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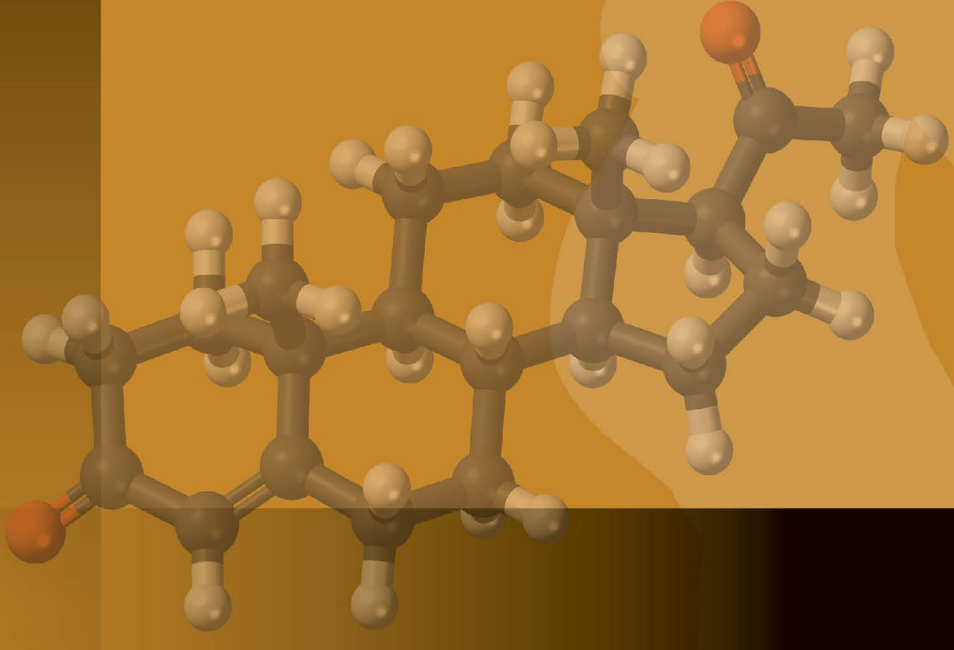
Use of Progestogens in Clinical Practice of Obstetrics and Gynecology



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CHAPTER

4 Routes of Administration and Bioavailability

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PHYSIOLOGICAL BLOOD LEVELS

In women, progesterone is produced from the ovaries and the adrenals, with the adrenals contributing a very minor fraction. The blood 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 diagram below. Progesterone levels tend to be <2 ng/mL prior to ovulation, and >5 ng/mL after ovulation. The levels range from 3 to 15 ng/mL during the luteal phase. The blood production rate is less than 1 mg/day in the preovulatory phase, which increases postovulation to 20–30 mg/day. If pregnancy occurs, human chorionic gonadotropin is released maintaining the corpus luteum allowing it to maintain levels of progesterone. Between 7 and 9 weeks the placenta begins to produce progesterone in place of the corpus luteum, this process is named the luteal-placental shift.[39] After the luteal-placental shift progesterone levels start to rise further and may reach 100–200 ng/mL at term. Whether a decrease in progesterone levels is critical for the initiation of labor has been argued and may be species-specific. After delivery of the placenta and during lactation, progesterone levels are very low.

Progesterone levels are relatively low in children and postmenopausal women.[40] Adult males have levels similar to those in women during the follicular phase of the menstrual cycle. Blood progesterone levels can be 50 times above normal in congenital adrenal hyperplasia. Blood test results should always be interpreted using the reference ranges provided by the laboratory that performed the results. Example reference ranges are listed below.

For comparative purposes, mid-luteal serum levels of progesterone are above 5–9 ng/mL, plasma levels in the first 4 to 8 weeks of pregnancy are 25–75 ng/mL, and serum levels at term are typically around 200 ng/mL. Production of progesterone in the body in late

pregnancy is approximately 250 mg per day, 90% of which reaches maternal circulation.[14,41,42]

ROUTES OF ADMINISTRATION

The different routes of administration for progesterone are orally, parenterally, intravaginally as a gel or insert and transdermal or subcutaneous.[43-47]

Oral Administration

- *Progesterone*: Following oral administration, it undergoes extensive first pass metabolism in gut wall and liver so that only ¼ of the dose reaches the circulation. The peak plasma levels are obtained in two hours that is equivalent to the luteal phase levels. The half-life is approximately 30 mins and baseline concentration is reached in 12 hours, thus requiring BD dosage.
- *Medroxyprogesterone acetate*: It is completely bioavailable and highly effective after oral administration. Its half-life is 2–3 days.
- *Dydrogesterone*: It has rapid oral absorption and reaches C_{max} in 1–2 hours. It has a half-life of 4–5 hours.
- *Norethindrone/Norethisterone acetate*: It has rapid oral absorption with 65% bioavailability and has a half-life of 8 hours.
- *Levonorgestrel*: It is completely bioavailable reaching C_{max} in 1–2 hours and has a half-life of 16 hours.
- *Gestodene*: It is 100% bioavailable with a half-life of 12–18 hours.
- *Desogestrel*: It is metabolized to 3-ketodesogestrel during first pass through gut wall and liver and is 75% bioavailable. It has a half-life of 12 hours.
- *Norgestimate*: Its pharmacokinetics is not well established.

