FOGSI FOCUS

PROGESTERONE
THE FEEL GOOD HORMONE

Editor :
DR. ASWATH KUMAR R

Sub Editor :
DR. NILESH UNMESH BALKAWADE

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Title:
PROGESTERONE THE FEEL GOOD HORMONE

Editors
Dr. Aswath Kumar Raghu
Dr. Nilesh Unmesh Balkawade

Year of Publication 2014

Published by
The Federation of Obstetric and Gynecological Society of India (FOGSI)
Model Residency, 605, Bapurao Jagtap Marg,
Jacob Circle, Mahalaxmi East, **Mumbai** 400 011, India
Ph: 32954564 / 23021648 / 23021654 / 23021343
Email: fogsi2007@gmail.com

Design : smritidesign.in

Dear Fellow FOGSIANS

It is indeed a great pleasure to write this message for the **FOGSI FOCUS** on 'PROGESTERONE THE FEEL GOOD HORMONE**'.**

My theme for this year is - ***'Empower Women Empower India - Pledge for Excellence'***.

We have carefully chosen some important subjects for our FOGSI FOCUS this year to empower our fraternity with the latest information .

Progesterone is considered to be the most important natural steroid hormone responsible for maintenance of pregnancy. The word is derived from the Latin word- 'Gestare 'meaning to bear or carry.

In our day to day obstetric practice we come across situations where we have to use progesterone derivatives in one or the other form. So this FOGSI FOCUS refreshes our knowledge and gets us acquainted with the armamentarium of various progesterones and its numerous applications which eventually benefit our patients .

There is no substitute for hard work.

Thomas A. Edison

I wish to congratulate Dr. Ashwath Kumar and his entire team for working hard to bring forth this wonderful focus !

Dr. Suchitra N. Pandit
President FOGSI 2014

From Editors Desk

DR. NILESH UNMESH BALKAWADE

DR. ASWATH KUMAR R

Dear colleagues,

It gives me great pleasure to bring to you this FOGSI Focus on Progesterone.

Progesterone is the 'feel good' factor amongst estrogen dominated environment. Situations like PCOD,DUB,Endometriosis are so common these days. Majority are due to estrogen dominance and altered Estrogen:Progesterone ratio. Answer to these and many other common and rare problems lies in the feel good effect of Progesterone. Its a boon for common problems like PCOD, Obstetric problems like Luteal phase defect to some rare diseases such as neuro degeneration on which research is going on. It has played a major role in advanced fields like IVF. New uses like that in preterm labor, cancer are being tried with variable success rate.

But this doesn't impede Research in this important yet enigmatic molecule called Progesterone.

Our president, Dr SuchitraPandit has really helped and encouraged us in making of this FOGSI Focus.I thank all our contributors who despite of their busy schedules have taken time to write these articles.

This FOGSI Focus would not have been possible with outthe support of INTAS pharmaceuticals, and we are really grateful to them for their wholehearted support.

I hope this FOGSI Focus on Progesterone will bring to you all the updated knowledge and information that you seek and go a long way in your practice.

Thanks

Editors

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History Of Progesterone: The 'Feel-Good' Hormone

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DR ASWATH KUMAR RAGHU
MBBS., M.D., FICOG
Dip. in Advanced Laproscopy, France
Additional Professor Dept of Gynaecology,
Jubulee Mission Medical College, Thrissur
Chairperson, FOGSI Quiz Committee

DR NILESH UNMESH BALKAWADE
M.S., D.N.B., F.I.A.G.E.
Assist. Prof. Dr. D. Y. Patil Medical College, Pune
MCM, Pune Obstetric & Gynaecological Society (POGS)

Life is how we look at it.

"So different are the colors of the life, as we look forward to the future, or backward to the past; and so different the opinions and sentiments which this contrariety of appearance naturally produces, that the conversation of the old and young ends generally with contempt or pity on either side"

—Samuel Johnson

The history of Progesterone is as old as the Walnut tree and as new as the ongoing research which has shown in animal experiments that progesterone and the progestin Nestoronea (®) have positive effects on neuroregeneration, repair of brain damage and myelin repair.[1]

The history of progesterone spans 500 million years which is generally accepted as the time frame of its existence. However, with the discovery, in 2010, of progesterone molecules in the walnut tree, the date of its origins has been pushed back.[2]

The researchers speculate that the hormone might be an ancient bio-regulator that evolved billions of years ago, before the appearance of modern plants and animals. The new discovery may change scientific understanding of the evolution and function of progesterone in living things.

Facts about progesterone
Molecular Formula C21H30O2 (Carbon 21, Hydrogen 30, Oxygen 2)

pregn-4-ene-3β-ol-3,20-dione *syn.* progesterone

Molecular weight 314.46
Synonym 4-pregnene-3, 20-dione
Melting point 126 C (259 F)
Bioavailability prolonged absorption
Protein binding 96%-99%
Metabolism hepatic to pregnanediols and pregnanolones
Terminal half-life 13.18 1.3
Excretion renal

Facts about plant sterols

Phytosterols are molecularly similar to cholesterol which is found in animals. Cholesterol is the starting point for the steroid hormones made naturally in animals, including humans.

Plants such as the soy bean, Dioscorea species of yams, fenugreek, sisal, calabar bean, some lilies, yucca, some solanum species, maize and many more contain phytosterols.

Some of which are stigmasterol, diosgenin, sitosterol, campesterol, hecogenin, sarsasapogenin, solasodine. As these sterols have a similar molecular structure to cholesterol, they are used as starting points for the synthesis of 'progesterone'.

Progesterone is then further synthesised into testosterone, estrogen, cortisone etc.

Modern history of progesterone:

The modern history of progesterone begins with its discovery and isolation by **Professor Willard Allen** who trained first as an organic chemist, then studied medicine. It was while working in Professor George Corners embryology laboratory that the two discovered a substance in the corpus lutuem that sustained pregnancy

On September 23rd, 1929 Willard Allen PhD, published the first paper on extracting progesterone from the corpus luteum.[3]

"In previous papers of the present series we have described the preparation and effects of extracts of the corpus luteum. These extracts, when injected into recently spayed female rabbits, regularly bring about a special histological and physiological state of the endometrium, characteristic of early pregnancy, and known by previous experimentation to be due to the corpus luteum... We have as yet proposed no name for this hormone of the corpus luteum, referring to it only as a hormone which induces the above-described characteristic effects in the rabbit. In so far as we are acquainted with its physiological behavior, its chief action lies in its ability, by alteration of the endometrium, to aid gestation in the castrated rabbit; and for this reason we wish to propose for it the name ***progestin****, i.e., a substance which favors gestation."*

Progestin, the original name of progesterone shouldn't be confused with progestin, a synthetic progestogen

It wasn't until 1933 that the pure hormone was isolated and later named progesterone. Willard Allen recounted the discovery and isolation in 1974 in an article entitled. Recollections of my Life with Progesterone

Considerable space has been devoted to the world-changing, female hormone progesterone. But little has been written about its remarkable discoverer, Willard M. Allen.

The day Allen isolated pure *progestin* (later named by him *progesterone*) was a very 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. ...*"[4]

In hindsight it was an unfortunate name, as it's now come to be regarded as a not only a 'female' hormone, but a 'sex' hormone too. So it's many other roles have been largely overlooked.

It is not a sex hormone; it plays no part in the secondary sexual characteristics which develop at puberty. These are governed by estrogen in females and testosterone in males. There are no great quantitative differences between men and women (at least outside the luteal phase).

It is secreted primarily by the ovaries in females and the testes in males, while smaller amounts are produced by the adrenal glands, the brain and glial cells.

It is the precursor to the sex hormones estrogen and testosterone. And to the adrenal hormones cortisol and aldosterone.

In 1929 Adolf Butenandt PhD, working in Germany, isolated oestrone, one of a group of steroids known collectively as estrogen. Edward Doisy, working independently in America, also discovered oestrone.

In 1931 Butenandt isolated androsterone. At the same time, he confirmed the existence of another estrogen, oestriol. In 1933 he showed for the first time the similarity between the molecular structures of androsterone and cholesterol. In 1934 he isolated a small sample of progesterone from the corpus luteum, corresponding with Willard Allen about their independent discovery.

By 1935 Ernst Laqueur had isolated testosterone from the testes. Shortly after this both Butenandt and Leopold Ruzicka, who was working independently, had synthesized testosterone from androsterone.

They were awarded the Nobel Prize for Chemistry in 1939.

At the same time, Percy Julian PhD extracted stigmasterol from the West African calabar bean (Physostigma venenosum), from which the name derives. Percy Julian was a remarkable chemist and was awarded 130 patents, and many honorary degrees. But he is best known for his work in the industrial synthesis of human steroids from plant sterols. His work later lead to the production of cortisone. In 1939 he isolated stigmasterol from soybean oil. By 1940 he was able in doing *bulk progesterone* production.

The Era of Marker Degradation:

In 1936 *Russell Marker* isolated the steroid pregnanediol from an extract of pregnant mare's urine. By 1937 he had converted this to progesterone.

In 1938 he found the sterol sarsasapogenin, from the sarsparilla plant, could be converted into progesterone using a technique which has since become known as the ***'Marker Degradation'***.[5]

Russell Marker spent much of the 1930s and 1940s in this Penn State lab, searching for synthetic methods for producing progesterone.

But sarsparilla was expensive, so undeterred, he searched for and found in 1941, the sterol diosgenin in the Dioscorea species of a *yam* growing wild in Mexico.

This could also be converted into progesterone. No pharmaceutical company was interested in his discovery. But again undeterred, he borrowed a friend's lab and converted the diosgenin into three kilograms of progesterone in 1943.

In 1944 he formed Syntex in Mexico City with two partners, a company which competed with Percy Julian's *'soybean progesterone'*.

When scientist Gregory Pincus first approached the pharmaceutical company G. D. Searle about funding research for an oral contraceptive, Searle's immediate response was no. In the early 1950s, the last thing Searle — or any of the other major drug companies — wanted to get involved in was the controversial area of birth control.

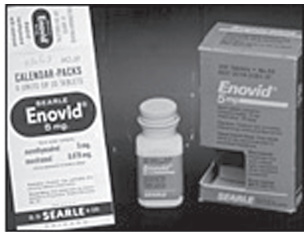
Marker's progesterone, because of its low cost, later became the preferred precursor to cortisone. In 1951, ***Syntex*** had developed the ***first oral contraceptive*** from progesterone.

The first orally active progestin, ethisterone (pregneninolone, 17á-ethynyltestosterone), the 17á-ethynyl analog of testosterone, synthesized in 1938 from dehydroandrosterone by adding acetylene either before or after oxidation of the 3-OH group to the ketone, with rearrangement of the 5,6 double bond to the 4,5 position, by Hans Herloff Inhoffen, Willy Logemann, Walter Hohlweg and Arthur Serini at Schering AG in Berlin, was marketed in Germany in 1939 as *Proluton C* and by Schering in the U.S. in 1945 as *Pranone*.[6,7,8,9.]

A more potent **orally active** progestin, norethisterone (norethindrone, 19-nor-17á-ethynyltestosterone), the 19-nor analog of ethisterone, synthesized in 1951 by Carl Djerassi, Luis Miramontes, and George Rosenkranz at Syntex in Mexico City, was marketed by Parke-Davis in the U.S. in 1957 as *Norlutin*, and was used as the progestin in some of the first oral contraceptives (*Ortho-Novum*, *Norinyl*, etc.) in the early 1960s.[6,7,8,9,10.]

The Pill:

Norethynodrel, an isomer of norethisterone, was synthesized in 1952 by Frank B. Colton at Searle in Skokie, Illinois and used as the progestin in *Enovid*,



marketed in the U.S. in 1957 and approved as the first oral contraceptive in 1960.[6,7,8,9,10.] In 1964 alone, Searle took in $24 million in net profits from Pill sales. The Pill, the contraceptive that no company initially wanted produce, turned out to be Searle's best selling product for years.

When birth control advocate Margaret Sanger asked Gregory Pincus to come up with a birth control pill, he knew one of the hardest parts of the process would be the large-scale human trials necessary for approval by the U.S. Food and Drug Administration (FDA). At a medical conference in the early 1950s, Pincus ran into an old acquaintance, Dr. John Rock. To his utter astonishment, Rock was already testing progesterone on his infertile female patients. He theorized that the drug would allow their bodies to "rest" from ovulation. Then, after stopping treatment, his hope was that the reproductive organs would "rebound" more vigorously and enable his patients to conceive.—'Rock rebound'. The research by Rock and Pincus was conducted in Puerto Rico to avoid US-FDA norms.[11]

After a lot of resistance, the pill came into the market

Progestins then further came up with following classes:

- First (estrane): norethindrone, norethynodrel, norethindrone acetate, ethynodiol diacetate
- Second (gonane): levonorgestrel, norethisterone, norgestrel
- Third (gonane): desogestrel, gestodene, norgestimate, drospirenone
- Fourth: dienogest, drospirenone, nestorone, nomegestrol acetate and trimegestone

Tanaproget is a non-steroidal progestin which is currently undergoing clinical trials.

Although history shows that some ethical issues were involved in various research projects, the invention of the newer molecules of steroids has been a boon to the mankind and will be so in the future

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PATH THROUGH THE BODY- PHYSIOLOGY & PHARMACOLOGY

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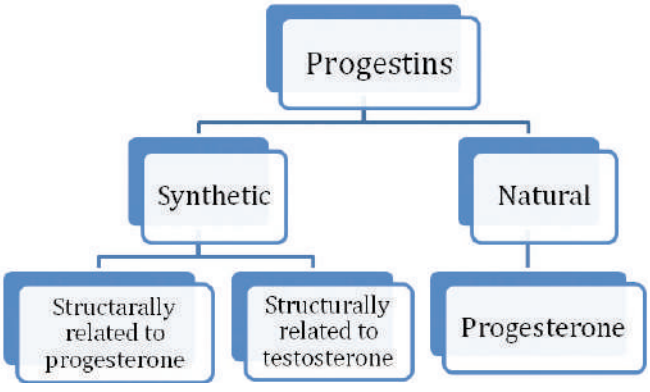
Dr Jyothika A Desai
Imm. Past President
Bangalore Society of Obstetrics and Gynaecology

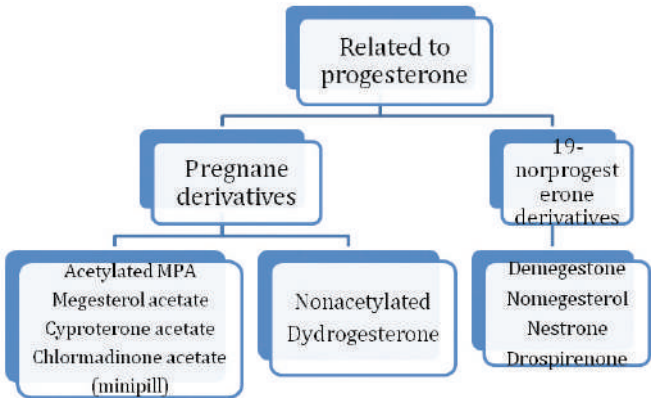
Dr Shailaja N
Associate Professor of OBG
PESIMSR, Kuppam – A.P.

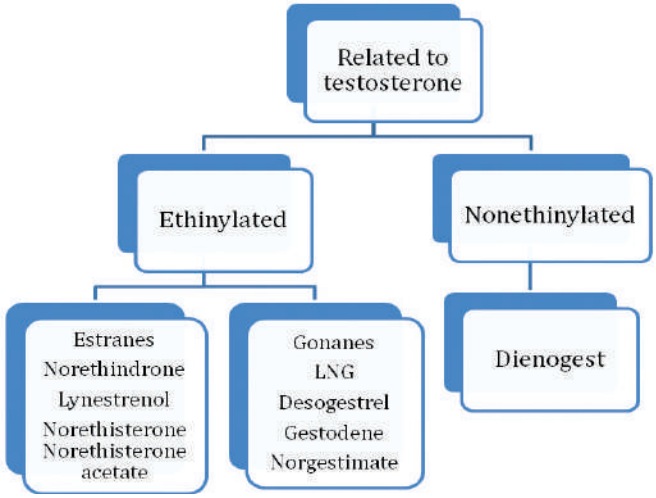
Progesterone also known as P4 (pregn-4-ene-3,20-dione) or more commonly, the pregnancy hormone, is a C-21 steroid hormone involved in the female menstrual cycle, pregnancy and embryogenesis of humans and other species.

Classification:

Prostesterones are classified based on their structure and on their introduction in the market







Pregnanes:

Medroxyprogesterone acetate–It has a similar action as the natural compound with lesser endometrial, stromal asynchrony. It is ideal for endometrial protection. Due to prolonged axis suppression it is not ideal for withdrawal bleeding.

Dydrogesterone -It induces production of progesterone induced blocking factor (PIBF), thereby decreasing harmful Th 1 cells and increasing Th 2 cells which increase clinical pregnancy rates.

Advantages :

- Being a diuretic it prevents sodium retention
- It has no adverse effect on B.P, weight, blood clotting factors and lipoproteins
- Adrenal and renal functions are unaffected

Cyproterone Acetate– It is a derivative of 17OHP with potent progestational and anti-androgen activity

Nomegestrol Acetate- It is a strong inhibitor of gonadotropin secretion without androgenic activity.

Estrane (Ist Generation) - norethisterone, norethynodrel and Gonane (IInd Generation) - levonorgestrel, d-norgestrel: Their strong inhibitory action on pituitary gonadotrophins and hemostatic activity make them effective contraceptives.

IIIrd Generation: Desogestrel, Gestodene, Norgestimate- they are lipid friendly & potent anti-ovulatory agents

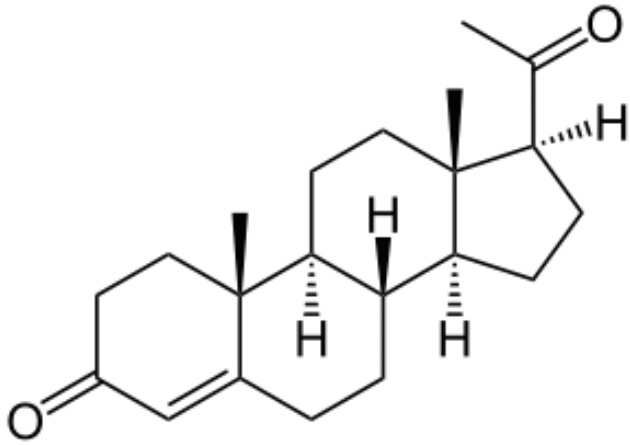
IVth Generation: Drospirenone – a progestin that is an analogue of Spironolactone. It has a high affinity for the mineralocorticoid receptor with anti-mineralocorticoid effects.

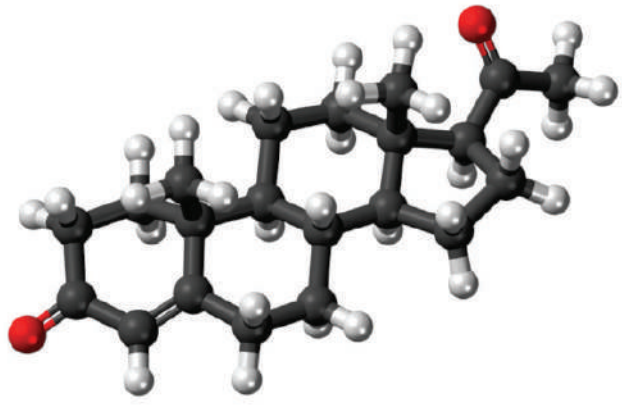
Micronized progesterone:

- It is a natural progesterone (decreasing the particle size increases absorption & bioavalability)
- Dose dependent increase of serum progesterone can be achieved
- To fully protect endometrium- 300mg/day in divided doses (mostly 100 mg by day & 200mg at night as sedation is a side effect) is required.
- Maximum absorption after food than on an empty stomach.
- Short acting and needs multiple doses
- Lipid friendly.
- Favours diuresis (so useful in HRT as cardioprotective)
- Suitable for treatment of LPD, DUB, HRT, premenstrual syndrome and for progesterone challenge test

Chemistry:

Progesterone is a compound with a 21carbon atom chain derived from cholesterol. It consists of four interconnected cyclic hydrocarbons, ketone and oxygenated functional groups, as well as two methyl branches. It is hydrophobic.





Source: Animal:

Progesterone is produced in the ovaries (by the corpus luteum), the adrenal glands and during pregnancy, in the placenta. Progesterone is also stored in adipose tissue.

In humans, during pregnancy, progesterone is produced initially from the corpus luteum that has been "rescued" by the presence of human chorionic

gonadotropins (hCG) from the conceptus. After the 8th week, production of progesterone shifts to the placenta.

An additional source of progesterone is milk products. After consumption of milk products, the level of bioavailable progesterone goes up.

Plant:

Progesterone-like steroid called diosgenin is found in *Dioscorea* species of the yam family (native to Mexico) like Dioscorea *mexicana*, *Dioscorea villosa* and *Dioscorea polygonoides*. Progesterone can be produced from this diosgenin.The human body is not able to make progesterone from diosgenin, so eating wild yam or soy will not boost one's progesterone levels. The term "natural progesterone" is really a misnomer since all progesterone available in the market is synthesized in the lab. Synthetic progesterone is called progestogen/ progestin/gestagen.

Advantages	Disadvantages
Bypasses first pass metabolism, rapid hepatic inactivation	Androgenic ill effects
Good oral absorption Good haemostat Good contraceptive	Fluid retention Decreases HDL PMS like symptoms
	Not able to convey many of the biological benefits of native progesterone

Synthesis:

Biosynthesis:

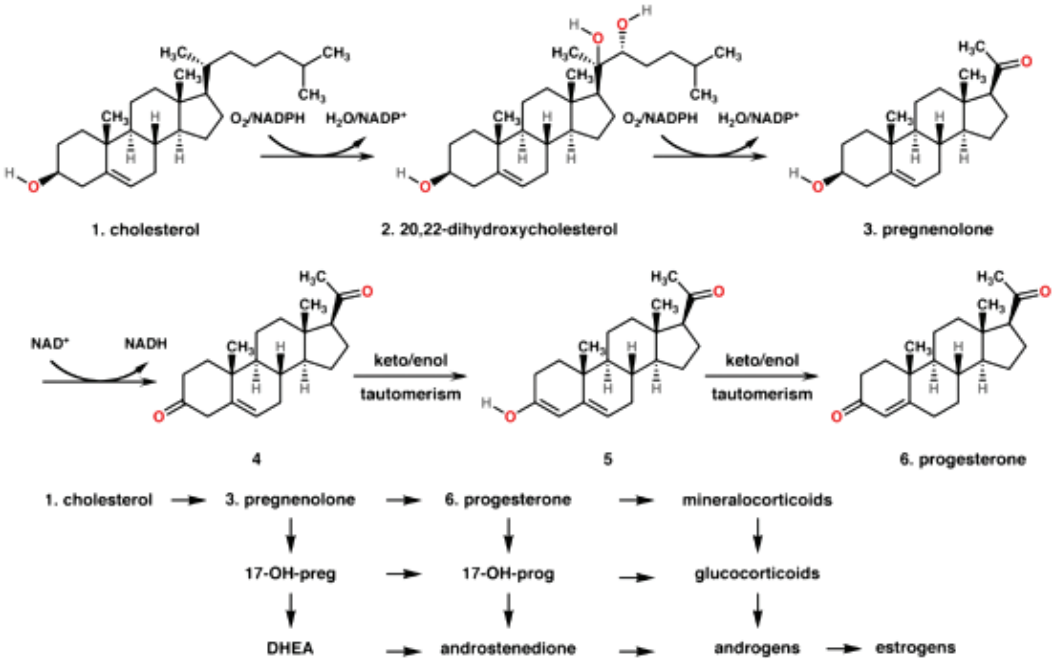
Top: Conversion of cholesterol (1) into pregnenolone (3) to progesterone (6).

