Obstetrical and Gynaecological Society of Malaysia

Progestogens in the Management of Miscarriage and Preterm Labour

Guidelines

1st Edition

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TABLE OF CONTENTS

FOREWORD

Early pregnancy bleeding is extremely common. Most of us would therefore encounter such clinical situations very often. While progestogens are commonly prescribed, good clinical guidance on when these options should be utilized, are scarce. Indeed, we sometimes question if progestogens are useful at all. In the era of evidence-based medicine, the reality is that evidence is unfortunately a moving target. Hence, one needs to keep constantly abreast with the shifts in equations. For many busy clinicians, this task can be quite daunting. We therefore took it upon ourselves, to delve into the intricacies of utilizing progestogens in the management of miscarriage. While the initial remits were confined to miscarriage, recent developments on the use of progestogens to manage late miscarriage and prevent preterm birth could not be ignored. This then led us to extend the review to include this very important area. The review was done in an extremely transparent manner and was then subjected to both internal and external review. It is our firm belief that the final product is robust and will withstand scrutiny.

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12th May 2020

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DECLARATIONS OF INTEREST

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All members of the guideline development group were asked to declare possible conflicts of interest by means of the disclosure forms.

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Summary of recommendations

1. Threatened Miscarriage

Recommendation 1	Level of evidence *(Strength of recommendation)*
In women without prior history of miscarriage; • Oral dydrogesterone can be considered. The quality of included studies however, were low to moderate. • Micronized vaginal progesterone is not recommended.	Level 1 *(Conditional)* Level 1 *(Strong)*
Recommendation 2	**Level of evidence** *(Strength of recommendation)*
In women with a history of ≥1 previous miscarriage; • Micronized progesterone 400 mg twice daily per vagina/ rectal or dydrogesterone 10 mg BD from the onset of bleeding up till 16 weeks of pregnancy may be considered.	Level 2 *(Conditional)*
Recommendation 3	**Level of evidence** *(Strength of recommendation)*
Dydrogesterone may be associated with fewer side effects than oral micronized progesterone.	Level 2 *(Conditional)*
Recommendation 4	**Level of evidence** *(Strength of recommendation)*
Bed rest, HCG or drugs to relax the uterus are not recommended in the management of threatened miscarriage.	Level 1 *(Strong)*

2. Recurrent Miscarriage

Recommendation 5	Level of evidence *(Strength of recommendation)*
Based on clinical outcomes, we support the proposal by the American Society of Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE) to define recurrent miscarriage as two or more miscarriages.	Level 4 *(N/A)*

Recommendation 6	Level of evidence *(Strength of recommendation)*
• Consider progesterone therapy in women with unexplained recurrent miscarriages as it potentially reduces the rate of miscarriage.	Level 1 *(Strong)*
• There is some evidence that oral dydrogesterone, if initiated when fetal heart activity is confirmed, is effective.	Level 2 *(Strong)*
Recommendation 7	**Level of evidence** *(Strength of recommendation)*
There is no clear evidence to indicate the superiority of a particular progestogen, dose or mode of administration.	Level 4 *(Strong)*
Recommendation 8	**Level of evidence** *(Strength of recommendation)*
Consider initiating progesterone in women with one or more previous miscarriages if they present with bleeding in early pregnancy.	Level 2 *(Conditional)*

3. Luteal Phase Prophylaxis

Recommendation 9	Level of evidence *(Strength of recommendation)*
• Progesterone prophylaxis is recommended to support the luteal phase in patients undergoing IVF.	Level 2 *(Strong)*
• Progesterone prophylaxis should be started either on the day of, or the day after oocyte retrieval.	Level 2 *(Strong)*
• There is no clear evidence to indicate the superiority of a particular progestogen option, dose or mode of administration.	Level 1 *(Strong)*

4. Preterm Labour

Recommendation 10	Level of evidence *(Strength of recommendation)*
Vaginal progesterone should be considered in asymptomatic women with a short cervix, regardless of history of prior preterm births (PTB). The reviewers recognize that cervical shortening would only be detected in women who are screened. Management in women without risk factors should be in accordance to the individual unit's screening policy for the detection of cervical shortening.	Level 1 *(Strong)*

Recommendation 11	Level of evidence *(Strength of recommendation)*
Vaginal progesterone prophylaxis should be offered to women with twin pregnancies and a short cervix. However, this benefit cannot be extrapolated to higher order pregnancies at the time of writing.	Level 1 *(Strong)*

Recommendation 12	Level of evidence *(Strength of recommendation)*
There is insufficient evidence for progesterone to be used in the treatment of preterm labour, either as a tocolytic or for maintenance after tocolysis.	Level 1 *(Strong)*

