

# Anderson Cesar Zani Head Organizer

# Current and future perspectives on health

**Brazilian Journals Editora 2024** 

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Diagramação: Editora Edição de Arte: Editora Revisão: Os Autores

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# Dados Internacionais de Catalogação na Publicação (CIP)

Current and future perspectives on health / Anderson Cesar Zani. São José dos Pinhais: Editora Brazilian Journals, 2024.

Formato: PDF

Requisitos de sistema: Adobe Acrobat Reader

Modo de acesso: World Wide Web

Inclui: Bibliografia

ISBN: 978-65-6016-073-6

1. Saúde. 2. Medicina.

I. Zani, Anderson Cesar. II. Título

Brazilian Journals Editora São José dos Pinhais – Paraná – Brazil www.brazilianjournals.com.br editora@brazilianjournals.com.br

# **PRESENTATION**

The book Current and Future Perspectives on Health offers the reader a thought-provoking view of the present and future of health in a world that is constantly changing. In an era marked by technological advances, demographic changes and global challenges, such as population aging and new threats to public health, understanding where we are headed has become more crucial than ever.

Throughout its pages, the book discusses how medicine and health sciences have evolved to meet the demands of modern society, exploring both current approaches and trends and innovations that promise to shape the future. Issues such as the incorporation of artificial intelligence into medical practice, the personalization of treatments and the growing emphasis on prevention and health promotion are addressed in an accessible yet in-depth manner.

We recommend this reading to anyone seeking to better understand the challenges and opportunities that arise in the field of health, whether you are a professional in the field, a student or someone interested in understanding the paths that medicine and health are taking. With an approach that combines critical analysis and optimism, this book aims to be a reflection on how we can build a healthier and more sustainable future, integrating science, technology and humanized care.

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# **CHAPTER 1**

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**ABSTRACT:** This study investigates the prevalence and impact of sexual dysfunction induced by selective serotonin reuptake inhibitors (SSRIs), which are widely used in the treatment of depression. SSRIs are associated with significant sexual side effects, including reduced sexual desire, difficulties in arousal, and delayed ejaculation, which negatively affect quality of life and treatment adherence. The review highlights the need for effective therapeutic approaches, such as dose reduction of SSRIs, substitution with medications with a lower sexual impact, or the addition of adjunctive medications. The methodology adopted involved conducting searches in recognized databases, resulting in an initial selection of 35 articles. Of these, 21 met the predefined criteria. The research emphasizes the importance of clear communication between physicians and patients for the proper management of these side effects.

**KEYWORDS:** selective serotonina reuptake inhibitors, sexual dysfunction, men, ejaculation, solutions.

RESUMO: Este estudo investiga a prevalência e o impacto da disfunção sexual induzida por inibidores seletivos da recaptação de serotonina (ISRSs), amplamente usados no tratamento da depressão. Os ISRSs são associados a efeitos colaterais sexuais significativos, incluindo redução do desejo sexual, dificuldades na excitação, e retardo na ejaculação, afetando negativamente a qualidade de vida e a adesão ao tratamento. A revisão destaca a necessidade de abordagens terapêuticas eficazes, como a redução da dose de ISRSs, substituição por medicamentos com menor impacto sexual ou a adição de medicamentos adjuvantes. A metodologia adotada consistiu na realização de buscas em bases de dados reconhecidas, resultando na seleção inicial de 35 artigos. Desses, 21 atenderam aos critérios previamente estabelecidos. A pesquisa enfatiza a importância de uma comunicação clara entre médicos e pacientes para o manejo adequado desses efeitos colaterais.

PALAVRAS-CHAVE: inibidores seletivos da recaptação de serotonina, disfunção sexual, homens, ejaculação, soluções.

# 1. INTRODUCTION

In the United States, about 7.9% of men and 12.1% of women are affected by depression, and in 2005, approximately 10% of the population used antidepressants. Selective serotonin reuptake inhibitors (SSRIs) are often recommended as the initial treatment for depression, although they take several weeks or months to reach full efficacy, making treatment adherence essential. (JING; Straw-Wilson, 2016).

In 2003, approximately 41.7% of men and 15.4% of women discontinued their psychiatric medications due to perceived sexual side effects. Among these, SSRIs were associated with sexual dysfunction in 40% to 65% of cases, which can exacerbate depressive symptoms and hinder treatment continuation. Although some studies suggest that the prevalence of these effects may be overestimated, sexual dysfunction remains a significant concern, often underreported. Only 14% of patients mentioned these effects on their own, while 58% did so only when directly questioned by physicians. (Jing; Straw-Wilson, 2016).

Selective serotonin reuptake inhibitor (SSRI) antidepressants are widely used in the treatment of depression, but their relationship with sexual dysfunction is a critical aspect that needs to be well understood. According to Kronstein et al. (2015), the difficulties in measuring sexual dysfunction in clinical trials for depression may lead to an underestimation of the adverse effects of these drugs, highlighting the need for more effective methods to assess and report sexual dysfunction, which is essential for a more accurate understanding of the impact of SSRIs on patients' sexual health.

The prevalence of antidepressant-induced sexual dysfunction has been extensively documented, as noted by Williams et al. (2006), who estimated the prevalence and impact of this side effect in two European countries. The study revealed that a significant proportion of patients using SSRIs experience sexual dysfunction, which can negatively affect treatment adherence and quality of life. The authors emphasize that sexual dysfunction is a significant side effect that should be carefully monitored to ensure effective and satisfactory treatment for patients.

Additionally, Rothmore (2020) reviews antidepressant-induced sexual dysfunction, noting that SSRIs, while effective in treating depression, are frequently associated with problems such as decreased libido, erectile difficulties, and delayed ejaculation. The study highlights that these side effects can be debilitating and need to

be addressed with appropriate strategies, such as dose adjustments or medication changes, to minimize their impact on men's sexual health.

Considering that SSRI-associated sexual dysfunction is often underreported and is considered a significant concern for patients using SSRIs, it is crucial for healthcare professionals to address this issue proactively and carefully to manage and mitigate these side effects, which have such a negative impact on patients' lives. The emphasis should be on the most common types of sexual side effects, the specific risks of each SSRI, and the alternatives should the treatment become intolerable. The study underscores the importance of clear and effective communication to improve both patient education and the quality of treatment provided. (Williams et al., 2006; Kronstein et al., 2015; Jing; Straw-Wilson, 2016; Rothmore, 2020).

In this context, and considering that this issue represents a global public health problem, this review aims to analyze the main therapeutic approaches for managing sexual dysfunction induced by selective serotonin reuptake inhibitors.

# 2. METHODOLOGY

This study is an integrative literature review, for which searches were conducted in renowned scientific databases such as the "Scientific Electronic Library Online" (Scielo), the "US National Library of Medicine" (PubMed), the "Latin American and Caribbean Health Sciences Literature" (LILACS), and Google Scholar, using the following descriptors: "selective serotonin reuptake inhibitors," "sexual dysfunction," "men," "ejaculation," and "solutions," separated by the Boolean term "AND," as well as their equivalents in Portuguese and Spanish, as listed on the DeCS platform (Health Sciences Descriptors).

From the database search, 30 articles were initially identified. Of these, 23 met the previously established criteria and were selected to compose the final set of this review. The inclusion criteria used in selecting references for this literature review involved the relevance of the studies to the central theme of the research, methodological quality, recency of the publications, type of study (primary or secondary), relevance of the population and sample studied, language, and accessibility of the articles, as well as publication in reliable sources. These criteria were adopted to ensure that the review was comprehensive, rigorous, and pertinent to

the field of study. As a justification for this research, the current relevance of the widespread use of selective serotonin reuptake inhibitors (SSRIs) is highlighted, given their significant role in treating depressive and anxiety disorders, conditions that affect a large portion of the global population. However, a crucial side effect of these medications is sexual dysfunction, which has become a growing global health concern. SSRI-associated sexual dysfunction can manifest as reduced sexual desire, difficulties in arousal, erectile dysfunction, and problems with orgasm, negatively impacting patients' quality of life and treatment adherence. The prevalence of these adverse effects can vary widely, influenced by factors such as the type of SSRI used and individual patient characteristics. This problem not only compromises the sexual health and well-being of individuals but also represents a significant challenge for healthcare professionals, who must balance the efficacy of antidepressant treatment with the appropriate management of side effects.

Therefore, the objective of the review was to analyze the main therapeutic approaches for managing sexual dysfunction induced by selective serotonin reuptake inhibitors.

# 3. RESULTS AND DISCUSSION

Sexual behavior is regulated by brain structures such as the medial forebrain bundle, the medial preoptic area of the hypothalamus, and the ventral tegmental area of the midbrain. The human sexual cycle involves desire, arousal, and orgasm, which are influenced by neurotransmitters. Desire is stimulated by dopamine, melanocortin, testosterone, and estrogen, and inhibited by prolactin and serotonin. Arousal is enhanced by nitric oxide, norepinephrine, melanocortin, testosterone, acetylcholine, and dopamine, while serotonin has a negative effect. Orgasm, linked to male ejaculation, is driven by norepinephrine and, to a lesser extent, by dopamine and nitric oxide, with a negative effect from serotonin. (Das, 2017).

Antidepressants can cause sexual dysfunction at any stage of the sexual cycle, including delayed ejaculation, difficulties with orgasm, reduced desire and arousal, erectile dysfunction, and decreased vaginal lubrication. All antidepressants have the potential to cause these effects, with a significantly higher prevalence among SSRIs, ranging from 10% to 80%. (Das, 2017).

SSRIs relieve depression symptoms by selectively inhibiting serotonin reuptake in the central nervous system. It is believed that various side effects associated with these medications result from increased serotonin in specific subtypes of serotonin receptors in different parts of the body. This increase may interfere with other hormones and neurotransmitters, such as testosterone and dopamine. Testosterone plays a role in sexual arousal, while dopamine is important for orgasm, which may lead to sexual dysfunction as a side effect. One of the most common sexual side effects of SSRIs is delayed ejaculation. Other effects include reduced sexual desire, less sexual satisfaction, anorgasmia, and impotence. (Jing; Straw-Wilson, 2016).

Sexual dysfunction is a common and often underestimated side effect of treatment with selective serotonin reuptake inhibitors (SSRIs), which can negatively impact patients' quality of life and lead to treatment discontinuation. (Jing; Straw-Wilson, 2016).

A prospective and descriptive clinical study with 344 participants showed that paroxetine caused more sexual side effects compared to fluvoxamine, sertraline, and fluoxetine. The incidence of sexual dysfunction was similar between fluoxetine and escitalopram. Side effects increased with higher doses of SSRIs, indicating the need to use the lowest effective dose. Paroxetine is associated with a higher risk of delayed ejaculation, reduced sexual desire, and impotence. Up to 42.5% of patients with sexual side effects considered discontinuing treatment. If sexual dysfunction persists, changing medication or adding a complementary antidepressant may be necessary. (Montejo-Gonzàlez et al., 1997; Stahl, 1998; Waldinger et al., 2004; Safa et al., 2013).

These findings are consistent with a similar study, which indicated that paroxetine caused more sexual dysfunction compared to fluvoxamine, sertraline, and fluoxetine. Although citalopram also appears to be associated with a high frequency of sexual dysfunction, this result has not been confirmed in other studies. Arlas et al. reported that sexual dysfunction occurred in 75.5% of cases with paroxetine and in 28.9% with citalopram. Both Arlas et al. and Waldinger et al. observed that citalopram resulted in less delayed orgasm and ejaculation compared to paroxetine. Based on these studies, paroxetine presents the highest risk of causing sexual dysfunction among SSRIs. (Arias et al., 2000; Waldinger; Zwinderman; Olivier, 2001; Hirschfeld, 2003).

Several approaches have been explored to mitigate the effects of SSRIs on male sexual function, aiming to improve patients' quality of life without compromising the treatment of underlying psychiatric disorders. One of the main approaches suggested in the literature is to reduce the SSRI dose, which may decrease the intensity of sexual side effects without losing therapeutic efficacy. However, this strategy should be pursued cautiously, as there may be a risk of depressive symptoms relapsing. Additionally, some studies indicate that switching to another SSRI with a lower risk profile for sexual dysfunction, such as fluvoxamine, or to antidepressants from another class, such as bupropion or mirtazapine, may be effective. Bupropion, in particular, is often cited as a substitution option, as it has a different pharmacological profile that may minimize sexual dysfunction. (Serretti; Chiesa, 2009; Jing; Straw-Wilson, 2016).

According to Das (2017), one of the main proposed solutions is medication modification. The article reports that switching from one psychotropic drug to another with a lower potential for causing sexual dysfunction can lead to substantial improvements. For example, replacing antidepressants with a high incidence of sexual side effects, such as paroxetine, with alternatives with less impact, such as bupropion, has shown positive results in several studies. The author mentions that in a specific study, switching to bupropion led to a reduction of up to 50% in the sexual dysfunction symptoms reported by patients.

Bupropion has been extensively studied as an effective alternative for managing SSRI-induced sexual dysfunction. Bupropion, an antidepressant that, unlike SSRIs, acts as a dopamine and norepinephrine reuptake inhibitor without directly interfering with serotonin levels, has shown good results in restoring sexual function without significantly interfering with depression treatment. This difference in mechanism of action is critical, as SSRI-associated sexual dysfunction is largely attributed to increased serotonin, which can inhibit dopamine release in brain areas related to sexual pleasure, while bupropion works by increasing dopamine release, a neurotransmitter related to pleasure and sexual desire. This improvement is particularly observed in areas such as sexual desire, arousal, and the ability to achieve orgasm. (Gitlin, 1994; Zisook et al., 2006).

Additionally, Zisook et al. (2006) emphasize that bupropion may be a suitable alternative for both patients starting antidepressant treatment and those already

suffering from SSRI-induced sexual dysfunction. Bupropion's versatility, whether used alone or in combination with other medications, allows for a more personalized treatment adaptation, aiming to maximize therapeutic effects while minimizing undesirable side effects. In this sense, bupropion emerges as a promising option for treating sexual dysfunction related to SSRI use, offering patients an approach that not only controls depressive symptoms but also contributes to improving sexual quality of life. Although further studies are needed to validate these results and investigate the mechanisms involved, the available evidence suggests that bupropion may be an effective therapeutic strategy in this context.

A placebo-controlled, double-blind study evaluated the use of sustained-release bupropion, administered at a dose of 150 mg twice daily, as an adjunct treatment to SSRIs in 55 patients who had SSRI-induced sexual dysfunction. Participants had been on citalopram, fluoxetine, paroxetine, or sertraline for at least 3 months. After 4 weeks of intervention, the bupropion group showed a significant increase in desire and sexual activity frequency compared to the placebo group. While there were also improvements in orgasm and overall sexual function in both groups, these changes were not statistically significant. Another study evaluated the use of bupropion as needed, starting with doses of 75 mg of immediate-release bupropion, administered 1 to 2 hours before sexual activity. Doses were adjusted based on the improvement of sexual dysfunction symptoms, with the maximum dose being 75 mg of immediaterelease bupropion three times a day. Overall, bupropion reversed SSRI-induced sexual dysfunction in 66% of patients when used regularly. When administered as needed, there was an improvement in sexual symptoms in 38% of cases. These findings indicate that bupropion may be a useful option as an adjunct to SSRI therapy in patients experiencing reduced sexual activity. However, it is important to note that the improvement in sexual dysfunction may be an indirect result of additional relief from depressive symptoms, which also impact sexual function. (Ashton; Rosen, 1998; Montejo et al., 2001).

In addition to bupropion, another strategy discussed by Jing and Straw-Wilson (2016) and Das (2017) is the addition of sildenafil (and other phosphodiesterase type 5 inhibitors) to the treatment, which, like bupropion, can mitigate the sexual effects of SSRIs. In particular, sildenafil has been widely studied to treat SSRI-associated erectile dysfunction and may be a viable solution for men experiencing this type of side

effect. Although the use of adjunctive medications has shown positive results in many cases, it is also noted that efficacy may vary and that continuous monitoring is necessary to adjust the approach according to the patient's response. Trazodone has also been investigated as a potential solution for sexual dysfunction caused by selective serotonin reuptake inhibitors (SSRIs). According to Stryjer et al. (2009), trazodone, an antidepressant that acts as a serotonin 5-HT2A receptor antagonist and as a serotonin reuptake inhibitor to a lesser extent, has a pharmacological profile that may counterbalance SSRI-induced sexual side effects.

This antagonism at 5-HT2A receptors is particularly relevant because these receptors are implicated in mediating serotonin's inhibitory effects on sexual function. Stryjer et al. (2009) highlight that trazodone administration, both as monotherapy and in combination with SSRIs, can lead to significant improvements in patients' sexual function. Trazodone, by partially reversing sexual dysfunction, can help restore sexual desire, arousal, and the ability to reach orgasm, areas often compromised by SSRI use. This effect is particularly important in patients whose sexual dysfunction does not improve with bupropion or other adjunct therapies. The ability of trazodone to mitigate SSRI-induced sexual dysfunction, without compromising the antidepressant effect of SSRIs, makes it an attractive option for treating this side effect.

# 4. CONCLUSION

Given the prevalence of sexual dysfunction in patients with depression, it is essential for healthcare professionals to conduct a comprehensive assessment and provide explanations regarding the potential side effects of antidepressant pharmacotherapy. For sexually active patients who require an SSRI, it is recommended to start with fluoxetine or sertraline, as they have a lower incidence of causing sexual dysfunction. Paroxetine should be the last choice, as it has the highest rate of sexual dysfunction. If an SSRI is chosen, patients should be maintained on the lowest effective dose to reduce the risk of adverse effects. If sexual side effects occur in patients stabilized on an SSRI, solutions include reducing the medication dose, implementing "drug holidays," switching to an alternative antidepressant, or adding an adjunctive antidepressant, such as bupropion, which has shown excellent results both as an adjunct and as a replacement for SSRIs.

The main limitation observed is that switching medications or introducing adjuncts does not always completely resolve sexual dysfunction and may, in some cases, result in additional side effects.

Moreover, various other strategies have been proposed to mitigate these adverse effects, and the choice of intervention should be individualized, taking into account the patient's characteristics and the severity of symptoms.

Lastly, patient education and open discussion about sexual side effects are crucial. Clear communication can help alleviate the anxiety and discomfort associated with sexual dysfunction and improve treatment adherence. Patients should be informed about potential side effects before starting therapy and encouraged to report any sexual issues that arise during treatment. This can help adjust the treatment more effectively and enhance overall satisfaction with antidepressant therapy.

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# **CHAPTER 2**

# THE INFLUENCE OF COMBINED ORAL CONTRACEPTIVES ON FEMALE LIBIDO AND SEXUAL FUNCTION

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ABSTRACT: Combined oral contraceptives (COCs) are effective contraceptive methods, but they raise concerns about their side effects, especially regarding libido, which affects numerous women worldwide. The prevalence of COC use varies across different populations, influenced by sociocultural and economic factors. Despite their efficacy, the relationship between COC use and female libido is a complex and debated topic, with studies pointing to potential impacts on sexuality. The objective of this review is to analyze and discuss the effects of combined oral contraceptives on female libido. The methodology used involved searches in renowned databases, initially selecting 35 articles, of which 21 met the pre-established criteria. The relationship between COC use and libido is complex and influenced by various factors, such as hormonal changes, like decreased testosterone levels and reduced natural lubrication in women, however, this is not a universal experience. Therefore, future studies are needed to investigate this issue in greater depth.

**KEYWORDS:** combined oral contraceptives, hormonal contraceptives, women, libido, sexuality.

**RESUMO:** Os anticoncepcionais orais combinados (AOCs) são métodos contraceptivos eficazes, mas levantam preocupações sobre seus efeitos colaterais, especialmente em relação à libido, o que afeta diversas mulheres ao redor do mundo. A prevalência do uso de AOCs varia entre diferentes populações, influenciada por fatores socioculturais e econômicos. Apesar de sua eficácia, a relação entre o uso de AOCs e a libido feminina é um tema complexo e debatido, com estudos apontando para possíveis impactos na sexualidade. O objetivo da presente revisão analisar e discorrer sobre os efeitos dos anticoncepcionais orais combinados na libido da mulher. A metodologia utilizada foi buscas em bases de dados renomadas, selecionados inicialmente 35 artigos, dentre os quais 21 se enquadraram nos critérios préestabelecidos. A relação entre o uso de AOCs e a libido é complexa e influenciada por diversos fatores, como por exemplo alterações hormonais, como a diminuição dos níveis de testosterona e diminuição da lubrificação natural da mulher, porém essa não

é uma experiência universal. Portanto, estudos futuros são necessários para investigar em maior profundidade o tema em questão.

**PALAVRAS-CHAVE:** contraceptivos orais combinados, contraceptivos hormonais, mulheres, libido, sexualidade.

# 1. INTRODUCTION

Combined oral contraceptives (COCs) are widely used hormonal contraceptive methods among women of reproductive age. These methods contain a combination of synthetic hormones, primarily estrogen and progestogen, which act in different ways to prevent pregnancy (Adriane Cristina Bovo et al., 2023). There are various types of COCs, including monophasic, biphasic, and triphasic pills, with different hormonal dosages and mechanisms of action. Since the 1960s, COCs have transformed family planning, offering women greater control over their reproductive lives. However, concerns about side effects have driven the development of new formulas with less estrogen and more progestogen, making them safer (Adriane Cristina Bovo et al., 2023).

The use of COCs is quite prevalent in many countries, being a contraceptive option chosen by many women due to their effectiveness and convenience. However, it is important to note that the prevalence of such medications varies among different populations, influenced by sociocultural, economic, and healthcare access factors (Zgliczynska et al., 2019).

The epidemiology of combined oral contraceptive use varies depending on the region and socioeconomic context. In Brazil, studies show that a significant portion of the female population of reproductive age uses COCs as their preferred contraceptive method. Data from a study indicate that among medical students, there is a high prevalence of use, reflecting both the reliability and easy access to these medications. However, while COCs are widely recognized for their contraceptive efficacy, there is growing interest and concern regarding their effects on sexual health, particularly concerning female libido (Cabral et al., 2018).

The high adherence to COCs, proven to be effective and safe, underscores their importance for reproductive health and family planning. UN data indicate that they are the fourth most commonly used contraceptive method globally, with over 151 million users. In Brazil, this number is even more significant, with nearly 30% of women opting for this method, contributing to improved maternal and child health and female empowerment (Adriane Cristina Bovo et al., 2023).

The relationship between hormonal contraceptives and female sexual desire is a complex and debated topic since their introduction to the market, with concerns about possible impacts on libido and adherence to the method. Despite three subsequent

decades during which a variety of new hormonal contraceptives with lower dosages and innovative administration systems have become available, the adverse effects on users' sexual desire remain a concern (Schaffir, 2006).

It is important to consider the role of sex hormones, particularly testosterone, in regulating female libido. Testosterone, although commonly associated with males, plays a significant role in female sexuality, influencing sexual desire and satisfaction. The use of COCs may interfere with hormonal levels, including testosterone, which could contribute to changes in libido.

Due to the great relevance of COCs, which are widely used worldwide, the objective of this literature review was to analyze and discuss the effects of combined oral contraceptives on women's libido.

# 2. METHODOLOGY

This study is an integrative literature review, for which searches were conducted in the databases "Scientific Electronic Library Online" (Scielo), "US National Library of Medicine" (PubMed), and Google Scholar, using the following descriptors: "combined oral contraceptives," "hormonal contraceptives," "women," "libido," and "sexuality," in addition to their corresponding terms in Portuguese, as listed on the DeCS (Health Sciences Descriptors) platform. It is worth noting that for the searches in these databases, the boolean term "AND" was also used between descriptors to ensure a more accurate selection of articles related to the proposed topic.

The inclusion criteria defined for the selection of articles that comprised the references for this review were: publications in English and Portuguese, thematically relevant to the review, indexed in the aforementioned databases, and study type, with a preference for randomized clinical trials and meta-analyses.

It is important to highlight that, in addition to recent studies from the literature, pioneering articles on the topic were also used to provide well-founded theoretical data for a more thorough discussion.

From the database searches, 35 articles were initially selected, of which 21 met the previously established criteria for the final selection of the research's literary collection.

The analysis of the selected articles enabled the gathering of information that contributed to the development of this study, which aimed to analyze and discuss the effects of combined oral contraceptives on women's libido, considering the current relevance of the topic, as oral contraceptives are widely used by women across all continents, highlighting an important public health issue today.

# 3. RESULTS AND DISCUSSION

Combined oral contraceptives (COCs) are one of the most common forms of hormonal contraception, widely used by women around the world. However, despite their efficacy, COCs have been associated with a range of side effects, including a decrease in libido or sexual desire. This literature review aims to explore the physiological and biochemical mechanisms by which COCs may negatively impact female libido, as discussed in previous studies.

One of the main mechanisms through which COCs affect libido is the alteration of sex hormone levels, particularly androgens. Androgens, including testosterone, are essential for regulating sexual desire in both men and women. According to Greco et al. (2007), the use of COCs is associated with a reduction in free testosterone levels in the blood. This occurs because COCs increase the production of sex hormone-binding globulin (SHBG), a protein that binds to testosterone, rendering it biologically inactive. As a result, the availability of free testosterone, which is crucial for libido, is reduced, potentially leading to a decrease in sexual desire.

If hormonal contraception had a consistent biological impact on sexual desire, androgens would be the main suspects in playing this role. Androgens have long been recognized as the primary hormonal influence on women's sexual desire. Reduced libido is a classic sign of androgen deficiency, and androgen replacement therapy has been shown to be effective in restoring normal libido in women with hypoactive sexual desire. Furthermore, it is observed that female sexual activity, including sexual initiation, tends to increase during the mid-follicular phase of the menstrual cycle, a time when androgen levels are elevated (Persky et al., 1982; Sherwin & Gelfand, 1987; Shifren et al., 2000; Bachmann et al., 2002; Schaffir, 2006).

Exogenous estrogen, in turn, is linked to a reduction in biologically active testosterone levels. This occurs because it increases the production of sex hormone-

binding globulin, resulting in greater binding of circulating testosterone. Therefore, it is expected that contraceptives containing estrogen reduce the amount of free testosterone and potentially exert a significant effect on sexual desire (Schaffir, 2006).

Moreover, Herzberg et al. (1971) observed that prolonged use of COCs may be associated with the development of depressive symptoms, which, in turn, may negatively impact libido. The authors suggest that the relationship between hormonal contraception and depression may be mediated by changes in hormonal balance, particularly through decreased androgen levels and increased SHBG production. Depression, being a factor that frequently coexists with low libido, may thus exacerbate the impact of COCs on female sexual desire.

The estrogens present in COCs also play a crucial role in modulating libido. While estrogen is necessary for maintaining sexual function, when administered in high doses, as in some COCs, it can lead to a hormonal imbalance that suppresses the natural production of testosterone by the ovaries (DEI et al., 1997). This imbalance contributes to a decrease in sexual desire, especially in women who are already sensitive to hormonal fluctuations.

Caruso et al. (2022) explore a more centered approach on "sexual acceptability," discussing how women's perceptions of the effects of COCs on their sexuality can directly influence their experience of sexual desire. The authors suggest that prior knowledge of potential adverse effects and adaptation to contraceptive use may mitigate the perception of reduced libido, implying that the negative impact of COCs may be both psychosomatic and physiological.

Another relevant factor is the influence of COCs on the menstrual cycle and, consequently, on the hormonal variations that occur throughout the cycle. The literature suggests that COCs, by suppressing ovulation, eliminate the natural hormonal peaks that typically contribute to increased libido during the fertile period. This uniformity in hormonal levels may lead to stabilization of libido at a lower level, without the peaks of sexual desire that occur in a natural menstrual cycle (Higgins et al., 2020).

The study by Cristina et al. (2023) corroborates these observations, highlighting that the reported decrease in libido among COC users may be attributed to both hormonal factors and the subjective perception of changes in sexual desire. The authors emphasize that, in addition to physiological changes, the psychosocial context

and the relationship with the partner also play a crucial role in the experience of female sexuality during COC use.

It is important to consider that individual variability in response to COCs also plays a significant role. Schaffir (2006) emphasizes that not all women experience a decrease in libido, and responses to COCs can vary widely depending on individual sensitivity to hormones, the specific formulation of the contraceptive, and psychosocial factors.

Davis and Castaño (2004) suggest that the choice of a specific COC formulation may help mitigate adverse effects on libido. Some women may benefit from COCs with lower doses of estrogen or those that utilize progestins that have a lesser impact on SHBG levels, resulting in smaller reductions in free testosterone. However, there is still a need for further research to identify which formulations are most favorable for maintaining libido.

Research indicates that the hormones present in COCs, primarily estrogens and progestins, may influence sex hormone levels, such as testosterone, and consequently affect libido (DEI et al., 1997; Greco et al., 2007; Hasegawa et al., 2022). Furthermore, psychological factors, such as anxiety, depression, and body image, may also be related to changes in libido among COC users (Herzberg et al., 1971; Higgins et al., 2020; Mark et al., 2016).

The relationship between the use of combined oral contraceptives and female libido is complex and multifaceted, reflecting the interaction of hormonal, psychological, and contextual factors. Various studies address this issue from different perspectives, suggesting that the impact of COCs on libido may vary according to hormonal composition, individual response, and other external factors, such as interpersonal relationships and the mental health of the user.

A classic study conducted by Davis and Castaño (2004) suggests that COCs may have a biphasic effect on libido, where some women report a decrease in sexual desire, while others do not experience significant changes or even perceive an increase in libido. This variability may be attributed to different COC formulations and how sex hormones influence sexual desire. Greco et al. (2007) explored the relationship between androgen levels and libido, highlighting that certain COCs may reduce free testosterone levels in the blood, which, in turn, may decrease sexual desire in some women.

Another relevant point discussed by Herzberg et al. (1971) and reaffirmed by Schaffir (2006) is the relationship between COC use and depressive symptoms, which may indirectly affect libido. The authors suggest that, in some women, prolonged use of COCs may be associated with the onset of depressive symptoms, which are often accompanied by a reduction in sexual interest. Hasegawa et al. (2022) corroborate this view, highlighting that users' perceptions of the effects of COCs on their sexuality are crucial for understanding the breadth of these effects.

On the other hand, more recent studies, such as that of Caruso et al. (2022), adopt a more centered approach on "sexual acceptability," considering not only the direct effects of hormones on libido but also how users perceive and adapt to the use of COCs concerning their sexual life. This study highlights that acceptance of the contraceptive method and satisfaction with it play a fundamental role in maintaining healthy libido, suggesting that the negative impact of COCs on sexual desire may be mitigated by a conscious and informed choice of method.

Additionally, Mark et al. (2016) conducted an analysis that considers the perspective of male partners, revealing that men's perceptions of their partners' sexual desire are also influenced by the type of contraceptive used. This study is particularly interesting as it broadens the debate to include relationship dynamics, suggesting that the sexual satisfaction of both partners should be considered when evaluating the effects of COCs on female libido.

While the reviewed literature shows a wide range of results, it is evident that COCs can have both positive and negative effects on libido, depending on multiple factors. Research by Cristina et al. (2023) and Gambrell (2024) emphasizes that individualized monitoring and adjustment of the contraceptive method may be necessary to minimize adverse effects and optimize the sexual well-being of users.

In a study conducted by Cabral et al. (2018), the prevalence of side effects was assessed among medical students at a private institution. The cross-sectional study included 100 women using COCs. The results indicated that 75% of participants reported some type of side effect, with decreased libido being one of the most frequently mentioned, present in 38% of users.

Another relevant study, conducted by Caruso et al. (2022), investigated how the use of COCs affects women's sexuality, focusing on the "sexual acceptability" of the contraceptive method. The research, which involved 1,000 women of different ages

and socioeconomic conditions, utilized a structured questionnaire to collect data on participants' sexual satisfaction. The results showed that 27% of women reported a noticeable reduction in libido after starting COC use, while 15% indicated a decrease in overall satisfaction with their sexual life. The authors suggest that these impacts may be related to both hormonal factors and subjective perceptions of contraceptive effects.

Davis and Castaño (2004) conducted a comprehensive review of available research on the relationship between COCs and libido in women. The review included studies with samples ranging from 50 to 2,000 participants, encompassing a wide range of methodologies, from observational studies to randomized clinical trials. The authors concluded that there is significant variability in results, with some studies reporting a decrease in libido in up to 40% of users, while others found no significant association between COC use and changes in sexual desire.

The existing literature suggests that COCs may influence libido through hormonal and psychosocial mechanisms, leading to reduced sexual desire in some women. However, the complexity of individual responses and the influence of contextual factors highlight the importance of personalized approaches when considering contraceptive methods. Future research should aim to investigate the effects of specific formulations of COCs on libido, taking into account the diverse experiences of women who use them.

# 4. CONCLUSION

Combined hormonal contraceptives (CHCs) are widely used contraceptive methods among women of reproductive age. Composed of a combination of estrogen and progestin, these methods serve as an effective and commonly employed tool for birth control. However, in addition to their contraceptive benefits, it is essential to understand the potential adverse effects, including those related to sexual health. Among the most frequent complaints associated with the use of CHCs is a reduction in libido.

The literature review indicates that, while CHCs may reduce libido in many women, this is not a universal experience, and various factors influence these outcomes, including the formulation of the contraceptive, the user's mental health, and

relationship dynamics. Some studies suggest that the use of CHCs may lead to decreased libido, while others find no significant association between these factors.

It is important to emphasize that the mechanisms by which CHCs may affect libido are complex, multifactorial, and not yet fully understood, necessitating the consideration of individual characteristics of each woman for an adequate understanding of the phenomenon. Some studies propose that the reduction in circulating androgen levels induced by the use of CHCs may contribute to decreased sexual desire. However, other factors, such as hormonal, psychological, and relational changes, may also play a significant role.

Moreover, it is crucial for women to be adequately informed about the possible side effects of CHCs, including those related to libido. Open communication between healthcare providers and patients is essential to identify and address any issues related to sexuality during the use of CHCs, facilitating the development of strategies that can help women maintain a healthy and satisfying sexual life while using hormonal contraceptive methods.

In conclusion, combined oral contraceptives affect female libido through multiple interrelated mechanisms, including the reduction of free testosterone levels, changes in the menstrual cycle, and psychosocial influences. While these effects may be significant for some women, the individual response to CHCs varies, and the choice of contraceptive method should take into account both physiological factors and the personal preferences and psychological well-being of the user.

Future studies are necessary to further investigate the mechanisms by which CHCs may affect libido, as well as to identify risk factors for the development of sexual problems related to the use of these contraceptive methods.

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# **CHAPTER 3**

# EATING PATTERNS AND ACADEMIC STRESS IN COLLEGE STUDENTS

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#### 1. INTRODUCTION

Human nutrition involves a series of actions, such as dietary habits, food selection and preparation, as well as the quantities consumed; all of this is referred to as eating behavior. This behavior is influenced by factors such as material well-being, satisfaction with body weight, sports, and family behavior (Dolich et al., 2022). Similarly, psychological factors (childhood traumas, depression, and anxiety) and personality traits (perfectionism and optimism) also determine an individual's eating habits and food choices (Adachi & Adachi, 2021; Ergun et al., 2023). Furthermore, in university environments, the educational atmosphere, pressures inherent to this setting, and generated stress play a crucial role in students' food choices and health (Law & Rasmussen, 2024; Maza-Pérez et al., 2022; Silva-Ramos et al., 2020).

Some psychological theories suggest that eating patterns can act as mechanisms for managing emotional responses and adaptive coping; this applies to nearly half of university students. In other words, emotional eating involves using food as an emotional refuge when individuals cannot manage stressors. Thus, in some individuals, stress can lead to increased food intake or modifications in their diet (Gusni et al., 2022; Joseph et al., 2022; Wardle & Gibson, 2016). Previous research has shown a relationship between academic stress and changes in eating behavior, including shifts in food choices, skipping meals or altering meal times, increased consumption of fast food, caffeine intake, and even binge eating episodes (Maqsood et al., 2023; Rani, 2023; Ulhaq et al., 2022).

On the other hand, a balanced and high-quality diet provides the essential nutrients that the body and brain need to cope with stress, depression, and anxiety, playing a protective role (Ling et al., 2024; Rani, 2023). Therefore, adequate nutrition, along with a healthy lifestyle and the development of positive coping skills, can enhance stress resilience and diminish its negative consequences (Kim et al., 2023; Ling et al., 2024). In this regard, a study conducted in South Korea demonstrated that a high-quality diet reduces the risk of stress and depression while improving quality of life, particularly among women (Kim et al., 2023).