Intramuscular Administration

With intramuscular injection of 10 mg progesterone suspended in vegetable oil, maximum plasma concentrations (C_{max}) are reached at approximately 8 hours after administration, and serum levels remain above baseline for about 24 hours.[34] Doses of 10 mg, 25 mg, and 50 mg via intramuscular injection result in mean maximum serum concentrations of 7 ng/mL, 28 ng/mL, and 50 ng/mL, respectively.[34] With intramuscular injection, a dose of 25 mg results in normal luteal phase serum levels of progesterone within 8 hours, and a 100 mg dose produces mid-pregnancy levels.[41] At these doses, serum levels

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of progesterone remain elevated above baseline for at least 48 hours, with a half-life of about 22 hours.[8,41] Due to the high concentrations achieved, progesterone by intramuscular injection at the usual clinical dose range is able to suppress gonadotropin secretion from the pituitary gland, demonstrating antigonadotropic efficacy (and therefore suppression of gonadal sex steroid production).[34]

Vaginal or Rectal Administration

With vaginal and rectal administration, a 100 mg dose of progesterone results in peak levels at 4 hours and 8 hours after dosing respectively, with the levels achieved being in the serum luteal phase range.[41] Following peak serum concentrations, there is a gradual decline in plasma levels, and after 24 hours, serum levels typical of the follicular phase are reached. Gels (4% and 8%) and inserts are available. It should not be administered with other vaginal preparations. If therapy with another agent administered intravaginally is needed, a gap of 6 hours before or after progesterone vaginal gel is recommended.[41]

- *Progesterone 4% vaginal gel*: Each prefilled applicator delivers approximately 1.125 g of gel (45 mg of progesterone).
- *Progesterone 8% vaginal gel*: Each prefilled applicator delivers approximately 1.125 g of gel (90 mg of progesterone).
- *Progesterone vaginal insert*: Each insert has 100 mg progesterone and comes in a pack of 21 inserts with applicator.

Transdermal Administration

Transdermal progesterone is about 5–7 times stronger than oral progesterone.[32] This is due to the fact transdermal administration bypasses first-pass metabolism. As such, 20–30 mg/day transdermal progesterone is equivalent to about 100–200 mg/day oral progesterone. Some researchers have reported that absorption of progesterone via the transdermal route is poor, impractical, and unsubstantiated, however they may have been measuring serum blood or urine levels.[48,49] Other studies have shown that transdermal absorption of progesterone cream is much higher when capillary blood or saliva testing is used.[50]

Subcutaneous Injection

Progesterone can also be administered alternatively via subcutaneous injection, with the new aqueous formulation Prolutex in

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Europe being intended specifically for once-daily administration by this route.[8,51,52] This formulation is rapidly absorbed and has been found to result in higher serum peak progesterone levels relative to intramuscular oil formulations.[52] In addition, subcutaneous injection of progesterone is considered to be easier, safer (less risk of injection site reactions), and less painful relative to intramuscular injection.[52] The terminal half-life of this formulation is 13 to 18 hours, which is similar to the terminal half-lives of oral micronized progesterone and intramuscular progesterone.[8]

STABILITY AND STORAGE

Oral Capsules

May be stored in tight, light-resistant containers at 25°C (may be exposed to 15–30°C).[45]

Parenteral Injection

The ideal temperature for storage is 15–30°C.[44]

Vaginal Gel and Inserts

Can be stored at 25°C (the range being 15–30°C).[46,47]

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Use of Progestogens in Clinical Practice of Obstetrics and Gynecology

This book is a monogram of an important hormone of female endocrinology, i.e. Natural Progesterone and its derivatives Progestogens. It includes basic principles, nomenclature, pharmacodynamics, description of individual progestogen and their clinical utility. It will enrich the readers with latest information and remarkably improve their prescription writing.

Anita MV is a practicing gynecologist and obstetrician in New Delhi. After her MD in OBGYN from Delhi University with top honors, she completed her Senior Residency in OBGYN from AIIMS. Subsequently, she worked as a Consultant and Senior Research Associate in AIIMS for three years. She has authored more than 25 publications in national and international OBGYN journals and has coauthored chapters in national and international OBGYN books. She has presented papers in AOGD and FOGSI conferences and won awards for her research papers. She has been actively participating in academic activities of OBGYN in all fora and at all levels.

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