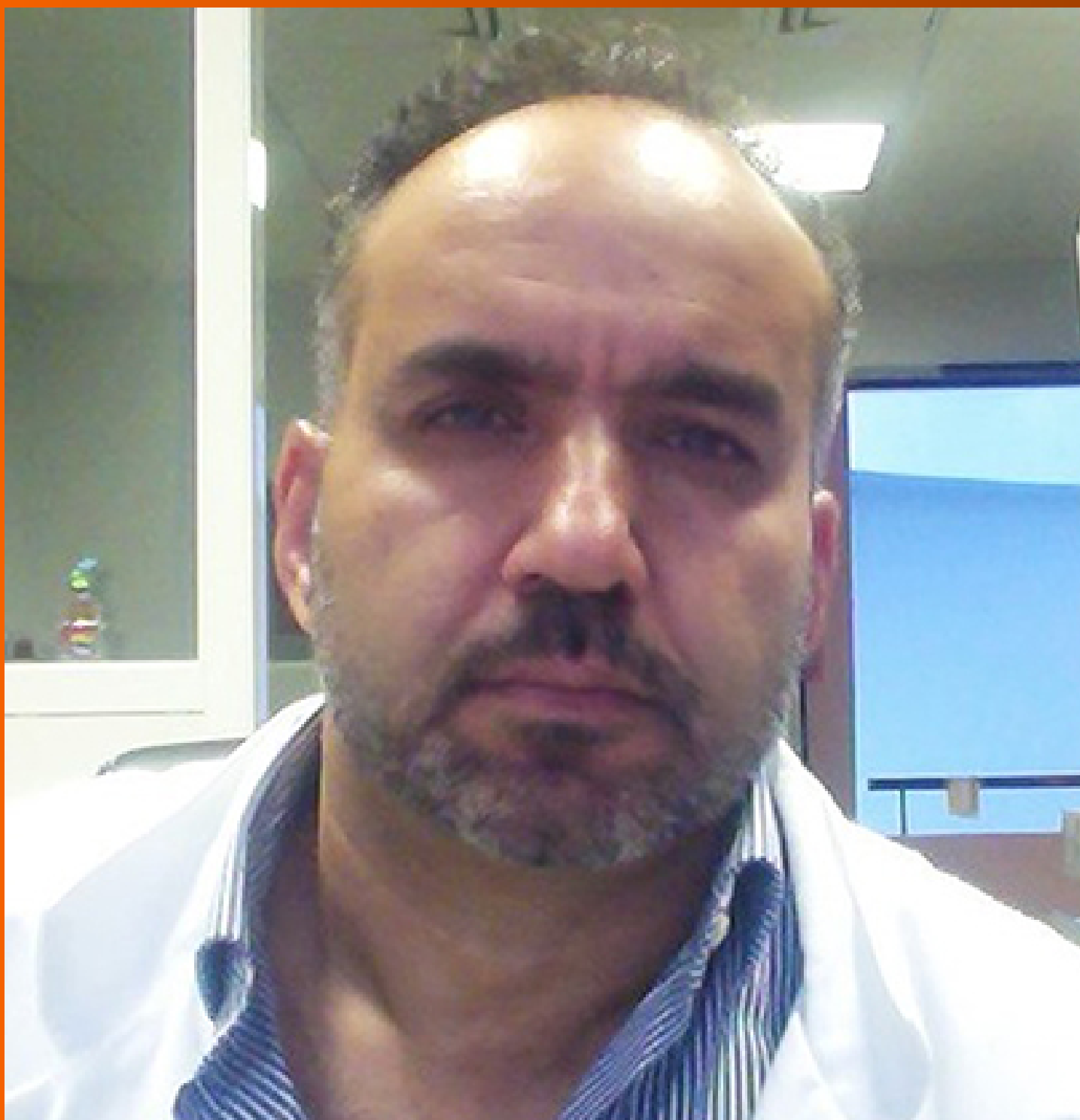


World Journal of *Biological Chemistry*

World J Biol Chem 2022 May 27; 13(3): 66-71



MINIREVIEWS

- 66 Progesterone in gender-affirming therapy of trans women

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RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Ying-Yi Yuan; **Production Department Director:** Xu Guo; **Editorial Office Director:** Yun-Xiao Wu.

