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GLICOCORTICÓIDES SINTÉTICOS E FERTILIDADE: UMA REVISÃO SOBRE OS MECANISMOS FARMACOLÓGICOS E O IMPACTO NO EIXO HIPOTÁLAMO-HIPÓFISE-GONADAL

GLUCOCORTICOIDES SINTÉTICOS Y FERTILIDAD: UNA REVISIÓN DE LOS MECANISMOS FARMACOLÓGICOS Y EL IMPACTO EN EL EJE HIPOTÁLAMO-HIPÓFISIS-GONADAL

SYNTHETIC GLUCOCORTICOIDS AND FERTILITY: A REVIEW OF PHARMACOLOGICAL MECHANISMS AND IMPACT ON THE HYPOTHALAMIC-PITUITARY-GONADAL AXIS

Apresentação: Comunicação Oral

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RESUMO

O objetivo desta revisão de literatura é avaliar o impacto dos glicocorticoides (GCs) sintéticos na fertilidade, analisando seus efeitos sobre o eixo hipotálamo-hipófise-gonadal (HHG) e as implicações clínicas do seu uso. Apoiada em uma revisão bibliográfica sistemática de artigos científicos, esta análise explora a complexa interação entre o eixo HHG, que regula a reprodução, e o eixo hipotálamo-hipófise-adrenal (HPA), ativado pelo estresse. Estudos como o de Whirledge e Cidlowski (2013, 2018) demonstram que o eixo HHG opera através de uma cascata hormonal (GnRH, LH, FSH) para governar a gametogênese e a esteroidogênese , enquanto o eixo HPA libera cortisol como principal mediador do estresse. Os resultados indicam que níveis elevados de GCs, endógenos ou farmacológicos, exercem um efeito supressor sobre o eixo HHG em múltiplos níveis, inibindo a secreção de gonadotrofinas e prejudicando diretamente a função gonadal. Em homens, isso resulta em espermatogénese deficiente e redução da testosterona. Em mulheres, causa desregulação do ciclo ovariano e pode comprometer a implantação embrionária. Contudo, a revisão revela um papel dual paradoxal,

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apresentado - dentre outros - por Silva *et al.* (2014), : os níveis fisiológicos de GCs são essenciais para a função reprodutiva, sendo que tanto a deficiência (adrenalectomia) quanto o excesso são prejudiciais. Este paradoxo estende-se ao uso clínico em tecnologias de reprodução assistida (TRA), onde, apesar de seu uso para modular a resposta imune, meta-análises não suportam sua eficácia rotineira para a população geral de FIV, embora subgrupos específicos com condições autoimunes possam se beneficiar. Conclui-se que a exposição a níveis supra fisiológicos de GCs representa um fator adverso significativo para a fertilidade. O manejo clínico de pacientes em idade reprodutiva deve, portanto, ponderar cuidadosamente os riscos de disfunção reprodutiva frente aos benefícios terapêuticos desses fármacos

Palavras Chave: Infertilidade, gametogênese, glicocorticóides, eixo hipotálamo-hipófise-gonadal.

