Pará Research Medical Journal

Artigo de Revisão Sistemática

SAÚDE DA MULHER

Advances in hormone therapy: a review of clinical effects and benefits of subcutaneous hormonal implants

Avanços na terapia hormonal: uma revisão dos efeitos clínicos e benefícios dos implantes hormonais subcutâneos

Beatriz Gili Moreira da Silva[1], José Abdon da Silva Filho[1], Paulo Cezar de Oliveira Junior[1], Thais Feres Menegario Zuppardo[2], José Roberto Mateus da Silva[3], Carlos Rocha Oliveira[1,4]

Summary **Purpose:** The aim of this review study is to evaluate and synthesize the existing literature regarding hormonal therapy through the use of subdermal implants in women, providing a comprehensive and up-to-date view on the role of hormonal implants in hormone replacement therapy. **Methods:** A systematic review using «Subdermal implants» and «Woman» like search terms. **Results:** Subcutaneous implants offer significant advantages in terms of treatment adherence, management, and relief of symptoms related to gynecological conditions, hormone replacement therapy, and treatment of hypogonadism symptoms during the pre- and post-menopausal periods. **Conclusion:** Therefore, hormonal implants are a valuable tool in managing hormonal conditions in women, offering a practical and effective alternative to traditional forms of hormone administration.

Keywords: drug implants; hormones; hormone replacement therapy.

Resumo: **Objetivo:** O objetivo deste estudo de revisão é avaliar e sintetizar a literatura existente sobre a terapia hormonal utilizando implantes subdérmicos em mulheres, fornecendo uma visão abrangente e atualizada sobre o papel desses implantes na terapia de reposição hormonal. **Métodos:** Realizou-se uma revisão sistemática com os descritores "implantes subdérmicos" e "mulher". **Resultados:** Os implantes subcutâneos apresentam vantagens relevantes em termos de adesão ao tratamento, manejo clínico e alívio de sintomas relacionados a condições ginecológicas, terapia de reposição hormonal e tratamento do hipogonadismo nos períodos pré e pós-menopausa. **Conclusão:** Os implantes hormonais constituem uma alternativa prática e eficaz às formas tradicionais de administração hormonal, sendo uma ferramenta valiosa no manejo das condições hormonais femininas.

Descritores: implantes farmacológicos; hormônios; terapia de reposição hormonal.

[1]Universidade Anhembi Morumbi, School of Medicine, São José dos Campos, SP, Brazil.
[2]Pontifícia Universidade Católica de Campinas, School of Pharmacology, Campinas, SP, Brazil.
[3]GAP Laboratory of Biotechonology, São José dos Campos, SP, Brazil.
[4]Universidade Federal de São Paulo, Post-graduation Program in Biomedical Engineering, São José dos Campos, SP, Brazil.
Funding: none
Conflicts of interest: The authors declare no conflicts of interest.
Received on: 10/12/2024
Accepted on: 02/25/2025

Work carried out at Universidade Anhembi Morumbi, São José dos Campos, SP, Brazil.

INTRODUCTION

The administration of sex hormones, both for hormone replacement therapy and contraception, became well established from the second half of the 20th century, driven by advances in medicine, particularly in the fields of sexual and reproductive physiology and endocrinology[1]. Initially, the first hormonal contraceptive was administered orally, followed by the development of other routes such as intramuscular, vaginal, transdermal, and subcutaneous[2].

The pharmaceutical industry sought increasingly effective and practical methods to facilitate the administration and dosing of hormones for various indications, resulting in the development of subcutaneous implants. In Brazil, these implants first appeared in the late 1960s, with studies conducted by Elsimar Coutinho[3]. Despite this, it was not until the 2000s that these implants entered the Brazilian pharmaceutical market as a safe, effective, and long-lasting option[4]. Currently, with technological advances, such implants are considered an accepted and effective method for hormonal treatment.

According to the United States Pharmacopeia, «Implant pellets are small, solid, sterile masses composed of an active pharmaceutical ingredient with or without excipients. They are usually administered through a special injector or by surgical incision. The release of the active ingredient from the pellet is typically controlled by diffusion and dissolution kinetics»[5].