Exploring the complex relationship between academic stress and modifications in eating patterns among university students through a review of existing literature highlights the significant relevance due to its consequences on the physical and mental

health of this group. Moreover, addressing these issues is crucial for developing effective strategies that promote healthy eating while fostering mental health among young university students, thereby achieving optimal health and a healthy lifestyle.

This topic also directly relates to the United Nations Sustainable Development Goals (SDGs), particularly SDG 3: "Good Health and Well-Being" and SDG 4: "Quality Education." SDG 3 promotes ensuring healthy lives and well-being for all people of all ages. Addressing dietary habits and academic stress among university students directly contributes to this goal, as good nutrition and effective stress management are fundamental for physical and mental well-being. Initiatives that encourage healthy eating habits and strategies for managing stress can reduce the incidence of mental health issues and chronic diseases in this population, thereby improving their quality of life and overall well-being.

Meanwhile, SDG 4 aims to ensure inclusive, equitable, and quality education and promote lifelong learning opportunities for all. The connection between nutrition, stress, and academic performance underscores the need for a comprehensive approach in higher education that includes health and well-being promotion. Educational programs that integrate psycho-nutrition and stress management techniques not only enhance students' academic performance but also equip them with the necessary tools to maintain a healthy lifestyle throughout their lives. In this way, addressing these topics contributes to creating an educational environment that supports the holistic development of students, aligning with the goals of SDG 4.

#### 2. PSYCHOLOGICAL THEORIES AND MODELS ON NUTRITION AND STRESS

La relación que existe entre la conducta alimentaria y el estrés es sumamente compleja, y con la finalidad de intentar entenderla se han propuesto una serie de teorías psicológicas. Una de ellas es el modelo de integración Gen X estrés, que señala especificamente al gen DRD2 (Gan et al., 2023). Este gen esta relacionado con el sistema de recompensa del cerebro, involucrado en las experiencias del placer y en la motivación para llevar a cabo comportamientos que producen recompensa (Blum et al., 2024). También se ha relacionado con riesgo de adicciones o comportamientos adictivos relacionado a sustancias como el alcohol, la heroína, entre otras, o incluso a cuestiones alimentarias (Blum et al., 2023; Lachowicz et al., 2020).

La participación del gen DRD2 en la modulación de la transmisión y recepción de dopamina, la motivación, la cognoción y el comportamiento de búsqueda de recompensa subraya el papel crítico en los mecanismos neurobiológicos involucrados en los comportamientos adictivos (Chaudhary et al., 2019; Gan et al., 2023). De acuerdo al modelo de integración Gen X estrés, las diferencias idividuales con respecto al estrés es lo que explica las variaciones en las elecciones de alientos (Gan et al., 2023).

Una teoría adicional postula el concepto de restricción y sugiere que el estrés, la restriccción dietética y la desinhibición interactúan para afectar las conductas alimentarias, resaltando la fuerte influencia de la desinhibición en la alimentación excesiva. Adicionalmente se sugiere que el esfuerzo para resistirse a limitarse en la comida puede llevar a reacciones emocionales como la ansiedad, el remordimiento o incluso el estrés crónico, lo que puede desencadenar en una disminución del control conductual e incrementar los efectos negativos, lo que puede llevar a episodios de atracones, obsesión por la comida, cambios en el metabolismo o ciclos de restricción y atracones (Cubic, 1992; Yeomans et al., 2008).

#### 3. INFLUENCE OF DIET ON BRAIN FUNCTION, MOOD AND BEHAVIOR

Although it may sound incredible, diet can have a direct effect on mood by influencing the neurotransmitters and neuropeptides involved in regulating mood and appetite. Examples of this include serotonin and dopamine, two neurotransmitters associated with feelings of well-being. Similarly, neuropeptides such as orexin and ghrelin are responsible for regulating appetite and energy balance; an imbalance in the production, transmission, or reception of these chemical messengers can lead to mood disturbances and reduced motivation (Bremner et al., 2020).

Conversely, dietary modifications such as the consumption of polyunsaturated fats or high sugar levels can cause acute changes in mood by promoting inflammation, obesity, and triggering chronic degenerative diseases, which can ultimately affect an individual's mood (Bremner et al., 2020).

On the other hand, certain foods have been shown to be beneficial in reducing stress by stimulating adaptation mechanisms, improving stress resilience, and minimizing its effects. Furthermore, adequate nutrition supports homeostasis,

enhances resilience, and reduces the burden of stress consequences (Akarachkova et al., 2020). In this regard, increased consumption of fruits and vegetables rich in vitamins, antioxidants, and minerals can reduce stress, inflammation, and the risk of developing cerebrovascular disease (CVD), as well as support the production of adaptation mechanisms (Akarachkova et al., 2020; Kang et al., 2023). Similarly, the consumption of whole grains, rich in dietary fiber, resistant starch, phenolic compounds, and mono- and polyunsaturated fatty acids, as well as antioxidant compounds, reduces oxidative stress and the development of chronic degenerative diseases (Bouchard et al., 2022; Özer & Yazici, 2019; Rani, 2023). Additionally, lean proteins aid in regulating lipid metabolism and the gut microbiome, both of which contribute to homeostasis and stress reduction, thereby improving overall physiological function (Bouchard et al., 2022; Rani, 2023).

In this sense, a healthy diet helps regulate hormone levels in the body, such as cortisol and adrenaline, which are heavily involved in the stress response. Likewise, a balanced diet reduces blood sugar levels, which can mitigate mood swings and stress.

#### 4. FACTORS DETERMINING EATING BEHAVIOUR

Eating patterns and eating behavior are closely related, yet each encompasses different aspects of nutrition. The former refers to "the guidelines that determine the quantity and combination of foods consumed daily to meet nutritional needs" (Abril-Ulloa et al., 2017). In contrast, eating behavior pertains to the actions and behaviors that establish the human relationship with food, encompassing aspects such as eating habits, food selection, culinary preparations, and the quantities consumed. Eating behavior is not limited to food intake; it also includes both internal and external factors affecting the individual (Esparza-Varas et al., 2022; Exome, 2016).

Eating behavior is influenced by a multitude of factors, including social elements such as socioeconomic status, education, income, occupation, physical environment, race and ethnicity, gender, age, culture, and family (Aguilar et al., 2023; Bowley & Blundell, 2016; Noll et al., 2020). Psychological factors such as stress, depression, loneliness, and boredom have been linked to emotional eating and unhealthy food choices (Ljubičić et al., 2023). In this regard, food-rich environments promote eating behaviors without emotional limitations, driven by exposure to and availability of

delicious foods, particularly affecting women and individuals under dietary restrictions (Medina et al., 2023).

Additionally, cultural beliefs are crucial factors that directly impact dietary patterns and habits due to traditions (including food taboos, restrictions, and recommendations, especially during certain life stages such as pregnancy and lactation), social norms, personal values, and religious or spiritual beliefs (de Diego-Cordero et al., 2021; Doshi, 2023; Joy-Telu & Aga Segi, 2023; Montes Quiroz et al., 2023).

#### 5. IMPACT OF ACADEMIC STRESS ON STUDENTS' EATING HABITS

The constant academic pressure felt by university students significantly influences their eating behavior. Various studies indicate that the stress experienced by students in educational institutions can lead to changes in their eating habits, such as reduced food consumption, overeating, skipping meals, altering the time spent eating, and increasing the intake of fast and low-quality food (Chanchal, 2024; Maqsood et al., 2023). Irregular meal schedules and a notable reliance on coffee have also been linked to anxiety, stress, and symptoms of depression, particularly during exam periods (Maqsood et al., 2023). Furthermore, variations in perceived stress levels have been associated with modifications in lifestyle, underscoring the importance of promoting adequate health habits and stress management strategies (Mohsen, 2023). Additionally, the emotional eating of students correlates with high levels of stress, neurotic personality traits, and unhealthy eating behaviors (Azalea & Noerfitri, 2023).

Distress, emotional confusion, anxiety, or sadness can lead individuals with limited emotional resources to adopt unhealthy eating habits as a coping mechanism for their internal struggles. Extreme dieting or binge-eating episodes are examples of actions that attempt to regain a sense of control or comfort. Concerns about body image can also result in disordered eating habits as a means to regulate emotions through food-related behaviors. In other words, as psychological distress increases, eating behaviors become more disrupted, which in turn exacerbates distress levels, perpetuating a negative cycle (Khadija et al., 2023). It has been shown that students tend to decrease their intake of fruits and

vegetables while simultaneously incorporating more fast food into their diets during periods of heightened academic stress (Michels et al., 2020).

# 6. STRATEGIES TO IMPROVE ACADEMIC STRESS AND VARIABILITY IN FOOD QUALITY

To effectively reduce stress and improve the eating behaviors of university students, a comprehensive approach is necessary. One strategy that has been shown to help decrease emotional eating behaviors triggered by stress is the implementation of skills development in individuals, such as tolerance for distress and discomfort, as well as life history-based interventions (Li et al., 2024). Mandatory psychological support, seminars, and workshops focused on stress management and eating behaviors are other strategies to safeguard students' well-being throughout their lives by fostering the development of healthy psychological and dietary habits (Chanchal, 2024). Additionally, the development of exercise programs, promotion of healthy foods on campus, and initiatives focused on mindfulness, time management, and relaxation techniques are crucial (Di Francesco, 2019).

Improving sleep quality is another strategy, as it has been observed to weaken the relationship between perceived stress and harmful eating behaviors, such as impulsive and emotional eating (Du et al., 2022). Furthermore, intervention strategies like lifestyle redesign programs have demonstrated positive effects on student well-being, including reduced stress levels and improved quality of life (An & Kim, 2024).

#### 7. CONCLUSIONS AND FUTURE RECOMMENDATIONS

In conclusion, the eating behaviors of university students are significantly affected by academic pressure and various psychological and social factors. The correlation between stress and eating habits is reciprocal. While stress can lead to adverse changes in dietary routines, a balanced diet can serve as a protective element that enhances students' ability to manage stress. It is essential to recognize that eating habits impact not only physical well-being but also the mental and emotional health of students.

To effectively address these issues, it is crucial to apply multidisciplinary approaches that encompass nutritional interventions, psychological support, and the promotion of healthy lifestyles. These strategies will not only improve students' well-being and health but also contribute to achieving sustainable development goals related to health and quality education.

Some suggestions for enhancing the approach to the presented issues include the implementation of regular workshops and symposiums to inform students about the importance of a balanced diet and how their dietary choices can influence their mental well-being and academic performance. Additionally, access to psychological support aimed at combating academic stress and unhealthy eating behaviors is necessary. Creating healthy food environments on campus is essential to improve the variety of nutritious and healthy foods available in university cafeterias and dining halls. Similarly, promoting regular physical exercise through classes and sporting events is vital.

Furthermore, the implementation of programs and resources to help students improve their sleep habits, along with lifestyle redesign interventions that holistically address time management, relaxation, meditation, and other positive coping techniques, is important. Finally, regular and continuous evaluations of the established programs will measure their effectiveness and allow for necessary adjustments. If these strategies are effectively implemented, they will not only improve the quality of life for university students but also contribute to their academic success and overall well-being, aligning with global objectives for health and quality education.

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## **CHAPTER 4**

#### REPAIR OF CHONDRAL INJURIES IN THE KNEE

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#### 1. INTRODUCTION

Articular cartilage lesions, particularly those affecting the knee, represent one of the greatest challenges in orthopedics, both in terms of diagnosis and treatment. Since William Hunter described them as "untreatable" in 1743, therapeutic strategies have evolved significantly [1]. Today, with advancements in repair techniques and the use of biological therapies, regeneration of damaged cartilage has become a reality, offering new treatment perspectives for patients with complex joint lesions.

Over the past 30 years, the field of chondral lesion repair has been transformed, combining surgical and biological approaches, along with improvements in diagnosis. The use of orthobiologics, stem cells, and collagen scaffolds has shown promising results in restoring joint structure, improving function, and reducing pain.

#### 2. EPIDEMIOLOGY OF CHONDRAL LESIONS

Chondral lesions in the knee are common among patients undergoing arthroscopy, with a prevalence of 16–19%, increasing to 36% among athletes [2]. These lesions may occur in isolation or be associated with other joint pathologies, such as meniscal or ligament injuries. They can be classified according to the International Cartilage Repair Society (ICRS) based on the degree of cartilage impairment, with grades 3 and 4 (deep lesions involving the subchondral bone) being the most complex and generally requiring surgical intervention [3].

#### 3. COMPREHENSIVE CLINICAL EVALUATION

Clinical evaluation is essential for selecting the appropriate treatment. The medical history should identify the patient's complaints, functional limitations, and recovery expectations. Analyzing the patient's sports profile and daily activities helps to define the functional demands on the affected knee. Comorbidities and prior injuries, such as ligament or joint issues, should also be assessed, as they may impact cartilage healing. Complementary exams, such as X-rays and magnetic resonance imaging (MRI), are necessary to assess the extent of the lesion and the presence of osteoarthritis (Figure 1).

**Figure 1.** Sagittal (a) and axial (b) magnetic resonance imaging section of the left knee showing a deep chondral lesion on the medial facet of the patella (thin arrows), associated with subchondral



Source: Prepared by the authors.

#### 4. CLASSIFICATION OF CHONDRAL LESIONS AND SURGICAL PLANNING

The classification of chondral lesions, according to the International Cartilage Repair Society (ICRS) system, divides lesions into four grades: Grade I: Superficial lesion, with cartilage softening or superficial fissures only, without significant tissue loss. Grade II: Deeper lesion, with a depth up to 50% of the cartilage thickness. Grade III: Significant defect reaching more than 50% of cartilage thickness, potentially involving the subchondral bone. Grade IV: Lesion extending through the full thickness of the cartilage and eroding the subchondral bone.

Surgical planning should be personalized. Although chondral repair techniques have evolved, surgical planning must be meticulous, considering not only the lesion but also factors like joint alignment and meniscal stability. Untreated coronal malalignment can compromise chondral repair outcomes. Many surgeons recommend joint alignment correction (osteotomies) along with cartilage repair to optimize results. Alignment correction is essential to prevent joint overload, particularly in medial compartment lesions. In extensive or multiple lesions, an overcorrection to 2° to 3° of valgus may be indicated [4].

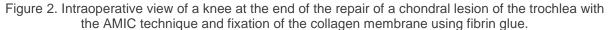
High-quality postoperative rehabilitation with physical therapy is crucial for treatment success. Well-structured protocols with early mobilization and supervised physical therapy ensure cartilage regeneration and efficient restoration of joint function

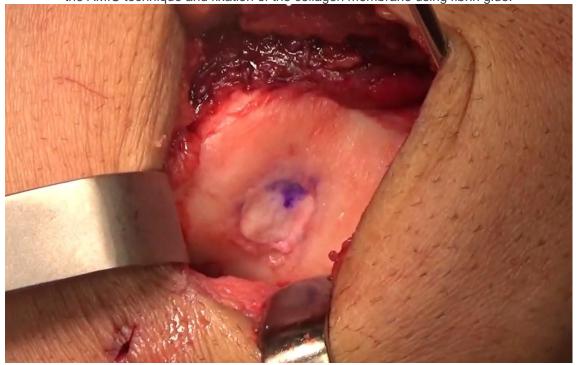
#### 5. CHONDRAL REPAIR SURGICAL TECHNIQUES

The choice of repair technique depends on the severity of the lesion. For smaller lesions, microfracture may be sufficient, while larger lesions or those at risk of failure require combined techniques, such as the use of biological grafts or biomaterials. The treatment choice also depends on factors such as lesion grade, location, defect size, patient age, and activity level.

Microfracture: a pioneering technique in chondral repair: Introduced by Steadman in 1997, microfracture is widely used for grade III and IV chondral lesions. It involves perforating the cartilage down to the subchondral bone, allowing bone marrow stem cells to migrate to the defect and form a blood clot (superclot), which serves as a biological scaffold for cartilage regeneration [5]. Although effective for smaller lesions, microfracture has limitations, such as the formation of fibrocartilage, which lacks the mechanical properties of original hyaline cartilage and may compromise long-term durability.

AMIC: Autologous Matrix-Induced Chondrogenesis: The use of collagen scaffolds can be combined with microfracture to promote hyaline cartilage formation in more extensive defects. The AMIC technique was developed to enhance microfracture outcomes. It uses a type I and III collagen membrane over the chondral lesion after microfracture (Figure 2). The membrane stabilizes the bone marrow clot and serves as a scaffold for stem cell differentiation into chondrocytes, promoting cartilage regeneration. Studies show that AMIC offers superior results compared to isolated microfracture, particularly in larger lesions, with improved quality of regenerated tissue and long-term clinical performance.





Source: Prepared by the authors.

Orthobiologics in Chondral Repair: Orthobiologics, such as bone marrow aspirate concentrate (BMAC), platelet-rich plasma (PRP), and mesenchymal stem cells (MSCs), have been widely used to enhance chondral lesion repair outcomes. MSCs can be extracted from bone marrow or adipose tissue, with adipose tissue offering an advantageous source due to its higher concentration of mesenchymal cells. These cells can differentiate into chondrocytes and other mesenchymal tissues, promoting more effective cartilage regeneration [6]. Additionally, the use of bone morphogenetic proteins (BMPs) and collagen matrix scaffolds has shown potential to enhance cartilage regeneration and improve the integration of new tissue with surrounding cartilage.

AMIC+: This technique combines AMIC with the use of mesenchymal stem cells derived from bone marrow (BMA) or adipose tissue (AD-MSCs). In the case of adipose grafting, the tissue is processed through microfragmentation to create a high-viscosity graft ideal for filling chondral defects. This biological stimulator, whether sourced from bone marrow or adipose tissue, is applied beneath a collagen membrane to maximize cartilage regeneration potential. These cells have a high potential to differentiate into cartilage and other mesenchymal tissues. The use of MSCs alongside the collagen membrane offers a promising treatment for focal chondral knee lesions. The AMIC+

technique combines biological regeneration with membrane coverage, delivering outcomes with higher-quality regenerated tissue, fewer complications, and reduced surgical times [7].

#### 6. CONCLUSION

The treatment of chondral lesions in the knee has advanced considerably, with technological and therapeutic innovations offering more effective and less invasive options. The combination of techniques such as AMIC and orthobiologics, especially adipose-derived stem cells, has shown promising short- and medium-term results. While the outcomes are encouraging, further research is needed to assess the durability of regenerated cartilage and to refine therapeutic approaches.

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## **CHAPTER 5**

TOTAL KNEE ARTHROPLASTY: A COMPARISON BETWEEN MECHANICAL AXIS AND PATIENT SATISFACTION IN NAVIGATED VERSUS CONVENTIONAL CASES

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#### 1. INTRODUCTION

Osteoarthritis (OA) is the most common form of joint disease and can lead to limitations in daily activities worldwide.<sup>1</sup> The global prevalence of knee OA is approximately 3.8%, a figure that has been increasing with population aging and the rise in obesity or overweight among the general population.<sup>1</sup>,<sup>2</sup>

Although knee OA is more prevalent among the elderly, it can also affect younger individuals, with treatment ranging from pain management through exercise, analgesics, education, and weight loss to total knee arthroplasty (TKA) when conservative treatment fails to control patient symptoms.<sup>2</sup>-<sup>6</sup>

One of the most determining factors in clinical and functional outcomes after TKA is lower limb alignment, with the restoration of the mechanical axis allowing for a margin of up to 3° in varus or valgus.<sup>3</sup>-9 In this context, computer-assisted surgery has improved surgical precision, particularly in an environment where the long-term efficacy of this treatment is increasingly crucial, given its growing use in younger patients.<sup>4</sup>,<sup>7</sup>-9

Currently, various techniques for correcting deformities in TKA are under discussion.<sup>1</sup>,<sup>10</sup> Besides mechanical alignment, which is widely used in Brazil, kinematic alignment appears to be of interest since a portion of the general population (32% of men and 17% of women) naturally has a constitutional varus with a natural mechanical axis of 3° or more.<sup>10</sup>-<sup>14</sup>

Studies show that approximately 25% of patients remain dissatisfied after undergoing TKA.<sup>15</sup>,<sup>16</sup> In addition to the type of prosthesis and surgical technique, factors such as gender, age, socioeconomic status, and psychological factors are also associated with postoperative clinical outcomes.<sup>2</sup>,<sup>5</sup>,<sup>6</sup>,<sup>11</sup>

The concept of quality of life has received significant attention in medical practice, resulting in an increasing number of tools aimed at evaluating it. <sup>18</sup> To assess clinical outcomes and patient satisfaction after TKA, there are both generic and specific instruments available.

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a questionnaire designed to assess treatment response in knee osteoarthritis patients. It is self-administered and captures relevant outcomes or consequences for

the patient. It includes 24 items divided into three subscales to assess pain, stiffness, and function, totaling 0–96 points, with a lower score indicating better outcomes.<sup>19</sup>

In addition to WOMAC, the Lysholm scale<sup>20</sup> was developed and later modified for evaluating knee symptoms and function. Comprising eight items that include gait, support, knee locking, instability, pain, and swelling, as well as difficulties with stair climbing and squatting, its primary use is for patients who have undergone treatment for anterior cruciate ligament injury, though it can also be used to assess patients post-TKA.<sup>21</sup>

The Short Form-12 (SF-12) is a generic questionnaire used to assess health-related quality of life, including questions on physical and mental health components.<sup>22</sup>,<sup>23</sup>

Considering the extensive international discussion on ways to achieve ideal alignment in TKA and the fact that mechanical alignment is the most commonly used approach in Brazil, we present here an evaluation and discussion on the degree of patient satisfaction in TKA using Navigated versus Conventional techniques.

The retrospective cross-sectional study presented here was approved by the Research Ethics Committee (REC) of Santa Casa de Misericórdia de Santos, under approval number 6.160.809. All patients who agreed to participate in this study signed the informed consent form, with confidentiality of their identities assured.

#### 2. MATERIAL AND METHODS

#### 2.1 DELINEATION

The sample consisted of patients who underwent TKA using navigated and conventional techniques at the same institution, performed by the same surgeon (T.R.S.) between 2019 and 2022. All patients with a diagnosis of OA who underwent primary TKA using the navigated and conventional techniques were included, performed with the Columbus system (Aesculap) for conventional cases and the OrthopilotTM system for navigated cases, by the same surgeon (T.R.S.) between 2019 and 2022. Patients who agreed to participate in the study by signing the Informed Consent Form (ICF) were included. Exclusion criteria were patients with whom contact could not be established and those who had difficulty responding to the questionnaires administered.

#### 2.2 DATA COLLECTION

Regarding data collection, a survey was first conducted of patients who underwent primary TKA in the selected institution's database, followed by telephone contact and scheduling of an appointment for radiographic evaluation and administration of postoperative questionnaires. The radiographic and functional assessments were performed by researchers independent of the study investigators.

The radiographic evaluation was conducted using pre- and postoperative panoramic radiographs of each patient, with the mechanical axis of the lower limbs calculated by drawing a line from the center of the femoral head to the center of the ankle joint. The mechanical axes of the femur (from the center of the femoral head to the femoral intercondylar point) and the tibia (from the center of the proximal tibia to the center of the ankle) were also traced, along with the vertical axis of the lower limbs. Additionally, the hip-knee angle, formed by the femoral mechanical axis and tibial mechanical axis (approximately 180°), was measured.<sup>7</sup>, <sup>11</sup>

The functional evaluation was performed using the WOMAC, Lysholm, and SF-36 questionnaires, all translated and validated for Brazilian Portuguese. This phase included demographic and identification data collection, followed by the application of the questionnaires.

#### 2.3 STATISTICAL ANALYSIS

To analyze a sample of n=20 patients, distributed into two groups: Conventional (N=10) and Navigated (n=10), descriptive and inferential statistical methods were applied. Qualitative variables were presented as absolute and relative frequency distributions. Quantitative variables were presented using measures of central tendency and variability, and their normality was assessed using the Shapiro-Wilk test.

In the inferential part, the following methods were applied: (a) The Chi-square test of independence was used to compare the proportional distribution of nominal categories, as recommended by Ayres et al.<sup>4</sup> (b) The Student's t-test was applied to compare quantitative variables; (c) Pearson's Correlation was used to assess the relationship between quantitative variables.

An alpha error of 5% was predefined for the rejection of the null hypothesis, and statistical processing was carried out using BioEstat version 5.3 and STATA release 17 software.

#### 3. RESULTS

A total of 20 patients participated in this study (n=15 females and n=5 males) who underwent total knee arthroplasty (TKA), with 10 in the Navigated Group and 10 in the Conventional Group. The characterization of the sample regarding gender, mechanical axis alignment of the knee pre- and post-operatively, and functional classification according to the Lysholm scale are available in Table 2.

The participants' ages ranged from 56.0 to 85.0 years. Table 1 presents a comparison of ages between the two groups and shows a mean difference of -3.3% with a p-value of 0.6101 by the Student's t-test, indicating that the difference was not significant. The Conventional Group had a slightly higher average age (69.4 years) compared to the Navigated Group (67.1 years). Both groups had a similar range of ages, with the Conventional Group ranging from 56.0 to 85.0 years and the Navigated Group ranging from 57.0 to 80.0 years.

Regarding the post-operative period, the average time was similar in both groups, with 2.5 years for the Conventional Group and 2.4 years for the Navigated Group.

The analysis of the WOMAC questionnaire domains showed a mean score of 12.4 for the Conventional Group and 9.1 for the Navigated Group in the functional capacity domain. In the WOMAC pain domain, the arithmetic mean was 2.7 for both groups. Furthermore, a mean score of 1.1 points was observed for the Conventional Group and 0.8 points for the Navigated Group in the stiffness domain, suggesting minimal stiffness in both groups with a total of eight points in this domain. Table 3 presents the difference in WOMAC scores between the Conventional and Navigated Groups.

In the physical domain of the SF-12 questionnaire, the mean score was 44.2 points for the Conventional Group and 45.1 points for the Navigated Group. In the mental domain, the Conventional Group had a mean of 50.1 points and the Navigated Group 49.1 points. The Lysholm score showed a mean of 76.4 points for the Conventional Group and 75.0 points for the Navigated Group (Table 4).

Table 5 presents the correlation matrix between quantitative variables. Noteworthy correlations include: the Functional Capacity domain with the Pain domain from the WOMAC questionnaire, showing a coefficient of  $r = 0.9245^*$  and a p-value of <0.0001\* (highly significant); the WOMAC Functional Capacity domain with Stiffness, showing a coefficient of  $r = 0.9036^*$  and a p-value of <0.0001\* (highly significant); WOMAC Pain with WOMAC Stiffness, with a coefficient of  $r = 0.8213^*$  and a p-value of <0.0001\* (highly significant).

Based on the statistics and the Student's t-test, no significant difference was found in WOMAC scores, SF-12, or Lysholm Scores between the two groups.

#### 4. DISCUSSION

The main finding of this study is the equivalence of results between patients undergoing total knee arthroplasty (TKA) using conventional and navigated techniques, suggesting the safety of both approaches. While the results of TKA with the conventional technique are well-documented in the literature, the navigated technique still requires further investigation. According to Hazratwala (25), TKA with navigation has proven to be predictable, reliable, and reproducible, with acceptable short-term revision rates.

The majority of patients in both groups were female (n=15, 75%). This is in agreement with previous national studies (26), which also identified a predominance of females, as the underlying condition (osteoarthritis, OA) that leads to the indication for TKA also affects this population due to increased mechanical load on the female knee (27).

One important factor for the success of TKA is the alignment of the mechanical axis and restoration of neutral angulation (Moser, 2019). In addition, factors such as mental health (28), pain (6), and patient satisfaction (11) have been shown to be highly predictive of clinical outcomes after TKA.

The factors influencing patient satisfaction after TKA appear to be similar for both genders. Both men and women experience negative factors that may lead to postoperative dissatisfaction, including pain, pain related to knee instability, mechanical issues, and low physical activity levels. On the other hand, satisfaction is associated with the ability to perform activities and walk long distances, followed by the functional characteristics of the knee (29). Additionally, mental health is a factor that influences patient satisfaction after TKA revision (28).

This study employed various assessment tools to measure functional outcomes and patient satisfaction after TKA. The Lysholm questionnaire and the WOMAC were used to evaluate specific knee symptoms and signs, while the SF-12 was chosen to provide an overall view of the surgery's impact on patient satisfaction and quality of life, recognizing that functionality does not always correlate directly with patient satisfaction after surgery.

A study (30) investigating the best questionnaires for assessing physical aspects in patients with knee osteoarthritis in the Brazilian population identified that the WOMAC and Lysholm questionnaires are valid for assessment, with WOMAC being more suitable for evaluating physical limitations and Lysholm for evaluating limitations related to pain.

The evaluation tools used in this study were selected for their simplicity, good validity, and reliability, as well as for providing a brief yet comprehensive evaluation of disease-specific conditions (WOMAC) and general health assessment (SF-12) (15).

The limitations of this research include an average postoperative follow-up period of only two years, which hindered an early assessment of potential changes in patient satisfaction over time. Additionally, being a retrospective study, it was not possible to conduct preoperative assessments using the same functional evaluation questionnaires.

The clinical relevance of this study lies in the use of a variety of assessment tools to investigate potential differences between the two surgical techniques, considering their impact on function, quality of life, and mental health. The results indicate no significant differences between the groups in terms of patient satisfaction, functional impact, or knee mechanical alignment. These findings suggest that the choice of surgical technique may depend on the surgeon's preference, as both approaches yield equivalent results.

#### 5. CONCLUSION

There are no significant differences between the functional results of patients undergoing conventional arthroplasty and those who underwent the procedure with navigation in relation to all variables examined, indicating that there is no support for stating that one surgical technique is superior to the other.

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#### **ANNEXES**

Table 1. Age and time of evaluation after surgery of n=20 patients, distributed in 2 groups: Conventional Surgery (n=10) and Navigated Surgery (n=10). São Paulo, Brazil, year 2023.

	Conventional (n=10)	Sailed (n=10)	General (n=20)	p-value*	Diff %
Age (years)	()	(	(11 20)	0.6101	-3.3%
Minimum	56.0	57.0	56.0		
Maximum	85.0	80.0	85.0		
Median	65.5	66.0	66.0		
1st Quartile	58.0	62.5	61.0		
3rd Quartile	82.2	70.5	76.2		
Arithmetic Mean	69.4	67.1	68.2		
Standard deviation	12.21	6.87	9.72		
Time after surgery					
(years)				0.9279	-4.0%
Minimum	1.0	1.0	1.0		
Maximum	6.0	10.0	10.0		
Median	1.0	1.5	1.0		
1st Quartile	1.0	1.0	1.0		
3rd Quartile	4.5	2.0	3.0		
Arithmetic Mean	2.5	2.4	2.4		
Standard deviation	2.05	2.76	2.37		

<sup>\*</sup>p-value by Student's t-test, comparing Conventional x Navigated. Source: Prepared by the authors.

Table 2. Characterization of n=20 patients, distributed into 2 groups: Conventional Surgery (n=10) and Navigated Surgery (n=10). São Paulo, Brazil, year 2023.

Features	Conventional		General	0/	n velve
General	(n=10)	(n=10)	(n=20)	%	p-value
Sex					0.3017
Masculine	1	4	5	25.0	
Feminine	9	6	15	75.0	
Pre axis					0.9999
Valgus	2	3	5	25.0	
Varus	8	7	15	75.0	
Post axis					0.4966
Valgus	3	3	6	30.0	
Varus	3	1	5	25.0	
Neutral	4	6	10	50.0	
Lysholm					
(classification)					0.1670
Bad	1	1	2	10.0	
Regular	6	4	10	50.0	
Good	2	0	2	10.0	
Excellent	1	5	6	30.0	

p-value by Chi-square test of independence.

Source: Prepared by the authors.

Table 3. WOMAC of n=20 patients, distributed in 2 groups: Conventional Surgery (n=10) and Navigated Surgery (n=10). São Paulo, Brazil, year 2023.

J.	Conventional	,	General		
WOMAC	(n=10)	(n=10)	(n=20)	p-value	Diff %
Rigidity				0.6935	-27.3%
Minimum	0.0	0.0	0.0		
Maximum	4.0	6.0	6.0		
Median	0.5	0.0	0.0		
1st Quartile	0.0	0.0	0.0		
3rd Quartile	2.0	0.0	2.0		
Arithmetic Mean	1.1	0.8	0.9		
Standard deviation	1.34	1.92	1.61		
<b>Functional Capacity</b>	y			0.5272	-26.6%
Minimum	0.0	0.0	0.0		
Maximum	42.0	37.0	42.0		
Median	11.0	5.0	8.5		
1st Quartile	7.7	3.0	3.0		
3rd Quartile	13.0	10.7	13.0		
Arithmetic Mean	12.4	9.1	10.7		
Standard deviation	11.48	11.41	11.26		
Womac Pain				0.9988	0.0%
Minimum	0.0	0.0	0.0		
Maximum	11.0	10.0	11.0		
Median	2.0	2.0	2.0		
1st Quartile	1.2	0.2	0.7		
3rd Quartile	2.7	3.0	3.0		
Arithmetic Mean	2.7	2.7	2.7		
Standard deviation	3.16	3.16	3.07		

p-value by Student's t-test, comparing Conventional x Navigated. Source: Prepared by the authors. Table 4. SF -12 and Lysholm score of n=20 patients, distributed into 2 groups: Conventional Surgery (n=10) and Navigated Surgery (n=10). São Paulo, Brazil, year 2023.

	Conventional	Sailed	General		
	(n=10)	(n=10)	(n=20)	p-value	Diff %
SF 12 PCS				0.8505	2.0%
Minimum	23.0	32.2	23.0		
Maximum	61.0	58.3	61.0		
Median	46.6	46.9	46.9		
1st Quartile	36.0	39.1	37.9		
3rd Quartile	52.2	51.8	52.3		
Arithmetic Mean	44.2	45.1	44.7		
Standard deviation	11.83	8.86	10.18		
SF 12 MCS				0.8122	-2.0%
Minimum	28.0	36.6	28.0		
Maximum	62.8	58.4	62.9		
Median	51.3	52.9	51.8		
1st Quartile	49.7	42.1	43.8		
3rd Quartile	57.2	55.0	55.8		
Arithmetic Mean	50.1	49.1	49.6		
Standard deviation	10.74	8.53	9.46		
Lysholm (score)				0.8767	-1.8%
Minimum	55.0	10.0	10.0		
Maximum	90.0	98.0	98.0		
Median	75.5	76.0	75.5		
1st Quartile	71.2	71.7	71		
3rd Quartile	85.7	93.0	88.5		
Arithmetic Mean	76.4	75.0	75.7		
Standard deviation	10.78	25.76	19.23		

p-value by Student's t-test, comparing Conventional x Navigated. Source: Prepared by the authors.

Table 5. Correlation coefficients between quantitative variables, n=20 patients.

	Age	Time Since cx	Womac Pain	Womac Rigidity	Womac C Functional	Lysholm	Sf 12 pcs	Sf 12 fcs
Age	1							
T From box	- 0.3248	1						
Womac Pain	- 0.2964	0.6894	1					
Rigidity	- 0.0819	0.6563	0.8213*	1				
C Functional	- 0.0941	0.6247	0.9245*	0.9036*	1			
Lysholm	0.0387	-0.2172	-0.2486	-0.2796	-0.2962	1		
Sf 12 pcs 12	- 0.1257	-0.3349	-0.6454	-0.6275	-0.759	0.3137	1	
Sf 12 pcs 12	0.4309	-0.1932	-0.134	-0.0608	-0.0291	-0.093	-0.0881	1

\*p-value <0.0001, Pearson linear correlation. Source: Prepared by the authors.

