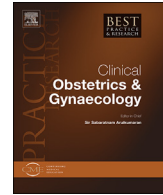




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Progesterone: History, facts, and artifacts

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A B S T R A C T

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Progesterone and its related molecules are a crucial tool in modern clinical practice, particularly in the fields of reproductive medicine. Its history is old, but still under development. Presently, the pharmacokinetic and pharmacodynamic profiles of progesterone are well-known and knowledge on natural progesterone (P4) and other molecules with progestational activity, namely progestogens or gestagens, are improved and their interest is still alive. Topics of great and current interest are progesterone and its role in assisted reproductive protocols, threatened and recurrent pregnancy loss, threatened preterm birth with favorable results on pregnancy, and perinatal outcomes. Moreover, progesterone provides several other positive effects on women's health. This paper describes the main chronological steps that characterized the history of progesterone, where scientific research and clinical practice are arrived and WHICH are the future perspectives on this hormone with a "never-ending history."

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Introduction

Progesterone and its related molecules represent a crucial tool in modern clinical practice, particularly in the field of reproductive medicine.

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The history of progesterone is old, but still in progress. A growing body of scientific evidences are available: several recent studies on its pharmacokinetic and pharmacodynamic features better define the pharmacological profile; increased knowledge on menstrual cycle and pregnancy help to understand and explain its implication in pregnancy establishment, maintenance, and labor activation from conception until delivery.

Presently, knowledge on natural progesterone (P4) and other molecules with progestational activity, namely progestogens or gestagens, are enriched and their interest is still alive. Topics of great and current interest are progesterone and its role in assisted reproductive protocols, threatened and recurrent pregnancy loss, threatened preterm birth with favorable results on pregnancy and perinatal outcomes.

Moreover, progesterone provides several other positive effects on women's health, such as adequate endometrial protection, suggesting to be the optimal progestagen in menopausal hormone therapy, in terms of cardiovascular protection, venous thromboembolism, probably stroke, and even breast cancer risk. In addition, neuroprotective effects of progesterone have also been demonstrated in several of experimental models, including cerebral ischemic stroke and Alzheimer's disease. Progesterone prevents sleep disturbances and modulates GH, TSH, and melatonin secretion in postmenopausal women. Finally, progesterone has been suggested to be effective for the treatment of hot flushes and night sweats in healthy women early in postmenopause and to prevent bone loss promoting bone health in pre- and possibly perimenopausal women [1,2].

Main chronological steps

Progesterone is the oldest hormone that we know about [3].

There is huge confusion in the scientific literature about *natural progesterone*, *progestagens*, *gestagens*, *progestogens*, and *progestins*.

The term *progesterone* should only be referred to 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 [4,5].

It should not be used as a generic one to design different natural or synthetic compounds [6]. The functional terms “*progestogens*” or “*progestagens*” refer to natural or synthetic molecules with progestational activity. The term “*progestins*” is used for synthetic compounds, designed to target the progesterone receptors, and belonging to different classes of molecules with sometimes very different even opposite pharmacological properties and modes of action [7–9].

The modern history of progesterone starts in the mid-1600s with the first book-length description of the female reproductive system (“*De mulierum organis generation inservientibus*” - published in 1672), when physician and anatomist Regnier de Graaf observed in cows that the presence and number of corpora lutea (CL) on the maternal ovaries correlated with pregnancy and the number of fetuses, and that the removal of the ovaries during pregnancy caused parturition [10].

Later, that first observation led Louis-August Prenant and Gustav Born in 1898 to propose that corpus luteum is an organ of internal secretion supporting the early embryo and facilitating the implantation process in the uterus [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].

Later, George W. Corner and Willard M. Allen proposed the term “progestin” to describe the molecule produced by CL that exerts “*pro-gestation*” activity [13–15] (Figs. 1, 2). The original name of progestin not to be confused with “progestin,” a synthetic progestogen identified later.

Willard M. Allen (1904–1993) was an American gynecologist. He showed a great interest in organic chemistry and this would come in handy for his medical school research that would reserve a special place for him in the annals of medical history. Allen studied medicine at the University of Rochester and supported himself by working as an assistant for his anatomy Professor, George W. Corner's embryology laboratory. George W. Corner (1889–1981) was an American physician and embryologist. The history of these researchers is interesting. Their first manuscript describing the effects of corpus luteum



Fig. 1. George W. Corner.