Bottom: Progesterone is important for aldosterone (mineralocorticoid) synthesis, as 17-hydroxyprogesterone is for cortisol (glucocorticoid), and androstenedione for sex steroids.

Cholesterol (1) undergoes double oxidation to produce 20, 22-dihydroxycholesterol (2). This vicinal diol is then further oxidized with loss of the side chain starting at position C-22 to produce pregnenolone (3). This reaction is catalyzed by cytochromeP450scc. The conversion of pregnenolone to progesterone takes place in two steps. First, the 3-hydroxyl group is oxidized to a keto group (4) and second, the double bond is moved to C-4, from C-5 through a keto/enoltautomerization reaction. This reaction is catalyzed by 3beta-hydroxysteroid dehydrogenase/delta (5)-delta (4) isomerase.

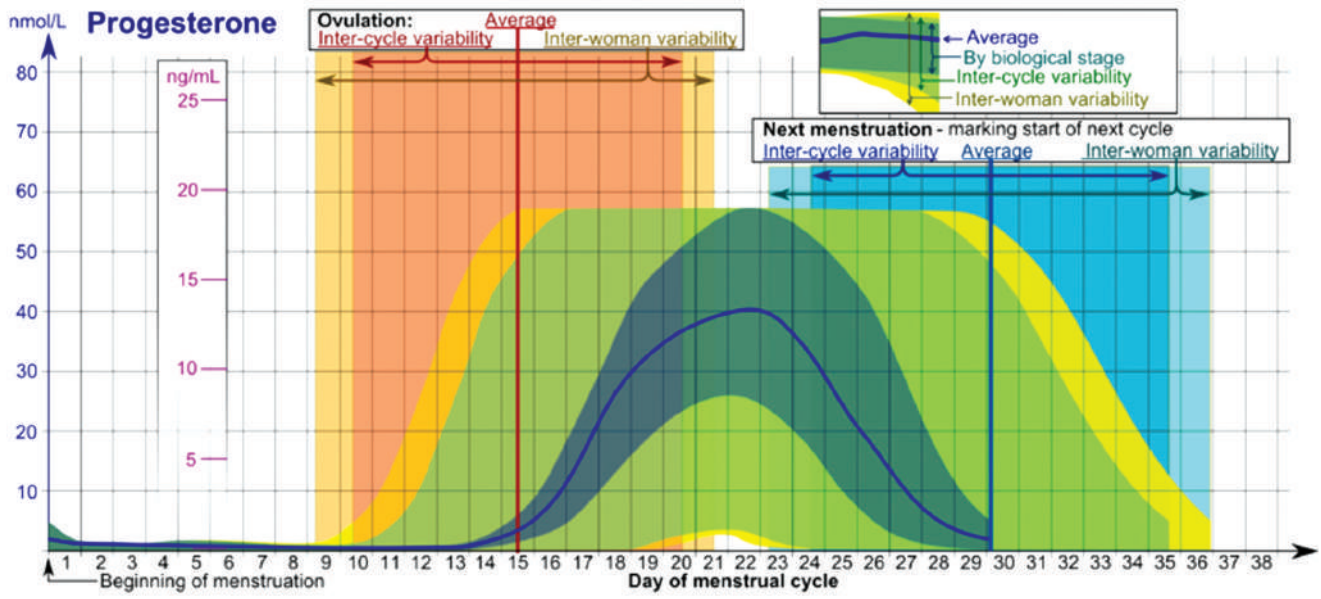
Progesterone in turn (see lower half of figure to the right) is the precursor of the mineralocorticoid aldosterone, and after conversion to 17-hydroxyprogesterone (another natural progestogen) of cortisol and androstenedione. Androstenedione can be converted to testosterone, estrone and estradiol.

Pregnenolone and progesterone can also be synthesized by yeast.



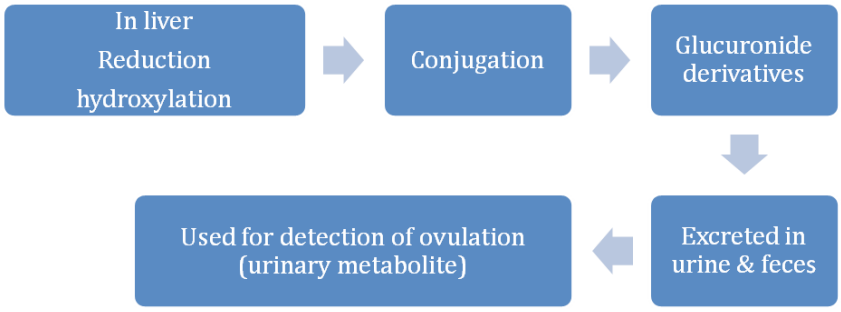
Levels

In women, progesterone levels are relatively low during the preovulatory phase of the menstrual cycle, rise after ovulation, and are elevated during the luteal phase, as shown in the diagram below. Progesterone levels tend to be < 2 ng/ml prior to ovulation and > 5 ng/ml after ovulation. After the luteal-placental shift, progesterone levels start to rise further and may reach 100-200 ng/ml at term.

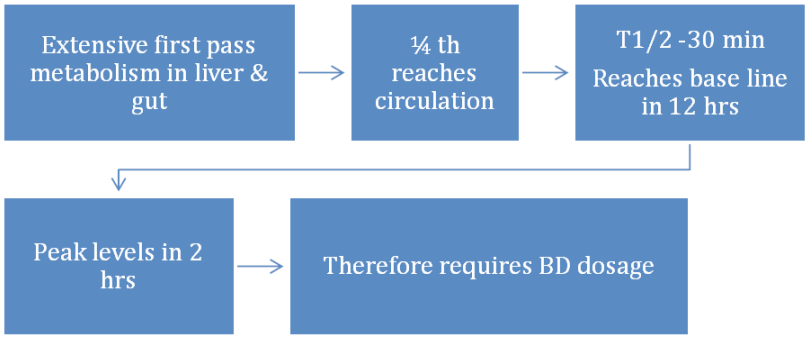


Progesterone levels are relatively low in children and postmenopausal women. Adult males have levels similar to those in women during the follicular phase of the menstrual cycle.

Blood test results should always be interpreted using the reference ranges provided by the laboratory that performed the tests.



Pharmacokinetics:

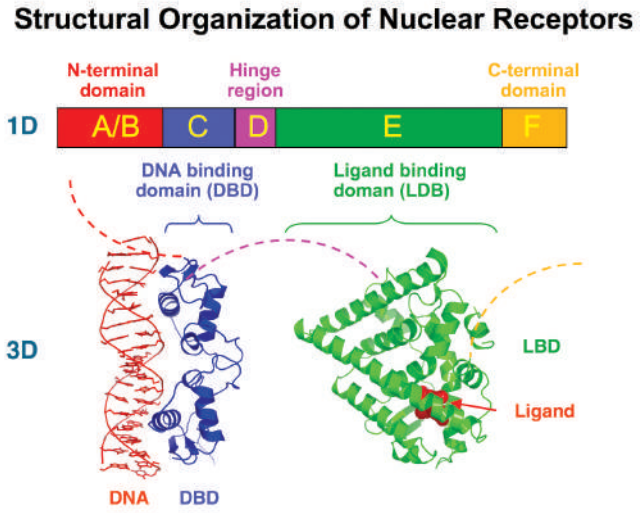


Preparations	T1/2
DMPA	2-3 days
Dydrogesterone	4-5 hrs
LNG	16 hrs
Gestodene	12-18hrs
Desogestrel	12 hrs
Norethindrone	8hrs

Physiological mechanisms:

- Progesterone exerts its primary action through the intracellular progesterone receptor although a distinct, membrane bound progesterone receptor has also been postulated.
- The mechanism includes: (1) steroid hormone diffusion across the cell membrane, (2) steroid hormone binding to receptor protein, (3) interaction of a hormone-receptor complex with nuclear DNA, (4) synthesis of messenger RNA (mRNA), (5) transport of the mRNA to the ribosomes, and finally, (6) protein synthesis in the cytoplasm that results in specific cellular activity.
- In addition, progesterone is a highly potent antagonist of the mineralocorticoid receptor (MR). It reduces the sodium-retaining activity of aldosterone.

The Progesterone Receptor:



- The progesterone receptor is induced by estrogens at the transcriptional level and decreased by progestin at both the transcriptional and translational levels (probably through receptor phosphorylation). The progesterone receptor (in a fashion similar to the estrogen receptor) has two major forms, designated the A and B receptors. The two forms are expressed by a single gene; the two forms are a consequence of transcription from distinctly different promoters, in a complex system of transcription regulation. Each form is associated with additional proteins, which are important for folding of the polypeptide into a structure that allows hormone binding and receptor activity. The molecular weight of A is 94,000 and B, 114,000, with 933 amino acids, 164 more than A.

On the progesterone receptor, TAF-1 is located in a 91-amino acid segment just upstream of the DNA-binding domain. TAF-2 is located in the hormone-binding domain. A fragment missing the hormone-binding domain activates transcription to levels comparable to full-length hormone-activated B receptors, and higher than that with the A receptor, thus beyond that of TAF-1 alone. In appropriate cells, therefore, BUS contains a third activation domain, TAF-3, and can autonomously activate transcription or it can synergize with the other TAFs. In the absence of hormone binding, the C-terminal region of the progesterone receptor exerts an inhibitory effect on transcription. Progesterone agonists induce a conformational change that overcomes the inherent inhibitory function within the carboxy tail of the receptor. Binding with a progesterone antagonist produces a structural change that allows the inhibitory actions to be maintained.

Effects

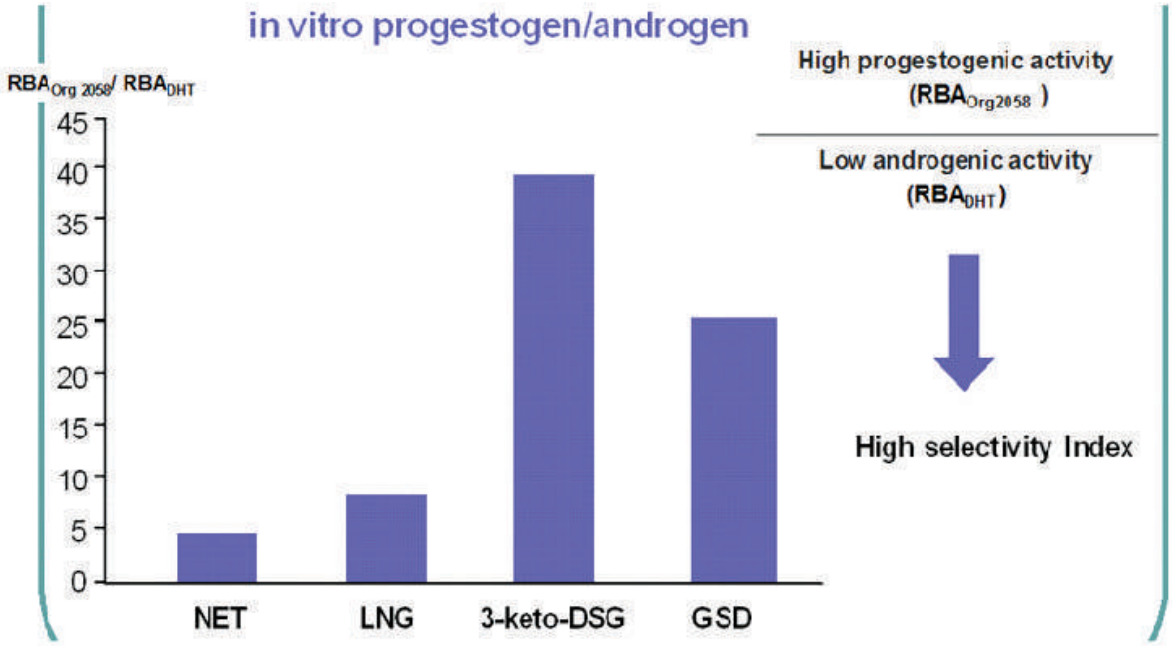
Progesterone has a number of physiological effects that are amplified in the presence of estrogen. Estrogen, through estrogen receptors upregulates the expression of progesterone receptors. Different Progestogens have different effects:Progestational effects, Androgenic effects and General effects

Progestational Effects: Refer to stimulation of the progesterone receptors (thereby helping to prevent ovulation and to lessen menstrual bleeding).

Androgenic Effects: Progestins with higher androgenic activity increase the chances of unpleasant androgen-related side effects which mainly include acne and Hirsutism

Progestational selectivity: The degrees to which progestational effects are maximized and androgenic effects are minimized. Typically, the goal of a birth control pill is to achieve a high level of progestational selectivity. Each progestin has a different potency, mg per mg, in terms of progesterone effect or androgen effect. However, a higher potency progestin may be used in a much smaller dose and thus be equivalent to a larger dose of a less potent progestin. For example, DSG is a very potent and androgenic progestin but its usual OC dose is 0.15 mg. Its progestin potency compared to NE would be 0.15 X 9.0 = 1.35 times. For androgenicity, it would be 0.15 X 3.4 = .51 or half as androgenic as a pill containing1mg of NE

Selectivity Index



NET: Norethisterone, LNG: Levonorgestrel, 3-keto-DSG: 3-keto-desogestrel, active metabolite of desogestrel (also known as etonogestrel), GSD: gestodene, RBA: Relative Binding Affinity

Some Progestational Compounds and their Biological Activities

Agent	Activities				
Progesterone & derivatives	**Estrogenic**	**androgenic**	**anti-estrogenic**	**antiandrogenic**	**anabolic**
Progesterone	-	-	+	-	-
Hydroxyprogesterone caproate	-/+	-/+	-	-	-
Medroxyprogesterone acetate	-	+	+	-	-
Megestrol acetate	-	+	-	+	-
17 ethinyl -testosterone derivatives & testosterone derivatives					
Dimethisterone	-	-	-/+	-	-
19-Nor-testosterone derivatives Desogestrel	-	-	-	-	
Norethynodrel	+	-	-	-	-
Norethindrone	-/+	+	+	-	+
Ethynodiol acetate	-/+	+	+	-	
L-Norgestrel	-	+	+	-	+

Progestin	Progestational activity	Androgenic activity
Norethindrone 1mg	1.0	1.0
Norethindrone acetate 1mg	1.2	1.6
Ethinodiol di acetate1 mg	1.4	0.6
LNG 1mg	5.3	8.3
dl-Norgestrel 1mg	2.6	4.2
Norgestimate 1mg	1.3	1.9
Norelgestromin 1mg	1.3	1.9
DSG 1mg	9.0	3.4
Drospirenone 1mg	1.5	0.0

Dickey R.P ,2000

Progesterone with affinity to steroid Receptor

Relative binding affinity	Progesterone	LNG	3-Keto-DSG	DNG	DRSP
Progesterone receptor	50	150	150	5	35
Androgen receptor	0	45	20	10	65
Estrogen receptor	0	0	0	0	0
Glucocorticoid receptor	10	1	14	1	6
Mineralocorticoid receptor	100	75	0	0	230

Binding affinity relative to: androgen receptor, metribolone=100%; estrogen receptor, estradiol 17=100%; glucocorticoid receptor, dexamethasone=100%; mineralocorticoid receptor, aldosterone=100%

LNG: levonorgestrel; 3-Keto-DSG: active metabolite of desogestrel (DSG); DNG: dienogest; DRSP: drospirenone

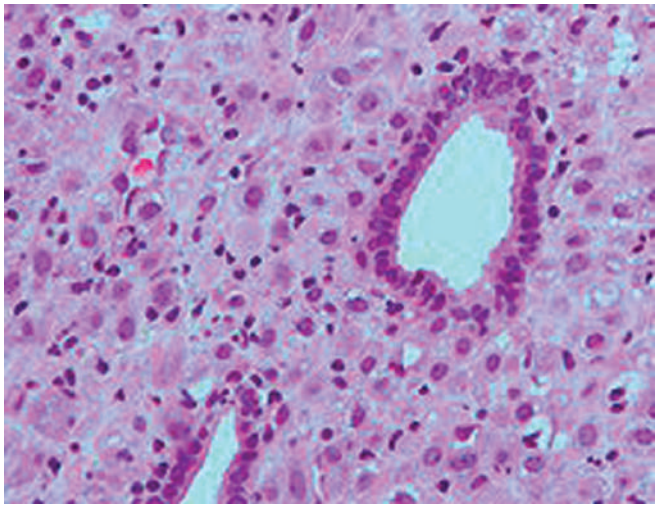
Schindler A. *Maturitas* 2008;**61**(1–2):171–180

Reproductive system:

- **It causes suppression of H-P-O axis, inhibits preovulatory surge and thereby ovulation.**

· Progesterone modulates the activity of CatSper (cation channels of sperm) voltage-gated Ca^{2+} channels. Since eggs release progesterone, sperm may use progesterone as a homing signal to swim toward eggs (chemotaxis).

· Progesterone converts the endometrium to its secretory stage to prepare the uterus for implantation. At the same time progesterone affects the vaginal epithelium and cervical mucus, making it thick and impenetrable to sperms. If pregnancy does not occur, progesterone levels will decrease, leading, in the human, to menstruation. Normal menstrual bleeding is progesterone-withdrawal bleeding. If ovulation does not occur and the corpus luteum does not develop, levels of progesterone may be low, leading to anovulatory dysfunctional uterine bleeding.



· During implantation and gestation, progesterone appears to decrease the maternal immune response to allow for the acceptance of the pregnancy.

· Progesterone decreases contractility of the uterine smooth muscle.

· In addition progesterone inhibits lactation during pregnancy. The fall in progesterone levels following delivery is one of the triggers for milk production.

· A drop in progesterone levels is possibly one step that facilitates the onset of labor.

· The fetus metabolizes placental progesterone in the production of adrenal steroids.

Nervous system

Neurosteroids (pregnenolone and dehydroepiandrosterone) affect synaptic functioning, are neuroprotective, and affect myelination. Its effect as a neurosteroid works predominantly through the GSK-3 beta pathway which improves memory and cognitive ability. Progesterone affects regulation of apoptotic genes.

Effects of Progesterone on Nicotine and Cocaine Addiction

· Progesterone reduces the urge to smoke cigarettes, "bad effects" from IV nicotine and "drug liking"

· Progesterone reduces craving and the feeling of being stimulated by cocaine by reducing the dopaminergic properties of the drug.

Metabolic effects:

Fat metabolism - stimulates lipoprotein lipase, promotes fat deposition and decreases HDL, increases triglycerides but has no effect on LDL.

Carbohydrate metabolism - increases basal insulin levels, increases insulin response to glucose, promotes glycogen storage (liver) and promotes ketogenesis.

Protein metabolism – no significant effect.

Other effects

· It raises epidermal growth factor-1 levels, a factor often used to induce proliferation, and used to sustain cultures of stem cells.

· It increases the core temperature (thermogenic function) during ovulation.

· It reduces spasm and relaxes smooth muscle. Bronchi are widened and mucus regulated. (Progesterone receptors are widely present in submucosal tissue)

· It acts as an anti-inflammatory agent and regulates immune response. It increases monocytes.

· It reduces gall-bladder activity.

· It normalizes blood clotting and vascular tone, zinc and copper levels, cell oxygen levels, and use of fat stores for energy. It may contribute to development of thrombosis in the predisposed.

· It may affect gum health, increasing risk of gingivitis (gum inflammation) and tooth decay.

- **It controls bleeding in DUB**

  Mechanism of action:

  Ø It reduces vascularity & enhances fibrinolysis.

  Ø It provides local stromal support.

- Ø It prevents glandular growth by antagonising estrogen action.
- Ø It increases thromboxane A2 leading to platelet aggregation.
- Ø It prevents endogenous ovarian steroid production

· It appears to prevent endometrial cancer (involving the uterine lining) by regulating the effects of estrogen.

- Ø Progesterone decreases synthesis of oestrogen receptors in the endometrium
- Ø It inhibits mitotic activity of the endometrial cells
- Ø It induces the enzyme oestradiol dehydrogenase — which degrades oestradiol in the endometrium into estrone which is a milder estrogen

· Progesterone plays an important role in the signalling of insulin release and pancreatic function, and may affect the susceptibility to diabetes or gestational diabetes

· It competes with aldosterone at the renal tubules: decreasing sodium reabsorption

· It promotes increased adrenocortical aldosterone secretion

· It causes alveolobular development of the breast secretory apparatus

· By acting on testosterone receptors, it decreases SHBG and is responsible for acne and hirsutism

· It stimulates osteoblastic mediated bone formation

· Progesterone also has a role in skin elasticity and bone strength, in respiration, in nerve tissue and in female sexuality, and the presence of progesterone receptors in certain muscle and fat tissue may hint at a role in sexually dimorphic proportions of these organs

Clinical applications:

The use of progesterone and its analogues have many medical applications. Because of the poor bioavailability of progesterone when taken orally, many synthetic progestins have been designed with improved oral bioavailability. Progesterone does not dissolve in water and is poorly absorbed when taken orally unless micronized in oil. Products are often sold as capsules containing micronised progesterone in oil. Progesterone can also be administered as vaginal or rectal suppositories or pessaries, transdermally through a gel or cream, or via injection (though the latter has a short half-life requiring daily administration).

Future direction:

Although significant progress has been made in understanding the physiological actions of progesterone in the mammalian reproductive system and the molecular structure and function of PR, there are still marked gaps in knowledge. There is a great deal to be learned about the biology and hormone responsiveness of the normal breast, and the relative paucity of models has been a limitation in this regard. More information is needed on the significance of PR A and PR B expression.

The role of coregulatory proteins in progesterone action needs further investigation to clarify whether progesterone regulates coregulatory protein expression and whether tissue levels of coregulatory proteins play a role in modulation of progesterone action.

New information on genes directly regulated by progesterone is urgently required, and techniques such as differential display PCR and similar approaches by which to identify progesterone-regulated transcripts, despite their limitations, are likely to yield important new knowledge in the near future.