These devices are available in various forms. However, two of the most commonly used are polymer-based forms, which may be either degradable or non-degradable, and mini-pumps, powered by osmotic pressure or mechanical forces. These devices are inserted subcutaneously into the loose interstitial tissues of the outer surface of the arm, the anterior surface of the thigh, or the lower abdomen[6].

Currently, there are various types of hormonal implants available on the market, each with different hormones in its composition. Among these, the etonogestrel implant, stands out as a long-acting contraceptive method. In Brazil, the duration of this implant is 3 years, as recommended by the manufacturer, and it is considered one of the most effective contraceptive methods. However, in other countries, this duration may be extended to up to 5 years of use[7].

For the purposes of hormone replacement therapy in women during perimenopause and postmenopause, as well as in cases of hormonal deficiency in specific situations, subdermal implants of estrogen, progesterone, and testosterone derivatives are used. These implants have shown high effectiveness in reducing and improving symptoms associated with these conditions[8].

Sex steroid hormones or ovarian hormones, such as estrogen, progesterone, and androgens, play a crucial role in female physiology, the reproductive system, and the success of pregnancy[9]. Throughout a woman's life, she experiences periods of biological transition, such as puberty, premenstrual regression of the corpus luteum, pregnancy/postpartum, and climacteric/menopause, which significantly affect the secretion and activity of sex hormones, particularly estrogens[10].

In women, three main estrogens—β-estradiol, estrone, and estriol—are responsible for maintaining secondary sexual characteristics. Among these, β-estradiol is the most important, secreted primarily by the ovaries and in smaller amounts by the adrenal glands[10]. Moreover, these hormones are also produced by adipose tissue and in the brain, where they act on specific receptors responsible for differentiation, modulate motor functions, pain sensitivity, and various cognitive functions, among other effects[10].

During the reproductive years, estrogen plays a crucial role in the proliferation and growth of specific cells in the female body, including the development of the breasts and external genitalia, as well as promoting pro-conceptive actions. This hormone also has a significant positive influence on bone and cardiovascular tissues. In addition to these physical functions, estrogen contributes to emotional, behavioral, and sexual characteristics typical of women by modulating cholinergic, serotonergic, noradrenergic, and dopaminergic systems, which directly impact mood[10].

Climacteric represents the transition from the reproductive phase to the non-reproductive phase in a woman's life, characterized by a significant reduction in estrogen levels compared to the reproductive years. Hypoestrogenism leads to a range of physiological impacts on the female population, including vasomotor symptoms, endocrine, metabolic, and genitourinary changes, among others[11].

Progestogens are steroid hormones that can be classified into two categories: natural and synthetic. Among natural progestogens, progesterones stand out, as they are found in high concentrations in the circulation and are produced in the ovaries and the reticular zone of the adrenal glands. Another example is 17α-hydroxyprogesterone, which is present in smaller quantities in the body[12].

In contrast, synthetic progestogens are divided into two main categories based on their chemical origin: progesterone derivatives and testosterone derivatives. Progesterone derivatives include compounds such as 17-hydroxyprogesterone and 19-norprogesterone. Testosterone derivatives, such as 19-nortestosterone, can be further subdivided into estranes (C-18) and gonanes (C-17). These synthetic progestogens are widely used for contraception and hormone replacement therapy[12].

Progesterone is a crucial endogenous hormone in the female biological cycle, closely associated with fertility and pregnancy. Its synthesis occurs from cholesterol via pregnenolone. During the menstrual cycle, progesterone is produced in the corpus luteum in the ovaries, and during pregnancy, by the placenta. Additionally, it is synthesized in smaller quantities by the adrenal cortex, adipose tissue, and nervous system, where it is produced by neurons and glial cells, exerting neurosteroid functions. Progesterone also acts in the nervous system tissues, serving as a neuroactive steroid[13-16].

From puberty to the reproductive years, this gonadal hormone is responsible for many essential physiological changes. Among its functions, it plays a key role in transforming the endometrium, which is crucial for maternal-fetal interaction, and in inhibiting the uncontrolled proliferation of the endometrium induced by estrogen. Additionally, progesterone contributes to the universal shedding of the endometrium and to a regular menstrual flow, as well as facilitating the secretion of endometrial glands, among other functions[10].