## **CHAPTER 6**

## ORAL INJURIES ASSOCIATED WITH THE USE OF COMPLETE PROSTHESIS: LITERATURE REVIEW

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**ABSTRACT:** Edentulism persists as a reality faced by many people, resulting in negative impacts on essential functions, such as chewing, swallowing and speaking. Rehabilitation using dental prosthetics appears as a solution to reestablish these functions, contributing to a significant improvement in the quality of life of affected individuals. However, it is crucial to address the challenges associated with inappropriate use and poor hygiene of dental prostheses, which can result in injuries to supporting tissues, alveolar mucosa, and oral soft tissues. This study seeks to explore the repercussions of poor adaptations and inefficient cleaning of complete removable dental prostheses, focusing on the most prevalent oral lesions identified by the research. Among these lesions, prosthetic stomatitis, angular cheilitis, inflammatory hyperplasia, candidiasis and traumatic ulcers stand out. By presenting a literature review, the aim is to provide a comprehensive understanding of these issues, contributing to a more informed and effective approach to managing and preventing complications associated with the use of dentures.

**Keywords:** denture, complete, quality of life, health of the elderly, geriatric dentistry.

**RESUMO:** O edentulismo persiste como uma realidade enfrentada por muitas pessoas, resultando em impactos negativos nas funções essenciais, como mastigação, deglutição e fonação, diante disso a reabilitação por meio de próteses dentárias surge como uma solução para restabelecer essas funções, contribuindo para uma melhoria significativa na qualidade de vida dos indivíduos afetados. No entanto, é crucial abordar os desafios associados ao uso inadequado e à higienização deficiente das próteses dentárias, que podem resultar em lesões nos tecidos de suporte, mucosa alveolar e tecidos moles bucais. Este estudo busca explorar as repercussões das más adaptações e da higienização ineficiente de próteses dentárias totais removíveis, com foco nas lesões orais mais prevalentes identificadas pela pesquisa. Entre essas lesões, destacam-se a estomatite protética, queilite angular, hiperplasia inflamatória, candidíase e úlceras traumáticas. Ao apresentar uma revisão de literatura, o objetivo é fornecer uma compreensão abrangente dessas questões, contribuindo para uma abordagem mais informada e eficaz na gestão e prevenção de complicações associadas ao uso de próteses dentárias.

**PALAVRAS-CHAVE:** prótese total, qualidade de vida: saúde do idoso, odontologia geriátrica.

#### 1. INTRODUCTION

Despite the advances in dentistry, the high frequency of dental losses is still a reality faced by the population, causing changes directly in the fundamental functions of chewing, swallowing and speech. One of the forms of rehabilitation is through the installation of removable prostheses. It is important to point out that caries, traumatisms and periodontal diseases are the main causes of edentulism, and may be related to conditioning factors and determinants of health, such as age, education and basic sanitation among others (Queiroz; Guedes, 2023).

The majority of users of Total Prostheses (PT) are elderly, a population that is growing globally (Brantes *et al.*, 2019). As people's life expectancy grows, so does the number of people who need dental prostheses. This type of rehabilitation aims to provide improvements in the quality of life for older people (Petry *et al.*, 2019). Currently, the use of total removable prostheses is still very common, especially for the elderly with a low socioeconomic level, because this has a lower value compared to dental implants.

Clinical and radiographic examination of the oral cavity is essential for proper treatment planning (Ercalik-Yalcinkaya, 2015). The functionality of the temporomandibular joint, the distribution of the masticatory forces, the tonicity of the musculature and the systemic conditions of the patient are important aspects to be taken into consideration by the dental surgeon, to prevent the dental prostheses from becoming ill adapted so that this treatment does not cause new problems to the patient.

It is worth pointing out that the success of prosthetic treatment is due to the good interaction between the professional and the patient, because the latter must correctly follow the dentist's guidelines, both when the correct form of hygiene, and the maintenance of the prostheses (Cordova *et al.*, 2016). This care on the part of the patient is crucial to guarantee the effectiveness of this rehabilitating medium.

However, we can say that the unsatisfactory result of rehabilitation with prostheses is due, in most cases, to the fact that these cause injury to the supporting tissues, or inadequate hygienization cause oral lesions in the supporting tissues and alveolar mucosa, as well as in adjacent tissues (Barcelos *et al.*, 2017).

Among the lesions related to the use of prostheses found in the research we can mention prosthetic stomatitis, angular cheilitis, inflammatory hyperplasia,

candidiasis and traumatic ulcers (Trindade *et al.*, 2018). Lesions resulting from the use of prostheses and dental losses not only negatively impact facial aesthetics, but also exert significant adverse effects on the mental health, phonetics and chewing capacity of individuals, thus compromising several essential aspects in their quality of life (Olchik *et al.*, 2013).

In view of this, the main purpose of the present study is to present, by means of a literature review, the oral lesions caused by the poor adaptation of the total prostheses as well as by the lack of efficient hygiene on the part of the patient, emphasizing the quality of life of the population.

#### 2. METHODOLOGY

This study is a literature review. To do so, three distinct researches were carried out. At the first moment, we searched for scientific articles in the databases SCIELO and MEDLINE, through the virtual library in health, using the keywords 'Dental Prostheses' and 'Lesions', using the prefix 'AND', where we obtained as a result of search a total of 22 articles. In this first phase of the research, 05 articles were selected.

In the second phase of the research, we also carried out an inspection in the SCIELO and MEDLINE databases, through the virtual library in health, but at that moment were used the key words 'quality of life' and 'dentures'. We obtained as a result of search a total of 27 articles, of which 06 were selected.

In the third phase of the research, we search for scientific articles in GOOGLE ACADEMIC, making use of the key words 'Oral injuries' and 'dental prosthesis'. We managed to select, through the theme and reading of the abstracts, a total of 09 articles.

In view of this, among the three studies, a total of 20 articles were included in this literature review, which were available in a complete form and were published in a period of, at the maximum, 20 years. They were in agreement with the theme addressed and in the English, Portuguese and Spanish languages. Those who did not meet the inclusion criteria were excluded.

#### 3. RESULTS AND DISCUSSION

Absence of teeth can cause a number of problems, including difficulty chewing and cosmetic damage, which directly impacts the individual's quality of life. The origin of edentulism may be associated with the presence of cavities, periodontal diseases and often lack of access to oral health services. (Marcelino *et al.*, 2023). The perception of toothless people regarding their quality of life is notably lower in those who have lost more than four teeth, evidencing that as the amount of missing teeth increases, the quality of life decreases. (Dornelas *et al.*, 2022).

Since edentulism is one of the oral problems commonly present in human life, it is necessary to use dental prostheses to replace the missing dental elements (Spezia, 2022). The use of prostheses can have significant improvements in chewing, aesthetics, self-esteem, speech, interpersonal relationships and in the possibility of recovering body image lost due to edentulism (Orestes *et al.*, 2015). According to our research it becomes evident that edentulism can lead to significant biopsychosocial disorders (Figueiredo *et al.*, 2019). This underlines the importance of prosthetic rehabilitation, since this aims not only to restore speech and chewing, but to play a crucial role in preserving the quality of life.

The use of higher total prostheses is still very common among the elderly population. This is considered a good oral rehabilitation option, but when not properly used it can cause several types of oral mucosal damage (Brantes *et al.*, 2019).

The continuity of care by the patient is not limited to the application of the total removable prosthesis; it also includes the guidance provided by the professional regarding the hygienization of the prosthesis and tissues in the oral cavity, and the importance of the return and maintenance consultation (Ercalik-Yalcinkaya, 2015).

Knowing that inadequate hygiene causes biofilm formation, accumulation of organic material and the proliferation of bacteria and fungi, and that a variety of injuries can arise due to the influence of various etiological agents, it is important to emphasize that lack of hygiene is one of the factors causing lesions in the mucosa related to prosthesis use (Barcelos *et al.*, 2017).

Besides hygienization, other factors are also directly linked to these types of oral lesions, such as the prosthesis's poor adaptation to the tissues of the oral cavity, the time it takes to make and use the prosthesis, and the occlusion relationship. Following

in this context, it is crucial to address the main oral lesions resulting from the inappropriate use of prostheses.

#### 3.1 PROTETIC STOMATITIS

Prosthetic stomatitis occurs in the oral mucosa and consists of one of the most frequent oral lesions in patients using removable prostheses (Silva *et al.*, 2021). The origin of prosthetic stomatitis is multifactorial, covering issues related to the general health of the individual and local factors such as the presence of bacterial plaque and fungi, along with mechanical aspects such as inadequate adaptation and hygienization of the total prosthesis, which can trigger infectious processes caused by microorganisms (Trindade *et al.*, 2018).

The action of the biofilm, composed of several species of bacteria and fungi including Candida Albicans favors the emergence of infectious conditions, including this has been the most prevalent in the diagnosis of stomatitis associated with dentures (Falcão *et al.*, 2019).

Other factors may trigger the emergence of prosthetic stomatitis as its use throughout the night (Freire *et al.*, 2023). Besides its time of use, that is, there is a significant relationship between the time of prosthesis use and the presence of prosthetic stomatitis (Alves *et al.*, 2020).

It is an inflammatory process, characterized by erythema of the oral mucous portion covered by the prosthesis. According to Trindade (2018), this inflammation as well as edema and hyperemia may be accompanied by hemorrhagic petechiae, it is worth emphasizing that this process is usually asymptomatic due to this fact often going unnoticed by the patient (Trindade *et al.*, 2018).

# 3.2 ANGULAR CHELITIS

Angular cheilitis emerges as a lesion closely associated with the elderly, since the physiological process of aging results in the loss of the vertical dimension of occlusion (Queiroz; Guedes, 2023). This phenomenon favors the accumulation of saliva in the region of the labial commissure, which plays a crucial role in the appearance of this lesion.

Its etiology is multifactorial and may be related to infectious agents, systemic diseases, and the loss of vertical dimension of occlusion (Trindade *et al.*, 2018). This type of injury may also result from the incorrect planning of prostheses, since they may cause losses in the establishment of the vertical dimension (Goiato *et al.*, 2005).

Angular cheilitis may manifest clinically bilaterally or unilaterally, presenting with a grayish white thickening and adjacent erythema. In addition, symptoms such as scaling, cracks, ulcers, and in some cases even bleeding are observed (Queiroz; Guedes, 2023). In addition, it is important to note that patients often report painful symptoms related to angular cheilitis.

# 3.3 INFLAMMATORY FIBROUS HYPERPLASIA

Hyperplasia can also be called cleft epulis, epulis caused by dentures or even a denture tumor (Trindade *et al.*, 2018). It is soft tissue lesions resulting from traumas caused by the maladaptation of the prosthesis, it is proliferative and not neoplastic, can develop anywhere in the oral cavity, however they develop more frequently in the region of the palate, tongue, lips, gum and jugal mucosa (Queiroz; Guedes, 2023). Although it is commonly linked to the inappropriate use of dental prostheses, inflammatory fibrous hyperplasia can be influenced by several other factors, such as diastemas, inadequate hygienization, professional iatrogenic practices, from this it is important to emphasize that there is a correlation between the increased incidence of this injury with the prolonged use of dental prostheses and the bone resorption of the edentulous patient.

Inflammatory Fibrous Hyperplasia presents as an exophytic or elevated lesion, well delimited, with consistency ranging from firm to flaccid to palpation. Its surface is smooth, sessile-based, or occasionally pediculated. The coloration of the lesion may vary from similar to adjacent mucosa to erythematous (Santos *et al.*, 2004). Usually this lesion is of reading growth and painless, but can cause discomfort to the patient in the face of speech and chewing.

# 3.4 CANDIDIASIS

Candida is an infection caused by yeasts belonging to the genus Candida, Candida Albicans being the most prevalent and frequently related species of infections in humans (Silva; Yamashita, 2023). The main conditions that favor the appearance of candidiasis are the lack of hygiene of the linked prosthesis and prosthetic traumatic issues, but its development is also closely linked to the state of health of the host. This lesion is often visualized in patients who use prostheses, because it makes the oral mucosa an environment conducive to the development and proliferation of yeasts, especially in those individuals who use poorly sanitized and ill-adapted prostheses (Queiroz; Guedes, 2023).

Lesions resulting from these fungal infections are identified by white plaques or nodules, with varying consistency, their edges may exhibit erythema (Silva; Yamashita, 2023). Such manifestations may be symptomatic or asymptomatic.

# 3.5 INJURY

One of the most common lesions in the oral cavity of the user of mucosupported dental prostheses is dealing with traumatic ulcers. They usually appear in the first or second year of use of the prosthesis. The origin of the appearance of these lesions covers everything from professional failures arising from iatrogenic issues in the manufature of the prosthesis to local irritating factors, highlighting the use of ill-adapted prostheses (Queiroz; Guedes, 2023).

It is characterized by an ulceration whether or not covered by a fibrinopurulent membrane and surrounded by a halo erythematosus. Patients commonly report painful symptoms, particularly during food intake. It is important to note that these ulcers may be acute or chronic depending on the patient's symptomatology and ulceration time (Trindade *et al.*, 2018).

# 4. CONCLUSION

Based on this study, we found that dental prostheses represent an effective solution for the treatment of edentulism. In this scenario, it becomes evident that

individuals resort to the use of dental prostheses in order to improve their quality of life. However, for this to be possible, it is necessary to establish a partnership between the dental surgeon and the patient.

It is crucial that the prostheses are properly made to provide comfort and restoration of masticatory function. In addition, the patient should carry out hygienization properly during use in order to prevent possible oral lesions such as prosthetic stomatitis, angular cheilitis, inflammatory fibrous hyperplasia, candidiasis, and traumatic ulcers, because these various oral mucosal lesions interfere with the quality of life of their users.

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# **CHAPTER 7**

# SERVICE-LEARNING EXPERIENCE OF UNIVERSITY STUDENTS IN ELEMENTARY SCHOOLS

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**ABSTRACT:** Service-learning experience carried out by students of the Bachelor in Human Nutrition in elementary schools, where educational nutrition interventions were implemented in a playful manner. The results were a service action with great community acceptance and significant learning in the undergraduate students.

**KEYWORDS:** community service, meaningful learning.

**RESUMEN:** Experiencia de aprendizaje-servicio realizada por estudiantes de la Licenciatura en Nutrición Humana en escuelas de nivel básico, donde se implementaron intervenciones educativas sobre nutrición de manera lúdica. Los resultados fueron una acción de servicio con gran aceptación comunitaria y aprendizaje significativo en los alumnos de licenciatura.

PALABRAS CLAVE: servicio comunitário, aprendizaje significativo.

# 1. INTRODUCTION

The educational model of the Universidad Autónoma Metropolitana Unidad Xochimilco in Mexico City, called the modular system, is characterized by forming human resources through the study of problems of reality, around which academic contents are integrated and which are developed through a scientific research exercise. As part of this research, community service work is carried out, which favors the integral training of students. This model is conducive to the implementation of the service-learning pedagogical strategy.

An example is presented below, in 2015, students of the Bachelor of Human Nutrition made the nutritional diagnosis in six basic level schools. A Based on the results, they developed health promotion programs that they implemented in the same schools. Table 1 presents the work done.

Table 1. Population studied and attended

Name of the investigation	Population studied	Program performed
The consumption of industrialized food	Primary"Ricardo Salgado	"Improving Your food."
products and physical inactivity as	Corral"	130 4th graders
determinants of the nutritional status of	86 4th graders	
schoolchildren in 5th year of primary of		
Coyoacán D.F.		
Dietary habits and physical activity in	"Moisés Sáenz Garza" High	"Rally-zando salud"
relation to nutritional status in	School	89 adolescents
adolescents of the Ranchería "La	89 adolescents	
Soledad" in San Felipe del Progreso		
State of Mexico		
Nutrition status in children of the	Primary "Simón Bolívar"	"Healthy eating"
"Simón Bolívar" Primary School from 7	112 schoolchildren from 2nd	186 schoolchildren from
to 10 years of age in relation to the	to 4th grade	2nd to 4th grade
consumption of energy-dense foods	D: ((0.1)	(1)
Eating habits and activity physics as	Primary "Cultural Center"	"Healthy eating and
determinants of nutritional status in a	Haim Weizmann"	More active children"
group of schoolchildren	90 school children from 4th to	90 school children from
	6th grade	4th to 6th grade
Relationship between habits	Primary"Carlos	"Promotion of Eating
Food and nutritional status in	D. II. "	habits
a group of 5th and 6th year students of	Pellicer"	Healthy."
the "Carlos Pellicer" Primary in the	100 schoolchildren from 5th to	
Coyoacán Delegation	6th grade	5th to 6th grade
Relationship between nutritional status	Secondary "Susana Ortiz	"The amount of food is in
(BMI) and risk behaviors associated	Silva"	your hands"
with eating disorders in adolescents	100 adolescents	100
T. 10	T	adolescents
Total 6 projects	Total: 477	Total: 695
	Individuals	attendees

Source: the authors

All the programs were developed with the same scheme, but included different contents and activities depending on each project, in all cases they were carried out in the school buildings themselves.

An antecedent to this type of experience is the project "Community Work Workshops" applied in the subject "Community Social Work" of the Social Work career of the University of Barcelona, implemented since 2003 with the perspective of Barbero (2003) which states: "it is about accounting for means and activities so that people can appropriate professional knowledge and skills, trying to increase the possibilities of self-determination".

The programs implemented by the UAM-X, sought to return results in a simple and practical way for children to recognize harmful behaviors to their health motivating positive changes; resuming the postulates of Carl Rogers (1989) who, in his principles on learning, defends that "the only learning that can significantly influence behavior is the one that the individual discovers and incorporates by himself".

In the programs, the activities had a playful character and were supported by very striking materials designed by the nutrition students to attract the attention of the minors and make them reflect on their habits. The topics that were included in addition to nutrition were physical activity and self-esteem. Each activity was brief but sufficient so that everyone had a prior explanation of the contents and the active participation of all minors was encouraged, for which, even though there was a person responsible for each activity, the entire nutrition team participated in all the dynamics.

In addition, it was emphasized the respect that peers must have in school coexistence. During the activities involving competition, the importance of collaborative work was emphasized and the participation of the entire group was recognized.

The materials designed for the implementation of the programs ranged from a rally with support of educational games in each "station", posters and playful materials applied in the classroom, to prints, presentations and a Facebook page called "NutriUAM" aimed at informing children and young people about recommendations to improve their habits.

# 2. RESULTS

The diagnosis of the research was the basis for the design of a health promotion program that was implemented in each school, with which they returned results and helped to improve their habits. Álvarez (2003) points out that health promotion begins with individual health and "the instruction-education that guides about various aspects of hygiene and personal health: food, physical and mental activity, rest, healthy fun, occupation of free time, adequate family relationships, etc."

The programs carried out did not aim to change the nutritional status found but to sensitize the population to the unhealthy practices detected and to provide alternatives for improving habits.

According to the evaluation carried out in all the programs, the population identified the nutrition problems that they presented and actively participated in dynamics where they proposed how to improve their lifestyle.

In this regard, Vincezi (2009) points out: "considering education and its relationship with the improvement of the quality of life implies assuming the responsibility of promoting, both from formal and non-formal education areas, the updating of the choice capacities of individuals, favoring the equivalence of opportunities to access resources that allow them to increase their autonomy."

The programs implemented provided the basic information necessary for children to make a better choice of food and motivated them to do physical activity in a fun and simple way.

This service experience was inserted into the research work, it should be remembered that within the modular system of the UAM-Xochimilco, research is an important tool of the training of students. As specified in its conceptual bases (2005) "the educational model encourages the collective exploration of knowledge and encourages students to develop their own research protocols and encourages them to enter the scientific world."

# 3. BENEFITS IN STUDENT TRAINING

The projects carried out had, as a first instance, a formative character for undergraduate students; in the application of the scientific method, in the integration

of acquired theoretical knowledge, as well as in the design and application of an educational program.

At the same time, a service was offered to the community through the service-learning pedagogical proposal, which as Puig (2006) points out: "it combines learning processes and community service in a single well-articulated project in which participants are trained and work on real needs of the environment with the aim of improving it".

This proposal has important contributions from Dewey, such as the principle of "activity associated with social projection", which consists of learning acquired during the real experience of the participants, working in cooperation to improve a social problem.

The benefits of this proposal are well documented. Among the most important, Mendía (2012) highlights: "the sets of competences are related not only to the development of academic and professional knowledge (learning to learn and learning to do), but also to social development (learning to live with other people) and personal development (learning to be) and are developed both in formal, nonformal and informal education. Service-learning is a powerful tool for the development of basic skills. Not based on simulations or assumptions, but from a real scenario that includes all the components: reality analysis, creation, planning, development and evaluation of a project."

In Latin America, there is a long tradition of service projects carried out by the higher education system, but the current perspective has as a main purpose of service-learning that students acquire values, attitudes and pro-service behaviors social. Prosociability is understood as "the effective satisfaction of the recipient, as well as the reciprocity or solidarity generated between both actors". (Cecchi, 2006)

In the end, the students felt that they were able to apply the knowledge acquired and indicated that they felt satisfied to work together with the population to improve their lifestyle.

# 3. COMMUNITY SERVICE

Álvarez, R. (2003) defines health education as "more than information about health knowledge. It is teaching that aims to lead the individual and the community to

a process of change of attitude and behavior, for the application of means that allow the conservation and improvement of health."

In this sense, any health education program measures its impact on the information acquired and that can be applied by the target population. The evaluation of all programs found that children and young people reproduced activities as planned, were motivated and said that they found them *easy to implement in their daily lives*.

In the final evaluation, the nutrition students considered that changes in the behavior of minors with long-term actions are feasible since the motivation and participation achieved was successful, but unfortunately their work would not have continuity because it corresponded to a quarterly project. For the above, the main limitation was the time dedicated to the programs.

The biggest weakness detected by the group was the lack of education actions for health and nutrition that are carried out in a permanent and fun way by schools, which if implemented on a regular basis would improve the health of minors.

Community service must be a permanent activity of universities, since it enables students to be trained and linked to disadvantaged groups. In some countries, it is even established by law. In relation to this, Contreras (2006) considers that: "the promotion of community service should not be seen as an addition to the institutional dynamic but as an expression of the Social Responsibility that the University assumes with the country."

At the Xochimilco Metropolitan Autonomous University, it is also considered this way. In its conceptual bases, it is stated that: "service as an application of knowledge will be a tangible reality. The link between theory and practice that is facilitates with the service, will enable the overcoming of fragmented and parceled education to achieve articulation with society, knowing that with this activity the Unit contributes to forging a more equitable and fair development project. Today, as social inequalities are becoming more acute, the Unit needs to articulate with society with service projects."

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# **CHAPTER 8**

ASSESSMENT OF THE QUALITY OF THE OPHTHALMOLOGICAL SERVICE AT THE HOSPITAL OF THE STATE PUBLIC SERVANT OF SÃO PAULO BASED ON THE NUMBER OF OMBUDSMAN CASES

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ABSTRACT: This study aims to highlight improvements in the quality indicators of ophthalmology services provided by the Hospital do Servidor Público Estadual de São Paulo, resulting from a significant change in the organization of the cataract surgery queue. The transition from an obsolete and inflexible system, represented by an outdated spreadsheet, to a dynamic virtual queue system had a positive impact on the operationalization of services. This research analyzes the reduction in both absolute and proportional complaints received through ombudsman channels, specifically related to cataracts, and the reduction in waiting time for surgery, emphasizing that most surgeries are now performed within the timeframe established by medical literature. Furthermore, it investigates the impact of ombudsman services on the evaluation of service quality, relying on relevant scientific evidence.

**KEYWORDS:** Cataract surgery, Virtual queue system, Service quality.

**RESUMO:** Este estudo tem como objetivo evidenciar melhorias nos indicadores de qualidade dos serviços de oftalmologia prestados pelo Hospital do Servidor Público Estadual de São Paulo, resultantes de uma mudança significativa na organização da fila de cirurgia de catarata. A transição de um sistema obsoleto e inflexível, representado por uma planilha ultrapassada, para um sistema dinâmico de filas virtuais teve impacto positivo na operacionalização dos serviços. Esta pesquisa analisa a redução das reclamações absolutas e proporcionais recebidas pelos canais de ouvidoria, especificamente relacionadas à catarata, e a redução do tempo de espera para cirurgia, enfatizando que a maioria das cirurgias passou a ser realizada dentro do prazo estabelecido pela literatura médica. Além disso, investiga o impacto dos serviços de ouvidoria na avaliação da qualidade dos serviços, apoiando-se em evidências científicas relevantes.

PALAVRAS-CHAVE: Cirurgia de catarata, Sistema de fila virtual, Qualidade do serviço.

# 1. INTRODUCTION

Ophthalmology is the medical specialty responsible for maintaining ocular health. The quality of ophthalmological services offered by public hospitals, such as the Hospital do Servidor Público Estadual de São Paulo, is crucial to meet the population's needs (BENGOA et al., 2006); (VARGAS et al., 2015). In this context, ombudsman services play a fundamental role in collecting patient feedback and identifying areas for improvement (SANTOS; COSTA; BURGER; TEZZA, 2019). The substantial change in the organization of the cataract surgery queue at this hospital, from an outdated spreadsheet with over two thousand registered patients, without ordering or any control over the patient's actual condition on their journey to cataract surgery, to a dynamic virtual queue with clear and precise patient ordering, presents an opportunity to assess how these improvements impact patients' perceived quality of care.

#### 2. METHODS

To assess the quality of ophthalmology services at the Hospital do Servidor Público Estadual de São Paulo, data were collected for the six months preceding and the six months following the change in the organization of the cataract surgery queue. Additionally, specific complaints and suggestions related to cataracts were recorded. The waiting time for surgery was compared to medical literature data to verify compliance.

# 3. RESULTS

In the six months preceding the change in the organization of the cataract surgery queue, a total of 104 ombudsman complaints were recorded, with 60 (57%) related to cataracts. Of these, 43 (72%) were complaints related to delays in surgical scheduling, with an undefined waiting time at that moment, as there was no well-established sequential queue for surgery. After transitioning to the dynamic virtual queue, in the following six months, the total number of complaints decreased to 85, representing an overall decrease of 18% in ombudsman cases. Of these, 42 were

associated with cataracts, showing a 30% decrease in absolute numbers during the period, with only 28 related to delays in surgical scheduling—a 35% decrease in absolute numbers compared to the previous period. Collectively, these data indicate a significant improvement in the quality of care.

Analyzing complaints related to waiting time in the six months following the change, it was found that 46% of complaints were due to a wait exceeding 90 days, while 54% represented complaints for waiting times less than 90 days, a timeframe considered appropriate by medical literature. Among those complaints made for a waiting period of less than 90 days, 53% were made very early, within the first 30 days after anesthesia clearance and placement of the patient in the surgical queue. The expected waiting time for surgery at the end of the analyzed period was less than 90 days. This indicates that the majority of cataract surgeries are now performed within the timeframe established by medical literature, representing a significant improvement.

# 3.1 COMPARISON WITH LITERATURE DATA:

Medical studies emphasize the importance of ophthalmic surgeries, including cataract surgery, being performed within ideal timeframes, generally not exceeding 90 days. Compliance with appropriate surgical timelines is crucial to avoid complications and enhance outcomes for patients (ZHANG *et al.*, 2022).

# 3.2 IMPACT OF OMBUDSMAN SERVICES ON SERVICE QUALITY ASSESSMENT:

Research highlights the positive impact of ombudsman services on the assessment of healthcare service quality. They provide valuable insights into patient satisfaction and assist in identifying areas that require improvement (ALMEIDA *et al.*, 2018). The reduction in the number of complaints after the change in the organization of the cataract surgery queue at the Hospital do Servidor Público Estadual de São Paulo reflects an improvement in perceived quality by patients.

# 4. CONCLUSION

The change in the organization of the cataract surgery queue at the Hospital do Servidor Público Estadual de São Paulo has resulted in significant improvements in the quality of ophthalmology services, with a noticeable reduction in complaints related to cataracts and waiting times. Further reductions in complaints are expected in the future, as the changes have a greater impact and are more widely perceived by users. Compliance with appropriate waiting times for cataract surgery already demonstrates more effective care. Additionally, the positive impact of ombudsman services on service quality assessment aligns with previous studies.

It is recommended that the hospital continue to monitor and improve its processes to maintain and possibly expand these gains in the perception of healthcare quality, with the aim of providing the best possible ophthalmological care to the population.

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# **CHAPTER 9**

# BIBLIOGRAPHIC REVIEW ON THE RELATIONSHIP BETWEEN PUBERTY AND RECOMMENDATIONS FOR INITIATING ANTI-HPV VACCINATION

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**ABSTRACT:** The Squamous-Column Junction (SCC) in the cervix is the transition area between the simple and paved stratified columnar epithelium, making it visible during puberty. This region is critical for HPV infection and is associated with a high risk of cervical malignancies. In Brazil, HPV vaccination, started in 2014, aims to prevent these infections and reduce the incidence of cervical cancer, especially considering the increasing incidence of precocious puberty. Objective: The objective of this study is to examine the current knowledge about the application of the HPV vaccine, its relationship with the JEC configuration and the progression of cervical cancer. Method: The study used a bibliographic review approach, analyzing scientific

articles and book chapters published in the last five years. The review focused on recent and significant advances related to HPV vaccine and its effectiveness in preventing cervical cancer. Results: The analysis shows the importance of HPV vaccination in the prevention of cervical cancer. The vaccine has been shown to be highly effective in reducing the incidence of cervical cancer and its complications, being one of the most cost-effective interventions globally. While there has been a significant decrease in cervical cancer cases, especially in developed countries, global membership still faces challenges such as a lack of clear information and vaccine resistance. The World Health Organization (WHO) has set targets for vaccinating 90% of girls between the ages of 9 and 14 by 2030, as well as expanding coverage for boys and individuals with specific conditions. In Brazil, vaccine coverage varies across states and has been negatively impacted by the COVID-19 pandemic. Conclusion: The effectiveness of vaccination is maximized when started in adolescence, before the onset of sexual activity. The integration of scientific evidence on the timing of vaccination and the histological configuration of JEC is essential for effective cervical cancer prevention strategies. It is crucial to further promote early vaccination and address global challenges to achieve cervical cancer eradication and improve global public health.

**KEYWORDS:** papillomavirus, cervical cancer, vaccine.

**RESUMO:** A Junção Escamo-Colunar (JEC), no colo uterino, é a área de transição entre os epitélios colunar simples e pavimentoso estratificados, tornando-se visível durante a puberdade. Esta região é crítica para a infecção pelo HPV e está associada a um risco elevado de neoplasias cervicais. No Brazil, a vacinação contra o HPV, iniciada em 2014, visa prevenir essas infecções e reduzir a incidência de câncer cervical, especialmente considerando a crescente incidência de puberdade precoce. Objetivo: O objetivo deste estudo é examinar o conhecimento atual sobre a aplicação da vacina contra o HPV, sua relação com a configuração da JEC e a progressão do câncer cervical. Método: O estudo utilizou uma abordagem de revisão bibliográfica, analisando artigos científicos e capítulos de livros publicados nos últimos cinco anos. A revisão focou nos avanços recentes e significativos relacionados à vacina contra o HPV e sua eficácia na prevenção do câncer cervical. Resultados: A análise evidencia a importância da vacinação contra o HPV na prevenção do câncer cervical. A vacina tem se mostrado altamente eficaz na redução da incidência de câncer cervical e suas complicações, sendo uma das intervenções mais custo-efetivas globalmente. Embora tenha havido uma diminuição significativa dos casos de câncer cervical, especialmente em países desenvolvidos, a adesão global ainda enfrenta desafios como falta de informações claras e resistência a vacinas. A Organização Mundial da Saúde (OMS) estabeleceu metas para vacinar 90% das meninas entre 9 e 14 anos até 2030, além de expandir a cobertura para meninos e indivíduos com condições específicas. No Brazil, a cobertura vacinal varia entre os estados e foi negativamente impactada pela pandemia de COVID-19. Conclusão: A eficácia da vacinação é maximizada quando iniciada na adolescência, antes do início da atividade sexual. A integração das evidências científicas sobre o momento da vacinação e a configuração histológica da JEC é essencial para estratégias eficazes de prevenção do câncer cervical. É crucial continuar a promover a vacinação precoce e enfrentar os desafios globais para alcançar a erradicação do câncer cervical e melhorar a saúde pública global.

PALAVRAS-CHAVE: papilomavírus, câncer de colo de útero, vacina.

# 1. INTRODUCTTION

The Squamous-Column Junction (SJC) or Transformation Zone (TZ) represents a critical anatomic region in the cervix, characterized by the transition between two distinct types of epithelium. This union between the simple columnar epithelium, which forms the endocervix, and the stratified paved epithelium, which originates the ectocervix, draws an area of significant importance for the health of the woman. ZT is influenced by age and female hormones, which play a crucial role in its exteriorization process (ORTOLAN; ZANINE, 2023).

Before puberty and after menopause, JEC remains trapped within the cervical canal and is invisible during specular examination. During the fertile age, however, it becomes external, located outside the external ostium, which makes it possible to visualize it and to collect material for examinations. The TZ plays a crucial role in the medical context, as it is through it that the human papillomavirus (HPV) penetrates the organism, initiating the uncontrolled and defective proliferation of cells. (TALLON *et al*, 2020).

After infection, the HPV inserts its genetic material as an episome (circular DNA) into the basal cells of the squamocolumnar junction (JEC) of the cervix. As these basal cells divide and migrate toward the surface of the ectocervical epithelium, the virus replicates, characterizing a lysogenic cycle. During the ascent of infected cells to the surface of the epithelium, viral particles are released along with viral oncoproteins when these cells reach the surface of the cervicovaginal epithelium. These oncoproteins, such as E6 and E7, play critical roles in oncogenesis. The HPV genes are divided into two main groups: the E genes, involved in the replication of the viral DNA, and the L genes, responsible for the transcription of the proteins of the viral capsid. The E1 protein, encoded by the E1 gene, is essential for the replication of epissomal DNA. The oncogenicity of the HPV manifests itself when the genetic material of the virus integrates itself into the human genome, a process that usually occurs with the rupture of the episome in the encoding region of the E2 gene. The E2 protein typically inhibits the oncoproteins E6 and E7; therefore, their rupture allows these oncoproteins to remain active. Oncoproteins E6 and E7 have the ability to form inactive complexes with the regulatory proteins of cell cycle P53 and Rb, respectively, which are products of tumor suppressor genes TP53 and RB. The oncoprotein E6 also

promotes the synthesis of the enzyme telomerase, which prevents the telomeric shortening required for apoptosis activation. This results in the formation of immortalized cells that proliferate incessantly, increasing the risk of accumulation of mutations and the development of neoplastic processes (ABBAS *et.al.*, 2016).

It is estimated that 50-70% of sexually active people will come across HPV at some point in their lives, and that 80% of women will have HPV contact before they turn 50, which may vary between different age groups and populations. In Brazil, this infection can be seen as epidemic, with an estimated 9 to 10 million people infected and about 700,000 new cases arising each year (FEDRIZZI, 2019).

Today, HPV is known to have more than 200 subtypes, with subtypes 6 and 11 often associated with genital warts, usually benign. In addition, subtypes 16 and 18 are strongly linked to the development of neoplasms, such as cervical cancer (BURLAMAQUI *et al*, 2018).

In 1984, in Brazil, the Program of Integral Attention to Women's Health (PAISM) was established as part of the Unified Health System (SUS), marking the first step towards the collection of material for the prevention of cervical cancer, although with an initially limited adherence. Only in 1998 was the program widely disseminated, becoming the National Cervical Control Program – Viva Mulher. Since then, the examination of oncotic cytology or Papanicolau has become an integral part of the comprehensive care of women's health, recommended for those between 25 and 64 years old, sexually active (CLARO; LIMA; ALMEIDA, 2021).

Uterine cervical cancer progresses slowly, with multiple stages, which highlights the importance of screening from the age of 25, since early detection increases the chances of cure (VITTO *et al.*, 2022). In Brazil, cervical cancer is the third most frequent among women (GALVÃO *et al.*, 2022). Thus, cervical cancer screening is of high importance as early detection of invasive lesions decreases mortality (MAGNO *et. al.*, 2020).

In 2007, Australia was the first country to implement HPV vaccination with high and sustained coverage, which led to a continuous drop in the incidence of precursor cervical cancer lesions (PATEL *et.al.*, 2018). Following this example, the Unified Health System (SUS) incorporated a vaccine against HPV in its National Immunization Plan in 2014, covering the most prevalent subtypes, being the main form of prevention. The vaccine is administered to both sexes between 9 and 14 years of age, with

availability to immunosuppressed individuals (DIAS; FREITAS, 2020). Free of charge, vaccination has been carried out since 2024 in a single dose schedule. In addition, the nonavalent vaccine against HPV is already available in the private network. Men and women aged 9 to 45 years can receive (BRAZIL, 2024).