RESUMEN

El objetivo de esta revisión de literatura es evaluar el impacto de los glucocorticoides (GCs) sintéticos en la fertilidad, analizando sus efectos sobre el eje hipotálamo-hipófisis-gonadal (HHG) y las implicaciones clínicas de su uso. Apoyada en una revisión bibliográfica sistemática de artículos científicos, este análisis explora la compleja interacción entre el eje HHG, que regula la reproducción, y el eje hipotálamo-hipófisis-adrenal (HPA), activado por el estrés. Estudios como el de Whirledge y Cidlowski (2013, 2018) demuestran que el eje HHG opera a través de una cascada hormonal (GnRH, LH, FSH) para gobernar la gametogénesis y la esteroidogénesis, mientras que el eje HPA libera cortisol como principal mediador del estrés. Los resultados indican que niveles elevados de GCs, endógenos o farmacológicos, ejercen un efecto supresor sobre el eje HHG en múltiples niveles, inhibiendo la secreción de gonadotropinas y perjudicando directamente la función gonadal. En hombres, esto resulta en una espermatogénesis deficiente y una reducción de la testosterona. En mujeres, causa desregulación del ciclo ovárico y puede comprometer la implantación embrionaria. Sin embargo, la revisión revela un papel dual paradójico, presentado —entre otros— por Silva et al. (2014): los niveles fisiológicos de GCs son esenciales para la función reproductiva, siendo que tanto la deficiencia (adrenalectomía) como el exceso son perjudiciales. Esta paradoja se extiende al uso clínico en tecnologías de reproducción asistida (TRA), donde, a pesar de su uso para modular la respuesta inmune, los metaanálisis no respaldan su eficacia rutinaria para la población general de FIV, aunque subgrupos específicos con condiciones autoinmunes puedan beneficiarse. Se concluye que la exposición a niveles suprafisiológicos de GCs representa un factor adverso significativo para la fertilidad. El manejo clínico de pacientes en edad reproductiva debe, por lo tanto, ponderar cuidadosamente los riesgos de disfunción reproductiva frente a los beneficios terapéuticos de estos fármacos.

Palabras Clave: Infertilidad, gametogénesis, glucocorticoides, eje hipotálamo-hipófisis-gonadal.

ABSTRACT

The objective of this literature review is to evaluate the impact of synthetic glucocorticoids (GCs) on fertility, analyzing their effects on the hypothalamic-pituitary-gonadal (HPG) axis and the clinical implications of their use. Supported by a systematic bibliographic review of scientific articles, this analysis explores the complex interaction between the HPG axis, which regulates reproduction, and the hypothalamic-pituitary-adrenal (HPA) axis, activated by stress. Studies such as those by Whirledge and Cidlowski (2013, 2018) demonstrate that the HPG axis operates through a hormonal cascade (GnRH, LH, FSH) to govern gametogenesis and steroidogenesis, while the HPA axis releases cortisol as the primary stress mediator. The results indicate that elevated levels of GCs, whether endogenous or pharmacological, exert a suppressive effect on the HPG axis at multiple levels, inhibiting gonadotropin secretion and directly impairing gonadal function. In men, this results in deficient spermatogenesis and reduced testosterone. In women, it causes deregulation of the ovarian cycle and can compromise embryo implantation. However, the review reveals a paradoxical dual role, presented—among others—by Silva et al. (2014): physiological levels of GCs are essential for reproductive function, with both deficiency (adrenalectomy) and excess being detrimental. This paradox extends to their clinical use in assisted reproductive technologies (ART), where, despite their use to modulate the immune response, meta-analyses do not support their routine efficacy for the general IVF population, although specific subgroups with autoimmune conditions may benefit. It is concluded that exposure to supraphysiological levels of GCs represents a significant adverse factor for fertility. The clinical management of patients of reproductive age must, therefore, carefully weigh the risks of reproductive dysfunction against the therapeutic benefits of these drugs.

Keywords: Infertility, gametogenesis, glucocorticoids, hypothalamic-pituitary-gonadal axis.

INTRODUCTION

Synthetic glucocorticoids are drugs characterized by their structural and functional similarity to cortisol, a steroid hormone naturally produced by the adrenal glands in response to stress and for metabolic regulation. Possessing potent anti-inflammatory and immunosuppressive effects, these compounds act by inhibiting inflammatory mediators such as cytokines—a group of proteins that modulate the immune response—and prostaglandins, lipid compounds involved in pain and inflammation. They are essential in the treatment and management of various pathologies, particularly autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis, as well as severe allergic and respiratory conditions like asthma and atopic dermatitis. Glucocorticoids also play a crucial role in preventing transplant rejection and are used as adjuvants in chemotherapy protocols (Kim, 2021).