Androgens are substances that serve as precursors to estrogens and play a crucial role in female sexual desire. Their primary sources of production are the adrenal cortex and the ovaries. This hormonal group includes several substances, such as testosterone (T) and its free fraction (TL), androstenedione (A), dehydroepiandrosterone (DHEA), and DHEA sulfate (S-DHEA). The most active form is dihydrotestosterone (DHT), which is notable for its higher potency and affinity for the androgen receptor[11].

Throughout the reproductive life, plasma levels of androgens and Sex Hormone-Binding Globulin (SHBG) progressively decrease, especially with the onset of menopause. It is known that the peak of androgens in women occurs between ages 18 and 24. However, in women at age 65, there is a considerable reduction of 55% in total testosterone, 49% in free testosterone (TL), 77% in DHEA, and 64% in androstenedione. The latter is of significant hormonal importance in the postmenopausal period, as it serves as a substrate for peripheral aromatization and the formation of estrone[11].

Androgen deficiency developed after menopause leads to various negative changes in a woman's overall health. These changes manifest in several ways, including a decrease in bone mineral density, which results in reduced bone mass and an increased risk of fractures. Body composition is also affected, with a reduction in lean mass due to the progressive decline in basal metabolism and energy expenditure. The decrease in lean tissue reduces resting energy needs, and when combined with reduced physical activity without a corresponding decrease in caloric intake, leads to an accumulation of body fat. Additionally, female sexual function is influenced by the decline in hormones, affecting sexuality and behavior both centrally, with impacts on arousal and desire, and peripherally, impairing mucus production and genital lubrication. These changes also affect quality of life, leading to alterations in overall well-being, energy levels, dysphoric mood, fatigue, and increased incidence of depression[17].

Hormone Replacement Therapy (HRT) plays a crucial role in supplementing women with hormonal deficiencies and encompasses various medical indications. Key indications for HRT include reducing the effects of hypoestrogenism in women with primary and secondary amenorrhea, managing symptoms during the climacteric (the menopausal transition and postmenopause), as well as its use during the reproductive years in patients using GnRH analogs, known as «add-back» therapy. Estrogen is the primary hormone used in HRT. For women with a preserved uterus, a combined hormonal therapy (estrogen and progestogens) is required to ensure endometrial protection. In addition to its effectiveness in treating hormonal deficiencies, estrogens and progesterones are also widely used for contraception[9].

The route of administration analyzed in this study offers several significant pharmacodynamic advantages. By maintaining an adequate plasma concentration of the drugs, this approach allows for both localized delivery and systemic circulation of the medications, bypassing the first-pass metabolism in the liver and gastrointestinal tract. Furthermore, reducing or eliminating the need for frequent dosing by the patient contributes to greater adherence to the treatment, thereby optimizing therapeutic outcomes[6].

Therefore, the objective of this review study is to evaluate and synthesize the existing literature regarding hormone therapy through subdermal implant administration in women, providing a comprehensive and up-to-date overview of the role of hormonal implants in hormone replacement therapy.

METHODS

For the selection of studies, a search was conducted in the electronic databases PubMed and ScienceDirect. The following search terms were used: «Subdermal implants» and «Woman» and combinations of these terms connected by the operator «AND.» The collected data was made using the protocol PRISMA (Figure 1)[18].