5. Serum Progesterone Monitoring

Recommendation 13	Level of evidence *(Strength of recommendation)*
There is currently no role for serum progesterone monitoring before or after starting progesterone.	Level 2 *(Strong)*

Suggested clinical protocols on the use of progestogens

Condition	Dose	Initiation	Cessation
Threatened miscarriage			
• No previous miscarriage	Oral dydrogesterone 10 mg BD[1]		1 week after bleeding has stopped
• ≥1 previous miscarriage	Vaginal/PR micronized progesterone 400 mg BD[2] OR Oral dydrogesterone 10 mg BD[1]	At diagnosis	16 weeks gestation 1 week after bleeding has stopped
Prevention of recurrent miscarriage	Oral dydrogesterone 20 mg OD[3]	Once pregnancy diagnosed	Up to 20 weeks
Luteal phase support in IVF	Oral dydrogesterone 10 mg daily TDS[4],[5] OR Vaginal micronized progesterone 200 mg TDS[4] OR 8% intravaginal progesterone gel 90 mg daily[5] OR Vaginal progesterone pessaries 400 mg BD[6]	On the day of oocyte retrieval OR Day after retrieval	12 weeks
Prevention of preterm labour in singleton pregnancies	Vaginal micronized progesterone 200 mg OD[7],[8]	At the time of diagnosis of short cervix <25 mm and <24 weeks	36 weeks
Prevention of preterm labour in twins	Vaginal micronized progesterone 400 mg OD[9]	At the time of diagnosis of short cervix <25 mm and <24 weeks	36 weeks

Chapter 1: **Introduction**

A miscarriage is defined as a pregnancy loss from the time of conception until 24 weeks of gestation.[10] It is considered as one of the most common complications of pregnancy, affecting up to 20% of pregnant women.[11] In addition to causing excessive bleeding, infection and other possible complications related to surgical treatment[12], miscarriages may also cause substantial psychological harm, including anxiety, depression and post-traumatic stress disorder.[13],[14]

There is however a lack of consensus with regards to defining miscarriages, with some considering 20 weeks as the upper gestational limit.[15] We have defined the period of viability as 22+0 weeks of gestation, consistent with the definition of viability by the World Health Organization (WHO) and the Ministry of Health, Malaysia.[16],[17] Therefore, miscarriages would encompass any gestation below this threshold.

Approximately 50-70% of miscarriages are associated with chromosomal abnormalities in the conceptus, with autosomal trisomy, especially trisomy 16, triploidy and monosomy X being the predominant chromosomal aberrations reported in the first trimester.[18],[19],[20] A smaller potentially preventable proportion of miscarriages may be caused by luteal phase deficiency, while in the remainder, the cause is not known.

Progesterone is produced by the corpus luteum in the ovary and is required to prime the endometrium for embryonic implantation. It is this physiological importance that has prompted the utilization of progesterone supplementation in early pregnancy to prevent miscarriages, largely in two circumstances;[21] the first, in women who have started to bleed during early pregnancy in an attempt to preserve the pregnancy, while the second, to prevent further loss in asymptomatic women with previous unexplained recurrent miscarriage. As a natural extension of this logic, many have also indulged in the prophylactic use of progesterone to prevent miscarriages (without history of previous recurrent loss) and a more extended use to prevent preterm labour. On the other hand, progesterone may have a more well-defined role in patients undergoing assisted reproduction.

Threatened miscarriage is diagnosed when a woman experiences vaginal bleeding with a viable intrauterine pregnancy and a closed cervix.[22] It occurs in 15-20% of pregnancies. A diagnosis of threatened miscarriage is associated with a 2.6-fold increase risk of progressing to fetal loss, occurring in up to 25.9% of women in one study.[23],[24] Furthermore, threatened miscarriage has been identified as a risk factor for a myriad of adverse pregnancy outcomes including pre-eclampsia, preterm delivery, intrauterine growth restriction, preterm premature rupture of membranes and placental abruption.[25]

The number of miscarriages used to define recurrent pregnancy loss remain in equipoise. It has previously been defined as the loss of three or more consecutive pregnancies by the Royal College of Obstetricians and Gynaecologists, while the loss of two or more clinical pregnancies were considered significant by the ASRM.[26],[27] Similarly, the ESHRE guideline development group settled on defining it as the loss of two or more clinical pregnancies.[28] We have chosen to adopt the definition proposed by the ASRM and ESHRE.

The rationale for this is well-supported by a large study which found that the likelihood of detecting an abnormality after two losses was similar to that after three or four or more losses.[29] In a society where women are delaying pregnancy and have greater expectations of their healthcare providers, it would not be unreasonable to intervene after a second loss.