NAME OF JOURNAL

World Journal of Biological Chemistry

ISSN

ISSN 1949-8454 (online)

LAUNCH DATE

July 26, 2010

FREQUENCY

Bimonthly

EDITORS-IN-CHIEF

Vsevolod Gurevich, Jean-Marie Exbrayat, Chunpeng Craig Wan

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1949-8454/editorialboard.htm>

PUBLICATION DATE

May 27, 2022

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<https://www.wjgnet.com/bpg/gerinfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/gerinfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Progesterone in gender-affirming therapy of trans women

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Specialty type: Endocrinology and metabolism

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Bansal C, India;
Cazzato G, Italy

Received: December 20, 2021

Peer-review started: December 20, 2021

First decision: February 21, 2022

Revised: February 28, 2022

Accepted: April 22, 2022

Article in press: April 22, 2022

Published online: May 27, 2022



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Abstract

Progesterone is an endogenous steroid hormone with an important role for the physiology of the female reproductive system and the mammary gland. It has additional significant actions in other tissues, such as the cardiovascular system, the central nervous system, and bones. The present article explores potential clinical implications from the addition of bioidentical progesterone to gender-affirming treatment of trans women. For this purpose, it provides an overview of the physiological action of progesterone in target tissues and speculates on possible benefits for gender transitioning. Progesterone is expected to exert moderate anti-androgen action through suppression of the hypothalamic-pituitary-gonadal axis and inhibition of the conversion of testosterone to dihydrotestosterone. It may also contribute to breast maturation. In the long-term, progesterone could prevent bone loss and protect cardiovascular health. The potential benefits are mainly inferred by extrapolating evidence from biological actions in cisgender women and medical assumptions and hence, clinicians need to be cautious when applying these data into practice. Further research is needed to ascertain the efficacy and safety of progesterone in current hormonal regimens.

Key Words: Progesterone; Transgender persons; Breast; Human; Gender dysphoria

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Core Tip: The addition of bioidentical progesterone to the gender-affirming treatment of trans women may be beneficial in many ways. However, since relevant studies are lacking, further research is needed.

Citation: Milionis C, Ilias I, Koukkou E. Progesterone in gender-affirming therapy of trans women. *World J Biol Chem* 2022; 13(3): 66-71

URL: <https://www.wjgnet.com/1949-8454/full/v13/i3/66.htm>

DOI: <https://dx.doi.org/10.4331/wjbc.v13.i3.66>

INTRODUCTION

Physiology of progesterone

Progesterone (P4) is an endogenous hormone with an important role for the physiology of the reproductive system of cisgender females. It is the major member of a class of steroid hormones (progestogens) that bind to and activate the progesterone receptor (PR). All steroid hormones consist of a common structure of a polycyclic (four-ring) complex which derives from the cholesterol molecule. The biosynthesis of steroid hormones follows the same pathways in all steroidogenic organs (the ovary, testis, adrenal cortex, and placenta), but the type and amount of the produced hormones vary depending on the presence and expression of specific enzymes in each tissue[1].

Like all steroid hormones in mammals, P4 is synthesised from pregnenolone. The conversion of pregnenolone to P4 is catalysed by the type 2 3 β -hydroxysteroid dehydrogenase/ Δ 5- Δ 4 isomerase through modification of the 3 β -hydroxyl group to a ketone and isomerisation of the C-5 to C-4 double bond[2]. P4 is a potent agonist of the nuclear PR. Ligand binding induces a signalling pathway which results in activation of genes containing P4 response elements. However, P4 also acts through non-classical signalling pathways, often mediated by non-genomic processes[3].