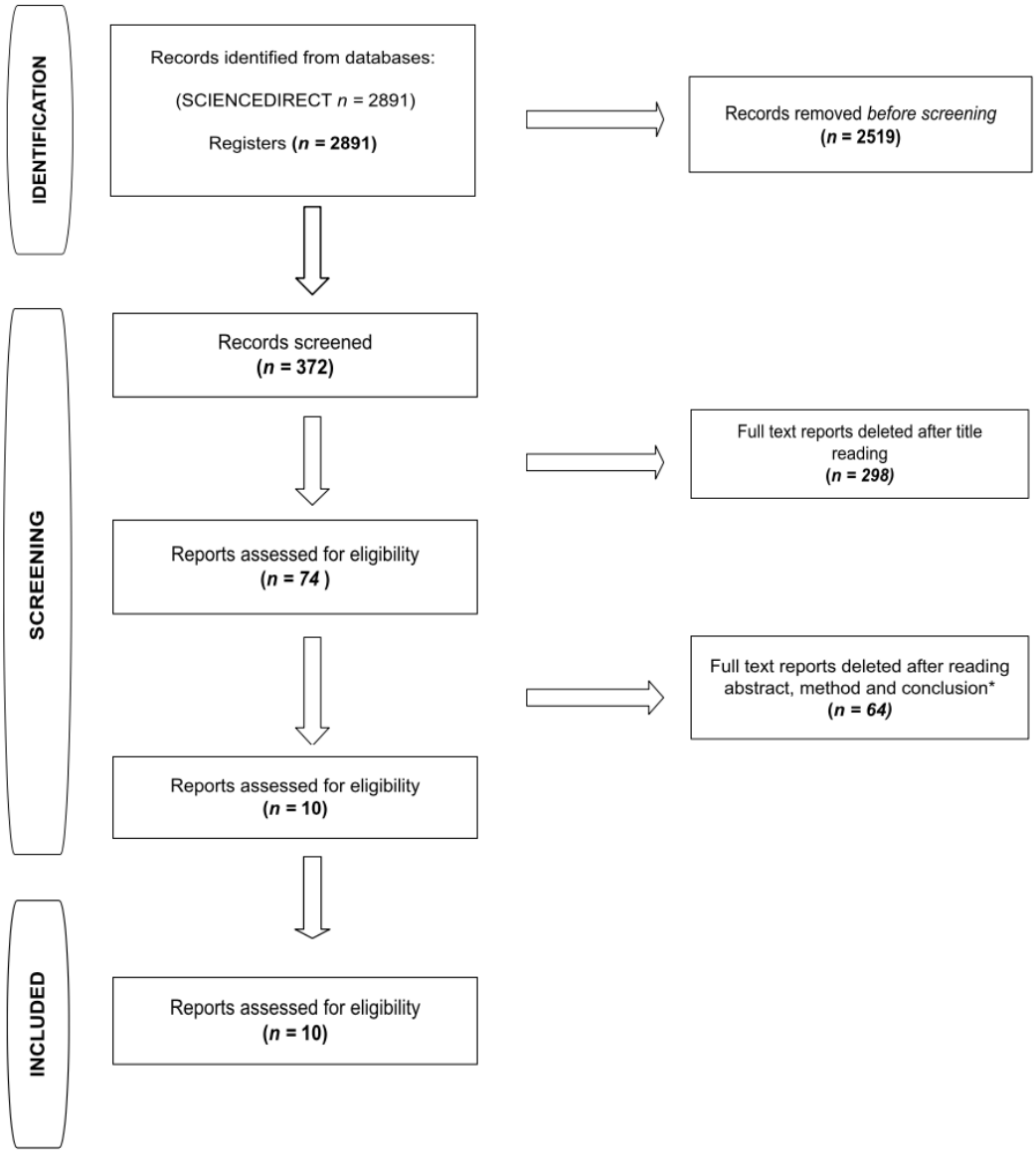

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for studies retrieved through the searching and selection process.

The inclusion criteria for the studies were: full-text publications, studies conducted between 2009 and 2024, clinical trials and reviews, studies involving human females who received hormones exclusively through subdermal implants (pellets) with no combination with other forms of administration. Exclusion criteria were: duplicates, articles not accessible in full, or those not meeting the inclusion criteria. Studies that did not appear in the initial search but met the objectives, intervention, and population of the review were included.

The study selection process was carried out in two stages. In the first stage, titles were examined to verify compliance with the inclusion criteria. In the second stage, the abstracts, methodologies, and conclusions of relevant studies were reviewed to confirm eligibility. Two independent reviewers conducted the selection, and any discrepancies were resolved by consensus or by a third reviewer.

As this is a literature review, no specific ethical approval was required. However, all included studies were conducted in accordance with applicable ethical principles and research standards.

RESULTS

The summary of results with study reference, used drugs and outcomes are ordered on Table 1.