Fig. 2. Willard M. Allen.

extracts on the uterus of the immature rabbit was ready for publication in the early summer of 1928, but this paper never left Corner's desk/laboratory. Being cautious he decided, before submitting the manuscript, to make an extract from start to finish all by himself. He reasoned that "if he, an anatomist, could do it anyone could." He was astonished to find that his extract was not potent. The next day, he drove to the University, which was at a distance of 18 miles and both Corner and Allen agreed to suppress the manuscript until they could find out why the extracts had not been potent. This dilemma was solved a few months later, when they realized that he had selected much smaller rabbits for testing. When they tested mature rabbits, the extracts were more powerful than the previous ones. The manuscript, which left his desk in December 1928, carried the following summary: "The experiment described ... shows that alcoholic extracts of the corpus luteum, freed from phospholipids, contain a substance which when injected into castrated adult female rabbits induces a characteristic alteration of the endometrium identical with the progestational proliferation previously shown to be due to the presence of CL in the ovaries ... Extracts of follicular fluid containing large amounts of estrin do not produce progestational proliferation, nor have extracts from human placenta given positive results. It appears therefore, that extracts of the corpus luteum contain a special hormone which has for one of its functions the preparation of the uterus for reception of the embryos by inducing progestational proliferation of the endometrium" [15].

They submitted a second manuscript. The summary stated: “These experiments demonstrate that in the presence of progestational proliferation induced by corpus luteum extracts, in rabbits deprived of both ovaries at the 18 h of pregnancy, the embryos may survive and grow normally and normal implantation may occur, whereas in the absence of progestational proliferation the embryos never survive beyond the fourth day. The evidence is now complete that in the rabbit, the corpus luteum is an organ of internal secretion which has for one of its functions the production of a special state of the uterine mucosa (progestational proliferation) and that in turn the function of the proliferated endometrium is to nourish or protect the free blastocysts and to make possible their implantation” [15,16]. In 1930, they decided to name the hormone “*progestin*.”

Allen remembered, in his paper “*My life with progesterone*,” the day in which he isolated pure progestin as a unique significant day in his life: “... The isolation of the hormone from the waxy material obtained by high-vacuum distillation was a laborious and exasperating experience. However, the month of May 1933 was a glorious month. On May 5, I had the crystalline corpus luteum hormone. On May 18, my daughter, Lucille, was born. My friends gave me double congratulations and I was sitting on top of the world ...” [17].

At the same time, various researchers, including Butenandt and Westphal in Danzig, Slotta in Breslau, and Hartmann and Wettstein in Switzerland, obtained progesterone in crystalline form. In 1934, both Corner and Allen purified and crystalized progestin from the organic extract of rabbit CL [18,19]. Wintersteiner completed the purification of Allen's molecule and determined the empirical formula [20].

Up to this point, progesterone, known generically as “corpus luteum hormone,” had been referred to by several groups by different names, including *corporin*, *lutein*, *luteosterone*, and *progestin*. Finally, in 1935, during the Second International Conference on the Standardization of Sex Hormones in London (England), a compromise was made between the experts and the name “**progesterone**” (for **progestational steroidal ketone**) was created, which referred to all biological and biochemical evidences acquired during the recent past years of researches [19,21] (Fig. 3).

At the beginning, the production of the progesterone crystalline pure form was difficult, very expensive and the price was as high as about 1000 dollars per gram [20].

In 1939, Professor Adolf FJ Butenandt (1903–1995, from Germany) synthesized the hormone from cholesterol and together with Leopold Ruzicka (1887–1976, from Croatia/Switzerland) he was awarded the Nobel Prize in Chemistry for their research on sex hormones [22] (see Fig. 4 and Fig. 5).

In 1938, Russell Earl Marker (American chemist, Fig. 6) found that the sterol sarsapogenin from the *Sarsaparilla* plant could be converted into progesterone. However, sarsaparilla was expensive and, continuing his research, in 1941, he isolated a sterol, named diosgenin, extracted from the *Dioscorea* species of a yam growing wild in Mexico (Fig. 7); this sterol could also be converted into progesterone using a cheaper technique known later on as the “Marker degradation” (Fig. 8) [23].

