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REVIEW ARTICLE

Use of Progesterone in Obstetrics: A Narrative Review

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ABSTRACT

Progesterone, a steroid hormone secreted by the ovaries, plays an indispensable role in reproductive physiology and obstetric care. Its functions span from maintaining uterine quiescence to immunomodulation, facilitating successful implantation and pregnancy maintenance. Progesterone acts by inhibiting prostaglandin synthesis, and reducing myometrial contractions. Additionally, it fosters endometrial changes conducive to embryo implantation by enhancing vascularity and oxygen supply. The immunomodulatory properties of progesterone involve a shift from Th1 to Th2 immune responses, crucial for fetal tolerance.

In assisted reproductive technology (ART), progesterone supplementation is critical due to the potential luteal phase defects caused by medical interventions. Studies have demonstrated the efficacy of natural micronized progesterone (NMP) in various forms, including oral, vaginal, and intramuscular (IM) administration. Oral NMP has shown comparable efficacy to IM forms in raising serum progesterone levels, thereby supporting luteal function and extending pregnancy duration. Comparative studies on different progesterone formulations indicate that oral sustained-release NMP (SR) is effective in maintaining adequate luteal phase progesterone levels, thus supporting pregnancy.

Clinical evidence highlights the beneficial effects of progesterone in preventing recurrent miscarriages and managing threatened abortions. Progesterone's role extends to reducing pro-inflammatory cytokines like IL-6 and TNF-α while increasing anti-inflammatory cytokines such as IL-10, thereby promoting a favorable environment for pregnancy continuation.

In summary, progesterone's multifaceted actions, including hormonal and non-hormonal mechanisms, underscore its essential role in obstetrics. Its application in managing luteal phase defects, recurrent miscarriages, and threatened preterm births demonstrates its critical impact on optimizing pregnancy outcomes. The distinction between natural progesterone and synthetic progestins is crucial, given their varying safety profiles and pharmacological effects. Large population studies have demonstrated safety of natural progesterone in pregnancy however, concern remains with synthetic progestin. Continued research and clinical application of progesterone will enhance its utility in reproductive medicine, providing better outcomes for patients experiencing reproductive challenges.

USE OF PROGESTERONE IN OBSTETRICS: A NARRATIVE REVIEW

Progesterone, also known as P4 (pregn-4-ene-3,20-dione), an endogenous steroid sex hormone primarily secreted by the ovaries, engages with specific receptors in the reproductive tract, mammary gland, and the central nervous system. Its historical utilization spans several decades notably in the maintenance of pregnancy with threatened miscarriage, luteal phase support, symptomatic therapy for postmenopausal symptoms, contraception, secondary amenorrhoea, and abnormal uterine bleeding. Over the last three decades, progestins, synthetic analogs of progesterone have found their utility in the various gynecological and obstetric conditions.

The evolving landscape of progesterone and their synthetic analogs with the discovery of previously unknown targets, including membrane associated progesterone receptors, xenobiotic transport proteins, mitochondrial pores and checkpoint signaling pathway proteins. These discoveries have opened new avenues in the clinical application of both progesterone and its synthetic analogues. The diverse

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range of targets underscores the versatility of progestogens, prompting further exploration of their potential roles in various physiological processes. [1]

HISTORY AND EVOLUTION OF PROGESTERONE

Modern history of progesterone begins with its discovery and isolation by Professor Willard Allen who published the first paper on extracting progesterone from corpus luteum. **(W.M. Allen, "Physiology of the corpus luteum, V: the preparation and some chemical properties of progestin, a hormone of the corpus luteum which produces pregestational proliferation", Am J Physiol 92 (1930), pp. 174 – 188)**

"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 behaviour, 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 favours gestation."

It was until later in 1933, that the pure hormone was isolated and later named 'progesterone'. This discovery and isolation was recorded by Willard Allen in 1974 in his article, "Recollection of my life with Progesterone" **(W. M. Allen, "My life with progesterone", Am J Obstetrics &Gynecology, 193 (4) 2005, pp. 1575–1577.)**

Progestin the original name of progesterone shouldn't be confused with progestin, a synthetic progestogen. While "progesterone" refers to the natural endogenous steroid sex hormone produced by the ovaries, "progestin" is a synthetic progestogen. The term 'progestin' encompasses a class of synthetic compounds designed to mimic the actions of progesterone. The term 'progestogen' includes both natural progesterone and synthetic progestins. This distinction is vital to avoid confusion, especially in the context of clinical applications where natural progesterone and synthetic progestins may serve different purposes and exhibit various pharmacological properties.

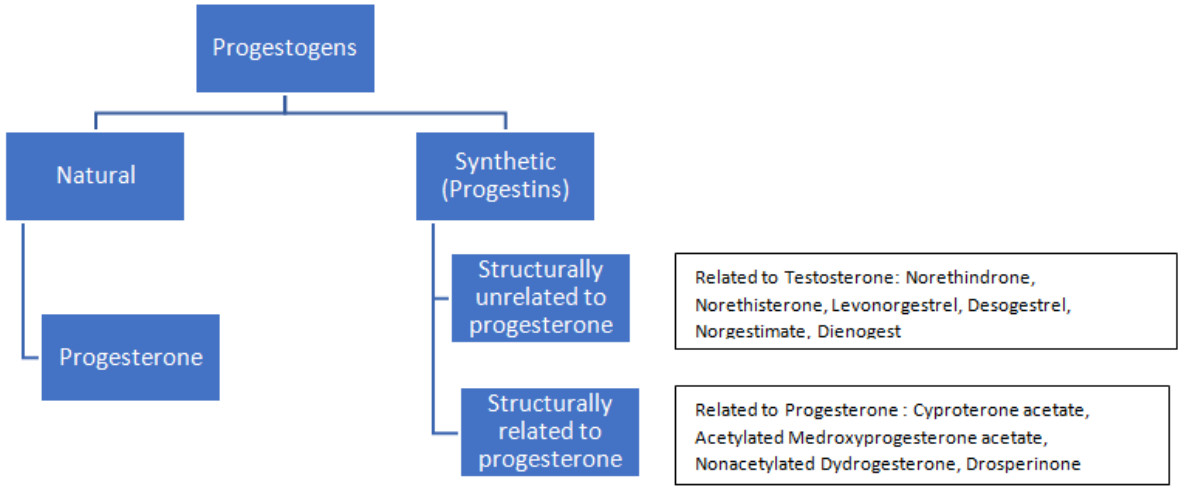

Fig1 : Classification of Progestogens: The term progesterone should only be referred to the natural hormone produced by the ovaries or included in a registered drug, qualified as "body identical" or "bioidentical" and different from custom-compounded bioidentical hormones.[2]

While the discovery motivated laboratory and clinical research to expand their knowledge on progesterone, one such personality in that effort was Georgeanna Seegar Jones (1912- 2005). Georgeanna, an American physician, described for the first-time luteal phase deficiency as a cause of infertility and pregnancy loss due to inadequate endometrium preparation and support. Thus, she is credited with using for the first-time progesterone to treat women with history of miscarriages. [2]

Another such leader in this field is Arpad Csapo who proposed that P4 maintains pregnancy by blocking parturition mechanism – 'P4 blocking hypothesis' and that withdrawal of this block induces labour activation. Early pregnancy luteectomyprofuces miscarriages through loss of progesterone support and contraction blocking action of progesterone shifted from the ovaries to the placenty – the luteo-placental shift was also found by him.[2]

THE REVOLUTIONARY PROCESS: MICRONIZATION

The routine uses of orally administered natural progesterone has been limited for years due to challenges related to poor absorption and rapid hepatic metabolism- the first pass effect. The

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relatively low bioavailability (<10%) associated with oral administration prompted the development of various synthetic progesterone derivatives. These synthetic alternatives aimed to overcome the limitations observed with natural progesterone, offering improved pharmacokinetics and enhanced effectiveness in clinical applications. Currently available synthetic progestins do not degrade rapidly by first pass metabolism. However, these synthetic compounds do not provide precise replication of the constellation of pure biological activities of the patent hormone progesterone such as antiandrogenic and ant mineralocorticoid and neuroprotective, regenerative and sedative effects due to its unique pharmacodynamic profile.

Around 1933, progesterone in an oil solution for intramuscular injection was introduced, marking the first pharmaceutical formulation of progesterone for medical use. A significant breakthrough in achieving a favorable balance between a good progesterone formulation and clinical efficacy came with the micronization process. Micronization of progesterone and suspension in oil-filled capsules, which allowed the progesterone to be absorbed severalfold more efficiently by the traditional oral route. Micronization of progesterone involves reducing size of progesterone particles to less than 10 micrometers, achieved by adding small progesterone crystals to long chain fatty acids. This increases the available surface area during stomach transit, enhancing the aqueous dissolution rate and intestinal absorption of progesterone. Combining micronized progesterone with oil suspension in gelatin capsules further accelerated and improved intestinal absorption. Numerous studies have demonstrated that physiologically relevant levels of progesterone can be rapidly achieved after the oral ingestion of at least 100mg of micronized progesterone with significantly elevated levels maintained for approximately 12 hours when administered in three divided doses.[2]

Soon after, Natural micronized progesterone Sustained Release (NMP-SR) was developed (Fig 2), utilizing the 'ERODingMATrix (EROMAT) technology.' This sustained-release formulation employs a hydrophilic matrix polymer designed to release micron-sized particles of progesterone gradually over 16–24 hours. The Hydrophilic matrix polymer ensures that significant amount of drug enters the colonic region. It limits the hepatic degradation of progesterone. Micellar solubilization of the micron sized drug particles by bile salts facilitate its absorption through lymphatic circulation. With an extended elimination half-life of 18 hours and high protein binding (90–99%), NMP-SR achieves and maintains serum progesterone concentrations within the luteal phase range (≥14 ng/mL) through once-daily dosing.[3]

Upon administering NMP-SR at doses of 200, 300, or 400 mg for 7 days, mid-luteal serum progesterone concentrations of 20.6, 36.1, and 46.2 ng/mL, respectively, were measured. The controlled release of drug particles during intestinal transit enhances lymphatic absorption into the systemic circulation from the small intestine and allows direct entry into the systemic circulation via the mucosal lining of the colon. This mechanism bypasses first-pass metabolism, ensuring that the active circulating drug achieves the desired therapeutic effect while minimizing the risk of metabolite-related adverse effects.In this way, NMP-SR effectively addresses the limitations associated with conventional oral NMP, offering a more controlled and sustained release that optimizes therapeutic outcomes and enhances patient safety.[3]

