Best Practice & Research Clinical Obstetrics and Gynaecology 69 (2020) 13–29

Contents lists available at ScienceDirect

Best Practice & Research Clinical Obstetrics and Gynaecology

journal homepage: www.elsevier.com/locate/bpobgyn

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The pharmacodynamics and safety of progesterone

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Keywords:
Progesterone
Progestogens
Progestins
Pharmacodynamics
Micronised progesterone
Pharmacokinetics

A B S T R A C T

Natural progesterone (P4) has a unique pharmacodynamic activity and safety profile compared to the synthetic progestins. As a result, a class effect does not exist for both P4 and synthetic progestins, in terms of both their efficacy and safety.

Progestogens act at the genomic level by binding to the nuclear receptors and modulating the expression of some target-genes. P4 and the synthetic progestins have a hugely variable affinity for binding not only to the P4 receptors but also to other members of the steroid receptor family including glucocorticoid receptor, androgen receptor and mineralocorticoid receptor. This leads to different and specific pharmacokinetic profiles, clinical pharmacodynamics, safety and efficacy.

P4 produced in the luteal phase of the menstrual cycle has several physiological effects regulating menses and, in the pregnant uterus, controlling the development of endometrial receptivity preparing the endometrium for implantation.

P4 and its associated metabolites are powerful biological agents through genomic action by the progesterone nuclear receptor with a finely tuned regulatory role throughout pregnancy, from conception until delivery. Extra-nuclear, non-classical mechanisms of action have also been identified, including steroid interactions with some membrane receptors [oxytocin receptors and γ-aminobutyric acid ($GABA_A$), and the induction of a direct relaxing effect on uterine contractility by blockage of calcium influx.

The extent of activity of P4 on the central nervous system (CNS) is modulated by the route of administration: oral P4 is affected by the presence of bacteria and associated enzymes secreted in the gut, the intestinal wall and by the liver, whereas vaginal P4 is not. P4 and two important metabolites, namely, allopregnanolone

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https://doi.org/10.1016/j.bpobgyn.2020.06.002
1521-6934/

(3a,5a-tetrahydroP4) and 3a,5a-tetrahydrodeoxycorticosterone, exert neuroprotective effects on neonates. They are also natural positive modulators of the neuronal $GABA_A$ receptor, providing a clear pathway to explain the rapid dose-dependent psychopharmacological actions including anxiolytic, antidepressant, anaesthetic, anticonvulsant and analgesic effects.

Fundamental structural differences exist between P4 and the synthetic progestins, resulting in different safety profiles when they are used during the menstrual cycle, in early and late pregnancy and in the alleviation of peri- or postmenopausal symptoms.

Introduction

Progestogens are compounds that exhibit progestational activity. They include both synthetic progestogens and natural progesterone (known as P4). Synthetic progestogens do not share a class effect with P4 and the affiliate molecules, in terms of both their efficacy and safety, The specific pharmacokinetic and pharmacodynamic characteristics of P4 differ from that all other progestogens; this unique "mother molecule" has different clinical effects on the cardiovascular and central nervous systems (CNS), breast and bone [1].

P4 and synthetic progestins bind not only to the P4 receptors, but also to many other steroid receptors, including the androgen and mineralocorticoid receptors (MR). Androgenic or anti-androgenic and glucocorticoid-like effects can occur. Very small changes in the structure of the molecules can lead to considerable differences in the effects seen [2,3]: for example, micronised P4 (but not synthetic progestins) and one of its major metabolites, allopregnanolone, have been shown to modulate γ-aminobutyric acid (GABA)ergic transmission with a similar potency or even greater efficacy, than those of alcohol, benzodiazepines or barbiturates [4].

A lack of appreciation of these differences in pharmacokinetic and pharmacodynamics properties between P4 and other progestogens has led to much confusion in the literature regarding the risks associated with their use.

This review explains why micronised P4 and synthetic progestins cannot be considered as a single pharmacological class, and looks at the impact that their different chemical structures, structure–function relationships, metabolism, pharmacokinetic and pharmacodynamic parameters have on their efficacy and safety profiles, particularly when used during pregnancy.

Differences in pharmacodynamics related to the route of administration

The route of administration is crucial in determining the optimal pharmacodynamic profile of P4, in terms of both the desired and reliable clinical effects, particularly during pregnancy (Table 1).

Oral P4

Oral (po) ingestion of micronised P4 in oily formulations, in soft capsules, results in rapid absorption, a maximal plasma concentration reached within 4 h with a bioavailability of about 8.6% compared to intra-muscular (i.m.) administration, and twice that when administered before food [5].

Orally administered P4 undergoes several successive metabolic steps in the gut (due to bacteria with 5β-reductase activity), in the intestinal wall (5α-reductase activity) and in the liver (5b-reductase, 3a-and 20a-hydroxylase activities). The resulting metabolites, 5α-pregnanolone (allopregnanolone) and 5β-pregnanolone, bind the $GABA_A$ receptor, while 5α-pregnanedione and 5β-pregnanedione exert anti-mitotic and tocolytic effects. The action of these metabolites may explain some of the observed side effects, such as drowsiness or sleepiness, as well as the therapeutic benefits in some specific

Table 1
Advantages and drawbacks related to the route of administration of progesterone in comparison with synthetic progestins.

