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Review

Systemic progesterone therapy—Oral, vaginal, injections and even transdermal?

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ABSTRACT

Several medicinal products containing progesterone are in widespread use orally for protection of the endometrium during concurrent oestrogen treatment, and injections or vaginally for support of luteal function during assisted reproduction. These indications have been established in extensive clinical testing programmes. In addition, the results of recent studies and meta-analyses suggest that vaginal progesterone is an effective method for preventing premature births in singleton pregnancies in women with a shortened cervix. In US, 17α-hydroxyprogesterone caproate is licensed to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. There is insufficient evidence from scientific studies to substantiate the transdermal application of progesterone. In particular, these preparations should not be used to oppose the effects of oestrogen on the endometrium, because even with low doses of estradiol a reliable progestogenic effect to protect the endometrium has not been proved. On the other hand, the application of transdermal progesterone preparations alone is not known to pose any risks to health.

Contents

1. Physiological effects of progesterone

Research into the physiological effects of the corpus luteum hormone began in the early decades of the 20th century [1]. Independent of each other, several research groups isolated a steroid hormone from extracts of corpus luteum that was called progestin in the USA and luteosterone in Europe. As a compromise, the name progesterone was agreed (structural formula, Fig. 1).

High blood concentrations of progesterone are reached in the female body in the luteal phase of the menstrual cycle and in pregnancy [2]. In non-pregnant women and in early pregnancy, progesterone is produced in the corpus luteum, in the later stages of pregnancy in the placenta [3].

Progesterone causes the secretory transformation of the endometrium from the oestrogen-induced proliferative phase [4].

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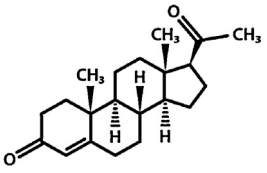

Fig. 1. Structural formula of progesterone.

Progesterone is necessary for implantation of the embryo and for the maintenance of a pregnancy, for example for the formation of decidua and uterine quiescence [3,5,6]. Progesterone is an essential component of the female reproductive system regulation not only in the uterus and ovaries but also in the breasts and in the central nervous system (CNS), where the effects are mediated by binding to specific receptors [3]. Progesterone receptors (PR) are ubiquitous [3,7] and exist in two different isoforms, PR-A and PR-B [7]. Both isoforms are coded by the same gene and are identical in sequence except that the N-terminus of PR-A is 164 aminoacids shorter than PR-B [8]. Binding of progesterone to the specific receptors leads to dimerisation, conformational change and – with the involvement of a large number of co-regulatory substances – binding to the distal elements of target genes, which is followed by regulation of gene transcription [7]. These processes are of a hitherto unforeseen complexity and include interactions with other signalling pathways [7]. Within one to two minutes, optically detectable aggregates are formed by the liganded progesterone receptor-coregulator complexes bound to the cell nucleus matrix and to DNA [9]. Increased amounts of such aggregates have been demonstrated in the endometrium of healthy women in the secretory phase (with high plasma progesterone concentrations) [10]. They had an average diameter of 0.65 μm and showed marked areas of high transcription activity [11].

2. Therapy with micronised oral and vaginal progesterone and with progesterone injections

As long ago as the 1940s, the chemist Russell Marker synthesised large amounts of pure progesterone from the plant substance diosgenin [12]. However, very high oral doses of the progesterone preparations available at that time were needed to achieve biological effects. Adequate absorption of progesterone was later achieved especially using micronised particles of the substance. In 1980, soft gelatin capsules containing natural micronised progesterone in an oily suspension were licensed in France as Utrogestan® [13].

The licensed indication of oral progesterone (Utrogest®) is protection of the endometrium in women undergoing oestrogen treatment for peri- and postmenopausal oestrogen deficiency symptoms or after surgically-induced menopause [14].

Various clinical trials have established that the sequential oral use of 200 mg progesterone daily offers reliable protection against undesirable effects of oestrogen on the endometrium, i.e. it prevents endometrial hyperplasia [15–17].

