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Ruan X, Mueck AO

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Systemic Progesterone Therapy – Parenteral, oral, vaginal and even transdermal?*

X. Ruan¹, A.O. Mueck^{1,2}

The therapeutic use of progesterone, which is identical to the female corpus luteum hormone, is becoming increasingly popular both for doctors and women. Several medicinal products containing progesterone are in widespread use orally (protection of the endometrium during concurrent estrogen treatment), parenterally or vaginally (support of luteal function in the course of assisted reproduction). These indications for progesterone 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 and practical method for preventing premature births in singleton pregnancies in women with a shortened cervix. In the United States, 17 α -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.

The administration of progesterone through the skin is also being promoted, although there is insufficient evidence from scientific studies to substantiate the transdermal application of progesterone. In particular, transdermal progesterone preparations should not be used to oppose the effects of estrogen on the endometrium, because even with comparatively low doses of estradiol (1 mg daily as a transdermal gel) 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.

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Key words: progesterone therapy, parenteral, oral, vaginal, transdermal

■ 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 estrogen-induced proliferative phase [4]. 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 [3–6]. Progesterone is an essential component of the female reproductive system regulation not only in the uterus and ovaries but also in the breasts

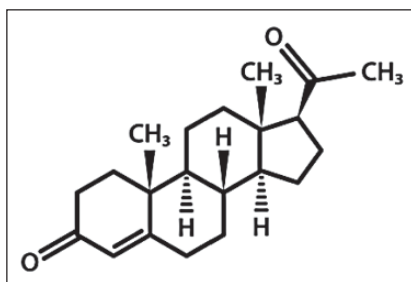


Figure 1. Structural formula of Progesterone

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-coregula-

tor 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 μ m and showed marked areas of high transcription activity [11].

■ Rational Therapy with micronised oral and vaginal Progesterone as well as 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

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From the ¹Department of Gynecological Endocrinology, Beijing Obstetrics & Gynecology Hospital, Capital Medical University, Beijing, China, and the ²Department of Gynecological Endocrinology and Centre of Research on Women's Health, University Women's Hospital of Tuebingen, Germany

Correspondence: Alfred O. Mueck, MD, PharmD, PhD, University Women's Hospital of Tuebingen, Head of the Sections Endocrinology and Menopause, Calwer Street 7, D-72076 Tuebingen, Germany; e-mail: Alfred.Mueck@med.uni-tuebingen.de

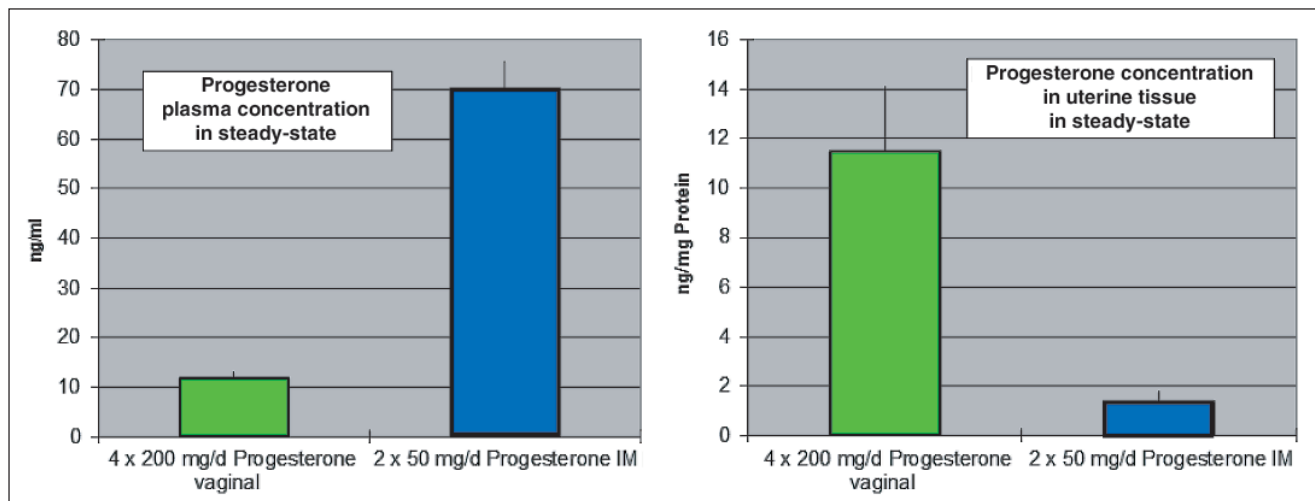


Figure 2. Plasma concentrations (mean $\pm$ standard error in ng/ml) and concentrations in uterine tissue (mean $\pm$ standard error in ng/mg protein) after repeated vaginal application of 4 $\times$ 200 mg/d progesterone ($n = 15$) or repeated i.m. injection of 2 $\times$ 50 mg/d progesterone in oil ($n = 5$). Data from [24].