	Oral P4	Vaginal P4	Transdermal P4	I.M. P4	Synthetic progestins	
					DHG	Others[a]
PK characteristics	- 1st hepatic passage [↑ inter-individual variability versus vaginal] - Fast increase in serum P4 followed by gradual ↘ [peaks and valleys] - Increase in 5-α & 5-β metabolites	- 1st uterine passage [↘ inter-individual variability]: high uterine tissue concentration - Constant and optimal P4 serum levels around the clock at the steady state	- No systemic exposure [Serum P4< 3 ng/mL]	- ↗↗↗ P4 serum levels [5–7fold higher versus vaginal - ↘ uterine tissue concentration - ↗↗ fluctuations in P4 blood levels compared to vaginal	- No ↑ in P4 serum levels	- No ↑ in P4 serum levels
Advantages	- Ease of administering/dosing - prevents the over-proliferation of the endometrial tissue - Anxiolytic, tranquilising and sedative effects via binding $GABA_A$ rec - Tocolytic and diuretic effects	- Convenience, ease and overall satisfaction of administering/dosing - Adequate secretory endometrial transformation (ART indications) - ↘ drowsiness or dizziness vs oral - Extensive clinical experience	- Patient acceptability - Well-established safety - Very good local tolerance	- Extensive clinical experience in ART - Cost-effectiveness in ART	- Ease of administering/dosing - No negative effect on the lipid profile. - Neutral effects on metabolic or vascular risks.	- High anti-gonadotropic potency ensuring suppression of ovulation combined or not with estrogen
Drawbacks and Possible side effects	- No or weak antiovulatory activity - Drowsiness and/or dizziness - Hypnotic effect [↗ sleepiness]	- Twice or three times a day application - Cost [depending the formulation] - Irritation or discharge depending the formulation	- No antiovulatory activity - Hypersensitivity to progesterone or any other component	- ↘ convenience, ease and overall satisfaction of administering/dosing vs vaginal - At least twice weekly and requires nurse assistance	- No antiovulatory activity - Safety concerns in early pregnancy	- Headaches, bloating, acne, mastalgia, weight gain, depression, mood swings, irritability, loss of libido, fluid retention, breakthrough bleeding - Cardiovascular, thrombotic and

(*continued on next page*)

Table 1 (*continued*)

	Oral P4	Vaginal P4	Transdermal P4	I.M. P4	Synthetic progestins	
					DHG	Others[a]
				- Granulomas [>oil], allergy and dry abscesses - Risk for acute eosinophilic pneumonia		breast cancer risk increase in HRT
Optimal indications	- djunctive use with oestrogen in HRT - Menstrual irregularities due to ovulation disorders or anovulation - Perimenopause. - Infertility due to luteal phase defect. - Threatened miscarriage or prevention of habitual miscarriage	- Supplementation of the luteal phase during ART cycles. - P4 support in women with partial or complete POI [oocyte donation]. - Threatened miscarriage or prevention of habitual miscarriage. - Prevention of PTB in women at risk	- Premenstrual mastodynia [hormone-induced breast pain before periods] - Benign mastopathy.	- Supplementation of the luteal phase during ART cycles.	- Adjunctive use with oestrogen in HRT - Menstrual irregularities - Infertility due to luteal phase defect. - Dysmenorrhea, endometriosis - Threatened miscarriage or prevention of habitual miscarriage [need for RCTs].	Hormonal contraception in oral or non-oral delivery systems [rings, patches, gels]

[a] Not all of side effects occur with all of the progestins. Side effects may be related either to the androgenic, the glucocorticoid properties or to its estrogenic effects. P4, Natural Micronised Progesterone. DHG, dydrogesterone. GABA, γ-aminobutyric acid. ART, Assisted Reproductive Technology. POI, Premature Ovarian Insufficiency. PTB, Preterm birth. RCTs, Randomised Clinical Trials.

indications, including the alleviation of mood, sleep disturbance and vasomotor symptoms (VMS), which are associated with menopause or premenstruum [6,7]. Recent data have shown that antagonism of receptors for neurokinin 3 improves VMS and slows pulsatility of luteinising hormone in the same way as oral P4 does in menopausal women [7].

The body of evidence suggests that oral P4 increases bone formation and adds significantly to oestrogen-related improvements in bone mineral density (BMD). It is thought that P4 stimulates the production of new osteoblasts from mesenchymal stem cells and also stimulates osteoblasts to create more bone matrix through a specific osteoblast receptor pathway [8]. Low "Peak Perimenopausal BMD" is likely to be the primary risk for fragility and may be related to cycle/ovulatory disturbances [9].

Vaginal P4

Compared with oral ingestion, vaginal administration of P4 results in only a small increase in the metabolite allopregnanolone and no change in 5β-pregnanolone levels, because normal vaginal bacteria are devoid of 5α- and 5β-reductases. This explains why the activity of P4 on the CNS is affected by the route of administration [6].

The vaginal route induces a lower C_{max} and higher P4 blood levels at steady-state compared to oral administration and similar $t_{1/2}$ values with more constant blood levels during the nychthemeral period [5]. As a result, P4 vaginal administration is highly effective in inducing the secretory transformation of the endometrium and in preventing premature shortening of the cervix. It is the preferred therapy for the maintenance of pregnancy, with only minor changes in the plasma levels of the "psychotropic" metabolites [6].

Vaginal administration of P4 avoids first-pass liver metabolism, and as a result, there is less stimulation of liver proteins. Even though at steady state the serum P4 level of a 800 mg/day vaginal dose is almost seven times lower than a 100 mg/day i.m. dose, the resulting endometrial P4 concentrations are almost five to seven times higher after vaginal administration than after i.m. administration [10]. Different mechanisms of action have been suggested to explain the "uterine first-pass effect", including direct diffusion through tissues, counter-current transfer between utero-vaginal veins or lymph vessels and arteries, intraluminal passage from the vagina to the uterus, and/or venous or lymphatic circulatory systems [11].