Thus, vaccination is essential for boys, who often present subclinical conditions, being asymptomatic carriers of the virus and can transmit it to sexual partners, and may present carcinomas of penis, anus and oropharynx (COSTA *et. al.*, 2019). In the case of girls, immunization occurs before puberty, preventing the virus from contacting the JEC while it remains indoors. However, it is observed that the average age of onset of puberty has decreased due to modern factors such as inadequate nutrition, overweight/obesity and early exposure to technology (NICOLI; *et al.*, 2022).

The most appropriate time for applying the HPV vaccine is before exposure to the virus. However, recent studies show that already infected women can also benefit from vaccination, including those with lesions of cervical intraepithelial neoplasia (CIN) 2/3, with a reduction in recurrences of approximately 75-88% among vaccinated women (FEDRIZZI, 2019).

Thus, this study has as its main objective to survey data from the literature that evidence the trend of precocious puberty in girls and its potential impact on the action of the HPV virus in their bodies. Furthermore, the study addresses the histological relationship of JEC during the various stages of the development of women and how the virus can proliferate in this context.

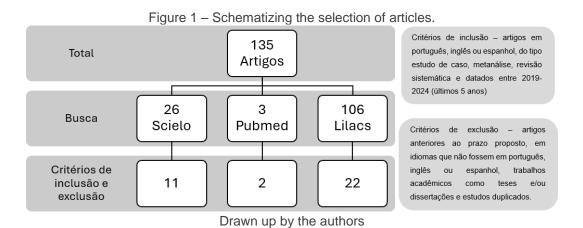
# 2. METHODS

This study will carry out a systematic review, using the methodological approach developed by Botelho, Cunha and Macedo (2011), widely recognized as the systematic review model. According to this structure, the investigative process will unfold into six sequential stages. Initially, the central question of the research will be outlined, followed by the definition of the search strategies and the selection of the databases to be used.

The subsequent stage will encompass the careful selection of materials, guided by rigorous inclusion and exclusion criteria. The abstracts of the selected articles will be submitted for analysis in the third phase, culminating in the organization of the studies that have aligned themselves with the predefined criteria. In the subsequent step, the studies will be categorized and submitted to an in-depth critical analysis.

The results of this analysis will be discussed in the fifth stage of the procedure. Finally, the sixth stage will comprise the detailed preparation of a document that systematizes the review conducted. To achieve these goals, the following databases will be used as information sources: United National Library of Medicine (PubMed), Latin American and Caribbean Literature in Health Sciences (LILACS) and Scientific Electronic Library Online (Scielo). The selection of articles is outlined in Figure 1.

Relevant articles will be identified by a combination of health science descriptors (DeCS): ('HPV' or 'Human Papillomavirus' or 'Human papillomavirus' or 'Papillomavirus Infections' or 'Papillomavirus Vaccines' or 'Quadrivalent Vaccine' or 'Human Papillomavirus Vaccine Quadrivalent') E ('Puberty' or 'Puberty' or 'Histology' or 'Histology').



#### 3. RESULTS

After the complete reading of the selected publications, a form was used to extract the relevant data. This information was organized in Table 1 with its main characteristics (stica) and organized in alphabetical order of the first author's name. After a careful reading by two reviewers, the results were submitted to a thematic analysis, which involved three stages: pre-analysis, exploration of the material and treatment of the results obtained. The objective of this analysis was to identify the main themes addressed by the selected publications (Minayo, 2013).

	Table 1. Characteristics of the articles selected for the study					
Title	First Author	Year	Magazine	Objectives	Results	
Human papilloma virus vaccination coverage in Northeast Brazil, 2013-2021: descriptive study	Matthew of Paula von Glehn	2023	RESS	The study aims to describe how adherence to vaccination against the human papillomavirus (HPV) has been in the Northeast region of Brazil, throughout the years 2013 to 2021.	For girls, vaccination coverage was 73.9% at the first dose and 54.3% at the second dose. For boys, the coverage was 49.7% in the first dose and 32.6% in the second dose. Only the states of Ceará and Paraíba managed to reach the target of 80% coverage in the first dose for girls; no state reached the target for both doses.	
Is vaccination against HPV justified in women aged 26-45?	Berta Lopez	2022	Ata Obstet Ginecol Port	The aim of the study is to conduct a survey of the age at which the HPV vaccination is to be carried out.	Vaccine administration to women over 26 years of age is justified by their ability to remain effective in producing antibodies, in addition to having proven safety and efficacy in preventing infections and developing benign, pre-invasive lesions and HPV-related cancers. Vaccination for women over 26 years of age should be considered individually, taking into account the specific risk factors of each patient. That is why universal vaccination until the age of 45 is not recommended by any scientific society, whether national or international.	
Adolescent knowledge, attitudes and practices about the human papilloma virus	Mariana Portela Soares Pires Galvão	2022	Rev Saude Publica	The study seeks to understand the level of knowledge, attitudes and practices of adolescents from public schools in Teresina-PI in relation to the human papillomavirus (HPV).	Among adolescents, 27.3% presented adequate knowledge, 34.1% showed positive attitudes and 74.6% exhibited adequate prevention practices. The multivariate analysis showed that the female sex (ORa = 15.62; 95%CI: 9.08-26.9), a good level of knowledge (ORa = 2.09; 95%CI: 1.15-3.81) and positive attitudes (ORa = 1.89; 95%CI: 1.10-3.23) are significantly associated with adequate preventive practices.	
Educational intervention effect for adherence of school adolescents to the human papillomavirus vaccine	Hellen Lívia Oliveira Catunda Ferreira	2022	Journal of USP's School of Nursing	Evaluate how the educational intervention "Get out, HPV!" impacts knowledge, attitude and adherence to human papillomavirus vaccination in adolescents.	Prior to the intervention, knowledge was insufficient, but the attitude was positive in both groups. After the intervention, the intervention group showed a significant increase in knowledge and appropriate practices. Having adequate knowledge and attitude after the intervention, in addition to being 12 years or older, significantly increased the likelihood of adhering to vaccination, explaining 70% of the practice.	
School-based HPV vaccination: The challenges of a Brazilian initiative	Julio Cesar Teixeira	2021	Rev Bras Ginecol Obstet	This study aims to evaluate the implementation and impact, after two years, of	The program invited 4,878 children through schools, representing 87.1% of the target population, with a refusal rate of 7.5%. Healthcare	

				a vaccination program against the human papillomavirus (HPV) in schools in a Brazilian city.	professionals' attention was divided due to several simultaneous events. First dose coverage among children aged 9 and 10 years increased from 16.1% in 2017 to 50.5% in 2018 (p < 0.0001).  Considering all ages, the administration of the first dose grew by 78% in 2018 compared to 2017 (6,636/3,733). However, in 2019, competing demands continued, resulting in a drop in first-dose coverage to 26.9%. In 2020, a municipal law began to require vaccination in schools and the creation of teams dedicated to vaccination, strategies that are still awaiting implementation and evaluation.
Human papilloma virus (HPV) vaccine coverage in Brazil: heterogeneity in space and among age cohorts	Lívia de Lima Moura	2021	REV BRAS EPIDEMIO L	Evaluate coverage of the first and second doses of the human papillomavirus (HPV) vaccine in Brazil, dividing by microregions and comparing groups of girls aged 14, 15 and 16 years in 2017. In addition, investigate how spatial variation in vaccine coverage relates to sociodemographic variables.	The proportion of microregions achieving adequate vaccine coverage was significantly higher for the first dose (ranging from 91.8% to 159.2%) regardless of age group. In contrast, the coverage of the second dose was lower (ranging from 7% to 79.9%), with differences associated with the degree of urbanization and the presence of private bathrooms in the municipality. The analysis of the random effect revealed a significant variation between the Brazilian states in obtaining vaccine coverage.
Human papilloma virus vaccination in males of pediatric age: what is the evidence?	Vanessa Filipa Guedes Silva	2019	Rev Port Med General Fam	Evaluate the efficacy of human papillomavirus (HPV) vaccination in boys in preventing malignant or pre-malignant diseases associated with HPV infection.	The three clinical guidelines heavily analyzed recommend (level A) vaccination against HPV in boys. Among the 11 articles reviewed, the majority point out that vaccination reduces the incidence of HPV infections and malignant or premalignant lesions.
ADHERENCE TO HPV VACCINE AMONG ADOLESCENTS: INTEGRATIVE REVIEW	Ayla Maria Calixto de Carvalho	2019	Text & Context – Nursing	This study seeks to identify the factors that influence adolescents' adherence to the human papillomavirus (HPV) vaccine.	Several factors have been identified as predictors of vaccine adherence, including knowledge about the risks of HPV infection, understanding the benefits of the vaccine, prevention of cervical cancer and genital warts, sexual activity, age above 14, mothers' intention to adhere to vaccination, mother-to-child communication about sexually transmitted infections, contraceptive and condom

					methods, school vaccine offering,
					recommendations from teachers
					and health care professionals, and the perception of vaccine safety
					and efficacy.
Human papillomavirus	Lídia Ester Lopes da	2019	Rev Panam	Analyze the acceptance of the human	A total of 212 articles were identified, of which 10 were
vaccine receptivity:	Silva		Salud	papillomavirus (HPV)	selected for further analysis. Most
a systematic review			Publica	vaccine and identify obstacles and incentives	studies have pointed to a favorable human papillomavirus (HPV)
				associated with its	vaccine receptivity, albeit with
				acceptance.	considerable variations, with a
					notable greater willingness to accept the vaccine compared to
					effective adherence, especially
					among female adolescents. A total of 11 facilitating factors and nine
					obstacles to this receptivity were
					identified, with special emphasis on the level of knowledge about the
					theme and the individual behavior
					in the face of the problem.
					It is important to point out that there is no universally standardized
					method for evaluating this theme,
					and the concepts associated with acceptance and adherence to
					vaccination have proved to be
					inaccurate. In this context, the present study proposed defining
					clear concepts for "acceptance"
					(referring to the voluntary intention
					to receive a vaccine or to agree that it represents an adequate
					preventive strategy) and
					"adherence" (related to the act of initiating vaccination and following
					the recommended dosing
PATIENT	Franciele	2023	Uningr	Examine the scientific	schedule).  Research revealed that most
PERCEPTION,	Batista do	2023	Unipar Health	information that is widely	studies focused on specific groups
KNOWLEDGE	Nasciment		Sciences	documented in the	of patients, notably parents, due to
AND SATISFACTION	0		Archives	literature regarding the patient's perception,	their involvement in the vaccination process of their children, pregnant
WITH THE				understanding and	women, post-natal women, and
VACCINATION PROCESS:				satisfaction with the vaccination process for	people with comorbidities. Adherence to vaccination,
INTEGRATIVE				the purpose of the	especially for influenza vaccine in
REVIEW				medical care provided.	pregnant women and HPV vaccine in parents, has been observed to
					decline significantly. The main
					reasons for delays in vaccination
					and refusal of immunization included a lack of knowledge about
					vaccines, an overbelief in natural
					immunity, a perception that vaccines are unnecessary, fear of
					adverse reactions, and
					dissatisfaction with the information provided.
	<u> </u>				provided.

					As regards the possible gaps in care, the lack of guidance from health professionals was highlighted. Therefore, in order to ensure that patient information is effectively communicated and that patients gain a more comprehensive understanding, it is crucial that healthcare professionals are constantly updated. This will allow them to offer clearer guidelines, resulting in better assimilation of knowledge by patients.
IMPACT OF HUMAN PAPILLOMAVIRUS IMMUNIZATION ON CERVICAL CANCER PREVENTION: AN INTEGRATIVE REVIEW	Arlan Maia Rebouças	2023	Unipar Health Sciences Archives	The present study aimed to identify, through bibliographic review, the scientific production that establishes a correlation between vaccination against Human Papillomavirus (HPV) and prevention of cervical cancer. The bibliographic search period spanned from March 24 to April 28, 2023, and followed inclusion criteria consisting of articles published in the last five years, written in Portuguese, English or Spanish, and classified with at least one Qualis CAPES B2. To achieve the purposes of this review, articles were meticulously selected from the analysis of their titles, abstracts and, later, full reading. At each stage, articles were excluded that did not fit the previously established criteria.	After carrying out a comprehensive search in the database, we managed to identify a total of 973 articles, 58 of which came from PubMed and 915 from the Virtual Library on Health. However, only eight articles met all the inclusion criteria and were therefore incorporated into this revision. These papers were originally published in the period between 2018 and 2022 in respected international journals. The literature analyzed provided multiple evidence confirming the relationship between vaccination against Human Papillomavirus (HPV) and prevention of cervical cancer. However, it is important to note that the rate of vaccine uptake still remains substantially low, even if it plays a crucial role in preventing this disease.
Relationship between awareness of cervical cancer and HPV infection and attitudes towards HPV vaccine among women aged 15-49 years: a cross-sectional study	Engin Yurtçu	2022	São Paulo Medical Journal	Analyze the association between the level of knowledge about cervical cancer, the presence of HPV infection and attitudes towards HPV vaccination in women aged 15-49 years.	The relationship between the consciousness questionnaire and the belief scale was elucidated through an analysis of simple structural equations. The mean score of women's knowledge of cervical cancer and HPV infection was 4.69 ± 4.02 when evaluated at 15 years of age. Women expressed fears regarding the diagnosis of cervical cancer and HPV infection, but demonstrated a lack of substantial information on the subject. They showed little familiarity with the anti-HPV

Knowledge and attitudes of parents of children/adolescent s about human papillomavirus: cross-sectional study	Louise Fernanda Santos Fernandes de Matos	2022	Acta Paulista de Enfermage m	Examine the attributes attached to those responsible for children and adolescents who obtained information about the human Papillomavirus, also evaluating the degree of knowledge about the infection and the willingness to vaccinate their children	vaccine, they were unaware of the procedures for obtaining the vaccine and they had limited knowledge about its benefits and associated risks. Notably, women who expressed fears about cervical cancer and believed they were at risk showed higher levels of information about the HPV vaccine  Among those taking part in the research, 327 (87.0%) reported having knowledge about the human Papillomavirus. A correlation was observed between the lack of knowledge about the infection and variables such as the male sex, between the ages of 18 and 25, and the conclusion of elementary schooling. Among those responsible who were aware of the Human Papillomavirus, 152 (46.5%) identified it as a sexually transmitted infection, 245 (74.9%)
					recognized transmission through unprotected sexual intercourse, 275 (75.5%) had no information about its symptoms, 218 (66.7%) erroneously believed in the possibility of curing the infection, and 283 (86.5%) were aware of the vaccine's existence. Notably, of all the interviewees, 98.1% indicated their intention to take their children to be vaccinated against the virus.
Environmental factors associated with human papillomavirus vaccine coverage in adolescents: analysis from 2016 to 2020	Bianca Maria Oliveira Luvisaro	2022	Rev. Latino-Am. Nursing	To examine the correlation between the elements present in the social context and the rates of adherence to vaccination against the human papillomavirus (HPV) among the adolescent population of the state of Minas Gerais.	The vaccination rates in the different regions analyzed are below the targets set by the Ministry of Health. Moreover, such rates are correlated with elements linked to the administration of the first dose, as well as with social context variables such as incidence of violence
HPV immunization in Brazil and proposals to increase adherence to vaccination campaign	Wagner Mesojedov as Santos	2023	Public Health Magazine	The objective of this study was to investigate the factors responsible for the low adherence to vaccination in the country, besides analyzing and comparing vaccination campaigns of HPV in Brazil and in the world, and to apply the quality tools in the identification of strategies that can raise CV vaccination coverage in relation to HPV.	In 2019, vaccination coverage in Brazil was only 49.6%, while other countries showed significantly higher rates: Australia reached 80.2% in 2017, Mexico reached 97.5% in 2019, and Peru recorded 91% also in 2019. These nations have succeeded in their vaccination campaigns, largely due to the application of social marketing strategies to engage the community.

	T	1	T		
Benefit of HPV vaccination in patients undergoing conization for removal of high-grade cervical intraepithelial lesion	Valentino Antonio Magno Virginia	2020	Amrigs Magazine	Do a literature review that gathers the latest scientific evidence on the benefits of vaccination against HPV (Human Papillomavirus) in women who have already undergone conization to treat pre-malignant lesions in the cervix.  To investigate the posture	The reviewed studies indicate that the vaccine has a significant protective effect in preventing recurrence of the disease.  67 pediatricians took part in the
recomiendan los pediatras de different providers de salud en Montevideo?	González	2021	Hey, Urug.	of certain pediatricians in Montevideo as to the recommendation of the vaccine against the HPV	study. Of these, 66 recommend the vaccine, 58 believe they have the necessary information about it, 64 know their indications and contraindications, 63 would like to receive official information from the Ministry of Public Health, 63 think that the patients do not have adequate information, 21 need 15 to 30 minutes to explain everything, and 65 believe that they can influence the parents' opinion about the vaccination.
Th1-Th2 profile in human papillomavirus (HPV) immune responses in vitro in men of the city of São Paulo, Brazil	Fernando Augusto Miranda da Costa	2019	Dst J. Bras. Sex Diseases Transm	Analyze the HPV-specific immune response in men, both those with virus-related lesions and those without such lesions, through in vitro testing.	Group A, made up of co-infected individuals (HIV+/HPV+), showed high levels of cytokines, especially of the Th2 profile, compared with the other groups analyzed. Levels of IL-6 and IL-10, cytokines associated with the Th2 profile, were found to be significantly higher in this group relative to the control group (HIV-/HPV-) (p<0.0001 for both).
Efficacy of the nonavalent vaccine in the prevention of infection by Human Papilloma Virus (HPV) and cervical cancer	Iván Enrique Naranjo Logroño	2018	Cienc. Serv. Salud Nutr	Evaluate the efficacy and safety of the nonavalent vaccine in the prevention of HPV and cervical cancer infections compared to the bivalent and quadrivalent vaccines.	"High risk" genotypes account for 90% of cervical cancer cases, while "low risk" genotypes account for the remaining 10%. The bivalent vaccine showed seroconversion rates of 100% in women 15 to 25 years after three doses. The quadrivalent vaccine showed seroconversion rates between 99% and 100% in women aged 16 to 26 years. The nonavalent vaccine has the potential to prevent approximately 90% of cervical, vulvar, vaginal, and anal cancers, and about 20% of cervical cancers associated with the five additional genotypes.
Effects of the age of vaccination on the humoral responses to a human papillomavirus vaccine	Francesco Nicoli	2022	npj Vaccines	Investigate the impact of age on the maintenance of the HPV vaccine immune response.	The results indicate that the efficacy of the immune response to the HPV vaccine at different ages is more related to the amount of immune cell precursors than to qualitative deficiencies in B cells. In addition, it was observed that adults also have a strong humoral

	immunogenic profile, suggesting that the inclusion of this group in
	recovery vaccination programs would be beneficial.

Source: Prepared by the authors.

The analysis of the selected articles allowed to identify a significant increase in the discussion on HPV vaccination in recent years, especially as of 2020. The interdisciplinary nature of the journals in which the articles were published showed that even publications outside the field of public administration brought pertinent discussions to the area. To identify the main discussions of the articles, a term frequency analysis was performed, where HPV was the most commonly used term, followed by the terms vaccination and prevention.

#### 4. DEBATE/DISCUSSION

The central theme addressed in all the articles included in this review is vaccination against Human Papillomavirus (HPV). All of these studies show significant similarities as far as vaccination is concerned, addressing its various modalities and approaches, taking into consideration the particularities of each country and the aspects assessed. These analyzes consistently converge on the importance of increasing vaccine coverage globally (REBOUÇAS *et al.*, 2023).

From the literature review, it becomes evident that increased vaccination coverage is a robust indicator of the importance of prevention and, potentially, future eradication of cervical cancers, as well as their complications (REBOUÇAS *et al.*, 2023).

Vaccines play a crucial role in stimulating the body's immune response, enabling the production of specific antibodies against infectious diseases (World Health Organization, 2020). In addition, immunization is recognized as one of the most cost-effective interventions at the global level, as it reduces the likelihood of outbreaks of infectious diseases, decreasing the need for health interventions and mitigating possible burdens on public services (World Health Organization, 2019).

Over the last decade, a decrease in the incidence of invasive cervical cancer has been observed, mainly in developed nations. This decline is attributed in part to the efforts of the World Health Organization (WHO), which promoted the adoption of targets to increase human papillomavirus (HPV) vaccine coverage as a primary prevention strategy in 194 countries. The purpose of this initiative is to accelerate the

eradication of cervical cancer (WHO, 2023). It is important to note that the World Health Organization (WHO) has issued a recommendation that emphasizes the need to implement vaccination programs in all countries with the aim of achieving a global target of 90% vaccination coverage. This objetive involves immunizing boys and girls simultaneously, covering the same age group, which comprises youngsters between the ages of 9 and 14. The Technical Chamber of Immunization Advice (CTAI), during its meeting held on May 30, 2022, decided to expand the guidelines to include also male individuals affected by HIV, patients undergoing transplants, and those diagnosed with oncological conditions. This decision was announced at the first meeting of CTAI, held on May 30 and 31, 2022, in Brazilia, Federal District, through oral communication. However, it is important to note that several countries still face considerable challenges in achieving this goal (Roteli-Martins et.al., 2022).

According to information from the ICO/IARC Information Center on Human Papillomavirus (HPV) and Cervical Cancer, approximately 80% of the sexually active population had contact with the virus at some point in their lives. The first peak of incidence is observed around the second decade of life, while the second peak is observed between the fifth and sixth decade of life. The first peak is associated with the onset of sexual activity, while the second peak can be attributed to new virus exposures or loss of immunity. It is worth highlighting that the immunity of adult women in relation to infection by the HPV is significantly lower than that of adolescents.

The human papillomavirus (HPV) vaccine is an essential tool to prevent cervical diseases, such as intraepithelial neoplasia (INE) 2 or 3 and adenocarcinoma in situ. Its effectiveness is greatest when given in early adolescence, before the onset of sex life. Vaccination is recommended from the age of 11 or 12 years, but it can be applied in people from 9 to 45 years (M. et al., 2021). There are some variants of the HPV vaccine available: the bivalent vaccine, which provides protection against subtypes 16 and 18 of the virus, the quadrivalent vaccine, which provides protection against viruses 6, 11, 16 and 18, and the nonavalent vaccine, which provides protection against 6, 11, 16, 18, 31, 33, 45, 52 and 58 (Quevedo et.al.,2016).

In Brazil, the Ministry of Health incorporated this immunization in its list of public health measures in 2014, being the first country in South America and the seventh in the world to offer, including vaccination against HPV in the Vaccination Calendar for adolescents, being indicated that all boys and girls from 9 to 14 years old carry out

immunization (Quevedo *et.al.*,2016). Because the immune system develops more intensively during childhood and adolescence, vaccination in this transitional phase induces specific IgG responses for 4 HPV viruses that are both high and long-lasting (NICOLI *et.al.*, 2022)

In addition, vaccinations that are not initiated in the recommended age range have been shown to be ineffective and have a low potential for prevention against cervical cancer, as well as other diseases caused by the virus (RAHANGDALE *et al.*, 2022). Previous research had already revealed a higher quantitative production of antibodies in children compared to adults, in addition to a noticeable decrease in vaccine efficacy as the age of immunization advances (WRIGHT JR *et al.*, 2019). In addition, studies indicate that the incidence and mortality of cervical cancer among women aged 15 to 24 years is significantly lower after immunization with HPV vaccine compared to those aged 25 to 39 years, which enhances the effectiveness of vaccination in younger women (TABIBI *et al.*, 2022). Despite evidence of vaccine efficacy, especially when the recommended age range is followed, there are significant challenges globally that prevent adherence to immunization in various spheres.

Barrier methods, such as condoms, can prevent about 70% of HPV infections. However, they do not protect completely because there are areas of skin that are not covered by the condom and also because of the incorrect use of them (GONZALES *et. al.*, 2021). In addition, screening programs often do not achieve significant coverage; the vaccine is therefore a key complementary tool in the prevention of UCC (PIREZ *et. al.*, 2021).

The Ministry of Health guarantees that the vaccine against the HPV is safe and effective. Just like all the vaccines offered by the National Immunization Program (PNI), it is going through a rigorous process of validation and registration with the National Health Surveillance Agency (Anvisa). Although, like any drug, it can cause post-vaccination adverse events, these are rare (TEXEIRA & MARTINS, 2019).

Even with the implementation of the National Immunization Program (NIP) there are still determinants for non-vaccination such as: lack of clear information from professionals in the field and lack of awareness about immunization and its importance, along with limited understanding by parents or guardians about the benefits of vaccination in relation to the associated risk, such as concern about vaccine safety and fear of adverse reactions from fake news (Lane *et al.*, 2018).

The study by Moura *et. al.* (2021) observed a significant variation in vaccine coverage across states, which may be linked to different state public policies, which affect the availability of vaccines to the population. Between 2013 and 2021, HPV vaccination coverage in the Northeastern states fell short of the 80% target established by the National Immunization Program (NIP), with vaccination coverage in boys being lower than for females (VON GLEHN *et. al.*, 2023).

Research shows that the COVID-19 pandemic has had a significant impact on public health, also affecting the extent of vaccination against the Human Papillomavirus (HPV) virus. However, this situation is not restricted to HPV vaccines alone, but also covers all other routine vaccines (Dinleyici *et.al.*, 2021; LaMontagne *et.al.*,2011).

Vaccination against HPV plays a key role in the WHO goal of eradicating cervical cancer, seeking to vaccinate 90% of girls by age 15 by 2030 (TEIXEIRA *et.al.*, 2021).

# 5. CONCLUSION

Literature analysis shows that the efficacy of HPV vaccine is optimized when administered in adolescence, before the onset of sexual activity. Vaccinating in this age group provides a robust immune response and protects the Squamous-Column Junction (SCC), an area vulnerable to viral infection and the development of precursor lesions of cervical cancer. Understanding the relationship between JEC histological configuration and vaccination reinforces the importance of initiating immunization early. Therefore, public health policies should prioritize vaccination in adolescence to prevent cervical cancer effectively and sustainably.

To this end, it is necessary to intensify vaccination campaigns through effective communication strategies, including the use of social media, in order to improve the population's understanding and adherence to immunization. These measures aim to increase vaccination coverage to reach the 80% target set. In addition, the implementation of vaccination programs in educational institutions may further enhance adherence and coverage, promoting a substantial increase in HPV protection.

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### **CHAPTER 10**

### USE OF FREEZE-DRYING MICROSCOPY IN BIOLOGICAL PRODUCTS IN THE PHARMACEUTICAL AREA FOR FREEZE-DRYING CYCLE

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ABSTRACT: Yellow fever is a serious public health problem in Brazil. This is due to the impossibility of eradicating the circulation of the virus in its wild cycle. One of the effective methods of acting, both preventively and correctively, is to administer the vaccine to the population in these areas. In this context, the Institute of Immunobiological Technology (Bio-Manguinhos), located at Fiocruz, is included, whose role is to provide vaccines to the population. This research seeks to study the critical stages of vaccine lyophilization, using lyophilization microscopy in the production process, with the aim of expanding production capacity and meeting national and export demand. Protocols were studied so that it would be possible to analyze the critical parameters of the product through lyophilization microscopy,

allowing the identification of the collapse temperature, freezing temperature, and melting temperature of an optimized 2-dose yellow fever vaccine formulation. The results showed that the freeze-drying microscopy (FDM) tool together with DSC contributed significantly to the study of the freeze-drying cycle of the optimized two-dose yellow fever vaccine, maintaining the efficacy and safety of the product regarding quality attributes.

**KEYWORDS:** Iyophilization, mass reduction %, residual humidity %, Iyophilization microscopy.

RESUMO: A febre amarela é apresentada como um grave problema de saúde pública no Brasil. Isso ocorre pela impossibilidade de erradicar a circulação do vírus em seu ciclo silvestre. Um dos métodos eficazes de agir, tanto de forma preventiva como corretiva ao problema, é a aplicação da vacina na população dessas áreas. Nesse contexto, insere-se o Instituto de Tecnologia em Imunobiológicos (Bio-Manguinhos), localizado na Fiocruz, cujo papel é fornecer as vacinas à população. Esta pesquisa busca estudar as etapas críticas da liofilização da vacina, fazendo o uso da microscopia de liofilização no processo produtivo, com o objetivo de ampliar a capacidade de produção e suprir a demanda nacional e exportação. Protocolos foram estudados para que fosse possível analisar os parâmetros criticos de produto por meio de microscopia de liofilização, permitindo identificar a temperatura de colapso, temperatura de congelamento, e a temperatura de fusão de uma formulação da vacina de febre amarela 2 doses otimizada. Os resultados mostraram que a ferramenta de microscopia de liofilização (FDM) juntamente com o DSC contribuiu significativamente no estudo do ciclo de liofilização da vacina de febre amarela otimizada de duas doses. mantendo a eficácia e a segurança do produto quanto aos atributos de qualidade.

PALAVRAS-CHAVE: liofilização, percentual de redução de massa, percentual de umidade residual, microscopia de liofilização.

#### 1. INTRODUCTION

Yellow fever (FMD) is a viral, infectious and non-contagious disease whose etiological agent is an arbovirus of the genus *Flavivirus*, belonging to the family *Flaviviridae*, being categorized into two types, urban and wild, and can be transmitted to humans and animals (Brazil, 2017).

According to Pivetta (2017), in Brazil, the predominance of wild yellow fever (FAS) is observed, in which the virus, through the mosquitoes of the *Haemagogus* and *Sabethes* genera, perpetuates the transmission cycle through the contamination of the monkeys. These types of mosquitoes do not live in an urban area; they breed only in tree holes, where the eggs are deposited, which hatch when bathed in rainwater. Contamination in humans occurs through contact with the contaminated mosquito present in the forests (Pivetta, 2017).

In the last few decades, FMD has been registered beyond the limits of the area regarded as endemic (the Amazon region) and critical in the eyes of public health. Accordingly, the adoption of surveillance, based on seasonality, introduced a period for monitoring the disease, which starts in July and ends in June of the following year. Human cases and epizootic diseases in non-human primates (NHPs) were reported in a large area of the country, generating a great challenge for the authorities (Ferreira *et al.*, 2011).

According to the Ministry of Health, yellow fever is a public health problem present in Brazil, so vaccination is an individual and collective prevention strategy, as quoted in the Brazilian Journal of Health Review, which can be considered an investment in health due to its excellent cost-effectiveness and the impact on disease prevention (Mizuta *et al*<sup>1</sup>., 2020).

According to Correia Junior, Silva and Trevisan (2021), vaccination has been expanded, facilitated and improved by the national immunization programs (PNI), in this context, in 1973 the National Immunizations Program (PNI) was created in order to reduce morbidity and mortality from preventable immune diseases in Brazil (Nóvoa et al., 2020).

The prevention and control of FMD involves vaccinating the population in areas at risk, as well as vector control and sanitation actions. Bio-Manguinhos is the only producer certified by the National Health Surveillance Agency (Anvisa) and the World

Health Organization (WHO) to meet the Single Health System (SUS) and countries in Africa and Asia, and the national and export demands, besides the regulatory systems, Bio-Manguinhos has been investing heavily in improvements in the production process of the yellow fever vaccine (Brazil, 2017).

Aiming at increasing the yield of the vaccine, Bio-Manguinhos inserted into its project improvements to the FA vaccine alternatives to expand its productive potential. One of the improvements prioritized was the optimization of the production of active pharmaceutical input (API) in the crushing stage, increasing its productive capacity (Brazil, 2017).

From this improvement, there was the need to evaluate the productive chain of the formulation, filling, freeze-drying, re-recording, overhaul and packaging. The critical step in the production process is lyophilization, as critical product attributes can impact critical quality attributes due to optimized API with and without sterilizing filtration. The proposal of this work aims to apply FDM, a freeze-drying simulator that aims to characterize the critical parameters of the product, allowing greater reliability to the critical quality parameters and minimize the risk to the process and the product, bringing innovation and technological prospecting to the pharmaceutical industry (Brazil, 2017). In this approach, the use of lyophilization microscopy (LDMP) brings robustness to the lyophilization cycles under development or already developed, by applying the quality by design approach (Tattini Junior, 2008).

#### 2. GOALS

Knowing that the quality of the immunobiological depends mainly on the drying rate (%) in the sublimation during the primary and secondary phases of lyophilization, the objective of this work is to propose a methodology for the study of the critical parameters of the product temperature, which impact on the quality of the two-dose attenuated AF vaccine, formulated with optimized API: quality impacts after the lyophilization process.

#### 3. THEORETICAL FRAME

#### 3.1 IMPACT OF CHANGE

There is a need to challenge the quality parameters of the new product with the commercial vaccine, ensuring safety and efficacy, making it a change process with moderate to minor impact (Brazil, 2022).

Criticality is how much this change is able to impact this product, that is, without changing its safety, effectiveness and quality. For this improvement proposal, the optimized API without antibiotic will be used, with a lesser impact already assessed by Anvisa in the formulation of the FA vaccine, maintaining all the ingredients of the formulation without the alteration of the excipient. The same commercial vaccine vial will be used.

After the production of the optimized API, the input follows the formulation stage with the others; however, with proportionality, being the FA vaccine with optimized IFA two doses, which maintains the low regulatory impact, since there is no change of inputs (Brazil, 2022).

The formulation of the product to be lyophilized is a mixture containing solvent, which will be removed over the cycle in the primary and secondary drying stages, which gives stability to the product. The duration of a lyophilization cycle depends on the composition of the AF vaccine with antibiotic-optimized API. (Brazil, 2017).

#### 3.2 LYOPHILIZATION PROCESS

Terroni *et al.* (2013), the freeze-drying process is a drying technology that consists of removing water through sublimation and is subject to very low pressure conditions. The product is placed in airtight chambers, the air from inside is removed through high vacuum pumps, creating the condition for the water to sublimate. It is a preservation technique that removes water from a solution at very low levels, so biological activities or chemical reactions are inhibited. In a simple way, it can be said that freeze-drying is a technique that allows separating liquid products previously frozen under vacuum (Terroni *et al.*, 2013).

Given the high costs of producing lyophilized vaccines, the restriction of available equipment and the long production time, the need to reduce the time of the lyophilization cycle through more assertive techniques becomes evident (Terroni *et al.*, 2013). Lyophilization usually consists of three steps:

- a) freezing: the freezing phase consists of reducing the product's temperature, so that most of the water (solvent) is crystallized. Solute segregation and the concentration of components in the liquid phase occur, which can lead to the growth of these ice crystals (Baruffaldi; Oliveira, 1998);
- b) primary or sublimation phase: this phase consists of the removal of ice by sublimation. In primary drying, sublimation begins at a very low pressure, at an optimum product temperature, in order to decrease this stage, which is the longest and most critical of the freeze-drying process (Pikal et al., 1990);
- c) **secondary phase or desorption:** moving on to the secondary phase, drying or desorption, the water left by the outlet of the ice crystals is removed, so that the product's RH remains at a real and ideal value. There is a greater reduction in chamber pressure to promote desorption of the residual ice and water still present. At this moment, when the frozen water is heated and removed by sublimation from a conventional freeze-drying process (Pikal *et al.*, 1990).

#### 4. METHODOLOGY

#### 4.1 SCOPE OF THE STUDY

Aiming to support the institutional strategic objectives, Bio-Manguinhos, along with its strategic planning, listed some demands as the institutional goal. Amongst them, there is the development of the cycle of the FA vaccine with an optimized two-dose API, a proposal from UNICEF to minimize losses in the field. This study was carried out at the Lyophilization Experimentation Laboratory (LALIF), in Bio-Manguinhos, an area for product development and improvement.

## 4.1.1 Proposal to study critical parameters of the two-dose yellow fever formulation with optimized API

#### 4.1.1.1 Use of lyophilization microscopy

To challenge the critical parameters in this stage, a tool of FDM was used, which allowed us to study the parameters of the product temperature by means of a freeze-drying simulator, with little sample (1 drop), without burdening the process costs in the experimental stage, in which the stages of development still take place.

The methodology made use of the FDM analytical tool. The equipment used for this research was Lyostat5, which comes equipped with quartz plates G16, used for the analysis of small volume samples of liquid products, with the purpose of determining critical limits of the product's temperature, such as Tc, Tf and Tcong.