Approximately 0.5% to 2% of women experience recurrent loss.[30] While there are some well-defined causes of recurrent pregnancy loss, in almost 50% of cases, the aetiology cannot be determined, and is therefore classified as explained.[29],[31] It has been suggested that these unexplained recurrent losses may be due to immunologic factors.[32]

While primary recurrent loss and secondary recurrent loss can be distinguished, the significance of this distinction is unclear. Primary recurrent loss is not associated with a previous viable pregnancy whereas secondary is associated with one or more previous pregnancies progressing beyond the period of viability. One small observational study suggested that the prognosis in secondary loss was better.[33]

Given the importance of immunological and inflammatory changes in implantation, progesterone has been investigated for its role as an 'immunomodulator'.[34] Progesterone not only induces secretory endometrial changes, but also potentially promotes a favourable inflammatory milieu.

In addition to its possible role in threatened miscarriage and recurrent pregnancy loss of unknown aetiology, progesterone is also used extensively in women undergoing assisted reproduction. On a broader clinical context, progesterone is also used in other 'high risk' pregnancies beyond the first trimester, including in women with previous mid-trimester miscarriage and women with a short cervix.

This guideline synthesizes the available evidence in a concise manner and provides some guidance on the contemporary role of progesterone.

Chapter 2: The role of progesterone in maintaining pregnancy and inhibiting loss

Progesterone is an essential hormone in achieving implantation and maintaining a healthy early pregnancy based on different mechanisms such as modulation of maternal immune response[35],[36],[37] and suppression of the inflammatory response,[38] reduction of uterine contractility,[39],[40],[41] improvement of utero-placental circulation and luteal phase support.[42],[43]

Modulation of maternal immune response seems to play an important role in ensuring that the product of conception, which is recognized as a semi-allograft, is not rejected by the mother.[43] The presence of progesterone and its interaction with progesterone receptors at the decidual level influences the maternal defence strategy. Immune tolerance is established in the maternal decidua, specifically in the feto-maternal interface by suppression of T-cell reactions and inhibition of natural killer (NK) cells.[44],[45] Several immunological effects of progesterone are mediated by progesterone-induced blocking factor (PIBF), a protein with inhibitory effects on cell-mediated immunity secreted by lymphocytes.[46] In contrast, when an alteration of the complex local immune network occurs, the maternal immune cells will reject the embryo, leading to implantation failure (Figure 1).[43]

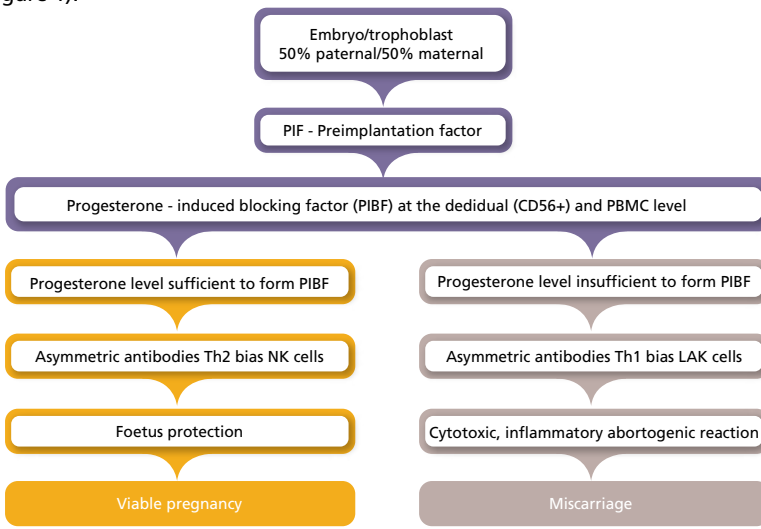


Figure 1. The pivotal role of progesterone receptor-mediated immunomodulation in successful pregnancy.
LAK cells: Lymphokine activated killer cell; NK: Natural killer cells; PBMC: Peripheral blood mononuclear cells

The association between pro-inflammatory cytokines and recurrent miscarriage may be attributed to an increase in cell-mediated immune response with a low antibody production. T helper cell 1 (Th1)-type cytokines [Interferon gamma (IFN-γ), interleukin-2 (IL-2), tumour necrosis factor alpha (TNF-α)] promote allograft rejection and compromise pregnancy.