Comparisons of i.m. and vaginal P4 dosing for luteal phase support (LPS) in infertility treatments has led to both controversial results and considerable debate over the best routes of administration, particularly in the USA. Studies have shown that despite discrepancies detected between serum levels and histological endometrial features after vaginal P4 application, adequate secretory endometrial transformation can be reached, with minimal undesirable systemic effects [12].

An updated worldwide web-based survey has assessed the real-life clinical practices regarding LPS in assisted reproduction: based on data obtained from 408 centres in 82 countries, representing 284,600 IVF cycles/year, it has been shown that most practitioners used a vaginal P4 product in more than 90% of the cycles (77% as a single agent and 17% in combination with i.m. progesterone) [13].

Differences in pharmacodynamics related to brain activity

As mentioned earlier, two important metabolites of P4, allopregnanolone (3α,5α-tetrahydroP4) and 3α,5α-tetrahydrodeoxycorticosterone, are natural positive modulators of the neuronal $GABA_A$ receptor. These provide a clear pathway that explains the rapid psychopharmacological actions, including anxiolytic, antidepressant, anaesthetic, anticonvulsant and analgesic effects seen with different dosages and routes of administration [14].

Neuroprotective effects of P4 and allopregnanolone have been suggested in neonates and demonstrated in many injury models, including cerebral ischemic stroke, excitotoxic damage of hippocampal neurons and traumatic spinal cord injury, in mouse models of spontaneous spinal motoneuron degeneration and in Alzheimer's disease [15,16].

During pregnancy not only the maternal brain but also the placenta may contribute directly and indirectly to an increase in allopregnanolone production and activity in the foetal brain, modulating neuroendocrine responses to stress. In pregnant rats allopregnanolone prevents activation of the

corticotrophin-releasing hormone (CRH) neurons inhibiting CRH release at the median eminence (ME) and preventing hypothalamic–pituitary–adrenal (HPA) axis responses to IL-1β through an opioid mechanism [17].

In the OPPTIMUM study (a multicentre, randomised, double-blind trial with vaginal P4 prophylaxis for preterm birth (PTB)) brain injury on ultrasound scan was significantly reduced by 50% in the progesterone group (OR = 0.50; 95% CI: 0.31–0.84 p = 0.008) [18].

In ageing and postmenopausal women, where sleep is fragmented and of lower quality, P4 appears to act as a "physiological" regulator of sleep disturbance, rather than as a hypnotic drug, by modulating (GABA)ergic transmission [19,20].

In a randomised, double-blind, cross-over study in healthy postmenopausal women, intranasal P4 was shown to have a sleep-endocrine promoting effect, compared to zolpidem and placebo. The spectral signature of intranasal P4 did not mimic the sleep-EEG alterations induced by GABA active compounds [21].

The view that the neuroprotective and regenerative effects of P4 in the brain may be primarily mediated by allopregnanolone has recently been challenged by the observation that P4 receptors play a key role in the viability of neurons after ischemic stroke and in the remyelination of axons after a demyelinating lesion, with potentially significant therapeutic implications in patients with multiple sclerosis and carpal tunnel syndrome [22]. Endogenous levels of P4 have also been shown to correlate positively with factors predicting better prognosis and survival of patients with amyotrophic lateral sclerosis [23].

Steroids, including P4, may be part of some cerebroprotective processes in relation to the key role of progesterone receptor (PR) signalling, in protecting against the cascade of changes that can lead to neural cell death. P4 may activate endogenous protective processes that counter the deleterious consequences of ischaemia and reinforce these intrinsic protective mechanisms: Recent results have been highlighted concerning differential changes in endogenous steroid levels in the brains of male and female mice and the importance of P4 receptors [PR] during the early phase after stroke. Finally, experimental studies provide evidence for the pleiotropic beneficial effects of P4 and its promising cerebroprotective potential in stroke [24].

More recently, a systematic review of the impact of endogenous and exogenous P4 exposure on stress biomarkers has been reported. This has concluded that HPAA activity was not affected by endogenous progesterone exposure across the menstrual cycle but might be reduced by exogenous MP application. In contrast, the autonomic nervous system (ANS) had a sympathetic predominance in the (P-dominated) luteal phase of the menstrual cycle [25].

A recent study in a small number of patients (N = 77), treated with P4 therapy compared to a control group, concluded that P4 lowers the intensity of depressive symptoms after preterm delivery based on the Depression, Anxiety and Stress Scale (DASS) scoring system, which is shown to be effective in early detection of postpartum depressive symptoms [26].

Are all progestogens including micronised P4 equal?

Micronised P4 and synthetic progestins exert their biological effects primarily by binding to progesterone receptors (PRs), the classical genomic pathway, but with different affinities. The variable affinity of progestogens for binding not only to the PR and but also to other members of the steroid receptor family, including glucocorticoid receptor (GR), androgen receptor (AR) and MR, plays a crucial role in differential intracellular progestogen actions (Table 2) [1,27,28].

P4 is a weak agonist for the GR and AR and is a full antagonist for the MR which is beneficial during pregnancy, and it has no significant activity via the oestrogen receptor (ER); counteracting possibly excess water retention induced by oestrogens [29–31].