endometrium in women undergoing estrogen treatment for peri- and postmenopausal estrogen 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 estrogen 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 three 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 estrogens (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 estrogen 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 estrogens or transdermal estradiol over a total of four 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 $\times$ 50 mg were substantially higher than after repeated vaginal application of 4 $\times$ 200 mg progesterone, the ratio was reversed in uterine tissue, with ten 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 progesterone 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 $\times$ 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, randomized trial in pregnant women with a history of spontaneous preterm birth found that weekly IM injections of 250 mg of 17 α -hydroxyprogesterone caproate (17 α -HCP) significantly reduced the risk of preterm delivery at each relevant gestational age by more than 30% [36]. Although the study was criticized because its very high rate of preterm birth in the placebo group, it finally led to authorization of 17 α -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%-CI: 0.42–0.80) in the primary endpoint, i.e. the rate of pre-term births ($< 33^{\text{rd}}$ week of pregnancy), in women treated with vaginal progesterone (12.4%) vs 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 the primary prevention of pre-term births in women with a history of prematurity or with a shortened cervix in singleton pregnancies [41, 42].

■ The Transdermal Use of Progesterone

The administration of progesterone through the skin was successfully promoted by the American doctor, **John R. Lee**. In his book “*Natural Progesterone*”, Lee described numerous positive effects of progesterone on menopausal symptoms, osteoporosis, cancer and diseases of the uterus, when the substance is applied as a cream to the skin. The tradition was continued in the USA by **Michael E. Platts**, a Californian doctor. In his book “*The Miracle of Bioidentical Hormones*”, he rates progesterone as the principal hormone for women. Many female complaints are said to be due to endogenous estrogen dominance. Progesterone can achieve a hormonal stabilisation; administration through the skin is supposedly sufficient.

The transdermal application of progesterone with the intention of systemic treatment is not to be equated with local treatment. Application of a progesterone gel to the breast led to a reduction in the increased proliferation of the breast epithelial cells caused by previous administration of estradiol to pre- and postmeno-

pausal women [43, 44]. Breast pain and breast tenderness were also abolished with a 1% progesterone gel [45]. The progesterone gel (Progestogel®) has been licensed by several regulatory authorities for the treatment of essential premenstrual mastodynia.

■ Creams or Gels with Progesterone – Pharmacokinetic Data

Reservations about the administration of progesterone through the skin principally concern the unreliable or inadequate therapeutic serum levels when progesterone is administered via that route [46]. These reservations also raise doubts about corresponding systemic effects [47]. To date, peak progesterone serum levels considerably > 1 ng/ml have only occasionally been measured after repeated transdermal application of various doses (predominantly 40 mg progesterone daily) [48, 49]. In the majority of studies [50–53], the average progesterone level was ≤ 1 ng/ml; this also applied to long-term transdermal use of 40 mg progesterone daily as a 6% cream (Progestelle®). However, as postmenopausal progesterone serum levels are usually very low (0.015–0.105 ng/ml, median 0.04 ng/ml) [55], significantly higher values in comparison with the daily use of a placebo cream were reported in more extensive controlled trials in which transdermal doses of 5–60 mg progesterone daily as a cream (Progestelle®) were used [56]. A systemic availability of progesterone was demonstrated in another study at a high dosage (2×40 mg daily) and therefore the supply of progesterone cream without a prescription or medical supervision was questioned in the USA as a matter of principle [57]. However, transdermal progesterone preparations (5–15 ng/ml) are generally unable to achieve luteal serum levels of progesterone (5–15 ng/ml) [46, 58].