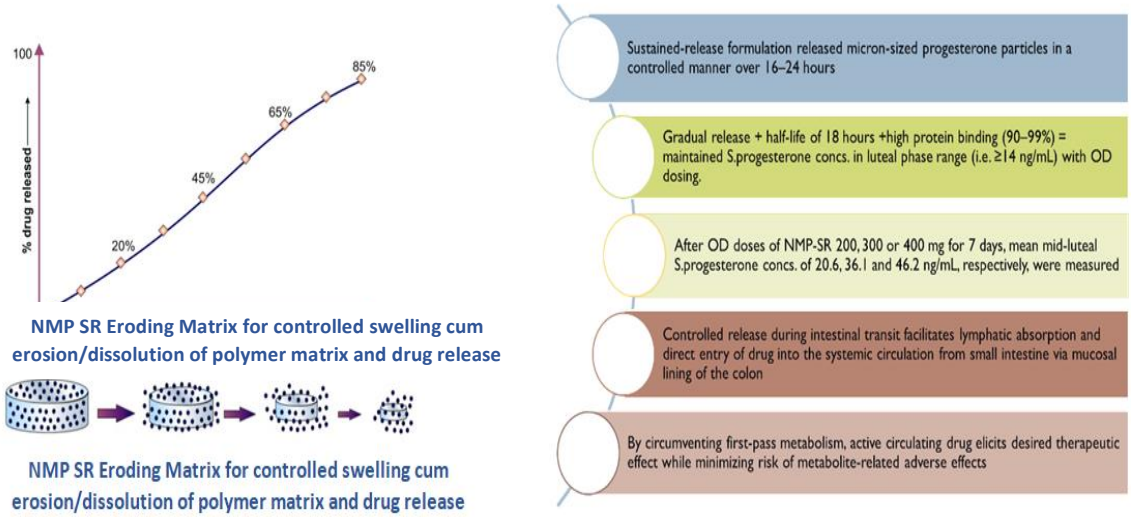

Fig 2: Natural Micronized Progesterone Sustained Release: Eroding Matrix technology. The formulation technology involves granulation of Micronized Progesterone and microboosters with release controlling polymer. Microboosters are the solubilizing agents that enhances the solubility of Progesterone and facilitate bioavailability enhancement of poorly soluble Progesterone.Rate controlling polymer is the release retarding polymer thatswells and releases Progesterone at controlled rate.

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In contemporary obstetrics, progesterone and other pregestational molecules have evolved into indispensable tools in daily practice. Enhanced knowledge of the biological basis underlying various mechanism leading to pregnancy complications has provided a solid foundation. Progesterone's pivotal role in pregnancy maintenance involves the modulation of the maternal immune response, suppression of the proinflammatory cascade, anti-inflammatory effects, inhibition of uterine contractility, and positive effects on uteroplacental perfusion.[2]

The management of threatened miscarriages, recurrent pregnancy loss, and threatened preterm birth now relies significantly on progesterone administration. This approach represents a very active and rapidly growing area of interest, particularly the immunomodulatory role of progesterone in managing the pregnancy complications. The widespread use of progesterone in these reproductive contexts highlights it indispensable role in optimising pregnancy outcomes and underscores its integration into various facets of contemporary obstetric care.

ROLE OF PROGESTERONE IN MAINTENANCE OF EARLY PREGNANCY

During the sixth day of fertilisation, the process of embryo implantation takes place. This depends on the local environment that develops as a result of progesterone secreted by the corpus luteum and hCG secreted by the blastocyst to maintain the corpus luteum. Progesterone stimulates the formation of blood vessels in the endometrium, which in turn allows the endometrial to secrete nutrients to nourish the uterine lining and support the pregnancy.[4]

Progesterone secretion by corpus luteum is required for success of early human pregnancy. Its hormonal action helps implantation of fertilized egg through:[5]

1. Stimulation of Uterine Growth creating a supportive environment for implantation.
2. Maintenance of uterine quiescence: Progesterone achieves this by stabilizing lysosomal membranes and inhibiting the synthesis of prostaglandins, contributing to a stable uterine environment.
3. Inhibition of myometrial contractions: Progesterone acts to inhibit contractions of the myometrium, preventing premature uterine contractions that could compromise implantation.
4. Endometrial Changes:Progesterone induces secretory transformation in the endometrium, increases vascularity of the endometrial lining, and stabilizes the endometrium, creating an optimal milieu for the implantation process.Improves blood flow & oxygen supply by increasing nitric oxide (NO) production

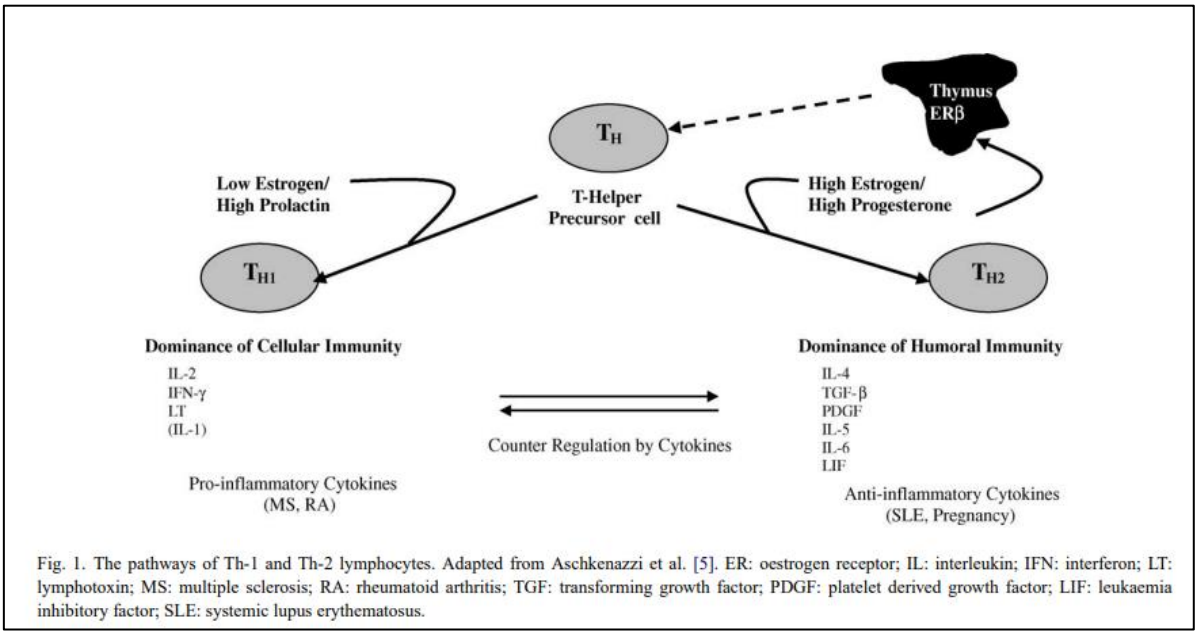

Fig. 1. The pathways of Th-1 and Th-2 lymphocytes. Adapted from Aschkenazzi et al. [5]. ER: oestrogen receptor; IL: interleukin; IFN: interferon; LT: lymphotoxin; MS: multiple sclerosis; RA: rheumatoid arthritis; TGF: transforming growth factor; PDGF: platelet derived growth factor; LIF: leukaemia inhibitory factor; SLE: systemic lupus erythematosus.

Fig: The pathways of Th-1 and Th-2 lymphocytes (Ref: J Steroid Biochem Mol Biol. 2005Dec;97(5):389-96. doi: 10.1016/j.jsbmb.2005.08.010.)[6]

In addition to its hormonal actions, progesterone exerts nonhormonal effects[5], including:

a) Immunomodulatory or Anti-inflammatory Effects: Progesterone, in conjunction with hCG and cortisol, inhibits tissue rejection and protects the conceptus. It blocks chemokines, leading to decreased prostaglandin synthesis and release. Furthermore, progesterone positively regulates factors such as PIBF (Progesterone-Induced Blocking Factor), NK (Natural Killer cells), HOX-10, and trophoblast HLA genes. This results in a favorable shift of the Th1-Th2 balance towards the Th2 type, supporting a conducive environment for implantation.

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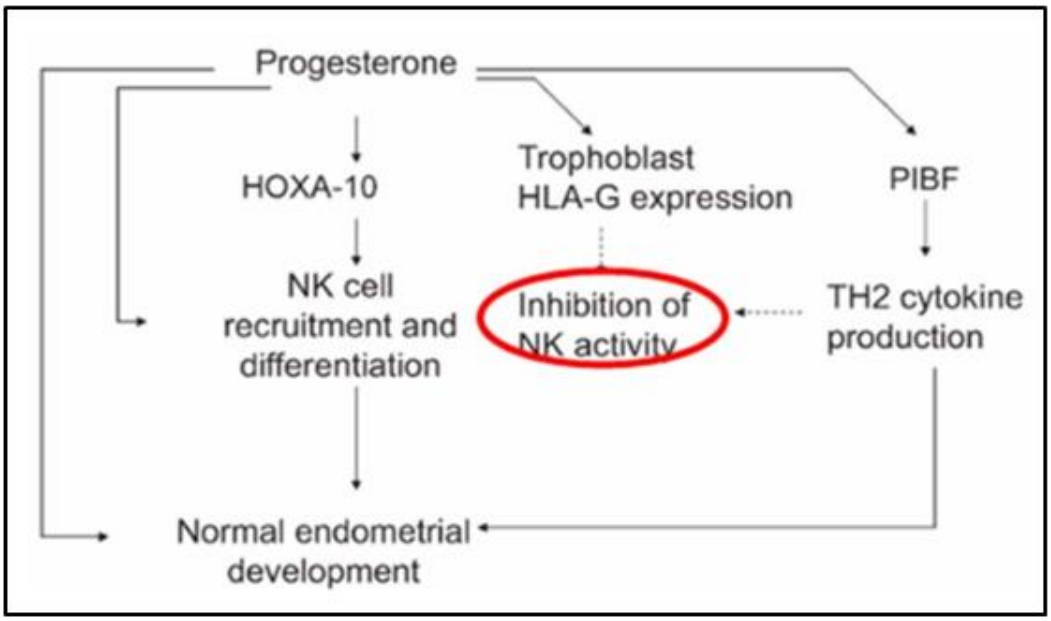

Fig: Non Hormonal action of Progesterone

b) Uterine Relaxant Properties: Progesterone acts as a uterine relaxant by blocking the effects of oxytocin, prostaglandin F2α, and α-adrenergic stimulation. It reduces intracellular calcium concentrations, lowering contractility and phosphorylated myosin levels, ultimately promoting myometrial relaxation.