This equipment has a quartz plate for freezing on a small scale. A drop of silicon oil was added to the orifice in the silver block, ensuring that it did not enter the opening and avoiding a false reading at the time of running the cycle.

For these procedures, a pipette was used to dispense the volume of 2µl from the liquid formulation for analysis and then, with the aid of a vacuum pen, a 13 mm diameter w13g glass plate was carefully inserted on top of the spacer, model, FDCS SP 70µm. After the sample is inserted into the slide, the intensity of the light has to be adjusted.

A 2µL sample containing FA vaccine was analyzed using a LyoStat5 microscope (Biopharma Process Systems Ltd.). The temperature was reduced to -50 °C (-40 °F) at a freezing rate of 10 °C/minute (rapid freezing) being the most critical. Once the stage reached -50 °C (-40 °F), the sample was held for five minutes to balance the temperature before the vacuum was applied.

4.1.1.2 Establishment of lyophilization cycle of commercial yellow fever vaccine (with commercial API) × two-dose yellow fever vaccine lyophilization cycle (with optimized API) with sterilizing filtration and without sterilizing filtration for simulation

For the commercial FA vaccine, in this study, the formulated batch was received at a storage temperature according to the therapeutic moment and after filling, freeze-

dried, with a slow freezing rate enabling the formation of the larger crystals, which facilitated sublimation for the formulated product.

In the experimental cycles, the working range for the variable pressure in mm bar and the average control limit of the collapse temperature for the product temperature were also evaluated. The cycles made use of experimental planning, to vary product temperature  $\times$  pressure  $\times$  vial type  $\times$  freezing rate, subsequently evaluating quality parameters for comparability of the AF vaccine (without improvement).

### 4.2 DEFINITION OF YELLOW FEVER FORMULATION CRITICAL TEMPERATURES TWO DOSES WITH OPTIMIZED API WITHOUT ANTIBIOTIC

Critical process parameters such as Tc, Tcong and Tf were evaluated in FDM, establishing a standard recipe containing freezing rate, fast freezing speed, i.e. in the worst case due to impact on sublimation, in addition to pressure and time. During the characterization of the critical parameters in the FDM freeze-drying simulator, the pressure was reduced to the maximum and maintained to dry the product. Once a good amount of dry material has been formed, the temperature is increased at a rate of 1 °C/minute until the material collapses, according to the recipe mentioned above.

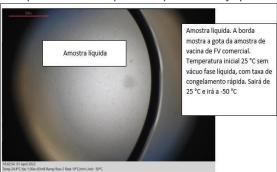
The lyophilization microscopy methodology for characterizing critical parameters in sterile drugs, made use of guidelines to meet EU Annex 1 in the pharmaceutical industry, setting strict requirements for manufacturing them applying, scientific basis as the rate of rapid freezing, so that crystals had a smaller structure, bringing the worst case (more difficult sublimation). For this reason, it was worked with 10 °C/minute (step 1), as shown in Figure 1.

The supply temperature used was 25 °C (step 2), according to Figure 2. At this stage, the product is frozen. It was maintained for one minute without vacuum to reach - 50 °C until it was with a homogeneous condition of the vials, remembering that this design simulates the process of freeze-drying under the same conditions (step 3), see Figure 3.

In step 4 (Figure 4), a vacuum was applied for five minutes, starting the sublimation step. In this stage, with the rate of rapid freezing, the effect of the Tc occurs, allowing the study of this critical parameter in the formulated product. In steps

5, 6 and 7, the secondary phase stage begins. At this same stage fusion takes place, which allows us to identify the Tf of the product.

Figure 1. Step 1 - Representative liquid sample under lyophilization microscope.



Source: The author (2023).

Figure 2. Step 2 - Solid-state frozen sample.



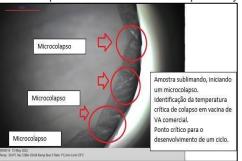
Source: The author (2023).

Figure 3. Step 3 - Sublimating sample, representative in lyophilization microscope.



Source: The author (2023).

Figure 4. Step 4 - Sample with representative micro-collapse in lyophilization microscope.



Source: The author (2023).

## 4.2.1 Critical establishments of the work bands in the formulation of yellow fever two doses with optimized API (data collection)

Graphically readings of critical temperatures were collected in three distinct samples, containing eight readings at different times. In this way, a data collection worksheet was assembled, containing n = 8 for three different samples of products such as commercial FA vaccine with common API, FA vaccine with optimized IFA without sterilizing filtration (unfiltered) and FA vaccine with optimized IFA with sterilizing filtration (filtered).

# 4.2.2 Proposal to establish working ranges in the formulation of yellow fever two doses with optimized API

The *Minitab* software was used, and several analyzes of the effect versus response were carried out: at critical collapse temperatures versus commercial vaccine; at critical collapse temperatures versusOptimized IFA with no antibiotic sterilizing filtration and no sterilizing filtration. The purpose of this methodology was to have the results by comparability and to evaluate the normality curve, the hypothesis test, the confidence interval and to establish the limits of control by way of control letters (1 sigma, 2 sigmas, 3 sigmas).

This part of the methodology establishes the safety limits to the product, minimizing risks and impacts to the quality parameters, since we are defining the safety bands, that is, what the work limit that my product will not be able to reach in a cycle, since it will have an impact of quality and risk of safety and effectiveness.

#### 4.3 ACCEPTANCE CRITERIA FOR QUALITY PARAMETERS

#### **4.3.1 Aspect**

All experimental batches had samples collected in parallel before verifying the residual moisture as well as the appearance of the evaluated lyophil. It should have uniform appearance, loosened gum from the bottom and well-formed without critical defects. Flasks containing defects such as malformed/non-standard particles, altered volume, broken, cracked or unstoppered flasks should be discarded. The visual inspection follows the regulatory standards of the Parenteral Drug Association (PDA, 2019).

#### 4.3.2 Solubility test of lyophilized vials: reconstitution time

In the solubility or homogeneity test, the lyophilized vials are reconstituted with dedicated water for injections (WFI) and their purpose is to evaluate if the lyophilized powder completely dissolves without forming visible clumps or waste, ensuring a homogeneous solution. As the vial is 4 ml and the tested vaccine was bottled in a volume of 0.22 to 0.25 ml in two doses, the volume of 2.5 ml will be dosed slowly to the vial containing the lyophil, with the aid of needle and syringe for ten seconds. The vial was shaken slowly and gently until a uniform, crystalline suspension was obtained. The whole procedure was timed and recorded. The minimum time to complete dissolution will be up to one minute.

#### 4.3.3 Residual humidity

All the residual moisture results obtained were statistically analyzed, so that the average of the five vials at each time was calculated, as well as their standard deviation to state the quality of the product, according to Brazilian pharmacopeia, specification of the product lower 3%.

#### 4.3.4 Power and thermostability

For the potency testing in the experimental batches, the 50% dose-infected cell culture method (CCID50 Cell Culture Infective Dose) was used, and the same test was routinely used for the batch of commercial AF vaccine. This test consists of determining the concentration of living particles, contained in a human dose (DH), when kept at 2°C to 8°C the lyophilized product, or being stored in *freezer* at -70°C the sample after formulation. For this purpose, dilutions were performed on each vial of FA vaccine with diluted API without antibiotic using factor 10.

The product is inoculated into rats (mice of the National Institute Health [NIH] lineage). For 21 days, the result is observed. For the thermostability test, the number of viral particles sufficient to immunize people is determined and the vaccine is conditioned at 37 °C for 14 days. To do so, it is necessary to prepare a Vero cell suspension and dilute the lyophilized vaccine in the plates containing the cell suspension and inoculate in a controlled environment. Conformant values for thermostability are: storage 2°C to 8°C and 37°C for 14 days - greater than or equal to 3.73 Log10 PFU/DH.

For immunobiological studies, stability studies should be conducted in accordance with Anvisa's RDC Resolution 50/2011. In this way, Figure 5, shows the conditions for conducting the stability studies of the finished product (Anvisa, 2011).

Figure 5. Finished product stability studies.

TEMPERATURA E UMIDADE- ESTUDO DE LONGA DURAÇÃO	TEMPERATURA E UMIDADE- ESTUDO ACELERADO
25 °C $\pm$ 2 °C/60% UR $\pm$ 5% UR (apenas produtos de uso restrito a hospitais) ou $30  ^{\circ}\text{C} \pm 2  ^{\circ}\text{C}/75\%  \text{UR} \pm 5\%  \text{UR}$	40°C ± 2°C/75% UR ± 5% UR
5°C ± 3°C	25 °C ± 2 °C/60% UR ± 5% UR ou 30 °C ± 2 °C/65% UR ± 5% UR ou 30 °C ± 2 °C/75% UR ± 5% UR
-20°C	Os parâmetros de temperatura e umidade serão definidos pelo fabricante

Source: Anvisa DRC Resolution 50 (2011).

#### 4.3.5 Critical process parameter

In this stage of the work, it is possible to identify the critical process parameters, such as the temperature of the product, the rate of freezing and the time. This fatora interferes critically with the process as a function of the exchange of heat that exists during the cycle, which makes possible the phases of sublimation and desorption. Among the parameters that interfere with sublimation one of the main ones is the type of bottle × volume packed.

Sublimation occurs as a function of product temperature, pressure as a function of time, so the larger the area of the bottle and the smaller the volume, the faster sublimation. Therefore, this evaluation of the kinetic behavior over the cycle becomes critical.

#### 4.3.6 Risk assessment of quality parameters and their impacts

According to United States Pharmacopeia (USP), based on the survey of causes and effects by means of the Ishikawa tool, to evaluate the risk of applying the FDM analytical tool, with the objective of characterizing critical process parameters that impact on product quality attributes, some possible causes and their possible effects for the problem critical quality attribute were scored; thus, the FDM tool minimized the risks, bringing greater safety and efficacy to the product (USP, 2020).

# 4.3.7 Experimental planning: five-dose yellow fever vaccine freeze-drying cycle with optimized API

For the experimental design addressing all interactions of variables with their responses was used, a complete factorial process planning with the variables of critical product parameters, and the response factor, were the quality attributes that ensured safety and efficacy: a) minimum product temperature (minimum limit) - TI; b) maximum product temperature (maximum limit) - TS; c) ideal product temperature (central point) - TC; d) 45 mm bar - PI; e) 60 mm bar - PC; f) 85 mm bar - PS; g) bottle 4.0 ml; h) bottle 2R.

### 4.3.8 Experimental planning design to challenge the cycle by correlating critical parameters with time

In the light of the experimental planning, it was possible to complete a planning with two central points, that is,  $2^3 + 2$  PC = 10 experiments for each type of flask. In this way, the critical process and product variables against quality parameters according to CPR Resolution 73/2016 were experimentally challenged in order to ensure safety and effectiveness to the patient (Anvisa, 2016).

#### 5. RESULTS AND DISCUSSION

#### 5.1 PRELIMINARY RESULTS OF LYOPHILIZATION MICROSCOPY

In order to identify the critical temperature parameters to improve the lyophilization cycle, the FDM tool was used in the formulation of the AF vaccine of the experimental batches, in order to identify the critical temperature parameters, allowing to design a cycle with possibility of shorter process time, product quality and better stability.

#### **5.1.1 Critical temperature characterization at primary stage**

Readings with n = 8 were performed on three samples of each product, evaluating the commercial FMD vaccine, the FA vaccine with optimized IFA without antibiotics prior to sterilizing filtration and the FA vaccine with optimized IFA without antibiotics after sterilizing filtration, and using the FDM tool for these results. The Minitab made it possible to generate some results of the first descriptive analysis. We have three samples, sample 1, sample 2 and sample 3, with three analyzes, Tc, freezing temperature and melting temperature.

#### 5.1.2 Result of comparability of vaccines

In the 24 samples, the variability between them is low and can be evidenced by the standard deviation, with a 95% confidence interval. For a commercial vaccine formulated with commercial API, with optimized IFA filtered and unfiltered, the critical temperature of the product with an average higher than the commercial vaccine. The results show a low standard deviation in front of samples and between vaccine comparabilities, which demonstrates that, regardless of API, Tc is critical against the formulation because of the sublimation time required for drying. The commercial vaccine had the Tc variable with a 95% confidence interval to a low standard deviation of 0,282 to 0,508, which demonstrates low variability between samples (with normality).

Figure 6 shows a statistical analysis demonstrating normality of critical product temperature parameters for commercial vaccine for Tc and Tcong.

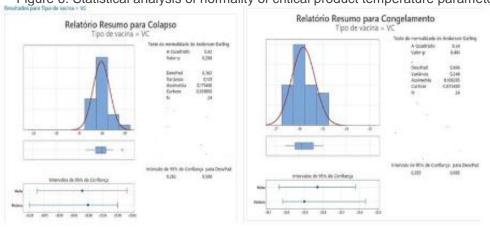
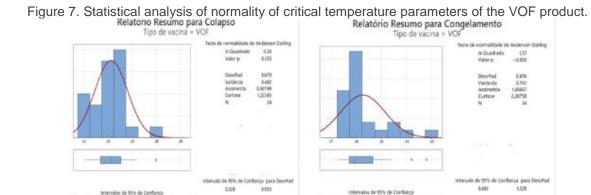


Figure 6. Statistical analysis of normality of critical product temperature parameters

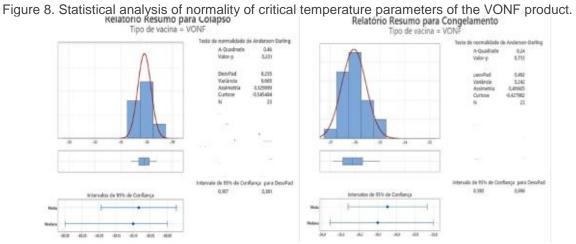
Source: The authors (2024)

The optimized filtered vaccine had the Tc variable with a 95% confidence interval with a low standard deviation of 0,528 to 0,953, which demonstrates low variability between samples (normally). For the freezing temperature variable with a 95% confidence interval, with a low standard deviation. Figure 7 shows a statistical analysis demonstrating normality, from critical product temperature parameters to optimized vaccine with sterilizing filtration, to collapse temperature, and freezing temperature.



Source: The authors (2024)

The unfiltered optimized vaccine had the Tc variable with a 95% confidence interval with a low standard deviation of 0,197 to 0,361, which demonstrates low variability between samples (normally). For the variable Tcong with a 95% confidence interval for the mean between -26,260° and -25,835°C with a low standard deviation. Figure 8 shows a statistical analysis demonstrating normality, from critical product temperature parameters to optimized vaccine without sterilizing (unfiltered) filtration, to collapse temperature, and freezing temperature.



Source: The authors (2024)

Table 1 shows that the sample measurements were analyzed by comparability demonstrating low variability and low standard deviation pointing out that there is no impact with sterilizing filtration, allowing optimization bringing the product the care to RDC658/2022, complying with Annex 1 EU GMP, RDC073/2016, bringing safety and

efficiency to the product and the patient as to the comparability of the three vaccines, which demonstrates risk mitigation to the process, the product and the quality attributes.

Table 1. Mean, standard deviation, analysis of variability between the three vaccines.

Tipo de vacina		DesvPad	IC de 95%
VC	24	0,496	(-26,040; -25,619)
VOF	22	0,563	(-26,147; -25,707)
VONF	23	0,492	(-26,263; -25,833)

DesvPad Combinado = 0,516847

Source: The authors (2024)

The hypothesis test was generated in two different conditions for each vaccine, when it collapses, and when it freezes, being evaluated the variable response temperature in different critical parameters, and measured the critical variable temperature, evaluating the homogeneity between the samples in each product, by means of variance test between the samples, where the curve is normal, i. e. lower 0.05. For the collapse in each sample was tested normality, and homogeneity and variance, where sample 1, 2 went on to show normality, and sample 3 presented outliers being evaluated the same, then being performed the Grubbs test, where The evaluation shows that there are no outliers being normal and the variance is from the sample, which shows Figure 9. In the equality test, Sigma Two, we evaluate if the variances are equal within the three samples, and with anew we evaluate if the medias are equal by doing a comparability test of the 3 samples as shown in Figure 10. When evaluated the collapse which is the most critical parameter, we do not use the normal test because one of the samples presented variability so the use of the Leuven test, where the hypothesis test was performed they are equal and are not significantly different, i.e. in the evaluation of variance of sample 1, of sample 2, and of sample 3, the results are overlapping and I accept the null hypothesis because the value of p is greater 0.05 and I am using 95% confidence (I accept the null hypothesis), that is to say they are overlapping it will never reject because at some point the variance of one hits on the variance of another then I can not reject then to Anova.

Figure 9. Anova for collapse and freezing versus type of vaccines.



Source: The authors (2024)

All the data values come from the same normal population we can follow by Anova, because I can assume that all variances are equal. Thus, following new, with 95% confidence, in terms of mean we cannot say that they are equal, therefore they are significantly different for sample 1 with 2 (rejects the hypothesis because p value gave 0.04), that is, the three are not equal and sample 1 is the one that shows the most variability, because the average (in terms of position) we obtained in sample 2 and in sample 1 are not equal but in terms of variability are equal (p value less 0.05), rejected the null hypothesis because to be equal the difference has to give close to zero. As Figure 10, presented in the statistical results, the three samples are not are equal statistically so we continue to evaluate the average by the Tucker test, as Figure 12, comparing 2 to 2 where we confirm that sample 1 is with a greater variability (more distant from all others) when compared with 1 and 3 that is ok and 2 and 3 that is ok. This test was done to challenge for comparability and to know if we can work safely with the three samples, so the low variability demonstrates that we can work with the methodology for the three samples.

Figure 10. Tukey's method for difference in medias.

Tipo de								
vacina_1	N Média	DesvPad	IC de	95%				
VC	24 -25,829	0,496	(-26,040;	-25,619)				
VOF	22 -25,927	0,563	(-26, 147;	-25,707)				
VONF	23 -26,048	0,492	(-26,263;	-25,833)				
DepvPad	Combinado	= 0,516847	,					
ompara	ções Emj	parelha	das de	Tukey				
Informa	acões de	Agrupa	mento	Usando	o Méto	do de T	ukev e 959	6 de Confia
Tipo de	.,							
	N Média	Agrupam	ento					
	24 -25.829		101110					
	22 -25.927							
	23 -26.048							
VONE								
	pue não comp	artilham u	ma letra si	ão significat	ivamente a	afferentes.		
		partilham ur	ma letra si	ão significat	livarmente o	ilderentes.		
Médias a	que não comp							
Médias a							dias	
Médias a	que não comp	eos de 1					fias	
Médias a	simultân	eos de 1 nça E	Tukey p	oara Dife	erenças	de Méd		
Médias a Testes S Diferenç de Nivei	sue não comp Simultâno a Diferer	eos de 1 nça E lias Difen	Tukey p P da ença IC	para Dife	erenças Valor-T	de Mée Valor-P Ajustado		
Médias a	Simultâne a Diferer s de Méd	eos de 1 nça E fias Difen 098 (	Fukey p P da ença IC 0,153 (-0,4	de 95% 464; 0,268)	Valor-T -0,64	de Méd Valor-P Ajustado 0,797		

Source: The authors (2024).

Table 2 presents statistical results from a descriptive analysis performed showing low variability between the samples for collapse temperature and freezing temperature, that is, in the set passes normality with 95% confidence interval, where for collapse the average temperatures of -30,662°C is the critical point for the three samples of lyophilized vaccines being the critical parameter in the lyophilization process in the primary stage.

Table 2. Descriptive statistics of critical product temperature parameters - comparability of vaccines.

#### Estatísticas

Variável	Total	Média	DesvPad	Variância	CoefVar	Minimo	Mediana	Máximo
Colapso	71	-30,662	0,978	0,957	-3,19	-32,900	-30,300	-29,100
Congelamento_1	69	-25,933	0.517	0.268	-1,99	-26,900	-26,000	-24,600

Source: The authors (2024).

#### 6. CONCLUSION

The preliminary results found were significant in comparison to the commercial vaccine and the vaccine with both filtered and unfiltered optimized API, showing that there is no variability of critical temperature parameters, regardless of the commercial API or optimized API. In this way, it is possible to define the critical parameters of Tc by means of the methodology of lyophilization microscopy. Thus, the use of lyophilization microscopy proved to be effective in tracing the limits of work control, allowing to proceed to the delineation of the cycle, evaluating the critical attributes of

product. Many studies on lyophilization focus on determining the collapse temperature, but there is a shortage of work using Freeze-Dry Microscopy (FDM) or lyophilization microscopy to measure this temperature accurately and reproducibly. A study published by Nail *et al.* (2002) in the *Journal of Pharmaceutical Sciences* examines the importance of lyophilization as a critical technique in the production of sensitive pharmaceutical products such as proteins and vaccines. The study highlights the use of simplified models to understand the fundamental mechanisms of the lyophilization process, but also recognizes that these models are rarely applied directly in pharmaceutical industrial contexts. Nail *et al.* (2002) argue that the application of techniques such as FDM, while valuable for understanding critical parameters in the laboratory, faces significant challenges when it comes to implementation on an industrial scale due to the lack of practical studies on real commercial products.

The gap identified in the literature, as highlighted by Nail *et al.* (2002), is justified by the inherent complexity of the transition from laboratory studies to pharmaceutical production environments for large-scale, sterile medicinal products. Most research, such as the one mentioned in the article, uses simplified systems to study lyophilization processes because they offer greater control over experimental variables, allowing a deeper understanding of fundamental mechanisms. However, the lack of application of these studies in real commercial products limits their practical relevance and the capacity for generalizing the results.

In addition, regulatory requirements such as the need to ensure compliance with regulations such as Good Manufacturing Practices (GMP) and FDA or EMA guidelines require validation of techniques in a real-world sterile drug production environment, where factors such as batch variability, quality control, and process robustness are critical and scalability challenges introduce an additional layer of complexity that is not addressed in simplified studies but few papers address the optimization of FDM or microscopy parameters to improve this measurement. Therefore, the proposed study demonstrates the efficacy of MDF in industrial environments, aligned with regulatory requirements and large scale production practices, where the applied methodology presents the accuracy in measuring the collapse temperature and ensures product stability.

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### **CHAPTER 11**

### INTEGRATIVE LITERATURE REVIEW: TREATMENT OF LIVEDOID VASCULITIS SECONDARY TO THROMBOPHILIAS

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ABSTRACT: Introduction: Livedoid vasculitis manifests exclusively in the lower extremities and mainly in the malleolar region. It can be primary or secondary. When secondary, the disease has a common relationship with thrombophilia and other diseases of the connective tissue. Objective: The present work aims to investigate, through an integrative literature review, the treatment of livedoid vasculitis secondary to thrombophilia. Methods: For the development of this research, the BVS, Scielo and PubMed databases were used. To carry out searches of relevant articles used in the development of the literature review, the following MESH terms were used: (livedoid vasculitis) AND (livedoid vasculitis treatment) OR (thrombophilia) AND (livedoid vasculitis secondary to thrombophilia). The period between 2010 and 2022, was one of the limiting criteria for selecting articles, which could be in Portuguese, Spanish or English. Twenty one articles were selected for analysis of this research. Results: Among the authors of the 21 analyzed articles, it showed that the use of low molecular weight Heparin and Direct Oral Anticoagulants were the most prevalent therapies in cases of Livedoid Vasculitis, however this does not indicate that the other therapies are ineffective. Since each clinical picture has its specificities. Conclusion: The treatment options for secondary livedoid vasculitis are varied, and the physician must evaluate and individualize treatment for each patient. Among the known and relevant

treatments are: therapy with low molecular weight heparin, therapy with direct oral anticoagulants, intravenous immunoglobulins, therapy with the use of Fenprocoumon and warfarin, and hyperbaric oxygen therapy. New studies comparing the different treatments for livedoid vasculitis secondary to thrombophilia are needed, especially in cases associated with Antiphospholipid Antibody Syndrome.

**KEYWORDS:** livedoid vasculitis, livedoid vasculitis treatment, thrombophilia livedoid vasculitis secondary to thrombophilia.

RESUMO: Introdução: A vasculite livedoide se manifesta exclusivamente nas extremidades inferiores e principalmente na região maleolar. Pode ser primária ou secundária. Quando secundária, a doença possui comum relação com a trombofilia e outras doenças do tecido conjuntivo. Objetivo: O presente trabalho tem por objetivo investigar por meio de uma revisão integrativa de literatura o tratamento de vasculite livedoide secundária a trombofilias. Métodos: Para o desenvolvimento desta pesquisa. foram utilizadas as bases de dados BVS, Scielo e PubMed. Para se realizar a pesquisas de artigos relevantes usados no desenvolvimento da revisão bibliográfica, utilizou-se os seguintes MESH terms: (livedoid vasculitis) AND (livedoid vasculitis treatment) OR (thrombophilia) AND (livedoid vasculitis secondary to thrombophilia). O período entre os anos de 2010 até 2022 foi um dos limitadores de critério para seleção dos artigos, podendo estes ser em idiomas português, espanhol ou inglês. Foram selecionados 21 artigos para análise desta pesquisa. Resultados: Entre os autores dos 21 artigos analisados, mostrou que o uso da heparina de baixo peso molecular e os anticoagulantes orais diretos foram as terapias mais prevalentes nos casos de vasculite livedoide, todavia isso não indica que as demais terapias sejam ineficazes. Visto que cada quadro clínico tem suas especificidades. Conclusão: As opções de tratamento para vasculite livedoide secundária são variadas, e o médico deve avaliar e individualizar o tratamento para cada paciente. Entre os tratamentos conhecidos e com relevância encontram-se: a terapia heparina de baixo peso molecular, terapia com anticoagulantes orais diretos, imunoglobulinas intravenosas, terapia com uso de fenprocumon e varfarina e oxigenoterapia hiperbárica. Novos estudos comparando os diferentes tratamentos para a vasculite livedoide secundária à trombofilia são necessários principalmente nos casos associados à Síndrome do Anticorpo Antifosfolípide.

**PALAVRAS-CHAVE:** vasculite livedoide, tratamento vasculite livedoide, trombofilia, vasculite livedoide secundária à trombofilia.

#### 1. INTRODUCTION

Livedoid vasculitis (LV) is a vascular disease that has a chronic course that affects the patient's quality of life, as it generates pain and discomfort in those affected. In addition to being a rare disease that does not yet have an established treatment, consequently, the treatment varies according to the clinical situation and comorbidities of the patient<sup>1</sup>.

This vasculopathy can be primary or secondary. The primary is not associated with pathologies. Secondary LV may be related to thrombophilia and connective tissue disorders<sup>2</sup>. Secondary LV has a known cause and may be related to systemic autoimmune disorders and hypercoagulability states, among the main ones the author cites systemic lupus erythematosus (SLE), systemic sclerosis, rheumatoid arthritis, Sjögren syndrome and antiphospholipid syndrome (PAS)<sup>3</sup>.

LV may be present without laboratory abnormalities, but patients usually report a burning pain that occurs year-round and is limited to the site of manifestation. Only the lower end is affected, mainly the ankle region. In addition, consideration should be given to the clinical triad livedo racemosa, ulceration with severe pain, and white atrophy. Depending on the course and early or late therapeutic intervention, the triad may be combined or isolated<sup>2.4</sup>.

VL causes vascular occlusion that progresses to ischemia with subsequent skin ulceration that provides a chronic and redeeming course<sup>5</sup>. The disease begins with erythematous plaques that are painful and possibly itchy and that are often bilateral in the lower limbs in the peripheral region, where it heals slowly and consequently forms residual atrophic white starry scars that are called white atrophy<sup>6</sup>.

LV has an approximate prevalence of 1 in 100,000 in North America and with a 3:1 ratio of women to men, i.e. most commonly in women preferentially middle-aged, but does not exclude all ages, including in childhood, plus an increased incidence during the summer months and pregnancy thus resulting significantly in impairments in citizens' quality of life <sup>7.8</sup>.

Authors articulate numerous hypotheses to explain the occurrence of LV in the absence of a definitive etiology, recalling that the diagnosis is carried out by exclusion according to the patient's history. Studies show that small arteries in the lower legs are susceptible to coagulation due to a variety of factors, i.e., there is a vaso-occlusive

disorder with intraluminal dermal vessel thrombosis without small vessel hypersensitivity vasculitis; progressing thrombi lead to skin necrosis, ulceration, and extremely delayed healing of the underlying skin. Even if the mechanism of LV is unknown, there is evidence that in 50% of the population studied there is a diagnosis of underlying thrombophilia with coagulation abnormalities or fibrinolysis<sup>5.9</sup>.

Within this context, the present study aims to investigate by means of an integrative literature review the treatment of LV secondary to thrombophilia.

#### 2. METHODOLOGY

The VHL, Scielo and PubMed databases were used for the development of this research. The following MESH terms were used to conduct research on relevant articles used in the development of the literature review: (livedoid vasculitis) AND (livedoid vasculitis treatment) OR (thrombophilia) AND (livedoid vasculitis secondary to thrombophilia). The period from 2010 to 2022 was one of the criteria limiting the selection of articles, which can be in Portuguese, Spanish or English. 21 articles were selected for analysis of this research.

Categorial analysis was used allowing the information to be more accurate, since the analysis is done on top of studies and research that have already been carried out. Categorial analysis will combine data from varied studies on the same topic, allowing these data to be differentiated and classified for a specific purpose<sup>2</sup>.

Three independent researchers analyzed the title and the summary of the articles retrieved during the search in the databases. When insufficient information was found in the title and the summary for the decision on eligibility, the full text was read.

Pre-selected articles were submitted to full text analysis to determine inclusion in the review based on eligibility criteria. In cases of divergence of opinion or doubt as to the pertinence of the article, it would be up to a third researcher to analyze the text in question in order to reach a consensus.

The inclusion criteria were: randomized controlled clinical trial, controlled clinical trial, cut study and/or case series and articles published in English, Spanish and Portuguese between the years 2010 and 2022. The exclusion criteria were pilot study and protocol study.

The study of the data was carried out through the analysis of categorial content, where the elements provide means to respond to the objective and describe the phenomenon that was under investigation, generating a new knowledge<sup>10</sup>.

#### 3. RESULTS

Articles were researched in a period of 12 years, and articles published in the respective banks used between January 2010 and October 2022 were eligible. At first, the search resulted in 932 articles. In the first analysis, the articles were removed outside the selected languages, without the specific approach, articles with methods other than those listed and with inconsistencies, as well as not contemplating the answers to the guiding question. Extensive research on the subject totaled 932 articles, in which 34 articles were removed, leaving 898 articles for a more in-depth analysis of the content, in which the other eligibility criteria were assessed, thus reaching 21 selected articles. The others were excluded because they did not comply with the previously scored selection guidelines. All processes are specified in the Prisma 2009 diagram, which accurately depicts the data from the article filter (Figure 1).

Registros identificados através da pesquisa de banco de dados (n=932)

Registros adicionais identificados através de outras fontes (n=0)

Registros duplicados removidos
(n=34)

Registros selecionados
(n=838)

Artigos de texto completo elegíveis
(n=478)

Artigos de texto completo excluídos, com razões (n=449)

Estudos incluídos na sintese quantitativa (metanálise) (n=21)

Figure 1 - Flowchart of selected articles.

Source: Self-Authored, 2023.

By consensus, the contents of the 21 articles were included, which were classified according to the inclusion criteria. Table 1 presents the articles selected to compose this study.

Table 1 - Selected articles.

Author(s)	Title	Year	Objectives
Araujo et al. <sup>11</sup>	Livedoid vasculitis: case report.	2019	The case of livedoid vasculitis is reported in a female patient aged 41 years with painful ulcers in lower limbs with a favorable outcome.
Santos <i>et al.</i> <sup>2</sup>	Livedoid vascular disease: a review of 5 clinical cases.	2018	Emphasize by means of a clinical case study the importance of the Dermatologist in the diagnosis of a pathology probably underdiagnosed, but which conditions significant morbidity.
Santos <i>et al</i> . <sup>3</sup>	Livedoid vascular disease: diagnostic challenge and favorable outcome after 5 years of rivaroxaban treatment.	2020	Report a relatively rare case of livedoid vasculopathy, associated with peripheral neuropathy, discussing its clinical presentation, its laborious diagnosis, and innovative treatment.
Bertequini and Pozo <sup>7</sup>	Multiple livedoid vasculitis mononeuropathy: case report.	2020	Report the case of a patient with this rare pathology to assist in her recognition as well as treatment.

Author(s)	Title	Year	Objectives
Abbade et al.4	Consensus on diagnosis and treatment of chronic leg ulcers - Brazilian Society of Dermatology.	2020	To bring together the experience of Brazilian dermatologists with the review of specialized literature for the elaboration of recommendations for diagnosis and treatment of the main types of chronic ulcers of lower limbs.
Bezerra <i>et al</i> . <sup>5</sup>	Livedoid vasculopathy: diagnosis and treatment in pregnant women.	2020	Describe the diagnosis and treatment in a young pregnant patient with excellent clinical response.
Spinel <sup>6</sup>	Analysis of serum levels and cutaneous tissue expression of lipoprotein (a) in patients with livedoid vasculopathy.	2017	To evaluate the serum and tissue expression of Lp(a) in patients with LV and to compare these findings with samples of apparently normal skin from healthy volunteers and with blood samples from patients with other dermatoses.
Goslan <i>et al</i> . <sup>12</sup>	Prophylaxis of deep vein thrombosis in bariatric surgery: comparative study with different doses of low molecular weight heparin.	2018	Compare the use of different doses of low molecular weight heparin (LMWH) for deep vein thrombosis (DVT) prophylaxis in patients who are candidates for bariatric surgery with respect to the risk of DVT, change in anti-Xa factor dosage, and pre-or post-operative bleeding.
Nobrega <i>et al</i> . <sup>13</sup>	Treatment of venous thromboembolism in neonates and children.	2020	Summarize information about the therapeutic use of unfractionated heparin (UFH) and low molecular weight heparin (LMWH) and the advantages in the treatment of VTE.
Fernandes et al.14	The new anticoagulants in the treatment of venous thromboembolism.	2016	Present the new anticoagulants in the treatment of venous thromboembolism.
Romero <sup>15</sup>	Vascor-Score sub- analysis on risk prediction of vascular complications in patients undergoing percutaneous cardiologic procedures at two reference centers.	2017	Perform a Vascor-Score sub- analysis on risk prediction of vascular complications in patients undergoing percutaneous cardiologic procedures at two reference centers.
Ardila <sup>16</sup>	Vasculitis livedoid.	2019	Focusing on the presentation and therapeutic approach of livenoid vasculitis, therefore, early detection of suspected cutaneous vasculitis, clinical, imaging, procedural, evaluation; and, correct interpretation and diagnosis of this dermatopathy can improve patients' quality of life and save lives, evaluation ensures timely detection of complications, depending on identification of typology and its causes, appropriate treatment, and

Author(s)	Author(s) Title Year		Objectives		
			effectiveness of compliance,		
			monitoring, and reassessment.		
Morita <i>et al</i> . <sup>17</sup>	Vasculitis update: overview and relevant dermatological points for clinical and histopathological diagnosis-Part I.	2020	Clarify recent concepts on the etiology of vasculitis, the classification advocated by the Chapel Hill Consensus Conference, and emphasize clues that may help suggest a specific group of vasculitis in clinical practice during the physical and/or histopathological examination.		
Creado <i>et al</i> . <sup>18</sup>	Lipoprotein(a) and livedoid vasculopathy: a new thrombophilic factor?	2015	The study assesses the condition of livedoid vasculitis with alteration in the immune system and autoimmune processes. It examines the possibility of the association of lipoprotein with the pathogenesis of livedoid vasculitis based on its effects on thrombogenesis.		
Kerk and George <sup>1</sup>	Livedoid vasculopathy: a thrombotic disease.	2013	Explanation of pathology: Livedoid vasculitis as well as features and aspects of it. It presents the modern therapeutic strategies resulting from their etiopathogenic associations with pro-thrombotic states.		
Di Giacomo <i>et al</i> .9	Frequency of thrombophilia determinant factors in patients with livedoid vasculopathy and treatment with anticoagulant drugs - a prospective study.	2010	Study to prospectively assess the frequency of thrombophilia and check the efficiency of the anticoagulant. Thirty-four patients were analyzed, of which 52% presented laboratory alterations of the procoagulant conditions.		
Micieli and Alavi <sup>8</sup>	Treatment for livedoid vasculopathy: a systematic review.	2018	The study conducted a review of 29 case series reports to investigate and systematize treatments for livedoid vasculitis. The studied population has a total of 339 participants and treatment with anticoagulants, antiplatelet agents, anabolic steroids, thrombolytics, hyperbaric oxygen, intravenous immunoglobulins, UV light and favorable combinations.		
Aldehaim and Alarfaj <sup>19</sup>	Livedoid vasculitis in a patient with sjogren syndrome successfully treated with methotrexate.	2022	It is a case report of primary Sjögren syndrome with Hydroxychloroquine-resistant cutaneous vasculitis of the lower limbs, azathioprine and rituximab. But with great success when treated with methotrexate.		
Herrera-Sánchez et al. <sup>20</sup>	Medium-pressure hyperbaric oxygen therapy for livedoid vasculopathy	2022	It reports the characteristics of Livedoid Vasculitis, as well as treatments used and with differential hyperbaric oxygen therapy (HBO).		
Ramphall et al.21	Comparative efficacy of rivaroxaban and immunoglobulin therapy	2022	This systematic review aims to compare the efficacy of rivaroxaban and intravenous immunoglobulin		

Author(s)	Title	Year	Objectives
	in the treatment of livedoid vasculopathy: a systematic review		(IVIG) therapy in the treatment of livedoid vasculopathy. Both rivaroxaban and IVIG have been shown to be effective treatment options with similar treatment response times.