Nevertheless, one study reported a significant although individually highly variable increase in salivary progesterone concentrations after a single application of a progesterone cream (64 mg). The increase was considerably greater in premenopausal (460 ± 372 nmol/l after 4 hours) than in postmenopausal women (58 ± 26 nmol/l after 1 hour) [59]. In one of the above-mentioned studies [53], groups of eight postmenopausal women

used an investigational product containing 20 or 40 mg/g progesterone or placebo $2 \times$ daily over two treatment cycles, each of three weeks. Here again, only the salivary concentrations substantially exceeded those after placebo, with peak levels of 82 ± 105 nmol/l for the lower dose and 60 ± 66 nmol/l for the high dose, compared to values of 0.4 ± 0.2 nmol/l with placebo. The variability was, however, considerable.

In a recently published American study [60] ten postmenopausal women applied 80 mg progesterone daily as cream or gel to the inner thigh. A sophisticated analytical technique was used to remove metabolites of progesterone that could interfere with the radioimmunoassay. As before, mean peak serum progesterone concentrations were < 1 ng/ml after 14 days of application. However, about 10-fold higher progesterone values were measured in saliva and 100-fold higher concentrations in fingertip capillary blood. Although the transport mechanism is unclear, the authors [60, 61] considered their results to be an indication that transdermal application of progesterone can achieve high tissue levels of progesterone that could be of therapeutic relevance.

An overview of the results of pharmacokinetic studies is given in Table 1.

■ Progesterone Administration through the Skin – Endometrial Protection

Topical progesterone is mainly of interest in connection with the treatment of (post)menopausal complaints and as an alternative to conventional HRT [46, 47].

A significant aspect of this use of progesterone – and progestogens in general – is protection of the endometrium during estrogen treatment. Blood or tissue concentrations are insufficient for topical progesterone to be used as endometrial protection; well-planned clinical trials with histological evaluation of biopsy material are needed [46, 58].

The European drug regulatory authorities stipulate that for this purpose, data from 300 women with evaluable biopsy material before and one year after treatment are required, whereby only about two cases of endometrial hyperplasia or serious histological findings may occur

Table 1. Overview of the results of pharmacokinetic studies.

Study	No. of patients	Dosage per day and treatment duration	Mean serum levels~	Mean salivary levels~	Further outcomes
Zargar-Shoshtari [62]	20	40 mg/day for 15 days	B: 0.1 ng/ml A: 1.4 ng/ml	B: 0.4 ng/ml A: 2.9 ng/ml	– High intraindividual differences – The low bioavailability of transdermal progesterone seems not to be caused by the metabolism by the 5-reductase
Lewis [53]	24	40–80 mg/day; 8 weeks (week 4 + 8 w/o use)	P: 0.3 nmol/l A: 1.5 nmol/l	P: 0.4 nmol/l A: 44.9 nmol/l	– Erythrocytes seems not to be involved in the transport of progesterone into peripheral tissues as progesterone was not concentrated in those cells (P: 0.4 nmol/l; A: 0.6–0.27 nmol/ml)
O’Leary [59]	6	1 × 64 mg	B: 2.5 nmol/l A: 3.6 nmol/l	B: 0.3 nmol/l A: 58 nmol/l (after 1 h)	– No increase in urinary excretion of progesterone and its metabolites after application of the cream
Cooper [51]	20	20–40 mg/day; 10 days	P: 0.7 nmol/l A: 2.9 nmol/l		– Oral (300 mg/day) but not percutaneous use resulted in adequate serum levels (> 3 ng/ml) in this crossover placebo-controlled trial (oral: 9.5 ng/ml)
Du [60]	10	80 mg/d; 2 weeks	B: 0.06 ng/ml A: 0.6–0.7*	A: 7.4–8.7 ng/ml* (baseline not shown)	– In contrast to serum, highly elevated levels of progesterone in capillary blood
Formby [63]	29	1 cycle: E2+ 25 mg/d in week 1 50 mg/d in week 2 100 mg/d in week 3 + 4; 6 months	n.d.	B: 135 ng/ml T: 2840 ng/ml#	– Significant relief in menopausal symptoms – No control of endometrium protection
Buray [48]	6	(i) 30 mg/day for 2 weeks; (ii) 60 mg/day for 2 weeks	B: 0.2 ng/ml A: (i) 1.6 ng/ml (ii) 2.3 ng/ml		– Strong intraindividual differences regarding C _{max} and T _{max} (1–12 h) – Transdermal absorption of progesterone correlated with the absorption of estradiol
Leonetti [64]	26	2 × 20 mg/day + CEE 0.625 mg/day 6 months	n.d.	–	– Results from endometrial biopsies suggest similar efficacy as MPA
Carey [52]	24	40 mg/day; 6 weeks	B: 0.0 nmol/l A: 2.8 nmol/l		
Leonetti [65]	102	20 mg/day; 12 months	n.d.		– No protective effect on bone density after 1 year – Significant improvement in vasomotor symptoms
Vashisht [54]	41	40 mg/day + 1 mg E2; 48 weeks	A: 2.3 nmol/l#		– One third of the subjects had evidence of inadequate endometrial opposition (proliferative or hyperplastic) – Significant reductions in menopausal symptoms
Benster [56]	223	60, 40, 20, 5 or 0 mg/day; 6 months	n.d.		– Progesterone cream was not more efficient in the treatment of menopausal symptoms as placebo
Wren [66]	27	16, 32 or 64 mg/day for 14 days per cycle + E2 patch 100 g/d	B: 0.4 nmol/l A: 1.2 nmol/l	B: 0.1–11.5 nmol/l T: 33.2– 2161.3 nmol/l	– No secretory effect on the endometrium – Salivary levels of progesterone were highly variable
Mircioiu [67]	32	1 × 90 mg	B: approx. 0.1– 0.2 ng/ml +* A: 1.0–2.3 ng/ml*		– The emulsion type base had a higher bioavailability as the hydrophilic or lipophilic base