These intricate hormonals and nonhormonal actions highlight the multifaceted role of progesterone in creating an optimal environment for successful implantation and early pregnancy development.Insufficient levels of progesterone in the luteal phase is one of the factors that results in implantation failure, miscarriages and assisted reproductive technique (ART) failure. Due to interventions in assisted reproduction, low progesterone environments are artificially generated. The corpus luteum's capacity to produce progesterone may be compromised by the use of gonadotrophin-releasing hormone analogues to stop the LH surge and aspiration of granulosa cells during the egg retrieval

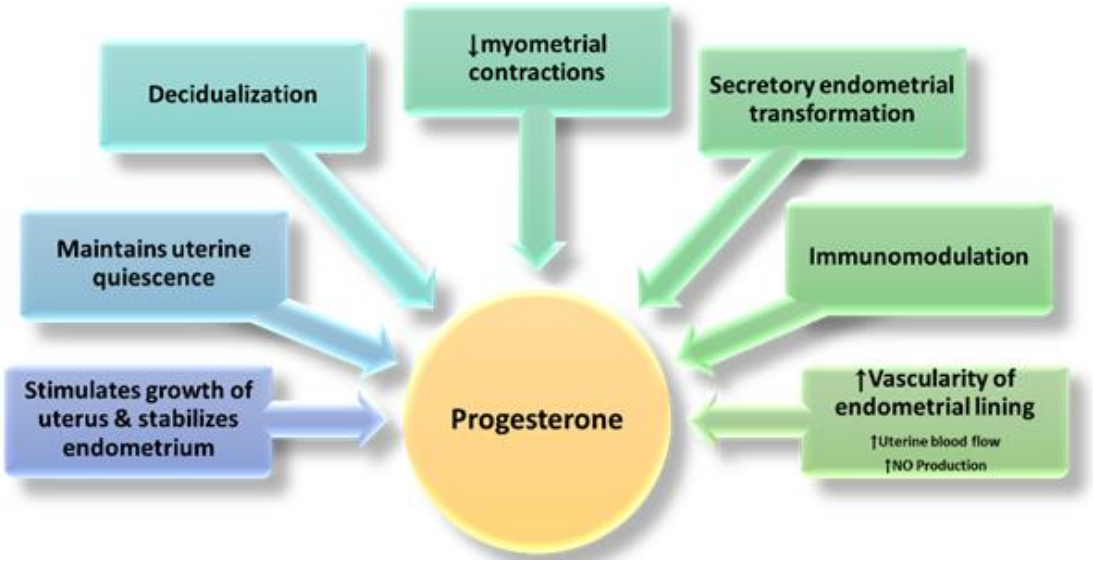

Fig: Progesterone action on uterus

IMMUNOMODULATORY ROLE OF PROGESTERONE IN EARLY PREGNANCY

Progesterone has long been considered “nature’s immunosuppressant”. Natural micronized progesterone when supplemented exogenously functions in the activation of various progesterone-regulated genes in the pregnant uterus along with development of endometrial receptivity to permit implantation. Its hormonal as well as non-hormonal actions deem progesterone supplementation necessary for the start of pregnancy. In patients using ART, oral natural progesterone at a dose of 200 mg per day has

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been utilised to increase luteal function while notably extending pregnancy. (Munshi et al. Am J Perinatol 2021;38:8–11. Accessed from https://fogsi.org/wp-content/uploads/fogsi-focus/fogsi-focus-maternal-fetal-and-neonatal-medicine-2020.pdf)

A study was carried out to in patients with infertility and paid volunteers were evaluated for both PIBF and progesterone at various times during the follicular phase and the luteal phase in both natural cycles and cycles involving embryo transfer after endogenous and exogenous progesterone exposure and after various synthetic progestins. Both intramuscular progesterone and oral micronized progesterone raise serum PIBF far greater than vaginal progesterone. Vaginal progesterone does, however, raise the PIBF level. Very interestingly, the rise in PIBF following ingestion of oral micronized progesterone is comparable, in fact, to IM progesterone.

Progesterone alone without exposure to the fetal allogeneic stimulus was able to produce a marked increase in serum PIBF. Neither a synthetic progestin (19-nortestosterone derivative) nor 17-hydroxyprogesterone caused an increase in PIBF.[7]

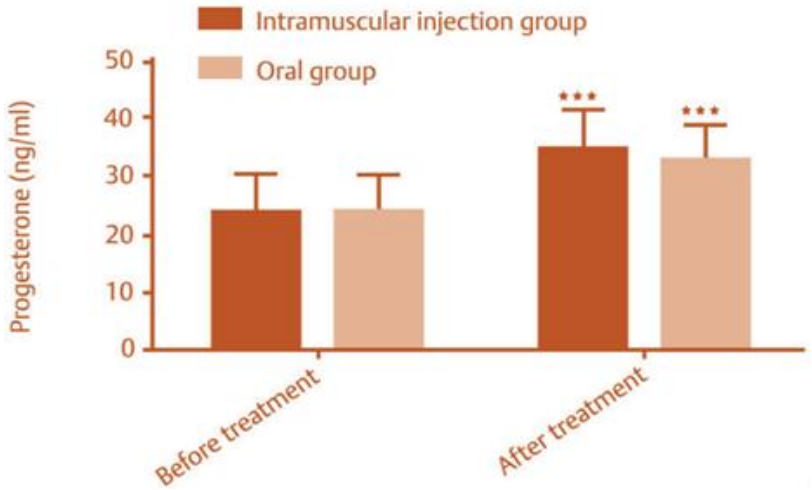

Fig: Increase in progesterone levels on supplementation.

In a study by Wang et al, the progesterone levels of pregnant women with threatened abortion receiving 200mg daily oral natural micronizedprogesterone or 20mg Intramuscular progesterone before and after treatment was evaluated. In both the groups, the progesterone levels after supplementation were significantly higher post treatment. However, the levels of progesterone in both groups after treatment were raised similarly that is, both oral and injectable natural progesterone showed a similar efficacy (Fig)

In addition, various studies report that in women receiving assisted reproductive technology (ART), the plasma levels achieved with therapeutic doses of oral natural progesterone are atleast as high as luteal phase levels. Study carried out by Gopinath and Desai, in over 90% women receiving ART treated with NMP SR as well as dydrogesterone achieved luteal phase plasma levels of progesterone.

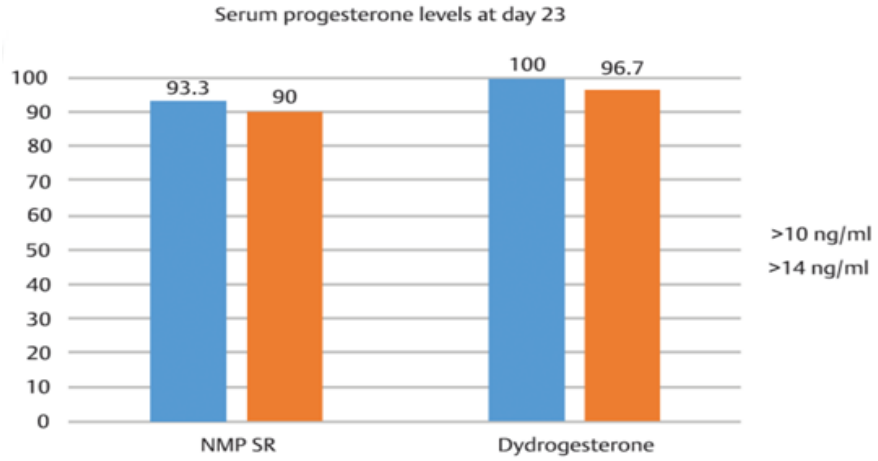

Fig: Progesterone levels in women receiving ART after oral supplementation. (Gopinath et al., Int J MedRes Health Sci. 2014; 3(4):933-936) ART, assisted reproductive technology; NMP SR, natural micronized progesterone sustained release

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Similar findings were also found by Malhotra and Krishnaprasad in the study on NMP SR and dydrogesterone. It was found that the percentage change of values was over 90% with a mean progesterone levels of 28.5 ng/ml.

In a study[8] assessing the clinical role of oral natural progesterone 200/300mg once daily at night or synthetic progesteronedydrogesterone 10mg twice daily for two weeks was administered during simulated IUI cycles for unexplained infertility. Mid-luteal sr. progesterone levels assessed in both groups on Day 21+/-2 showed mean levels of 30.7 and 28.5 ng/ml in both the groups for Dydrogesterone and oral NMP SR group respectively. Serum Progesterone levels in Dydrogesterone and Oral NMP SR groups. Pregnancy was observed amongst 5 (11%) and 10 (30%) patients treated with oral NMP SR and Dydrogesterone respectively during the 'First' cycle of IUI.

A real world, retrospective study on the effectiveness of natural micronized progesterone in luteal phase support showed 88% (14/16) clinical pregnancy rate and 93% (13/14)continuation of pregnancy more than 20 weeks (Modi S et al, Effectiveness of the oral sustained release formulation of natural micronized progesterone (NMP SR) in obstetrics: A retrospective, multicentre, real world study. Eposter presented at: FOGSI South Zonal Conference With Yuva; 2023 Mar 10-12; Calicut, Kerala, India)

Table summarising studies evaluating oral natural micronized progesterone along with sustained release preparations for luteal phase support during assisted reproduction

Study	Study Design	Ovarian Stimulation	Luteal Support	Results
Colwell and Tummon 1991	RCT/39	CC + hMG	Oral NMP 200 mg qds vs no luteal support	Serum P levels higher in oral NMP group vs no-luteal-support group on days 2, 4 and 11 (all p<0.001) Mean ± SD duration of luteal phase longer after oral NMP (17.0 ± 1.3 vs 13.7 ± 3.0 days, p<0.05). No significant difference in ongoing pregnancy rates (20% vs 0%)
Pouly et al. 1996	RCT/283	hMG	Oral NMP (100 mg in am, 200 mg in pm) vs vaginal NMP 8% (90 mg/day)	Mean ± SD blood P level higher in oral NMP group vs vaginal NMP group on day 8 (50.9 ± 81.9 vs 29.9 ± 56.4 ng/mL, p<0.001) No differences between oral NMP and vaginal NMP groups for rates of implantation (29.9% vs 35.3%), clinical pregnancy on day 30 (25.0% vs 28.8%) ongoing pregnancy on day 90 (22.9% vs 25.9%), abortion after day 90 (3.0% vs 11.1%), deliveries per patient (22.2% vs 23.0%) or deliveries per embryo transferred (11.1% vs 11.7%)
Friedler et al. 1999	RCT/64	GnRH + hMG	Oral NMP 200 mg qds vs vaginal NMP 100 mg bd	No difference in serum P levels between groups in conception cycles Higher serum P levels on days 11 and 15 in oral NMP group vs vaginal NMP in nonconception cycles (p=0.032) Lower implantation rate with oral NMP vs vaginal NMP (10.7% vs 30.7%, p<0.01) but no significant differences in rates of pregnancy (33.0% vs 47.0%), miscarriage (40.0% vs 12.5%), or ongoing pregnancy (20.0% vs 41.1%)
Licciardi et al. 1998	RCT/43	GnRH downregulati	Oral NMP 200 mg tds vs IM P 50	No difference in serum P levels between groups Lower