On the other hand, T helper cell 2 (Th2)-type cytokines [Interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-10 (IL-10), transforming growth factor-beta 2 (TGF β2)], have an

opposite effect by inhibiting Th1 response, thereby promoting normal pregnancy. The circulatory cytokines levels are of Th2 bias in normal pregnancy and a Th1 bias in cases of recurrent miscarriages. IL-13, also a Th2-type cytokine, has been shown to be produced by human trophoblast cells.[46]

In women with a successful pregnancy, there are markedly higher concentrations of IL-4 and IL-10-producing T-cell clones, in both peripheral blood mononuclear cells (PBMC) and at the maternal–fetal interface, than are found in women with recurrent miscarriage.[47] Therefore one therapeutic target is to find drugs to downregulate pro-inflammatory cytokines or to up-regulate anti-inflammatory cytokines, or both.[43] Micronized progesterone and dydrogesterone are believed to have a role in this respect.[46]

Modulation of utero-placental circulation is another pertinent mechanism to sustain a healthy pregnancy. Oestrogen and progesterone have direct effects on the synthesis and release of angiogenic factors by placental cells, which regulates trophoblastic invasion and uterine artery remodelling. Progesterone activates decidual reaction in the endometrial stromal cells, influences vascular permeability and increases the number of uterine natural killer (uNK) cells. Progesterone also secretes various angiogenic factors to promote vascular development of the decidua during early pregnancy.[48],[49] In addition, it promotes the differentiation of decidual cells into endothelial and smooth muscle cells, consistent with a role in angiogenesis in the placenta.[50] It is believed that recurrent pregnancy loss is associated with increased uterine arterial impedance due to low level of progesterone.

The endometrial lining is also primed by progesterone to maintain early pregnancy once blastocyst implantation has occurred. Many studies suggest the role of luteal progesterone in establishing and maintaining pregnancy. The production of progesterone by the luteal cells depend on the availability of its circulating cholesterol substrate and is facilitated by a low-level luteinising hormone (LH) stimulation.[51] Luteal cells appear in two morphologic forms; small cells contain more LH and beta human chorionic gonadotrophin (bHCG) receptors while large cells have a greater capacity for steroidogenesis.[52] This combination provides mechanisms that allow responses to LH stimulation, hence maintaining the production of progesterone.

Uterine contractility is also suppressed by progesterone during pregnancy.[39],[40],[41] Its action is modulated by two progesterone receptors; progesterone receptor-A (PR-A) and progesterone receptor-B (PR-B), via ligand-activated gene expression. Progesterone appears to relax the myometrium by repressing the expression of genes. A study on mice has also found that progesterone represses the expression of two critical contraction-associated protein (CAP) genes, connexin43 (CNX43), which encodes a major gap-junction protein that helps synchronize contractile activity, and the oxytocin-receptor gene (OXTR), which determines the responsiveness of myometrial cells to oxytocin.[53] These genes were down regulated by miRNA- 200 in the mouse uterus; targeting specific repressive factors, zinc finger E-box binding homeobox proteins 1 and 2 (ZEB 1 and ZEB 2) which are also found in the human uterus. These exciting findings have opened doors to more discovery of novel pathways to explain the quiescent stage of the uterus during pregnancy.

Attempts to maintain pregnancy by ensuring that optimum levels of progesterone are achieved have been explored. It has been shown that a serum level of 25 ng/ml is associated with a lower risk of first trimester miscarriages in all reproductive women.[47] In addition, serum progesterone level has a linear increment in normal pregnancies from 5 to 13 weeks of gestation. This pattern is not observed in women with spontaneous miscarriages. Lower linear increment is usually associated with threatened miscarriages and a subsequent complete miscarriage at 16 weeks.[54]

Chapter 3: Basic science and pharmacology of progesterone

3.1 Introduction

Progesterone is a steroid hormone produced by the adrenal glands, and the gonads. The major physiological actions of progesterone include its effects on the uterus and ovaries, where it regulates induction of ovulation, facilitation of implantation and maintenance of early pregnancy.[55] Progesterone, a 21-carbon derivative of cholesterol, is hydrophobic and plays an important role in the pathway of hormonal synthesis; a precursor to oestrogen, testosterone and cortisol (Figure 2). The word progesterone is derived from the Latin word 'Gestare' meaning to 'bear' or 'carry'.[56]