In 1944, Marker formed the Syntex Company in Mexico City, named *Syntex SA*, with two partners, Emeric Somlo and Federico Lehmann. In March 1944, the company produced its first kilogram of progesterone, which was sold at \$50/gram. After a dispute with the company in 1945, Marker severed ties with Syntex SA. Because Marker was the only person in the company who knew how to make progesterone, they could no longer produce the drug. Marker, however, went to work with Botanica-Mex, a company based in Texcoco. Later, the company was sold to Gedeon Richter Ltd. where they started using both *Cabeza de negro* and *barbasco* (yam) to make progesterone.

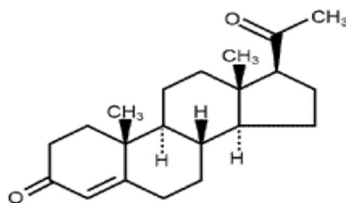


Fig. 3. Progesterone biochemical formula.



Fig. 4. Leopold Ruzicka.

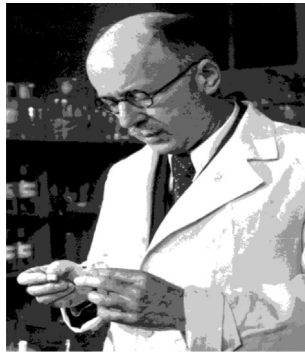


Fig. 5. Adolf Butenandt.



Fig. 6. Russel Earl Marker.

Improving the extraction procedure and using the *Dioscorea barbasco* (the richest source of diosgenin), he was able to obtain progesterone in larger quantities, which would be put on the market at \$10/gram and then at \$5/gram [24].



Fig. 7. Dioscorea.

DIOSCOREA

(natural progesterone source)

DIOSGENIN (alkaloid extraction)

P4 – heme synthesis (Marker degradation)

Fig. 8. Progesterone extraction from Dioscorea

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 [25].

Those discoveries motivated laboratory and clinical research to improve their knowledge on progesterone (P4), which contributed later to reproductive medicine.

A relevant personality in that effort was Georgeanna Seegar Jones (1912–2005) (Fig. 9), American physician, the director of Johns Hopkins' Laboratory of Reproductive Physiology in 1949, who described for the first time luteal-phase deficiency as a cause of infertility and pregnancy loss due to inadequate endometrium preparation and support. Thus, she was credited with using for the first time progesterone to treat women with a history of miscarriages [26,27].

In 1950s, another leader in this field was Arpad I. Csapo, who proposed that P4 maintains pregnancy by blocking parturition mechanism (the so called "P4 block hypothesis"), and that withdrawal of this block induces labor activation. Csapo (1918–1981) (Fig. 10) was a Hungarian scientist. He devoted his career to study what he defined as "the qualitative physiology of uterine function." 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 [28,29]. He also found that early pregnancy luteectomy produces miscarriages through the loss of



Fig. 9. Georgeanna Seegar Jones.



Fig. 10. Arpad Csapo.

progesterone support and that the contraction-blocking action of the progesterone shifted from the ovaries to the placenta, the so-called “luteo-placental shift” [30,31].

In detail, in one of his experiments he stratified four patients' groups: 1) < 7 weeks of gestation and tubal ligation (control group); 2) < 7 weeks of gestation, tubal ligation plus luteectomy; 3) > 8 weeks of gestation plus luteectomy, 4) < 7 weeks of gestation, tubal ligation plus luteectomy plus progesterone administration. He observed no miscarriage in the early pregnant group with luteectomy and progesterone replacement, confirmed his theory on progesterone role as an essential “guardian of pre-natal life” [30,31].

Csapo laid the foundation for explaining a really complex phenomenon, such as pregnancy and its related mechanisms. One significant aspect of Csapo's work involved his efforts to promote international cooperation in uterine physiology research. From 1950s onward he participated in several research projects.

However, until now there is still no absolute agreement on the exact nature of the physiological processes that control the maintenance of pregnancy and the onset of labor, although progesterone is certainly recognized as an essential “player.”

Micronization: “a revolutionary process”

The oral administration of natural progesterone has not been used routinely for years because of poor absorption and rapid hepatic metabolism (so called “first-pass effect”). The relatively low bioavailability of orally administered progesterone prompted the development of multiple synthetic

progesterone derivatives. Most of these compounds were C-17 derivatives of progesterone (e.g., medroxyprogesterone acetate - MPA) or C-19 nortestosterone derivatives (e.g., norgestrel). However, these synthetic compounds do not replicate precisely the constellation of pure biological activities of the parent hormone progesterone, such as antiandrogenic, antimineralocorticoid and neuroprotective, regenerative, and sedative effects due to its unique pharmacodynamic profile.