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		on, FSH or hMG, or FSH + hMG	mg/day	implantation rate with oral NMP vs IM P (18.1% vs 40.9%, p=0.004) No difference in clinical pregnancy rates (45.8% vs 57.9%)
Tomic et al. 2011	Case control/370	GnRH agonist, FSH	Oral NMP 100 mg tds + vaginal NMP 8% (90 mg/ day) vs vaginal NMP 8% (90 mg/day)	No difference in ongoing pregnancy rate between combination of oral + vaginal NMP vs vaginal NMP alone (39.5% vs 33.5%, p=0.48) but lower abortion rate with combination therapy vs monotherapy (6.4% vs 15.6%, p<0.05)
Güven et al. 2016	OL, OB/591	FSH	Oral NMP 200 mg vs no luteal support	All patients had unexplained infertility Evaluation of IUI cycles that developed a single follicle Higher clinical pregnancy rate in oral NMP group vs no luteal support group (24.3% vs 15.0%, p=0.021) Higher live birth rate in oral NMP group vs control group (19.8% vs 9.8%, p=0.004)
Chi et al. 2016	RET, OB/1779	NA	Oral NMP vs vaginal NMP vs DYD	No difference in rates of biochemical pregnancy, clinical pregnancy, early miscarriage, or ectopic pregnancy between recipients of oral NMP vs vaginal NMP vs DYD
Malhotra and Krishnaprasad 2016	OL, OB/78	CC + hMG	Oral NMP-SR 200 or 300 mg od vs oral DYD 10 mg bd	All patients had unexplained infertility In the first cycle, mid-luteal serum P levels of ≥ 14 ng/mL were achieved in 82.2% of oral NMP-SR recipients vs 78.8% of DYD recipients Biochemically confirmed pregnancy rate in the first cycle was 11% in oral NMP-SR group vs 30% in DYD group
Gopinath and Desai 2014	OL, OB/60	Natural or stimulated (CC ± hMG	Oral NMP-SR 400 mg/day vs oral DYD 10 mg bd	All patients had unexplained infertility In the first cycle, mean serum P levels were maintained at ≥ 14 ng/ mL in the mid-luteal phase in 93.3% of patients (oral NMP-SR 90.0% vs DYD 96.7%) Overall first-cycle biochemicallyconfirmed pregnancy rate 5% (oral NMP-SR 6.7% vs DYD 3.3%) Possible reasons for the low pregnancy rate were monofollicular development in patients undergoing natural IUI cycles, a trend towards a low-motility fraction, and evaluation of the first cycle only

[a]Subsequent ovulation induction was achieved using administration of human chorionic gonadotropin. [b]Publication in Chinese; additional details not available in English abstract.bd, twice daily; CC, clomiphene citrate; DYD, dydrogesterone; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; hMG, human menopausal gonadotropin; IM, intramuscular; IUI, intrauterine insemination; N, number of subjects; NMP, natural micronized progesterone; OB, observational study; OL, open label; P, progesterone; qds, four times daily; RCT, randomized controlled trial; RET, retrospective; SR, sustained release; tds, three times daily.

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Progesterone supplementation serves as a crucial element for luteal support after in vitro fertilization (IVF), commonly administered vaginally, although practices may vary geographically. A meta-analysis of randomized controlled trials (RCTs) revealed that the route of administration (intramuscular, vaginal, oral) or the type of progestogen did not significantly impact outcomes in luteal phase support for assisted reproduction techniques (ARTs), encompassing IVF and intracytoplasmic sperm injection (ICSI), concerning live birth/ongoing pregnancy, clinical pregnancy, or miscarriage rates.

Oral NMP supplementation after IVF has demonstrated an increase in luteal phase serum progesterone levels and prolonged luteal phase duration compared to no supplementation. Studies comparing oral and vaginal NMP found similar rates of clinical and ongoing pregnancy, though one study reported a lower implantation rate with oral NMP. Another randomized study comparing oral NMP with intramuscular progesterone found a lower implantation rate with oral NMP, but no significant difference in clinical pregnancy rates. Additionally, a case–control study indicated that a combination of oral plus vaginal NMP yielded similar ongoing pregnancy rates but a lower abortion rate compared to vaginal NMP alone.

THREATENED OR RECURRENT MISCARRIAGE

Miscarriage, defined as the spontaneous loss of a pregnancy before 24 weeks gestation, is common, with about 25% of women experiencing one at some point in their life and 15% to 20% of pregnancies ending in miscarriage. Miscarriage is a frequent pregnancy problem that can have serious physical and psychological consequences. Vaginal bleeding with or without abdominal pain is a sign of threatened miscarriage. While the cervix is closed and the foetus remains viable inside the uterine cavity. Unfortunately, half of the threatened abortion pregnancies ended in miscarriage, which had a significant psychological impact on women and their families. Physiological studies have revealed that progesterone is involved in a variety of actions, ranging from preimplantation to the entire pregnancy, including endometrium transfer and decidualization, regulation of extravillous trophoblast invasion, control of uterine contractions, protection of the semi-allogenic foetus from the mother's immune system, and so on.

Corpus luteum progesterone production is critical for pregnancy maintenance until the placenta takes over this function at 7 to 9 weeks of gestation. In fact, removal of the corpus luteum or administration of a progesterone receptor antagonist readily induces abortion before 7 weeks (49 days) of gestation. Progesterone induces secretory changes in the lining of the uterus, which are important for implantation of the fertilized ovum. A large RCT called the PRISM (progesterone in spontaneous miscarriage) trial evaluated the role of progesterone in women with bleeding in early pregnancy included 4,153 women and found that progesterone therapy administration during the first trimester did not result in a significantly higher incidence of live births than placebo. Vaginal micronized progesterone of 400 mg, administered twice daily, was associated with increasing live birth rates according to the number of previous miscarriages. In a subgroup analysis among women with a history of one or more miscarriage(s) and bleeding in current pregnancy, the live birth rate was 75% (689/914) with progesterone versus 70% (619/886) with placebo (rate difference 5%; risk ratio = 1.09, 95% confidence interval: 1.03–1.15; p = 0.003). The benefit was greater for the subgroup of women with three or more previous miscarriages and current pregnancy bleeding.

Progesterone used to treat imminent abortion reduces the levels of proinflammatory cytokines, such as IL-6 and TNF-α while increasing those of the anti-inflammatory cytokine IL-10 in proportion to the dose administered. Progesterone can prevent abortion by generating an anti-inflammatory environment.

IMMUNOMODULATORY ROLE OF PROGESTERONE IN PREVENTION OF MISCARRIAGES

Progesterone dependent pibf immunomodulation

Progesterone binds to Progesterone receptor on T cells that are activated having already interacted with fetal/paternal antigen. PIBF is subsequently released, binds to the PIBF receptor, which forms a heterodimer IL-4 receptor and activates the Jak1/Stat6 pathway, leading to increased production of Th2 cytokines. This contributes to a Th2 dominant cytokine pattern. On Th1 cells, PIBF inhibits the Jak/STAT4 pathway to inhibit Th1 cytokine production

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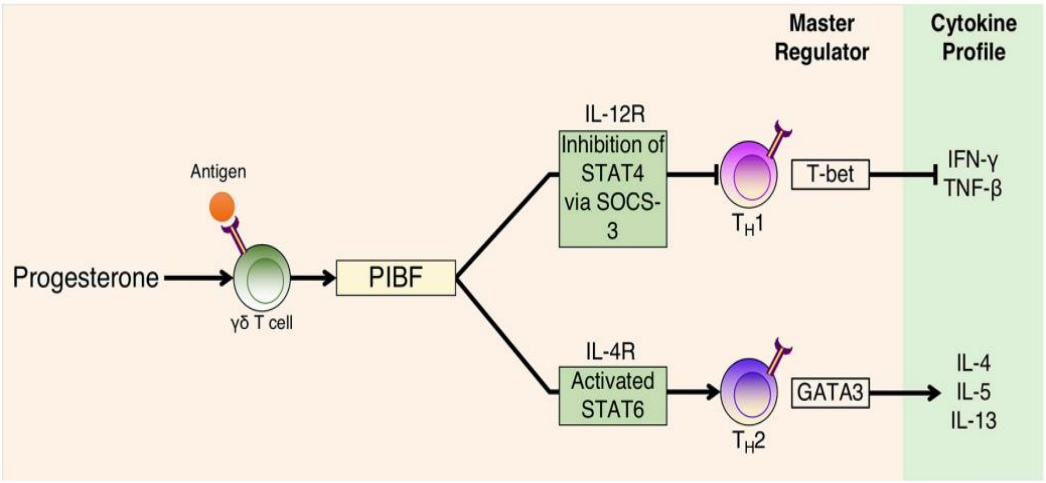

Fig: Progesterone dependent PIBF action on T cell differentiation and cytokine production[11]

1. **In the periphery,** Progesterone affects T cell activation and differentiation directly by

a) **T cell activation:** modulation of T cell receptor (TCR) signal transduction or

b) **Induce tolerance:** inducing tolerant antigen-presenting cells (APCs) including DC that suppress T cell activation during TCR engagement, as well as indirectly via induction of Tregs that subsequently modulate T cell differentiation.

c) **Cytotoxicity:** Progesterone can also suppress cellular cytotoxicity, predominately via PIBF to block degranulation.

d) Induce tolerance at maternal fetal interface.

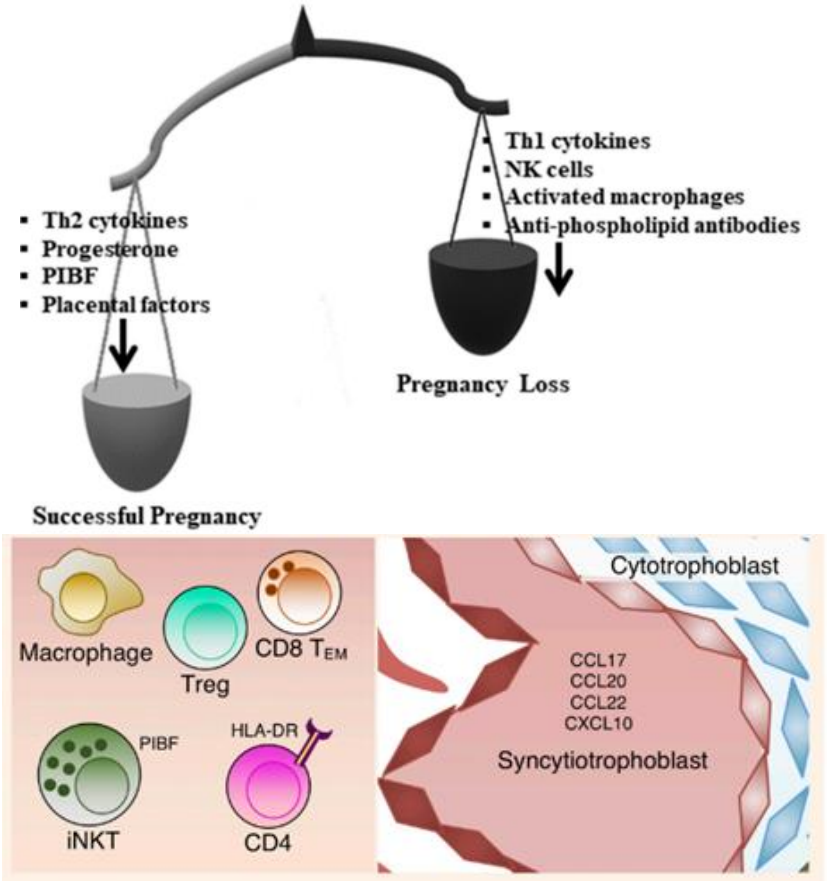

Fig4 : Progesterone induces tolerance at the maternal Fetal interface[11]