Table 1. Summary of results containing: study reference, drug used, population studied and outcomes.

Hormone	Population	Dose of drug administered	Outcome	References
Etonogestrel	Adolescents with PCOS	Not specified	Good adherence to treatment compared to other routes of administration	Buyers et al. (2020)[19]
Etonogestrel	Women with endometriosis	Etonogestrel implant - 68 mg	↓pelvic pain,↓serum levels of CD23 and CA-125. Control of dysmenorrhe	Carvalho et al. (2018)[20]; Margatho et al. (2020)[21]
Testosterone	Women in premenopause and postmenopause with symptoms of androgen deficiency	Not specified	↓Irritability, ↓depressive symptoms, ↓anxiety, ↓vaginal dryness, ↓urogenital complications, ↓sexual dysfunction, ↓mental exhaustion, ↓muscular discomfort, ↓headache.	Glaser et al. (2011)[22]; Glaser et al. (2012)[23]
Testosterone (T) or Testosterone + Anastrozole (T + A)	Women with hormonal deficiency	Not specified	Protective factor for breast cancer	Glaser et al. (2013)[24]
Estradiol and Testosterone	Postmenopausal women	17-β-estradiol 4 x 50 mg; testosterone 2 x 40 mg	↑Bone matrix density	Renata et al. (2010)[25]
Estradiol	Women without a uterus experiencing menopausal symptoms	80-100 mg for 12 months	↓ Headache, ↓palpitations, ↓sleep disturbances, ↓tiredness, ↓fatigue, ↓paresthesias, ↓irritability, ↓loss of concentration, ↓depressive symptoms, ↓Hot flashes, ↓pain during intercourse, ↓vaginal dryness. ↑Serum levels of HDL.	Ione et al. (2009)[26]
Estradiol + Monogestrel Acetate	Women with a uterus experiencing menopausal symptoms	70-100 mg for 12 months	↓Headache, ↓palpitations, ↓sleep disturbances, ↓tiredness, ↓fatigue, ↓paresthesias, ↓irritability, ↓loss of concentration, ↓depressive symptoms, ↓Hot flashes, ↓vaginal dryness. ↑Serum levels of HDL.	Ione et al. (2009)[26]
Nestorone	Postmenopausal women	50 mg	↑Improved quality of life, ↑vitality, ↑social and mental health, ↑sexual function. ↓Pelvic pain, ↓fatigue.	Renke et al. (2023)[27]; Donovitz et al. (2023)[28]

PCOS: Polycystic Ovary Syndrome, HDL: High-Density Lipoprotein.

DISCUSSION

The use of etonogestrel implants in patients with Polycystic Ovary Syndrome (PCOS) has been meticulously described by Buyers et al.[19]. As an outcome, significantly higher adherence to treatment with etonogestrel implants was observed compared to other administration routes, such as pills and injections. Factors contributing to this outcome include the convenience provided by the implants, the reduction in the need for frequent medical interventions, and the mitigation of perceived adverse effects.

Women with endometriosis also benefited significantly from the use of subdermal implants. Clinical trials demonstrated effective control of pelvic pain and dysmenorrhea in patients with endometriosis who used etonogestrel implants[20]. Additionally, another clinical study found that in the group of women who received etonogestrel implants, there was a reduction in serum levels of CD23 and CA-125, biomarkers associated with endometriosis and other gynecological conditions such as gynecological tumors and pelvic inflammatory diseases[21].

The use of testosterone implants in pre- and postmenopausal women with symptoms of androgen deficiency revealed significant benefits. There was a reduction in irritability, depressive symptoms, and anxiety. Additionally, a decrease in vaginal dryness and urogenital complications was observed. Improvements were also noted in sexual dysfunctions, mental exhaustion, and muscle discomforts, as well as a reduction in the frequency of headaches[22,23].

Another study utilizing testosterone implants and/or testosterone combined with anastrozol in women with hormonal deficiency observed a significant reduction in the incidence of breast cancer in premenopausal and postmenopausal women[24].

Additionally, in postmenopausal women using implants of testosterone combined with estradiol, an increase in bone matrix density was observed in patients who used these implants[25].