"Study the past if you would define the future." – Confucius

PROGESTERONE RAINBOW: NATURAL TO SYNTHETIC PROGESTERONES

3

Dr. Gorakh Mandrupkar
MBBS DGO FCPS FICMCH MCSEP (i)
Consultant, Reproductive Medicine,
Pristine Women's Hospital, Kolhapur
Mandrupkar Clinic, Islampur (ISO 9001:2008)
Joint Secretary, FOGSI

Dr. R D Shriwastav
MD DGO
Assistant Prof. Sangita Hospital,
Andheri (W), Mumbai
Dept. OBGY, Bharti Medical Collage & Hospital, Sangli

Introduction

Progesterone is a steroid hormone produced by the adrenal glands in both men and women, and by the testes and ovaries in men and women respectively. It plays a role in menstrual cycle and pregnancy and circulates throughout the body binding to receptors in the brain, the cardiovascular tissue, breast tissue and more.

It is secreted during pregnancy by the placenta. During menopause, the total amount of progesterone produced declines to less than 1% of the premenopausal level.[1]

Progesterone is made from pregnenolone, which is in turn product of cholesterol.

The word progesterone is derived from the Latin word 'Gestare' meaning to 'bear' or 'carry'.

Progesterone occupies an important position in the pathway of hormonal synthesis. In addition to being the precursor to estrogen, it is also the precursor of testosterone and cortisol.

Functions of progesterone

Progesterone has several biological actions.

1. Progesterone acts primarily as an antagonist to estrogen.
2. It brings about the changes in endometrium which enables the implantation of a fertilized ovum.
3. It serves to promote survival and development of embryo and fetus.
4. It prevents contractions of the uterus and helps in maintaining pregnancy.

Progestogens

The term progestagens or progestogens include endogenous, natural as well as the synthetic steroids (Progestin: progesterone that mimics the actions of endogenous progesterone.)

Several new progestins have been synthesized in the recent past for use as contraceptives as well as hormone therapies (HTs). [2,3]

Classification: Natural and Synthetic progesterones

- **Natural progesterones**

In at least one plant, *Juglansregia*, progesterone has been detected.

In addition, progesterone-like steroids are found in *Dioscorea Mexicana*. This plant is part of the yam family native to Mexico.

It contains a steroid called 'diosgenin' that is taken from the plant and is converted into progesterone.

It is true that the natural progesterone now available has

been synthesized but it is not synthetic, that it is not unnatural.

Micronisation refers to creamy white crystalline particulate powder. The particles are suspended in oil and are dispensed in soft gelatin capsules. Nowadays, technology has made it possible to make water soluble oral preparations of same. All these natural micronized preparations are safe and easy to use. Oral, vaginal, intramuscular, as well as topical routes are available.

Mostly used in treatment of PCOS, Luteal phase defects, prevention of preterm labor[4], for maintenance after different assisted reproductive techniques.

Advantages of natural progesterones:

They are well tolerated.

They are safe in pregnancy.

Available in all routes of administration.

Improved bioavailability

Typical 'progesterone' side effects of bloating, breast tenderness, mood changes etc. are less.

No change in coagulation process or blood pressure.

Synthetic progesterones:

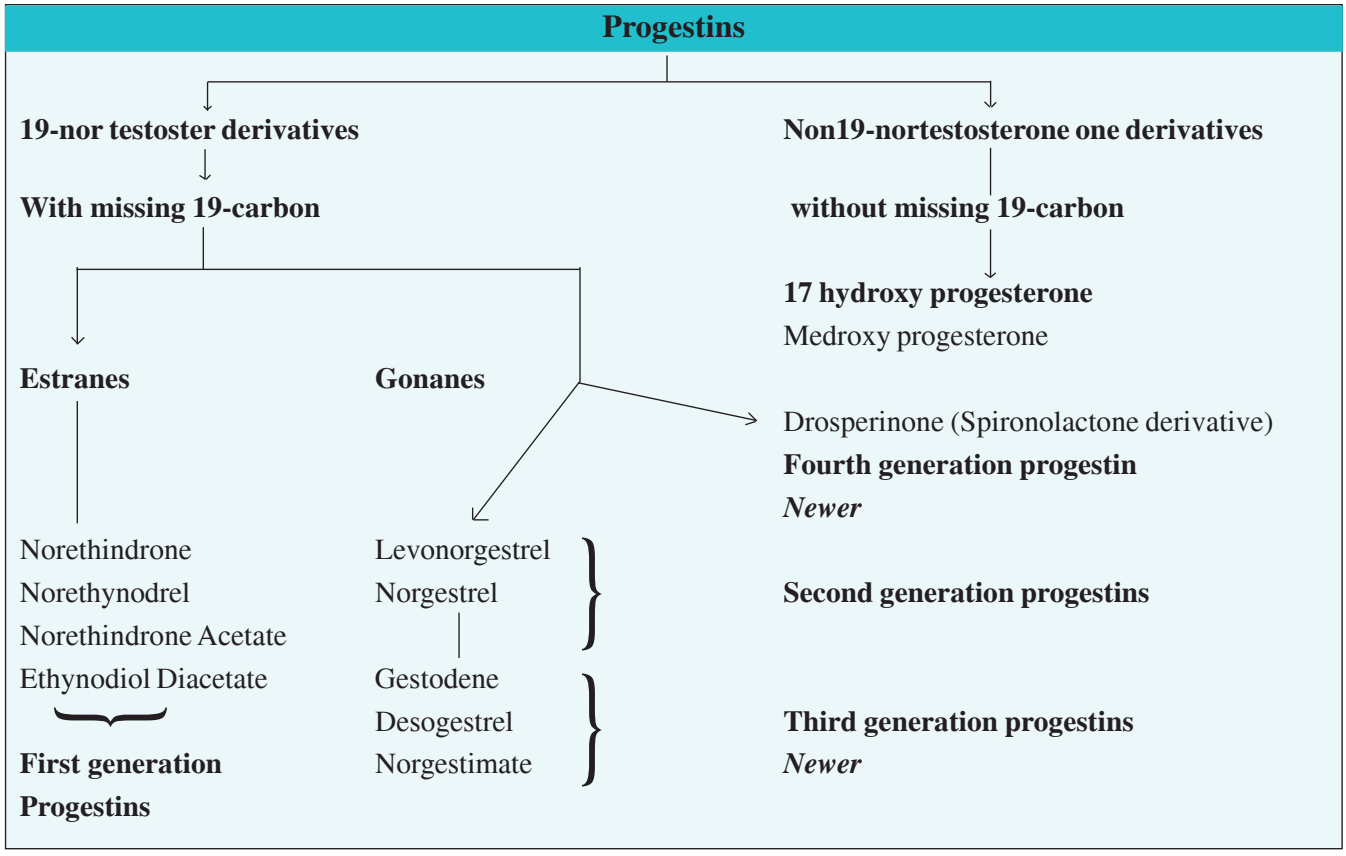
These are derived from steroids and further classified according to steroid from they are derived.

These are also classified generation wise.

- **Uses of synthetic progesterones:**
  1. Abnormal uterine bleeding
  2. Endometriosis
  3. Contraception
  4. Premenstrual syndrome
  5. Hormone replacement therapy

Classification: Newer and Older Progestins

Progestins are classified into four generations based on the steroid from which they are derived, which then determines their molecular structure.



Pregnanes	Estranes 1st generation	Gonanes 2nd generation	Gonanes 3rd generation	Other/unclassified
Medroxyprogesterone acetate	Norethindrone acetate	dl-Norgestrel	Desogestrel	Drospirenone
Cyproterone acetate	Ethynodiol diacetate	Levonorgestrel	Gestodene	
Chlormadinone acetate	Lynestrenol		Norgestimate	
Nomegestrol, Nestorone	Norethynodrel Dienogest			

Structure and Activities of the Progestins

The newer progestogens, namely, desogestrel, norgestimate, gestodene share the common property of having weak or no androgenic effects. However, there is great variation between these agents in their pharmacokinetic properties and hormonal activities. Both desogestrel (precursor of 3-keto-desogestrel) and norgestimate (precursor of levonorgestrel) are prodrugs. All these newer progestins are 19-nortestosterone derivatives. Desogestrel norgestimate and gestodene belong to the subgroup of 13-ethyl-gonanes with an ethinyl group at C17.

The most potent progestogens are gestodene and desogestrel and may moderately reduce SHBG levels and counteract the stimulating effect of ethinyl estradiol on hepatic serum proteins.

The first and second generation progesterones exert anti androgenic effects except the hydroxy progesterone derivative, Medroxy progesterone which has low such activity.

The newer most fourth generation progesterone, drosperinone is a Spironolactone derivative. It has not only progestogenic activity but also it has anti androgenic activity. Its benefit is that it has anti mineralocoticoid activity which does not cause water retention and hence very few typical 'progesterone' side effects.[5]

Conclusion

- Progesterone acts as a precursor to many steroid hormones and regulates many biological and metabolic effects in the body.
- Progestogens encompass both natural and the synthetic compounds which mimic the actions of endogenous progesterone.
- The progestins available for contraception are not similar.
- Initial data supports that the newer agents are well-tolerated and super added anti mineralocoticoid activity along with anti-androgenic activity of Drosperinone may create revolution in PCOS management.

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PROGESTERONE FOR SAFE MOTHERHOOD

4

Dr. Neetha George M.S, D.G.O
Consultant in OBGYN,
Jubilee Mission Medical College,
Thrissur, Kerala.
georgeyogiaveedu@gmail.com

Dr. Elavarasi Elamaran D.G.O
Senior Resident,
Jubilee Mission Medical College,
Thrissur.
arasi5984@gmail.com

Progesterone otherwise known as progestational steroid ketone is an undisputed molecule in pregnancy maintenance through its endocrine, paracrine and immunological effects on fetal and maternal tissues.

Its ***role in safe motherhood*** includes its use in

Luteal Phase Defect

Recurrent Pregnancy Loss

Preterm labour

Multiple pregnancy and

Assisted Reproductive Techniques

It is an important component of many contraceptive preparations as well but in this chapter, we will be concentrating on the role of progesterone in preterm labour

INTRODUCTION:

On February 3, 2011, the US Food and Drug Administration (FDA) approved the use of progesterone supplementation (17 hydroxy progesterone caproate, 17-OHP-C) during pregnancy to reduce the risk of recurrent preterm birth in women with a history of at least one previous spontaneous preterm delivery. This is the first time that the FDA has approved a medication for the prevention of preterm birth, and represents the first approval of a drug specifically for use in pregnancy in almost 15 years [1]

What does Evidence Based Medicine Say?

The National Institute of Child Health and Human Development (NICHD) Maternal Fetal Medical Units (MFMU) Trial [2] showed the effectiveness of progesterone in reducing preterm birth. 463 patients at high risk for preterm birth because of a prior preterm birth were randomized to weekly 17-OHP or placebo at 16-20 weeks until 37 weeks.

There was significantly reduced risk of preterm delivery in the progesterone exposed women (RR=relative risk, CI= confidence interval)

Delivery<37weeks (36% v 55% [RR, 0.66; 95% CI 0.54-0.81])

Delivery<35weeks (21% v 31% [RR, 0.67; 95% CI 0.48-0.93])

Delivery<32weeks (11% v 20% [RR, 0.58; 95% CI 0.37-0.91])

In the 17-OHP exposed infants *there was*

- Less perinatal mortality,
- Reduced rates of necrotizing enterocolitis, intraventricular hemorrhage and need for supplemental oxygen,

- There was no evidence of virilization of female offspring.

Prior Preterm labor is typically treated with weekly injections of 17-OHP, and cervical insufficiency is typically treated with cerclage. ***Dr. Temming et al*** wanted to see if 17-OHP to women treated with cerclage decreases preterm labor (PTL) risk. It was found that 17-OHP plus cerclage reduced risks [3]

de Fonseca and colleagues (Brazilian Trial) published an RCT of 157 women at high risk for preterm delivery (a history of prior spontaneous preterm birth (PTB), prophylactic cerclage, or uterine malformation) who were administered a vaginal progesterone suppository (100 mg) or placebo nightly from 24 to 34 weeks. This study found a 13.8% rate of preterm births of less than 37 weeks in the progesterone group compared to 28.5% in the placebo group and a 2.8% rate of preterm births of less than 34 weeks in the progesterone group compared to 18.6% in the placebo group.[4]

In 2009, ***Rai and colleagues*** [5] conducted a randomized double-blind, placebo-controlled trial of 150 women with at least one preterm birth who received 100 mg of oral micronized progesterone or placebo twice a day from recruitment (18–24 weeks) until 36 weeks or delivery. This study found a reduction in preterm birth in the first group compared to controls (39.2% vs 59.5%, *P* - .0002). There was also a reduced risk of NICU admission, low birth weight, and duration of NICU stay.

RECENT RANDOMISED TRIALS ON PROGESTERONE Table 1[6]

MECHANISM OF PROGESTERONE IN PTL:

Table 1
Recent randomized trials of progesterone

Author	Date, Site	Subjects	Primary Outcome	Intervention	Results
da Fonseca et al[33]	2003, Brazil	157 women at "high risk" for preterm birth	Preterm birth <37 weeks	Intravaginal progesterone (100 mg) or placebo, 24–28 weeks	RR 0.49 (95% CI 0.25–0.96)
Meis et al[32]	2003, USA	463 women with prior spontaneous PTB	Preterm birth <37 weeks	17-hydroxy-progesterone caproate (250 mg weekly) or placebo, 16–20 to 36 weeks	RR 0.66 (95% CI 0.54–0.81)
O'Brien et al[34]	2007, Multinational	659 women with prior SPTB	Preterm birth <32 weeks	Daily vaginal progesterone gel (90 mg) or placebo	RR 1.08 (95% CI 0.76–1.52)
Fonseca et al[46]	2007, UK, Brazil, Greece	250 women with cervical length ≤15 mm	Preterm birth <34 weeks	Nightly intravaginal pessary (200 mg micronized progesterone) or placebo,24–33 + 6 weeks	RR 0.56 (95% CI 0.36–0.86)
Rouse et al[39]	2007, USA	661 twin pregnancies	Composite of delivery or death prior to 35 weeks'	Weekly IM injection of 250 mg 17-hydroxy-progesterone caproate or placebo (castor oil) from 16 to 20 + 3 weeks until 34 completed weeks	RR 1.1 (95% CI 0.9–1.3)
Hassan et al[47]	2011, USA	458 singleton pregnancies	Preterm birth before 33 weeks	Daily vaginal progesterone gel or placebo from 20 to 23 6/7 until 36 6/7 weeks	RR 0.55 (95% CI 0.33–0.92)

Progesterone is thought to enhance quiescence of the uterus by inhibiting uterine contractions.[7] This was initially proposed as a see-saw theory in which high levels of progesterone prevent contractions and low levels promote contractions. There are many biochemical changes in the uterus that are thought to lead to a "functional progesterone withdrawal."

Indeed, this functional withdrawal of progesterone may be related to the decreasing ability of the progesterone receptor to regulate genes that lead to uterine quiescence.[8,9]

It has been shown that the progesterone receptor antagonizes nuclear factor- K-Beta-activation of cyclooxygenase-2 (COX-2)–induced contractility in the uterus.[10] *Condon* demonstrated a decline in levels of progesterone receptor coactivators in the pregnant uterus at term, which may again lead to a functional progesterone withdrawal, making the uterus more contractile while not altering the levels of circulating progesterone.[11] Progesterone causes Th2 shift,[12] P induced blocking factor decrease decidual NK cell activity Progesterone stimulates transcription of ZEB1 and ZEB2 (zinc finger E box binding homeobox protein) which inhibit connexion 43 and oxytocin receptor gene.[13]

Administration of progesterone decrease PR-A/ PR-B (progesterone receptor) ratio which makes uterus quiescent.

Progesterone may also act at the level of the cervix.[14] Progesterone decreases levels of inducible nitric oxide synthase (iNOS) and COX-2, which are associated with cervical ripening[15]. Progestational agents have been found to modulate gene expression in the cervix, both in the presence and absence of inflammation, postulating another mechanism by which progesterone may prevent preterm births.[16] Degradation of type I collagen in the dilated cervix in labor was stimulated by the addition of physiologic concentrations of 17-estradiol. This process was blocked by the addition of progesterone.[17,18,19]

Basal and interleukin-1 (IL-1) induced IL-8 production in uterine cervical fibroblasts is down-regulated by progesterone at the transcriptional level. Progesterone decreases stromal degradation, inhibits cervical ripening and acts as barrier to ascending infection.[17,18,19]

The maternal immune response is another area of research. Studies have found that giving 17-OHP-C suppresses the maternal immune response. In patients who received exogenous 17-OHP-C, lipoteichoic acid (LTA) or lipopolysaccharide (LPS) stimulated induction of IL-6 was significantly decreased compared with controls.[20] The addition of exogenous progesterone has been shown in vitro to protect fetal chorion and human decidua cells from induced cell death.[21] It has been shown that the addition of progestin to term decidua cells diminishes production of IL-11, a cytokine known to enhance production of prostaglandins.[22]

SUMMARY OF PROGESTERONE IN PRETERM LABOUR [23]

Proposed mechanisms of action reported for progestogens to prevent preterm birth[9–17]

Stimulate transcription of ZEB1 and ZEB2, which inhibit connexin 43 (gap-junction protein that helps synchronize contractile activity) and oxytocin-receptor gene
Decrease prostaglandin synthesis, infection-mediated cytokine production (antiinflammatory effects) by fetal membranes/placenta
Changes in PR-A and PR-B expression (decreased PR-A/PR-B ratio keeps uterus quiescent)
Membrane-bound PR in myometrium
PRs, when stimulated by progesterone, help selected gene promotion, or prevent binding of other factors
Interfere with cortisol-mediated regulation of placental gene expression
Nongenomic pathways
Reduce cervical stromal degradation in cervix
Alter barrier to ascending inflammation/infection in cervix
Reduce contraction frequency in myometrium
Attenuate response to hemorrhage/inflammation in decidua
Alter estrogen synthesis in fetal membranes/placenta
Alter fetal endocrine-mediated effects

PR, progesterone receptor; *ZEB1*, zinc finger E-box binding homeobox protein 1; *ZEB2*, zinc finger E-box binding homeobox protein 2.

SMFM. Progesterone and preterm birth prevention. Am J Obstet Gynecol 2012.

Lastly, there may be autocrine and paracrine effects. Research suggests a role for placental corticotropin-releasing hormone (CRH) in the timing and initiation of labor. Rising levels of CRH are noted to precede the onset of both term and preterm labor in humans, acting as a "placental clock" to control the timing of parturition[24]. Cortisol and progesterone have competing effects on the pregnant uterus, with cortisol increasing prostaglandin production and progesterone preventing it. Other studies have investigated the rising fetal cortisol levels at the end of gestation and show CRH and adrenocorticotropic hormone (ACTH) both work to down-regulate progesterone, suggesting an autocrine and paracrine effect in the initiation of human labor.[25,26,27]

PROGESTERONE FOR THE PREVENTION OF PRETERM BIRTH-*when and how?*

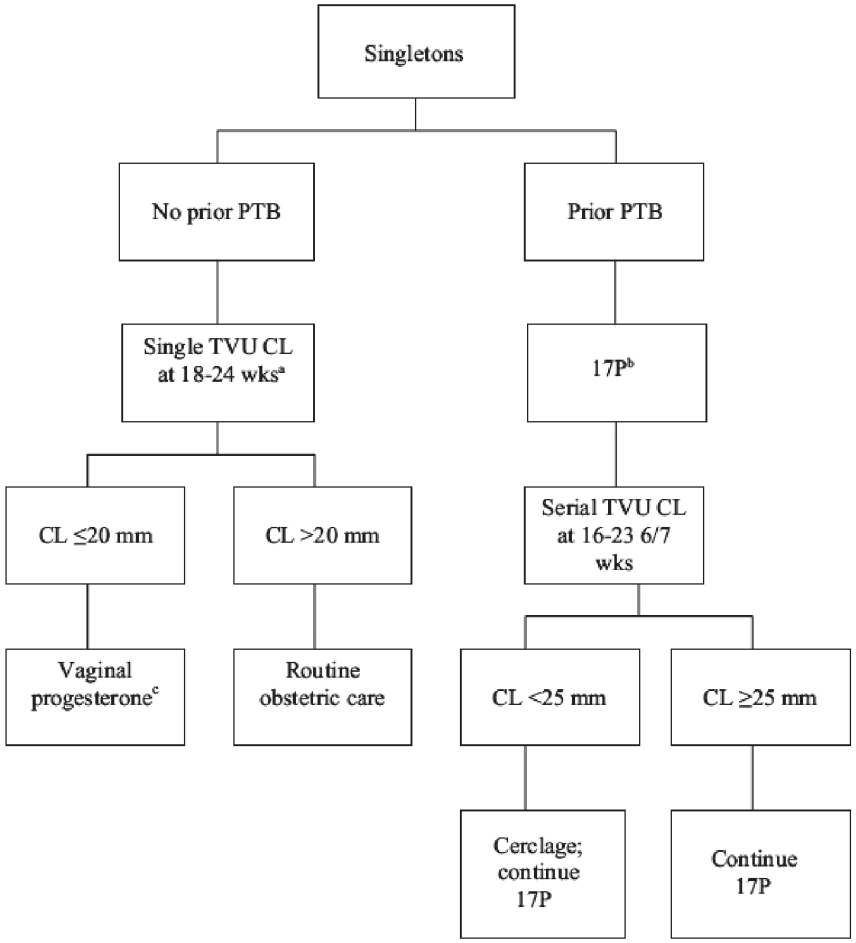
Summary of recommendations of ACOG and SMFM (Society For Materno Fetal Medicine([23,28]

1. There is insufficient evidence to recommend the use of progestogens in singleton gestations with no prior PTB, and unknown CL.

2. In women with singleton gestations, no prior SPTB, and short TVU CL<20mm at <24 weeks, vaginal progesterone, either 90-mg gel or 200-mg suppository, is associated with reduction in PTB and perinatal morbidity and mortality, and can be offered in these cases. Cerclage should be done in these cases. CL measurements 21-25 mm are re-examined once in 7-14 days for presence of other factors for PTL.

Table 3[23]

FIGURE
Algorithm for use of progestogens in prevention of PTB in clinical care



[a]If TVU CL screening is performed; [b]17P 250 mg intramuscularly every week from 16-20 weeks to 36 weeks; [c]eg, daily 200-mg suppository or 90-mg gel from time of diagnosis of short CL to 36 weeks.
CL, cervical length; *PTB*, preterm birth; *17P*, 17-alpha-hydroxy-progesterone caproate; *TVU*, transvaginal ultrasound.
SMFM. Progesterone and preterm birth prevention. Am J Obstet Gynecol 2012.

3. The issue of universal TVU CL screening of singleton gestations without prior PTB for the prevention of PTB remains an object of debate. CL screening in singleton gestations without prior PTB cannot yet be universally mandated. Nonetheless, implementation of such a screening strategy can be viewed as reasonable, and can be considered by individual practitioners. Practitioners who decide to implement universal TVU CL screening should follow strict guidelines. Practitioners who choose to screen low-risk singleton gestations may consider offering vaginal progesterone, either 90-mg gel or 200-mg suppositories, for short TVUCL <20mm at <24 weeks along with cerclage .