P4 is slightly anti-androgenic because it also binds to 5-α reductase enzyme and will therefore interact with the conversion of testosterone in dihydrotestosterone, its active metabolite [2]. Both allopregnanolone and micronised P4 are natural positive modulators of the neuronal $GABA_A$ receptor conferring on this molecule a unique pharmacodynamic profile (Fig. 1) [15].

The classical view that PRs mediate P4 effects by acting as transcriptional factors to facilitate target gene expression has undergone substantial modifications in recent years in the light of the discovery of

Table 2
Biological activities of natural progesterone and synthetic progestins (depending on their tissue concentration and binding affinity to the receptors) [3].

	PR	Anti-E	EST	AND	A-A	A-M	$GABA_A$
Progesterone	+	+	-	-	+	+	+
Drospirenone	+	+	-	-	+	+	-
Dydrogesterone	+	+	-	-	-	-	-
MPA	+	+	-	±	-	-	-
LNG	+	+	-	+	-	-	-

PR, progestogenic; Anti-E, antiestrogenic; EST, estrogenic; AND, androgenic; A-A, antiandrogenic; A-M, antimineralocorticoid activity; $GABA_A$, positive modulation of $GABA_A$ receptor, LNG, levonorgestrel.
+, effective; ± slightly effective; -, not effective.

extra-nuclear, non-classical mechanisms of P4 regulation [32]. Recent evidence has demonstrated that membrane P4 receptors (mPRs) mediate most of the non-classical P4 actions that cannot be currently explained by their genomic action via nuclear receptors [33,34].

The pharmacodynamics of P4 before implantation and in early pregnancy

Exogenous micronised P4 has been shown to induce endometrial secretory changes, including decidualisation and vasodilation (decreasing apoptosis). Signs of apoptosis in the human endometrium apparent by Day 26 of the menstrual cycle can be reduced with either human chorionic gonadotrophin (hCG) or P4 treatment. The clinical utility of these findings includes a rational use of LPS for the treatment of women with infertility and/or recurrent pregnancy loss (RPL) [35]: In an observational

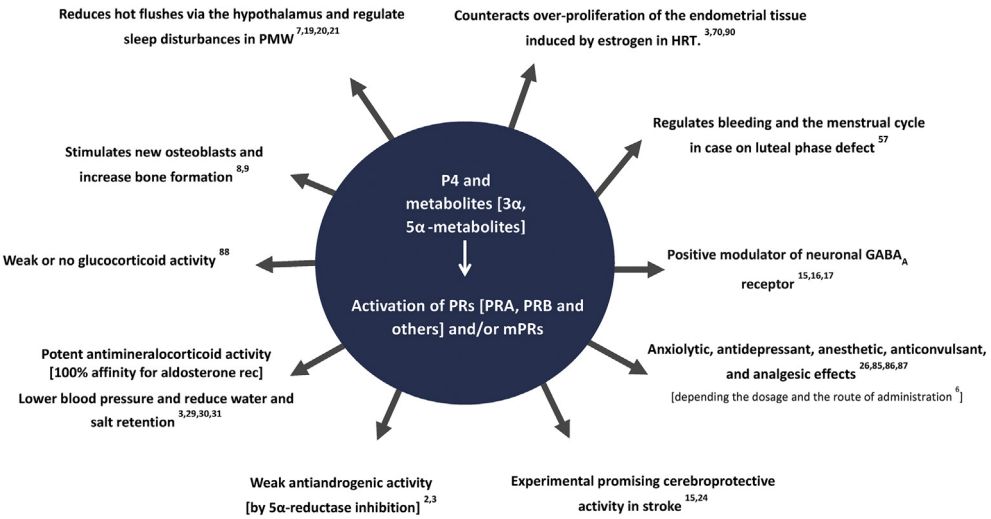

Fig. 1. Pharmacodynamic profile of micronised progesterone [P4] in gynaecology.

cohort study using prospectively collected data, the use of luteal start vaginal micronised P4 was associated with improved pregnancy success in a strictly defined cohort of women with RPL. It was suggested that luteal start vaginal micronised P4 leads to improved endometrial gland development, optimising the local environment for early maintenance of pregnancy [36].

During the luteal phase of the cycle, P4 prepares the endometrium for implantation of the embryo by ensuring that it is spongy, thick, and full of nutrients. The interaction between an activated blastocyst and a receptive uterus is part of the complex process that leads to implantation and the early stages of placental development [37,38].

Just after conception the genes regulated by P4 control the development of endometrial receptivity, recruitment and differentiation of decidual natural killer (NK) cells, and the promotion of extravillous trophoblast (EVT) invasion in the maternal decidua by inhibiting apoptosis of EVTs remodelling the local vasculature and regulating angiogenesis [39–41].

P4, but not synthetic progestins, is transformed to several isomers: Two isomers of dihydroP4, four pregnanolone isomers, and eight isomers of pregnanediol [1]. Due to this unique pharmacodynamic profile P4 modulates maternal immune responses protecting the semi-allogenic foetus, reducing the uterine contractility antagonising oxytocin receptor, suppressing the foetal immunoplacental inflammatory response, improving the utero-placental circulation, and maintaining uterine quiescence and cervical integrity throughout pregnancy (Fig. 2) [35,39,42–51].