2. **At the maternal fetal interface**,

Progesterone promotes placental tissue growth and invasion by inducing immune-tolerant phenotypes of macrophages, natural killer (NK) and T regulatory (Treg) cells, whilst promoting exhaustion of activated

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CD4 and CD8 T cells that have interacted with placental-derived fetal-paternal antigens

IMMUNOMODULATORY ROLE OF EXOGENOUS PROGESTERONE

Clinically, Exogenous progesterone is used to treat infertility, miscarriage and PTL, for which its role has been explored. Low progesterone levels have been linked to increased risk of first trimester miscarriage.[12] A Study by Kishore K et al, compared the changeover in Th1 cytokines in subjects with RPL on supplementing with 200mg of oral micronized progesterone. The levels of Th1 cytokines TNF-α, IL-6 and PTX-3 was found to be reduced at every time point in treated cases of RPL as compared to untreated ones along with better pregnancy outcomes ($p<0.005$) [13] Agarwal N et. al. showed that oral micronized progesterone led to increased rise of Th2 cytokines like IL6 ($p=0.001$) and less rise of Th1type cytokines like TNF α ($p=0.012$) supporting the immunomodulatory effects of progesterone.[14]

Peripheral blood mononuclear cells from women with unexplained RPL showed production of the type 2 cytokines IL-4, IL-6 and IL-10 by lymphocytes from the RPL and PTL groups and of IL-4 and IL-10 by lymphocytes from healthy pregnant women was significantly increased upon exposure to PIBF. Ratios of type 1:type 2 cytokines were decreased, suggesting a shift towards Th2 type cytokine pattern. [15] Cohen et al compared the rise in PIBF levels after exposure to different forms of progesterone. Progesterone alone without exposure to the fetal allogeneic stimulus was able to produce a marked increase in serum PIBF. Neither a synthetic progestin (19-nortestosterone derivative) nor 17-hydroxyprogesterone caused an increase in PIBF. [7]

In another study, the peripheral blood mononuclear cells from women with and without unexplained recurrent pregnancy loss were cultured with progesterone was found to specifically block Th1 immunity to trophoblast, as was IL-10. Progesterone also appeared to upregulate TGF-beta secretion in response to trophoblast.[16]AbdulHussain et al noted that progesterone significantly down-regulated the secretion of the Th1 cytokines IFN-α and TNF-γ, and the Th17 cytokine IL-17A, and IL-23. Whereas, the secretion of the Th2 cytokine IL-6 was upregulated.[17]

All progesterone, vaginal, intramuscular and oral micronized progesterone raise serum PIBF, however the raise in intramuscular and oral is far greater than vaginal progesterone. Very intriguingly, the increase in PIBF following oral micronized progesterone consumption is comparable to that following IM progesterone administration. [7]

Observations from the evidence section:

Oral NMP

- The most common dose used was 200mg BD
- Doses used were 100mg BD, 200mg BD, 300 mg BD and 400 mg BD
- Range of efficacy in prevention of abortion ranges from 57.1% to 91.8%
- In RCTs, oral NMP was as efficacious as vaginal NMP and Dydrogesterone
- In one RCT, Oral NMP was determined to be superior to vaginal NMP
- In a prospective cohort observational study, Oral NMP was as efficacious as Dydrogesterone in maintaining pregnancy upto 28 weeks

Oral NMP SR

- Doses used were 200mg OD, 300 mg OD and 400mg OD
- Duration of therapy averaged 10 weeks
- Range of efficacy in prevention of abortion ranges from 94% to 100%
- Oral NMP SR was seen to be as efficacious as Vaginal NMP

Based on clinical data of orally administered NMP, the efficacy seems to be at par with oral dydrogesterone and vaginal NMP. NMP-SR has also shown a trend of efficacy similar to vaginal NMP. So, the benefit risk ratio seems to favor NMP SR with further reduction in dosing frequency compared to vaginal NMP.

In a prospective, single center, randomized controlled trial[18] evaluating the different progesterone doses on the concentration of proinflammatory and into inflammatory cytokines in pregnant women in threatened abortion (n=221) found that progesterone can prevent imminent abortion by generating an anti-inflammatory environment. In the study, Group 1 consisted of IL-6, IL-10, and TNF-α values in pre-treatment blood samples from 221 patients diagnosed with imminent abortion. Group 2 included 81 patients who received natural oral 100 mg micronized progesterone MP twice a day for two weeks. Group 3 included 83 patients who were administered oral 200 mg of natural micronized progesterone MP twice a day for two weeks. Group 4 included 57 patients who received oral 200 mg of natural micronized progesterone MP twice a day for two weeks, and one depot progesterone was added to the treatment by administering it at a dosage of 500 mg/day intramuscularly.IL-6 values between groups were lower in group 4 compared to group 3 ($p=0.007$). When IL-10 values were compared between the groups, the IL-10 ratio was highest in group 4 and lowest in group 2 ($p<0.001$, $p=0.003$, $p<0.001$). When the TNF-α values between the groups were compared, the value in group 4 was decreased compared to groups 1 and 2 ($p=0.031$, $p<0.001$). In the logistic regression analysis, the IL-6 value above 12.01 increased the abortion imminens rate 1.01 times, and a TNF-α value above 11.04 increased the abortion imminent rate 1.21 times

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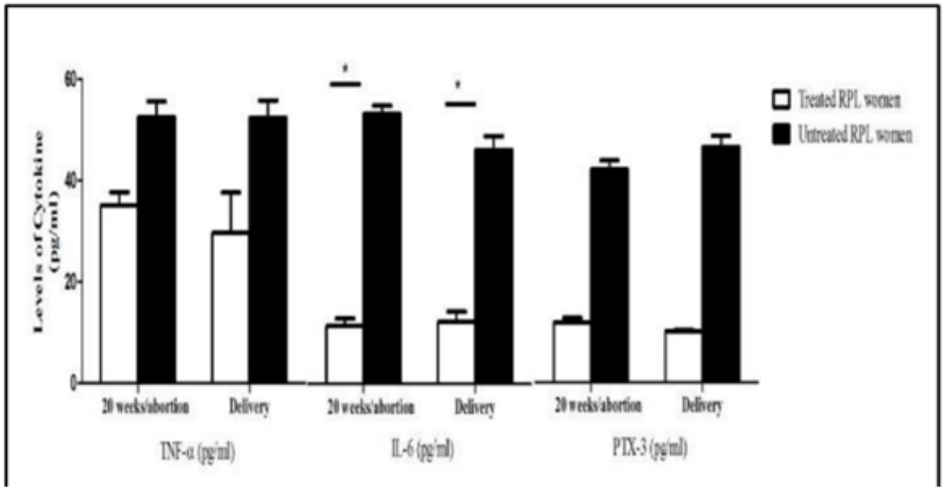
Group		IL-6	IL-10	TNF-α
Group 1	Mean± SD	14.15±1.46	10.63±2.4	11.55±1.32
Group 2	Mean±SD	12.24±1.91	11.30±1.28	11.43±1.44
Group 3	Mean±SD	10.31±2.26	12.91±2.37	10.41±1.37
Group 4	Mean±SD	9.07±1.63	14.01±1.93	10.01±1.21
p-value		<0.001	<0.001	<0.001

The study concluded that Progesterone used to treat imminent abortion reduces the levels of proinflammatory cytokines, such as IL-6 and TNF-α, while increasing those of anti-inflammatory cytokine IL-10 in proportion to the dose administered.

In another study by Kishore K. et al,[13] studied the the association of serum cytokines IL-6, TNF alfa , Pentraxin 3 and progesterone. In RPL, the continuous rise in the levels of Th1 cytokines TNF-α, IL-6 cytokines and PTX-3 has an adverse impact on pregnancy outcome. The changeover in the levels of Th1 cytokines was studied in two major groups; Gp I (N=30) comprised of RPL subjects with two or more consecutive spontaneous miscarriages history and Gp II (N=30) comprised of normal pregnancy controls .The efficacy of oral micronized progesterone was assessed in regulation of cytokine levels ,with GpIa (N=15) treated with 200 mg oral micronized progesterone and GpIb (N=15) comprised of untreated RPL subjects and its role in improving pregnancy outcome was also determined. The present study determined the levels of cytokine TNF-α, IL-6 and PTX-3 in serum samples for all the subjects at three time points at the time of enrolment, with (GpIa) or without (GpIb) progesterone administration at 20 weeks or abortion if earlier and at the time of delivery. The results indicated that the levels of Th1 cytokines (TNF-α [37.80 versus 78.09], IL-6 [16.93 versus 81.12] and PTX-3 [17.42 versus 73.53]) was found to be reduced at every time point in the treated cases with an RPL history as compared to untreated ones. Further, the cases treated with with oral micronized progesterone were found to have better pregnancy outcomes s ($p< 0.005$ significant number of live births). The study concluded that r exogenous progesterone decreases the Th1 pro inflammatory response and efficiently improves the pregnancy outcomes by modulation of cytokine levels.

Evidences on oral natural micronized progesterone for threatened abortion

Figure 1: Levels of cytokines at enrolment 20 weeks and at delivery in RPL vs. controls.



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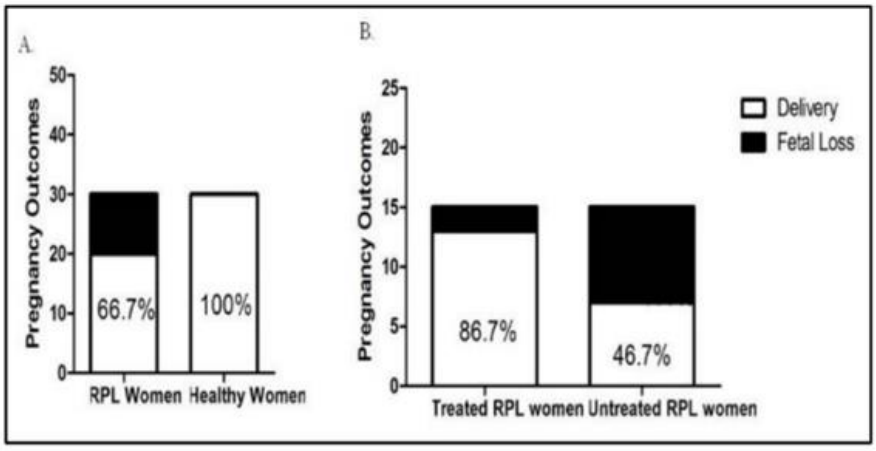

Figure 3: A) pregnancy outcome in RPL women vs. controls, B) pregnancy outcome in RPL treated vs. untreated cases.

