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REVIEW

The history of natural progesterone, the never-ending story

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ABSTRACT

The term progesterone should only be used for the natural hormone produced by the ovaries or included in a registered drug. The modern history of progesterone begins with the first book-length description of the female reproductive system including the corpus luteum and later with the Nobel Prize winner, Adolf Butenandt who took a crucial step when he succeeded in converting pregnanediol into a chemically pure form of progesterone, the corpus luteum hormone. The deficient production of progesterone was shown first to be the cause of the luteal-phase deficiency responsible for infertility and early pregnancy loss due to inadequate secretory transformation of the endometrium. Later, progesterone was confirmed to be the best and safest method of providing luteal-phase support in assisted reproductive technology. Progesterone provides adequate endometrial protection and is suggested to be the optimal progestagen in menopausal hormone therapy in terms of cardiovascular effects, venous thromboembolism, probably stroke and even breast cancer risk. Neuroprotective effects of progesterone have also been demonstrated in several of experimental models including cerebral ischemic stroke and Alzheimer's disease. Vaginal progesterone was shown to decrease the risk of preterm birth in women with a mid-trimester sonographic short cervix and to improve perinatal outcomes in singleton and twin gestations.

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Introduction

There is a lot of confusion in the literature about natural progesterone, progestagens, progestogens and progestins. The term progesterone should only be used for the natural hormone produced by the ovaries or included in a registered drug, qualified as 'body identical' or 'bioidentical' and different from custom-compounded bioidentical hormones[1,2]. It should never be used as a generic one to design different natural or synthetic compounds[3]. The functional terms 'progestogens' or 'progestagens' refer to natural or synthetic molecules with progestational activity, those which prepare the uterus for pregnancy. The term 'progestin' is used for synthetic compounds, designed to target the progesterone receptors, and belonging to different classes of molecules with sometimes very different pharmacological properties and modes of action[4–6].

Progesterone in early pregnancy

In fact, the history of progesterone spans 500 million years and it is the oldest hormone that we know about[7]. However, the 'modern' history of progesterone begins with Regner de Graaf, a young Dutchman of Delft who published in 1672 his *De mulierum organis generation inservientibus*, the first book-length description of the female reproductive system, including the corpus luteum[8].

In 1898, 226 years later, the French histologist Louis-Auguste Prenant and, at about the same time, the great embryologist Gustav Born of Breslau suggested that the corpus luteum is an organ of internal secretion protecting the early embryo and facilitating its implantation in the uterus[9]. About 10 years later, the French embryologist Paul Ancel and the histologist Paul Bouin correctly supposed that the histological alterations of the endometrium that they had discovered were produced by endocrine activity of the corpus luteum[10].

Finally, while working in Professor George Corner's US embryology laboratory, Professor Willard Allen, an organic chemist who went on to study medicine, discovered the hormone in the corpus luteum that sustained pregnancy and that was essential for survival of the preimplanted embryo in rabbits[11]. It is noteworthy that the term 'hormone' was coined by the British physiologist Ernest Starling during one of his lectures in 1905, to define chemical signaling molecules produced by glands in multicellular organisms that are transported by the bloodstream to target distant organs and referring to a so-called endocrine mode of signaling[12].

The corpus luteum hormone was obtained in crystalline form from corpus luteum in 1931 and 1932 by various workers including Butenandt and Westphal in Danzig, Slotta in Breslau, and Hartmann and Wettstein in Switzerland[9]. It was isolated later by Allen in 1933[13]. Oscar Wintersteiner of New York completed the purification of Allen's progesterone and determined the empirical formula[14].

In the autumn of 1934, Professor Adolf F. J. Butenandt and Schmidt succeeded in converting pregnanediol into a chemically pure form of the corpus luteum hormone, which

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was given the name progesterone, a contraction of '*proges*tin' and 'luteo-*sterone*' in agreement with all the above contributors during a garden party given by the English pharmacologist Sir Henry Dale; he was Chairman of the conference of the Health Organization of the League of Nations (London, 1935) charged with setting up International Standards for some of the sex hormones including the new hormone of the corpus luteum[14].

At the same time, Fernholz synthesized the hormone from stigmasterol but the production of this crystalline pure form was extremely difficult and time-consuming, and prices of progesterone were as high as $1000 per gram[15].

In 1939, the synthesis of this pregnancy hormone from cholesterol was carried out by Professor Adolf Butenandt in a straightforward way and he was awarded the same year, together with Leopold Ruzicka, the Nobel Prize in Chemistry for their work on sex hormones.