Inadequate secretion of P4 in early pregnancy has been linked to the aetiology of miscarriage. P4 supplementation is an established treatment for threatened miscarriage to prevent spontaneous pregnancy loss [52,53]. Around one in four pregnancies end in miscarriage (the loss of pregnancy in the first 23 weeks) [54]. A relatively recent prospective cohort study has highlighted the pivotal role of endogenous P4 in supporting early pregnancy; lower serum P4 is associated with threatened miscarriage and a subsequent complete miscarriage at 16 weeks gestation [55]. The use of vaginal micronised P4 (Utrogestan®) in the first trimester has been evaluated in two large, high-quality, multicentre placebo-controlled trials; one targeting pregnant women with unexplained recurrent miscarriages (the PROMISE Trial) and the other targeting women with early pregnancy bleeding (the PRISM Trial) [56–58]. The PROMISE trial studied 836 women with unexplained recurrent miscarriages at 45 hospitals in the UK and The Netherlands and found a 3% higher live birth rate with use of P4 in the first trimester. The PRISM trial studied 4153 women with early pregnancy bleeding at 48 hospitals in the UK, and found a 5% increase in the number of babies born to those who had previously had one or more miscarriages and who had been given P4 in the first trimester, compared to those given a placebo.

A key finding, first observed in the PROMISE trial and then replicated in the PRISM trial, was that treatment with vaginal micronised P4 was associated with an increase in live birth rates according to

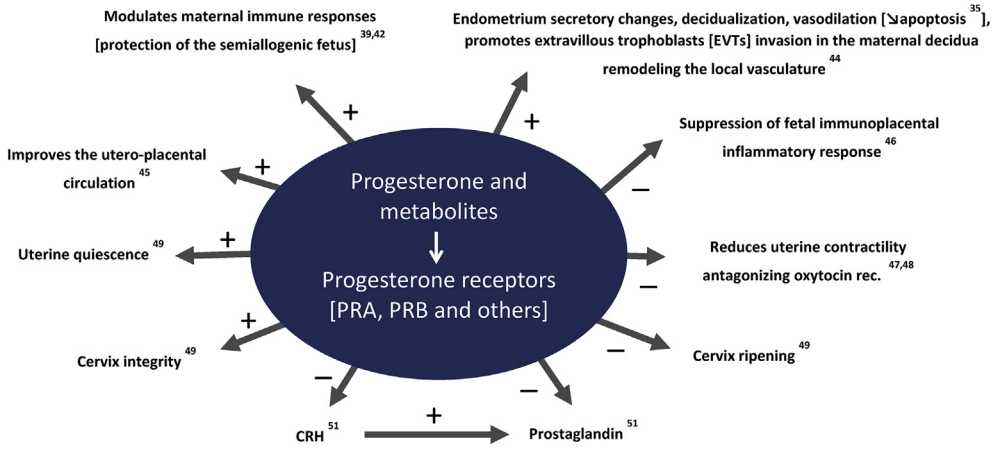

Fig. 2. Pharmacodynamic profile of micronised progesterone [P4] in pregnancy maintenance.

the number of previous miscarriages. It has been shown that the risk of a future miscarriage increases with the increase in the number of previous miscarriages [59]. In a critical evaluation of the randomised data from this study, it was concluded that women with a history of miscarriage who present with bleeding in early pregnancy may benefit from the use of vaginal micronised progesterone 400 mg twice daily. Therefore, women and their care providers should use these findings for shared decision-making [58].

Finally, an economic evaluation, based on the PRISM trial, has concluded that the use of progesterone is likely to be cost-effective, particularly for women who have had previous miscarriage(s) [60].

The pharmacodynamics of P4 in luteal phase support in Assisted Reproductive Technology

Luteal P4 and oestradiol are an essential requirement for preparing the uterus for implantation. When no other apparent causes of infertility are detected, assisted reproduction techniques (ARTs) can be avoided and replaced by individualised P4 supplementation during the early luteal phase in a natural cycle [61].

P4 is crucial for the establishment of pregnancy because of its roles in activating several P4-regulated genes in the pregnant uterus and in the development of endometrial receptivity to permit implantation [40]. Early in pregnancy P4 is produced by the corpus luteum and the rise in P4 production is fundamental for the maintenance of pregnancy until the placenta takes over this function at 7–9 weeks of gestation [62].

At term, the placenta produces about 250 mg P4 per day. Placental P4 maintains many of the distinct properties of the pregnant uterus and cervix, including immunological and anti-inflammatory functions.

P4 and some progestins can affect the serum concentrations of other hormones, particularly oestrogen. Oestrogenic effects are modified by P4 or progestins, either by reducing the availability or stability of the hormone receptor complex or by turning off specific hormone-responsive genes by direct interaction with the P4 receptor in the nucleus. Oestrogen priming is necessary to increase progestogen effects by up-regulating the number of P4 receptors and/or increasing P4 production, causing a negative feedback mechanism that inhibits oestrogen receptors. This negative feedback system protects the pregnancy by ensuring that the correct amount of oestrogen and P4 are present to maintain the lining of the uterus, prevent contractions of the smooth muscle, trigger the development of the foetal organs, etc.

Ovarian hyperstimulation for IVF shortens the luteal phase resulting in advanced luteolysis. In the absence of LPS in controlled ovarian stimulation (COS) cycles, maturation of the endometrium is unsatisfactory, and the histological dating never corresponds to the expected cycle day. After administration of exogenous micronised P4, the endometrial morphology is indistinguishable from that of a natural cycle. A study in women with ovarian failure (primary or secondary) preparing for embryo transfer (ET) following oocyte donation has shown that after i.m. administration of P4, the endometrial morphology may be less homogeneous than following vaginal administration, with 43.5% of specimens showing delayed maturation and 9% of specimens showing glandular/stromal asynchrony [63–65].