B: Baseline; P: Placebo; A: After treatment; CEE: Conjugated equine oestrogen; MPA: Medroxyprogesterone acetate; E2: Estradiol; ~ C_{max} or measured at study endpoint; * Range indicates different formulations; + Estimation based on a figure; # Median is shown; no baseline value available

during the treatment period [68]. A proliferative endometrium is regarded as not abnormal. To date, no results of such extensive studies with topical progesterone are known.

In the most comprehensive study on endometrial safety yet published, 54 postmenopausal women aged 57 ± 5 years were given 1 mg estradiol as a gel plus

40 mg progesterone as 6% cream daily for 48 weeks; 41 women were evaluable [69]. After 24 weeks a weak progestogenic protective effect was confirmed in six women with proliferative endometrium (15%), after 48 weeks in 12 women (32%), of whom a proliferative endometrium was diagnosed in ten cases and hyperplasia in two (5%). Consistent with a weak progesterone effect, the ultrasound

endometrial thickness increased significantly from an initial average of 3.3 ± 1.7 mm to an average of 5.3 ± 3.3 mm after 24 weeks and 5.5 ± 2.8 mm after 48 weeks. Significantly higher endometrial thickness was measured in women with a proliferative endometrium or hyperplasia than in the other women. The recording of bleeding episodes also reflected a weak progestogenic effect, be-

cause the proportion of women with complete amenorrhoea fell during the study from 48% after 24 weeks to 35% after 48 weeks. Due to inadequate endometrial protection, the authors did not recommend the combination of 6% cream at the chosen dosage of 40 mg daily and an estrogen preparation. However, the 5% (two cases) incidence of hyperplasia as a significant criterion after almost one year was not particularly noteworthy. An increased incidence of cases of proliferative endometrium compared to oral administration was also measured with the transdermal use of estradiol plus norethisterone acetate [70]. A dependence of the frequency of diagnosis of a proliferative endometrium on the progestogen dose was, for example, demonstrated for oral combinations of 1 mg estradiol with 0.5 mg to 3 mg drospirenone, but in view of the simultaneous absence of hyperplastic findings after one year of treatment, was not considered relevant for endometrial safety [71].

Taking second place among the studies on endometrial safety with transdermal progesterone was a cross-over study by Leonetti et al [64] in which 33 postmenopausal women with a mean age of 57 years (range 49–75) were enrolled, of whom only 26 completed the study and provided evaluable data. The women had already been treated with oral CEE plus MPA and after a two-week pause in treatment, a baseline endometrial biopsy was obtained. They were then randomised to a group who continued their oral treatment with 0.625 mg CEE plus 2.5 mg MPA daily for six months, or to a second group who received 0.625 mg CEE plus transdermal 20 mg progesterone daily as Progest® cream for six months. They then underwent a second endometrial biopsy and, after a two-week pause in treatment, were switched to the other treatment for six months. A third biopsy was carried out at the end of the study. In not a single biopsy sample was hyperplasia or a serious result found. A proliferative endometrium was diagnosed in five of 26 women (19%) after the combination with transdermal progesterone and in seven women (27%) after the combination with oral MPA. Bleeding, which consisted exclusively of spotting and did not require any special hygiene measures, was reported by five women (19%) during the combination with transdermal progesterone and by

seven (27%) with oral MPA. At the end of the study, 20 women (77%) preferred the combination with transdermal progesterone and five (19%) the combination with oral MPA. The authors regarded the lack of hyperplastic changes as encouraging, despite the small collective and the short treatment pauses between the different regimes.