In a study conducted on women who had undergone hysterectomy and were experiencing menopausal symptoms, the outcomes provided by the use of estradiol implants were elucidated. The treatment proved effective in alleviating headaches, palpitations, sleep disturbances, fatigue, tiredness, paresthesia, irritability, concentration deficit, and depressive symptoms. Additionally, there was a significant reduction in hot flashes, dyspareunia, and vaginal dryness, along with an increase in serum HDL levels[26]. In the same study, another group of women with a uterus and experiencing menopausal symptoms were treated with implants of estradiol in combination with monogestrel acetate. A significant reduction in headaches, palpitations, sleep disturbances, tiredness, fatigue, paresthesia, irritability, concentration deficit, and depressive symptoms was also observed. Additionally, there was a decrease in hot flashes and vaginal dryness, as well as an increase in HDL levels[26].

The use of nestorone implants in postmenopausal women resulted in improvements in quality of life, energy levels, social and mental health, and sexual function. Additionally, there was a reduction in pelvic and physical pain[27,28].

The administration of sex hormones, particularly through subcutaneous implants, represents a significant advancement in hormone replacement therapy and contraception, providing enhanced efficacy, convenience, and patient adherence to treatment. This study reviews the existing literature on the use of hormonal implants, focusing on therapeutic benefits and patient acceptance.

Subcutaneous implants offer significant advantages in terms of treatment adherence. The elimination of frequent dosing, as observed in studies with etonogestrel in patients with Polycystic Ovary Syndrome (PCOS), highlights the convenience and efficiency of this administration route. Adherence to treatment is crucial, especially in chronic conditions, where consistency in medication administration can determine therapeutic efficacy. The convenience of implants reduces the reliance on frequent medical interventions, a factor that contributes to improved quality of life for patients.

The efficacy of hormonal implants in managing gynecological conditions such as endometriosis is notable. Studies indicate that the use of etonogestrel implants results in effective control of pelvic pain and dysmenorrhea, as well as a reduction in serum levels of biomarkers associated with endometriosis, such as CD23 and CA-125. These findings suggest that implants not only mitigate symptoms but may also positively influence the pathogenesis of the disease.

Testosterone therapy with implants in premenopausal and postmenopausal women has shown significant benefits, including reduced irritability, depressive symptoms, anxiety, and vaginal dryness, along with improvements in sexual dysfunctions and overall quality of life. These findings are particularly relevant given the complexity of symptoms associated with androgen deficiency. Furthermore, the combination of testosterone with anastrozole demonstrated a reduction in breast cancer incidence, a crucial benefit that could significantly impact the clinical management of these patients.

Estradiol implants, especially when combined with testosterone, have demonstrated a positive impact on bone density in postmenopausal women. This effect is fundamental for the prevention of osteoporosis and fractures, conditions that profoundly impact morbidity and mortality in this population. The improvement in bone matrix density underscores the importance of hormonal implants in maintaining bone health in postmenopausal women.

The use of hormonal implants has proven effective in enhancing the quality of life and overall well-being of patients. Studies with estradiol implants in hysterectomized women reported alleviation of symptoms such as headaches, sleep disturbances, fatigue, irritability, and depressive symptoms. Additionally, the combination of estradiol with monogestrel acetate in women with a uterus demonstrated similar benefits, suggesting that this combination may be effective across a broader spectrum of patients.

CONCLUSION

Hormonal implants represent an effective and convenient form of hormonal therapy, offering significant benefits in terms of treatment adherence, symptom control, and improvement in patients' quality of life. The evidence reviewed in this study supports the use of hormonal implants as a viable and effective option for hormonal replacement therapy and contraception. However, individualization of treatment, considering the specific characteristics and needs of each patient, is crucial to maximize the benefits and minimize the risks associated with hormonal therapy.

Ongoing development and research on new hormonal formulations and combinations are essential to further enhance the efficacy and safety of hormonal implants. Additionally, long-term studies are necessary to evaluate the long-term effects of hormonal implants, particularly concerning cardiovascular health and cancer incidence.

In conclusion, hormonal implants are a valuable tool in the management of hormonal conditions in women, offering a practical and effective alternative to traditional forms of hormonal administration.