P4 is mainly secreted by the ovary after ovulation and by the placenta during pregnancy. Before ovulation, ovarian granulosa cells in the follicle synthesise and secrete oestrogens. After the rupture of the follicle and the release of the ovum, these granulosa cells mature to form the corpus luteum. The latter produces P4 (and oestrogens) in the luteal (secretory) phase of the cycle. If fertilisation does not occur, the corpus luteum will further enlarge for the next 10-12 days and then it will regress and discontinue the release of P4 (and oestrogens). In case of fertilisation, the corpus luteum will continue to grow and function for the first 2-3 months of pregnancy. Afterwards, it will gradually regress as the placenta assumes the role of hormonal biosynthesis. The release of P4 from the corpus luteum is influenced by a number of hormones. Luteinising hormone (LH) exerts the primary action, whilst follicle stimulation hormone (FSH), prolactin, prostaglandins, activin, follistatin, and beta-adrenergic agents play a secondary role in the control of P4 production[4].

Reproductive function is inextricably related to P4. The latter is involved in the endometrial transition from the proliferative to the secretory phase during the menstrual cycle, the facilitation of the implantation of the blastocyst, and the maintenance of pregnancy. However, P4 has additional significant actions in other tissues, besides the reproductive system, including the mammary gland, the cardiovascular system, the central nervous system, and bones[5]. The actions of oestradiol (E2) and P4 are well balanced and coordinated in order to result in a healthy physiology[6]. Table 1 presents the main roles of P4.

P4 is the only natural progestogen that is used therapeutically. Micronised crystals of P4 allow for a better gastrointestinal absorption. Progestins are a variety of synthetic progestogens with a different potency and pharmacokinetics from P4. Although these compounds mimic some of the effects of P4, they may have different actions on PR at the same target tissues[7]. The present article explores the effects of bioidentical P4 on gender-affirming therapy of transgender females. Nevertheless, hypotheses about progestins can be drawn according to their degree of P4-like effects.

Gender-affirming hormonal therapy

Transgender individuals are persons whose gender identity is compatible with the opposite sex or with a variance that falls outside the classical binary definition of male/female. In particular, transgender females (also called trans women) are individuals who self-identify as females but were assigned male gender at birth. Gender-affirming therapy in trans women aims at inducing physical changes towards feminine biologic characteristics[8]. Treatment with E2 (mainly oral or transdermal) and anti-androgens (usually cyproterone acetate and less frequently spironolactone) or gonadotrophin-releasing hormone (GnRH) agonist is expected to result in redistribution of body fat and decrease in muscle mass, softening of the skin, breast development, and decreased terminal hair growth accompanied by decreased sexual desire and erections, testicular atrophy, and reduced sperm production. These changes evolve over a period starting from the first months of the administration until more than three years later. The relevant possible risks include thromboembolic disease, enlargement of an underlying prolactinoma, breast cancer, coronary artery and cerebrovascular disease, cholelithiasis, and hypertriglyceridaemia[9].

P4 AS A COMPONENT OF FEMINISING TREATMENT

Hormonal treatment in transgender persons aims at suppressing the secretion of the endogenous sex hormones and replacing them with the hormones of the desired gender. The therapeutic interventions need to maintain sex hormone blood levels within the respective normal range of the affirmed gender [10]. As P4 constitutes an important hormone in cisgender females, it is hypothesised that a daily or cyclic treatment with oral P4 could be a beneficial component of gender-affirming therapy of trans women, in addition to E2 and anti-androgen regimens. According to this perspective, the importance of P4 for transgender health is expected to be due to metabolic and anti-androgen effects. However, the

Table 1 Known physiological actions of progesterone

Uterine endometrium	Inhibition of proliferation and differentiation of the endometrium into a secretory organ for the potential implantation of a fertilised ovum
Uterine cervix	Inhibition of cervical mucus secretion
Breast tissue	Ductal side branching and lobulo-alveolar development; increase of the areolar size
Skeleton	Bone formation (in conjunction with oestradiol)
Arterial endothelium	Amplification of the actions of endogenous nitric oxide
Brain	Mitigation of central stress hormone responses; induction of deep sleep

relevant potential benefits are mainly inferred by extrapolating evidence from biological actions in cisgender women and thus, clinicians need to be cautious when applying these data into practice[11].