In another smaller investigation, the same research group confirmed an anti-proliferative effect of four weeks of daily transdermal progesterone after two weeks' previous treatment with 0.625 mg CEE daily [72]. On the other hand, the Australian researchers led by Wren [73] showed no progestogenic effect of the sequential addition of transdermal progesterone 16–64 mg daily given for 14 days per 28-day cycle to continuous use of 100 µg estradiol daily; about 90% of the women showed a proliferating endometrium after three cycles. Such small short-term studies are, in principle, unsuitable for investigating a protective effect against estrogen-induced endometrial hyperplasia.

Overall, even proponents of transdermal progesterone consider further clinical trials are needed before use for endometrial protection along with estrogen treatment could be recommended [64]. Results of such studies are still awaited.

■ Progesterone Administration through the Skin – Effect on Menopausal Symptoms

Although estrogens or estrogen-progestogen combinations are the most effective form of treatment for menopausal symptoms [74], it has been known for a long time, that progestogens alone such as MPA [75, 76] or megestrol [77, 78] can relieve hot flushes (US-flashes) [79]. Yet recently, a randomised, placebo-controlled trial showed, that the frequency and severity of vasomotor symptoms can be reduced by the use of oral progesterone [80]. In more extensive studies with progestogens, the effectiveness was demonstrated particularly when treating hot flushes in patients following breast cancer [81, 82]. Progestogens can be considered as a “non-estrogen option” in patients with breast cancer, although safety has not been definitively proved to date [83].

A recent systematic review from Canada of progesterone cream analysed three randomised controlled studies on the treatment of vasomotor symptoms [84].

In a study published in 1999 by the American group of Leonetti [65], 43 postmenopausal women used 20 mg transdermal progesterone daily as a cream and 47 an identical placebo cream over the planned period of one year and could be included in the analysis. At the outset, 30 women in the progesterone group and 26 in the placebo group reported vasomotor symptoms. After four months and at the end of the study, 25 of the 30 women (83%) in the progesterone group reported an improvement or disappearance of the vasomotor symptoms, but only five of the 26 (19%) in the placebo group. The difference was significant ($p < 0.001$). However, there was no detailed analysis of the frequency and severity of the symptoms.

The Australian group of Wren [66] recruited 80 postmenopausal women with an average age of 54 years with at least one hot flush per day. 38 used 32 mg transdermal progesterone daily as a cream (ProFeme®) and 42 women a placebo cream for three months. 72 women ended the study as planned. Symptoms were assessed using the Greene Climacteric Scale or a questionnaire on menopause-specific quality of life. No information was given about sample size planning.

Serum progesterone concentrations increased significantly with the progesterone cream from 0.11 ng/ml to 0.31 ng/ml ($p < 0.001$). Overall, there were no significant changes in the parameters measured. The authors interpreted this as proof that no therapeutic effects can be achieved with the dose of progesterone cream used.

In the largest study [56], 223 postmenopausal women aged between 40 and 60 years with moderate to severe symptoms were randomly assigned to five groups each of 43 to 46 women, who used a placebo cream or a cream containing 5, 20, 40 or 60 mg progesterone (Progestelle®) daily for six months. The primary analysis was based on the Greene Climacteric Scale. Vasomotor, psychological and somatic symptoms decreased in all groups including placebo. A dose-dependent

Table 2. Indications of a rational systemic progesterone therapy according to route of administration.

Route of administration of progesterone	Indication	Dosage	Licence
Oral	Peri-/postmenopause: – Protection of endometrium during simultaneous oestrogen therapy	200–300 mg daily	Yes
	Pre-/perimenopause: – Treatment of dysfunctional bleeding	200–300 mg daily	(Yes)*
Parenteral (IM, SC)	After assisted reproduction: – Support of luteal function	25 (SC), 50–100 mg (IM) daily	IM (Yes)* SC pending
	Later pregnancy (only 17 α -HCP): – Prevention of premature births in singleton pregnancies in women who have a history of singleton spontaneous preterm birth	250 mg weekly (IM)	Yes (in USA)
Vaginal	After assisted reproduction: – Support of luteal function	90–600 (800) mg daily	Yes
	Later pregnancy: – Prevention of premature births in singleton pregnancies in women with a shortened cervix	90–200 mg daily	No
Transdermal	Not recommended for systemic treatment!		No