RECOMMENDATIONS FOR TVU CL SCREENING:[29]

All women with prior PTL

All women with risk for PTL-RR>1.5

All pregnancies conceived after infertility treatment

History of cervical instrumentation

History of 1 or more pregnancy termination

History of current genitourinary infection

Uterine anomalies

Women who smoke, are depressed, or BM1<19.6

All African Americans

Current pregnancy risk factors:

Current pregnancy symptoms - premenustrual symptoms, cramps, pelvic pressure, change in vaginal discharge

TAS CL < 3cm < 24wk

Unexplained vaginal bleed < 14weeks

4. In singleton gestations with prior SPTB 20-36 6/7 weeks, 17P 250mg IM weekly preferably starting at 16-20 weeks until 36 weeks is recommended. In these women, if the TVU CL shortens to <25 mm at <24 weeks, cervical cerclage should be offered.

5. Progestogens have not been associated with prevention of PTB in multiple gestations, or PPROM.

The observation that progesterone supplementation does not prevent preterm birth in multiple pregnancy suggests that the mechanism leading to preterm labor and delivery in multiples—namely excessive uterine stretch—is different from that in singleton. This argument is supported by a recent study showing that progesterone does not inhibit stretch-induced MAPK activation or gene expression in myometrial cells in vitro.

6. There is currently insufficient evidence to recommend progestogens for primary, adjunctive, or maintenance tocolysis

7. For patients undergoing assisted reproduction, progesterone supplementation is essential since GnRH agonist or antagonist used to prevent premature LH surge frequently results in poor luteal function due to suppression of pituitary LH secretion.

8.Biochemical and endocrine markers (including estriol, corticotrophin-releasing hormone, and activin A) are predictors for preterm birth. The only test that is currently FDA approved and recommended by The American College of Obstetricians and Gynecologists (ACOG) is the measurement of fetal fibronectin (fFN) in cervicovaginal secretions. Elevated levels of cervicovaginal fFN (defined as > 50 ng/mL) at 22-0/7 through 34-6/7 weeks of gestation are associated with an increased risk of preterm birth. However, in a low-risk population, the positive predictive value of a positive fFN test at 22 to 24 weeks of gestation for spontaneous preterm delivery prior to 28 weeks and 37 weeks of gestation is only 13% and 36%, respectively. Therefore supplemental progesterone is not at present indicated for preterm birth prevention with positive fFN without signs of preterm labour in low risk population.

The Royal College of Obstetricians and Gynaecologists (RCOG) endorses current recommendations that, in women at high risk of preterm delivery, progesterone administration should be restricted to clinical trials to determine whether its use is associated with improved fetal, neonatal and/or infant outcome.

Administration of Progesterone:

The optimal progesterone formulation, route of delivery, and dose for the prevention of preterm birth has not yet been determined.[30-33]

Intramuscular progesterone preparations have slow release but optimal blood levels.Vaginal progesterone has a half-life of approximately 13 hours. It should be administered daily. Doses of 90 to 400 mg have been recommended. Authors favoring this formulation point to its natural formulation and higher endometrial concentration than via intramuscular administration, with a 14 times greater increase in the ratio of endometrial to serum concentration after vaginal dosing. Micronized progesterone can be administered either orally or vaginally, but the latter route is preferable because of more absorption,enhanced bioavailability and the absence of undesirable side effects. Vaginal progesterone

bypass hepatic metabolism therefore has vaginouterine first pass effect.[34-36]

Recent formulations of sustained release preparations 300mg or 400mg can deliver a high concentration of progesterone with least side effects of oral preparations.

Currently, intramuscular 17-OHP is the only US Food and Drug Administration (FDA) approved formulation of progestin with the indication of prevention of PTL .17-OHP is a natural progesterone with no androgenic activity that is produced by both the corpus luteum and placenta. Exogenous 17-OHP is administered intramuscularly. Doses have ranged from 250 mg every 5 days to 1000 mg weekly, beginning as early as 16 weeks of gestation. Because the half-life of 17OHP is approximately 7 days, weekly dosing would seem most appropriate. Although actively metabolized in the placenta, significant concentrations of exogenous 17-OHP and its metabolites do cross the placenta.

Gel or dispersible tablets have better bioavailability and less local discomfort.

Timing of Initiation and Cessation of Progesterone:

The optimal timing for initiation of progesterone treatment depends on the indication.[6]

Dose of Progesterone:

When opting for intramuscular progestin, the most widely studied dose is 250 mg weekly intramuscular 17-OHP-C ,though natural progesterone preparations are available with equal efficacy. If opting for vaginal progesterone, a dose of either 100 to 200 mg micronized progesterone capsules vaginally nightly (compounded) or 90 mg 8% gel nightly.

For oral preparations, 300 mg sustained release preparations may have more compliance

SAFETY OF PROGESTERONE:

Side effects:

Side effects are fairly common with injectable progestogens, including injection site reactions and urticaria (3.1%), but importantly leading to drug discontinuation in only 0.6% patients.[37] The most common complaint among users of vaginal progesterone gel is vaginal discharge in 8-9%[33].Other undesirable side effects such as sleepiness, fatigue, headaches and gastrointestinal disturbances are more with oral plain preparations than with vaginal and oral sustained release preparations.

Risk of congenital malformations:

There is a large body of literature on the use of progestins in the first trimester for assisted reproduction[38-40]. No virilisation of female fetus has been found. The only concern that persists is a possible increased risk of hypospadias in male offspring exposed to exogenous progestins, even if real, however, this risk is limited to exposure prior to 11 weeks of gestation[1]

NEWER CONCEPTS:

1. Advances in the prevention of spontaneous preterm birth (SPTB) with 17-OHP can be made if women most likely to respond to 17-OHP can be identified prospectively by genotype and if an appropriate individualized prevention regimen can be outlined. If this strategy is applied to nulliparous women with other risk factors for preterm birth (such as a personal history of mullerian anomalies or a family history of preterm birth), those women with a high-risk genotype could be studied to determine whether treatment with 17-OHP during their first pregnancy could reduce the risk of primary SPTB. There are 8 genes in the nitric oxide synthase pathway with different allele frequencies between responders and nonresponders; including SPTA2, GA2L2, DMD,SYNE1,NOS1, MICA2, SMTL2, and DESP.[41]
2. There is rising evidence that PCOS is a leading cause of cervical incompetence and PPROM. Progesterone supplementation prevents onset of miscarriage and PTL in these pts., but doesn't replace the role of cerclage in patients with short cervix. [42]
3. There are studies which show that altered calcium homeostasis leads to cell death in chorion and decidual cell of fetal membranes especially in PPROM and Progesterone offers protective role by decreasing Calcium influx through voltage gated Ca channels[43]

To summarise, in ideal candidates, progesterone supplementation has been shown to prevent recurrent preterm birth in one-third of subjects. The reasons of SPTB should be evaluated and the treatment individualised.

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PROGESTERONE CAFETERIA IN CONTRACEPTION

5

Prof. Dr. Suchitra N. Pandit
MD., MAO (IRL) DGO, DFP,
FRCOG (UK) FRCPI (IRL) FICOG,
FICMCH, PGD, MLS (Law)
President FOGSI & ICOG 2014
President MOGS (2013-14)

Dr. Swati Bhargav
MS OBG
Dept. of Obs & Gyn
M.G.M Medical College
M.Y Hospital, Indore (M.P)

Introduction:

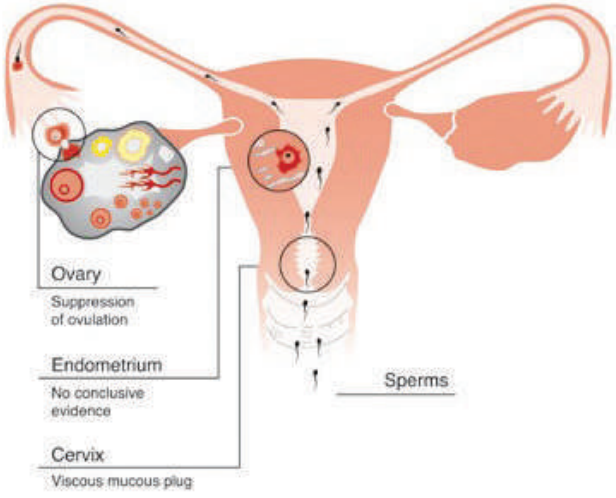
Contraception is a choice to prevent conception. The **cafeteria approach** offers a bouquet of products for a woman to choose from. All the devices available are informed to the couple allowing them to make a decision that would be right for them. A patient's choice of contraceptive method involves factors such as efficacy, safety, non-contraceptive benefits, cost, and personal considerations. The Family Welfare Program has adopted this "cafeteria approach," since the 1960s.

Progesterone has been used for contraception for more than 30 years. It was recognized to play this role so as to have a contraceptive method devoid of the metabolic or clinical side effects associated with the use of estrogens. As a result of this endeavor, various methods for the progesterone use were considered as: oral progestins, implants, injectables, intrauterine hormonal systems, and vaginal rings.

Mechanism of action:

All progesterone only contraceptive methods, regardless of their route of administration:

1. Affect cervical mucus, making it hostile
2. Reduce sperm penetrability
3. Reduce sperm transport



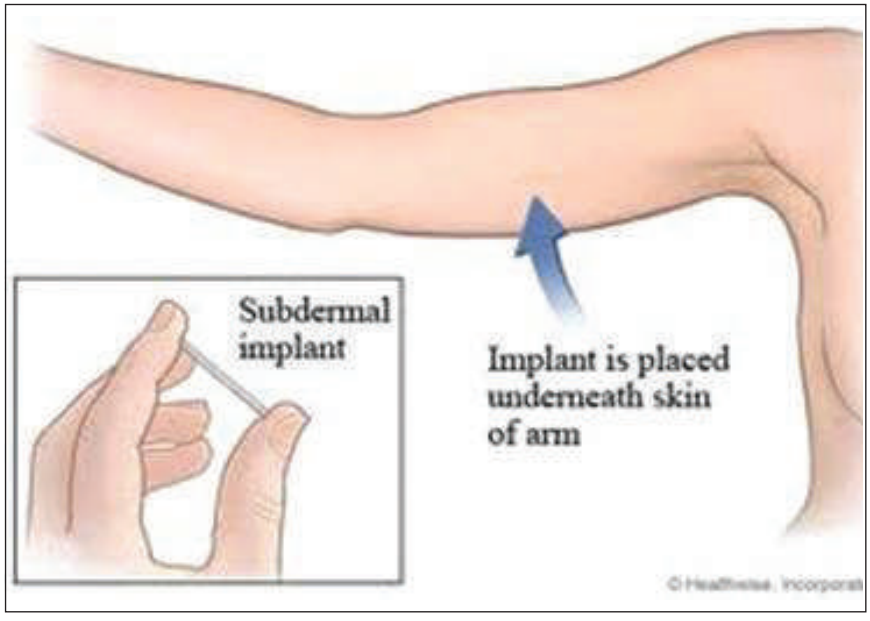
4. Inhibit ovulation
5. Compromise endometrium foe implantation

Mechanism of action of each depends on progesterone activity and dose.[1]

These progestins act by binding to their receptors located in diverse target cells, which are distributed along the hypothalamic-pituitary-gonadal-genital tract axis.

Oral Contraceptives:
Numerous progestin only pills for contraception are used as contraceptive. They are often called as minipills or progestin-only pills (POPs).
Progestin-only contraceptives may be preferable in some situations, which have absolute or relative contraindications to estrogen, lactation, and comfort and feasibility of formulations for long-term use and also as emergency contraception.
The pills come in packs of 28 and contain 35-75% less progestin than the combination pill. It has to be taken at the same time every day.
Clinical effectiveness: With perfect use, the pregnancy rate for POP users is 0.3 %.[2]
For typical use rate of effectiveness is almost 92 %.

Implants:
In addition to oral contraceptives, **implants** are also used. Norplant was released as an implant form of contraception in 1990. These are mainly used subdermally for contraceptive purpose. They are more effective than oral and barrier contraceptives. The implants consist of levonorgestrel or desogestrel metabolite, 3-keto-desogestrel. The levonorgestrel implants consist of the drug enclosed in silastic rods, 6 or 2 in number, each containing 36 mg or 70 mg of levonorgestrel respectively. The daily release of is of 50 µg .The 3-keto-desogestrel implant is a single rod containing 68 mg of the drug. The initial release is 60-70 µg /day. This reduces to 25-30 µg/day by the use of 3 years.



The contraceptive efficacy of levonorgestrel implants is 5 and with desogestrel is 3 years.
Formulations are implanted subdermally with minimal incision under local anesthesia.

Clinical Effectiveness:
Failure rate for implants with both perfect and typical use is 0.05.[2]

Injectable contraceptives:
Depot Medroxy Progesterone Acetate **(DMPA)** is a good injectable progesterone alternative in contraception cafeteria. The FDA approved it, in 1992 as an injectable contraceptive.
It is administered every 3 months, each containing a dose of depot medroxy progesterone acetate 150 mg. It can be detected in systemic circulation within 30 min of administration.

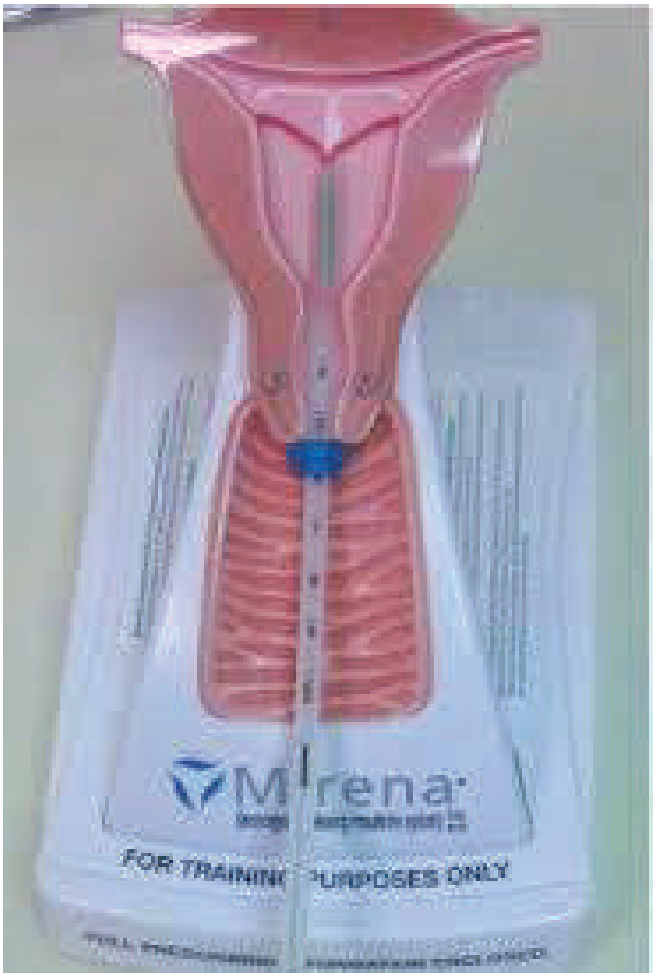
Clinical effectiveness:
With perfect use, the pregnancy rate DMPA is 0.3 %.[2]
For typical use rate of failure is almost 3 %.
Black box warning: Women using DMPA may loose bone mineral density, so calcium supplementation must be given.

Emergency contraception
It is hormonal contraception that is used by a woman after she has had unprotected intercourse, ideally within 72 hours.
As sperms are viable for several days, and women can't be sure of the exact timing of ovulation, it may be possible to prevent fertilization by a contraceptive method that blocks or delays ovulation. This is the principal mode of action of emergency contraceptives.
One dose of 0.75mg Levonorgestrel is advised as soon as possible after unprotected intercourse followed by same dose 12 hours later, both doses within 72 hours.
WHO recommends single 1.5mg dose of levonorgestrel to be as effective as two doses.

Progesterone vaginal ring
It is used to extend the contraceptive effectiveness of lactational amenorrhea among breastfeeding women.

Progesterone vaginal rings are inserted in the vagina for continuous use for up to three months and replaced with a new ring if breastfeeding is continued and extended contraception is desired. Women can use these rings continuously for up to one year. It functions by diffusing a continuous flow of progesterone through the vaginal walls—approximately 10mg per day.
The progesterone ring does not provide protection from sexually transmitted infections, including HIV.

Intrauterine progesterone contraceptive (LNG-IUS)
LNG-IUS is the hormonal intra uterine system containing Levonorgestrel. It contains 32 mm long, flexible plastic T-shaped frame impregnated with barium sulphate.



A cylindrical reservoir is wrapped around vertical stem of about 52 mg of Levonorgestrel (LNG). It releases 20mcg of hormone per day through poly-dimethyl-siloxane membrane into uterine cavity.
Other advantages of LNG-IUS[3]

1. Reduction in menstrual flow
2. Reduction in menstrual pain
3. Reduction in size of fibroid.
4. Reduction in endometrial hyperplasia / cancer.

Precautions:
Difficulties during insertion are reported.
Pregnancy must be ruled out.
Clinical effectivess:
After 5 years it should be removed as its contraceptive efficacy gets over.
Pregnancy failure rate is 0.1 % on perfect as well as typical use.[2]
Disadvantages:

1. High cost of insertion
2. No protection against STIs
3. The need to be inserted /removed by a clinician.

Thus there are a vast variety of options in the cafeteria approach of Progesterone use as a method of contraception ranging from oral, injectable, implants, rings to devices. Its use at varied periods like lactation, emergency contraception and other times, draws the attention to mark its importance in this field.

Side effects of progesterone contraceptive agents

Oral	Injectables	Implants
Irregular bleeding	Irregular bleeding	Irregular bleeding
Intermenstrual spotting Amenorrhea	Breast tenderness Depression And Reduction in bone mineral density	Infection (Less common) Follicular cysts

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PROGESTERONE – ANSWER TO ESTROGEN DOMINANCE

6

Dr. Manjula Anagani, M.D.
Chief Laparoscopic surgeon, Obst & Gyn,
Beams Hospitals, Jubilee Hills, Hyderabad
Visiting Consultant – Rainbow Hospitals,
Care Hospitals & Yashoda Hospitals,
Hyderabad

Dr. Anitha Nelakuditi,
D.N.B, Consultant gyn,
Lalitha Gayathri Hospitals

INTRODUCTION:

The term 'Estrogen Dominance'is coined by late Dr. John Lee. (1) Estrogen dominance is a theory about metabolic states where the level of estrogen over weighs the level of progesterone. This means -

1) estrogen can be high with normal level of progesterone or
2) normal level of estrogen with low level of progesterone or
3) the level estrogen level is reduced but not ceased and progesterone production ceases leading to estrogen dominant state - as seen during menopausal transition

Estrogen dominance can start as early as menarche to menopausal transition. Today , the age of menarche is dropping as low as 10 years, endometriosis is affecting 10% of perimenopausal women, PMS is affecting 30% of perimenopausal women,(2) uterine fibroids are seen in 25% of women of age 35 to 40 years and breast cancer affecting close to 10 % of women. This necessitates the need of understanding the Estrogen dominance & the use of Progesterone in those conditions.

CAUSES OF ESTROGEN DOMINANCE:

- STRESS (excessive need for cortisol depletes progesterone as some of it is converted to cortisol to support Stressed/tired adrenal glands)
- POOR DIET (usually high in carbohydrates, low fibre diet):
- Estrogen is excreted in bowel. Studies have shown that low fiber diet causes constipation leading to increased reabsorption of estrogen when stools remain for a long time in the intestine & thus higher Estrogen levels
- NUTRIONAL DEFICIENCIES (especially magnesium, zinc, copper and B complex vitamins):
- Vitamin B6 and magnesium are required for neutralization of estrogen in liver. Deficiencies lead to elevated estrogen levels. Too much estrogen inturn leads to deficiency of zinc , magnesium, and vitamin B. Increased sugar ,fast food and processed food leads to depletion of magnesium
- ADRENAL FATIGUE
- LUTEAL PHASE INSUFFICIENCY
- ANOVULATORY CYCLES

- USE OF ORAL OR INJECTABLE CONTRACEPTIVES
- UNOPPOSED ESROGEN AS A PART OF HRT
- XENOESTROGEN EXPOSURE:

Growth hormone used in livestock and poultry contains fat soluble estrogen. Organochlorides, PCB'S, PCV'S and other plasticizers act as estrogen. Consumption of these xenoestrogen can cause Estrogen dominance.

- OBESITY (in postmenopausal women, estrogen is made in the fat cells; excess fat cells make excess estrogen)

ESTROGEN EFFECT VERSUS PROGESTERONE EFFECT:

Progesterone acts as an antagonist to estrogen. The following table clearly shows how progesterone and estrogen balance each other.

Table 1(1)

ESTROGEN EFFECT	**PROGESTERONE EFFECT**
Causes endometrium proliferate	Maintains secretory *to* endometrium
Causes breast stimulation that can lead to breast cancer	Protects against fibrocystic breast and prevents breast cancer
Increases body fat	Helps use fat for energy
Increase endometrial cancer risk	Progesterone controls the estrogen-primed endometrial glands by decreasing the number of estrogen receptors thus preventing endometrial cancer
Restrains ***osteoclast***	Promote **osteoblast** function,
function slightly	leading to bone growth
Reduces vascular tone	Restores vascular tone
Increase blood clot risk	Normalize blood clot

According to Late Dr. John Lee – for optimum health, the Progesterone to Estrogen ratio should be between 200 – 300: (1).

DISEASES OR PROBLEMS DUE ESTROGEN DOMINANCE:

- Weight gain
- Fibrocystic breast diseases
- Certain types of PMS Edema (water retention), mood swings and depression.
- Migraines
- Menstrual disturbances—irregular and heavy bleeding
- Endometriosis
- Fibroids
- Ovarian cysts
- Breast cancer

I. ESTROGEN DOMINANCE IN MENARCHIAL & REPRODUCTIVE AGE GROUP:

1) PRECOCIOUS PUBERTY & ESTROGEN DOMINANCE:

One of the causes for gonadotropin independent precocious puberty is exposure to exogenous estrogen. Prolonged or repeated estrogen exposure can cause early maturation of HPO axis resulting in gonadotropic independent precocious puberty.

Incessant Maturation has been associated with increased pathological conditions such as infertility, endometrial and breast cancer, fibroids, anemia, migraine, endometriosis etc.

2) PCOS & ESTROGEN DOMINANCE:

Due to chronic anovulation the endometrium is exposed to unrelenting estrogen stimulation & the endometrium is predisposed to abnormal pattern of growth. The risk of endometrial cancer may be increased by three fold.

Estrogen – progestin contraception treatment induces cyclic menses and attenuate endometrial growth and thereby preventing endometrial hyperplasia.

3) PREMENSTRUAL SYNDROME & ESTROGEN DOMINANCE:

· Irritability:

Acting as a Central Nervous System stimulant by inhibiting monoamino Oxidase (MAO) and thus increasing free norepinephrine, high Estrogen levels leads to irritability.