REFERENCES

1. Oudshoorn N. Beyond the Natural Body. Routledge; 2003.
2. Bruton LL, Hilal-dandan R. As bases farmacológicas da terapêutica de Goodman e Gilman. 13th ed. Porto Alegre: Grupo A; 2018.
3. Coutinho E. Menstruação, a sangria inútil. São Paulo: Gente; 1996.
4. Manica DT. A desnaturalização da menstruação: hormônios contraceptivos e tecnociência. Horiz Antropol. 2011;17(35):198-226. https://doi.org/10.1590/S0104-71832011000100007
5. United States Pharmacopeia (USP). USP Nomenclature Guidelines [Internet]. Rockville (MD): United States Pharmacopeia; [cited 2024 Set 2]. Available at: https://www.usp.org/sites/default/files/usp/document/usp-nomenclature-guidelines.pdf

6. Sinko PJ. Martin's physical pharmacy and pharmaceutical sciences. 8ª ed. Philadelphia: Lippincott Williams & Wilkins; 2023.

7. Manica DT. Supressão da menstruação: ginecologistas e laboratórios farmacêuticos representando natureza e cultura [Master's dissertation]. Campinas: Instituto de Filosofia e Ciências Humanas, Universidade Estadual de Campinas; 2003.

8. Manica DT. Contracepção, natureza e cultura: embates e sentidos na etnografia de uma trajetória [Doctoral thesis]. Campinas: Instituto de Filosofia e Ciências Humanas, Universidade Estadual de Campinas; 2009.

9. Lasmar RB. Tratado de Ginecologia. São Paulo: Grupo GEN; 2017.

10. Aires MDM. Fisiologia. 5ª ed. Rio de Janeiro: Grupo GEN; 2018.

11. Benetti-Pinto CL, Fernandes CE, Filho ALDS. Hormônios em ginecologia. São Paulo: Manole; 2023.

12. Freitas F, Costa-Paiva L, Pinto-Neto AM, Makuch MY, Pedro AO. Papel dos progestagênios na terapia hormonal do climatério [Internet]. São Paulo: Federação Brasileira das Associações de Ginecologia e Obstetrícia (FEBRASGO); 2006 [cited 2024 Set 2]. Available at: https://www.febrasgo.org.br/media/k2/attachments/06-PAPEL_DOS_PROGESTAGENIOS_NA_TERAPIA_HORMONAL_DO_CLIMATERIO.pdf

13. Sundström-Poromaa I, Comasco E, Sumner R, Luders E. Progesterone – Friend or foe? Front Neuroendocrinol. 2020;59:100856. https://doi.org/10.1016/j.yfrne.2020.100856

14. Zhang Y, Nadeau M, Faucher F, Lescelleur O, Biron S, Daris M, et al. Progesterone metabolism in adipose cells. Mol Cell Endocrinol. 2009;298(1-2):76-83. https://doi.org/10.1016/j.mce.2008.09.034

15. Rossato M, A Nogara, M Merico, Ferlin A, Foresta C. Identification of functional binding sites for progesterone in rat Leydig cell plasma membrane. Steroids. 1999;64(1-2):168-75. https://doi.org/10.1016/s0039-128x(98)00104-4

16. Stoffel-Wagner B. Neurosteroid metabolism in the human brain. Eur J Endocrinol. 2001;145(6):669-79. https://doi.org/10.1530/eje.0.1450669

17. Strufaldi R, De L, Pompei M. No 5 Androgênios na pós Menopausa [Internet]. [cited 2024 Aug 31]. Available from: https://www.febrasgo.org.br/images/comissoes/Androgenios_na_pos_menopausa_-_revisado.pdf

18. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71

19. Buyers E, Sass AE, Severn CD, Pyle L, Cree-Green M. Twelve-month continuation of the etonogestrel implant in adolescents with polycystic ovary syndrome. J Pediatr Adolesc Gynecol. 2021;34(1):33-9. https://doi.org/10.1016/j.jpag.2020.08.017