* Depending on country

trend towards a reduction in the weekly incidence of hot flushes and night sweats was found, but was not significant even with the highest dosage of 60 mg progesterone daily ($p = 0.07$). A non-significant effect on the vasomotor components of the Greene Climacteric Score was also measured with 40 mg progesterone ($p = 0.06$). A slight effect on vasomotor symptoms, which would have required larger patient groups for it to be confirmed, can therefore not be excluded.

The studies published to date – although of adequate duration of treatment – do not take account of the existing testing requirements of drug regulatory authorities concerning the choice of patients, the parameters or the methods used to evaluate them in order to estimate drug effects on vasomotor symptoms, especially hot flushes [68, 85].

In the summary of the systematic review, the authors state that, given the current state of knowledge, progesterone cream cannot be recommended for the treatment of menopausal symptoms and that further studies are needed [84].

■ Progesterone Administration through the Skin – Effect on Bone Metabolism, Lipids, inflammatory and clotting Parameters and Atherosclerosis

In the already cited study by Leonetti et al [85], no differences were found in the changes in bone mineral density in the

lumbar spine, femoral neck or hips measured by X-ray absorptiometry (DEXA) after one year of treatment with progesterone cream or placebo. The lipid values also showed no differences between the groups.

Similarly, no effects of progesterone cream on lipids or parameters of bone metabolism were observed in the 12-week study by Wren et al [66] and also no differences compared with placebo – although the informative value of the study is considerably reduced due to the limited period of treatment.

Likewise, no effects on various parameters of coagulation or inflammation were seen in a small cross-over study with 30 postmenopausal women who applied 20 mg progesterone daily as a cream or a placebo for four weeks [86].

In the largest study conducted on this question so far, 131 postmenopausal women between 50 and 75 years, each with at least one atherosclerotic plaque detected by ultrasound were divided into groups and instructed to use 40 (2 × 20) mg progesterone as cream (pro-juven®) or placebo for three years [87]. Outcomes measured during the course of the study were plaque thickness, intima-media thickness, bone mineral density of the femoral neck and lumbar spine and various laboratory values (especially lipids). In each group 56 women were evaluable for the analysis. No significant differences between progesterone cream and placebo were found for any of the parameters measured. The authors con-

cluded that in the dosage used, the progesterone cream has no influence on the course of atherosclerosis or the preservation of bone.

■ Rational Therapy with Progesterone – Conclusions (Tab. 2)

Progesterone opposes the effects of estrogens on the endometrium. This is the basis of the licensed indication of endometrial protection for oral progesterone and also the treatment of dysfunctional bleeding in pre- and postmenopausal women.

In addition, progesterone is necessary for the implantation of the embryo and for the maintenance of a pregnancy. This explains the successful use of parenteral or vaginal progesterone to support luteal function after assisted reproduction, which is another licensed indication. A further area of rational use has opened up for the use of parenteral or vaginal progesterone for preventing premature births in singleton pregnancies in women at risk.

In contrast, reservations exist about the administration of progesterone through the skin, largely because the serum levels are low, which in turn raises doubts about corresponding systemic effects. The therapeutic significance of higher progesterone values in saliva or capillary blood is unclear. The data on the use of progesterone cream for endometrial protection during simultaneous use of estrogen, or as sole treatment for menopausal symp-

toms, are contradictory and overall inadequate. Studies conducted to date with progesterone cream have shown no consistent effects on bone metabolism, lipids, inflammatory and clotting parameters or on the progression of atherosclerosis.

According to the current position statements of the North American [71] and the International Menopause Society [88] bioidentical hormone preparations, including progesterone creams compounded in pharmacies, have not been adequately tested with regard to efficacy and risks and should therefore not be used as a general rule. However, experience to date shows no serious risks. Transdermal use of progesterone can produce local effects, for example, on the breast. Nevertheless, application through the skin is currently not a form of rational systemic progesterone therapy.

Conflict of Interest

Both authors have received funding for the research and education activities from manufacturers developing sexual steroids including progesterone. They have been investigators of trials in this field sponsored by various pharmaceutical companies. Both authors serve on the board of several societies and journals covering this field of treatment using sexual steroids.

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