Despite their therapeutic efficacy, the extensive and prolonged use of these drugs is associated with a range of adverse effects impacting multiple physiological systems. Conditions such as osteoporosis, hyperglycemia, myopathies, and mood disorders are common among patients undergoing continuous treatment, representing a significant clinical challenge (Schimmer and Farrow, 2019). Among these, the impact on the hypothalamic-pituitary-gonadal (HPG) axis (see Figure 1) is particularly notable. According to Aires (2021), this axis begins with the release of gonadotropin-releasing hormone (GnRH) by the hypothalamus, which then stimulates the anterior pituitary to secrete the gonadotropic hormones FSH and LH. These, in turn, act on the male and female gonads. This system is vital for the hormonal regulation of reproductive function through the coordinated secretion of GnRH, gonadotropins, and sex hormones such as testosterone and estrogen. Dysregulation of this axis can result in numerous complications affecting both male and female fertility (Quenby et al., 2005).

Thus, this literature review aims to evaluate the alterations that occur in the hypothalamic-pituitary-gonadal axis when exposed to synthetic glucocorticoids and their impact on fertility. It also seeks to identify the physiological role of this axis and its consequence on gonadotropin release; verify the mechanisms of suppression by glucocorticoids on the action of GnRH (Gonadotropin-releasing hormone); and finally, analyze how impairment in users' fertility manifests clinically.

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THEORETICAL FRAMEWORK

Reproductive function is regulated, in both men and women, by the central nervous system—more specifically, in the hypothalamus (Joseph and Whirledge, 2017). This organ acts as the main command center, integrating neural and hormonal signals to govern reproduction. The primary hypothalamic effector agent is GnRH, Gonadotropin-Releasing Hormone, a decapeptide that is synthesized and secreted by specialized neurons located predominantly in the arcuate nucleus of the hypothalamus (Whirledge and Cidlowski 2018; Guyton and Hall, 2021).

After GnRH synthesis, it is not released directly into the general systemic circulation. Instead, it is secreted into the hypothalamic-hypophyseal portal system. This system directly connects the hypothalamus to the anterior pituitary (adenohypophysis) (Whirledge and Cidlowski, 2013). It ensures that GnRH reaches its destination in high concentrations, thus preventing dilution or degradation, which allows for precise and rapid control over pituitary function (Guyton and Hall, 2021).

As stated by Molina (2021), a fundamental characteristic for the physiological action of GnRH is its pulsatile secretion, that is, an intermittent release that occurs in pulses with varying frequency and amplitude. This is extremely important for stimulating the pituitary to secrete its gonadotropins. A continuous (i.e., non-pulsatile) secretion of GnRH leads to the desensitization of its receptors in the pituitary, resulting in the suppression of the response and, consequently, the inhibition of the entire reproductive axis (Joseph and Whirledge, 2017).

When GnRH reaches the anterior pituitary through the portal system, it binds to specific membrane receptors on a population of cells called gonadotrophs (Wagner and Claus, 2004). The activation of these receptors by GnRH triggers an intracellular signaling cascade, resulting in the synthesis and release of Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH). Both are glycoproteins that act as messengers between the brain and the gonads (Falhammar et al., 2012).

According to Guyton and Hall (2021), once secreted into the general circulation, LH and FSH travel through the body until they reach their target organs, the gonads. It is there that these hormones exert their final functions, stimulating the production of sex steroid hormones (steroidogenesis) and the development and maturation of gametes (gametogenesis) (Whirledge and Cidlowski, 2013).

In the testes, LH and FSH act on distinct cell types to orchestrate testicular function: LH primarily targets the Leydig cells, located in the interstitial tissue, while FSH acts on the Sertoli cells, located inside the seminiferous tubules (Falhammar et al., 2012). The function of LH in

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this context is to stimulate these cells to produce testosterone, the main male androgen. FSH initiates spermatogenesis, aided by the high concentration of testosterone, ensuring the continuous and efficient production of mature sperm (Wagner and Claus, 2004).

In the ovaries, the action of LH and FSH governs the phases of the menstrual cycle, making it dynamic, cyclical, and orchestrated. FSH is the dominant hormone in the first half of the cycle, the follicular phase (Cauldwell et al., 2025). Its function is to stimulate the recruitment and growth of a group of ovarian follicles. As these follicles develop, their cells (especially the granulosa cells) produce increasing amounts of estrogen, primarily estradiol (Vila and Fleseriu, 2020).