20. Carvalho N, Margatho D, Cursino K, Benetti-Pinto CL, Bahamondes L. Control of endometriosis-associated pain with etonogestrel-releasing contraceptive implant and 52-mg levonorgestrel-releasing intrauterine system: randomized clinical trial. Fertil Steril. 2018;110(6):1129-36. https://doi.org/10.1016/j.fertnstert.2018.07.003

21. Margatho D, Carvalho NM, Bahamondes L. Endometriosis-associated pain scores and biomarkers in users of the etonogestrel-releasing subdermal implant or the 52-mg levonorgestrel-releasing intrauterine system for up to 24 months. Eur J Contracept Reprod Health Care. 2020;25(2):133-40. https://doi.org/10.1080/13625187.2020.1725461

22. Glaser R, York AE, Dimitrakakis C. Beneficial effects of testosterone therapy in women measured by the validated Menopause Rating Scale (MRS). Maturitas. 2011;68(4):355-61. https://doi.org/10.1016/j.maturitas.2010.12.001

23. Glaser R, Dimitrakakis C, Trimble N, Martin V. Testosterone pellet implants and migraine headaches: A pilot study. Maturitas. 2012;71(4):385-8. https://doi.org/10.1016/j.maturitas.2012.01.006

24. Glaser RL, Dimitrakakis C. Reduced breast cancer incidence in women treated with subcutaneous testosterone, or testosterone with anastrozole: A prospective, observational study. Maturitas. 2013;76(4):342-9. https://doi.org/10.1016/j.maturitas.2013.08.002

25. Britto R, Araújo L, Barbosa I, Silva L, Rocha S, Valente AP. Hormonal therapy with estradiol and testosterone implants: bone protection? Gynecol Endocrinol. 2011;27(2):96-100. https://doi.org/10.3109/09513590.2010.489131

26. Barbosa IC, Coutinho EM, Oladapo L, Noronha CF, Mota RL, Lopes AC, et al. An open-label study of subdermal implants of estradiol-only versus subdermal implants of estradiol plus nomegestrol acetate: effects on symptom control, lipid profile and tolerability. Gynecol Endocrinol. 2009;25(4):269-75. https://doi.org/10.1080/09513590802632480

27. Renke G, Callizo C, Paes R, Antunes M, Michels G, Concha L, et al. Clinical approaches to nestorone subdermal implant therapy in women's health. Biomedicines. 2023;11(9):2586. https://doi.org/10.3390/biomedicines11092586

28. Donovitz G, Cotten M. Breast cancer incidence reduction in women treated with subcutaneous testosterone: testosterone therapy and breast cancer incidence study. Eur J Breast Health. 2021;17(2):150-6. https://doi.org/10.4274/ejbh.galenos.2021.6213

Autora correspondente

Beatriz Gili Moreira da Silva Universidade Anhembi Morumbi, Escola de Medicina Avenida Deputado Benedito Matarazzo, 6070
CEP: 2230-002, São José dos Campos, SP, Brasil. Email: beatrizmoreiraa1808@gmail.com

Informações sobre os autores:

BGMS, é acadêmica de medicina na Universidade Anhembi Morumbi. JASF é acadêmico de medicina na Universidade Anhembi Morumbi. PCOJ é acadêmico de medicina na Universidade Anhembi Morumbi. TFMZ é Farmacêutica pela Pontifícia Universidade Católica de Campinas. JRMS é médico pela Universidade Anhembi Morumbi e proprietário da GAP Laboratory of Biotechnology. CRO é PhD em Farmácia pela Universidade Federal de São Paulo.

Contribuição dos autores:

BGMS: Escrita – Primeira Redação, Escrita – Revisão e Edição, Curadoria de Dados. JASF: Escrita – Primeira Redação, Escrita – Revisão e Edição, Curadoria de Dados. PCOJ: Escrita – Primeira Redação, Escrita – Revisão e Edição, Metodologia, Administração do Projeto. TFMZ: Conceituação, Escrita – Revisão e Edição JRMS: Conceituação, Escrita – Revisão e Edição CRO: Conceituação, Supervisão, Escrita – Revisão e Edição, Validação, Análise Formal, Administração do Projeto.

Todos os autores leram e aprovaram a versão final submetida ao Pará Research Medical Journal.