Clinical study	Study population and design	Effects/Results
Turgal et al[76]	Randomized controlled trial A total of 60 women with TA were selected and randomly assigned to one of two groups: oral micronized progesterone group (400 mg/day; *n* = 30) and control group (*n* = 30)	Placental volume difference was significantly higher in the OMP therapy group (336%) than in the control group (141%)
El-Zibdeh and Yousef[103]	Open-label, randomized/threatened miscarriage, viable fetus, *n* = 86, Dydrogesterone + standard supportive care	No adverse effect, one neural tube defect, one heart disease
Prabhat and Korukonda[77]	Retrospective study, 185 patients with high-risk pregnancy at 40 centers OMP SR group was administered in a mean dosage of 271 mg for 18 ± 5 weeks	Long-term administration of oral NMP SR group suggests therapeutic compliance and a safety profile for high-risk pregnancy
Marinov et al [104]	Retrospective study, 68 women were treated for TA with a daily dose of 400-mg MP (orally twice daily)	The preventive treatment with MP in women caused dull pain and weight issues. MP can be recommended in tablet form twice daily with proper indications
Friedler et al[75]	Retrospective study, a total of 64 patients were prospectively randomized into two groups: oral (200 mg × 4 times a day) and vaginal (100 mg × two times a day) requiring intracytoplasmic sperm injection	Higher rate of implantation vaginally as compared with oral administration of MP. Difference in the pregnancy miscarriage patients and ongoing pregnancy rates were not significant statistically. No side effects were reported
Yassaee et al[50]	Single-blind clinical trial study, 60 pregnant women were prospectively divided into two groups: the control group, without any treatment, and the case group, received 400 mg of vaginal progesterone suppository	Rate of abortion in women treated with progesterone suppositories was reduced. Among 60 patients in the case group, the number of abortions (6 cases, 20%) was lower than that in the control group, which had 10 abortions (33.3%)
Wahabi et al[105]	Identification of seven randomized trials, 696 women were recruited to compare the use of natural progestogens in the treatment of threatened miscarriage with either placebo or no treatment	Reduction in the rate of miscarriage with the use of progesterone compared with placebo or no treatment (RR: 0.53; 95% CI: 0.35–0.79) The results suggested that the use of progesterone is effective in the treatment of threatened miscarriage
Czajkowski et al[106]	Randomized, parallel-group, double-blind, double dummy-controlled study, 53 patients with threatened miscarriage and a living embryo, 300 mg of micronized vaginal progesterone or 30 mg of oral dydrogesterone daily supplementation for 6 weeks	Vaginal progesterone administration results in the decrease in the spiral artery pulsatility and resistance index and diastolic ration as compared with oral dydrogesterone treatment

Abbreviations: CI, confidence interval; MP, micronized progesterone; NMP, natural micronized progesterone; OMP, oral micronized progesterone; RR, risk ratio; SR, sustained release; TA, threatened abortion.

NMP EFFECT ON FETAL PLACENTAL VOLUME IN FIRST TRIMESTER THREATENED ABORTION[19]

A RCT carried out on womwn (n=60) enrolled with threatened abortion and a singleton pregnancy from 6–8 6/7 weeks of gestation were administered OMP (400mg/day) n=30 and control group (n=30). After treatment, placental volume difference was significantly higher in the OMP group (336%, 67–1,077) than in the control group (141%, 29– 900) (p 5 0.007). The mean differences in gestational sac, amniotic sac, and embryonic volumes between the OMP and control groups were not statistically significant. The study concluded that Hormonal

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support with OMP is associated with increased placental volume in firsttrimester threatened abortion when compared with the control group.

Comparison of Pre- and Posttreatment Differences for Gestational Ages, Laboratory Parameters, and Volume Measurements Using XI VOCAL Method Between Oral Micronized Progesterone Group and Controls

Parameter	OMP Group (n = 30)	Control Group (n = 30)	*p* Value
Gestational age (weeks)	54 ± 16	47 ± 13	0.07†
CRL (mm)	425 (145–1,280)	258 (88–936)	0.02*
Progesterone (ng/ml)	50 (35–252)	37 (31–133)	0.50*
β-HCG (mIU/ml)	576 (184–2,623)	515 (132–2,853)	0.56*
Gestational sac volume (cm^3)	356 (54–1,100)	249 (7–1,447)	0.07*
Amniotic sac volume (cm^3)	549 (44–2,070)	350 (13–2,395)	0.07*
Placental volume (cm^3)	336 (67–1,077)	141 (29–900)	0.007*
Embryo volume (cm^3)	1,046 (87–8,671)	1,069 (156–4,329)	0.42*

Abbreviations: CRL, crown rump length; HCG, human chorionic gonadotropin.
*Mann-Whitney *U* test.
†Independent sample *t* test.

In a paper [20] that aimed to explore the efficacy of progesterone with different administrations in the treatment of patients with early threatened abortion, 124 patients with early threatened abortion were retrospectively analysed and divided into an intramuscular injection group (progesterone was intramuscularly injected) (n = 62) and an oral medication group (progesterone was orally administrated) (n = 62) according to different administrations. After treatment, the fetal heart rates in the two groups were significantly higher than those before treatment (both P < 0.001), and the rate after treatment in the intramuscular injection group was higher than that in the oral medication group (P > 0.05).

Table 7. Comparison of fetal heart rate changes

Groups	Intramuscular injection group (n = 62)	Oral medication group (n = 62)	t	P
Before treatment	103.67 ± 10.37	102.85 ± 10.29	0.442	0.659
After treatment	120.38 ± 11.46	118.26 ± 10.57	1.071	0.284
t	8.224	7.846		
P	< 0.001	< 0.001		

Women presenting with threatened miscarriage are at an increased risk of adverse reproductive outcomes and under great psychological stress. To diagnose the treatment options for prognosis, it is crucial to determine the clinical history of miscarriage and examination, serum biochemistry of pregnant women, and ultrasound. Bed rest, hCG, and using uterine muscle relaxants have not been shown to be effective in threatened miscarriage. The lower serum progesterone is associated with threatened miscarriage. The clinical supplementation with progesterone is required for the maintenance of pregnancy for early embryonic development, implantation, and fetal development, suggesting therapeutic compliance and a safety profile for long-term administration. Several routes of administration (i.e., oral, vaginal, IM, transdermal) and various formulations of progesterone are available and clinically used in the treatment of threatened miscarriage. The oral progesterone may be preferable in view of patient compliance. Oral supplementation with sustained release progesterone may show improved patient compliance. In conclusion, large-scale multicenter randomized controlled and comparative studies are needed to better evaluate the superiority of different types and routes of progesterones in first-trimester threatened miscarriage.

PRETERM BIRTH

Preterm birth contributes to almost 10 Lac deaths worldwide. Children born preterm have several life-long problems. Timely diagnosis helps guide antenatal decisions and avoids any associated risks. Interventions like tocolysis, steroids, in-utero transfer and magnesium sulfate for neuroprotection can be planned. As per WHO and FIGO spontaneous preterm labour is labour resulting in birth before 37 completed weeks.[9]

The ‘causes’ of preterm birth are multifactorial with social, psychological and biological factors playing a role. The most significant and consistently identified risk factor is previous history of preterm birth, Recurrent preterm birth is estimated to be approximately 22.5%, a 2.5 times higher relative risk

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as compared with women with no previous spontaneous preterm birth.

ROLE OF PROGESTERONE IN PRETERM LABOUR

The mechanism of onset of preterm labour is a complex with uterine activity mediated by prostaglandin. Progesterone is essential in maintaining pregnancy primarily through uterine quiescence, this is achieved by suppression of calcium-calmodulin-myosin light chain kinase system reducing calcium flux and altering the resting potential of smooth muscle. [10]

In humans, the progesterone receptor (PR) has two major subtypes PR-A and PR-B. Binding of progesterone to PR-A, the short form of the receptor, not thought to be associated with intra-cellular pathway mechanisms, prevents the actions of progesterone mediated by PR-B. An increase in the myometrial PR-A to PR-B expression ratio occurs at the onset of labor at term, resulting in an increase in myometrial PR-A, and in effect a functional withdrawal of progesterone, with increasing sensitivity to contractile stimuli. Prostaglandins produced prior to the onset of labor, also act to increase the PR-A/PR-B expression ratio, and therefore the potential to initiate a functional withdrawal of progesterone. In many animals the onset of labor is associated with a decrease in progesterone concentrations, but this has not been shown to occur in women before term or preterm birth, with no apparently detectable changes to circulating steroid hormone levels evident[10]

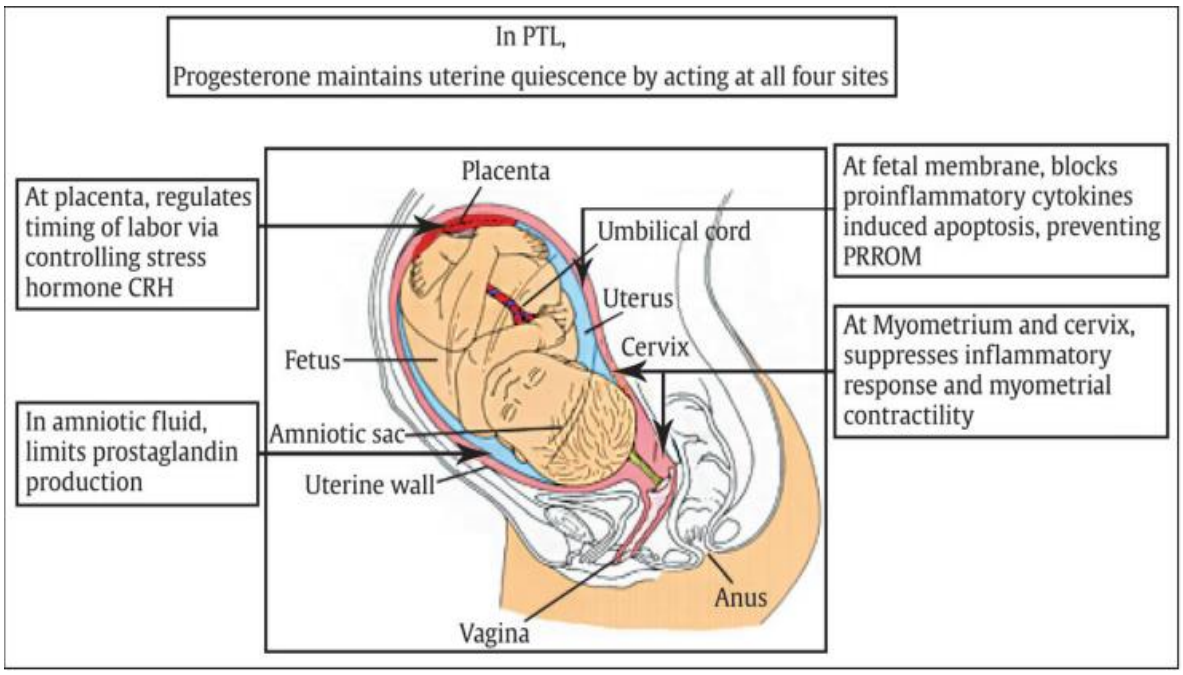

Fig: Mechanisms of action: progesterone in prevention of PTL. CRH, corticotrophin-releasing hormone; PRROM, preterm premature rupture of the membranes; PTL, preterm labor.