The net consequences of premature P4 elevation on IVF-ET outcome might result from a balance between two antagonistic parameters: good embryo quality is associated with a good ovarian response to COS correlated with higher P4 levels but impaired receptivity of the endometrium resulting from premature endometrial exposure to P4 [66].

It has been suggested that serum P4 levels of greater than 1.5 ng/mL on the day of hCG administration may be associated with lower ongoing pregnancy rates following IVF/ICSI cycles, irrespective of the GnRH analogue used for pituitary down-regulation [67]: For example, in a single-centre prospective randomised controlled trial (RCT), it was shown that the initiation of progesterone supplementation one day after oocyte retrieval (OR) did not decrease the clinical pregnancy rate, implantation rate or live birth rate in women undergoing IVF-ET cyles with the use of the GnRH agonist long protocol [68]. Therefore, exogenous P4 for optimal LPS should start the evening before the day of OR and not later that two days after OR to reach optimal P4 levels during the window of implantation (6–10 days after ET).

The pharmacodynamics of P4 in preterm labour and induction of labour

P4 relaxes the uterus throughout pregnancy by inhibiting the expression of oestrogen receptor alpha (ER-α) and reducing sensitivity to oestrogen [69]. P4 has multiple functions on the myometrium, which may contribute to its role in the prevention of PTB: it has been shown to induce high levels of cyclic adenosine mono phosphate (cAMP) and time-dependent stimulation of nitric oxide synthetase (NOS), as well as to inhibit the formation of myometrial gap junctions (channels made of connexin 43). P4 and its metabolites induce uterine quiescence both through interactions between nuclear and membrane P4 receptors and by maintaining low levels of the inflammatory prostaglandins (via cyclooxygenase), oxytocin and intracellular calcium [70–72].

In summary, exogenous and endogenous P4 inhibit inflammatory responses associated with preterm parturition and promote myometrial relaxation. The actions of P4 on the cervix and pelvis contribute to the maintenance of mid-gestation pregnancy and uterine muscle quiescence prior to labour and preparation for delivery [37,73–75].

PTB is the leading cause of perinatal morbidity and mortality. The mechanism by which labour is initiated in humans is unclear. The physiological pathways that may lead to PTB and pathological processes implicated in the preterm parturition syndrome (PPS) were proposed and updated by Romero et al., in 2013; the proposed aetiology of PPS includes infection, vascular, stress-nutrition factors, uterine overdistension, cervical disease, hormonal, abnormal allogenic recognition, allergy or even unknown causes [76].

In many animal species, there is a reduction in the amount of circulating P4 before the onset of labour. While these changes have not been shown to occur in women, it has been suggested that there is a "functional" withdrawal of P4 related to changes in the expression of P4 receptors in the uterus [73,75,77,78]. At term, the myometrial sensitivity to P4 changes, with more expression of P4 receptors-A (PR-A) relative to P4 receptors-B (PR-B) [69,78]. The change in ratio of PR-A relative to PR-B leads to functional P4 withdrawal. This, in turn, leads to elimination of the suppressive effect of P4 on ER-α expression, leading to functional oestrogen activation and increased myometrial sensitivity to oestrogen [77].

This interaction between the PR and ER systems in the myometrium seems essential for the control of human parturition. The onset of labour in humans and the functional withdrawal of P4 explains why disruption of P4 alone could trigger the full parturition cascade [69].

Birth is a result of complex, partially defined, events that are tightly regulated by a variety of mechanisms and mediators within the endocrine, nervous and immune systems. The following factors are probably involved in human parturition: changes in levels of oestrogen and P4; increased production of prostaglandins and oxytocin; and increased levels of CRH and cortisol. Inflammatory reactions and the release of cytokines are among the most accepted theories for term and preterm labours [79].

Recent mechanistic evidence shows that effector and activated T cells cause pathological inflammation at the maternal–foetal interface inducing birth. This effect can be prevented by treatment with P4, leading to the avoidance of preterm labour and adverse neonatal outcomes (Fig. 3) [80].

The effect of progestogens on the vaginal microbiome is a matter for debate: a retrospective observational cohort study of women has shown that intravaginal P4, but not 17-alpha hydroxyprogesterone caproate (17-OHP-C), was associated with a significant (40%) decrease in the prevalence of rectovaginal group B streptococcus (GBS) colonisation at term [81]. Not only exogenous micronised P4, but also numerous 5α- and 5β-reduced progesterone metabolites such as 5β-pregnanolone and 5β-pregnanedione exert tocolytic effects on spontaneous uterine contractility of pregnant women at term [48]. This rapid and reversible relaxing effect, which is not through a receptor-mediated genomic action, is suggested to determine the pattern of motility, ensuring the necessary quiescent environment to prevent abortion during gestation.

If progesterone reduces myometrial oxytocin-induced contraction, 17 OH-progesterone is not able to directly inhibit uterine contractility and does not delay the interval to delivery after successful preterm labour. However, there is evidence of a reduction in neonatal sepsis and intraventricular haemorrhage [82–86].