Progesterone acts as antagonist to estrogen. When the progesterone levels are insufficient, estrogen dominates and PMS symptoms can me more pronounced.

Progesterone creates and promotes an enhanced sense of emotional wellbeing and psychological self-sufficiency.

· Water retention:

Estrogen alters aldosterone –renin functions involving regulation of sodium and potassium in the blood, potentially leading to fluid retention.

Progesterone serves as a natural diuretic.

· Insomnia and sleeplessness :

Women with estrogen dominance sleep restlessly whereas women with progesterone supplements tend to have less insomnia

· Migraine & premenstrual headache :

The constriction of blood vessels followed by rebound dilation is the key factor for migraine. Estrogen causes water retention and vasodilation which causes headache. Estrogen dominance causes depletion of magnesium & Magnesium is required for maintaining normal vessel tone.

A logical treatment for severe PMS, is to suppress ovulation and the ensuring cyclical endocrine/ biochemical changes that cause the distressing symptoms.

Progesterone offers many benefits to the PMS sufferer.

Progesterone helps by acting as a natural anti-depressant, restoring libido, normalizing blood sugar, facilitating thyroid hormone, serving as a natural diuretic, restoring proper cell oxygen levels, protecting against fibrocystic breasts, helping use fat as fuel and normalizing zinc and copper levels. [**1**].

Assurance and life style modifications with low fat intake and high fibrediet , adequate vitamin intake should be the first step.

Combined oral and contraceptive pills – espthose containing anti-mineralcorticoid and anti-androgenic progestogen, drospirenone has been effective.

Progestogens:

a) Cyclical progesterones- from 5th day of the cycle for 20 days - A recent meta analysis showed no significant benefit for the treatment of severe premenstrual syndrome with progestogens and progesterone(**3**) .

b) Depomedroxyprogesterone acetate (Depo*Provera),* etonorgestrel rod (Implanon) and anovulation suppression 'progestogen-only pill' (Cerazette) - all have ovulation suppressant activity and as such would be expected to have greater treatment efficacy. However, cyclical symptoms are often replaced with continuous low-grade symptoms due to the PMS-like side effects of synthetic progestogens . So as a Second-line treatment, oral cyclical progestogen has been used with estrogen for longterm endometrial protection (e.g. Oestradiol patches (100mcg) +duphaston 10mg D17-D28)

c) Levonorgestrel intrauterine system - Incidence of progestogenic PMS like physical and psychological side effects is less.On its own it may benefit the PMS ,by improving menorrhagia ,dysmenorrhea thus reducing depression associated with PMS expectancy symptoms (**4**)

4) FIBROCYSTIC DISEASE OF BREASTS ANS ESTROGEN DOMINANCE:

The pathophysiology of fibrocystic disease is determined by estrogen predominance and progesterone deficiency that results in hyper proliferation of connective tissues, which is followed by facultative epithelial proliferation. The risk of breast cancer is increased to two fold to four fold in these patients.

Cyclic administration of progesterone modulates the mammary effect of estrogen.

5) AUB AND ESTROGEN DOMINANCE:

Majority of DUB is due to anovulatory cycles. The continuous release of estrogen secretion unopposed by progesterone in anovulatory cycle leads to endometrial hyperplasia leading to menorrhagia or metrorrhagia or menometrorrhagia.

Use of progesterone either continuous or cyclical form help to restore normal menstrual cycle.

Oral route: Progestogen therapy is administered cyclically either in the second half (luteal phase treatment from the 15th to the 25th day)(**3**) or throughout the menstrual cycle (whole cycle treatment-from the 5th to the 25th day).

Depot preparation of Norethisterone and medroxyprogesterone acetate: If used for long enough they induce amenorrhoea, but during the early months bleeding tends to be unpredictable and can be heavy leading to higher discontinuation rates&systemic side effects are a problem(**3**)

LNG IUS: causes profound changes within the endometrium ,thinning of the of endometrium ,atrophy of endometrial glands ,decidualisation of endometrial stroma ,capillary thrombosis . There seems to be an increase in biochemical modulators in women using LNG IUS which mediate a reduction in cell proliferation & increase in programmed cell death.(5)

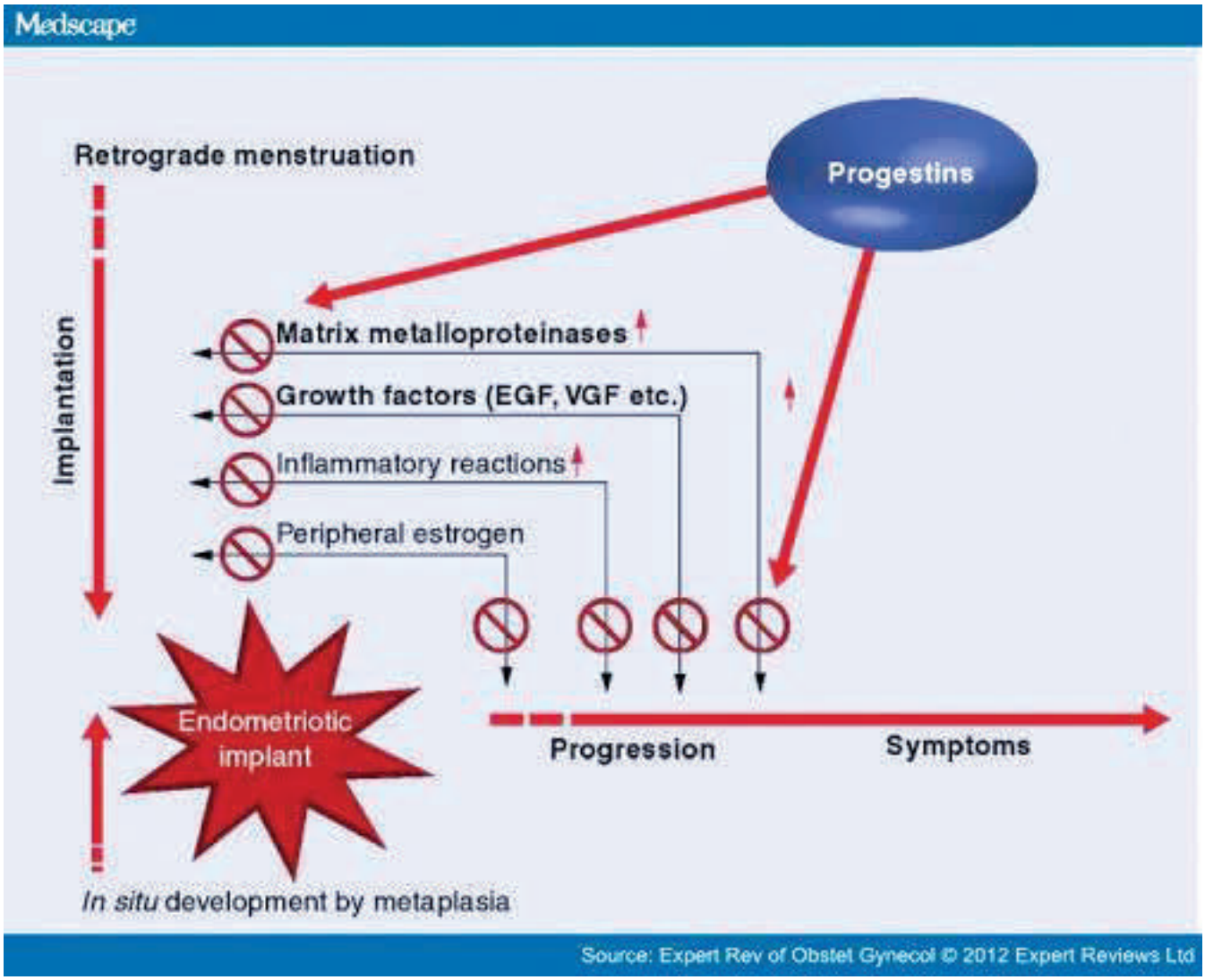
6) ENDOMETRIOSIS AND ESTROGEN DOMINANCE:

Estrogen in Endometriosis is derived from three sources.

1. Estrogen secreted by ovary into circulation.
2. Estrogen released directly into the peritoneal cavity at ovulation.
3. Estrogen derived from adipose tissue.

Progesterone inhibits endometrial growth first by inducing decidualization, then atrophy. High doses can inhibit pituitary gonadotropin secretion and ovulation, inducing amenorrhea.

Fig 1(**mechanism of action of progestins in treatment of endometriosis**)



Progestogens – alone or in combination with lowdoseestrogen :longterm – around 6 mths or intermittently repeated medication seem to be effective & are relatively well tolerated.(6)

Depot provera – very effective in symptoms but possibility of delayed resumption of ovulatory cycles and systemic effects on bone makes it less advisable in reproductive age group.

LNG –IUS – positive effects on endometriosis – related pain & Deep infiltrating endometriosis(Rectovaginal Endometriosis)(8)

7) FIBROIDS & ESTROGEN DOMINANCE:

Fibroid is predominantly an estrogen dependent tumor .Estrogen dependancy is evidenced by its growth

potentiality being limited during child bearing period, increased growth during pregnancy ,no occurrence of the tumor before menarche and cessation of the growth following menopause and its frequent association with anovulation .

The goals of medical therapy for leiomyoma are to temporarily reduce symptoms and to reduce size of the tumor .

Progesterones have been indicated in menorrhagia secondary to fibroids. Norethisterone / medroxyprogesterone acetate 5-10 mg is administered cyclically from day of the cycle for 20 days.

LNG- IUS –effective for menorrhagia but not generally recommended in fibroids distorting the cavity due to technical difficulty in insertion.6

8) POSTPARTUM DEPRESSION AND ESTROGEN DOMINANCE:

About 300-400mcg of progesterone are daily produced during pregnancy. Following delivery, the fall of progesterone level leads to a state of estrogen dominance.

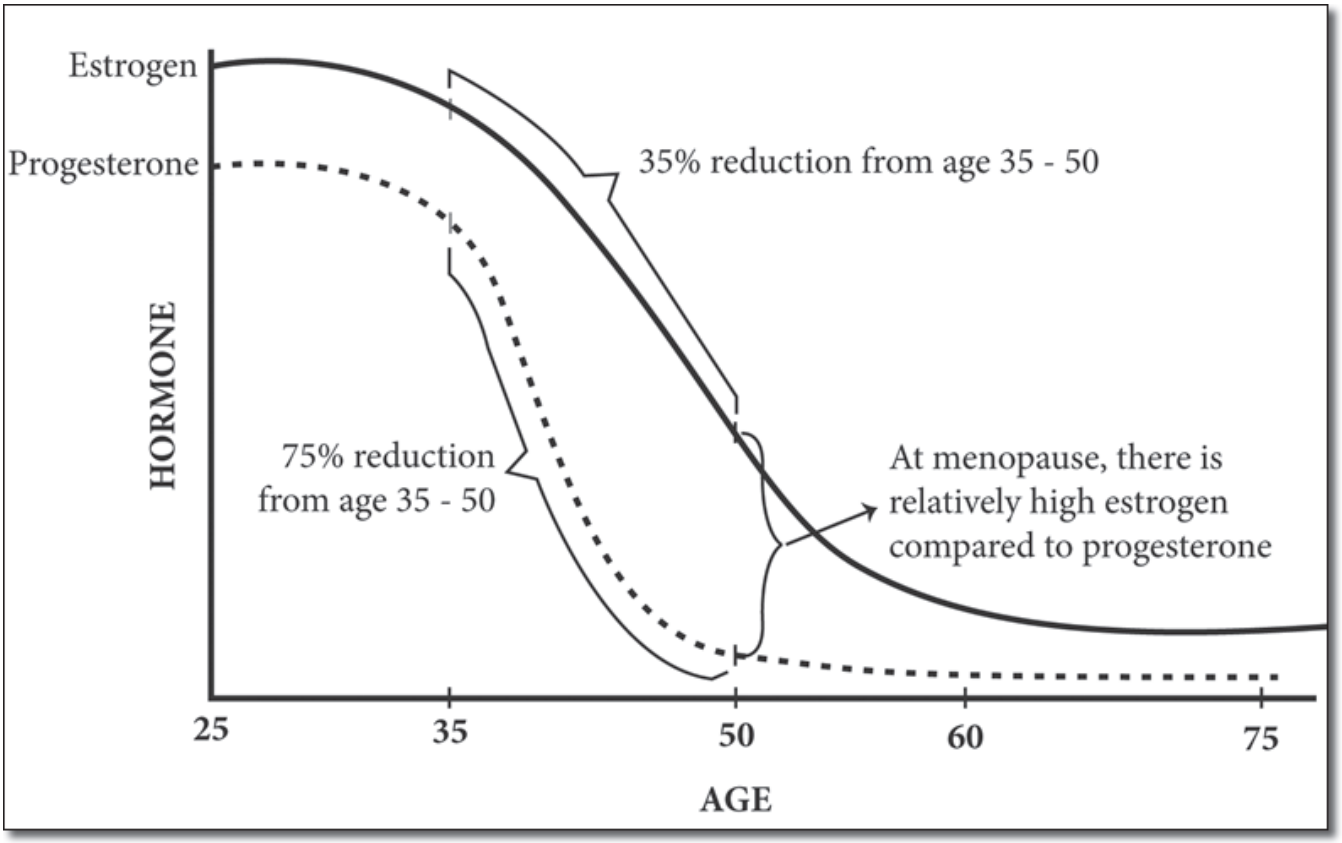
The progesterone counterbalance the effects of estrogen. Estrogen has an excitatory effect on the brain whereas progesterone has calming effect.

Postpartum depression can be easily treated with supplementation of progesterone.

II. ESTROGEN DOMINANCE IN PERIMENOPAUSAL WOMEN:

From age of 35 to 50 years, there is a 75% reduction in progesterone estrogen declines only by 35%. By menopause, the total amount of progesterone is extremely low compared to estrogen which is still half its premenopausal levels.

Fig 2(1)



The causes for estrogen dominance here are:

1. Anovulation:

   When there is anovulation, the corpus luteal is not formed and there is no increase in progesterone. Laboratory measures show both low estrogen and progesterone level. The lack of estrogen with relative estrogen dominance leads to symptoms like PMS, mood swings, breast tenderness, etc.

2. Luteal insufficiency:

   Here the ovum is produced but corpus lutem malfunctions. Hence progesterone levels are low with high estrogen.

III. ESTROGEN DOMINANCE IN MENOPAUSAL WOMEN:

1. During menopause, the estrogen produced from the ovaries decreases but there is no drastic reduction of androstenedione. Fat calls convert androstenedione to estrogen and absolute deficiency of progesterone leads to estrogen dominance.
2. Use of unopposed estrogen as part of harmone replacement therapy has been associated with significant increase in breast cancer(5.4 times) , water retention, fibrocystic disease of breast, depression, headache, breast swelling & endometrial cancer.

PROGESTERONES TREATMENT IN PERI MENOPAUSAL AND POST MENOPAUSAL WOMEN WITH ESTROGEN DOMINANCE:

- Many peri- or post-menopausal women with clinical signs of hypothyroidism, such as fatigue, lack of energy, intolerance to cold, are actually suffering from unrecognized estrogen dominance and will benefit from supplementation with natural progesterone.
- Natural progesterone is preferred in perimenopausal women as it is a natural diuretic and prevents the cell's uptake of sodium and water, thus preventing hypertension.
- Natural progesterone can be beneficial to both those with diabetesand those with reactive hypoglycemia as it stabilizes the impaired homeostatic control of glucose levels due to estrogen dominance.
- Progesterone serves a role in keeping brain cells healthy. A disorder such as premature senility (Alzheimer's disease) may be, at least in part, another example of disease secondary to progesterone deficiency.
- Progesterone is essential for the healthy development of the myelinsheath which protects the nerve cells. Low progesterone levels lead to recurring aches and pains.
- Progesterone is responsible for enhancing the libido.

ENDOMETRIAL CANCER AND PROGESTERONE TREATMENT:

Progesterone agents have been extensively used in patients with advanced or recurrent endometrial cancer. Nevertheless, most studies do support low-grade histology, long disease-free interval, and expression of estrogen and/or progesterone receptors as important prognostic factors that predict a favorable response to progestin.(**9,10**)

LIFESTYLE MODIFICATION REQUIRED IN ESTROGEN DOMINANCE

- Reduce stress
- Limiting the exposure to Xenoestrogen
  - Eating organic meat and dairy products
  - Heating the food in glass or porcelain rather than plastic in microwave.
  - Avoiding drinking from plastic bottles or Styrofoam cup.
- Consuming of phytoestrogen (soya bean, yams, alfalfa, licorice) can be beneficial as it binds to estrogen cell receptor and prevents xenoestrogen from binding.

CONCLUSION:

A healthy lifestyle with a balanced nutritious diet and relaxation seems to be the main stay of treatment along with hormonal supplementation for symptoms associated with estrogen dominance . Counseling and awareness regarding the need for longterm medication and the side effects associated with it help in improving the acceptance rates of therapy .Progesterones in various routes of administration have been proven to alleviate and treat the symptoms associated with estrogen dominance .Levonorgestrel releasing Intrauterine system has been an emerging trend with proven wider clinical applications beyond contraceptive capabilities .Careful preinsertion counseling regarding the unscheduled vaginal bleeding in the initial months has been associated with better acceptance rates

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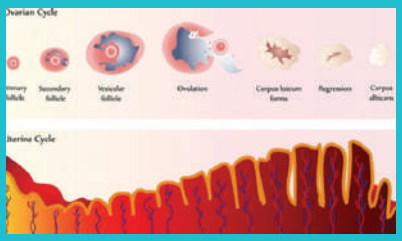


LUTEAL PHASE DEFECT

7

DrAlok Sharma,
MD, MICOG, DHA.MD,
Incharge Infertility Clinic
Shimla, Himachal Pradesh.
Email id – md.alok@gmail.com

Dr Sandeep Singh Rathore
KNSH for M & C, Indira Gandhi
Medical College, Shimla. (HP)

Luteal phase insufficiency or Luteal phase deficiency (LPD) was first described by Georgeanna Jones in 1949.[1] It is defined as a condition in which there is either deficient production of endogenous progesterone by corpus luteum or suboptimal response of the endometrium to otherwise normal progesterone concentrations.[2] Hence there is inadequate secretory changes of the endometrium after the ovulation of the dominant follicle.[3,4.]

Since, then there has been an evidence based change of definition as follows:

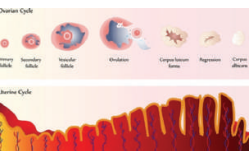
- Delay in endometrial maturation more than 2 days in 2 successive endometrial biopsies beyond the actual cycle day in the histological development of the endometrium.
- Low integrated luteal phase progesterone.
- Consistently short luteal phase duration (less than 13 days), most accurately delineated by the interval from detection of midcycle LH surge to the onset of menses.

It affects women of all races during their reproductive years. Random cycles of normally menstruating women may be affected by it.[5] Therefore, the diagnosis of LPD can be made only after repeated testing in normal fertile women. Number of factors like dieting[6], recent child birth[7], lactation[8], extremes of reproductive age[9,10,11], affects its incidence in normal women. LPD is clinically relevant if it is present in most menstrual cycles in a patient. The incidence of LPD is reported between 6.6% and 51% depending on the diagnostic criteria used.[12] In women with infertility the reported prevalence of LPD ranges from 3.7% to 20%.[13,14] In women with recurrent pregnancy losses LPD is reported in 25% to 40% cases.[15]

Pathophysiology

The pathophysiology of LPD involves formation and function of corpus luteum and the endometrial changes subsequent to it. It can result from abnormalities at the level of the hypothalamus/ pituitary, the ovary or the endometrium.

Normal luteal phase length is relatively fixed at 12-14days. The follicular phase abnormalities like low follicular FSH levels, altered follicular FSH/LH ratio, abnormal FSH & LH pulsatility lead to defect in formation and function of dominant follicle. This further forms deficient corpus luteum. STAR protein governs the cholesterol transport, which is the rate limiting step in steroidogenesis. Pulsatile LH action is mandatory for normal corpus luteum function. Corpus luteum becomes refractory to LH action in late luteal phase.



Daily progesterone production is 25-50 mg which is secreted in approximately 90- minute pulses.

Large cells develop from granulosa cells and produce basal progesterone under pulsatile LH stimulus, while small cells are from theca interna cells which produce progesterone mainly after human chorionic gonadotrophin stimulus. [16,17]

In adequately estrogen- primed endometrium there occurs leutinisation changes in endometrium. The leutinisation threshold has been suggested to present between 1ng/ml and 5ng/ml. There is no consensus regarding lower levels of progesterone needed for normal luteal phase changes.[18]

In addition to the well recognized associations noted previously various other conditions like hyperprolactinemia[19], thyroid disease; in particular hypothyroidism[20], hyperandrogenism[21], endometriosis[22] result in LPD.

Diagnosis

LPD diagnosis is neither straightforward nor completely accurate. Diagnostic tests influenced by and based upon following physiologic observations.

1. Duration of luteal phase is 12-14 days normally
2. Peak levels of progesterone is observed 6-8 days after ovulation and it is secreted in pulses
3. Follicular phase estrogen and luteal phase estrogen and progesterone cause characteristic endometrial response
4. After implantation the rising levels of HCG affect the progesterone secretion by the corpus luteum
5. Failure of increase of HCG level causes corpus luteum failure and decrease in progesterone level

The tests available to assess luteal phase functioning are indirect tests like Basal body temperature and direct tests like progesterone and estrogen level in blood, serum and saliva and endometrial sampling.

1. BBT charts

The usefulness of BBT in LPD was questionable right from beginning.[23]

Ovulation is indicated by 0.2p C (0.5p F) increases in body temperature above that of previous 6 days and increase persisting for at least 11 days.[24] It is difficult to interpret by the patient and physician and therefore is not recommended these days.

2. Progesterone levels

Another common method used for diagnosis of LPD is measurement of Serum progesterone levels. Its production begins after LH surge and is nonpulsatile in early luteal phase. In mid and late luteal phase it is secreted in pulsatile manner reflecting LH pulses.[25] Its levels are not constant due to its pulsatile release and levels may vary upto 8 folds within 90 minutes.[26] Therefore single value of progesterone does not serve any purpose in diagnosing LPD. No minimum serum progesterone levels define 'fertile' luteal function so random progesterone levels is not a valid diagnostic test to define LPD. It is suggested that sum of three midluteal levels taken between day 5 and day 9 after ovulation of > 30 ng/ml has a sensitivity of 100% and specificity of 80%.[27] Once pregnancy is established, the corpus luteum is simulated by HCG to produce progesterone and its levels have some value in determining whether pregnancy is viable or extrauterine.[28]

3. Endometrial biopsy

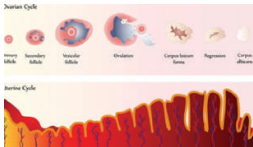
It is considered to be the most important diagnostic test to evaluate LPD by many. But there are concerns regarding timing of biopsy, number of biopsies, definition of out of phase biopsy – 2 days or 3 day, its interpretation and inter and intra- observer variability.