Source: Self-Authored, 2023.

#### 4. DISCUSSION

Diagnosis of VL can be made based on the clinical and histological setting and laboratory values can be used beyond diagnosis<sup>16</sup>. In parallel, the detection of prothrombotic parameters has only diagnostic relevance in conjunction with histology and clinical signs, and detection alone is not sufficient for diagnosis<sup>5</sup>.

Tissue damage can be prevented by rapid initiation of therapy because the prognosis is usually severe. The author highlights the associated use of vasodilators (does not report the medicines used) and acetylsalicylic acid for the improvement of the lesions of the patient where, after 90 days, the patient presented improvement of hyperalgesia. During the periods of hospitalization of the patient, the medicines of choice were alprostadil (Prostavasin®) with cyclophosphamide, prednisone and pentoxifylline. Subsequently, the metrotexate was introduced, and ultimately azathioprine was responsible for a significant improvement in lesions, this being the drug of choice<sup>7</sup>. ó When contraception emerged, the use of prednisone, azathioprine, mycophenolate mofetil, mycophenolate sodium, and pentoxifylline did not present ulcer remission in their study<sup>21</sup>.

Also, if therapy is not started as soon as possible, irreversible skin damage and necrosis occur. On the other hand, the same author talks about therapeutic strategies in a differentiated way. The population studied was composed of five patients, all of whom made use of pentoxifylline, and four of them made use of antiplatelets (acetylsalicylic acid and dipyridamole) and venotropics (bioflavonoids, diosmin and vaccinium myrtillus). Other associated therapies were used only in two patients, intravenous immunoglobulin (IgEV), calcium channel blockers (nifedipine) and immunosuppressants: prednisolone, methotrexate and azathioprine. Anticoagulants (low molecular weight warfarin and heparin), sulfone, danazol and vitamin supplements (folic acid, vitamin B12 and vitamin B6) were used in only one patient. The only situation in which a factor may occur that is procoagulant and may influence

the therapeutic decision is in the case of hyperhomocysteinemia. In this situation, the VL seems to have a good result for the treatment with folic acid and vitamins of the B<sup>2</sup> complex. This class includes pentoxifylline 400mg in 8/8hrs orally and buflomedil chloride 150mg 3 to 4 times a day or 300mg 2 times a day, as pentoxifylline does not have good results in its isolated use, but has a good tolerance profile and with few side effects<sup>6</sup>.

The authors report a case of primary Sjögren syndrome with LV with resistance to hydroxychloroquine, azathioprine, and rituximab use, but with satisfactory results with methotrexate use. Hydroxychloroquine was administered at a daily dose of 400mg, and azathioprine at a dose of 100mg for 3 months, but, as already stated, there was no success in remitting the lesions. He then started treatment with rituximab 1g intravenously (IV) at the next dose after 15 days, when he showed a partial response. The authors maintained the use of this drug for 6 months, but new ulcers developed, and thus suspended the use of both rituximab and azathioprine. They started with methotrexate 10mg along with folic acid 10mg, weekly orally (VO), observing improvement of the condition and healing of the ulcers without the appearance of new lesions 19.

Use of glucocorticoids (oral prednisone 0.5 mg/kg/day), acetylsalicylic acid (100 mg/day), and ciclosporin orally (3 mg/kg/day), with no positive results after 90 days of use. Therefore, continuous treatment with rivaroxaban 15 mg/day and then duloxetine 60 mg/day was initiated and improvement was observed in the following months<sup>3</sup>.

Therapy of choice was composed of pentoxifylline 400mg daily and acetylsalicylic acid (ASA) 325mg 2x/day. After two weeks, the lesions began the healing process, but new lesions appeared and hyperalgesia was present. Therefore, the pentoxifylline dose was increased (doubled the dose), the ASA was maintained and added to the tramadol 50mg prescription of 8/8 hours for pain<sup>11</sup>.

As much as LV is common in a middle-aged age group, it is possible even in children, so there are studies about the therapy for this group. Low molecular weight heparin (LMWH) therapy is possible in children. This is off-label therapy. Heparin-induced thrombocytopenia (HIT) may occur as a side effect of LMWH therapy. In addition, the dose should be reduced in case of severe renal insufficiency. Regular laboratory checks are recommended during therapy<sup>13</sup>. This same therapy is advocated for use in adults, which should be used as first-line therapy, because it has a large

number of advantages, including a more predictable pharmacokinetic profile, in addition to its easy handling and use. The author highlights as the most used, enoxaparin (30mg 12/12hrs subcutaneous (SC)) and dalteparin (2,500 IU to 5,000 IU, once a day), where both drugs can be associated with warfarin, but being used 1mg/kg, via SC<sup>6</sup>.

However, low molecular weight heparin anticoagulant therapy should be performed at the total therapeutic dose: 1mg/kg SC route, but the author does not describe association with warfarin. After initiation of therapy, there is usually a rapid response with improvement in pain within 2 to 4 days. If symptoms improve and ulcerations heal, the dose should be reduced to maintenance therapy by half the therapeutic dose<sup>12</sup>.

Also noteworthy is direct oral anticoagulant (DOAC) therapy, which can be used as first-line therapy<sup>14,21</sup>. DOACs include factor Xa inhibitors (rivaroxaban (Xarelto®), apixaban (Eliquis®), edoxaban (Lixiana®), and the thrombin inhibitor dabigatran (Pradaxa®). Rivaroxaban can be used at a dose of 10 mg twice daily for exacerbation or relapse and 10 mg once daily for maintenance therapy<sup>14</sup>. The use of rivaroxaban highlighted a significant improvement in algia and skin ulcers at 10mg/day over a 4-week period, in addition to the efficacy in the prevention of pain and new ulcers, in which it demonstrated a rapid and continuous response. This drug has been shown to be safe and anti-haemorrhagic and well tolerated by VL patients, mainly by improving quality of life and without any notable adverse effects. The study also explains better the patients' adherence to rivaroxaban, which is a choice in cases of patients who show resistance to heparin because it is a drug applied to the skin. It has an additional benefit of not requiring daily injections or laboratory monitoring, which provides better adherence to therapy for patients. In addition to demonstrating, in some studies, a significant improvement of algia and skin ulcers with the use of this medicine².

In patients with antiphospholipid antibodies (PAS), there is an increased risk of recurrent thrombotic events during DOAC therapy. Therefore, there is a contraindication at first for patients at high risk, i.e. those who have the three positive antiphospholipid tests: lupus anticoagulant (LAC), anticardiolipin antibodies (aCL) and antibodies to beta2 glycoprotein1 (B2GP1). Thus, in patients with FAS there is a preference for making use of vitamin K<sup>4</sup> antagonist drugs.

In addition to LMWH and DOAC, intravenous immunoglobulins (IVIg) are recommended as first-line therapy. This therapy does not have a totally enlightened action, but it probably acts from the neutralization of circulating and immunocomplex antibodies deposited in the tissues. IVIg tested positive for LV at a dose of 0.5g/kg/day. Due to the high costs, IVIg therapy should be used primarily in cases refractory to the initial choice therapy. Ultimately, however, the indication is the responsibility of the physician<sup>6</sup>. The combination of rivaroxaban and IVIg, where IVIg acted in the cure of most LV ulcers at around 2-3 months, however showed little improvement in algia, while rivaroxaban showed significant improvement in both algia and ulcers with a mean response time of 2-4 months from the start of treatment<sup>21</sup>.

Next, one should discuss second-line therapies. Phenprocoumon and warfarin can be used as second-line therapy. They inhibit vitamin K-dependent coagulation factors and anticoagulant proteins C and S, relevant for microcirculation, and should be used only in exceptional cases<sup>15</sup>. From the same point of view, there are reports about the antagonist drugs of vitamin K that has as its main medicine warfarin that best represents this category of drugs<sup>14</sup>. This drug interferes with the cyclic conversion of vitamin K and its 2,3-epoxide by blocking the synthesis of its dependent coagulation factors, factors II, VII, IX, and X. Therefore, its effect does not occur until the factors already present in the circulation are metabolized; such a process typically takes 1 to 3 days.

Hyperbaric oxygenation therapy (HBO) was not used as first-line therapy, but was performed in one study patient in combination with danazol, resulting in remission of LV<sup>8</sup>. Similarly, a guaranteed effect of HBO is reported to be improvement of microvascular perfusion, where it is probably related to a stimulus of nitric oxide synthesis by hyperbaric oxygen<sup>6</sup>. Low-pressure OHB as adjunctive therapy in a female patient with a 60-minute session ÿ 100% O2 to 1.45 Atmosphere Absolute (ATA), being, in the first two weeks, the treatment done 3 times per week and, after, 2 times per week. After 12 weeks, there was a significant reduction in pain and complete healing of lesions. The study also reports that there was no recurrence of lesions within 16 months of treatment<sup>20</sup>.

#### 5. FINAL CONSIDERATIONS

The treatment options for secondary VL are varied and the physician should evaluate and individualize the treatment for each patient. Among the known and relevant treatments are: low molecular weight heparin (LMWH) therapy, DOAC therapy, intravenous immunoglobulins (IVIg), therapy with phenprocoumon and warfarin use, and hyperbaric oxygen therapy.

Among all the authors analyzed, the use of low molecular weight heparin, direct oral anticoagulants and IVIg were the most indicated therapies. However, this does not indicate that other therapies are ineffective. Since each clinical picture has its specificities, associations or not of these drugs are considered, taking into consideration the comorbidities and resistances of each patient.

In short, therapies such as LMWH and DOAC are known to achieve good results rapidly, the first being subcutaneous and the second oral. The only harm of IVIg therapy is its high cost. However, they all require constant follow-up to the patient so that possible complications and/or adverse effects involving thrombosis do not occur and are properly monitored.

New studies comparing the different treatments for livedoid vasculitis secondary to thrombophilia are required primarily in cases associated with Antiphospholipid Antibody Syndrome.

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# **CHAPTER 12**

# POLYPHARMACY IN THE ELDERLY: A CASE STUDY

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**ABSTRACT:** The advent of polypharmacy among the elderly population is increasingly common. It consists of the administration of more than five medications or a larger number of clinically necessary medications. The present case study seeks to demonstrate, through a case report of a long-term resident, that the evaluation by a multidisciplinary team, identification and management of the condition bring significant benefits on the well-being and health of the elderly. The constant evaluation by a multidisciplinary team is important, given the limiting diseases, frailty and low functionality of the elderly. In this case, early identification and management becomes essential.

**KEYWORDS:** polypharmacy, long stay institution, multidisciplinarity.

**RESUMO:** É cada vez mais frequente o advento de casos de polifarmácia entre a população idosa. Consiste na administração de mais de cinco medicações ou de um maior número de medicamentos clinicamente necessários. O presente estudo de caso procura demonstrar, por meio de um relato de caso de uma moradora de instituição de longa permanência que a avaliação por uma equipe multidisciplinar, identificação e manejo do quadro trazem benefícios expressivos sobre o bem-estar e saúde do idoso. A avalição constante por uma esquipe multidisciplinar é importante, haja vista doenças limitantes, fragilidade e baixa funcionalidade do idoso. Neste caso torna-se fundamental a identificação e manejo precoce.

**PALAVRAS-CHAVE:** polifarmácia, instituição de longa permanência, multidisciplinaridade.

#### 1. INTRODUCTION

With population aging, drug consumption has increased significantly, especially among the elderly. However, this combination of drugs may not be beneficial to the patient due to polypharmacy. This refers to concomitant use of drugs, measured as single counts of drugs (above five) or as administration of a greater number of drugs than clinically indicated. In this report, the case of polypharmacy is discussed in a patient living in a long-term institution. (ILPI).

#### 2. CASE REPORT

A 74-year-old female patient living in ILPI, she started to experience dizziness, limited walking, and a falling episode. The only history described was of systemic arterial hypertension, in use of antihypertensives (losartan 50mg and anlodipine 5mg), but also made use of biperiden 2mg. After this complaint, meclizine hydrochloride 50mg, promethazine 25 mg and betasistin 24mg were introduced for external medical evaluation, without improvement of the condition. Patient was then evaluated by multidisciplinary team, when the positive postural hypotension test and Katz score reduction from 6 to 4, corresponding to partial dependence for activities of daily living, were noted. There were also no signs of Parkinson's disease. Therefore, meclizine 50 mg dihydrochloride, promethazine 25 mg and anlodipine 25 mg and biperiden 2 mg have been suspended. In reassessment after fifteen days, the patient presented normal pressure and ambulation levels, with improvement of complaints of dizziness. Withdrawal of betaistine 24mg was also indicated, maintaining improvement of the condition.

#### 3. DISCUSSION

Elderly patients, especially ILPI residents, are susceptible to polypharmacy, given their limiting diseases, frailty, and poor functionality. Such a situation increases the risk and severity of adverse drug reactions, drug interactions, cumulative toxicity, and leads to medication errors, reduces treatment adherence, and raises morbidity and mortality. Factors that contribute to polypharmacy are related to medical

interaction (iatrogenics, lack of knowledge), patient (age, sex, susceptibility, self-medication), and drug (side effects, interactions, and toxicity).

# 4. CONCLUSION

Polypharmacy is a frequent problem in the care of the elderly, mainly in ILPIs, so it is important to constantly reassess

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# **CHAPTER 13**

# TUBERCULOSIS PULMONARY: CONCEPTIONS ABOUT TREATMENT AND DIAGNOSIS

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#### 1. INTRODUCTION

Tuberculosis is an infectious and transmissible disease caused by the bacteria Mycobacterium tuberculosis, also known as Koch bacillus. The disease primarily affects the lungs (lung form), although it can affect other organs and/or systems. The extrapulmonary form, which affects organs other than the lung, occurs more often in people living with HIV, especially those with immunologic impairment.

The pulmonary form, besides being more frequent, is the main responsible for the maintenance of the transmission chain of M. tuberculosis.

Signs, symptoms, and radiological manifestations depend on the type of TB presentation. Classically, the main forms of presentation are the primary form, the post-primary (or secondary) form, and the miliary form. Classic symptoms, such as dry or productive persistent cough, evening fever, night sweats, and slimming, can occur in any of the three presentations.

Primary pulmonary TB usually occurs after the first contact of the individual with the bacillus and is therefore more common in children. Clinical manifestations may be insidious, with the patient presenting with irritability, low fever, night sweats, and inappetence. Cough is not always present. Physical examination may be inexpressive.

Postprimary or secondary pulmonary TB can occur at any age, but is more common in adolescents and young adults. Its main characteristic is a dry or productive cough. In places with high TB incidence rates, anyone who seeks the health facility because of prolonged cough (passive search) should have TB included in their diagnostic investigation.

In cases where cough is productive, the sputum may be purulent or mucoid, with or without blood. Evening fever, without chills, usually does not exceed 38.5 oC. Night sweats and anorexia are common. Physical examination usually shows facies of chronic disease and slimming, although individuals with good general condition and no loss of appetite may also have pulmonary TB. Pulmonary auscultation may have decreased vesicular murmur, an amphoric murmur, or even be normal.

Miliary TB refers to a specific pulmonary radiological aspect, which can occur in both the primary and secondary forms of TB. It is a severe form of the disease, which is most common in immunocompromised patients, such as people infected with HIV in advanced stages of immunosuppression. The clinical presentation may be acute or

subacute, most commonly in children and young adults. In a more unusual way, miliary TB presents as a chronic disease (the elderly) or even fever of obscure origin. Symptoms such as fever, asthenia, slimming, and cough occur in 80% of cases.

Physical examination may show hepatomegaly (35% of cases), central nervous system disorders (30% of cases), and erythematomaculo-papulo-vesicular (uncommon) skin changes.

# 2. DEVELOPMENT

Pulmonary tuberculosis is a global public health challenge, with millions of new cases and annual deaths. Influenced by factors such as poverty and limited access to health, its control is complex. Early diagnosis and effective treatment are essential, but they face challenges, such as a lack of sensitivity in diagnostic methods and drug resistance.

A bibliographic review article analyzes current approaches, highlighting gaps in knowledge and exploring diagnostic methods, treatment strategies, and future directions for improving disease control. Analyze conceptions on current approaches to the diagnosis and treatment of pulmonary tuberculosis. A systematic review examined studies on the treatment and diagnosis of pulmonary tuberculosis, including social, cultural, and antimicrobial resistance factors.

Articles, clinical studies and meta-analyzes of the last 20 years were selected in the PUBMED, LILACS and SCIELO databases. Traditional diagnostic methods, such as bacilloscopy and sputum culture, have limitations, highlighting the need for new approaches, such as molecular techniques and chest imaging.

In treatment, antibiotic-based protocols are recommended, but complementary approaches, such as nutrition and alternative therapies, are explored. The social stigma surrounding TB impacts the search for medical care, requiring culturally sensitive awareness strategies. Future challenges include antimicrobial resistance and the need for more effective public health policies, as well as education and awareness for disease prevention and control.

Coordinated efforts are essential to reduce the overall burden of TB and achieve its elimination as a threat to public health. Pulmonary tuberculosis is a global public health challenge, marked by social, economic and biological complexities.

Early diagnosis, effective treatment and overcoming of cultural barriers are key. Despite advances such as diagnosis and treatment, persistent challenges such as antimicrobial resistance and health access disparities persist.

Integrated and collaborative approaches, focusing on innovation, strengthening health systems and public awareness, are essential to reduce the overall burden of TB and improve health outcomes.

Drug therapy for TB is effective, but can be complex to manage by people in their daily lives. In addition to that it causes adverse effects that impact the organism and alter the day-to-day of the individual. Even more, the use of other complementary therapies, such as assistants in the treatment, needs to be known and considered by health professionals, especially regarding the possibilities of interactions with the active ingredients of allopathic medicines.

Diseases generally have an impact on human lives, individually and socially. When it comes to a contagious infectious disease, such impacts reverberate both in the personal and public spheres and this is evidenced in the practical life of people with TB. The treatment works like a more effective strategy for the return of the previous state, regarded as functional, understood as being an opponent to the current state, diseased.

TB brings with it different changes in daily life: family life, with self-isolation; work life, when the patients stop working or change the rhythm of work; social life, with the restriction of living together; psychological life, generating shame, guilt, fear of death and transmission to the people closest to them. Such alterations have the stigma and prejudice shading various places of coexistence of people living with TB. Diagnostic confirmation interferes with the patients' self-image and self-esteem, which has repercussions on interpersonal relationships, because prejudice is evident and leads to rejection of the patient's person.

The imagination about TB is that of a separatist disease, which is growing in importance today, even with biomedical advances as far as treatment and cure are concerned. Faced with this, prejudice flourishes in the conceptions of the participants by way of reports of situations lived in daily life.

Revealing the diagnosis triggers prejudice and social withdrawal, which can even lead people to fear the loss of their job. The results of a study on the social

representations of patients with TB indicate that the preservation of secrecy about the disease has as its objetive the protection of prejudice that guides it.

The prejudice of others and self-prejudice persist, directly or indirectly, even through the guidelines on the modes of transmission of the disease, the treatment and its effect on the bacillus, which makes it incapable of infecting other people in the first months of treatment. Nonetheless, beliefs about contagion still populate the social imagination, and superstitious beliefs flourish, which generate self-discriminatory attitudes such as: separating clothes, crockery and cutlery; sleeping in separate rooms even at the end of treatment. Similar attitudes emerged in a study on leprosy, indicating that they are relatively common in diseases linked to stigma and prejudice.

When discriminatory acts leave from close people, such as family and friends, they produce feelings and attitudes of spontaneous isolation and seclusion. This distancing is justified as a way of preserving the health of the family and that of other loved ones. The social representations about the disease reveal that stigma and prejudice lead the patient to social isolation, compulsory or voluntary.

Patient care with health education and the dissemination of technical information about transmission and treatment have effects on self-care and should be stimulated and reinforced in Primary Health Care and in health programs aimed at people with communicable diseases. In the conceptions of participants, it is evident that the guidelines carried out by the health team during consultations with different health professionals reached the objectives, reflecting on their attitudes of self-care.

On the other hand, the technical-scientific information coexists with beliefs and imaginary about contagion and separatism and is expressed in real situations experienced by other patients and also in the fear they feel of transmitting it to their relatives, even when doing the treatment in the health unit and receiving guidance about the disease.

Conventional drug treatments are widely disseminated, but they do not go beyond practices rooted in the sociofamiliary traditions of the so-called traditional medicine demarcated by culture. The knowledge that sustains and builds such practices was historically constructed through ancestry and passed down from generation to generation by orality, establishing interactions with other knowledge in time and space, transforming it and adding new historical-social elements, transforming it into a know-how related to therapeutic resources.

According to the National Policy of Integrative and Complementary Practices (PNPIC) in the SUS, such practices are ways of stimulating natural ways of dealing with signs and symptoms of the disease and/or with possible aggravations. These must be taken into consideration by welcoming listening, since it is a way of man's interaction with the environment in which he is inserted.

TB patients resort to some of these traditional practices in search of solutions to their problems concerning the prevention and the aggravation of diseases by the use of medicinal plants, understood as palliative measures, to relieve the side effects of the medicines.

The difficulty in managing the treatment and in inserting it into the activities of daily life (ADL), mainly as a result of the pulmonary limitations caused not only by the disease, but also by the treatment, is a reality in patients' lives. This has a negative impact on work activities, resulting in financial losses and costs for accessibility to the unit.

The fear of having life condemned as a result of the disease, given that its routine is altered by labor limitations, even, strengthens the conceptions that the TB patient is an incapacitated being, since work is an important activity for the configuration of human dignity. The return to routine activities is a perspective of the sick portrayed in expressions such as going back to what he was doing before he became ill and leading a normal life.

The commitment to self-care in favor of a cure comes from the revision of unhealthy habits of life in an attempt to recover the health that it had before becoming ill with TB. Adherence to treatment provides an opportunity for a new beginning of life, however, this new beginning demands changes in the way of operating daily life, especially for those already marginalized before becoming ill, which is very characteristic of these people.

This review of habits can be conceived as a positive side of the disease, since it leads the person to reflect on the importance of care for themselves, such as: improving food; increasing water intake; not smoking; not drinking alcohol; protecting oneself from rain and sun.

#### 3. FINAL CONSIDERATIONS

It is concluded that the conceptions of people who experience pulmonary TB about the diagnosis and treatment of this disease converge on the importance of correct information about transmission, guided by the health team, denoting a differential in the process of acceptance of oneself and of living with family members in their homes in such a way that, from the guidelines, several feelings, such as fear, were attenuated.

It was concluded that the need persists for patients to (re)mean TB during treatment, and it is fundamental that the health team knows these concepts, in order to subsidize care that includes physical and biopsychosocial aspects before the unit's Tuberculosis Control Program.

Regarding treatment, even if patients consider the importance of regular and correct intake of medication, they are dissatisfied with its adverse effects and seek to mitigate them with palliative measures, drawing attention to the need to know and consider the different therapeutic itineraries used by the patient in order to alleviate his ailments.

It is appropriate to point out that the convictions about the condition of illness of the participants generated reflections about its altered functionalities, mainly considering the departure from their works, which brought concerns of financial and social aspects, which implied a thought of loss on the period of treatment, provoking the will to cure and change of life after this phase.

The findings of this study bring, as implications for professional practice, the targeting of care strategies and follow-up of participants diagnosed with TB, ensuring an integral, longitudinal care, as well as focused on the needs of this audience, expressed through their speeches.

As to the limitations of this study, it is highlighted the fact that it does not have, as an aid, the knowledge of sign language for the possible approaches with patients who could have the hearing acuity decreased. In addition, the unreadability, by some records present in the register of the presented unit, made it impossible to collect some information, and it is necessary not to include it as a record of information in this study.

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# **CHAPTER 14**

# QUALITY AND SAFETY IN HEALTH. PUBLIC POLICIES FROM APRIL 25 TO THE END OF THE 20TH CENTURY

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RESUMO: A Revolução de abril de 1974 deu início ao período de democratização em Portugal. A Constituição da República Portuguesa (CRP), aprovada pela Assembleia Constituinte em 1976 estabeleceu pela primeira vez "O direito à protecção da saúde, realizado pela criação de um Serviço Nacional de Saúde...", concretizado em 1979. O Ministério da Saúde só veio a ser criado em 1983. A Direção-Geral da Saúde foi extinta em 1984 e, de novo, criada em 1993. A Lei de Bases da Saúde criada em 1990, estabeleceu pela primeira vez, a proteção da saúde perspetivada não só como um direito, mas também como uma responsabilidade conjunta dos cidadãos, da sociedade e do Estado, em liberdade de procura e de prestação de cuidados. O início da abordagem da qualidade deu-se com a organização do Seminário Internacional Évaluation des services de soins de santé primaires (1985) e o início da história da qualidade, com a avaliação da qualidade (1993). Na segunda metade da década de 90, o Ministério da Saúde assumiu a qualidade como uma prioridade. A Qualidade, como prioridade, enquanto orientação estratégica, foi enquadrada na Primeira Estratégia de Saúde – "Saúde um Compromisso" (1998-2002), sendo assim definida pela primeira vez uma política de qualidade na saúde. Não obstante as atribuições da qualidade em saúde cometidas à Direção-Geral da Saúde a partir de 1993 e das medidas estabelecidas, foi criado o Instituto da Qualidade em Saúde em 1999.

PALAVRAS-CHAVE: direito à saúde, lei de bases da saúde, qualidade na saúde, política de qualidade na saúde

ABSTRACT: The Revolution of April 1974 began the period of democratization in Portugal. The Constitution of the Portuguese Republic (CRP), approved by the Constituent Assembly in 1976, established for the first time "The right to health protection, realized by the creation of a National Health Service...", which came to fruition in 1979. The Ministry of Health it was only created in 1983. The Directorate-

General for Health was abolished in 1984 and, again, created in 1993. The Basic Health Law created in 1990, established for the first time, the protection of health from a perspective not only as a right, but also as a joint responsibility of citizens, society and the State, in freedom to seek and provide care. The beginning of the quality approach occurred with the organization of the International Seminar Évaluation des services de soins de santé primaires (1985) and the beginning of the history of quality, with quality assessment (1993). In the second half of the 90s, the Ministry of Health assumed quality as a priority. Quality, as a priority, as a strategic orientation, was framed in the First Health Strategy – "Health a Commitment" (1998-2002), thus defining a health quality policy for the first time. Despite the responsabilities of quality in health assigned to the Directorate-General for Health from 1993 and the established measures, the Institute of Quality in Health was created in 1999.

**KEYWORDS:** right to health, basic health law, quality in health, health quality policy.

#### 1. INTRODUCTION

The Revolution of 25 April 1974 started the period of democratization in Portugal. The political and social conditions created later made possible the creation of the National Health Service (NHS).

In the Portuguese Health System (SSP), there are three systems: the National Health Service (SNS), health subsystems (special social health insurance schemes for certain professions) and, also, private health insurance.

Portugal applied to join the European Communities in 1977 and signed the Accession Treaty on 12 June 1985. On 1 January 1986, Portugal became a member of the Communities, known as the European Union since 1993, by virtue of the Maastricht Treaty of 1992. Each Member State (MS) defines public health policies, taking into account the principle of subsidiarity enshrined in the Maastricht Treaty (1992), with the exception of deliberations on certain measures, which were established at the beginning of the new millennium (e.g. safety of medicines and medical devices). The Council's Health Committee, appointed in 1995, established a committee of quality specialists, which recommended to the ministers of health the establishment of a system for improving the quality of health care at all levels, recommendations adopted in 1997 (WHO, 1994, cited by WHO 2003, according to Martins d'Arrábida C., 2023).<sup>a</sup>

In 1998, the 51st World Health Assembly renewed the commitment to strengthen, adapt and reform, as appropriate, health systems to ensure universal access to evidence-based, good quality and sustainable health services. The aim was to ensure the availability of essential primary healthcare as defined in the Alma-Ata Declaration (WHO, 1999).<sup>b</sup>

Since 1980, the WHO European Region (51 countries) had adopted a common policy framework for health development with objectives and strategies and could be used to transform national policies into operational programs at local level. In 1985,

<sup>&</sup>lt;sup>a</sup> World Health Organization (2003). Quality and accreditation in health care services: a global review. Geneva. World Health Organization. WHO/EIP/OSD/2003.1 209 p. Accessed at http://www.who.int/iris/handle/10665/68410

https://www.portaldiplomatico.mne.gov.pt/index.php?option=com\_content&view=article&id=519:uniao -europeia&catid=119

<sup>&</sup>lt;sup>b</sup> Adopted by International Conference on Primary Health Care, Alam-Ata, 6-12 Sptember 1978 and endorsed by the Thirty-second World Health Assembly in Resolution WHA32.30.

the 38 Targets were established to support the European regional strategy "Health for All in the Year 2000", with Target 31 - Ensuring the quality of healthcare - defined by the creation of mechanisms for the quality of healthcare until 1990.

The review of the policy, approved by the WHO Regional Committee for Europe in September 1998, to be reviewed later in 2005, is the result of a thorough scientific analysis and consultations with all the Member States and numerous important organizations in the region (WHO, 1999, Brown, Cueto, Fee, 2006). The objective of HEALTH2, with its 21 targets for the 21st century, embodies the quality of health care and one of its attributes (equity) and the reduction *burden* of health problems and injuries, aiming to achieve the full health potential for all people.

This article aims to share the analysis carried out from 25 April to the end of the 20th century, with emphasis on the period of the first legislature of a new political cycle, between 6 November 1985 and 5 January 1990 since the beginning of the approach to quality in health, as well as the approval of the Hospital Management Law and the creation of centers of responsibility. In the second legislature, between January 5, 1990 and October 28, 1995, with a ministerial change on December 7, 1993, the focus is the creation of the Health Basic Law, the beginning of quality evaluation, the beginning of quality in health as a priority with strategic guidelines for quality assurance and regional strategies and the definition of a quality policy for the first time.

After a political cycle of 10 years, with a parliamentary majority of eight, a new political cycle with a parliamentary minority began on 28 October 1995, ending on 25 October 1999. In the second parliamentary term of the political cycle from 25 October 1999 to 6 April 2002, there was a ministerial change on 25 October 1999. This new cycle highlights the dissemination of the Charter of Patients' Rights and Duties, the creation of family health units (FHU), responsibility centers, Quality assignments in the Directorate-General for Health (DGS) and the creation of the Health Quality Institute.

### 2. RIGHT TO HEALTH PROTECTION

The Constitution of the Portuguese Republic (CRP) of 2 April 1976 established for the first time "The right to health protection is achieved by the creation of a universal, general and free national health service, by the creation of economic, social and cultural conditions that guarantee the protection of childhood, youth and old age, and

by the systematic improvement of living and working conditions, as well as by the promotion of physical and sporting, school and popular culture and by the development of the health education of the people." (Decree of Approval of the Constitution of 10-04-1976).

#### 2.1 MEDICAL SERVICE TO THE PERIPHERY

Between 1975 and 1982, the period during which the outlying medical service took place, it was possible to verify its impact on population coverage, in terms of supply and demand for health care. Only three years after the creation of the NHS was it possible for doctors to go into areas of specialization. In the results of the significant reduction in the infant mortality rate, in addition to the population coverage, through the medical service to the periphery, "the action of voluntary medical organizations, outside the official system, who moved to the interior, doing health promotion, medical acts..." (Carapinheiro G. and Gameiro Pinto M., 1987, cited by Martins d'Arrábida C., 2023).

# 2.2 ESTABLISHMENT AND STATUS OF THE NATIONAL HEALTH SERVICE (NHS)

The 'Arnaut Ordinance', published in 1978 (anticipation of the National Health Service (SNS)), established that access to the Medical-Social Services was guaranteed to all citizens, in a universal way, free of charge, regardless of the ability to pay, and accompanied by the participation of medicines (Ministerial Order of the Office of the Minister of Social Affairs), referred to by Martins d'Arrábida C., 2023).

In 1979, the National Health Service (SNS) was created, a pillar of the Portuguese health system, with the aim of guaranteeing the right to health services to all Portuguese and foreign citizens, regardless of their economic condition - universal, general and free (Law No 56/79 of 15 September).

The NHS gives concrete expression to the right to health protection enshrined in Article 64 of the CRP, allowing the implementation of a network of health organizations and global health care services for the entire population as a response to the need for universal and equitable coverage of health services and financed through taxes. An integral part of the process of political and social democratization,

after April 25, 1974, the SNS is part of a wider movement of southern European countries (Italy (1978), Greece (1983) and Spain (1986), according to Sakellarides C. *et al.* (2016).

The approval of a new statute of the National Health Service took place in 1993, under the regulation of the then Law on Health Bases (paragraph 2 of base XII of Law No 48/90 of August 24), making it imperative, with the constant concern to provide users with comprehensive and high quality care, in order to bring it into line with the principles enshrined in Chapter II of that law (Decree-Law 11/93 of January 15).

Considering that the traditional dichotomy between primary care and differentiated care had proved to be a source of organizational dysfunctions, the creation of integrated health care units was established, which would make possible the indispensable linkage between personalized groups of health centers and hospitals, in which one of the essential aspects of the new organization of the National Health Service is rooted (Decree-Law 11/93 of January 15).

# 2.3 CREATION OF THE MINISTRY OF HEALTH

The Ministry of Health became independent from the Assistance in 1973, one year before April 25 (Decree-Law No. 584/73 of November 6). The Salvation Board transformed it into the State Secretariat of Health of the Ministry of Social Affairs in 1974 (Decree-Law No. 203/74 of May 15), referred to by Martins d'Arrábida C., 2023)<sup>c</sup>.

The Ministry of Social Affairs was abolished and the Ministry of Health was created in 1983 (Decree-Law No. 344-A/83 of July 25, approving the Organic Law of the IX Constitutional Government).

Maldonado Gonelha, Minister of Health (1983-1985), was the first of the Ministry of Health designated, after the 25 April 1974.

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c https://www.historico.portugal.gov.pt/pt/o-governo/arquivo-historico/governos-cons/gc19/os- minister ios/ms/quero-saber-mais/quero-aprender/historia-sns.aspx

# 2.4 REGIONAL HEALTH ADMINISTRATIONS (ARS) AND HEALTH CENTERS

The regional health administrations (ARS) were created in 1982, as part of the development of the policy of regionalization of health adopted by the Government, with the aim of ensuring the right to health protection (Decree-Law No. 254/82 of June 29).

The health centers, established by Decree-Law No. 413/71 of September 27, were regulated, remaining in the organic and functional dependence of the ARS (Ordinance No. 97/83, February 28).

The regional health administrations and their heritage were transferred to the new regional health administrations, and the following health regions were established, which aimed to improve integration between the various levels of health care (i) North, based in Porto, (ii) Center, based in Coimbra, (iii) Lisbon and Tagus Valley, based in Lisbon, (iv) Alentejo, based in Évora, (v) Algarve, based in Faro. In each health region there has been a regional health administration (ARS) (Decree-Law 11/93 of January 15), referred to by Martins d'Arrábida C. (2023).