The USA PEPI study [15] is still regarded as a *Landmark Trial* [18] in terms of the endometrial safety of hormone replacement therapy (HRT). A total of 875 women were treated for 3 years with various HRT regimes, including one arm with oral administration of 200 mg micronised progesterone daily on 12 days of every month as an addition to a standard dose of 0.625 mg conjugated equine oestrogens (CEE) daily. With this form of added progestogen and also with sequential or continuous addition of medroxyprogesterone acetate (MPA), the incidence of endometrial hyperplasia was of a similarly low order as that found under placebo (1–4% of the women), whereas the 3-year use of oestrogen alone led to such hyperplasia in 62% of the women. The clinical safety of a combination of progesterone (200 mg daily, p.o. sequentially on 12 days per month) and oral conjugated oestrogens or transdermal estradiol over a total of 4 years were confirmed in the KEEPS study, which still has to be published in detail [19].

The transition from the reproductive to the post-reproductive phase in a woman's life lasts several years [20]. It is characterised by cycle disturbances ranging from dysfunctional bleeding to secondary amenorrhoea, which can be treated with oral micronised progesterone [21,22].

In women with non-functioning ovaries, the availability of progesterone measured after vaginal application was higher than after oral use of the soft gelatin capsules, whereas the blood levels after intramuscular administration were excessively high [23]. It was also shown that although plasma progesterone concentrations after repeated intramuscular injection of 2×50 mg were substantially higher than after repeated vaginal application of 4×200 mg progesterone, the ratio was reversed in uterine tissue, with 10 times higher concentrations after vaginal compared with intramuscular administration (Fig. 2) [24]. These and other investigations demonstrated that there is an accumulation of progesterone in uterine tissue after vaginal application—a so-called uterine first-pass effect [25].

Progesterone is a standard of care to support the luteal phase in assisted reproduction cycles [26].

In the United States, progesterone in oil injected intramuscularly (IM) has traditionally been the most popular form of luteal support [27,28]. As a new option, an aqueous progesterone preparation becomes available for subcutaneous (SC) injection with similar exposure as an equivalent dose of IM progesterone in oil but with higher and prompter progesterone peak concentrations [29]. When used as luteal support in assisted reproduction, the SC progesterone in a daily dose of 25 mg produced similar pregnancy and live birth rates in comparison with a vaginal progestone gel (90 mg daily) [30].

Vaginal progesterone has been used for more than 20 years to support luteal function and early pregnancy after assisted reproduction [31,32]. A meta-analysis [33] showed that the vaginal application of 3×200 mg micronised progesterone in the luteal phase is often used in trials and may therefore be recommended on a broad empirical basis. Supplementation with vaginal progesterone up to the 8th–12th week of pregnancy is common practice in IVF centres throughout the world [34].

Over the last ten years there has been a rekindling of interest in the use of progesterone to prevent premature births in spontaneous pregnancies [35]. A double-blind, randomised trial in pregnant women with a history of spontaneous preterm birth found that weekly IM injections of 250 mg of 17α-hydroxyprogesterone caproate (17α-HCP) significantly reduced the risk of preterm delivery at each relevant gestational age by more than 30% [36]. Although the study was criticised because its very high rate of preterm birth in the placebo group, it finally led to authorisation of 17α-HCP to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth in the United States [37].

Vaginally applied progesterone was used in women with a shortened cervix in two large [38,39] and other smaller clinical trials. The meta-analysis of individual patient data from these studies in pregnant women with a cervical length ≤25 mm showed a significant reduction of 42% (relative risk 0.58; 95% confidence interval 0.42–0.80) in the primary endpoint, i.e. the rate of pre-term births (<33rd week of pregnancy), in women treated with vaginal progesterone (12.4%) versus placebo (22.0%) [40]. There were also significant reductions in all secondary endpoints, including peri- and neonatal morbidity and mortality, with vaginal progesterone compared to placebo. In terms of safety, there were no untoward effects with vaginal progesterone. In the meantime, treatment with progesterone is the most promising pharmacological approach to

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