In theory whether the maturation is delayed by inadequate ovarian hormone secretion or is delayed because of an intrinsic endometrial abnormality, luteal phase deficiency affects the normal implantation or early placental development. Midluteal endometrial biopsy depicts implantation window.[29] The common practice is to perform endometrial biopsy in two cycles[30], but there is no consensus. When there is no difference in sporadic appearance of out of phase endometrium in normal and infertile women.[31] Recent prospective, blinded, randomized clinical trials suggested that endometrial biopsy is an imprecise tool for differentiating fertile women from women with LPD (infertility).

To summarise none of the available test is good enough to make the diagnosis of LPD.

Treatment of Luteal Phase Defect

The first approach to treatment of potential LPD is the correction of any underlying condition like hypothalamic dysfunction, thyroid dysfunction or hyperprolactinemia. Empirical treatment of LPD is neither justified nor warranted as per the present evidence. Although it is given to promote endometrial maturation, to increase endometrial receptivity and to



support implantation and development of early pregnancy.

Ovulation inducing drugs like clomiphene treat LPD by improving the quality and quantity of follicle has been suggested by few studies. There is no evidence that progesterone is beneficial in natural, unstimulated cycles. They are useful in controlled ovarian stimulation cycles for IVF.[32,33,34] Similarly there is no substantial evidence to support routine supplementation with estrogen and HCG in natural or unstimulated cycles. Though they are beneficial in ART cycles.

SUMMARY

LPD is a subtle disorder of corpus luteum function and has a multifactorial cause

The diagnosis is best made by measuring serum progesterone levels daily throughout the luteal phase. This method is impractical, however, except in a research setting. The best means of estimating luteal phase function available to clinicians is three pooled mid luteal progesterone levels.

To conclude at the moment testing and treating LPD in non- IVF cycle is not recommended. LPD as an independent entity causing infertility has not been proven so far.

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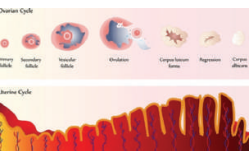

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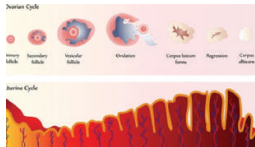

PROGESTERONE IN RPL

8

Dr.Ajay Mane

Dr.Ajay Mane – Chairperson-Sexual Medicine Committee,FOGSI (2014-16)

Dr.Rajendrasinh Pardeshi

Dr.Rajendrasing Pardeshi – Chirperson –Food,Drugs and Medico-surgical equipment committee,FOGSI (2012-14)

Introduction:

Recurrent miscarriage is known to affect 0.5-2% of pregnant women, and the standard investigative protocol fails to identify a specific cause in 50% of cases.[1]

Progesterone appears to be necessary to support an early pregnancy, and it has been used for this purpose for several decades. It has been suggested that some women who experience spontaneous abortions may not be producing enough progesterone, so by administering exogenous progesterone it may be possible to prevent miscarriage. Progesterone produces a small but significant decrease in miscarriage among pregnant women with 3 or more unexplained pregnancy losses.[2]

Recurrent Pregnancy Loss:

Three or more abortions consecutively within the period of 20 weeks of gestation in respective pregnancy are called as recurrent pregnancy loss **(RPL)** or recurrent miscarriage or habitual abortions.

Etiology of RPL:

In certain cases more than one factor or a single cause may be seen.

Anatomical abnormalities : These account for 10% to 15% of cases of RPL.

Endocrine disorders : It shares about approximately 17% to 20% of RPL.

Infectious diseases : The incidence of 0.5% to 5 % (6)

Genetic causes : 3.5% to 5% of RPL are associated with a parental balanced structural chromosome rearrangement. (4).

Immunological causes : The incidence is 20-50%. APS is main reason.

Other causes : Thrombotic disorders Environmental causes Idiopathic (Almost 10%)

Progesterone…the hormone for maintenance of pregnancy:

Progesterone is very necessary for the occurrence and pregnancy maintenance.

1. Progesterone helps the endometrium for the process of implantation.
2. The pre-ovulatory increase in the secretion of 17â-estradiol (E_2) promotes the proliferation and differentiation of uterine epithelial cells. Then the production of progesterone takes place causing the proliferation and differentiation of stromal cells.
3. Progesterone acts on the endometrium via specific receptors.
4. It causes conversion of TH1 to TH2; as a response producing progesterone induced blocking factor (PIBF) and performs reduction of NK cells activity.

Corpus luteum is the only source of progesterone during the luteal phase of the normal/routine menstrual cycle and in pregnancy.

The corpus luteum as well as the trophoblast is the source of progesterone.

Role of progesterone in recurrent pregnancy loss:

1. Progesterone as an immunomodulatory molecule.[5]

Increased progesterone sensitivity of pregnancy lymphocytes is due to activation-

induced appearance of progesterone binding sites in the lymphocytes.

Following recognition of derived antigens gamma/ delta TCR+ cells develop progesterone receptors. Progesterone binding results in the synthesis of a mediator protein named the progesterone-induced blocking factor (PIBF).

PIBF by acting on the phospholipase A2 enzyme interferes with arachidonic acid

metabolism, induces a Th2 biased immune response, and by controlling NK activity exerts an anti-abortive effect.

2. In the management of luteal phase defect.

LPD is a recurrent post – ovulatory deficiency in the production of progesterone from the corpus luteum leading to infertility or habitual abortion.

Typical patient is subfertile or shows h/o of recurrent pregnancy loss

` Clinical characteristics are indicative of deficient progesterone production:

a. advanced age,
b. low body weight, and/or
c. shortened menstrual cycles that are often accompanied by premenstrual spotting

A growing body of considerable evidence indicates that in addition to women with luteal phase defects, women with idiopathic recurrent miscarriage may benefit from progestogen treatment.[1]

3. Prevention of second trimester loss / preterm labor.

Role of injectable progesterone (17-á-OH progesterone) is not only recommended but also approved by FDA.

In known cases of cervical shortening from diagnosis till 36 weeks the use of vaginal micronized progesterone is also recommended nowadays.

Clinical evidences:

1. **Int Immunopharmacol. 2001**
   Increased progesterone sensitivity of pregnancy lymphocytes is due to activation-induced appearance of progesterone binding sites in the lymphocytes…..exerts an anti-abortive effect.

2. **J Fam Pract. 2005**
   Progesterone produces a small but significant decrease in miscarriage among pregnant women with 3 or more unexplained pregnancy losses

3. **Best Pract Res Clin Obstet Gynaecol. 2008**
   A growing body of considerable evidence indicates that in addition to women with luteal phase defects, women with idiopathic recurrent miscarriage may benefit from progestogen treatment,… Some studies have revealed a remarkable improvement in pregnancy outcome after progestogen supplementation in women suffering from recurrent miscarriage. As most studies on this topic are of unsufficient statistical power, further research on the efficacy of progestogen treatment in affected women is required.
4. **Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD003511. DOI: 10.1002/ 14651858.CD003511.pub2.**
   There is no evidence to support the routine use of progestogens to prevent

miscarriage in early to mid-pregnancy. However, there seems to be evidence of benefit in women with a history of recurrent miscarriage. Treatment for these women may be warranted given the reduced rates of miscarriage in the treatment group and the finding of no statistically significant difference between treatment and control groups in rates of adverse effects suffered by either mother or baby in the available evidence. Larger trials are currently underway to inform treatment for this group of women.

Different formulations in different situations:

1) **<u>Natural Progesterones</u> (Micronized Progesterone):**
   These can be administered by oral, vaginal, rectal, and intramuscular or transdermal routes.
   Nowadays better oral water soluble preparations are available. Dose: 200 - 800 mg daily in divided doses.
2) **<u>Synthetic Progestins:</u>**
   17 á-hydroxy progesterone is administered as 250 - 500 mg deep intramuscular injection.
3) **<u>Progesterone derivatives:</u>**
   Dydrogesterone is administered as oral tablets.
   Dose : 10 to 30 mg daily.

Conclusion:

Progesterone has been used to support early pregnancy since so many years.

Growing evidence shows that not only women with luteal phase defects, but also women with idiopathic recurrent miscarriage may benefit from progestogen treatment. However, the studies so far conducted are of insufficient power of statistics. Further research, RCTs are required.

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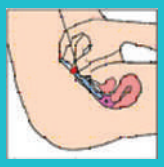

PROGESTERONE SUPPLEMENTATION DURING IN VITRO FERTILIZATION (IVF) CYCLES

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Dr Fessy Louis T
Consultant & IVF Coordinator
CIMAR Fertility Center, Cochin
FOGSI International Academic
Exchange Committee Chairperson

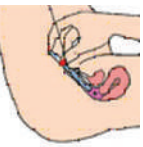
Progesterone is a hormone produced by the ovary. Progesterone prepares the lining of the uterus (endometrium) to allow a fertilized egg (embryo) to implant. If a pregnancy does not take place, progesterone levels will fall and endometrium sheds. If an embryo implants in the uterus, the ovary will produce progesterone which will decrease after ten weeks of the pregnancy. After that time, progesterone will be produced by the placenta throughout the rest of the pregnancy.

Luteal phase is deûned as the period between ovulation and either the establishment of a pregnancy or the onset of menses two weeks later. The luteal phase of a natural cycle is characterized by the formation of a corpus luteum, which secretes steroid hormones, including progesterone and estradiol (E2). If conception and implantation occur, the developing blastocyst secretes human chorionic gonadotrophin (hCG). The role of hCG produced by the embryo is to maintain the corpus luteum and its secretions [1].

The role of progesterone in the luteal phase: Progesterone induces a secretory transformation of the endometrium in the luteal phase. By inducing this change after adequate estrogen priming, progesterone improves endometrial receptivity. Progesterone also promotes local vasodilatation and uterine musculature quiescence by inducing nitric oxide synthesis in the decidua. Decreased endometrial receptivity is considered largely responsible for the low implantation rates in IVF. The uterine-relaxing properties of progesterone were supported by a study of IVF embryo transfer outcomes by Fanchin et al [2]. This study results indicated that a high frequency of uterine contractility on the day of embryo transfer hindered transfer outcome, possibly by expelling embryos out of the uterine cavity. A negative correlation between uterine contractility frequency and progesterone concentrations was detected underlining the benefits of progesterone in IVF. The importance of progesterone during the first weeks of a pregnancy was demonstrated by Csapo etal. In their initial study, the removal of the corpus luteum prior to 7 weeks of gestation led to pregnancy loss. They also found that pregnancy could be maintained even after removal of the corpus luteum by external administration of progesterone [3].

The cause of the luteal phase defect in stimulated IVF cycles:

Initially, it was thought that the removal of large quantities of granulosa cells during the oocyte retrieval (OR) might diminish the most important source of



progesterone synthesis by the corpora lutea, leading to a defect of the luteal phase. However, this hypothesis was disproved when it was established that the aspiration of a preovulatory oocyte in a natural cycle neither diminished the luteal phase steroid secretion nor shortened the luteal phase. Another theory suggested that the prolonged pituitary recovery that followed the GnRH agonist co-treatment designed to prevent spontaneous LH rise in stimulated cycles resulting in lack of support of the corpus luteum, would cause a luteal phase defect. It was also suggested that the hCG administered for the final oocyte maturation in stimulated IVF cycles could potentially cause a luteal phase defect by suppressing the LH production via a short-loop feedback mechanism [4].

Options of luteal support in ART:

To correct the luteal phase defect in stimulated IVF/ ICSI cycles, progesterone and /or human chorionic gonadotrophin (hCG) can be administered. The addition of estradiol to progesterone luteal support is currently debated and the final situation in luteal phase support needs further studies.

Human chorionic Gonadotropin:

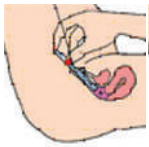
Since it was found that the corpus luteum can be rescued by the administration of hCG, this treatment has become the standard care for luteal support since the late 1980s. By stimulating the corpora lutea, hCG is an indirect form of luteal support. It is known to generate an increase in E2 and progesterone concentrations, thus rescuing the failing corpora lutea in stimulated IVF cycles. Despite the variety of protocols that exist for the use of hCG in luteal phase support, there appears to be no rationale behind either the dose frequency (every 2 days, every 3 days, varying intervals) or the total daily dose (1000, 2500 or 5000 IU). There has been no study to date which has been able to show that luteal phase support with hCG is superior to that provided by progesterone. HCG is associated with a greater risk of OHSS. Luteal support with hCG should be avoided if E2>2700 pg/ml and if the number of follicles is 10. Due to the same efficacy of hCG and progesterone, but the increased OHSS risk with hCG, progesterone should be the first choice for luteal phase support following ovarian stimulation in the long protocol. The question is, by what route progesterone should be given [5].

Progesterone:

In response to progesterone, the glands become tortuous and secretory and there is an increase in stromal vascularity, thus making the endometrium both morphologically and functionally well prepared for implantation. Progesterone preparations can be divided into two groups: natural progesterone and synthetic preparations. Synthetic derivatives or progestins are 1) 17-hydroxyprogesterone derivatives and 2) 19-nortestosterone derivatives. The 19-nortestosterone synthetic derivatives resist enzymatic degradation if given orally, but have a high incidence of secondary effects and have been associated with mood changes, depression, virilization, decrease in high-density lipoproteins, luteolysis and a possibly teratogenic effect that limits their use during fertile cycles. Natural progesterone has no adverse effects on high-density lipoproteins, no teratogenic effects and is more effective than the derivatives in inducing secretory changes at the endometrium. Currently available formulations of progesterone include oral, vaginal, rectal and intramuscular. Progesterone administered orally is subjected to first pass prehepatic and hepatic metabolism. This metabolic activity results in progesterone degradation to its 5a- and 5b-reduced metabolites. Parenteral administration (vaginal, rectal and IM) of progesterone overcomes the metabolic consequences of orally administered progesterone [6].

Oral progesterone:

Oral micronized progesterone was used for luteal support in IVF with poor results until the end of 1980s [7]. Devroey et al. in 1989 reported an absence of the secretory transformation of the endometrium in patients with premature ovarian failure (POF) who had been treated with oral micronized progesterone when compared with patients treated with IM injections or vaginal micronized progesterone [8]. This finding suggested that oral administration reduced the hormone's bioavailibility. To overcome this problem, dydrogesterone (DG) was introduced to support the luteal phase of stimulated IVF cycles [9]. DG, a retroprogesterone with good oral bioavailability, is a biologically active metabolite of progesterone and has an anti-estrogenic effect on the endometrium, achieving the desired secretory transformation. Chakravarty et al in 2005 undertook a prospective, randomized study (n = 430) that compared the efficacy, safety and tolerability of oral DG with vaginal micronized progesterone as LPS after IVF [10]. Both DG and progesterone were associated with similar rates of successful pregnancies. Although both routes had more or less comparable cycle outcome the cited studies did not comment on sedative effects of oral



synthetic dydrogesterone compared with vaginal micronized progesterone.

Vaginal progesterone:

The intravaginal route of progesterone supplementation in IVF has gained wide application as a first choice luteal support regimen, mainly due to patient comfort and effectiveness [11]. Following intravaginal administration of progesterone, high uterine progesterone concentrations with low peripheral serum values are observed, due to counter-current exchange in progesterone transport between anatomically close blood vessels and due to the uterine first pass effect, where liver metabolization is absent. Natural progesterone has been incorporated in different forms for vaginal administration, e.g. vaginal tablets or capsules, vaginal pessaries and vaginal gel. The tablets absorb the vaginal secretions and disintegrate into an adhesive powder that adheres to the vaginal epithelium, thus facilitating sustained absorption and reduced perineal irritation.

IM progesterone:

Intramuscular progesterone, supplementation is given as an injection of natural progesterone in oil In 1985, Leeton et al. first demonstrated the extension of the luteal phase of stimulated IVF cycles treated with 50 mg IM progesterone [12]. The doses of IM progesterone used for LPS vary between 25 and 100 mg/day without any significant difference concerning the outcome. This route of administration is often associated with a number of side effects, including painful injections and a rash causing a lack of enthusiasm for this treatment modality. In addition to this, injections of progesterone in oil can also cause inflammatory reactions and abscesses.

In an open-label trial in 1184 women from 16 US centers, by Levine evaluated the clinical and ongoing PR in IVF cycles involving vaginal and IM progesterone it was found to have comparable clinical and ongoing PR A meta-analysis published in 2002 by Pritts and Atwood included five prospective randomized trails comparing IM administration of progesterone with vaginal application [13] . Clinical PR and delivery rate were significantly higher when IM progesterone was used. Despite the conclusion of Pritts and Atwood's meta-analysis, vaginal administration of progesterone is a viable alternative to the IM injections of progesterone which are associated with a high number of side effects.

Rectal progesterone:

A number of publications have evaluated the rectal use of natural progesterone in women undergoing IVF/ ICSI. In 1987 Chakmakijan and Zachariah studied the bioavailability of micronized progesterone by measuring sequential serum progesterone concentrations after a single bolus of 50–200 mg given sublingually, orally (capsule and tablet), vaginally and rectally (suppositories) during the follicular phase of a group of normally menstruating women. When compared with other modes of administration, rectal application resulted in serum concentration during the first 8 h twice as high as other forms [6].

Comparison of different progesterone preparations for vaginal administration:

A limited number of progesterone preparations are currently available that can be administered vaginally.

Progesterone capsules containing 100/ 200/300 mg natural progesterone per capsule can be used.

The dose used in most studies is 600 mg/day, which therefore requires capsules to be administered twice or three times a day.

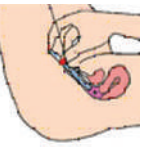
A variety of progesterone pessaries are also available, the majority of which appear to have equivalent pharmacokinetic properties to progesterone capsules.

8% vaginal gel a preparation that contains 90 mg natural progesterone, is available in an applicator specially developed for vaginal administration. Various studies have shown that 90 mg administered once daily seems to be at least as effective as 600 mg capsules for luteal phase support in the course of IVF treatment [14] . The essential difference between progesterone capsules or suppositories and 8% vaginal

gel is that the former contains an oil emulsion, while the latter is an oil-in-water emulsion on a polycarbophil base. While the polycarbophil ensures that the preparation adheres to the vaginal epithelium, the oil-in-water emulsion guarantees the continuous release of progesterone directly from the aqueous phase. Replenishment of the hormone in the aqueous phase is with micronized progesterone from the depot oily phase [15].

Progesterone with E2:

The two most important hormones produced by the corpus luteum are progesterone and E2. The role of progesterone as luteal support in stimulated cycles is well



established. However, it has not yet been clearly demonstrated whether additional supplementation of E2 in stimulated IVF cycles may be beneficial. Two meta-analyses has shown that the addition of E2 to progesterone for luteal phase support in IVF/ICSI cycles has no beneficial effects on pregnancy rates [16]. Further studies are needed to clarify the exact role of E2 luteal support in long agonist vs. antagonist, normal responder vs. high responder and low responders.

The onset of Luteal Phase Support:

Timing of LPS remains the subject of debate. Current clinical practice involves beginning LPS on different days. In one study by Williams etal, delaying LPS until 6 days after OR resulted in a decreased PR of 24% when compared with patients who began luteal support 3 days after OR [17] . Where as in another study by Baruffi et al no difference has been found when LPS was started at OR compared with starting at embryo transfer [18] . Further, studies are needed to establish best timing of onset of the LPS. Referring to the published data, it is evident that the timing of LPS should not be later than day 3 after OR. The HCG administered for final oocyte maturation covers the luteal phase for a maximum of 8 days. However, taking the uterolytic effect of progesterone in account, it is recommended to start treating the patients with progesterone at least as early as the day of embryo transfer (if day 3 following the day of OR).

Duration of Luteal Support:

Theoretically, progesterone would be of benefit to only 'fill in the gap' between clearance of exogenously administered hCG and the increase in endogenous hCG production. As soon as endogenous hCG production increases, the corpus luteum secretes an appropriate amount of progesterone [19]. However most IVF centers extend luteal support for varying durations after positive pregnancy test. There were no studies to either support or contest the generally accepted practice of prolonging progesterone supplementation during early pregnancy**.**

Summary:

In luteal phase support in IVF following ovarian stimulation

—in principle, luteal phase support is necessary to optimize the results of treatment

— Luteal phase support with hCG is not superior to luteal phase support with progesterone;

— Supplementary administration of hCG brings no advantage when progesterone is administered;

— Luteal phase support with hCG brings an increased risk, as compared with luteal phase support with progesterone, of OHSS and its corresponding potential complications;

—the administration of estradiol to supplement luteal phase support is probably not worthwhile, although a definitive conclusion cannot be drawn due to the controversial nature of the data available;

— The use of oral progesterone is clearly inferior to i.m. or vaginal administration, and is associated with an increased rate of side-effects due to unphysiological metabolites;

— At present, insufficient data are available for a direct comparison of i.m. with vaginal progesterone, but there is no reason to expect a disadvantage with vaginal progesterone administration.

Luteal Phase Support with HCG or progesterone after assisted reproduction results in an increased Pregnancy rates. In the coming years, IVF stimulation may evolve into a more physiological process, a milder stimulation, with the significant fringe benefit of reducing or eliminating the current luteal phase defect

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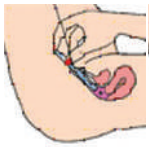

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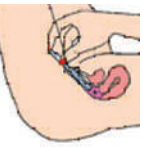

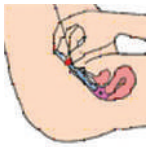

PROGESTINS IN ENDOMETRIOSIS

10

Dr Pratik Tambe MD FICOG,
Nirmiti Fertility and IVF, 1st Floor,
Parasmani,
Near Naupada Police Station,
MG Road, Thane West 400602.
drpratiktambe@gmail.com
0225035095, +919820066010

Dr Lata Rajput MD
Nirmiti Fertility and IVF, 1st Floor,
Parasmani, Near Naupada Police Station,
MG Road, Thane West 400602.

Introduction

Endometriosis is a chronic debilitating disease that has a variety of symptoms and manifestations and reduces the quality of life in women suffering from this disorder. Treatment requires a medical approach, surgery or a combination of both. Long-term or repeated medication is often necessary. Therefore, the efficacy, tolerability and costs of a drug are relevant.

Progestins

For over 40 years, oral progestins lacking an estrogen component have been demonstrated to be effective in the treatment of endometriosis. Different derivatives of progesterone (medroxyprogesterone acetate [MPA] and dydrogesterone) or derivatives of C19-nortestosterone (norethisterone, lynestrenol, desogestrel and dienogest, for example) have been used in treatment. They differ with respect to their pharmacological profile and potency of action on the hypothalamic–pituitary axis, metabolic processes, breast tissue and genital organs.

Mechanism of action

The details of the mechanisms of action and the morphological changes induced by progestins in humans have only been partly understood, even though they have been used in the treatment of endometriosis in many different countries for a number of years. The therapeutic effect is via secretory transformation of estrogen-primed uterine endometrium. The doses required to achieve this differ amongst the different derivatives.