According to Yong et al. (2002), LH has a dual and crucial function. During the follicular phase, it acts on the theca cells of the follicles to produce androgens, which are readily converted into estrogen by the adjacent granulosa cells (a process known as the two-cell, two-gonadotropin theory). The exponential increase in estrogen culminates in the mid-cycle LH surge, the endocrine event that serves as the indispensable trigger for ovulation, i.e., the release of the egg (Jeon et al., 2023). After ovulation, in the luteal phase, LH sustains the corpus luteum (the remaining structure of the follicle), which becomes the body's main source of progesterone (Whirledge and Cidlowski, 2013). Local regulation of glucocorticoids, through the expression of 11β-HSD enzymes in granulosa cells, also plays an important role; expression shifts from the type 2 (inactivating) isoform to the type 1 (activating) isoform during luteinization, favoring the accumulation of active cortisol in the pre-ovulatory follicular environment (Thurston et al., 2003).

However, for everything to happen in a coordinated manner, the hypothalamic-pituitary-gonadal axis is regulated by a feedback system, in which gonadal hormones modulate the activity of the hypothalamus and pituitary. It is through this control that hormonal homeostasis and the adjustment of reproductive function to the body's physiological needs are achieved (Joseph and Whirledge, 2017).

In practice, negative feedback in men works through testosterone, which exerts it at two levels: in the hypothalamus, by inhibiting the frequency of GnRH pulses, and in the pituitary, by decreasing the sensitivity of gonadotrophs to GnRH, which mainly reduces LH secretion. To control FSH, Sertoli cells, upon being stimulated for spermatogenesis, secrete a peptide hormone called inhibin (Kirby et al., 2009). Inhibin acts directly on the pituitary to selectively inhibit FSH secretion without significantly affecting LH. Thus, the system has two control circuits: one for testosterone (via LH) and another for spermatogenesis (via FSH) (Falhammar et al., 2012).

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In women, during most of the menstrual cycle (early follicular phase and luteal phase), estrogen (at moderate levels) and progesterone exert potent negative feedback on the hypothalamus and pituitary, keeping FSH and LH levels relatively low. This is important to allow only one follicle to become dominant and to prevent new follicular recruitment after ovulation. Exclusive to the female cycle, positive feedback is the event that enables ovulation (Whirledge and Cidlowski, 2018).

In the late pre-ovulatory phase, the rapidly growing dominant follicle produces exponential levels of estrogen. When the estrogen concentration exceeds a critical threshold and remains high for a sustained period (approximately 48 hours), its effect on the axis reverses: from inhibitory, it becomes stimulatory. This positive feedback causes an increase in the frequency of GnRH pulses and, most importantly, drastically increases the pituitary's sensitivity to GnRH, culminating in the so-called "LH surge." It is this LH surge that induces the final maturation of the egg and the rupture of the follicle, i.e., ovulation (Jeon et al., 2023). Conditions such as spondyloarthritis can impact female fertility through mechanisms involving inflammation and hormonal imbalances, and the use of glucocorticoids is common in its treatment, although with mixed effects on fertility (Bindoli et al., 2024). Furthermore, women with hypopituitarism or primary adrenal insufficiency also face significant fertility challenges and require careful management of hormone replacement, including hydrocortisone, during pregnancy to ensure favorable outcomes (Cauldwell et al., 2025).

These mechanisms have been studied in various living beings, showing that the need to reallocate resources during stress directly contributes to the individual's fertility. Since the body is directing its stimuli to respond to situations of anxiety, malnutrition, and various stressors, glucocorticoids end up decelerating the production and circulation processes of LH, FSH, and testosterone in males (Falhammar et al., 2012; Whirledge and Cidlowski, 2010). Furthermore, as discussed in the research by Whirledge and Cidlowski (2010), endogenous and synthetic glucocorticoids also play a role in ovarian development. Endogenous GCs, in situations of infectious stress, suppress LH action, either through the action of prostaglandins (PGs) or tumor necrosis factor-α (TNF-α). However, the same authors argue that pre-treatment with glucocorticoids can reduce the suppression induced by TNF-alpha in studies with rats, exhibiting GCs as a factor in maintaining the secretion of this hormone in cases of inflammatory stress (Orazizadeh, Khorsandi, & Hashemitabar, 2009).