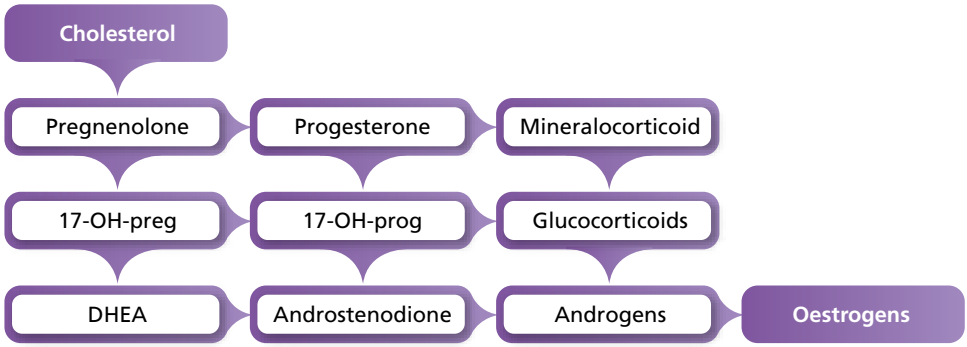


Figure 2. Synthesis of progesterone

DHEA: Dehydroepiandrosterone; 17-OH-preg: 17-hydroxypregnenolone; 17-OH-prog: 17-hydroxyprogesterone

3.2 Classification Of Progesterone

Unlike oestrogen which is a generic term for oestrogenic hormones, progesterone denotes a specific endogenous progestogen, while its synthetic counterpart is known as progestins. Progesterone are classified based on their structure and their sequence of introduction into the market. Both the natural progesterone and synthetic progestins interact not only with the progesterone receptor (PR) but also with other steroid receptors. Therefore, depending on the derivative molecule (either progesterone or testosterone), these progestins may, exert androgenic, anti- androgenic, mineralocorticoid or glucocorticoid-like effects.[57],[58]

3.2.1 Natural Progesterone

Natural progesterone is primarily obtained from plant sources such as soya bean and Mexican yam roots. It contains a steroid called diosgenin and is converted into progesterone. However, the human body is not able to make progesterone from diosgenin and eating wild yam roots will not increase the progesterone levels.[59],[60] Therefore, the term "natural progesterone" is a misnomer since all progesterone available in the market is synthesized in the lab.

The following are the benefits of natural progesterone:

- They are well-tolerated
- Well-established safety profile in pregnancy
- Multiple routes of administration
- Improved bioavailability
- Decrease high-density lipoprotein (HDL) cholesterol levels

Micronized progesterone is a form of natural progesterone used clinically in the prevention of threatened miscarriage and preterm labour.