In 1938, Russell Earl Marker found that the sterol sarsasapogenin from the *Sarsaparilla* plant could be converted into progesterone. However, sarsaparilla was expensive and, continuing his research, he isolated in 1941 a sterol, named diosgenin, extracted from the *Dioscorea* species of a yam growing wild in Mexico; this sterol could also be converted into progesterone using a technique which has since become known as the 'Marker degradation'[15]. After using a friend's lab to convert diosgenin into three kilograms of progesterone, he formed in 1944 the Syntex Company in Mexico City with two partners. Because of the low cost of Russell Marker's progesterone, it later became the preferred precursor to cortisone and, by 1951, Syntex developed the first oral contraceptive from progesterone[16].

Georgeanna Seegar Jones, who became in 1949 the director of Johns Hopkins' Laboratory of Reproductive Physiology, was credited with using progesterone to treat women with a history of miscarriages, thus allowing many of them not only to conceive, but to deliver healthy babies. She was the first to describe luteal-phase deficiency, a cause of infertility and pregnancy loss caused by inadequate secretory transformation of the endometrium, resulting from deficient production of progesterone[17]. In 1978, when she and her husband left Hopkins for the Eastern Virginia Medical School in Norfolk (EVMS), they created their own *in vitro* fertilization (IVF) program at EVMS. On December 28th, 1981, their procedure gave birth to Elizabeth Jordan Carr, the first American IVF baby after the birth of the first test-tube baby in the world, Louise Joy Brown, on July 25th, 1978 in England[18].

Arpad Csapo claimed that progesterone both causes the uterus to prepare itself for pregnancy and guards the embryo against premature birth by inhibiting the contraction of uterine muscle. As a pioneer, he isolated actin and myosin, two proteins responsible for contractible properties of the muscle, and developed the theory that progesterone blocks the contraction of muscles in the pregnant uterus[19,20]. However, until now there is no agreement on the exact nature of the physiological processes that control the onset of labor. He also found that early pregnancy luteectomy produces miscarriages through loss of progesterone support and that the contraction-blocking action of the progesterone shifted from the ovaries to the placenta, the so-called 'luteo-placental shift'[21,22].

Progesterone and brain

In the early 1940s too, it was shown by Hans Seyle that high doses of progesterone can very rapidly modulate brain excitability by inducing anesthesia in rats[23]. In the 1970s, Karavolas and collaborators showed that progesterone was converted to 5α-dihydroprogesterone and allopregnanolone within the rat hypothalamus and pituitary gland[24]; in 1986 came the demonstration that both allopregnanolone (3α,5α-tetrahydroprogesterone) and 3α,5α-tetrahydrodeoxycorticosterone are natural positive modulators of neuronal $GABA_A$ receptors, providing a mechanistic insight into the rapid psychopharmacological actions of progesterone and its metabolites, including anxiolytic, antidepressant, anesthetic, anticonvulsant, and analgesic effects[25].

In 2008, progesterone was suggested to act as a 'physiologic' regulator in case of sleep disturbances rather than as a hypnotic drug in aging and postmenopausal women, where sleep is fragmented and of lower quality (Figure 1)[26,27].

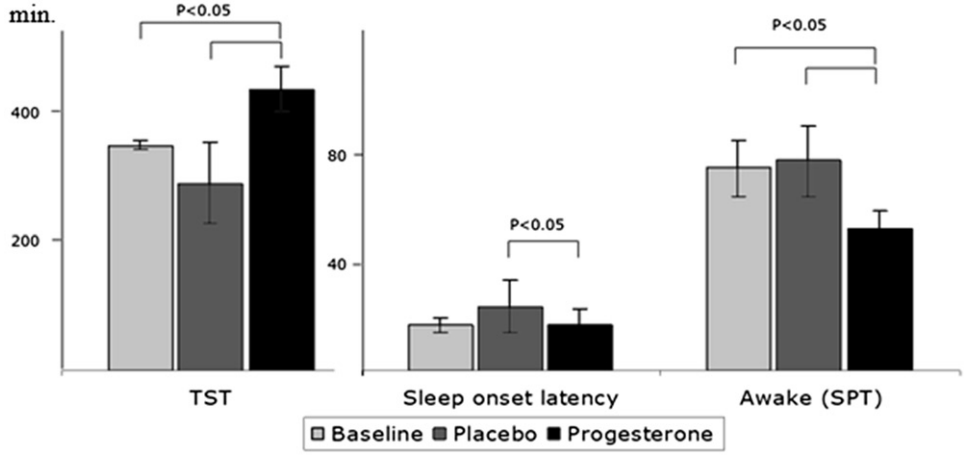

Figure 1. Sleep EEG parameters (minutes) before treatment (baseline), at day 21 placebo and day 21 oral progesterone treatment, 300 mg once a day in postmenopausal women. Total sleep time (TST) is the total time spent asleep. Sleep period time (SPT) is the time between sleep onset and last epoch of sleep in the morning. Awake SPT: awake corresponding to sleep period time. Data are given as mean ± standard deviation. Adapted from Schüssler[26].

