# FOGSI POSITION STATEMENT ON THE USE OF PROGESTOGENS

## Under the guidance of GCPR Incharge, Dr Sanjay Gupte, in the FOGSI Presidential tenure of Dr Prakash Trivedi (2015) and Dr Suchitra Pandit (2014)

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## PROGESTERONE AND ITS ROLE IN EARLY PREGNANCY

- Progesterone is an essential hormone needed to maintain pregnancy.
- After ovulation, endogenous progesterone is produced by the corpus luteum and it rises sharply and peaks the following week.
- If the ovum is not fertilized, ovarian progesterone production falls, triggering endometrial shedding and menstruation. If the ovum is fertilized and it implants into the endometrium, the corpus luteum continues to secrete progesterone to prevent endometrial shedding, thereby protecting the developing fetus.
- Later in pregnancy, the placenta takes over progesterone production, a switch that is regulated by the hormone human chorionic gonadotrophin (hCG).

## MICRONIZED PROGESTERONE AND DYDROGESTERONE

- Endogenous Progesterone is derived from cholesterol steroids and produced mainly by the corpus luteum and the placenta, with some contribution from the adrenal glands.
- It has a half-life of about 5 minutes and is metabolized mainly by the liver to pregnanediol. In the bloodstream, progesterone is bound mostly to albumin. When taken orally, exogenous progesterone is absorbed rapidly, but almost

the entire dose is expected to be metabolized completely in one pass through the gut and liver. Hence, the vaginal route or injectable route is preferred for administration of exogenous progesterone.

- Both micronized progesterone and dydrogesterone are derived from a plant source. i.e. Diosgenin (a plant source - Dioscorea villosa )
- Micronization is the process of reducing the average diameter of particles such that the particles that are produced are only a few micrometers in diameter.
- Dydrogesterone (6-dehydro-retroprogesterone) is a progestogen that has high specific affinity for progesterone receptors, no affinity for androgen, mineralocorticoid, glucocorticoid, and estrogenic receptors.
- Both micronized progesterone and dydrogesterone are closely related to endogenous progesterone, both in its molecular structure as well in pharmacological effects.
- Progesterone is currently used in early pregnancy for various indications by oral, vaginal, IM route and as tablets, capsules, vaginal pessaries, injections and gels.

## PROGESTERONE SUPPLEMENTATION FOR LUTEAL SUPPORT IN ASSISTED REPRODUCTIVE TECHNIQUES (ART)

- Luteal function is usually compromised in ART cycles both in GnRH agonist and antagonist protocol.
- Adequate luteal phase support is required during ART to improve implantation and pregnancy rates, which can be achieved by either hCG (human chorionic gonadotropin) or directly by using progesterone.
- Endogenous progesterone deficiency is responsible for implantation failure and early miscarriages.
- Progesterone supplementation is advisable starting just after Oocyte Retrieval/Embryo Transfer.
- The duration of exogenous progesterone therapy generally varies up to 10-12 weeks of gestation.
- The following are routes of administration and doses based on the currently available evidence on progesterone in ART cycles
    - Intramuscular progesterone: 50-100mg/day
    - Vaginal micronized progesterone: 600-800mg/day
    - Oral Dydrogesterone: 20-30mg/day
    - Vaginal progesterone Gel: 8% (90mg) once daily

## PROGESTERONE SUPPORT IN RECURRENT PREGNANCY LOSS AND THREATENED MISCARRIAGE

- About 10% to 15% of the clinically recognizable pregnancies result in spontaneous miscarriages. Increase in the number of miscarriages would lead to an increase in the rate of subsequent miscarriage (13-17% after first miscarriage and 55% after the third miscarriage).
- Recurrent spontaneous miscarriage is spontaneous loss of 3 or more consecutive pregnancies before 20 weeks of gestation
- Threatened miscarriage is a pregnancy complicated by bleeding before 20 weeks gestation.
- Inadequate secretion of endogenous progesterone in early pregnancy has been linked as one of the etiological factors for recurrent miscarriage.
- Progesterone induces secretory changes in the endometrium essential for endometrial maturation, endometrial stabilization and embryo implantation and proper regulation of inflammatory mediators to create adequate positive immune response in early pregnancy, preventing pregnancy loss.
- Dydrogesterone is known to have immunomodulatory properties such as decreasing pro-inflammatory and increasing anti-inflammatory cytokines in early pregnancy[3,8,9].
- A large multicenter study called PROMISE study (http://www.medscinet.net/promise) is currently underway to assess vaginal micronised progesterone supplementation in women with unexplained recurrent miscarriages.
- Similarly the world's largest Phase III study called Lotus I and Lotus II is ongoing in several European, Middle East, Asian countries to assess the role of Dydrogesterone, Micronised Progesterone vaginal tablets and Micronised Progesterone gel as Progesterone support in Artificial Reproductive Techniques, including IVF.
- Based on the available clinical data, progesterone support (vaginal micronized progesterone & dydrogesterone) is beneficial in women

presenting with a clinical diagnosis of threatened miscarriage with relative risk reduction in the miscarriage rate of 47% with the use of progesterone (risk ratio (RR) 0.53; 95% confidence interval (CI) 0.35 to 0.79). [1,7]

- The argument for use of progesterone (vaginal micronized progesterone & dydrogesterone) is that there is no evidence of harm and some evidence of benefit, although not coming from huge multicentric trials. The decision should be based on clinician's discretion until strong evidence is available to recommend routine use
- The doses of progesterone that are generally used in clinical practice as per current evidence are as follows:
- Recurrent Miscarriage:
    - Oral dydrogesterone 10 mg BD till 20 weeks of pregnancy
    - Micronized Progesterone : 400mg /day vaginally till 20 weeks of pregnancy

- Threatened Miscarriage :

    - Micronized Progesterone : 400mg /day vaginal till bleeding stops.

    - Dydrogesterone :40 mg loading dose followed by 20-30 mg daily till 7 days after bleeding stops.

- There is no role of progesterone supplementation in normal healthy pregnant women for prevention of miscarriage.

## SAFETY OF PROGESTERONE

- Available evidence strongly supports the safety of progesterone when used in pregnancy (based on the available clinical data on vaginal progesterone and dydrogesterone).
- There is no statistically significant difference in the congenital abnormalities seen in the clinical studies between the newborns of the mothers who received progesterone and those who did not.
- The adverse effects reported with oral progesterones are;
    - common adverse event: breast tenderness, bloating, headache,
    - other adverse events include: constipation/diarrhea, itching/urticarial rash, fatigue, irritability, anxiety/depression somnolence.
    - In addition, intramuscular progesterone adverse effects include redness at the injection site, pain and inflammation.
    - Transvaginal use of progesterone can cause discharge, vaginal irritation in some patients.
- Progesterone should be used with caution in patients with cardiovascular diseases and in patients with impaired liver function and cholestasis.

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