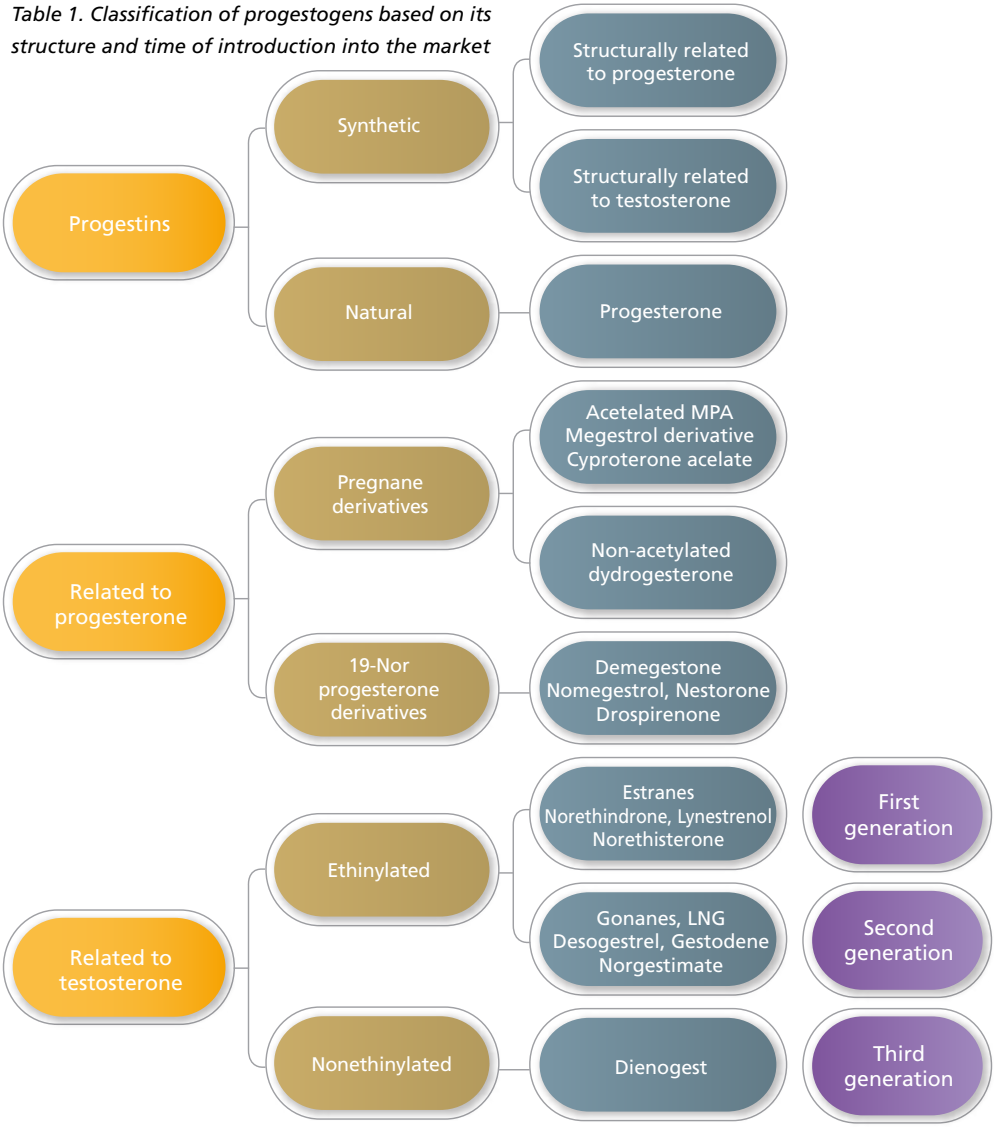
3.2.2 Synthetic Progesterone

These differ from natural progesterone in terms of its interaction with other receptors, videlicet androgen effects such as acne, glucocorticoid effects such as salt and water retention, bloating or mineralocorticoid effects such as decreased weight and water retention.[61] Anti-androgenic progestins may act by exerting competitive inhibition of the androgen receptor or bind to the enzyme 5-alpha reductase and inhibit the conversion of testosterone into dihydrotestosterone, its active metabolite. The synthetic progestins used in clinical practice are derived either from testosterone (19-nortestosterone) or progesterone (17-OH progesterone and 19- norprogesterone). Of note, the designation of first-, second-or third-generation progestin is based on time since market introduction and not on structural and physiologic differences or efficacy.[62],[63],[64] Dydrogesterone is a synthetic progesterone with enhanced oral bioavailability and is referred to as a retroisomer of natural progesterone. It is widely used in the prevention of threatened miscarriage with its exceptional progestogenic effects and negligible androgenic, glucocorticoid and mineralocorticoid effects.

3.3 Mechanism Of Action

The primary action of progesterone is through the intracellular progesterone receptors, with A and B receptors as the major forms. The progesterone-receptor complex interacts with nuclear deoxyribonucleic acid (DNA), producing messenger RNA (mRNA) which is transported to the ribosomes resulting in cytoplasmic synthesis of proteins with specific cellular activity.[65] The progesterone receptor is induced by oestrogens at the transcriptional level and decreased by progestin at both the transcriptional and translational levels through receptor phosphorylation. The metabolic effects of progesterone are amplified in the presence of oestrogen.[66] The structural classification of progestogens and its respective timelines of introduction into the market are depicted in Table 1.

Table 1. Classification of progestogens based on its structure and time of introduction into the market



LNG: Levonorgestrel; MPA: Medroxyprogesterone acetate

3.4 Physiological Effects Of Progesterone

The extent to which the progestational effects are maximized and androgenic effects are minimized is referred to as progestational selectivity. A selective progestin has progestational effects at relatively low concentrations or doses and androgenic effects at only relatively high concentrations or doses. To minimize the androgenic side effects associated with the older progestins, the doses

used in oral contraceptives (OC) have been reduced over the years. These measures have decreased the potential for undesired androgenic effects but also have negatively affected cycle control. Newer generation of progestins generally have higher progestational selectivity.[67],[68] The metabolic effects of selected progestins in comparison to progesterone are listed in Table 2, while the types of progesterone and their respective routes of administration are listed in Table 3.

Table 2. Metabolic effects of selected progestins compared to progesterone

	Progestational activity	Anti-mineralocorticoid activity	Glucocorticoid activity	Androgenic activity	Anti-androgenic activity
Progesterone	+	Moderate	None	None	Weak
Dydrogesterone	+	Weak	None	None	Weak
Cyproterone acetate	+	None	Weak	None	Very strong
Dienogest	+	None	None	None	Moderate
Drospirenone	+	Moderate	None	None	Moderate
Medroxyprogesterone	+	None	Weak	Moderate	None
Norethisterone	+	None	None	Moderate	None
Norgestimate	+	None	None	Moderate	None
Levonogestrel	+	None	None	Strong	None
Desogestrel	+	None	None	Moderate	None
Gestodene	+	Weak	None	Moderate	None
Nestorone	+	None	None	None	None
Trimegestone	+	Weak	None	None	Weak

(+) effective, (+) weakly effective (-) not effective

Table 3. Types of progesterone and their routes of administration in clinical practice

Types of progesterone	Routes of administration
Micronized progesterone	Oral, vaginal gel, or suppository
17α-hydroxy progesterone caproate	Intramuscular injection
Dydrogesterone	Oral

3.5 Pharmacokinetics

The pharmacotherapeutic considerations determine the chosen route of administration of progestogens. In general, absorption of any drug from the site of administration is dependent on three factors; (1) the pharmaceutical form such as tablets, suppositories, gel etc; (2) the solubility of the drug at the tissue level; (3) the hematic flow at the tissue level.