Neuroprotective effects of progesterone and allopregnanolone have been suggested in neonates[28] and demonstrated in many injury models, including cerebral ischemic stroke[3,29], excitotoxic damage of hippocampal neurons[30], traumatic spinal cord injury[31], in mouse models of spontaneous spinal motoneuron degeneration and Alzheimer's disease[32,33]. The view that the neuroprotective and regenerative effects of progesterone in the brain may be primarily mediated by allopregnanolone has recently been challenged by the observation that progesterone receptors play a key role in the viability of neurons after ischemic stroke and in the remyelination of axons after a demyelinating lesion[29,34], with also potential significant therapeutic implications in patients with multiple sclerosis and carpal tunnel syndrome[3]. Endogenous levels of progesterone were also found to correlate positively with factors predicting better prognosis and survival of patients with amyotrophic lateral sclerosis[35].

Progesterone in menopausal hormone therapy

In 1966, Robert A. Wilson's book informed women that menopausal symptoms were completely preventable, advising them to take estrogen with the promise of remaining '*Feminine forever*'. When it later became obvious that the risk of endometrial cancer was increased at least by 2.7 times in women treated with estrogen compared to untreated women, the medical community suggested progestagen to protect the uterus[36–38].

Initially, an oral formulation of progesterone was not used for menopausal hormone therapy (MHT) because of poor bioavailability, rapid hepatic metabolism and hence a rapid clearance rate. In the late 1970s, it was shown that decreasing the size of progesterone particles below 10 μm through micronization substantially increased the bioavailability of the hormone, partly suspended in peanut oil and partly in solution[39,40]. The first approval for an oral progesterone capsule prepared by the Besins Company (France), under the brand Utrogestan®, was granted in the early 1980s[41]. Interestingly, apart from its main progestational action, natural progesterone exerted antiandrogenic, antimineralocorticoid and neuroprotective, regenerative and sedative effects due to its unique pharmacodynamic profile[4,42–44].

In the meantime, synthetic analogs of progesterone were developed to make the hormone available orally for use as a contraceptive agent, but many of these compounds bound to receptors for glucocorticoids, androgen and mineralocorticoids, inducing possible side-effects such as acne, weight gain, depression, mood swings, irritability and increased breast cancer risk in MHT users. No synthetic progestin could mimic the same hormonal activities as the native progesterone hormone[41].

In 1983, researchers led by Malcolm Whitehead at King's College Hospital Medical School (London) showed dose-dependent effects of oral progesterone on the estrogenized postmenopausal endometrium[45]. Later, adequate endometrial protection was demonstrated in MHT when micronized progesterone was administered as a cyclic combined regimen (200 mg for 12 days each month) or as a continuous