# 2.5 ORGANIZATION AND BUSINESS MANAGEMENT OF HOSPITALS

The Hospital Management Law, adopted in 1988, established the principle of organization and business management in hospitals and the creation of centers of responsibility as "functional structures that should group, as a rule, several cost centers with homogeneous or similar activities and can constitute intermediate levels of administration" (Decree-Law No. 19/88 of 21 January).

The general regime to which the creation of responsibility centers integrated into hospitals and hospital centers of the SNS was to be subject was established by Decree-Law No 374/99 of 18 September 1999.

In the following two decades, their development as intermediate management bodies was not observed (Martins d'Arrábida C., 2023).

## 2.6 THE LAW OF HEALTH BASES

The Basic Law on Health (Law No 48/90 of 24 August) established, for the first time, the protection of health, which is intended not only as a right but also as a joint

responsibility of citizens, society and the State, in freedom of demand and care.<sup>d</sup> Healthcare was provided by government agencies and establishments or, under the supervision of the state, by other public bodies or by private entities, without or for profit. The private sector has found a stimulus in the area of health and the private management of NHS hospitals has begun.

The rights of patients, inserted and enshrined in the Basic Law of Health and those previously established in the Hospital Statute (Decree-Law No. 48357 of April 27, 1968) constituted the specific legal framework (Martins d'Arrábida C., 2023).

#### 2.7 NATIONAL HEALTH COUNCIL

It was established that the National Health Council (CNS) was the consultation body of the Ministry of Health (Decree-Law No. 10/93 of January 15).

#### 2.8 LETTER OF PATIENT RIGHTS AND DUTIES

In 1997, the Charter of the Rights and Duties of the Patient was released, addressed to patients of the National Health Service (Barros, Machado e Simões, 2011, cited by Martins d'Arrábida C., 2023).

# 2.9 CREATION OF FAMILY HEALTH UNITS (FUS)

In 1999, the system for the creation, organization and operation of health centers was established, structuring them into functional units, and for the first time the Family Health Unit (FHU) was created - "The elementary unit for providing health care to a population identified through registration in users' lists" (Decree-Law No 157/99 of 10 May).

#### 2.10 HEALTH 24

In 1999, under the aegis of Maria de Belém Roseira, the SAÚDE 24 Pediatrics "Dói-Dói-Trim-Trim" was launched, a national helpline aimed at parents and children

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d Cf. Point 4 of Base I of the Health Bases Law of 24 August.

up to the age of 14. In 2002, the Public Health Line was created, based in DGS and with the merger of the two services, Line Saúde 24 was created, on April 25, 2007 (Martins d'Arrábida C., 2023).

# 2.11 NATIONAL VACCINATION PROGRAM (PNV)

Further progress in vaccination continued in this period. From 1999 onwards, the National Vaccination Program (PNV) included the hepatitis B and *Haemophilus influenzae* type b *vaccines* (Cabral C., Pita J., 2015, cited by Martins d'Arrábida C., 2023).

# 2.12 PORTUGUESE OBSERVATORY OF HEALTH SYSTEMS (OPSS)

The Portuguese Observatory of Health Systems (OPSS) was created in 1999. The government took health as a priority, with demanding targets such as health financing and waiting lists, not associated with intervention measures with a strategic framework. The first report of the OPSS came to be published in 2001 "Knowing the Paths of Health".

#### 3. QUALITY IN HEALTH APPROACH

Since it is now part of the area of Patient Safety, after the first reference to infection control, by the Directorate-General for Health, under the direction of José Alberto de Faria, 49 years later, Resolution (72) 31 of the Council of Europe was circulated to all health units by the Directorate-General for Hospitals in 1979. It called for the establishment of infection control committees in public or private health institutions, as part of the national health care network, in conjunction with the National Health Service, as part of infection surveillance (Information Circular No 6/79 of 9/2/79 DGH, 1979), referred to by Martins d'Arrábida C., 2023).

The beginning of the approach to quality in health can be considered, the organization of the International Seminar Évaluation des services de soins de santé primaires with the collaboration of the World Health Organization (WHO) and the Public Health Schools of the Universities, Free of Brussels and Hebrew of Jerusalem, in 1985,

followed by the seminar "Evaluation and quality control in health services, co-organized by the Department of Health Studies and Planning, WHO and the Directorate General of Primary Health Care (DGCSP) in 1985 (Pisco L., Biscaia J., 2001, cited by Martins d'Arrábida C., 2023).

At the national level, the beginning of the history of quality, nowadays, was due to Emílio Imperatori (1993). Between 1987 and 1989, the Iberian Program also allowed the definition of strategies in the area of quality (Campos, Saturno and Vaz Carneiro (2010). This perspective is shared, in terms of quality assessment, taking into account the very definition of a list of indicators for health centers and the introduction of the review of use by the Department of Financial Management (DGF) (Martins d'Arrábida C., 2023).

#### 3.1 ABOLITION OF THE DIRECTORATE-GENERAL FOR HEALTH

On 2 March 1984, the Directorate-General for Health had been abolished and had 'long since ceased to satisfy doctors and other public health professionals, because concepts in this field have obviously evolved, postulating today the view that is usually called Community health', and the Directorate-General for Primary Health Care (DGCSP) was created. Several areas of intervention have been integrated in this Directorate, ensuring the coordination of health promotion, prevention and treatment of the disease (Decree-Law No. 74-C/84 of 2 March), referred to by Martins d'Arrábida C., 2023).

In 1991, the DGCSP drew up strategic guidelines for quality assurance for 91-93 (Campos, Saturno and Vaz Carneiro, 2010) and regional strategies 92-95, for quality assurance (Information Circular No 8/DPA of 16/5/91 and Information Circular No 9/DPA of 3/6/91, respectively), referred to by Martins d'Arrábida C. (2023).

In the period 1986-1996, approximately one third of the funding under the second Community framework was spent on quality training in health, eventually being developed by various entities in a poorly integrated way and, without direct consequence, in the realization of integrated quality improvement projects (Pisco L., Biscaia J., 2001, cited by Martins d'Arrábida C., 2023).

In the second half of the 1990s, the Ministry of Health assumed quality as a priority. In September 1998 the Health XXI program was adopted, and its Objective 16

emphasized the importance of delivering quality as the final measure. For the first time, the quality of health care has been included in the Third Community Support Framework (Health Operational Program - Health XXI), through a financial envelope for a policy to promote quality in health (Pisco L., Biscaia J., 2001).

The National Program for the Humanization and Quality of Health Services, with the task of promoting the improvement of the quality of care and human of the institutions and services of the National Health Service (SNS) was approved in 1992 by order of the Minister of Health of 8-10-92, referred to by Martins d'Arrábida C. (2023). In the following year, the National Commission for Humanization and Quality of Health Services was established and it was established that in all hospitals and health centers of the NHS, commissions of the Program should be constituted (Order of the Secretary of State for Health of January 16).

#### 3.2 ESTABLISHMENT OF THE DIRECTORATE-GENERAL FOR HEALTH

The Organic Law of the Ministry of Health, adopted in 1993, enshrined in its preamble the principle of indivisibility of health, which implied that the tasks and competences of the Directorates-General for Primary Health Care and Hospitals were polarized in the Directorate-General for Health (DGS). In this way, these Directorates-General were abolished and the DGS (Decree-Law No. 10/93 of 15 January) was created. DGS has become the central service for regulating, guiding, coordinating and supervising health promotion, disease prevention, health care provision and health care institutions and services, even if not integrated into the health system (Martins d'Arrábida C., 2023). It was also established that the National Health Council (CNS) was the consultation body of the Ministry of Health, with the composition, competence and functioning defined in regulatory decree (Decree-Law No. 10/93 of January 15).

The Infection Control Project developed at national level between 1988 and 1999 was abolished as part of the activities of the Health Service Management Information Systems (SIGSS) of the State Department of Administration and later at the IGIF (Instituto de Gestão Informática e Financeira da Saúde), and replaced by the National Program for Infection Control (PNCI), by order of the Director-General for Health, on 14/05/1999 (Information Circular of the Directorate-General for Health No. 20/GAB/DG of 30/7/99), according to Martins d'Arrábida C. (2023). In 1993, the DGS

had set up the infection control committees (CCI), called for in Council Resolution (72) 31 (Normative Circular No 4/93 of 10/2/93), referred to by Martins d'Arrábida C. (2023).<sup>e</sup>

The organization of the Directorate-General for Health was approved and created in the then "Directorate of Services for Promotion and Quality Assurance", the Division of Accreditation and Audit (Art. 24) (Decree-Law No. 345/93 of 1 October, cited by Martins d'Arrábida C., 2023).

With regard to the prevention and control of healthcare associated infections (HCAI), the DGS defined in 1996 the roles and competences of hospital infection control commissions throughout the network of public and private sector hospitals (Order of the Director-General for Health of 23/10/1996).

The tasks and competencies defined for the Department of Health Studies and Planning were integrated into the Directorate-General of Health (DGS) in 1997. The DGS was entrusted with the study and support in the definition, development and implementation of the global health policy, technical support to international cooperation, as well as guidance, coordination and supervision of prevention activities and the provision of health care (Decree-Law No. 122/97 of May 20).

In 1997, the Quality Division within the Directorate for Care Services (DSPCS) was set up within the organization of the Directorate-General for Health. Under Article 25(h) of the Quality Division of Decree-Law No 122/97 of 20 May 2011, the Information Circular No 15/DSPCS of 23/03/98 of Sakellarides, 'Free and Informed Consent', was published, addressed to the Management Bodies, Doctors of Health Centers and Hospitals.

The organizational quality model "MoniQuor", which aimed to monitor the quality of health centers, at the level of Primary Health Care (PSC), was put into action in 1998, but evolved into a process of cross-analysis: each health unit supervised another that was supervised by a third (Barros *et. al.*, 2011, Pisco L. Biscaia J., 2001, cited by Martins d'Arrábida C., 2023).

In the analysis of the strategic management of the National Health Service, Ferrinho, Guerreiro and Portugal (2018) identified as the first technical cycle of strategic planning in the health sector, led by Sakellarides, as Director-General of

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<sup>&</sup>lt;sup>e</sup> The Information Circular No. 6/79 of 9/2/79 DGH, 1979 released Resolution (72) 31 of the Council of Europe which called for the creation of infection control commissions in public or private health institutions integrated into the national healthcare network.

Health and which led to the elaboration of the First Health Strategy -"Health a Commitment" (1998-2002), according to De Oliveira D. (2020), Mintzberg, Ahlstrand, Lampel (2009), Craveiro I., Ferrinho P. (2001), Ministry of Health (1999), cited by Martins d'Arrábida C. (2023).

In the second legislature of the political cycle (1999-2002), the Health Strategy - "Health a Compromise" (1998-2002) was maintained. It served as an orientation for DGS and many health professionals, but no longer with political support. Based on a set of values and principles, it was constituted by strategic guidelines for the development of an overall vision of the SNS, goals, objectives and priority areas of action (cf. Ferrinho, Guerreiro and Portugal R., 2018, cited by Martins d'Arrábida C., 2023).

#### 3.3 INSTITUTE OF QUALITY IN HEALTH

Despite the attributions of Quality in the Directorate-General for Health, the Institute of Quality in Health (IQS) was created in 1999 and endowed with scientific, technical and administrative autonomy, for the definition and development of standards, strategies and procedures for the improvement of quality in the provision of health care (Ordinance No. 288/99 of April 27).

In a partnership, established on 17 March 1999, between the Institute for Quality in Health (IQS) and the King's Fund *Health Quality Service* (KFHQS) (Order No 17960/99 of 15 September (Pisco L., Biscaia J., 2001), the Accreditation Program was first implemented in September 1999 in five hospitals, in early 2000 in two hospitals and in September 2000, 1993 more nuine hospitals (Institue of Quality in Health, 1993, Pisco L., Biscaia J., 2001, cited by Martins d'Arrábida C., 2023). The partnership, consolidated by Order No 14584/2003 of 26 July 2003, started the Hospital Accreditation Program.

#### 4. ENDNOTES

Between 1974 and 1986, with the beginning of the democratic process, the coverage of healthcare by the medical service to the periphery, in terms of supply and demand-use of health services, the approval of the Constitution of the Portuguese Republic (CRP) and the enshrining of the right to health protection, the creation of the NHS, stand out.

The Ministry of Health was only created in 1983, the Directorate-General for Health (DGS) was abolished, and the Directorate-General for Primary Health Care (DGCSP) was created.

The beginning of the approach to quality in health was the organization of the International Seminar Évaluation des services de soins de santé primaires with the collaboration of the World Health Organization (WHO) and the Public Health Schools of the Universities, Free Brussels and Hebrew Jerusalem, in 1985. The beginning of the history of quality, with the evaluation of quality, was due to Emílio Imperatori (1993). A policy of quality in health came to be defined only with the First Health Strategy - "Health a Commitment" (1998-2002).

The approval of the Organic Law of the Ministry of Health led to the abolition of the Directorates-General for Primary Health Care and Hospitals and the creation, once again, of the Directorate-General for Health (DGS). The approval of the organization of the Directorate-General for Health led to the creation of the infection control committees in 1993 and the Quality Accreditation and Audit Division in the Directorate of Quality Promotion and Assurance Services in 1993. The Quality Division in the Directorate of Care Services (DSPCS) was established in 1997. Currently integrating into the area of Patient Safety, in 1999 the National Infection Control Program replaced the Infection Control Project. Currently, also in the area of Patient Safety, Information Circular No. 15/DSPCS of 23/03/98 "Free and Informed Consent" was published.

In spite of the initiatives in the area of Quality in Health, the Institute of Quality in Health was created in 1999, with scientific, technical and administrative autonomy, also in the dependence of the Director-General of Health.

The European Union (EU), in the framework of the financing of the II Community Framework, applied in quality health training and in particular the III Community Support Framework (Health Operational Program - XXI Health), through a financial envelope for a policy to promote quality in health may have contributed to national initiatives in this area.

Alongside EU support, WHO initiatives, notably WHO-Europe, the scientific academy and relevant national actors may have contributed to the national decision on policy measures in the area of Quality and Safety in Health in the period after 25 April until the end of the 20th century.

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# **CHAPTER 15**

# PNEUMONIA ASSOCIATED WITH MECHANICAL VENTILATION: PROFILE OF HOSPITAL INFECTION IN INTENSIVE CARE UNIT

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**ABSTRACT** 

**KEYWORDS:** 

**RESUMO:** 

PALAVRAS-CHAVE:

#### 1. INTRODUCTION

Lower respiratory tract infections, especially pneumonia, represent one of the main complications acquired in the hospital environment. Among the risk factors for the development of the disease is mechanical ventilation, and the therapy to which patients who have some kind of respiratory insufficiency are submitted. The study aimed to analyze the microbiological profile and resistance of bacteria that cause hospital pneumonia associated with mechanical ventilation in the Intensive Care Unit of the Emergency and Emergency Hospital.

Mechanical ventilation-associated pneumonia (VAP) develops at least 48 hours after endotracheal intubation. The most common pathogens are gram-negative bacilli and Staphylococcus aureus; however, antibiotic-resistant microorganisms are a significant concern. In patients on mechanical ventilation, pneumonia usually manifests with fever, increased white blood cell counts, worsening oxygenation, and increased tracheal secretions, which may be purulent. Diagnosis is presumed based on clinical manifestations and chest x-ray, confirmed by blood culture or by lower respiratory tract bronchoscopy. Treatment is with antibiotics. In general, the prognosis is poor, partly due to comorbidities.

The most common cause of pneumonia associated with mechanical ventilation is microaspiration of bacteria that colonize the oropharynx and upper airways in extremely ill patients.

Endotracheal intubation is the main risk factor for pneumonia associated with mechanical ventilation. Endotracheal intubation breaks airway defenses, compromises cough and mucociliary clearance, and facilitates microaspiration of bacterial-filled secretions that accumulate above the cuff of the inflated endotracheal tube. In addition, the bacteria form a biofilm on and within the endotracheal tube, which protects them from antibiotics and host defenses. The greatest risk of pneumonia associated with mechanical ventilation occurs during the first 10 days after intubation. Mechanical ventilation-associated pneumonia occurs in 9 to 27% of patients on mechanical ventilation.

#### 2. DEVELOPMENT

Pathogens and antibiotic resistance patterns vary significantly between institutions and may vary within institutions over short periods (eg, month to month). Institutional-level local antibiograms that are updated regularly are essential to determine appropriate empirical antibiotic therapy. In general, the most important pathogens are: *Pseudomonas aeruginosa; Staphylococcus aureus* sensitive to methicillin; *methicillin-resistant S. aureus* (MRSA).

Other important pathogens include enteric gram-negative bacteria (mainly species of Enterobacter, Klebsiella pneumoniae, Escherichia coli, Serratia marcescens, Proteusspp, and Acinetobacter bacteria).

Methicillin-sensitive S. aureus, Streptococcus pneumoniae, and Haemophilus influenzae are commonly involved when pneumonia develops within 4 to 7 days of hospitalization, while enteric SARM and gram-negative microorganisms become more common with increasing duration of intubation or hospitalization.

Prior intravenous antibiotic treatment (within the last 90 days) significantly increases the likelihood of infection by antibiotic-resistant organisms, especially MRSA and *Pseudomonas* infection in mechanical ventilation-associated pneumonia. Infection with resistant organisms greatly increases mortality and morbidity.

Other risk factors for antibiotic-resistant organisms specific for mechanical ventilation-associated pneumonia include: Septic shock at the time of mechanical ventilation-associated pneumonia; Acute respiratory distress syndrome (ARDS) preceding mechanical ventilation-associated pneumonia; Hospitalization for ≥ 5 days before the occurrence of mechanical ventilation-associated pneumonia; Renal replacement therapy before the onset of mechanical ventilation-associated pneumonia.

High doses of corticosteroids increase the risk of Legionella and Pseudomonas infections. Chronic suppurative pulmonary disorders such as cystic fibrosis and bronchiectasis increase the risk of gram-negative pathogens, including strains resistant to antibiotics.

The present study shows that the majority of patients (82.4%) presented PAVM by multiresistant microorganism and that, in this group, mortality was higher (61.3% vs. 25%, p = 0.008). Some methodological aspects, however, need to be analyzed.

First, it should be considered that although the absence of quantitative culture for processing endotracheal secretion samples is critically amenable, the population studied shows the reality of most ICUs, where the diagnosis of pneumonias is clinical, and the identification of agents carried out only through qualitative analysis.

Considering the high negative predictive value of endotracheal aspirate for the diagnosis of VAP, we use as mandatory criterion the positivity of the culture associated with the clinical criteria.

The method for collecting the material in a non-invasive manner also portrays reality, since the fibrobronchoscope is not always available at the moment of the diagnostic suspicion.

On the other hand, there is a lack of data that are absolutely unequivocal in demonstrating the superiority of invasive methods over non-invasive methods for the diagnosis of VWP. Ruiz et al. showed no difference in mortality in patients whose treatments were based on invasive methods when compared to those based on non-invasive methods.

The study conducted by Fagon et al., which so far has included the largest number of patients studied with VWP, demonstrated a reduction in mortality of patients treated based on the results of invasive methods at fourteen days, without, however, differing at 28 days. In this study, the group called clinical management did not use quantitative cultures for the analysis of endotracheal aspirate. A recently published meta-analysis suggests that clinical criteria represent the best benchmark for daily clinical practice.

The same authors say that studies evaluating the accuracy of diagnostic tests should not include tests as part of the definition of what is VWP. Second, it should be considered that this is a retrospective study, and that although the clinical and laboratory criteria have been as strict as possible in order to rule out other causes of pulmonary infiltrates and other foci of infection, the possibility of overestimating the occurrence of VWP always exists, especially when quantitative culture and bronchoalveolar lavage or protected bronchial brushing are not used, even if highly desirable.

Another diagnostic possibility that should always be considered is purulent tracheobronchitis, which is why it is important to exclude edema as a cause of lung infiltrate, in addition to using quantitative cultures when available.

Thirdly, it should be taken into account that the sample size and the predominance of patients with multi-resistant microorganisms can, by themselves, explain the higher mortality trend in the group, since the clinical and severity characteristics between the two groups were not different.

Although the most prevalent microorganisms are Gram-negative bacilli, S. aureus was, in isolation, the most frequent bacterium and 86.7% of them were resistant to oxacillin. This high rate of oxacillin resistance supports the recommendation of the Brazilian Consensus on Pneumonias that all S. aureus should be considered as resistant to oxacillin in the composition of empirical treatments of hospital pneumonia, especially when associated with mechanical ventilation.

The highest prevalence of S. aureus was also found by Balthazar et al. in an elegant study designed to compare the quantitative culture of bronchoalveolar lavage with the quantitative culture of post morten lung biopsy. The data from the Sentry Program, though, show, through samples collected from various Brazilian hospitals, that S. aureus was the second most prevalent microorganism (19.6%) and that close to half of the strains were of S. aureus resistant to oxacillin.

Carrilho also demonstrated that S. aureus was the second most prevalent bacterium in hospital pneumonias in the ICU of a university hospital in the north of Paraná. Korn et al. studied 100 patients admitted to two ICUs and observed that at the time of admission, 46% of them were colonized by oxacillin-resistant S. aureus, 28 patients became colonized and 16 developed respiratory or urinary infection.

The authors did not find any risk factors in the sample evaluated, but they pointed out that 20% of the patients colonized in the admission did not have previous hospitalizations, nor did they come from another hospital internment unit. To evaluate the utility of LBA in patients under empirical treatment for VAP and considered under therapeutic failure in a clinical ICU in São Paulo, Gomes et al. found Acinetobacter baumannii (37.1%), Pseudomonas aeruginosa (17.7%) and oxacillin-resistant S. aureus (16.1%) as the main causative agents of pneumonia.

Pseudomonas aeruginosa was the agent most frequently reported by the Sentry Program, and showed resistance to most antibiotics tested. In the present study, Pseudomonas aeruginosa was the second most prevalent agent, and 15.9% were considered multidrug resistant.

Acinetobacter baumanni, isolated in 8 patients, was multi-resistant in 7 of them. Stenotrophomonas malthophilia has been isolated in only 2 patients, but deserves to be analyzed, since it has increasingly been identified as a cause of hospital-acquired respiratory infection, especially in transplanted patients and patients with malignancies.

Similar to other non-fermenting species, S. malthophilia is intrinsically resistant to many of the antibiotics commonly used in empirical treatment schemes for hospital pneumonia. On the other hand, the drug of choice for this agent, sulfamethoxazole-trimethoprim, does not figure among the various antimicrobial regimens used empirically.

The use of broad-spectrum antibiotics determining greater selective pressure and the difficulties in implementing measures to control hospital infection have been pointed out as responsible for the emergence of increasingly resistant agents. General control measures such as hand washing, identification of colonized patients, and the use of contact precautions, even if neglected, have as their major goal to prevent the spread of microorganisms through health professionals and visitors.

On the other hand, the ideal strategy of reducing the antimicrobial spectrum after the isolation and identification of the agent determines a certain fear in the assistant team, which tends not to modify the treatment in the face of the improvement presented by the patient, and thus promotes the emergence of multi-resistant microorganisms, since the longer the exposure time to an antimicrobial, the greater the chance of colonization and infection by these microorganisms.

Isolation of more than one agent occurred in 14 episodes of pneumonia. The decision to call them probable cases of polymicrobial pneumonia lies in the limitation of the method used to collect respiratory secretions (already discussed above). Combes et al. showed an incidence of 48% of polymicrobial PAVM, which however did not determine differences in morbidity and mortality.

Trouillet et al. identified, through logistic regression, three variables associated with a higher chance of developing VWP by multi-resistant microorganisms: duration of mechanical ventilation, previous use of antibiotic and previous use of broadspectrum antibiotic.

In the present study, no associations were demonstrated with the time of mechanical ventilation, with the days of hospitalization in the ICU or in the hospital.

However, the time of ventilation and hospitalization were more prolonged in patients who developed pneumonias by sensitive bacteria, which is probably due to higher mortality in the group of patients with multi-resistant microorganism pneumonia.

Also, no relationship with previous use of antibiotics was observed. Very possibly these findings are due to the small number of cases studied and also to the predominance of multi-resistant microorganisms. The data showed that patients with MVAP by multi-resistant microorganisms were associated with higher mortality. In this group of patients, a greater number of inadequate treatments occurred.

Chastre and Fagon demonstrated, by combining several studies, that early empirical therapy seems to play an important role in the prognosis of these patients. The prognosis of VWPs by aerobic gram-negative bacilli is considered worse than by gram-positive when these agents are susceptible to antibiotics.

Mortality associated with Pseudomonas pneumonia is particularly high, usually above 70% to 80%. Kollef et al. showed that patients with VAP by microorganisms considered high-risk (Pseudomonas aeruginosa, Acinetobacter spp. and Stenotrophomonas malthophilia) had higher mortality when compared to patients with pneumonia developed late by other agents.

#### 3. FINAL CONSIDERATIONS

It is concluded that bacterial multiresistance has been associated with higher mortality, as can be demonstrated in this and other studies. If, among the various prognostic factors, adequate empirical antibiotic therapy becomes more and more important, the challenge in the elaboration of empirical schemes is permanent, since the bacterium can modify its resistance mechanisms in the same patient at different moments of the treatment.

Although this work illustrates the real way in which the diagnosis of VWP is made in most ICUs, the increase in the use of quantitative cultures, with their respective cutoff points, depending on the material used, is important for greater specificity, without, however, ending the discussions about the diagnosis. In the light of this knowledge, prevention seems to be the most sensible thing to do, and it is therefore necessary to implement more prophylaxis strategies, some of them very simple, such as hand washing.

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# **CHAPTER 16**

A COMPARATIVE STUDY BETWEEN PROPOFOL AND ETOMIDATE IN THE ANESTHETIC INDUCTION OF HYPOVOLEMIC PATIENTS: A BIBLIOGRAPHIC ANALYSIS

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#### 1. INTRODUCTION

Anesthetic induction in hypovolemic patients is challenging due to hemodynamic instability caused by reduced circulating blood volume. This condition is common in emergency scenarios such as trauma and hemorrhage, where choosing the appropriate inducing agent is crucial to minimize risks of hypotension and ensure patient safety.

The aim of this study is to critically review the literature on the comparison between the use of propofol and etomidate in anesthetic induction of hypovolemic patients, aiming to improve anesthetic practices.

An exploratory and qualitative literature review was conducted in bases such as PubMed, SciELO, LILACS and Google Academic. Descriptors used included "Propofol", "Etomidate", "Hypovolemia" and "Anesthetic Induction". The search covered publications from 2019 to 2023, selecting studies that directly addressed the effects of agents on hemodynamic stability in hypovolemic patients. After applying inclusion and exclusion criteria, nine studies were selected for detailed analysis.

Propofol, although widely used for its rapid onset of action, presents significant risks of hypotension, especially in hypovolemic patients. Etomidate, on the other hand, offers greater hemodynamic stability, but with the risk of adrenal suppression. Analysis of the studies shows that while propofol increases the risk of adverse clinical outcomes by its propensity to cause hypotension, etomidate, although more stable haemodynamically, may complicate management of critical patients due to possible suppression of cortisol production.

The choice between propofol and etomidate should not be based on a fixed protocol, but rather on a careful assessment of the patient's specific conditions. Both agents have their merits and risks, and the decision should consider the hemodynamic and endocrine needs as well as the patient's clinical situation. The development of evidence-based guidelines is essential to optimize the safety and efficacy of anesthetic induction in hypovolemic patients, thereby increasing positive clinical outcomes.

Anesthetic induction in hypovolemic patients represents a significant clinical challenge, since decreasing circulating blood volume affects hemodynamic stability and may worsen hypotension during administration of inducing agents (Miller et al., 2020). This condition is frequent in emergency settings, such as trauma, surgical

hemorrhages, extensive burns, and septic shock, where adequate control of blood pressure and cardiac output is critical to prevent severe complications. In the light of this panorama, the appropriate choice of the inducing agent becomes crucial, with the objetive of minimizing the risk of cardiovascular instability and guaranteeing the patient's safety in the perioperative period.

#### 2. DEVELOPMENT

Traditionally, propofol is widely used in anesthetic induction due to its rapid onset of action, predictable recovery and favorable anesthetic profile. However, its significant blood pressure lowering effect has been a point of concern, especially in patients with compromised intravascular volume (Morgan & Mikhail, 2018).

In contrast, etomidate is recognized to maintain more pronounced hemodynamic stability, providing induction with less incidence of significant hypotension. This profile makes it an attractive alternative in hypovolemic situations, although concerns about adrenal suppression lead to controversy about its use in critical cases (Cuthbertson et al., 2020).

Current evidence on the safety and efficacy of propofol and etomidate in hypovolemic patients is still limited and sometimes conflicting, evidencing the need for more robust investigations. Well-designed clinical trials and recent meta-analyzes can provide input for clearer anesthetic protocols, taking into account aspects such as fluid replacement, concurrent administration of vasopressors, and advanced hemodynamic monitoring (Gu et al., 2015; Bloom etal., 2021). In addition, innovative therapeutic strategies, such as coinduction with other agents or multimodal approaches, can optimize cardiovascular stability during induction in these high-risk patients (Vallee et al., 2019).

Given the challenges and the ongoing debate about the choice of the ideal agent for anesthetic induction in hypovolemic patients, this study aims to critically review the literature on the comparison between propofol and etomidate. By consolidating up-to-date and relevant information, the aim is to contribute to the improvement of scientific knowledge and anesthetic practices, fostering the development of more effective, safe and individualized therapeutic approaches for this group of patients.

Hypovolemia, characterized by reduced effective circulating blood volume, is a common condition in critical patients, victims of trauma, extensive burns, and surgical hemorrhages, as well as in cases of septic or anaphylactic shock (Miller et al., 2020). These individuals present hemodynamic instability that requires caution in choosing the anesthetic inducing agent, since induction may aggravate hypotension and compromise tissue perfusion (Morgan & Mikhail, 2018). In this context, the comparison between propofol and etomidate has become relevant due to pharmacodynamic and pharmacokinetic differences and their impacts on cardiovascular stability.

Propofol is a widely used hypnotic agent due to its rapid onset of action, efficient hepatic metabolism and more predictable arousal. However, its main adverse effect is the significant reduction in systemic blood pressure, due to peripheral vasodilation and myocardial depression, which can be critical in hypovolemic patients (Morgan & Mikhail, 2018; Gu et al., 2015). In contrast, etomidate is known to better maintain hemodynamic stability during induction, with a lower incidence of hypotension compared to propofol (Gu et al., 2015; Bloom et al., 2021).

Studies show that in hemodynamically unstable patients, induction with propofol can result in pronounced falls in blood pressure, with risk of coronary and cerebral hypoperfusion (Niemi & Greenblatt, 2023). (2015) concluded that etomidate, when compared to propofol, was associated with a lower incidence of significant hypotension in critical and potentially hypovolemic patients. Although these findings reinforce the role of etomidate as a safer option in hemodynamic terms, concerns about adrenal suppression, especially with repeated use or prolonged infusions, cannot be ignored (Cuthbertson et al., 2020).

The main controversy involving etomidate concerns the inhibition of the enzyme 11β-hydroxylase, leading to transient reduction in cortisol production (Masson, 2019). This adrenal suppression may be clinically relevant, especially in septic or critically ill patients, in whom the stress response is vital (Cuthbertson et al., 2020). Although the impact of a single dose of etomidate on mortality is debated, the balance between immediate hemodynamic stability and risk of adrenal insufficiency should be weighed (Rund & Schulte, 2021).

On the other hand, propofol, while not suppressing adrenal function, can increase the risk of severe hypotension, which can lead to adverse clinical outcomes such as myocardial ischemia, organ dysfunction and worse prognosis in patients

already hemodynamically compromised (Morgan & Mikhail, 2018). In this sense, the clinical decision involves considering not only the hemodynamic stability profile and endocrine effects, but also the individual characteristics of the patient, including fluid reserve, etiology of hypovolemia and presence of comorbidities.

The choice between propofol and etomidate in anesthetic induction of hypovolemic patients does not follow a rigid and universal protocol. The literature suggests that etomidate is a valid option to minimize pressure falls, ensuring greater cardiovascular stability at the time of induction (Gu et al., 2015; Bloom et al., 2021).

However, in scenarios in which endogenous stress response is critical, etomidate-induced adrenal suppression may be disadvantageous (Cuthbertson et al., 2020; Masson, 2019). In addition, strategies such as coinduction with other drugs (e.g. ketamine) have been investigated, aiming to minimize the hypotensive effects of propofol and promote hemodynamic stability in hypovolemic patients (Vallee et al., 2019). Thus, the optimal therapeutic approach may involve combining agents, dose adjustment and adopting advanced monitoring, as well as adequate fluid replacement before induction, where possible.

Additionally, although the current literature points to etomidate as a more stable agent hemodynamically, it is important to stress that its use must be contextualized within a broader anesthetic protocol. Experienced professionals can choose etomidate, in a single dose, for high-risk induction in hypovolemic patients, ensuring advanced monitoring and carefully evaluating the risk-benefit (Cuthbertson et al., 2020).

In addition, strategies to mitigate adrenal suppression may include simultaneous administration of replacement steroids, although this practice still requires more robust evidence before it is routinely adopted. On the other hand, the introduction of multimodal protocols, including goal-directed fluid therapy and the use of short-acting vasopressors, may make the use of propofol safer in hypovolemic patients.

The refinement of monitoring techniques, such as systolic volume analysis, pulse pressure variability index and dynamic evaluation of volemic response, allow early and personalized intervention, reducing propofol-induced hemodynamic fluctuations (Morgan & Mikhail, 2018).

These technological and pharmacological advances may eventually balance the hemodynamic disadvantages of this hypnotic agent in critical contexts. Finally, the

choice between propofol and etomidate in anesthetic induction of hypovolemic patients illustrates the complexity of clinical reasoning in perioperative medicine.

Decision-making depends on multiple factors, such as initial volemic state, patient response to stress, the need to preserve cardiac output, and the expected duration of anesthesia (Gu et al., 2015; Bloom et al., 2021). With the ongoing evolution of research, future studies, including randomized and well-designed clinical trials, are expected to help establish clearer guidelines, optimizing anesthetic care and consequently improving safety and prognosis of critical patients.

Induction of anesthesia is associated with mild to moderate hemodynamic variation depending on many factors. In our study, we observed that propofol caused significant hypotension and tachycardia in induction compared to etomidate. Hypotension occurs with propofol mainly due to reduced sympathetic activity, which causes vasodilation, or its direct effect on vascular smooth muscles.

Sudden hypotension and tachycardia have deleterious effects on maintenance of circulation to vital organs in patients with coronary artery disease, valvular stenosis, uncontrolled hypertension, and shock. On the other hand, the hemodynamic stability observed with etomidate may be due to its singular lack of effect on the sympathetic nervous system and baroreceptor functions.

Etomydate is not limited to normotensive patients because of its hemodynamic peculiarity. In several studies, etomidate showed less cardiovascular depression and minimized the use of vasoconstrictive agents than another induction agent in sepsis and in critically ill patients. Although etomidate may cause adrenal insufficiency in these patients in the postoperative period, its clinical consequence is still obscure in relation to its advantage of preventing hypotension in induction.

In conclusion, etomidate is better than propofol due to its hemodynamic stability and lower incidence of pain at injection. The only disadvantage of etomidate was the high incidence of myoclonus. We suggest, therefore, that etomidate is a better option in patients particularly prone to hemodynamic fluctuation in induction, such as uncontrolled hypertension, sepsis, critically ill patients, and those with coronary artery disease.

#### 3. FINAL CONSIDERATIONS

The comparison between propofol and etomidate in the anesthetic induction of hypovolemic patients provides evidence of a challenging clinical scenario in which hemodynamic stability and adrenal function need to be carefully balanced. Etomidate emerges as a promising option to minimize hypotension during induction, contributing to improved immediate safety in critical patients. However, the possibility of adrenal suppression, albeit temporary, imposes a therapeutic dilemma that demands a careful evaluation of the patient's clinical condition, the etiology of hypovolemia, and the surgical context.

In turn, propofol, widely used and with favorable pharmacokinetics, presents a clear disadvantage in patients with reduced volume reserve due to the increased risk of hypotension.