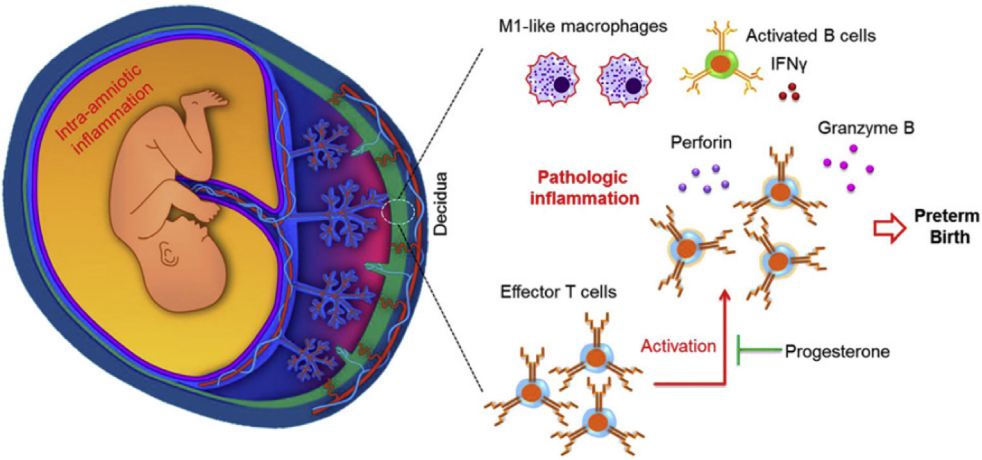

Fig. 3. Conceptual framework. Activated T cells, preterm labor and birth prevented by treatment with progesterone [80].

In-vitro models have shown that the combination of micronised P4 with nifedipine or indomethacin, but not $MgSO_4$, might be used to effectively suppress preterm labour. The mechanism of action is not clear but perhaps P4 may act on potassium channels and alter the behaviour of the β-adrenergic receptors [87].

What about safety related to pharmacodynamics?

P4 and synthetic progestins do not exhibit a class effect, in terms of both efficacy and safety [1,3]. In contrast to micronised P4, medroxyprogesterone acetate (MPA) and androgenic synthetic progestins are partial to full agonists for the AR and GR but have no significant activity via the MR or ER. The following clinical adverse effects have been reported indicating their interactions with these receptors [2]:

- AR: acne, hirsutism, weigh gain, lipid deleterious effects;
- GR: salt and water retention, bloating, breast cancer risk increase.

Another progestin, dydrogesterone (DYD: also known as "retroprogesterone") is characterised by a conspicuous change in the configuration of the P4 molecule with a clear difference in structure, metabolism, pharmacologic activities and effects [1]. Compared to natural P4, synthetic progestins including DYD are devoid of tranquilising, antiandrogenic, diuretic, tocolytic and neuroprotective effects, all of which may be of great importance during maintenance of pregnancy from conception until delivery [15–17,26,29–31,84–86,88–90].

In terms of breast safety, a relative consensus has been reached that a long-duration of exposure to pharmacological progestogen levels combined with oestrogen, either through use of contraceptives (transient, albeit small elevation in the risk with current use) or by menopausal hormone therapy (MHT) (primarily with oestrogen + progestin formulations, but not oestrogen + progesterone or DYD), increases breast cancer risk [91].

It has been suggested that in normal luminal breast cells and in breast cancer cells, P4 and MPA combined with oestradiol (E2) treatment have opposing mitogenic effects due to interaction with GR. GR activity seems to discriminate between P4 and MPA effects in breast cells [92]. After two months of treatment with oral conjugated equine oestrogens (CEEs), MPA induced a highly significant increase in breast cell proliferation/apoptosis ratio markers (Ki-67 and bcl-2) and significantly enhanced mammographic breast density – an important risk factor for breast cancer. Similar effects were not

seen with the use of percutaneous oestradiol in combination with oral micronised P4, which showed less adverse effects and different gene regulations than oral CEE/MPA in the breasts of healthy women *in vivo*. These findings were supported by a significant increase in proliferative MKi-67 gene expression with MPA but not with oral micronised P4 [93,94].

P4 may increase anti-proliferative effects when coupled with an ERα antagonist in the breast tissue. Progestogens are thought to function as a molecular rheostat to control ERα chromatin binding and transcriptional activity, and this has important implications for prognosis and therapeutic interventions. In a mouse xenograft study of oestrogen-induced tumour growth, the effect of P4 alone, tamoxifen alone or P4 + tamoxifen was studied. P4 antagonised oestrogen-induced tumour formation, as did tamoxifen alone, but the combination of tamoxifen plus progesterone had the greatest tumour inhibitory effect [95].

There is limited evidence that oestrogens combined with oral micronised P4 and perhaps DYD given for more than five years are associated with an increased breast cancer risk in MHT [96]. However, the risk ratio (RR) associated with oestrogen + DYD has been shown to be significantly above 1 for lobular breast cancer. Use of oestrogen + other progestogens has been associated with the increase in the risk of both ductal and lobular carcinomas, and of ER+/PR+ and ER+/PR-carcinomas [97].

Interactions with several steroid receptors, growth factors, oncogenes, co-activators and inhibitors, and with the cell-cycle and oestrogen-metabolising enzymes may be different for each progestogen [98]. Different chemical structures, metabolisms, pharmacokinetics, and potencies will induce different responses in the breast tissue and breast cancer tumorigenesis [99,100].

A high 3aHP-to-5aP concentration ratio in the microenvironment may foster normalcy in noncancerous breast regions. However, the production of 5 aP greatly exceeds that of 3aHP in ER/PR-negative tumours and treatment with 3aHP can effectively block tumorigenesis and cause existing tumours to regress [101].

It has been suggested that progesterone receptor membrane component 1 (PGRMC1), which is known to be overexpressed in some types of aggressive and poor prognosis breast cancers, increases the breast-cell proliferation effects of certain progestogens, including norethisterone and other synthetic progestins, including DYD. In contrast to P4, but not during oestradiol-induced proliferation for P4 and DYD, either in vitro or in a xenograft animal model based on a prospective, randomised, blinded, placebo-controlled four-arm study (45–50 days) performed to investigate if growth can be correlated with both blood concentrations and tissue expression of PGRMC1 [102].