In some cases, authors advocate for the use of corticosteroid therapy to improve fertility, especially in assisted reproductive technologies (ART), such as in vitro fertilization (IVF). This is a central theme in the debate on using glucocorticoids to improve fertility,

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precisely because of their potent anti-inflammatory and immunosuppressive action, which would increase the chances of success in the procedures (Robertson et al., 2016). The theory is that by suppressing an "abnormal" immune response, they could improve endometrial receptivity and embryo implantation rates, especially in women with repeated implantation failure or recurrent miscarriage. Some studies have suggested that they could "normalize" immune cell populations in the uterus, such as Natural Killer (NK) cells (Kim, 2021). However, for the general population of IVF patients, there is no clear evidence of benefit. The Cochrane meta-analysis (Boomsma et al., 2012) found no significant improvement in the live birth rate with the use of glucocorticoids. There was a borderline significant increase in the pregnancy rate in standard IVF cycles (but not in ICSI), but this did not translate into more babies born (Leroy et al., 2015).

Parallel to the reproductive axis, the body has a central system for responding to stress stimuli (whether physical, like an infection, or psychological): the Hypothalamic-Pituitary-Adrenal (HPA) axis. The cascade begins in the hypothalamus with the secretion of Corticotropin-Releasing Hormone (CRH). CRH travels through the pituitary portal system to the anterior pituitary, where it stimulates corticotrophic cells to release Adrenocorticotropic Hormone (ACTH) (Kim, 2021). ACTH, in turn, enters the systemic circulation, and its main target is the cortex of the adrenal gland. There, it stimulates the synthesis and secretion of cortisol, the main endogenous glucocorticoid in humans. As in the HPG axis, cortisol exerts strong negative feedback on the hypothalamus and pituitary, inhibiting the secretion of CRH and ACTH to end the stress response when the stimulus ceases (Whirledge and Cidlowski, 2018). Cortisol is vital for survival, orchestrating responses aimed at restoring homeostasis, such as increasing blood glucose (to provide energy), modulating the immune response, and suppressing inflammatory processes (Joseph and Whirledge, 2017).

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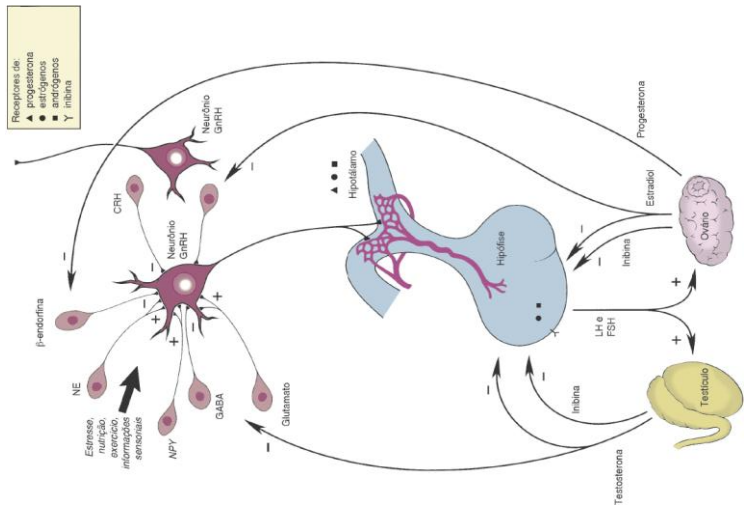
Figure 1. Hypothalamic-Pituitary-Gonadal Axis



Source: Aires (2018).