Anti-androgen effects

The direct anti-androgen action of P4 on the androgen receptors (AR) appears to be minimal[12]. Nevertheless, the treatment with exogenous P4 at pharmacological dosages is expected to exert negative feedback on the hypothalamic-pituitary-gonadal axis[13] and hence generate an indirect anti-androgen activity. According to this mechanism, the suppression of LH will eventually lead to a reduction of the synthesis and secretion of gonadal testosterone (Te) by Leydig cells[14]. In addition, exogenous P4 may possibly enhance the impairment of spermatogenesis in Sertoli cells by decreasing intratesticular Te and suppressing FSH[15]. Therefore, the administration of sufficient doses of P4 in daily regimens, rather than cyclically, may enhance the anti-androgen action of gender-affirming therapy in trans women and could be clinically useful until orchiectomy is performed.

The 5-alpha-reductase enzyme family consists of three isoenzymes which catalyse the conversion of Te to 5-alpha-dihydrotestosterone (DHT) by promoting an irreversible break of the double bond between carbons 4 and 5 of the Te molecule with nicotinamide adenine dinucleotide phosphate (NADPH) acting as a cofactor[16]. DHT has a several-fold more potent androgen action in comparison with Te. As 5-alpha-reductase is highly expressed in the skin, hair follicles, and prostate gland, DHT is mainly involved in facial, axillary, pubic, and body hair growth, as well as scalp pattern hair loss and prostate enlargement in males[17]. P4 is an inhibitor of 5-alpha-reductase and as such, it might mitigate masculinising effects of DHT in target tissues. However, the inhibition of 5-alpha-reductase by P4 is rather weak and thus can only be demonstrated at supraphysiological concentrations[18].

Breast maturation and enlargement

P4 is substantially involved in breast tissue development. Indeed, it appears to have a potentiating or accelerating role in oestrogen-mediated mammary ductal development and alveolar expansion during puberty. Moreover, P4 enhances the actions of oestrogens on proliferation of the epithelial and stromal compartments in the adult mammary gland[19]. During pregnancy, P4 acts synergistically with prolactin in order to promote lobulo-alveolar development of the mammary gland. The goal is to prepare the breast for lactation after parturition[20]. Oestrogens enhance the action of P4 on breast tissue[21]. Therefore, treatment of transgender females with exogenous oestrogen and P4 may be beneficial for glandular development. However, it should be noted that although oestrogens are undisputed breast tissue mitogens, the role of P4 action in breast cancer is unclear[22] and any therapeutic intervention should be followed with caution.

Bone health

It is established that the role of oestrogens is critical for skeletal homeostasis as they regulate bone remodelling, partly through the osteoprotegerin/receptor activator of nuclear factor kappa-B ligand (RANKL) system. Furthermore, oestrogen deficiency upregulates bone turnover and causes bone loss [23]. In contrast, the actions of P4 on the promotion of bone health are largely unrecognised. P4 likely acts complementarily with oestrogens in bone formation and hence, it may have an active role in maintaining women's bone health in osteoporosis prevention. *In vitro* studies of human osteoblasts indicate that it enhances osteoblast proliferation and promotes their maturation and differentiation[24]. Therefore, micronised P4 in conjunction with E2 may be effective in prevention of osteoporosis in trans women. However, further research is needed to confirm the contribution of P4 to clinically significant bone formation.