PROGESTERONE'S IMMUNOMODULATION IN PRETERM LABOUR

In labor, term as well as preterm, there is an increase in inflammatory markers tumor necrosis factor (TNF) -alpha, interleukin-1 (IL-1) and interleukin-6 (IL-6), and down-regulation of the anti-inflammatory interleukin-10 (IL-10). Inflammatory cytokines may alter enzyme expression, increasing prostaglandin production prior to the onset of labor. These maternal inflammatory mediators may then interact at the feto-placental unit, precipitating preterm birth. In particular, inflammatory cytokines interleukin-1 and TNF-alpha act to increase prostaglandin production, while both IL-10 and progesterone have a negative effect on prostaglandin production.

It is in this context that progesterone may exert its anti-inflammatory properties, raising a possible link between inflammatory process, alterations in progesterone receptor expression and the onset of preterm labor. While it has been postulated that the effect of progesterone on preterm birth is related to its anti-inflammatory properties, the specific mechanism of action remains unclear.

Elovitz and colleagues have developed a mouse model of intra-uterine inflammation with intrauterine injection of lipopolysaccharide (LPS). In these experiments, pre-treatment with progesterone was associated with suppression of activation of contraction-associated genes and inflammatory mediators, as well as prevention of the cervical ripening response to intrauterine inflammation. Pre-treatment with progesterone was associated with a reduction in preterm labor and preserved fetal viability in the mouse. In a subsequent experiment, the influence of progesterone on Toll-like receptors was evaluated. Toll-like receptors are involved in both

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the initiation and modulation of the inflammatory response, and regulation of these receptors may be one mechanism whereby intrauterine inflammation mediates the onset of labor, and therefore modifiable by the administration of progesterone. Pre-treatment of mice with progesterone prior to the creation of an intra-uterine inflammatory environment, was associated with a decrease in the LPS induced up-regulation of receptors in both the cervix and placenta. The authors concluded that this may be a potential mechanism whereby progesterone acts to reduce the risk of preterm birth.

Other investigators have evaluated the anti-inflammatory effect of progesterone at the feto-placental unit. Placental chorionic plate arteries were exposed to either lipopolysaccharide alone or in combination with progesterone. Exposure to LPS alone was associated with an increase in the production of the inflammatory cytokine IL-6. Pre-treatment of the arteries with progesterone was associated with reduced production of IL-6 after LPS exposure, although there was no demonstrable effect on the concentrations of TNF-alpha or IL-10. Similarly, exposure to progesterone was associated with a reduction in both fetal and maternal mononuclear cell expression of IL-6 after exposure to LPS, again suggesting these cell populations as possible targets for the anti-inflammatory effects of progesterone, and a potential mechanism for the observed reduction in preterm birth following progesterone. [10]

EVIDENCES ON EXOGENOUS PROGESTERONE IN PRETERM LABOUR

Study	Study Design	Patient profile	Intervention	Results
Rai et al. 200930	DB, RCT/150	History of sPTD 20–<37 weeks Singleton pregnancy	Oral NMP 100 mg bd vs placebo From 18–24 to 36 weeks or delivery	Rate of PTD (<37 weeks) lower with oral NMP vs placebo (39.2% vs 59.5%, p=0.002) Mean ± SD gestational age at delivery greater with oral NMP vs placebo (36.1 ± 2.66 vs 34.0 ± 3.25 weeks, p<0.001) Oral NMP prevented sPTD between 28–<32 weeks (2.7% vs 20.3%; RR 0.20, 95% CI 0.05–0.73, p=0.001) but not between 32 and <34 weeks (RR 0.86, 95% CI 0.60–1.22, p=0.85) or between 34 and <37 weeks (RR 0.83, 95% CI 0.48–1.45, p=1.00) [RR of PTD with oral NMP vs placebo with gestational age ≥37 weeks as reference] Among patients requiring tocolysis, mean tocolysis-to-delivery interval longer with oral NMP vs placebo (49.7 vs 26.8 hours, p=0.058)
Ashoush et al. 201731	DB, RCT/212	History of sPTD<37 weeks Singleton pregnancy	Oral NMP 100 mg qds vs placebo From 14–18 to 37 weeks or delivery	Risk of sPTD (<37 weeks) lower with oral NMP vs placebo (44.7% vs 63.7%; RR 0.7, 95% CI 054–0.92, p=0.01) Mean ± SD gestational age at delivery greater with oral NMP vs placebo (35.4 ± 2.7 vs 33.9 ± 2.9 weeks, p=0.01) Patients who required tocolysis had a longer mean tocolysis-to-delivery interval (87 ± 45.5 vs 36 ± 14.2 hours, p<0.001)
Glover et al. 201132	DB, RCT/33	History sPTD>20 to <37 weeks Singleton pregnancy	Oral NMP 400 mg/day vs placebo From 16–19 to 33 weeks	Rate of sPTD (<37 weeks) numerically lower with oral NMP vs placebo, but statistical significance not achieved (26.3% [5/19] vs 57.1% [8/14]; RR 0.55, 95% CI 0.26–1.16, p=0.15) Mean ± SD gestational age at delivery not significantly longer with oral

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				NMP vs placebo (37.0 ± 2.7 vs 35.9 ± 3.8 weeks, p=0.3)
Boelig et al. 201933	Meta-analysis30–32 /386	History of sPTD<37 weeks Singleton pregnancy	Oral NMP vs placebo	Risk of preterm birth decreased at <37 weeks' gestation (relative risk [RR] 0.68; 95% CI 0.55–0.84) and at <34 weeks' gestation (RR 0.55; 95% CI 0.43–0.71) with oral NMP vs placebo Increased gestational age at delivery (mean difference 1.71 weeks; 95% CI 1.11–2.30) with oral NMP vs placebo
Tariq et al. 201734	OB/345	History of PTD Singleton (95%) or multiple pregnancy	Oral NMP 400 mg/day From 15–20 weeks to delivery	Oral NMP prevented PTD (< 37 weeks) in 67% of patients, and PTD occurred in 33% of patients despite treatment Mean gestational age at time of delivery 37.51 ± 1.34 weeks
Natu et al. 201735	RET/30	High risk for preterm labour (history of preterm labour or abortion; infection or multiple gestation in current pregnancy) Singleton or multiple pregnancy	Oral NMP vs vaginal progesterone suppository From first trimester[a]	PTD rate was 40% (6/15) with oral NMP vs 26.7% (4/15) with vaginal progesterone; statistical analysis was not performed
Maintenance tocolysis				
Noblot et al. 199136	DB, RCT/44	Arrested preterm labour (tocolysis with ritrodrine)	Oral NMP 400 mg qds × 24 h then tds vs placebo From start of tocolysis to 35 weeks or delivery	Pregnancy prolongation (6.0 vs 6.4 weeks) or number of deliveries before 37 weeks (6 vs 8) not different between oral NMP and placebo Total ritrodrine dose (863 vs 1370 mg; p<0.05) and number of days of hospitalization (13.6 vs 17.8; p<0.05) lower with oral NMP vs placebo
Choudhary et al. 201437	DB, RCT/90	Arrested preterm labour (successful tocolysis with nifedipine) Singleton pregnancy	Oral NMP 200 mg/day vs placebo From 48 hours after tocolysis to 37 weeks or delivery	Mean ± SD latency period (days gained until delivery) longer with oral NMP vs placebo (33.29 ± 22.16 vs 23.07 ± 15.42 days, p=0.013) Rate of PTD lower with oral NMP vs placebo (33% vs 58%, p=0.034)

International guidelines and references supporting the use of progesterone for prevention of PTB

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Reference	Patients at risk	Daily dose and duration
Western Australia 2017	Short cervix between 16 and 24 wk gestation	200 mg until 36 wk
	Cervix length is <10 mm, management can include cervical cerclage, vaginal progesterone, or both	
	History of spontaneous preterm birth (with or without preterm pre-labor rupture of membranes) between 20 and 34 wk gestation	200 mg each night from 16 to 36 wk gestation
European Association of Perinatal Medicine 2017	Short cervix (25 mm) at mid gestation, either with singleton or twin pregnancy and regardless of their obstetrical history	–
French Clinical Practice Guidelines 2016	Threatened late miscarriage characterized by an isolated undilated short cervix (< 25 mm) and no uterine contractions	90–200 mg upto 34 wk
NICE Guideline 2015	With or without history of spontaneous preterm birth or mid-trimester loss between 16–34 wk and short cervix at 16–24 wk	–
FIGO 2015	Short cervix (<25 mm at 19–24 wk)	90–200 mg from diagnosis of short cervix up to ~37 wk
StratOG 2015	As an alternative to cervical cerclage in woman with prior PTB or short cervix CL <25 mm at 20 to 37 wk	Up to 37 weeks
ACOG 2012	Woman with or without prior PTB and short cervix CL ≤ 20 mm at ≤ 24 wk	From 16–24 wk of gestation
SOGC 2008	Prior PTB or Short cervix CL <15 mm at 22–26 wk	100 or 200 mg

Abbreviations: CL, cervical length; PTB, preterm birth.

SAFETY OF ORAL NATURAL MICRONIZED PROGESTERONE

Progesterone is an essential hormone and plays a critical role in the maintenance of pregnancy. The sustained-release tablet formulation of natural oral micronized progesterone (NMP SR) contains natural progesterone that is slowly released in the gastrointestinal tract thereby avoiding sudden drug release and loss of drug to the first-pass metabolism. Additionally, this may also potentially reduce the dose-related side effects.

The clinical usage and safety profile of NMP SR in pregnancy has been recently assessed in several studies. The largest of those was the NAP-DELAY study[18] which was a multicenter drug utilization surveillance study conducted in 2016 on 185 high-risk pregnancies receiving NMP SR. In this retrospective case-cohort analyses, the oral NMP SR formulation was prescribed for several indications, including patients with bad obstetric history with first or second trimester loss, cervical factor, still birth, threatened miscarriage with or without spotting, placenta previa, primary and secondary prophylaxis of preterm birth (PTB), elderly primi, polyhydramnios, uterine fibroid, twin gestation, and septate uterus. Mostly, the oral NMP SR formulation was initiated between 16 and 26 weeks of pregnancy and was continued until 34 weeks. The most common preferred dosage in the study was 300-mg single dose, with the mean dose of NMP SR used in the study ranging from 271.4 to 311.1 mg, depending on the indication. According to the results of the NAP-DELAY study, in all the 185 cases, the pregnancies continued till 34th week with no significant adverse events, except for two cases of spotting, who were receiving 200-mg once daily for subchorionic hemorrhage, or 400-mg once daily for uterine fibroid with subchorionic hemorrhage. The other adverse events comprised gastritis, vomiting, drowsiness, and dizziness, with none of them requiring hospitalization or referral

The study also noted that the rates of these centrally mediated adverse events were comparatively lower than those previously noted with the immediate-release formulations of oral natural micronized progesterone. Therefore, the study concluded that the natural progesterone remained a physiological and safer option for long-term progesterone supplementation in high-risk pregnancies.

In a multi-center prescription event monitoring study by Purandare and colleagues [19] reported the safety profile of oral NMP SR in the outpatient settings on 153 patients for luteal phase support in unexplained infertility, bad obstetric history, and secondary amenorrhoea, supplemented with NMP SR for 2 months following induction. Again, the 300-mg once daily was the most commonly prescribed formulation. The formulation was well tolerated, and the side effects comprised drowsiness (0.6%), hyperemesis (1.3%), and giddiness (0.6%), which were all mild and transient.