Corroborating these facts, Matsuwaki et al. (2003) showed in their tests with rodents that injections of tumor necrosis factor-alpha caused a severe suppression of pulsatile luteinizing hormone secretion in ovariectomized and adrenalectomized rats, while only slightly affecting the pulsatility of luteinizing hormone in ovariectomized rats, suggesting that the adrenal gland has a protective effect on the gonadotropin-releasing hormone pulse generator in stressful conditions. Subsequently, this pulsatility recovered after replacement with corticosterone (similar to human cortisol) in rats that underwent both procedures. Betamethasone treatment in rats has also been shown to reduce epididymal sperm count and fertility rates (Gouyandeh et al., 2015).

Synthetic glucocorticoid drugs, such as prednisone, dexamethasone, and methylprednisolone, are developed to mimic and, in most cases, amplify the anti-inflammatory and immunosuppressive actions of cortisol (Leroy et al., 2015). They exert their effects by binding to the same intracellular glucocorticoid receptors (GRs) that cortisol uses, which are present in virtually all tissues of the human body (Whirledge and Cidlowski, 2018).

The main difference between endogenous cortisol and synthetic GCs lies in their pharmacological potency and duration of action. Many synthetic compounds are significantly more potent and have a longer half-life than cortisol. When administered in pharmacological doses (usually much higher than physiological levels of cortisol), these drugs exert extremely potent negative feedback on the HPA axis, leading to the suppression of endogenous CRH and

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ACTH production. It is this potent action, both in peripheral tissues and in the central nervous system, that makes them effective therapeutic tools, but also the source of their multiple adverse effects (Kim, 2021)

Therefore, it can be inferred that the interaction between the HPA and HPG axes is antagonistic, as the function of the HPA is to prioritize survival. In situations of high stress, whether through endogenous corticosteroids or the use of drugs that increase corticosteroid levels in the body, reproductive function is suppressed (Joseph and Whirledge, 2017).

METHODOLOGY

This explanatory study presents a quantitative-qualitative approach and was conducted through a bibliographic search in the following databases: Google Scholar, PubMed, and Scielo. To ensure reproducibility, the following descriptors were used in all 3 databases: *corticosteroids and fertility*, *betamethasone and fertility*, *dexamethasone and fertility*, *hypothalamic-pituitary-adrenal*, *Hypothalamic-Pituitary-Gonadal*, *glucocorticoids and fertility*, *glucocorticoids and adverse effects*. These sites were selected due to the ease of conducting searches within the pre-established criteria that will be presented throughout the text.

Initially, only journals published from the year 2000 onwards were selected. This ensures the recency of the data used in this research, since, for a study based on medical and pharmaceutical concepts, the timeliness and accuracy of the facts are of utmost importance. However, exceptions to this chronological period were made for the books: "Endocrine Physiology" by Molina (2021), "Physiology" by Aires (2018), and "Textbook of Medical Physiology" by Guyton and Hall (2021). This was only done because these works are considered classics in their fields of research and are widely disseminated within the academic community.

In parallel with this limitation, the Qualis Capes classification of the articles was also used as a selection criterion, thus ensuring the reliability of the works used. Therefore, only journals from strata A and B were used, which, together with the classic works, created a theoretical foundation with well-regarded and widely circulated academic productions. Due to these specifications, it was also decided to select articles from the bibliographic references of the journals retrieved from the databases. However, for these productions, only the chronological limitation was applied to maintain their contemporaneity.

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Based on the adopted procedures, the obtained results were systematized and cataloged in the form of summaries and spreadsheets, using Excel and Google Docs software. The mention of specific glucocorticoids in the selected scientific articles was counted and analyzed, with theoretical works (books and manuals) being excluded. This organization allowed for the creation of a structured database, ensuring not only the preservation and secure storage of the information but also facilitating data retrieval for subsequent consultations and analyses, which formed the basis for the discussion of the results presented in the study.

RESULTS AND DISCUSSION

The analysis of these studies allowed for the identification of patterns regarding the mechanisms of action of GCs and their impact on fertility, as well as the observation of a clinical paradox in the therapeutic use of these medications. When searching the seven descriptors, the results described in the table below were found.