Cardiovascular protection

The protective functions of P4 in the cardiovascular system have not been extensively studied. Existing evidence suggests that P4 decreases vasoconstriction and causes natriuresis. In addition, it promotes endothelial nitric oxide synthase activity and calcium influx in vascular endothelial and smooth muscle

cells, respectively, and hence, it lowers blood pressure[25]. P4 is expected to have a neutral effect on blood lipid levels[26]. The vascular actions of P4 may assist in preventing cardiovascular disease in trans women. However, the cardiovascular benefits of P4 have not been clinically confirmed and thus claims about potential cardiovascular protection are controversial[27]. Moreover, some synthetic progestins may have a negative effect on cardiovascular health with regard to lipid changes, atheroma development, or vasomotion[28].

DISCUSSION

The number of individuals, with gender dysphoria, who seek cross-sex treatment, has increased over the past years[29]. The administration of oestrogen (combined with GnRH agonist or anti-androgen in case of present testes) is the mainstay of hormonal regimens in transgender females. However, the clinical results of gender transitioning are sometimes less than satisfactory and additional therapy may be required. P4 is a natural endogenous steroid hormone with multiple important physiologic effects, including anti-androgen activity, mammary gland growth, reduction of bone resorption, and anti-mineralocorticoid action[30]. Therefore, pairing bioidentical P4 with oestrogen could be a novel approach to gender-affirming treatment. P4 is not typically recommended in the hormonal treatment of trans women because of a lack of thorough evidence concerning its safety and efficacy[31,32]. The advocacy of the use of bioidentical P4 as part of the feminising treatment is currently anecdotal and is driven by the prospect of mirroring, in trans women, the hormonal status of cisgender females.

The anti-androgen effect of P4 consists of suppression of the hypothalamic-pituitary-gonadal axis and inhibition of the conversion of Te to DHT. As discussed earlier, feminising treatment includes either a GnRH agonist to suppress gonadal Te levels or an anti-androgen to block the AR. Nonetheless, GnRH analogues are expensive pharmaceutical products, whilst maximum AR blockade with anti-androgens (such as cyproterone acetate and spironolactone) has potential serious side effects. The addition of micronised P4 could theoretically lead to a considerable reduction of the needed dosage of GnRH agonist or anti-androgen for gender transitioning until the testes are surgically excised.

Breast development is a major goal of cross-sex hormonal treatment of trans women. However, transgender females most usually do not achieve the same shape and level of breast enlargement compared with their cisgender counterparts[33]. At present, mammoplasty is the only option for constructing a fully developed female breast in trans women[34]. The administration of P4 on top of usual oestrogen treatment could hypothetically promote breast development in transgender females. However, there have been no reliable studies of the role of exogenous P4 in breast development in trans women so far[35].

CONCLUSION

In conclusion, oral micronised P4 is identical to the natural hormone and could be added to E2 in gender-affirming treatment of trans women. Indeed, P4 may aid anti-androgen action through two main pathways: (1) Suppression of the hypothalamic-pituitary-testicular axis; and (2) inhibition of Te conversion to DHT. Furthermore, it may promote physiological feminine breast maturation. In the long-term, P4 could also prevent bone loss and protect cardiovascular function. Nevertheless, the clinical usefulness of P4 in trans women's health is currently based mainly on clinical assumptions emerging from physiologic mechanisms, observational data, and daily experience. Further nonclinical and clinical trials are necessary to investigate the efficacy and safety of the addition of P4 to current hormonal treatment regimens. Then, commissioned systematic review on the available data could provide relevant clinical guidance.

FOOTNOTES

Author contributions: Milionis C and Ilias I performed the majority of the writing and prepared the table; Ilias I and Koukkou E provided input in writing the paper; Koukkou E coordinated the writing of the paper.

Conflict-of-interest statement: The authors state that they have no conflict of interest to report.

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S-Editor: Liu JH

L-Editor: Wang TQ

P-Editor: Liu JH

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