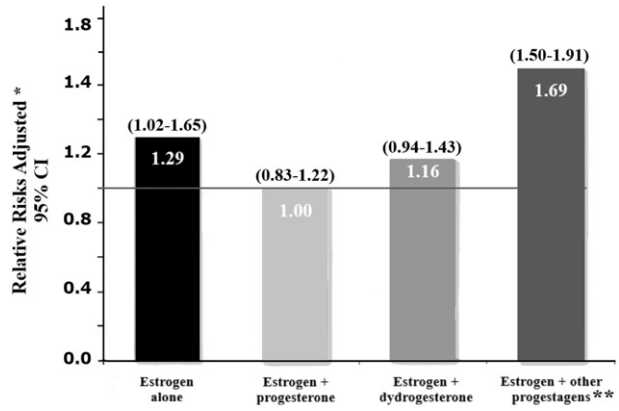

Figure 2. Relative risks for invasive breast cancer by type of hormone replacement therapy (HRT) and progestogens compared with HRT never-use in the E3N cohort study. *Adjusted for time since menopause (time scale), age at menarche (<13/≥13 years old), parity and age at first full-term pregnancy (nulliparous/first full-term pregnancy at age <30, 1 or 2 children/first full-term pregnancy at age <30, 3 or more children/first full-term pregnancy at age ≥30), breastfeeding (no/< 12 months/≥ 12 months/unknown), age at menopause (continuous), type of menopause (artificial/natural or unknown), personal history of benign breast disease (yes/no), family history of breast cancer in first-degree relatives (yes/no), family history of breast cancer in other relatives (yes/no), body mass index (≤20/[20–25]/[25–30]/> 30 kg/m^2), physical activity (<34/[34–47]/[47–62]/≥ 62 MET-h/week), previous mammography (yes/no, time-dependent variable). Further stratified on year of birth ([1925–1930]/[1930–1935]/[1935–1940]/[1940–1945]/[1945–1950]). **Other progestagens: medrogestone, chlormadinone acetate, cyproterone acetate, promegestone, nomegestrol acetate, norethisterone acetate, medroxyprogesterone acetate. Adapted from Fournier[57].

combined regimen of 100 mg per day, typically >2 years post final menstrual period[46–50]. The same dose appeared to be devoid of side-effects on blood pressure, lipid profile and thrombotic risk, contrary to those caused by 19-nortestosterone derivatives and other synthetic progestins[51–55].

Finally, in a meta-analysis, observational studies suggested that, in menopausal women, use of estrogen and progesterone may be associated with lower breast cancer risk compared to synthetic progestin (Figure 2)[56]. This systematic review was mainly based on the results of the E3N cohort study[57,58] and supported by experimental evidence suggesting that the opposing effects of medroxyprogesterone acetate (MPA) and micronized progesterone on breast tissue are related to the non-specific effects of MPA, including glucocorticoid activity and differences in the regulation of gene expression[50,59,60]

Progesterone in luteal-phase deficiency and assisted reproductive technology

The premature onset of menses was recognized as indicative of a luteal-phase deficiency of progesterone production, which was shown to be correctable by exogenous progesterone administration[17]. The luteal phase in a natural cycle was defined as defective when serum mid-luteal progesterone levels decreased to less than 10 ng/ml, but it appeared very quickly that there was no correlation between plasma levels of progesterone, tissue levels and the histological pattern[61,62]. The most reasonable consensus on a defective luteal phase was suggested as a lag of more than 2 days in endometrial histological development compared to the

expected day of the cycle, based on the criteria of Noyes, even if there was delayed endometrial development in the luteal phase in about one-quarter of women[62].

In the early 1980s, two famous pioneers in IVF, Robert G. Edwards in Europe and Howard W. Jones in the US reported a shortened luteal phase when human menopausal gonadotropins (hMG) alone were used to induce multiple follicular growth for *in vivo* and *in vitro* fertilization. The use of gonadotropin-releasing hormone agonists for a combined therapy with hMG suppressed the output of preovulatory luteinizing hormone (LH), deleterious for embryo quality; supraphysiological levels of steroids such as estradiol, secreted by a high number of corpora lutea during the early luteal phase of stimulated cycles, inhibited the LH release via negative feedback actions at the level of the hypothalamic–pituitary axis, inducing premature luteolysis[63,64]. Because LH support during the early luteal phase is entirely responsible for the maintenance and the normal steroidogenic activity necessary to prepare the endometrium for embryo implantation, low implantation and pregnancy rates were observed if no adequate exogenous luteal-phase support (LPS) was provided[64].

Progesterone was recognized to be the best method of providing LPS in assisted reproduction technology (ART), as it was associated with higher rates of live birth or ongoing pregnancy than placebo, with lower rates of ovarian hyperstimulation syndrome[65]. Based on an updated world-wide web-based survey obtained from 408 centers (82 countries), representing 284 600 IVF cycles/year, and assessing the real-life clinical practices regarding LPS, most practitioners (80% of cycles) started LPS on the day of egg collection; a vaginal progesterone product was used in >90% (77% as a single agent and 17% in combination with intramuscular progesterone), and administered until 8–10 weeks' gestation or beyond. The most commonly used vaginal progesterone preparation was a vaginal tablet, preferred in 46% of cycles[66].

The vaginal progesterone capsule is supported now by more than 20 years of evidence from randomized controlled trials in about 6000 patients, providing optimal ongoing pregnancy and live birth rates in ART procedures with a level 1 of evidence.

Progesterone in prevention of preterm birth

Preterm delivery is a leading cause of neonatal morbidity and mortality[67]. In 2010, an estimated 14.9 million babies were born preterm, 11.1% of all livebirths world-wide[68]. Preterm parturition is a syndrome caused by multiple etiological factors such as intra-amniotic infection, extrauterine infections, vascular disorders, decidual senescence, disruption of maternal–fetal tolerance, a decline in progesterone action, uterine overdistension, cervical disease, or maternal stress[69].