Table 1. Number of results per database for each search term

	Scielo	PubMed	Google Academic
Glucocorticoids and fertility	0	816	52.400
Corticosteroids and fertility	1335	1423	48200
Betamethasone and fertility	75	21	4580
Dexamethasone and fertility	575	228	46100
Hypothalamic-pituitary-adrenal	117	16,524	421000
Hypothalamic-Pituitary-Gonadal	15	3458	61500
Glucocorticoids and adverse effects	9	55135	399000

Source: Author (2025).

The main finding in the literature is the dual use of glucocorticoids. At normal levels, cortisol is essential for ensuring homeostasis and proper reproductive function. Studies such as that by Silva et al. (2014) demonstrate that the absence of GCs results in testicular dysfunction and decreased spermatogenesis, which highlights the need for these hormones to maintain reproductive life. During the follicular phase, before the LH peak that triggers ovulation, there is a suppression of the expression of the 11ßHSD2 enzyme and an increase in 11ß-hydroxysteroid dehydrogenase type 1 (11ßHSD1), which primarily acts as a reductase,

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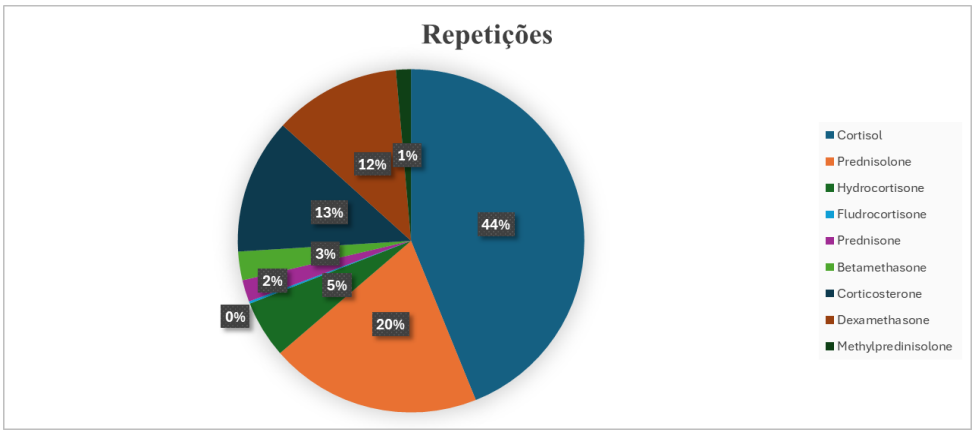
activating cortisone into cortisol. This increase in cortisol production functions as an endogenous anti-inflammatory mechanism to resolve ovulatory inflammation and assist in the formation of the corpus luteum (Yong et al. 2002). Similarly, Whirledge et al. (2015) show that the glucocorticoid receptor in the uterus is indispensable for embryo implantation and decidualization.

However, exposure to high levels of glucocorticoids, whether from stress or drug use, has been shown to be detrimental, acting as a suppressor of the hypothalamic-pituitary-gonadal (HPG) axis. Articles such as Whirledge and Cidlowski (2013, 2018) detail that this occurs via the modulation of neuropeptides, which in turn interrupt the signaling necessary for reproduction to occur. In the testes, GCs induce apoptosis of Leydig cells, which directly impairs spermatogenesis. Studies in rodents, as demonstrated by Gouyandeh et al. (2015) with dexamethasone and betamethasone, confirmed a reduction in sperm count and consequently in fertility. In the ovaries, inflammation can be considered analogous to a natural inflammatory process (Whirledge and Cidlowski, 2013), and therefore, while glucocorticoids can help regulate it locally, exogenous excess dysregulates this cycle, having more adverse than favorable actions.

During the research, it was observed that "cortisol" is the most discussed corticosteroid, appearing 407 times in the selected articles, which was expected, as it is the main endogenous hormone in studies on the physiology of the HPA axis in response to stress. Furthermore, other drugs were also cited several times, as shown in Figure 2. Regarding the visibility and quantity of studies focused on synthetic glucocorticoids, a significant increase in the repetition of GRs was observed when their names are used as descriptors, as shown in Figure 3.

Figure 2. Pie chart showing the frequency of drug mentions.