Although the implementation of advanced monitoring, targeted fluid therapy strategies, and multimodal approaches can mitigate this effect, their use remains more risky in cases of significant hypovolemia.

In short, the decision between propofol and etomidate is not based on a rigid protocol, but rather on an individualized analysis, taking into account hemodynamic, endocrine and metabolic variables. Improved monitoring technologies and more robust prospective studies could provide additional evidence to guide this complex choice.

In this sense, the development of clearer and more substantiated guidelines will contribute to improve anesthetic care in hypovolemic patients, increasing their safety and improving clinical outcomes.

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# **CHAPTER 17**

#### PITUITARY APOPLEXY

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**ABSTRACT**:

**KEYWORDS:** 

**RESUMO:** 

PALAVRAS-CHAVE:

#### 1. INTRODUCTION

Pituitary apoplexy is a rare but potentially fatal endocrinological emergency characterized by sudden hemorrhage or acute ischemic infarction of the pituitary gland, usually within a pre-existing pituitary adenoma (Mayol *et al.*, 2023), leading to an abrupt increase in pressure within the sella turcica (Mendelson, 2022). This event can result in a rapid neurological and endocrinological deterioration, requiring emergency medical intervention (Mclemore *et al.*, 2021).

The incidence of pituitary apoplexy is estimated to be between 1.5% and 27% of patients with pituitary adenomas, most commonly in tumors larger than 10 mm, with only 10% being symptomatic tumors. Some authors even suggest changing the nomenclature to "Pituitary tumor apoplexy" given the higher incidence in these conditions. There is a prevalence in men that varies in the age group from 37 to 60 years (Donegan *et al.*, 2022; Mayol *et al.*, 2023). Despite being a rare complication, its actual occurrence may be underestimated due to subclinical cases that are not diagnosed (Herman *et al.*, 2021).

Management of pituitary apoplexy evolved over time, with an increasing focus on early intervention. In the past, treatment was predominantly conservative, but recent clinical studies have shown that early surgical decompression can significantly improve visual and neurological outcomes (Rajasekaran *et al.*, 2011). In addition, immediate hormone replacement therapy has become standard practice to prevent acute adrenal failure and other endocrine complications (Briet *et al.*, 2016).

## 2. PHYSIOPATHOGENY

The pituitary gland is a small endocrine gland located at the base of the brain, within the sella turcica, a bone cavity of the sphenoid bone (Melmed *et al.*, 2021). It is divided into two main parts: the adeno-pituitary (anterior lobe) and the neuro-pituitary (posterior lobe). The adeno-pituitary secretes hormones that regulate various bodily functions, including growth, reproduction, and metabolism. These include growth hormone (GH), prolactin (PRL), adrenocorticotropic hormone (ACTH), and gonadotrophic hormones (LH and FSH). The neuro-pituitary gland, in turn, stores and releases oxytocin and vasopressin (ADH) produced in the hypothalamus (Guyton *et al.*, 2020).

Vascularization of the pituitary is complex and is provided mainly by the upper and lower pituitary arteries, which are branches of the internal carotid artery. The adeno-pituitary is supplied by the postpituitary system, with relatively low pressure, while the neuro-pituitary receives blood directly from the lower pituitary arteries, with higher pressure. Therefore, when apoplexy occurs due to low pressure or hypovolemia, the adeno-pituitary is affected in a general manner, while the neuropituitary is usually preserved (Biagetti *et al.*, 2022). This rich vascularization makes the gland susceptible to changes in blood flow, blood pressure, and bleeding and ischemic events (Muller *et al.*, 2022).

The pathophysiology of pituitary apoplexy is not yet defined, but some hypotheses try to explain this phenomenon. It occurs when there is a sudden hemorrhage or a heart attack in a pituitary adenoma, leading to tumor expansion and a rapid increase in pressure within the sella turcica. This increased pressure can cause compression of neighboring structures, such as optic chiasm, resulting in acute neurological and visual symptoms (Lefebvre *et al.*, 2017). In addition, disruption of blood supply can cause tissue necrosis, further aggravating the clinical picture (Serri *et al.*, 2021) undergoing hormonal dysfunction due to sudden disruption of hormone release (Mayol *et al.*, 2023). Other studies suggest that adenomas have high metabolic demand, limited angiogenesis, and weaker blood vessels with lower density and low amount of endothelial growth factor when compared to the normal pituitary gland. In addition, studies indicated that adenoma cells cannot survive in the absence of reduced glucose concentrations, the tumor becomes susceptible to ischemia in the face of any factor that disrupts the balance between tissue perfusion and increased metabolic demand (Donegan *et al.*, 2022; Muthukumar, 2020).

#### 3. ETIOLOGY

In up to 30% of cases, some studies identified predisposing factors associated with the occurrence of pituitary apoplexy (Iglesias, 2024).

The main cause of pituitary apoplexy is the presence of nonfunctioning pituitary adenomas, especially macroadenomas (>10 mm), which are more prone to hemorrhages due to their abundant vascularization and tissue structure (Randeva *et al.*, 1999). In most cases patients are unaware of the tumor (Mayol *et al.*, 2023). It is

believed that because they are non-secreting tumors, they become symptomatic in more advanced stages, which makes them larger at the time of diagnosis and thus more susceptible to heart attacks and bleeding (Muthukumar, 2020). Among pituitary-functioning tumors, prolactinomas are the most frequent (Donegan *et al.*, 2022).

Cranial trauma can result in direct damage to the pituitary gland or precipitate a bleeding event in a pre-existing adenoma, leading to apoplexy due to changes in blood pressure or intracranial pressure (Sibal *et al.*, 2004). Significant hemodynamic and hormonal changes occur during pregnancy, such as increased gland volume, blood supply, and hormonal activity. These changes can make diagnosis difficult, since symptoms resemble those of preeclampsia. In addition, some events may be related to lactotrophic hyperplasia (Donegan *et al.*, 2022; Muthukumar, 2020; Powell *et al.*, 2020).

Conditions affecting blood circulation, such as hypertension and uncontrolled diabetes mellitus, may increase the risk of pituitary apoplexy by compromising the vascular integrity of the pituitary gland (Ferri, 2019). Other less common factors include infections, such as sinusitis, which can spread to the sella turcica, and surgical or radiotherapy procedures that directly affect the pituitary gland (Tiraboschi et al., 2018). In addition to these predisposing factors, there is hormone treatment with gonadotropin releasing that can cause an acute increase in the size of the gland. Patients who use anticoagulants are at risk of up to 3 times more bleeding, and those who are susceptible to thrombocytopenia due to conditions such as dengue may also develop apoplexy due to their increased propensity to bleeding. The use of drugs as dopaminergic agonists or somatostatin analogs, in addition to mechanical ventilation and Sheehan's syndrome, characterized by pituitary necrosis secondary to heavy bleeding during childbirth are predisposing factors (Mayol et al., 2023; Vilar, 2020). This syndrome is most prevalent in countries with lower socioeconomic status, where adequate medical follow-up is limited (Iglesias, 2024). Symptoms and signs usually manifest gradually, over months or even years. In some cases, diagnosis can occur 20 to 30 years after delivery. Lactation is often absent (agalactia) due to prolacting deficiency (Vilar, 2020). Less often, infarction can occur soon after delivery, even without the presence of overt bleeding. If blood loss is severe, especially if accompanied by hypotension, the patient should be evaluated and treated promptly for adrenal insufficiency. Other hormonal deficiencies can be analyzed four to six weeks after such evaluation. (Snyder, 2024).

Although less frequently, there is an association between apoplexy and Rathkeilitis fissure cysts, craniopharyngiomas, pituitary metastases, mainly from renal cell carcinoma, as well as pituitary tuberculosis and hypophysitis (Iglesias, 2024).

Recently, cases of seizure events have been reported in several patients with COVID-19 and also in individuals after vaccination against the virus. The suggested acute mechanism involves increased SARS-CoV-2-associated coagulopathy and binding of the virus to the angiotensin 2-converting enzyme in the cerebral vasculature, which leads to its reduction and accumulation of angiotensin 2, which is a potent vasoconstrictor, predisposing ischemia and bleeding events (Donegan *et al.*, 2022).

#### 4. CLINICAL PICTURE

Among the symptoms, sudden and severe headache, located in the frontal or retro-orbitary region is the most common (80% to 90%) and characteristic of pituitary apoplexy, often described by patients as "the worst headache in life" (Briet *et al.*, 2016). This headache is often accompanied by nausea, vomiting, and photophobia. It occurs due to an abrupt increase in pressure within the saddle and involves mechanisms such as the division of the upper part of the trigeminal nerve within the cavernous sinus, meningeal irritation, compression of the dura mater, and enlargement of the saddle walls (Mayol *et al.*, 2023; Sibal *et al.*, 2004).

Visual changes are frequent and include bitemporal hemianopsia (vision loss in the lateral visual fields) and diplopia (double vision), which occur due to compression of the optic chiasm and cranial nerves that control the eye muscles (Rajasekaran *et al.*, 2011). Occulomotor nerve involvement is the most common and patients may present with ptosis, lateral deviation of the eye, and ipsilateral pupillary dilation to injury (Mayol *et al.*, 2023). Visual loss may indicate severe neurological damage and requires immediate intervention (Verrees *et al.*, 2013).

In addition, pituitary apoplexy can lead to changes in the level of consciousness in up to 22% of patients (Muthukumar, 2020), which range from mild confusion to coma, depending on the severity of the bleeding event and the impact on brain perfusion (Bills *et al.*, 2021). The presence of obtundation or loss of consciousness is a medical emergency signal requiring immediate intervention (Casanueva *et al.*, 2007).

An apoplectic event can cause a rapid fall in hormone levels due to disruption of pituitary function. This can result in systemic complications such as acute adrenal insufficiency, one of the most serious clinical problems and occurring in more than two-thirds of patients with apoplexy. In addition to hypothyroidism (35% to 70%) and hypogonadism (50% to 75%), it is more common in women (Capatina *et al.*, 2015; Donegan *et al.*, 2022; Mayol et al., 2023).

The lack of secretion of adrenocorticotropic hormone (ACTH) leads to a reduction in cortisol secretion, which is crucial for the maintenance of blood pressure and the vasopressor response to catecholamines. Lack of cortisol leads to peripheral vasodilation and inability to maintain blood pressure, resulting in distributive shock, which can be life-threatening if not promptly treated with corticosteroid replacement and adequate hemodynamic support (Snyder *et al.*, 2024). In adrenal crisis the patient may present hypotension, hypothermia, hypoglycemia, lethargy, coma and electrolyte disorders such as hyponatremia (Donegan *et al.*, 2022; Mayol *et al.*, 2023).

Although rare, pituitary apoplexy may present with fever, which may make diagnosis difficult by simulating central nervous system infections such as meningoencephalitis. Fever in these patients tends to result from a sterile inflammatory response due to necrosis and hemorrhage, rather than from infection. In some cases, it can be caused by hypothalamic dysfunction, due to compression of the hypothalamus, which regulates body temperature (Huang, 2009).

#### 5. DIAGNOSTICS

Diagnosis of pituitary apoplexy is initially clinical, suspected in one or more of the findings: sudden, severe headache, visual changes, nausea/vomiting, altered mental status, and acute endocrine dysfunction (Donegan *et al.*, 2022). Clinical history should include a detailed evaluation of symptoms and possible precipitating factors such as anticoagulant use, trauma and history of pituitary adenomas (Casanueva *et al.*, 2007).

To establish the diagnosis, an imaging test is required. Non-contrast-enhanced computed head tomography is often the first imaging test done due to its wide availability and speed. CT can detect intrasellar hemorrhages in 20% to 40% of cases and some bone changes, but is less sensitive than MRI in detecting ischemic lesions

(Donegan *et al.*, 2022; Nawar *et al.*, 2008). Contrast tomography can be done later to define tumor dimensions more precisely (Mayol *et al.*, 2023). At CT, bleeding appears hyperdense, which makes the test optimal within the first 6 hours of symptom onset. However, in the hyperacute phase bleeding may be isodent, making diagnosis difficult. In both hemorrhagic and non-hemorrhagic apoplexy, contrast causes peripheral enhancement in lesions (Donegan *et al.*, 2022).

Magnetic resonance imaging is the test of choice for detailed evaluation of pituitary apoplexy. It has 90% sensitivity (Iglesias, 2024). MRI provides high-resolution images of the sella turcica and allows for clearer visualization of hemorrhages, ischemia, edema and the extent of compression of adjacent structures (Lefebvre *et al.*, 2017). Specific sequences such as T1 and T2 with contrast are particularly useful in characterizing lesions (Sibal *et al.*, 2004). The characteristic finding that MRI reveals is an increased and peripheral-enhanced mass in the selar/suprasellar region around a low-intensity center (Mayol *et al.*, 2023).

Laboratory and hormonal evaluation is indispensable, since approximately 80% of the patients with apoplexy show deficiency of at least one of the hormones of the adeno-pituitary gland. The most common deficiency is GH (90%), ACTH (70%), and TSH (50%) (Mayol *et al.*, 2023, Snyder, 2024). However, it also includes the dosage of other hormones that may be altered, such as cortisol, LH, FSH and prolactin (Casanueva *et al.*, 2007).

Dynamic pituitary function tests can be performed to evaluate the functional reserve of the gland, especially in subacute (diagnosis after 72 hours) or chronic cases (Briet *et al.*, 2016; Donegan *et al.*, 2022). These tests help determine the need for long-term hormone replacement and monitor functional recovery after treatment (Capatina *et al.*, 2015).

#### 6. TREATMENT

There is no consensus in the literature on the treatment of apoplexy. Initial management of an apoplectic event should focus on stabilizing the patient, ensuring adequate hemodynamic support. This includes administration of intravenous fluids to correct hypotension, electrolyte disturbances and shock, and continuous monitoring of vital signs (Rajasekaran *et al.*, 2011).

Immediate hormone replacement is crucial, especially to correct adrenal insufficiency. All patients should be treated with corticosteroids, even in the absence of symptoms of adrenal crisis. Corticosteroids are given in high doses to stabilize cardiovascular function and prevent distributive shock (Rajasekaran et al., 2011). In addition to treating adrenal insufficiency, they help reduce cerebral edema and inflammation, relieving compression of neural structures and improving neurological symptoms (Nawar et al., 2008). The recommended starting dose is 100-200 mg intravenous hydrocortisone bolus followed by maintenance every 6 hours at 50-100 mg. Alternatively, a continuous infusion of 2 to 4 mg/hour after initial bolus may be chosen (Mayol et al., 2023). Use of 2 to 3 doses of dexamethasone 2 to 16 mg daily orally or intravenously may be useful to reduce edema in cases where early surgical decompression has not been performed. In some situations, combination with mannitol may be necessary. Once there is improvement in acute episode, it is indicated to adjust the dose of glucocorticoid to 20 to 30 mg daily of hydrocortisone, in up to three oral doses (Iglesias, 2024). The thyroid hormone replacement, if necessary, should be administered only after the glucocorticoids have been administered, as otherwise it may worsen adrenal insufficiency, and investigations should not delay treatment. Patients with lactotrophic adenoma (prolactinoma), dopamine agonist administration is indicated to reduce adenoma size (Snyder, 2024).

Emergency surgery is indicated in cases of pituitary apoplexy with progressive visual impairment, significant neurologic deficits, or deterioration of mental status that does not respond to conservative treatment (Capatina *et al.*, 2015). The transsphenoidal approach is the preferred surgical technique for pituitary adenoma decompression, due to direct access and lower associated morbidity (Casanueva *et al.*, 2007). Craniotomy may be necessary in cases of large adenomas with significant suprasellar extension for complete resection or when the transsphenoidal approach is not feasible (Verrees *et al.*, 2013). By opting for conservative treatment, in cases of mild impairment, without altered sensory and without severe comorbidities, close clinical monitoring is essential to quickly detect any sign of deterioration of the condition (Muthukumar, 2020). It is ideal that the neurological evaluation is done initially every hour, and can be extended to 4 to 6 hour intervals if clinical improvement improves (Iglesias, 2024). Hypopituitarism and visual changes may resolve spontaneously as blood is reabsorbed, a process that can take weeks to months after bleeding (Snyder,

2024). Further studies are still needed to better stratify patients who could benefit from surgery, although the rarity and acute nature of this condition still limit research.

#### 7. DIFFERENTIAL DIAGNOSTICS

They include conditions with visual and neurological symptoms, such as ophthalmoplegic migraine, aneurysm, subarachnoid hemorrhage, retrobulbar neuritis, temporal arteritis, meningitis, hypophysitis, cavernous sinus thrombosis, hypertensive encephalopathy, basilar artery infarction, and carotid dissection (Donegan *et al.*, 2022; Mayol *et al.*, 2023).

#### 8. COMPLICATIONS

Complications of pituitary apoplexy can be divided into immediate and delayed. Among the immediate complications, adrenal crisis stands out as a life-threatening condition. (Rajasekaran *et al.*, 2011). Adrenal insufficiency can lead to severe hypotension, requiring immediate intervention with intravenous fluid replacement and appropriate hormonal therapy (Nawar *et al.*, 2008).

Among late complications, many patients may develop permanent pituitary failure after apoplexy, requiring long-term hormone replacement therapy (80%) (Casanueva *et al.*, 2007; Mayol *et al.*, 2023). In addition, although most patients recover vision after surgery, some may have persistent visual deficits due to irreversible damage to the optic chiasm (Verrees *et al.*, 2013).

Another complication that can arise in a small group of patients is central diabetes insipidus (Mayol *et al.*, 2023), by inappropriate secretion of antidiuretic hormone, in the involvement of the neuro-pituitary. This condition may be transient, either after apoplexy or after surgery, and therefore should be reassessed during follow-up (Donegan *et al.*, 2022).

#### 9. PROGNOSIS AND PREVENTION

Postsurgical prognosis is usually good, particularly when intervention is done early. Most patients show good recovery from visual function and extraocular muscle

paralysis (Muthukumar, 2020). Early surgery, especially in children, may improve clinical outcomes, as tumors tend to be more aggressive than those seen in adults (Mayol *et al.*, 2023).

Mortality is 1.6% to 1.9% and recurrence of apoplexy is rare, especially after complete surgical removal of the pituitary adenoma. However, patients should be closely monitored for signs of recurrence (Nawar *et al.*, 2008).

Patients with known pituitary adenomas should be followed regularly through imaging and hormonal evaluation to detect early changes that may predispose to apoplexy (Casanueva *et al.*, 2007). Assessment of visual acuity, eye movements and visual fields is essential. Cortisol dosing at 8:00 is the indicated initial postoperative examination in patients without steroid therapy. Thyroid function (TSH and free T4) should be checked between the third and fourth day after surgery and reassessed at 6 to 8 weeks if normal (Iglesias, 2024).

In addition, it is important to instruct patients with known adenoma to identify warning signs, such as sudden and severe headache and visual changes, so that they seek medical attention immediately (Mayol *et al.*, 2023). Patients using anticoagulants should be carefully monitored, and the use of these drugs should be reviewed in case of pituitary adenomas (Rajasekaran *et al.*, 2011). In addition, pregnant women with pituitary adenomas should be closely monitored due to increased risk of apoplexy during pregnancy (Powell *et al.*, 2020).

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# **CHAPTER 18**

#### PSYCHIATRIC EMERGENCIES DURING PREGNANCY: A LITERATURE REVIEW

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**ABSTRACT:** Pregnancy is a period marked by profound biological, psychological, and social changes that can exacerbate or trigger psychiatric disorders in predisposed women. Psychiatric emergencies, such as mood disorders, anxiety, psychosis, and substance use, require prompt interventions due to their impact on maternal health and obstetric outcomes. The objective of this research was to explore the main emergency psychiatric conditions, their implications for maternal-fetal health, and the most appropriate therapeutic approaches for each case. Renowned databases were searched, selecting 16 reference articles that met the pre-established criteria. Managing these psychiatric conditions requires a multidisciplinary and individualized approach, considering the effects of treatments on the fetus and balancing teratogenic risks with benefits for the mental health of the pregnant woman. Thus, the management of psychiatric emergencies during pregnancy is a complex field that demands coordination among healthcare professionals.

**KEYWORDS:** emergency, psychiatry, pregnancy.

**RESUMO:** A gestação é um período marcado por profundas mudanças biológicas, psicológicas e sociais, que podem exacerbar ou desencadear transtornos psiquiátricos em mulheres predispostas. As emergências psiquiátricas, como transtornos de humor, ansiedade, psicose e uso de substâncias, requerem intervenções rápidas devido ao seu impacto na saúde materna e nos desfechos obstétricos. O objetivo dessa pesquisa consistiu em explorar as principais condições psiquiátricas emergenciais, suas implicações para a saúde materno-fetal e as abordagens terapêuticas mais adequadas para cada casos e para sua confecção, foram realizadas buscas em bases de dados renomadas, selecionando-se 16 artigos referenciais que se enquadraram nos critérios pré-estabelecidos. O manejo dessas condições psiquiátricas exige uma abordagem multidisciplinar e individualizada, considerando os efeitos dos tratamentos no feto e equilibrando os riscos teratogênicos com os benefícios para a saúde mental da gestante. Assim, a gestão das emergências psiquiátricas na gestação é um campo complexo que demanda coordenação entre profissionais de saúde.

PALAVRAS-CHAVE: emergências, psiquiatria, gestação.

#### 1. INTRODUCTION

Pregnancy is a period of intense biological, psychological, and social changes, marked by challenges that can exacerbate or trigger psychiatric disorders in predisposed women. The most common psychiatric emergencies during pregnancy include anxiety disorders, severe depression, psychoses, suicidal ideation, and substance use disorders. Such emergencies require rapid and appropriate interventions due to the significant impact on both maternal health and obstetric outcomes. The occurrence of these conditions is a complex and multifaceted issue involving biological, emotional and contextual factors (MILLS; BERKOWITZ, 2011; AHMED et al., 2023).

Hormonal changes, psychological stress, lifestyle changes, and social pressures associated with pregnancy can contribute to the onset or worsening of psychiatric disorders. According to Goodman, Chenausjy and Freeman (2014), anxiety disorders, which include panic disorder, are frequent during pregnancy, with an estimated prevalence of between 6.6% and 15%. According to Altshuler, Hendrick and Cohen (2000), mood and anxiety disorders are highly prevalent, affecting between 10% and 20% of pregnant women.

These disorders, if not adequately treated, can lead to severe obstetric complications, such as placental abruption, as described by Cohen, Rosenbaum and Heller (1989). In addition, chronic anxiety and maternal stress are associated with an increased risk of premature delivery and low birth weight (DOLE, 2003; WADHWA et al., 1993).

Another important aspect to be considered are mood disorders, especially depression and bipolar disorder, which may worsen during pregnancy. Yonkers et al. (2011) highlight that depression is one of the most prevalent disorders in this period, affecting about 10% to 20% of pregnant women. Untreated depression is strongly associated with suicidal behaviors and other adverse outcomes, making it a high-priority clinical condition. Inadequate management of these conditions can result in devastating effects for the mother and fetus, including increased maternal mortality rates, especially in developed countries (ALTSHULER; HENDRICK; COHEN, 2000).

Pregnancy psychosis is a less common but potentially devastating psychiatric emergency. According to Watkins and Newport (2009), gestational psychosis can

manifest itself both in women with a prior psychiatric history and in those without any history of mental disorders. This condition requires immediate intervention, often with the hospitalization of the patient and the use of antipsychotics, although the safety of these drugs during pregnancy is still a topic of continuous debate (OYEBODE et al., 2012; WEBB; HOWARD; ABEL, 2004).

In addition to mood and psychotic disorders, substance abuse during pregnancy is a significant psychiatric and obstetric concern. Use of illicit drugs, alcohol, and tobacco during pregnancy is associated with a wide range of complications, including intrauterine growth restriction, premature delivery, and fetal death (Committee Opinion No. 473, 2011). These emergencies require a multidisciplinary approach, with psychiatric support and adequate obstetric interventions to minimize the risks to both the mother and fetus.

Given the scenario of multiple risks involved, managing psychiatric emergencies during pregnancy involves complex and individualized care. Ahmed et al. (2023) reinforce the need for an approach that considers not only the psychological well-being of the pregnant woman, but also the potential effects of treatments on the fetus. The use of psychotropics during pregnancy, although necessary in many cases, should be carried out with caution, balancing the teratogenic risks with the benefits of maternal mental health treatment (OYEBODE et al., 2012).

Therefore, it is evident that psychiatric emergencies during pregnancy constitute a vital and challenging clinical care area, requiring immediate and coordinated interventions among psychiatrists, obstetricians and other health professionals. The literature review on the topic aims to explore the main emergent psychiatric conditions, their implications for maternal-fetal health and the most recommended therapeutic approaches, based on the most recent and relevant studies in the area.

#### 2. METHODOLOGY

This review was conducted through a bibliographic survey using the PubMed, Scielo and Cochrane Library databases, and the following keywords: "emergency" "psychiatry" and "pregnancy". Sixteen articles published between 1987 and 2024 were used, selected based on their relevance for psychiatric emergencies during pregnancy.

The inclusion criteria included clinical studies, systematic reviews, and case studies that discussed the management of emergency psychiatric conditions in pregnant women. Exclusion criteria included studies that focused exclusively on the postpartum period or did not address therapeutic interventions. References used include articles such as Ahmed et al. (2023), which reviews major psychiatric emergencies in pregnancy, and Wadhwa et al. (1993), which explores the association between prenatal stress and obstetric complications.

As a justification for the research, the current relevance of the theme in question and the constant need for updates is highlighted, since psychiatric emergencies during the period of pregnancy can lead to serious damages in the life of the pregnant woman and of the baby in formation.

The objective of the review was to explore the main emergent psychiatric conditions, their implications for maternal-fetal health and the most recommended therapeutic approaches, based on the most recent and relevant studies in the area.

#### 3. RESULTS AND DISCUSSION

Pregnancy is a period of significant physiological and psychological transformations that can precipitate or exacerbate emergency psychiatric conditions. Common psychiatric emergencies during pregnancy include anxiety disorders, mood disorders, psychoses, suicidal behavior, and substance use disorders. These conditions require proper management due to the potential implications for both pregnant women's health and fetal development (AHMED et al., 2023). Thus, the results of this research were divided according to the main psychiatric complications during pregnancy.

#### 3.1 MAJOR DEPRESSIVE DISORDER

Major depressive disorder is highlighted as one of the most prevalent psychiatric emergencies in pregnancy, and may evolve into severe depression and suicidal behavior. The article by Mills and Berkowitz (2011) stresses that depression during pregnancy can be aggravated by hormonal and psychosocial factors, increasing the risk of complications such as premature delivery and low birth weight. In severe cases,

hospitalization may be necessary to ensure patient safety. Antidepressant therapy is a viable option, but the risk-benefit of treatment should be carefully assessed, considering the possible teratogenic effects of some medications.

#### 3.2 POST-TRAUMATIC STRESS DISORDER

The study conducted by Yonkers et al. (2014) explores the relationship between post-traumatic stress disorder (PTSD) in pregnant women and the risk of premature delivery. Using a sample of pregnant women followed throughout pregnancy, the article investigated how the presence of PTSD symptoms can affect pregnancy outcome, in particular the occurrence of premature births. The results indicate that women with PTSD have a significantly higher risk of premature delivery when compared to women without the disorder.

The article demonstrated that the severity of PTSD symptoms is directly correlated with the increased risk of obstetric complications, especially premature delivery. Women with more severe symptoms were more likely to deliver before 37 weeks gestation, regardless of other risk factors such as age, ethnicity, or socioeconomic status. This finding suggests that PTSD alone is a critical risk factor and should be considered a priority in prenatal care.

In addition, Yonkers et al. (2014) have highlighted that the presence of PTSD in pregnant women may be underdiagnosed due to lack of adequate screening during prenatal care. The study emphasizes the importance of including mental health assessments as a routine part of obstetric care in order to identify PTSD symptoms early and intervene appropriately. Addressing this disorder early is crucial to minimize the risks of gestational complications.

The management of pregnant women with PTSD requires a multidisciplinary approach, involving obstetricians, psychiatrists and mental health professionals. Cognitive-behavioral therapy (CBT) is cited as one of the most effective interventions to treat PTSD during pregnancy. In addition, psychosocial interventions and, in more severe cases, controlled use of drugs may be necessary to stabilize the patient's mental health. Yonkers et al. (2014) underline that by adequately treating PTSD, it is possible to reduce the risk of premature delivery and improve maternal-child outcomes.

Finally, the article suggests that the inclusion of PTSD evaluation protocols in prenatal care can significantly improve the care offered to pregnant women, promoting both mental and physical health. Yonkers et al. (2014) argue that obstetric care should include continuous monitoring of the pregnant woman's mental health, ensuring that conditions such as PTSD are promptly identified and treated, which in turn will reduce complications such as premature delivery.

#### 3.3 PREGNANCY ANXIETY DISORDERS

Anxiety disorders, including panic disorder, generalized anxiety disorder (GAD), and social anxiety disorder, are often seen in pregnant women. Studies indicate that the prevalence of anxiety in pregnant women can vary from 13% to 21%, and is a significant risk factor for obstetric and neonatal complications, such as premature delivery and low birth weight (GOODMAN et al., 2014). In addition, severe panic attacks may be associated with acute obstetric events, such as placental abruption, which highlights the need for early identification and management of these conditions (COHEN; ROSENBAUM; HELLER, 1989).

Panic disorder, for example, can manifest itself as sudden crises of extreme anxiety, with physical symptoms such as tachycardia, sweating, and shortness of breath, which can be mistaken for obstetric emergencies. Management of these crises includes pharmacological interventions, such as the use of benzodiazepines in acute cases, and psychotherapeutic interventions, such as cognitive-behavioral therapy (CBT), with the long term objetive of stabilizing the patient. (MILLS; BERKOWITZ, 2011)

Management of anxiety disorders in pregnancy requires a multidisciplinary approach. Treatment should balance the benefits of the medication with the potential risks to the fetus. Psychologic therapies, such as cognitive-behavioral therapy (CBT), have been widely recommended as first line of treatment (AHMED et al., 2023). However, in more severe cases, the use of anxiolytic drugs, such as selective serotonin reuptake inhibitors (SSRIs), may be considered, although with close monitoring due to possible teratogenic effects.

#### 3.4 MOOD DISORDERS

Mood disorders, especially depression and bipolar disorder, are prevalent conditions during pregnancy. It is estimated that between 10% and 20% of pregnant women suffer from depression, which can result in adverse outcomes for both mother and fetus, such as intrauterine growth restriction and premature delivery (ALTSHULER; HENDRICK; COHEN, 2000). Bipolar disorder, in turn, may manifest more severely during pregnancy, and is often associated with severe manic or depressive episodes requiring immediate intervention (YONKERS et al., 2004).

Treatment of depression and bipolar disorder during pregnancy presents significant challenges. Antidepressants, such as SSRIs, are often used to manage depression, while mood stabilizers, such as lithium and lamotrigine, are essential for controlling bipolar disorder. However, both types of drugs present potential risks to the fetus, such as neonatal withdrawal syndrome and congenital malformations, respectively (OYEBODE et al., 2012). Thus, the management of these disorders should be highly individualized, considering the risks and benefits for both the mother and the fetus (YONKERS et al., 2011).

#### 3.5 PSYCHOSES IN PREGNANCY

Psychoses, particularly schizophrenia, brief psychotic disorder, or exacerbation of a bipolar disorder during pregnancy, represent one of the most serious psychiatric emergencies during pregnancy. Schizophrenia affects approximately 1% of the world population, and pregnancy can trigger acute exacerbations of the disease, requiring immediate hospitalization (WATKINS; NEWPORT, 2009). In addition, postpartum psychosis, which occurs at 1 to 2 in every 1000 births, is considered a high-risk psychiatric emergency, mainly due to the risk of self-harm and infanticide (O'HARA, 1987; MILLS; BERKOWITZ, 2011).

Treatment of psychoses during pregnancy requires immediate intervention due to the risk of violent or suicidal behavior, which can endanger both the mother and the fetus. It involves the judicious use of antipsychotics for stabilization of the patient. The choice of antipsychotic should take into account both efficacy in symptom control and fetal safety. Atypical antipsychotics, such as olanzapine and risperidone, have been

preferred over typical antipsychotics because of their more favorable side effect profile. However, the use of antipsychotics during pregnancy remains a controversial topic, with studies still diverging on long-term safety for the fetus. (WEBB et al., 2004; MILLS; BERKOWITZ, 2011).

#### 3.6 SUICIDAL RISK

Suicidal behavior is a major cause of maternal mortality, accounting for approximately 5% to 20% of maternal deaths in developed countries (WILSON et al., 2015). Pregnant women with mood disorders, especially those with severe depression or bipolar disorder, are at increased risk of suicidal ideation and suicide attempts (YONKERS et al., 2004). Early recognition of suicidal behaviors and the implementation of preventive interventions are crucial for the protection of the life of the pregnant woman and the fetus.

Management of suicidal risks during pregnancy should be immediate and intensive. In addition to hospitalization in severe cases, drug therapies and psychotherapies are required to stabilize the patient. Studies indicate that lithium, despite its teratogenic risks, can significantly reduce the risk of suicide in patients with bipolar disorder, provided that it is used under strict monitoring (YONKERS et al., 2011). However, the use of antidepressants in pregnant women with suicidal ideation should be done with caution, since these medications may, in some cases, increase the risk of impulsive behavior. In addition, in some cases, electroconvulsive therapy (ECT) may be considered, especially in patients with refractory depression or with imminent risk of suicide, due to its efficacy and safety during pregnancy (MILLS; BERKOWITZ, 2011).

#### 3.7 SUBSTANCE USE DISORDERS

The use of substances during pregnancy is a growing concern, especially due to its adverse impacts on fetal development. Use of alcohol, tobacco, and illicit drugs can lead to severe obstetric complications such as premature delivery, intrauterine growth restriction, neonatal withdrawal syndrome, congenital malformations, and fetal death. In addition, pregnant women with substance use disorders are more likely to

have psychiatric comorbidities, such as depression and anxiety, which further aggravates the clinical picture. (Committee Opinion No. 473, 2011; MILLS; BERKOWITZ, 2011).

Management of substance use disorders in pregnancy should include multifaceted interventions, ranging from supervised detoxification to ongoing psychosocial follow-up. Methadone or buprenorphine treatment programs have been effective in managing opioid dependence in pregnant women, reducing the risk of neonatal complications and improving maternal and fetal outcomes (AHMED et al., 2023). In addition, the involvement of multidisciplinary teams is essential to ensure comprehensive support and reduction of risks associated with substance use.

#### 3.8 EPIDEMIOLOGY AND MANAGEMENT

Epidemiological studies indicate that about 20% of pregnant women will experience some kind of psychiatric emergency during pregnancy or in the postpartum period (AHMED et al., 2023). These figures highlight the importance of early detection and adequate interventions to minimize negative impacts on maternal and neonatal health. Management of psychiatric emergencies during pregnancy should be based on specific clinical protocols that consider the particularities of this population, including the interactions between psychiatric treatments and obstetric risks.

In terms of management, continuous psychiatric follow-up during pregnancy is fundamental to ensure the emotional stability of the pregnant woman and to prevent complications. The use of psychotropic drugs, although often necessary, should be closely monitored, with dose adjustments according to the stage of pregnancy and potential teratogenic risks (OYEBODE et al., 2012). In addition, psychological support, counseling and participation in support groups can significantly improve psychiatric and obstetric outcomes.

#### 4. CONCLUSION

Psychiatric emergencies during pregnancy represent a significant challenge for health care professionals due to the need to balance the appropriate treatment of the mother with the safety of the fetus. Common psychiatric conditions include anxiety disorders, depression, bipolar disorder, and psychosis, which can have severe outcomes if left untreated. The management of these emergencies requires a multidisciplinary approach, involving carefully chosen pharmacological interventions and psychosocial support.

Early identification, proper management, and ongoing support are essential to minimize risks to the pregnant woman and fetus. Given the complexity of the interactions between mental health and the course of pregnancy, ongoing research and the development of specific clinical protocols are necessary to improve care for this vulnerable population.

The literature review suggests that, with proper management, it is possible to reduce the risks for both the mother and the fetus, although more research is still needed to improve the treatment of these conditions during pregnancy.

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Agência Brazileira ISBN ISBN: 978-65-6016-073-6