Progestins reduce the frequency and increase the amplitude of pulsatile GnRH release, resulting in a reduction in FSH and LH secretion. Their continuous application leads to a suppression of ovarian steroidogenesis with anovulation and low serum levels of ovarian steroids. The hypoestrogenic and hypergestagenic status causes decidual transformation of the eutopic endometrium. As continuous progestin therapy results in low serum estradiol levels, breakthrough bleeding is a common occurrence.[1]

Effects on Target Tissue

The mode of action on the endometriotic implant is still a contentious issue. Earlier studies on the subject postulated activities via the steroid receptor mechanism as known from the uterine mucosa, meaning that secretory changes in ectopic lesions were followed by decidual transformation and atrophy. Later studies have cast doubt over this hypothesis.

Endometriotic foci either contain progesterone receptors in very low concentrations, or else they are absent[2], and enzyme systems differ widely between eutopic and ectopic endometrial tissue.[3] Progestins reduce the synthesis of receptors, resulting in diminished sensitivity of the implants during long-term treatment. Morphological studies have revealed different reactions of endometriosis: after long-term use (9 months) of progestin influence, some implants remained unchanged; however, some demonstrated arrested epithelium and some had abortive secretory reactions, but decidual reaction and necrosis could not be demonstrated.[4]

On comparative ultrastructural examinations, endometriotic foci are delayed and still proliferative in the luteal phase.[5] This insensitivity to the influence of progestins- known as progesterone blockage - may be caused by specific changes in enzyme systems,[6] in addition to low or reduced receptor concentrations. The 17-â-hydroxysteroid-dehydrogenase type 2 is defective and cannot be activated by progestins, resulting in increased proliferation, as estradiol is not inactivated.[7]

TNF-á and estradiol induce proliferation of endometriotic stromal cells, whereas progestogens were found to reduce TNF-á activation. Progestins also induce suppression of matrix metalloproteinases, which are involved in the implantation and progression of ectopic endometrium.

Dienogest, a C19 steroid with a cyanomethyl group at C17 and a double bond between C-9 and C-10, inhibits angiogenesis in the ectopic endometrium through structural changes in the microvessels and decreased microvessel density, which can reduce the development and progression of endometriotic implants.[8] Furthermore, dienogest can inhibit proliferation of endometrial stromal cells *in vitro* due to an increase in the arrest of cells in the G0/G1 phase of the cell cycle.[9]

Clinical Experience

Oral administration of different progestins at low doses (5–20 mg/day) has a wide range of different results reported in mainly retrospective studies. These results vary little from estrogen–progestin combination therapy. Improvement in subjective complaints varies between 60[10]and 94%[11]. The advantages of progestins over oral contraceptives relate to the avoidance of estrogen-induced side effects. The disadvantages are spotting and bleeding problems, which have to be treated through increasing dosages, additional estrogen medication or interruption of the medication for 5–7 days.

Dienogest 2 mg daily, reduces endometriosis-related pain. However, in 95% of cases spotting was reported, which persisted in 60% of women, even with increased doses of 4 and 6 mg/day[12]. Dienogest does not reduce sex hormone-binding globulin, is bound unspecifically to albumin and does not accumulate using oral doses of 2 mg/day. It has typical progestogenic properties: good tolerability, antiandrogenic action and weak antigonadotropic activity, combined with typical characteristics of 19-norprogestins: strong suppressive action on the endometrium in low doses, a short half-life and high bioavailability.

Endometriosis Associated Pain

Two recent published prospective randomized studies tested dienogest 2 mg daily against placebo[13]or versus leuprorelin depot[14], and showed a significant improvement in endometriosis-related symptoms. Bleeding problems were the main side effects and occurred in up to 80% of patients within the first 3 months of treatment, and were reduced during the following months of medication. After finishing the abovementioned study, the women (n = 168) were enrolled in a long-term treatment study (up to 53 weeks) and a 6-month follow-up[15]. The drug showed a good safety and efficacy profile, with a progressive decrease in symptoms and bleeding irregularities during medication use and the decrease in pain persisted for at least 6 months after cessation of therapy.

In a prospective, randomized trial with MPA, there was a 50% regression rate of ectopic implants and 13% partial regression with scar formation.[16] Pain reduction with MPA was as effective as danazol, using medication after diagnosis of endometriosis or after surgical excision as well[17].

In deep-infiltrating rectovaginal endometriosis, the guidelines[18] recommend complete excision, but it is also possible to treat with progestins symptomatically. In a prospective randomized controlled trial using norethisterone acetate (NETA) versus a combination of estrogen and cyproterone acetate (CPA)[19] , dyschezia, pelvic pain, deep dyspareunia and dysmenorrhea were reduced significantly with both treatment regimens. CPA monotherapy for 6 months versus OCs improved quality of life and psychiatric profile significantly in treated women[20].

When comparing GnRH analogues with low-dose progestins, there is significant reduction of pain symptoms during and 1 year after treatment, but no

differences between the medications used[21]. There is a significant reduction of deep dyspareunia and cyclic pain in both groups; goserelin is superior to OCs. At repeat laparoscopy, there is significantly more pronounced reduction of endometriotic implants in the leuprorelin group. The improvement of symptoms like chronic pelvic pain and dyspareunia did not differ significantly. Primarily, a medication with GnRH agonists is indicated, but progestins are also very useful for long-term treatment or repeated medication.

In conclusion, different progestins have different effects on the different types of endometriotic foci. Pain relief using adequate dosages of progestins is identical with the medication of danazol or GnRH analogues.

Infertility

Pregnancy rates following MPA, lynestrenol or norethisterone acetate regimens vary from 5 to 90% depending on the stage of endometriosis and whether they were surgically corrected or not. All these publications are observational or retrospective studies[22,23] . There is no randomized controlled trial that has proven an improvement in fertility after any progestin medication.

Dydrogesterone[24] does not inhibit ovulation it can be used for symptomatic treatment of pain and for reduction of bleeding problems. It can be used cyclically, has no androgenic side effects and is well tolerated. When used in doses between 10 and 60 mg/day, for various numbers of days per cycle over periods of 3–9 months, the majority of women became symptom-free or experienced a significant reduction in the number/severity of symptoms. These findings were supported by laparoscopic examination in several of the studies.

Side Effects

Negative side effects of progestins are disturbances of lipid and carbohydrate metabolism and the clotting system, more seen in C19-derivatives, as well as negative influences on mood swings and depression, more seen in C17-derivatives. Weight gain and bleeding problems are further causes for the cessation of long-term medication.

For levonorgestrel, spotting, breakthrough bleeding, bloating, weight gain and headache was reported in up to a third of the patients; for lynestrenol, hot flushes, acne and sweating were the main problems in up to 59%; and for MPA spotting, bloating and weight gain occurred in almost two-thirds of treated women.[25,26] For dienogest, which was introduced in the European market last year, acne, hot flushes, headache, breast tenderness, loss of libido and fatigue are reported between 10 and 38%.[27]

Recurrence Rate

Only a few follow-up studies have been published concerning the recurrence rates after cessation of progestin medication. They reported a relatively high rate of recurrence of symptoms in the first year after the end of treatment. Long-term follow-up shows recurrence rates above 50% in general.Endometriosis is a chronic disease and medical treatment will not eradicate the implants or cysts. Therefore, long-term medication is required, but no data are currently available for progestin therapy lasting longer than 6–12 months.

Alternative Routes

Depot injections of MPA are very effective in suppressing endometriosis-related complaints. A significant drawback to the use of depot preparations is the possible prolonged interval to resumption of ovulatory cycles after discontinuance. Therefore, this type of application is recommended only in elderly patients, who do not desire pregnancy. The injectable depot MPA was as effective as a combination of oral contraceptive with low-dose danazol (50 mg/daily), but significantly more bleeding problems were observed in the MPA group.

To reduce the adverse side effects of medical treatments, a new aspect is the intrauterine administration of progestogens, which can be an effective treatment of symptomatic endometriosis. The C19 progestogen levonorgestrel is delivered directly in the uterine cavity with a rate of 20 µg/day during a period of 5 years. There are positive effects on endometriosis-related pain and deep infiltrating endometriosis also.[28,29] The pain and bowel symptoms were alleviated and the size of the nodules was reduced, as demonstrated with transrectal sonography. This is in contrast to the general opinion that deep infiltrating lesions are not responsive to medical therapy.

A 3-year follow-up study found a pain-free continuation rate of 56% for the levonorgestrel intrauterine device[30]. However, reduction of symptoms was higher in patients receiving GnRH analogs, whereas other prospective randomized studies have been in favor of the local administration of levonorgestrel. Irregular bleeding during the initial months after application is common, but by the end of the study 70% of the women

were amenorrheic. In comparison, all GnRH analogue users became amenorrheic in a shorter time.

A new approach to improve the use of progestins in endometriosis is the development of subcutaneous implants of MPA[31]. When compared to GnRH analogues, no differences were observed in the reduction of pain symptoms, but demineralization of bone and hypoestrogenism side effects were found in the GnRH agonist group and bleeding problems were frequent in the MPA group.[32]

Conclusions

It is clear that if sufficient dosages for suppression of the cycle and stopping the growth of the endometrium are used, progestins are effective treatment. Because endometriosis is a chronic disease, long-term medications or repeated medications are needed. Since their side effects are often tolerable, metabolic disturbances are clinically unimportant and they are inexpensive, progestins have found excellent application.[33,34]

There is a lack of sufficient prospective randomized trials comparing different progestins and different dosages, which is a need for the future. The new drugs under development for the medical treatment of endometriosis are targeting different steps in the pathogenesis –inhibitors of vascular epithelial growth factors, matrix metalloproteinase inhibitors or immunomodulatory substances like TNF-á inhibitors. Results in laboratory or animal studies are promising, but their use in humans is far from being achieved. For the next 5–10 years, progestins alone or in combination with pain-relieving strategies are very important for the medical treatment of endometriosis in general, whereas GnRH analogues have their place in special indications.

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(1937 words, excluding references)

ROLE OF PROGESTERONE IN CANCERS

11

Dr.SebantiGoswami
Associate Professor G&O,
Medical College Kolkata

Progesterone is a hormone uniquely known for its role in maintenance of pregnancy and in a spectrum of pregnancy related complications. When the association of progesterone and cancers is the subject the arena of discussion becomes skewed.

Progesterone mainly has a role in the treatment of endometrial hyperplasia which is a forerunner of endometrial cancer and in early endometrial carcinoma in women where preservation of the uterus is of concern.

The treatment for patients diagnosed with endometrial neoplasia is surgery, including total abdominal hysterectomy and bilateral oophorectomy .This is true for both endometrial adenocarinoma and atypical endometrial hyperplasia.Hysterectomy may not be an acceptable option for young women diagnosed with complex atypical hyperplasia and/or endometrial cancer prior to completing childbearing. This may also be true for patients with multiple comorbidities who are poor surgical candidates. In this subset of patients with either complex atypical hyperplasia of endometrium or clinical stage 1A low-grade uterine tumors, progesterone therapy may be an acceptable alternative for primary management.

Progestin Therapy in Endometrial Hyperplasia

Consistently, studies have shown that progestins are effective for treatment of endometrial hyperplasia. Progestin therapy has an impact on the endometrial cells as early as ten weeks after initiation of treatment, but most recognize the need for a minimum of three months of progestin therapy before assessing for a response.[1,2] Reversal of endometrial hyperplasia by progestins is thought to occur through activation of PRs, resulting in stromal decidualization and subsequent thinning of the endometrial lining. The doses and types of progestins for treating endometrial hyperplasia vary depending on presence or absence of atypia. Studies have shown regression of hyperplasia without atypia to normal endometrium in 80 to 90% of patients when treated with either medroxyprogesterone acetate (MPA), 10 mg daily for 12 to 14 days each month, when treated for 3 to 6 months.[3-6] In a larger prospective study from the United Kingdom (n = 105), patients with endometrial hyperplasia were treated with a levonorgestrel intrauterine device (LNG-IUD). A reported 90% (94 of 105) of patients had histologic regression after 2 years. Out of this group, only 67% (6 of 9) of patients had "atypical" endometrial hyperplasia with most (88 of 96) having hyperplasia without atypia.[7] Other successful

treatments demonstrated for atypical hyperplasia include use of continuous oral megestrol acetate, starting 80 mg daily up to 160 mg per day, and oral MPA, 600 mg daily.[8,9] A reported 82% complete (14 of 17) and 18% partial response rate was found using the MPA regimen in a multicenter trial with only six recurrences found within 25- to 73-month follow-up.[10]

Progestin Therapy in Primary Endometrial Cancer

Studies investigating the efficacy of progestin therapy in endometrial cancer have been limited to case series and pilot studies. Ramirez et al[11] reviewed 27 articles for a total of 62 patients with stage 1A endometrial cancer treated with progestins. Although 76% responded to treatment after 12 weeks, 24% who initially responded recurred. Seven of the patients with recurrence were retreated with progesterone, with five of seven having a complete response rate with no evidence of disease at 46-month follow-up.[11] In a prospective, multicenter trial, 22 women with stage 1A endometrial carcinoma in women < 40 years of age were treated with oral MPA for 26 weeks followed by cyclic estrogen-progestin therapy for six months. Twelve (55%) achieved a complete clinical response, seven with partial response and three had no change.[10] In a review of articles published between January 1966 and January 2007 describing patients with endometrial cancer treated with hormonal therapy, 133 patients were identified who were treated for an average duration of 6 months and who demonstrated an average response time of 12 weeks.[12] Of these 133 patients, 51% demonstrated a lasting complete response, 25% showed a temporary response, and 24% never responded to treatment. These studies highlight a 50 to 70% overall response rate for patients treated with high-dose progesterone therapy as primary therapy and also emphasize the need for close follow-up even in the responders because of the substantial rate of recurrence.[8-11,13] Progestin-releasing IUDs used in patients with endometrial cancer with high surgical risk factors have yielded mixed results. Montz et al[14] used the "progestasert" as the IUD in selected grade 1 endometrial cancer without any evidence of myometrial invasion, with a reported (75%) complete response rate (six of eight patients) at 12 months. However, Dharet al[15] reported a case series of four patients with only 25% complete histologic regression at 6 months when using the LNG-IUD.

Progestin Therapy in Recurrent Endometrial Cancer

Progesterone agents have been extensively used in patients with advanced or recurrent endometrial cancer. Many of these patients have already undergone surgical procedures, chemotherapy, or both, with progressive disease or present with multiple comorbidities at an advanced age where hormonal therapy may be a therapeutic alternative. Early studies reported response rates as high as 56% with various treatment regimens (MPA, hydroxyprogesterone caproate);[1,18,19] however, with more stringent response criteria and larger multicenter cooperative studies, the objective response rates ranged from 15 to 20%.[20,21] In a major Gynecologic Oncology Group study, women with advanced or recurrent endometrial cancer were randomized to either low-dose (200 mg/day) or high dose (1000 mg/day) oral MPA, with complete response rate of only 17% and 9%, respectively.[21] Progression-free survival was 3.2 versus 2.5 months with overall survival of 11.1 versus 7.0 months for low-dose versus high-dose group, indicating that high-dose regimens yielded worse response. The lower response seen with high doses may be explained by the downregulation of progesterone receptors.[21] It is not clear why so many receptor-positive tumors do not respond to therapy and why some ER/PR-negative tumors do respond. Nevertheless, most studies do support low-grade histology, long disease-free interval, and expression of estrogen and/or progesterone receptors as important prognostic factors that predict a favorable response to progestin.[20,21]

Endometrial adenocarcinoma is highly associated with unopposed estrogen action. The significance of progesterone in controlling estrogen-driven proliferation is underlined by its efficacy in preventing endometrial cancer. Progestins are used in the clinic effectively to eradicate some but not all endometrial hyperplasia and well-differentiated endometrioid endometrial cancer. It is also a mode of palliative therapy for recurrent endometrial cancer and does not eradicate the disease. The fact that progestin therapy is often associated with recurring disease is highly suggestive that progesterone response in the normal endometrium is very different from that of neoplastic or malignant tissues. Malignant cells are not the same as normal cells, and therefore mechanisms of progesterone action are expected to be different. Furthermore, the tissue composition of the normal endometrium is very different from the diseased endometrium. One example is the significant decrease

in the amount of stroma observed in endometrial cancer compared with cycling endometrium. The stroma is highly responsive to progesterone and dynamically influences the epithelium in a paracrine manner. Without sufficient stroma, progesterone response would be compromised. Thus progesterone responsiveness may be dictated not only by the hyperplastic or malignant epithelium but also by the stroma. There is very little known of the role of stroma in response to progesterone in modulating glandular transformation and would be an area worth investigating to further understand how to prevent or to treat endometrial carcinoma.

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PROGESTERONE IN MENOPAUSAL THERAPY

12

Dr. Abha Rani Sinha
D.G.O., M.S., FICOG
Associate Professor
Dept. of Obst&Gynae
Patna Medical College, Patna
Secretary, Patna Obstetric & Gynaecological Society
Email: drabharanisinha@rediffmail.com

Dr. Sushma Singh
D.G.O., M.S.,
Senior Resident
Dept. of Obst&Gynae
Patna Medical College, Patna
Email: drsushmakrishn@gmail.com

With increasing life expectancy, majority of women would spend one third of their life in post menopausal age. Many of these women need treatment for variety of conditions which may range from few mild complaints to multiple severe symptoms. In these women, HRT is of relevance. Since menopausal symptoms are due to deprivation of estrogen, the administration of this hormone will alleviate majority of menopausal symptoms. Progestogen should be added to systemic estrogen for all women with a uterus to prevent endometrial hyperplasia and cancer.[1,2]

The ideal progestogen in HRT should neither negate the beneficial effects of estrogen nor produce cyclic or irregular bleeding and, in addition, should be well tolerated. Progesterone can be given cyclically or in the form of continuous combined regimen[3]. If the last menstrual period has occurred less than one year prior to starting HRT, a sequential combined regimen should be started, i.e. continuous estrogen with progestogen (12–14 days per month).This regime will allow monthly withdrawal bleed. In women who wish to avoid a monthly withdrawal bleed and has taken a minimum of one year of HRT, or is starting HRT one year after the last menstrual period should switch to a continuous combined regimen which will allow a bleed free HRT – this will also minimise the risk of endometrial hyperplasia. If breakthrough bleeding occurs after switching to continuous combined HRT and does not settle after three to six months, then the woman should be switched back to a sequential regimen for at least another year. If bleeding is heavy or erratic on a sequential regimen, the dose of progestogen can be doubled or duration increased to 21 days. A persistent bleeding problem beyond six months necessitates investigation with ultrasound scan and/or endometrial biopsy.

With both the regimens, there may be some erratic bleeding to begin with, but 90% of those that persist with these regimens will eventually be completely bleed free.

In the following situations progesterone along with estrogen may be indicated even in hystrectomized women.

(i) Women with past history of endometriosis – because adenocarcinoma has been reported in patients with pelvic endometriosis being treated with unopposed estrogen[4].

(ii) Supra cervical hysterectomy

(iii) Endometriod tumours of the ovary[5].

(iv) Adenocarcinoma of the endometrium

Side effects

One of the main factors for reduced compliance with HRT is that of progestogen intolerance[6]. Typical side effects include breast tenderness, bloating and depression[7,8]. Symptoms of fluid retention are produced by the sodium retaining effect of the renin-aldosterone system, triggered by stimulation of the aldosterone receptors. Androgenic side effects such as acne and hirsuitism are a problem of the testosterone derived progestogens due to stimulation of the androgen receptors.

Mood swings and Premenstrual syndrome like side effects result from adverse stimulation of the central nervous system progesterone receptors.

To minimise progestogenic side effects, the dose can be halved and duration of progestogen can be reduced to seven to ten days.This may sometimes result in bleeding problems and hyperplasia. So in these women there should be a low threshold for ultrasound scanning and endometrial sampling, if clinically indicated.

Micronized progesterone and dydrogesterone generally have fewer side effects due to progesterone receptor specificity.

Benefits of Progesterone in HRT

Vasomotor Symptoms

Progestogen alone also reduces vasomotor symptoms but is not as effective as estrogen[9].

Quality of life (QOL)

Micronized progesterone may exert superior effects on mood compared with MPA containing regimens[10].

Two metabolities of progesterone allopregnanlone & pregnanlone are responsible for progesterones unique sedative effect. Treatment regimens with micronized progesterone should be taken at bed time and with Estrogen, this is a good choice for women with sleep disturbances.

Osteoporosis

Progestational agents are considered antioestogenic but they have been reported to act independently to reduce bone resorption[11]. When added to estrogen,Progestins can apparently exhibit a synergistic increase in bone formation associated with a positive calcium balance[12,13].The synergistic result of combining estrogen with progestin is determined by the type of progestin. This effect is observed with progestins belonging to 19 –nortestosterone family[14].

Risks

Breast cancer

Diagnosis of breast cancer increases with EPT use beyond 3 to 5 years. In the WHI overall, this increased risk, in absolute terms, was eight additional breast cancers per 10,000 women using EPT for 5 or more years. Studies have not clarified whether the risk differs between continuous and sequential use of progestogen, with observational studies suggesting that risk may be greater with continuous use of progestogen. Data from a large observational study suggest that EPT with micronized progesterone carries a low risk of breast cancer with short-term use but carries an increased risk of breast cancer with all EPT formulations with long-term use[15,16].

Ovarian Cancer

In the WHI, the only RCT to date to study ovarian cancer, EPT was not associated with a statistically significant increasein ovarian cancer after a mean of 5.6 years of use. Therewere 4.2 cases per 10,000 for HT users and 2.7 cases per 10,000 per year for the placebo group[17].

Stroke

The WHI EPT and ET trials demonstrated an increased risk of ischemic stroke and no effect on the risk of hemorrhagic stroke. In these trials, when the entire cohort was analyzed, there were eight additional strokes per 10,000 women per year of EPT and 11 additional strokes per 10,000 women per year of ET. In recent analyses that combined results from the WHI EPT and ET trials, HT in younger women (ages 50-59 y) at study entry had no significant effect on risk of stroke (relative risk [RR], 1.13; 95% CI, 0.73-1.76)[18,19,20].

Dose and route of administration

Progestogens can be used in different doses and different regimes for providing endometrial safety. Typically the lowest effective doses is used - 1.5 mg medroxyprogesterone acetate, 0.1 mg norethindrone acetate, 0.5 mg drospirenone, or 100 mg micronized progesterone. A long-term Finnish observational study reported that continuous use of EPT reduced the risk of endometrial neoplasia compared to no use of HT, and sequential progestogen therapy with ET increased the risk, particularly with long-cycle progestogen. In this study, all progestogens performed similarly within a given regimen[21].