Natural progesterone is available as oral, injectable and intravaginal formulations. Oral micronized progesterone is developed by the process of micronizing as its name suggests, designed to increase the half-life of progesterone and reduce its destruction in the gastrointestinal tract.[69],[70],[71] The serum concentrations reach maximal levels much more rapidly with micronized progesterone than with injected progesterone. The routes of administration of progesterone and their respective effects are detailed in Table 4.

Table 4. Routes of administration of progesterone and their effects

Route of administration	Pharmacokinetics	Clinical consideration	Side effects
Oral	a. Rapid metabolism and clearance rate b. Poor bioavailability c. Enterohepatic passage results in formation of secondary (2^0) metabolites d. 2^0 metabolites such as 5a- and 5b-reduced pregnanolone have a high affinity for Gamma-Aminobutyric Acid (GABA) receptors present in the reproductive organs and their activation may adversely affect pregnancy outcomes[72]	a. High acceptability b. Requires higher and more frequent dosing c. 2^0 Metabolites cause adverse effects such as dizziness and nausea d. Micronized formulation has the advantage of reduced intestinal passage and thus, adverse effects[66],[67] e. Oral micronized progesterone has lower implantation rates per embryo compared to intramuscular (IM) in luteal phase support for in vitro fertilization (IVF) cycles[73]	Sleepiness, fatigue, headaches and gastrointestinal disturbances[74]
Vaginal	Rapid absorption and avoids first-pass hepatic metabolism	a. Allows increased bioavailability at target tissues such as the endometrium, without requiring high plasma levels, thus reducing side effects b. In assisted reproduction, vaginal progestins appears to have lower pregnancy rates compared to IM[75],[76],[77]	Vaginal discharge in 8-9%[78]

Route of administration	Pharmacokinetics	Clinical consideration	Side effects
Intramuscular (IM)	Perhaps more aptly described as 'intragluteal administration', injection into the gluteus results in a longer half-life compared to other sites, such as the deltoid. This is referred as the depot effect and is related to the adiposity of the muscle, to which progesterone shows a high affinity[79]	Allows a single daily administration of progestins despite a short plasma half-life (5-20 min)	Injection site reactions and urticaria (3.1%)[74]
Others	a. Transdermal route is convenient and offers good compliance. Does not achieve adequate plasma level as the lipophilic progesterone is not easily absorbed by the skin[80] b. Other routes of administration such as rectal, sublingual and trans-nasal are without much bibliographic support[81]		

Chapter 4: The role of progestogens in the management of threatened miscarriage

4.1 Overview

Progesterone secreted by the corpus luteum is essential for the maintenance of early pregnancy. The most recent Cochrane review on the use of progesterone for this specific indication included seven trials involving 696 participants, with low to moderate quality of evidence.[82] The results indicated that treatment of threatened miscarriage with progestogens compared to placebo or no treatment probably reduces the risk of miscarriage; (risk ratio (RR): 0.64; 95% confidence interval (CI): 0.47 to 0.87; 7 trials; 696 women), while treatment with oral progestogen compared to no treatment also probably reduces the miscarriage rate (RR 0.57, 95% CI 0.38 to 0.85; 3 trials; 408 women). However, treatment with vaginal progesterone compared to placebo, probably has little or no effect in reducing the miscarriage rate (RR: 0.75; 95% CI: 0.47 to 1.21; 4 trials; 288 women). The review thus concluded that treatment of threatened miscarriage with progestogens compared to placebo or no treatment probably reduced the risk of miscarriage. However, the use of vaginal progesterone probably had little or no effect when compared to placebo.