In 1933 or 1934, Schering introduced progesterone in oil solution as a medication administered by intramuscular injection. This was the first pharmaceutical formulation of progesterone to be marketed for medical use. Over the coming years, several studies were conducted, and new formulations were proposed with advantages and disadvantages for medical purposes. The most important revolution that led to a better compromise between progesterone formulation and good clinical effects was the *micronization process*. Micronization of progesterone and suspension in oil-filled capsules, which allowed progesterone to be absorbed severalfold more efficiently by the traditional oral route, was first studied in the late 1970s and described in literature in 1980s [32–36]. Micronization in oil is a chemical process that adds small progesterone crystals to long chain fatty acids thus, decreasing the size of progesterone particles below 10 μm . Fitzpatrick et al. described that the micronization of progesterone to particle sizes of <10 μm increases the available surface area of the drug during the stomach transit and enhances the aqueous dissolution rate and intestinal absorption of progesterone. Suspension in oil in a gelatin capsule has been shown to further accelerate and improve the intestinal absorption of the product [37]. The first approval for an oral progesterone capsule (Utrogestan®) developed by Besins Company in the early 1980 was granted in France. Initially, oral micronized progesterone (OMP) was first introduced in Europe and later in the United States in 1998 [38,39]. By 1999 and until now, oral micronized progesterone had been marketed in more than 80 countries [39]. Over the coming years, numerous studies on clinical pharmacokinetics of OMP have demonstrated that physiologically relevant levels of progesterone can be obtained rapidly after the oral ingestion of at least 100 mg of micronized progesterone, and that significantly elevated levels of progesterone can be maintained for approximately 12 h [37]. Interest in the micronization process continued and researches also focused on the advantages of vaginal first-pass effect [40]. Vaginal micronized progesterone soft capsules first in the early 1990s and gels or pessaries later on were introduced for medical use, particularly in reproductive medicine indications. Thus, from a simple particles' size reduction in oil derived a progesterone formulation complete in all its effects and well absorbed by mucosal surfaces. Studies on micronization continue and nowadays micronized progesterone products are preferred and largely used for many medical purposes.

Where are we now?

Currently, P4 and other progestational molecules are essential tools in daily clinical practice in obstetrics. Enriched knowledge on the biological basis of different mechanisms leading to pregnancy complications are now available [41]. The role of progesterone in the maintenance of pregnancy comprises the modulation of maternal immune response, the suppression of the pro-inflammatory cascade, the inhibition of uterine contractility, and its beneficial effects on utero-placental perfusion.

Certainly, a very active and growing area of interest with regard to the role of progesterone in the management of the threatened preterm birth [42].

In the last few years, significant advances have been made in biochemical progesterone formulations and routes of administration (for example vaginal soft capsule, dry effervescent tablet, pessary and even suppository are now available). These improved areas of knowledge continue to stimulate experts to deepen their bioequivalence profile to define the “best therapeutic way” in terms of efficacy and safety, daily dose, adverse event, cost-effectiveness, patient compliance, and tolerability [42,43].

The standard management of threatened miscarriages, recurrent pregnancy loss, and threatened preterm birth are now based on progesterone administration, mainly vaginally applied. In addition, the use of these drugs in assisted reproductive technology cycles as luteal phase support is mandatory not only in fresh but also in frozen-thawed embryo transfer cycles.

Therapeutic equivalence based on clinical endpoints needs to be well established even if pharmacokinetic characteristics are similar, taking also into consideration that progesterone products are highly variable drugs with significant inter- and intra-individual variability. Scientific interest in all aspects of

Table 1

Progesterone history: main chronological steps.