Even if Emile Papiernik in France was the first in 1970 to suggest progesterone for the prevention of preterm birth[70], it took another 30 years before two trials confirmed that daily vaginal progesterone administration (100 mg between 24 and 34 weeks of gestation) and weekly injections of 17α-hydroxyprogesterone caproate (250 mg intramuscularly between 16 and 36 weeks) reduced the rate of preterm birth (≤ 37 weeks)[6,70,71].

A short cervix, conventionally defined as a transvaginal sonographic cervical length ≤25 mm in the midtrimester of pregnancy, and a history of spontaneous preterm birth to a lesser extent, are powerful risk factors for spontaneous preterm birth; they have a high predictive accuracy for spontaneous preterm birth at <34 weeks of gestation, and a moderate to low predictive accuracy for spontaneous preterm birth at <37 weeks of gestation in both singleton and twin gestations[72,73]. In two meta-analyses of individual patient data, vaginal progesterone decreased the risk of preterm birth in women with a midtrimester sonographic short cervix[74,75], was cost-effective and improved perinatal outcomes in singleton and twin gestations, without any demonstrable deleterious effects on childhood neurodevelopment[28,76,77].

Conclusion and future directions

Natural 'body-identical' oral progesterone is devoid of any androgenic and glucocorticoid activities, it is slightly hypotensive due to its antimineralocorticoid activity, and it appears to be the optimal progestogen, in synergism with estrogen, in MHT in terms of cardiovascular effects, blood pressure, venous thromboembolism, probably stroke and even breast cancer risk, as opposed to synthetic progestagens and particularly MPA, which appear to be mitogenic on breast cells[2,78]. Further studies will contribute to a better understanding of the effects of progesterone on some target tissues such as the breast. The risk of breast cancer attributable to MHT is small, it decreases progressively after treatment is stopped and it may be lower with micronized progesterone than with synthetic progestins[63]. However, the risk of breast cancer associated with MHT in women over 50 years remains a complex issue, probably related also to duration of use.

Progesterone has both unpredictable proliferative and differentiating actions on normal and breast cancer tissue. Identification of genes whose transcription is directly modulated by progesterone is a crucial step in understanding the effects of progesterone on these complex processes[45].

It is suggested, for example, that the progesterone receptor (PR) is an estrogen receptor-α (ERα)-associated protein that may function as a molecular rheostat to control ERα chromatin binding and transcriptional activity within breast cancer cells, with a possible good clinical outcome in the presence of agonist ligands obtained with a unique gene expression program. Progesterone inhibits estrogen-mediated growth of $ER\alpha^+$ cell-line xenografts and primary $ER\alpha^+$ breast tumor explants, and increases antiproliferative effects when coupled with an ERα antagonist[79].

As a first step to validate this hypothesis, ongoing trials will evaluate whether treatment with oral progesterone in combination with ER-directed therapy, such as tamoxifen, will result in a significant reduction in the proliferation marker Ki-67 by immunohistochemistry in women with ER-positive, PR-positive, HER2-negative breast cancer.

Recent improvements in freezing embryos and oocytes in more user-friendly ART, including vaginal progesterone for luteal-phase support, represent a real breakthrough in reproductive biology without jeopardizing the best chances of success, giving the opportunity to move away from the standard sequence of ovarian stimulation–retrieval–transfer and constraints associated with the potential harmful effects of the hormonal environment on endometrial receptivity and those associated with the risk of ovarian hyperstimulation syndrome[80]. However, more research is needed with randomized controlled trials and medico-economic studies with a sufficient number of patients, to confirm the outcomes in new protocols, e.g. using vaginal progesterone in the follicular phase to block the LH surge. During frozen–thawed embryo transfer cycles, the optimal dose, timing, duration and cost-effectiveness of vaginal progesterone for luteal-phase support remain to be further evaluated in well-designed, comparative, randomized controlled trials.

Since the early 1970s and first evidences by Papiernik and Csapo suggesting progesterone for early implantation, pregnancy maintenance, prevention of early or late miscarriage and prevention of preterm birth, there remain important questions unanswered, e.g. how a shift in the estrogen/progesterone ratio is achieved and how estrogen and progesterone signaling interacts at the level of the cervical cells before the onset of labor[81]. Therefore, in symptomatic women undelivered after an episode of preterm labor, the efficacy of progesterone to prevent preterm birth remains to be clarified[82].

For sure, previous and future clinical developments with progesterone are indeed a never-ending story.

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