In MHT, not only the type of progestogen but also the route of administration, timing, duration and dose have also been studied in a systematic review. This review concluded that only transdermal oestradiol, alone or in combination with micronised P4, should be considered as suitable for use in women with increased baseline venous-thromboembolic (VTE) risk or even stroke risk, when alternative non-hormonal medication was not effective [103]. Strong biological plausibility supports observational studies that suggest a lower risk of vascular effects when oral low-dose or transdermal oestradiol are used concomitantly with micronised P4 in MHT. In contrast, some progestogens, such as MPA and norpregnane derivatives, have been shown to be associated with worsened lipid profiles, glucose tolerance and a greater risk of VTE in postmenopausal women [104–106].

In a case–control study published in the Lancet, use of DYD during the first trimester of pregnancy was associated with a higher frequency of children born with congenital heart disease (75 of 202) than in the control group (36 of 200; adjusted odds ratio OR = 2.71, 95% CI 1.54–4.24, $p < 0.001$) [107,108]. In a 2.5 million patient database (Maccabi Health Services), the rate of congenital malformations among babies exposed to DYD *in utero* during the first trimester of pregnancy was higher than in those not exposed. It has been suggested that DYD conferred teratogenic effects after exposure to the recommended doses in pregnant women. The risk of hypospadias and cryptorchidism has biological plausibility, because of the known effects on male genitalia, as is the risk for spina bifida, caused by a proven decrease in folic acid levels. Some of these adverse foetal effects appear to be further augmented by concomitant use of IVF and ART [109].

Even though some evidence from two RCTs show no difference in the rate of congenital anomalies compared with vaginal natural P4 in LPS in controlled ovarian hyperstimulation fresh cycles in ART [110,111], the ESHRE Reproductive Endocrinology Guideline Group GDG considers these data insufficient to make a firm statement, because DYD is an orally active progestogen different in structure from

natural progesterone. Instead, the guideline states that there are some concerns regarding safety for the offspring, and there is a lack of long-term offspring health studies [112].

A retrospective descriptive study of 1050 women undergoing IVF/ICSI at the Reproductive Unit of Singapore General Hospital between 2000 and 2011 evaluated the live birth rate and safety profile of DYD for LPS in ARTs. In this study, seven women terminated their pregnancies following detection of foetal anomalies and 291 women delivered live birth babies [113].

In contrast, data are available from several well-designed randomised double-blind, placebo controlled trials (PREDICT, FMF study, PROMISE, PRISM and OPPTIMUM) that have investigated the neonatal effects, health and neurophysiological development of offspring and the cost-effectiveness of the use vaginal micronised P4 in the early luteal phase in ART cycles or throughout pregnancy up to 37 weeks of gestation [18,56,57,114,115].

Vaginal P4 does not appear to impact the vaginal microbiota in pregnancy; the use of vaginal pessaries has not indicated a significant "infection risk" [116].

In contrast to micronised P4, 17-OHP-C injection, which is used for the prevention of recurrent PTB, has been associated with increased rates of gestational diabetes in a prospective cohort study and in retrospective data from a large database containing information from women who received outpatient perinatal services for pregnancy-related conditions through Matria Healthcare [117,118]. The lack of efficacy of 17-OHP-C injection was confirmed in the PROLONG study, an international multicentre, randomised, double-blind trial. This lack of efficacy was not associated with increased foetal/early infant death [119].

Summary

A single class effect does not exist for micronised P4 and synthetic progestins, due to their specific pharmacokinetic and pharmacodynamic characteristics, and their genomic and/or non-genomic mechanisms of action in most of the target organs, including the uterus, breast, endothelial network, bone and brain.

This may explain why divergent clinical efficacy and safety profiles have been clearly demonstrated, not only in experimental models but also in recent well-designed randomised clinical trials.

Declaration of competing interest

The author is a consultant at Besins Healthcare Global.

Practice points

- The role of P4 in the physiopathology of pregnancy is crucial from conception until delivery and there is strong biological plausibility for the supplementation of exogenous progesterone for the management of LPS in ART, prevention of PTB in women at risk with a short cervix and/or a history of preterm delivery, and in prevention of threatened or recurrent miscarriage.
- In MHT the continuous or sequential combination of so-called "body identical" hormones, including transdermal and low-dose oestradiol and micronised P4 in standardised dosages remains the best choice for reducing risks, including deep venous thrombosis, stroke, and gallbladder diseases, without having an impact on the breast when administered in the early menopause and for a duration of at least 5–7 years.

Research agenda

- Determine the optimal daily dose of P4, route of administration and duration:
  - ✓ on endometrial receptivity during the implantation window.
  - ✓ in LPS in fresh and in frozen-thaw ET cycles in ART.
  - ✓ in symptomatic women and in pregnancy maintenance after tocolysis.
- Identify biomarkers or the pregnant women at risk who will benefit from P4 intervention for prevention of PTB, threatened miscarriage and recurrent miscarriage.
- Confirm the important role of progesterone in bone formation, improvement of VMS and sleep improvement for peri- and postmenopausal women.
- Establish the mid- and long-term safety profile of body-identical hormones in MHT.

Acknowledgements

I thank Helen Erwood from ESPL for her expertise and help in reviewing the manuscript.

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