<ul style="list-style-type: none"> • 1672 – Regnier de Graaf 	<ul style="list-style-type: none"> - “<i>De mulierum organis generation inservientibus</i>”: first book-length description of the female reproductive system. - Corpus luteum is recognized as the organ involved in pregnancy success [8]
<ul style="list-style-type: none"> • 1898 - Louis-August Prenant and Gustav Born 	<p>Corpus luteum is described as an organ of internal secretion supporting the early embryo and facilitating implantation process in the uterus [9].</p> <p>He coined the term “<i>hormone</i>”</p> <ul style="list-style-type: none"> - They obtained progesterone in crystalline form - They purified and crystalized progestin from the organic extract of rabbit corpora lutea - He completed the purification of Allen's molecule and determined the empirical formula <p>A compromise was made between the experts and the name progesterone (progestational steroidal ketone) was created</p>
<ul style="list-style-type: none"> • 1905 - Ernest Starling • 1930s – Butenandt, Westphal, Slotta, Hartmann, Wettstein • 1934 - Corner and Allen • Wintersteiner 	<p>They were awarded the Nobel Prize in Chemistry for researches on sex hormones</p> <ul style="list-style-type: none"> - He obtained progesterone by natural precursors (the less expensive was extracted from the <i>Dioscorea</i> – mainly represented in Mexico). - 1944: the Syntex Company in Mexico City was born. - He contributed to obtain <i>larger and cheaper quantities</i> of progesterone - She described for the first time luteal-phase deficiency as the cause of infertility; - She was credited with using progesterone to treat women with a history of miscarriages [22,23]
<ul style="list-style-type: none"> • 1935 - Second International Conference on the Standardization of Sex Hormones, London (England) • 1939 – Butenandt and Ruzicka 	<p>Syntex Company developed the first oral contraceptive from progesterone [21].</p> <ul style="list-style-type: none"> - “P4 block hypothesis”; - actin and myosin experiments; - luteectomy ± progesterone replacement experiments were related with miscarriages
<ul style="list-style-type: none"> • 1940s – Russell Marker • 1949 - Georgeanna Seegar Jones 	<p>Micronized progesterone</p> <ul style="list-style-type: none"> - Micronization: biochemical process; decreased size of PG particles <10 µm; - improved pharmacokinetic and pharmacodynamic profile; - for oral and vaginal use; - worldwide spread and currently widely being used in medical practice
<ul style="list-style-type: none"> • 1950s • Csapo 	<p>Interest in progesterone role in obstetrics has not gone away:</p> <ul style="list-style-type: none"> - growing body of scientific data available; - progesterone and pro-gestational molecules are universally used in clinical practice; - periconceptional period is recognized as a “<i>key window</i>” for action; - most important results in obstetrics derived from:
<ul style="list-style-type: none"> • Late 1970s – Early 80s 	<ol style="list-style-type: none"> 1) luteal-phase support in ART cycles; 2) recurrent pregnancy loss; 3) threatened miscarriage; 4) preterm birth prevention
<ul style="list-style-type: none"> • “Modern progesterone era” - where we are now 	<ul style="list-style-type: none"> - Progesterone is still a matter of large interest in many fields: gynecology, endocrinology, oncology, neurology, pharmacology, biology, and chemistry.

progesterone life (pharmacodynamic profile, pharmacokinetic profile, natural and synthetic molecules, absorption features, routes of administration, randomized studies, and pregnancy outcomes) led to significant changes in modern clinical practice and probably it will bring further growth to the body of data.

Moreover, evidences suggest and stress the concept of the role of *pre-conceptional period as a key window of action* during which progesterone support seems to be essential, particularly in high-risk patients.

Summary

Conclusion and future perspectives

This paper tells the dynamic history of progesterone and how it has gradually proven to be an essential hormone for pregnancy in all its main chronological stages. The scientific and clinical interest in progesterone and its related molecules is still high and engages researchers in many fields, such as pharmacological, biochemical, gynecological and obstetric, and endocrinological.

Further studies will probably contribute to a better understanding of the effects of progesterone on some target tissues thus leading to an optimal use in clinical practice.

[Table 1](#) lists the main chronological steps of the progesterone history and gives a brief overview on “where we are now” in terms of clinical use.

Practice points

- Progesterone is the oldest hormone that we know about
- Natural progesterone (P4) and other molecules with progestational activity are crucial in women’s health, particularly in reproductive medicine
- Scientific researches have improved pharmacodynamic and pharmacokinetic profile of these molecules
- Nowadays, P4 and other molecules with progestational activity are largely used in assisted reproductive protocols, threatened and recurrent pregnancy loss, threatened preterm birth with favorable results on pregnancy and perinatal outcomes

Research agenda

- Scientific and clinical interest in P4 and other progestational molecules is still high.
- Many fields such as pharmacological, biochemical, gynecological and obstetric, endocrinological, and neurological are conducting research on this topic.
- Further studies can contribute to a better understanding of the effects of progesterone on some target tissues, thus optimizing its clinical use.

Declaration of competing interest

The authors have no conflicts of interest.

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