Oral progestogens, combined with systemic estrogen, and combined progestogen-estrogen matrix patches have demonstrated endometrial protection. The transdermal estrogen and progesterone combination incorporate norethidrone acetate in a daily dose of 0.140 or 0.250mg or LNG in daily dose of 0.007, 0.015 or 0.030 and 0.04mg/daily and in sequential regimenorethidrone acetate 0.250 mg or LNG 0.010mg.

Progesterone can be administered in a vaginal gel which allows the delivery of a very low dose that can effectively protect the endometrium with low systemic levels because of bypass effect on the uterus[22]. The administration of 90mg every 2 days produces secretary changes in the endometrium. An application of the 4% commercial preparation twice weekly protects the endoemetrium and is associated with amenorrhoea in most patients[23].

Progesterone IUCD (MIRENA)

It protects the endometrium against hyperplasia and cancer. The local site of action provides endometrial protection and escapes systemic progestin side effects. There is irregular break through bleeding in the first six months and after one year approximately 60-70% of the women are amenorrheic.

A small study reported that when used with systemic ET in perimenopausal and postmenopausal women, the progestin-containing intrauterine system was found to provide endometrial protection equivalent to protection provided by systemic progestogen administered continuously and superior protection compared with progestogen given sequentially[24,25,26].

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PROGESTERONE: DIFFERENT DRUG DELIVERY SYSTEMS

13

Dr. Mrs. Saie G. Mandrupkar
MBBS DGO
Consultant, Ob-Gyn
Mandrupkar Clinic,
Islampur (ISO 9001:2008)
Prakash Memorial Clinic, Islampur

Dr. Mrs. Sonali Bichkar
MD
Consultant, Ob-Gyn
Bichkar Hospital, Karad

INTRODUCTION

Progesterone is a natural steroidal hormone (21 carbon steroid) derived from cholesterol. It is secreted primarily from the corpus luteum of the ovary during the second half of the menstrual cycle and from the placenta during pregnancy.

A number of compounds are synthesized having progesterone like activities and can be given by different routes. These are called progestational agents, progestogens or progestins.

ROUTES OF ADMINISTRATION

Apart from traditional oral route progesterones can be given by intramuscular, vaginal, rectal, topical and as intrauterine system as well.

Oral Route

A. <u>Synthetic progestins</u>:

These either alone or as COCs i.e. in combination with estrogens, are used for:

1. Contraception
2. PCOS, Acne, Hirsutism
3. Abnormal uterine bleeding (AUB)
4. Dysmenorrhea
5. Postponement of menses.
6. Treatment of Endometriosis
7. Premenstrual syndrome (PMS)
8. Premenstrual dysphoric Disorder (PMDD)

B. <u>Natural progesterones:</u>

Plant source for these is *Dioscorea Mexicana.* It contains a steroid called diosgenin that is taken from the plant and is converted into progesterone.

Nowadays, all natural progesterones are synthesized and are suspended in oil in as creamy white crystalline particulate powder and are dispensed in soft gelatin capsules. The process of micronization has benefitted the oral absorption of progesterone.

Micronized natural progesterone is now a safe and effective alternative to synthetic and natural progesterone formulations for variety of clinical and research applications. [1]

It is widely used in infertility and assisted reproductive techniques (ART). Other obstetric uses of progesterone

include treatment of threatened abortion and preterm labor. The disadvantage is nausea and decreased bioavailability.

Intramuscular injections

The gynecological use of I.M. progesterone mainly includes contraception while natural one is used in pregnancy maintenance.

In 1992, the food and drug administration (FDA) approved the marketing of DMPA as contraceptive agent.

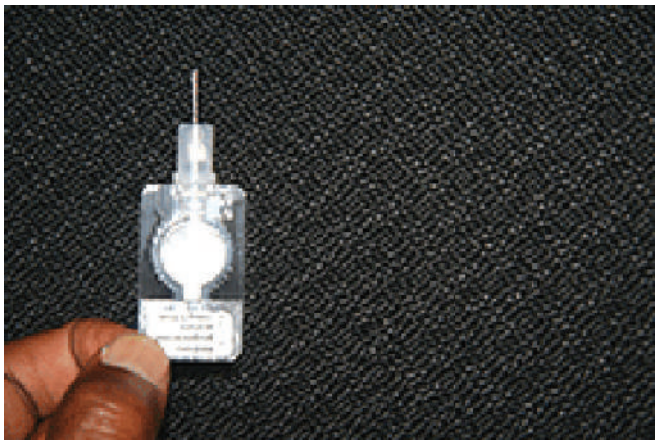
It is given as a deep I.M. injection in gluteal region with large bore needle every 3 months (90 days).

Advantages:

- It is independent of coital activity.
- No estrogen-related side effects
- It does not interfere with milk production.

Disadvantages:

- 70% incidence of irregular bleeding
- Loss of bone mineral density. The bone loss is greater with longer duration of usage of drug.



A new micronized preparation as **subcutaneous DMPA** is approved by US FDA. It has a lower dose of progestin (104 mg instead of 150 mg) every 3 months.

Obstetric uses of progesterone include early pregnancy support and prevention of preterm labor. Though vaginal route is favored, in some cases where bioavailability and patient factor is there intramuscular injections of natural micronized progesterone is used. Disadvantage is oily daily injection with thick needles producing soreness and inflammation at injection sites.

Implants

These are mainly used subdermally for contraceptive purpose. They are more effective than oral and barrier contraceptives. The implants consist of levonorgestrel or desogestrel metabolite, 3-keto-desogestrel. The levonorgestrel implants consist of the drug enclosed in silastic rods, 6 or 2 in number, each containing 36 mg or 70 mg of levonorgestrel respectively. The daily release of is of 50 µg.

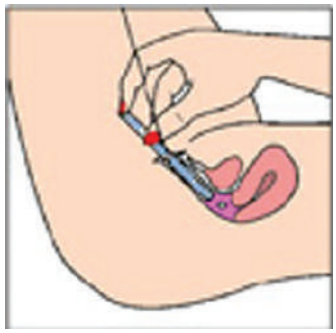
The 3-keto-desogestrel implant is a **single rod** containing 68 mg of the drug. The initial release is 60-70 µg /day. This reduces to 25-30 µg/day by the use of 3 years.

The contraceptive efficacy of levonorgestrel implants is 5 and with desogestrel is 3 years.

Formulations are implanted subdermally with minimal incision under local anesthesia.

Progesterone implants as contraceptives are long acting, highly effective, reversible, and have no effect on bone marrow density (which is a side effect of DMPA).

Vaginal Route



Progesterone can be used by vaginal route in the form of capsule, tablet, suppository, vaginal gel, cream or ring. Use of natural micronized progesterone by the vaginal route is now most favorable route for obstetric indications.

Suppository contains progesterone in a wax base. Upon insertion, the suppository melts due to warmth of body and drug is released.

Tablets are effervescent and they dissolve in vaginal secretions.

Gel helps to coat the vaginal walls.

Rectal administration can be done alternatively if vaginal administration not possible due to causes such as bleeding.

Natural micronized progesterone is recommended by vaginal route in prevention of preterm labor. [2,3]

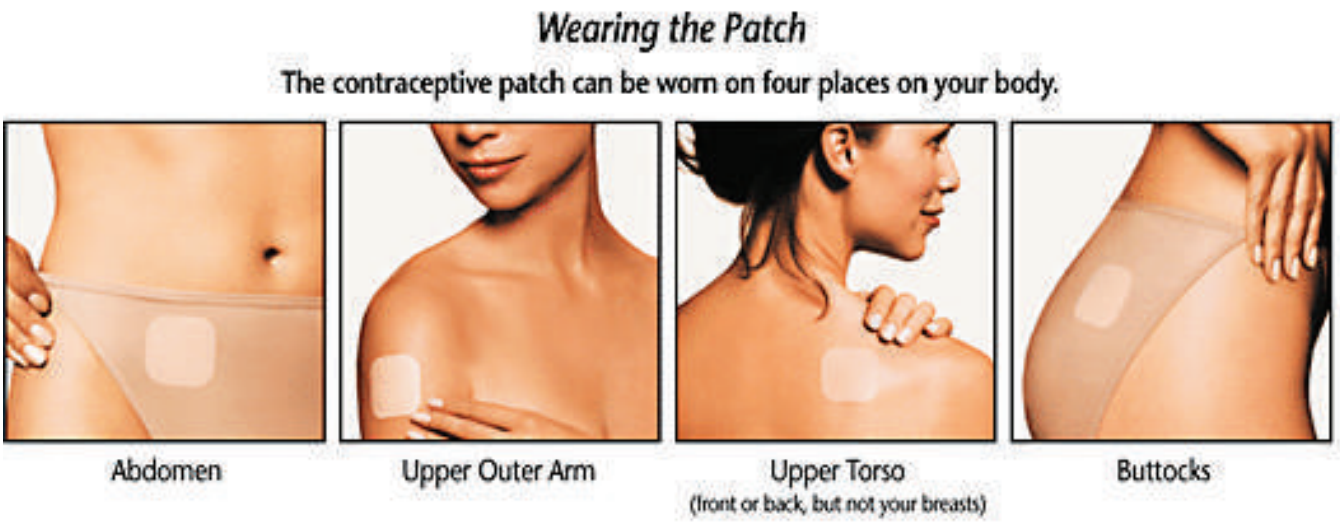
Topical Route

Advantages:

- Patient compliance
- Rapid absorption
- High bioavailability.
- Avoidance of first pass hepatic metabolism.

A combined hormonal contraceptive vaginal ring made up of ethinyl vinyl acetate containing estrogen and progestin, releasing 15 µg of estrogen (ethinyl estradiol EE) and 120 µg of progestin (etonorgestrel) per day is available for contraceptive use.

Only progestin containing rings, available in some countries, are found to be less effective.



Source: Ortho-McNeil Pharmaceutical, 2001.

Progesterone is available in the form of gel, cream, spray and patches.

Ø Alcohol- based **gels** are effective with once a day application.

Ø **Creams** tend to get poorly absorbed through the skin.

Ø A contraceptive **patch** releasing 20 µg EE and 150 µg norelgestromin is available for contraception.

A new patch is applied each week for 3 weeks and then 4thweek is patch free when patient gets withdrawal bleeding.

Ø Progesterone is also available as **skin spray** for hormone therapy. It is administered as 1-5 sprays daily on the skin rotating the site of application in the second half of the cycle. Each 0.19 ml spray contains 6 mg of natural progesterone.

This is effective, easy to use, well tolerated, and safe.

Due to avoidance of first pass effect of liver dosage required is much less.

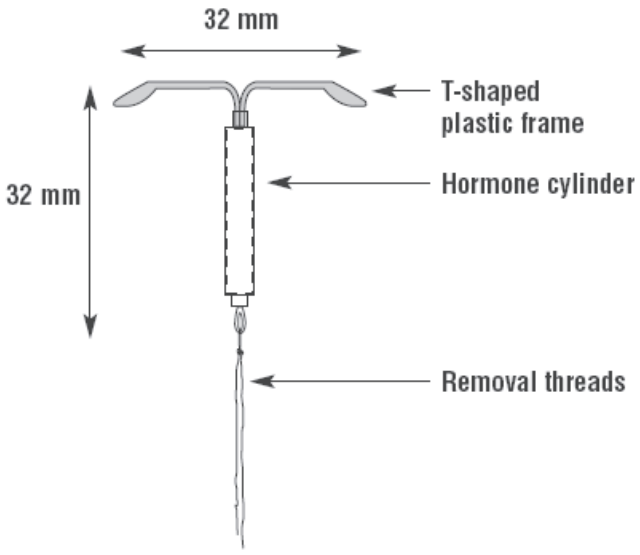
Impregnated lntra-uterine Contraceptive Device

Intra- uterine contraceptive device impregnated with progesterone is used for contraception. Also called intra-uterine progesterone contraceptive devices, these have the advantage of being devoid of the side effects of estrogen and decreased IUCD-related menstrual side effects. Some formulations have been shown to be of help in treatment of fibroid and DUB and possibly in adenomyosis and endometriosis.

Nasal Spray

Use of progesterone in nasal spray form for contraception has been studied by the world Health Organization (WHO) in 1978. However, this did not become popular for clinical use.

LNG IUS (Intra uterine progesterone contraceptive)



Levonorgestrel intra uterine system (LNG-IUS) is the hormonal intra uterine system that contains Levonorgestrel.

It has 32 mm long, flexible plastic T shaped frame impregnated with barium sulphate for making it radio-opaque.

Cylindrical reservoir contains 52mg Levonorgestrel which is released in uterine cavity at a rate of 20 µg /day initially and 10µg/day later on after 5 years.

It is not only licensed for contraception but also one of the promising treatments of dysfunctional uterine bleeding.

Other advantages:

§ Reduced menstrual pain.

§ Reduction in size of fibroids

§ Symptomatic improvement in endometriosis

§ Reduction in endometrial ca/ hyperplasia.

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NEW RESEARCH ON PROGRESTERONE AND ITS METABOLITES

14

DR. NAZIA ISHRAT
M.S. (OBST. & GYNAE)
Asst. Prof. Obstetrics & Gynecology
J.N.Medical College, AMU, Aligarh
E MAIL-
ishrat.nazia@rediffmail.com

PROF. SEEMA HAKIM
MD, FICOG, FICMCH
Professor, Obstetrics & Gynecology
J.N.Medical College, AMU, Aligarh
E Mail: -
drseemahakim@rediffmail.com

Progesterone is a naturally occurring steroid hormone which regulates postovulatory menstrual cycle and maintains pregnancy. Besides natural progesterone, there are different classes of synthetic progestins and its derivatives[1]. According to the progesterone component oral contraceptive pills (OCPs) are classified[2] into four generations. Third and fourth generation progestins desogestrel, gestodene, dienogest, drospirenone, nomegesterol acetate are called as new progestins[1,2]. The development of new generations of progestins with improved selectivity profiles has been a great challenge.

Desogestrel[3] is prodrug transforms to active metabolite 3-keto-desogestrel also known as etonogestrel. ***Norgestimate***[4] a new prodrug and its active metabolite norelgestromin are very similar to levonorgestrel. All 3rd generation progestins like **desogestrel**, **gestodene** and **norgestimate** have negligible androgenic activity because of increased binding to Serum Hormone Binding Globulin (SHBG) and decreased free testosterone levels.

Nomegesterol Acetate (NOMAc) [4], a new 17 a-hydroxy 19-norprogesterone derivative is highly antigonadotropic. It undergoes enterohepatic recirculation has no glucocorticoid or mineralocorticoid activity but somewhat antiandrogenic.

Nesterone[5] is only active parenterally because of quick metabolization in liver. It shows high binding affinity to progesterone receptor but binding to androgen receptor is negligible. It shows high ovulation inhibition effect and evolved for contraception in the form of vaginal ring, subcutaneous implant and transdermal delivery system.

Dienogest[6] is a 19-nortestosterone with a cynomethyl group instead of ethyl group at C-17 and an extra double bond. Introduced as an oral contraceptive in combination with ethinyl valerate it is also being used in Abnormal Uterine Bleeding (AUB).

Drospirenone[7] is a spironolactone derivative which shows high affinity for progesterone, mineralocorticoid and androgenic receptors. Oral contraceptive pills (OCPs) containing 3 mg drospirenone and 30 gEE shows equal contraceptive efficacy to second generation OCPs with good cycle control, decrease in body weight and blood pressure and improvement of acne.

RECENT ADVANCES IN CLINICAL USES OF PROGESTERONE

(a) Combined Estrogen -Progesterone Contraceptive-

Recent OCPs contains low dose estrogen and new progestins. Because of less androgenicity, they do not cause weight gain, acne and hirsutism[5]. New progestins do not impair carbohydrates tolerence. They also have a favourable lipoprotein profile & thus protects against cardiovascular diseases[8]. But a WHO collaborative study has shown 2.6 times greater risk of venous thromboembolism with OCPs containing desogestrel and gestodene than the OCPs containing levonorgestrel[9]. This inference may be due to some confounding factors like prescribing new progestins to smokers, new users, carriers of factor V Leiden mutation, women with family history of thrombosis.

(b) **Progesterone Only Contraceptives**- They are preferably used in lactating women, women over age 40, diabetics, hypertensive women and women with history of thromboembolism[3].

Depo-subQ Provera 104 a new low dose depot medroxyprogesterone acetate (DMPA) is being administered subcutaneously[10]. Subcutaneous DMPA showed complete ovulation inhibition for 13 weeks along with decrease in anemia, PID, ectopic pregnancy and endometrial cancer. It also benefits patient of sickle cell disease by inhibiting sickling and increasing hemoglobin level[2].

Progesterone Only Pills (POPs) containing norgestrel or levonorgestrel are taken daily at the same time but new desogestrel containing POPs allow a 12 hour grace period and a greater ovulation inhibition[4].

Progesterone containing IUCDs like **Mirena**, levonorgestral releasing intrauterine system (LNG-IUS) contains 52 mg LNG releasing 20µg /day for 5 years. **Fibroplant**, a new shorter device releasing 14µg LNG per day is being developed for the treatment of endometrial hyperplasia and menorrhagia in the peri-and post menopausal women[11].

(c) Emergency Contraception- Levonorgestrel alone in 2 doses of 0.75 mg 12 hours apart is better than the combined estrogen-progesterone pills. Single dose of 1.5 mg levonorgestrel is also equally effective.

(d) ***Post partum Contraception-*** POPs can be a good choice after 3 weeks postpartum. LNG-IUS is an equally effective alternative. It can be used even during cesarean section[12].

NON CONTRACEPTIVE USES OF PROGESTERONE

(1) Prevention of Pre term labour- Progesterone is recommended for patients at risk of pre term labour. In European trial for patients with short cervix (<2 cm) on TVS at 24 weeks were prescribed 200 mg micronized progesterone vaginally upto 34 weeks of gestation[13].

(2) Luteal phase support- During ART, progesterone is standard protocol for luteal phase support and can be given by oral, vaginal and intramuscular route. Micronised natural progesterone when given vaginally is more effective than oral route[14].

(3) Acne and Hirsutism- Oral contraceptive pills containing third generation progesterone or drospirenone show improvement in acne and hirsutism. 50-100mg Cyproterone acetate is added to first 10 days of cycle with COCs (reverse sequential regimen) in case of severe hirsutism and acne[2].

(4) Primary dysmenorrhea- Extended regimens (84 days) are effective in treating dysmenorrhea by decreasing frequency of mensus. Vaginal ring, Implant and LNG-IUS have demonstrated reduction in dysmenorrhic symptoms.

(5) Pre-menstrual tension or Premenstrual dysmorphic disorders- Drospirenone containing OCPs are observed to improve water retention, behavioral changes and mood changes[7]. Drospirenone is an antimineralocorticoid which is associated with weight loss due to natriuretic action.

(6) Abnormal Uterine Bleeding (AUB) - Progesterone are more effective in anovulatory AUB. Progesterone therapy is ideal in puberty, adolescent and women approaching menopause[15].

(7) Uterine fibroids- LNG-IUS reduces menstrual blood loss and dysmenorrhea upto 50% in patients of uterine fibroids. There is decrease in uterine volume but hemoglobin and serum iron level rises. Estrogen-Progesterone combination when added with GnRH agonists for long term use in fibroid, there is no reduction in the bone mass density[16].

(8) Endometriosis- Progesterone induces a hyperprogestogenic hypoestrogenic state causing decidualization of endometrium. Progestins are first choice for treatment of endometriosis because

comparable effectiveness as danazol or GnRH analogue. LNG-IUS has beneficial effects in the treatment of endometriosis by reducing pain, better suppression than the GnRH agonists with fewer side effects and providing ongoing contraception[17]. A trial with dienogest 2mg given daily for 6 months demonstrated equal results to depot leuprolide acetate in relieving pain associated with endometriosis[18].

(9) Endometrial Hyperplasia and Endometrial carcinoma- The medical therapy depends upon the number of estrogen and progesterone receptors. Due to the local action on endometrium LNG-IUS is very effective in endometrial hyperplasia and menorrhagia. The results are comparable with surgery or endometrial ablation[19] Well differentiated grade I endometrial carcinoma are suitable for progesterone therapy...

(10) Hormone Replacement Therapy (HRT) - Progesterone in combination with estrogen is used as an HRT for post menopausal women whose uterus is present. Progestin can be used cyclically for last 12 to 14 days of the cycle or continuously.

RECENT RESEARCHES IN PROGESTERONE

Role of progestins in breast cancer- Proliferative changes in breast cancer cells are due to ovarian hormones, as one third of the patients show some response to estrogen therapy, but some are unresponsive. So the progesterone molecule seems to be implicated in breast carcinoma. Researches are going on to determine progesterone metabolism in breast tissue and cell lines to establish whether progesterone metabolizing enzymes can alter the drugs to pro or anti-cancer moieties. A specific cell membrane protein PGRMC-1 is found to block cell death in breast cell which is affected by progestins used in HRT[21].

Role of progesterone in brain injury – Progesterone increases neuronal survival and synthesis of myelin specific proteins by oligodendrocytes. Progesterone and 19-nor progesterones increase Bcl-2 expression preventing cell death. In a 3 year Phase III trial on the patients of head injury, progesterone was given shortly after the brain trauma has shown reduced risk of death and long term disability[22].

Role in epilepsy- Progesterone and its metabolites like allopregnanolone and pregnanolone regulate neuronal signaling. They interact with several neurotransmitter receptors- GABA, glycine, serotonin 3, nicotinic cholinergic receptors. Progesterone has an antiseizure effect due to its metabolite 3-alpha, 5-alpha-THP and action at GABA receptor complex. It increases seizure threshold and reduces epileptiform activity[23].

Role in stress- Progesterone and allopregnanolone are neurosteroids which regulate catecholamine secretion during stress[24]. It modulates reward system and improves cognitive function.

Role in nicotine addiction Progesterone inhibits breakdown of serotonin and enhances serotonin receptor function in the brain. So people resort to nicotine like substances that enhance serotonin activity when progesterone levels are low. Progesterone is being evaluated for treatment of nicotine addiction[25].

Role in coronary hyperreactivity Low levels of progesterone can cause decrease in vascular thromboxane prostanoid receptors causing coronary hyperreactivity which can cause coronary artery disease.

Role in male contraception Progesterone stimulated Ca^{+2} increase seems to be related with sperm motility, sperm capacitation and biosynthesis of testosterone in Leydig cells. Progesterone in combination with testosterone enanthate is being used for male contraception[26]. Progesterone can be used in erectile dysfunction in males.

Role in skin elasticity and bone density skin5-alpha reductase activity is inhibited by progesterone and 19-nor derivatives. Topical 2% progesterone increases skin elasticity and firmness in peri and postmenopausal women[27].

SUMMARY

Progestins are not similar in their action due to large differences in their structure, metabolites and pharmacological actions. The new progestins developed for contraception and hormone replacement therapy are similar to natural progesterone, less androgenic and well tolerated. But they should be prescribed cautiously to the smokers, women with facter V Leiden mutation and women with family history of thromboembolism. Epidemiologic studies have created controversies among role of progestins in HRT in causing breast carcinoma. Neuroprotection and myelin regeneration by progesterone can be a scope of future research and development.

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