In an open-label prospective observational study by Gopinath and Desai [20] on 60 patients receiving intrauterine implantation, the 400-mg dose of oral NMP SR, once daily was well tolerated and none of the patients reported any central side effects.

In an open-label, prospective, multi-center, investigator initiated observational surveillance study by Malhotra and Krishnaprasad[8] on 120 patients receiving intrauterine insemination (IUI), a total of 22 and 23 patients received 200- and 300-mg NMP SR, respectively. Oral NMP SR was found to be safe and well tolerated in both cohorts, with occurrence of three cases of drowsiness and one case of nausea with NMP SR.

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Pope Paul VI study[21], analysed the fetal safety of progesterone administration during the course of 1310 pregnancies over a period of 35year period of time. The total number of anomalies observed in n those taking progesterone was 29 (in 1,310) for an incidence of 2.2%. The total number of anomalies observed in those who did not take progesterone was 10 (in 453) for an incidence also of 2.2%. By Chi square analysis, this is not statistically significant (p=0.99). Looking at the individual anomalies, there was no statistically significant difference between those that were on progesterone and those that were not on progesterone for any of the anomalies identified. The various fetal anomalies that were observed, both in those patients who took progesterone (n=1,310) and those who did not take progesterone (n=453) is shown in Table 1.

1 = Chi-square analysis (Chi-square = 1.727,1)
2 = Chi-square analysis (Chi-square = 0.0848,1)
3 = Chi-square analysis (Chi-square = 0.0010,1)
4 = Chi-square analysis (Chi-square = 0.0915,1)
5 = Chi-square analysis (Chi-square = 0.6914,1)
6 = Chi-square analysis (Chi-Square = 0.6176,1)
7 = Chi-square analysis (Chi-square = 0.3458,1)
8 = Based upon 549 females exposed to progesterone and 218 not exposed, Chi-square analysis, (Chi-square = 0.3976,1)
9 = Based upon 570 males exposed to progesterone and 226 not exposed, Chi-square analysis (Chi-square = 0.3970,1)
10 = Chi-square analysis (Chi-square = 2.887,1)
11 = Chi-square analysis (Chi-square = 6.049e-005,1)

Specific Fetal Anomalies Observed in Patients On Progesterone (n = 1,310) vs. Those not on Progesterone (n = 453)

Pope Paul VI Institute for the Study of Human Reproduction (1979 – 2014)

Anomaly Observed	On Progesterone (n = 1,310) n	%	Not On Progesterone (n = 453) n	%	P Value
Down syndrome	5	0.4	0	0.0	0.19[1]
Cardiac anomaly	4	0.3	1	0.2	0.77[2]
Trisomy 13	3	0.2	1	0.2	0.97[3]
Cleft lip/palate	3	0.2	1	0.2	0.97[3]
Other chromosome Anomalies	2	0.2	1	0.2	0.76[4]
Polydactyly	2	0.2	0	0.0	0.41[5]
Renal anomalies	1	0.1	1	0.2	0.43[6]
Omphalocele / BW	1	0.1	1	0.2	0.43[6]
Imperforate anus/ club foot/ectopic anus	2	0.2	0	0.0	0.41[5]
Aqueductal stenosis	1	0.1	0	0.0	0.56[7]
Labial fusion	1	0.2[8]	0	0.0	0.57[8]
Hypospadias	1	0.2[9]	0	0.0	0.53[9]
Wilms tumor	1	0.1	0	0.0	0.56[7]
Rhabdomyoma of Heart	1	0.1	0	0.0	0.56[7]
Wiskott Aldrich Syndrome	1	0.1	0	0.0	0.56[7]
Dandy Walker Malformation	0	0.0	1	0.2	0.089[10]
Pyloric stenosis	0	0.0	1	0.2	0.089[10]
Tracheal atresia	0	0.0	1	0.2	0.089[10]
UPJ Obstruction	0	0.0	1	0.2	0.089[10]
Total	29	2.2	10	2.2	0.99[11]

TABLE: ANOMALIES OBSERVED IN PATIENTS IN POPE PAUL VI INSTITUTE.

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The number of anomalies in the progesterone versus the non-progesterone group, whether they were chromosomal or non-chromosomal was not significantly different from those that were not on progesterone.

In a systematic review by Simons NE et al[22], the long term effects of prenatal exposure of progesterone in children was evaluated. All studies compared progesterone to placebo in second and/or third trimester for the prevention of preterm birth. 2 meta-analyses (890 children; aged 6 months to 8 years) showed no difference in neurodevelopment as assessed by Bayley-III Cognitive Composite score at 2 years between children exposed to progesterone versus placebo. (Standardised Mean Difference -0.04, 95% Confidence Interval -0.26 to 0.19), I 2 = 22%. Heterogeneity prohibited additional meta-analyses. Other long-term outcomes showed no differences.The systematic review concluded no harm in offspring prenatally exposed to progesterone treatment for the prevention of preterm birth.

Some key findings from USFDA review were reported by ASRM Practice committee in the Fertility and sterility journal[23]. As per the review by USFDA in controlled studies no increase in congenital anomalies including genital abnormalities in male or female infants was seen resulting from maternal exposure to progesterone during early pregnancy. Analysis of the published literature relating to maternal progestogen exposure during pregnancy and virilization of the genitalia in female infants indicates that most reported cases involved high doses of progestins derived from androgens, particularly ethisterone and norethindrone. Most reported cases of masculinized female infants are associated with maternal exposure to methyltestosterone, methandriol, and danazol. The FDA concluded that class labeling for all progestogens warning of an increased risk of birth defects was inappropriate because it would apply without regard to the indication for which the drug is prescribed. The FDA also noted that use of micronized progesterone for luteal phase support in IVF cycles had become routine and that the agency had itself recently approved a P gel for use in infertile women under treatment with ART

The safety profile of vaginal progesterone in the first trimester of pregnancy is supported by extensive data from patients who received this agent during the course of assisted reproductive technologies. The FDA has approved the marketing of vaginal progesterone for luteal support in the first trimester of pregnancy. Safety during the second and third trimesters in the prevention of preterm birth is based on 2 large randomized clinical trials that included >1000 patients.[24] There was no difference in the profile of adverse events between patients who were exposed to vaginal progesterone or placebo. A 2-year follow-up evaluation of fetuses who were exposed to progesterone in utero was completed by O'Brien et al,76 and no differences between vaginal progesterone and placebo were reported. During the review of the application of vaginal progesterone for the prevention of preterm birth in patients with a short cervix, the FDA did not find a safety signal.

Data are available from several well designed randomized double-blind, placebo controlled trials (PREDICT, FMF study, PROMISE, PRISM & OPPTIMUM) that have investigated the neonatal effects, health and neurophysiological development of offspring and the cost-effectiveness of the use vaginal micronized Progesterone in the early luteal phase in ART cycles or throughout pregnancy up to 37 weeks of gestation

Current evidences[23] indicates that progesterone supplementation during early pregnancy pose no significant risk to mother or fetus. One retrospective case control study has observed an association between maternal exposure to exogenous synthetic progestogens during early pregnancy and an increased risk for hypospadias in their infants (OR 2.2, 95% CI 1.0–5.0) (19). However, for 30 of the 42 cases described in the report, the type and duration of progestogen treatment was not known or specified. Because certain progestogens possess weak androgenic and antiandrogenic properties, it is quite possible that the observed association between early maternal progestogen exposure and the risk of hypospadias may be attributed largely, if not entirely, to use of progestins that bind to the androgen receptor. There is no direct evidence to indicate that supplementation with Progesterone itself during early pregnancy poses any significant risk of hypospadias or other types of birth defects. The increased risk for hypospadias observed in infants conceived by intracytoplasmic sperm injection (ICSI) most likely can be attributed to genetic factors related to paternal subfertility

Global Guidelines on the safety of progesterone in pregnancy: Australian TGA[25] has classified natural micronized progesterone as pregnancy category A: Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

Similarly, US FDA[26] has classified Natural micronized progesterone as pregnancy category B: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. Other product forms are not recommended or are contraindicated during pregnancy

Hydroxyprogesterone caproate exposure in first trimester was associated with an increased risk of cancer (adjusted HR, 2.57).[27]17-Hydroxyprogesterone caproate approval was withdrawn by USFDA in April 2023.[28]

In a recent pharmacovigilance study[29] reporting on the use of oral dydrogesterone in assisted reproductive technology presented at 39th Hybrid Annual Meeting

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of the ESHRE, Copenhagen – Denmark on June 2023 reported that among 29,120,563 case safety reports, 50,653 were related to the use of drugs for ART. Of these, 375 were cases of birth defects, including 60 (16%) with dydrogesterone. 44 cases out of 60 (73.3%) were compatible with major birth defect (MBD) cases according to EUROCAT classification. These cases contained a total of 55 MBD, consisting mainly in genital defects such as hypospadias (n ¼ 18, 32.7%), congenital heart defects (n ¼ 15, 27.3%) limb defects (n ¼ 10, 18.2%) and digestive system defects (n ¼ 6, 10.9%). In the primary analysis, a significant disproportionate reporting of birth defects was found with dydrogesterone when compared to any other drug (ROR 5.4, 95%CI [3.9-7.6]) and to any other ART agent (ROR 5.9, 95%CI [4.2-8.4]). In a head-to-head comparison to progesterone, the large study found an increased reporting of birth defect with dydrogesterone (ROR 5.4, 95%CI [3.7- 7.9]). These results were confirmed in both sensitivity analyses. Earlier studies published in The Lancet[30]&Pediatric Cardiology[31] indicated risk of congenital heart defect with usage of Dydrogesterone in early pregnancy.

CONCLUSION

A single class effect does not exist for natural micronized progesterone and synthetic progestins, due to their specific pharmacological characteristics and this explains the divergent safety profiles of these molecules as evidenced by experimental models as well as well-designed randomised clinical trials. Natural micronized progesterone has been studied in diverse obstetric and gynaecological conditions such as luteal phase defect, threatened abortion, recurrent miscarriage, prevention of preterm labour, high risk pregnancy, secondary amenorrhea, dysfunctional uterine bleeding, hormone replacement therapy etc. In term of route of administration, oral route is most commonly preferred by patients hence, oral progesterone usage has been more from decades but, oral progesterone capsule formulation has limitation of multiple daily dosage requirement & sedation/dizziness compliant which reduces compliance. Advent of Sustained release oral natural micronized progesterone (NMP-SR) formulation has addressed limitation of existing formulation and has been mainstay of formulation for progesterone prescription. Number of evidences show effectiveness of oral progesterone formulation in threatened & recurrent miscarriage. This chapter also covers specific points with respect to dose dependent immunomodulation with oral progesterone, fetal heart rate increase post-treatment, feto-placental volume increase in threatened abortion patients. Current evidences point toward little to no fetal harm or impaired fertility with the use of natural micronized progesterone whereas synthetic progestins have been associated with increased risk of birth defects.

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