Source: Author (2025).

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Figure 3: Relationship between authors, titles, and the number of repetitions of glucocorticoids.

Autores	Título	Glicocorticoides (n° de repetições)
Leroy et al. (2015)	Regulation of 11β-hydroxysteroid dehydrogenase type 1 Immunosuppressive drugs and fertility	Cortisol (19) -
Kim (2021)	Glucocorticoid therapy in assisted reproduction	Prednisolone (2), Dexamethasone (4)
Kawasaki, Fuji e Winters (2000)	Follistatin production by skin fibroblasts and its regulation by dexamethasone	Dexamethasone (22)
Joseph e Whirlegde (2017)	Stress and the HPA Axis: Balancing Homeostasis and Fertility	Cortisol (26), Corticosterone (5), Dexamethasone (9)
Jeon et al. (2023)	Cortisol/glucocorticoid receptor: a critical mediator of the ovulatory process and luteinization in human periovulatory follicles	Cortisol (79), Corticosterone (10)
Gouyandeh et al. (2015)	Long-term Effects of Betamethasone on Epididymal Tissue, Epididymal Sperm Counts and Fertility in Male Mice.	Betamethasone (24), Dexamethasone (3)
Falhammar et al. (2012)	Fertility, sexuality and testicular adrenal rest tumors in adult males with congenital adrenal hyperplasia	Prednisolone (2), Hydrocortisone (2), Fludrocortisone (2)
Cauldwell et al. (2025)	Pregnancy Outcomes in Women With Primary Adrenal Insufficiency: Data From a Multicentre Cohort Study	Cortisol (2), Presnisolone (4), Hydrocortisone (27)
Bindoli et al. (2024)	Fertility issues in women of childbearing age with spondyloarthritis	Prednisone (3)
Amin et al. (2021)	ABVD and BEACOPP regimens' effects on fertility in young males with Hodgkin lymphoma	Prednisolone (2)
Revelli et al. (2009)	A retrospective study on IVF outcome in euthyroid patients with anti-thyroid antibodies: effects of levothyroxine, acetyl salicylic acid and prednisolone adjuvant treatments	Prednisolone (8)
Quenby et al. (2005)	Prednisolone reduces preconceptual endometrial natural killer cells in women with recurrent miscarriage	Prednisolone (28)
M. Orazizadeh, L. S. Khorsandi & M. Hashemitabar (2009)	Toxic effects of dexamethasone on mouse testicular germ cells	Dexamethasone (4)
Kirby et al. (2009)	Stress increases putative gonadotropin inhibitory hormone and decreases luteinizing hormone in male rats	Corticosterone (18)
Dan et al. (2005)	Unexplained Recurrent Miscarriage and in Routine Intracytoplasmic Sperm Injection: A Meta-Analysis	(2)
Boomsma et al. (2022)	Peri-implantation glucocorticoid administration for assisted reproductive technology cycles (Review)	Prednisolone (35), Prednisone (5), Dexamethasone (14, Methylprednisolone (13)

Source: Author (2025).

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CONCLUSIONS

This review has demonstrated the relationship between synthetic glucocorticoids and the hypothalamic-pituitary-gonadal axis, which confirms the impact of drugs with this formulation on fertility. It was also verified that the administration of GCs acts as a suppressor of the Hypothalamic-pituitary-gonadal axis (Whirledge and Cidlowski, 2013, 2018). Clinically, this impairment will manifest in men as a reduction in spermatogenesis due to apoptosis of Leydig cells, proven by animal studies, and with the dysregulation of the ovarian cycle in women. In general, a significant decrease in fertility is manifested (Matsuwaki et al. 2003).

Paradoxically, authors were found who advocate the use of these medications for treatment and to increase success rates in cases of patients who underwent in vitro fertilization. However, current evidence does not present consistent arguments to justify such a practice broadly. The research thus reiterates that the exposure of patients to high levels of synthetic glucocorticoids is a significant adverse factor for fertility, making awareness of these risks extremely relevant in the clinical management of patients of reproductive age (Boomsma et al., 2012).

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