Recommendation 1	Level of evidence *(Strength of recommendation)*
In women without prior history of a miscarriage;	
• Oral dydrogesterone can be considered. The quality of included studies however, were low to moderate.	Level 1 *(Conditional)*
• Micronized vaginal progesterone is not recommended.	Level 1 *(Strong)*

By far the largest to date, the recently published Progesterone in Early Pregnancy Bleeding (PRISM) trial was a multicentre, randomized, double-blinded, placebo- controlled trial.[2] A total of 12,862 women were eligible, of which 4153 were randomly assigned to receive either progesterone (2079 women) or placebo (2074 women). The trial showed that among women with bleeding in early pregnancy, progesterone therapy administered during the first trimester of pregnancy did not result in a significantly higher incidence of live births. However, subgroup analysis showed that progesterone had possible benefits in women with bleeding in early pregnancy and a previous history of miscarriage. Interestingly, 8709 or two-thirds of the 12862 women who were eligible for randomization declined to participate.

An economic evaluation subsequent to this, using the same PRISM cohort found that progesterone was likely to be a cost-effective intervention in women with a previous miscarriage. Despite an additional £76 per patient in the progesterone arm, the cost-effectiveness acceptability curve for the base-case analysis was favorable. The discordance between clinical and health economic outcome was attributable to the estimation and quantification of the uncertainty around clinical end-points.[83]

A recent meta-analysis of ten randomized controlled trials included findings from PRISM and specifically re-examined live birth as the primary outcome. The authors found that progestogens increased the incidence of live birth (RR 1.07,95% CI 1.00 to 1.15; P=0.04; I2 =18%) but the benefit was only seen in with oral progestogen (RR 1.17, 95% CI 1.04 to 1.31; P=0.008; I2 =0%) and not in vaginal progestogen (RR 1.04, 95% CI 1.00 to 1.08; P=0.07; I2 =0%;). Similarly, oral progestogen reduced the risk of miscarriage (RR 0.73, 95% CI 0.59 to 0.92), but not when administered vaginally.[84]

Recommendation 2	Level of evidence *(Strength of recommendation)*
In women with a history of ≥1 previous miscarriage; • Micronized progesterone 400 mg twice daily per vagina/ rectal or oral dydrogesterone 10 mg BD from the onset of bleeding up till 16 weeks of pregnancy may be considered.	Level 2 *(Conditional)*

A small, open-labelled randomized controlled trial involving 141 women directly investigated the efficacy of oral micronized progesterone compared to dydrogesterone.[85] The authors did not find any difference in the primary outcome of miscarriage prior to 16 weeks of gestation (10.2% micronized progesterone versus 15.2% dydrogesterone; p=0.581) or resolution of bleeding by day 4-10 (89.7% micronized progesterone versus 96.6% dydrogesterone; p=0.272). Significantly more women on oral micronized progesterone complained of drowsiness and giddiness during treatment.

Recommendation 3	Level of evidence *(Strength of recommendation)*
Dydrogesterone may be associated with fewer side effects than oral micronized progesterone.	Level 2 *(Conditional)*

4.2 Other treatment options in threatened miscarriage

4.2.1 Bed rest

Bed rest is perhaps the most frequently dispensed advice in the management of threatened miscarriage. However, there is little evidence of its value. Physical activity is rarely associated with an increased risk of miscarriage. In fact, a sedentary lifestyle can lead to a number of other complications such as thromboembolic events, back pain, muscle atrophy and bone loss.[86]

4.2.2 Human chorionic gonadotrophin (HCG)

A meta-analysis showed that there was no significant difference in the incidence of miscarriage between HCG and "no HCG" (placebo or no treatment) groups. When HCG and bed rest alone were compared, there was a significant reduction in the risk of miscarriage. Good quality research is needed to assess the impact of HCG on miscarriage.[87]

4.2.3 Uterine Muscle Relaxants

Uterine muscle relaxant drugs have been used for threatened miscarriage in an attempt to relax the uterine muscle and thus reduce the risk of miscarriage. There was only one poor quality trial with 170 women studying beta-agonist, a tocolytic, to prevent miscarriage compared to placebo. The results demonstrated a lower risk of intrauterine death (miscarriage and stillbirth) in the beta agonist group (RR: 0.25; 95% CI: 0.12 to 0.51), but no difference in preterm birth. Overall, there is insufficient evidence to recommend uterine muscle relaxants to prevent threatened miscarriage.[88] A proportion of miscarriages are caused by genetic abnormalities and its unlikely that progestogens could prevent a miscarriage of this aetiology.

Recommendation 4	Level of evidence *(Strength of recommendation)*
Bed rest, HCG or drugs to relax the uterus are not recommended in the management of threatened miscarriage.	Level 1 *(Strong)*

4.3 Key messages

- In women with threatened miscarriage, the benefit of progesterone appears to increase with the number of previous miscarriages experienced
- The largest trial involving women with threatened miscarriage and previous pregnancy losses were performed using micronized progesterone

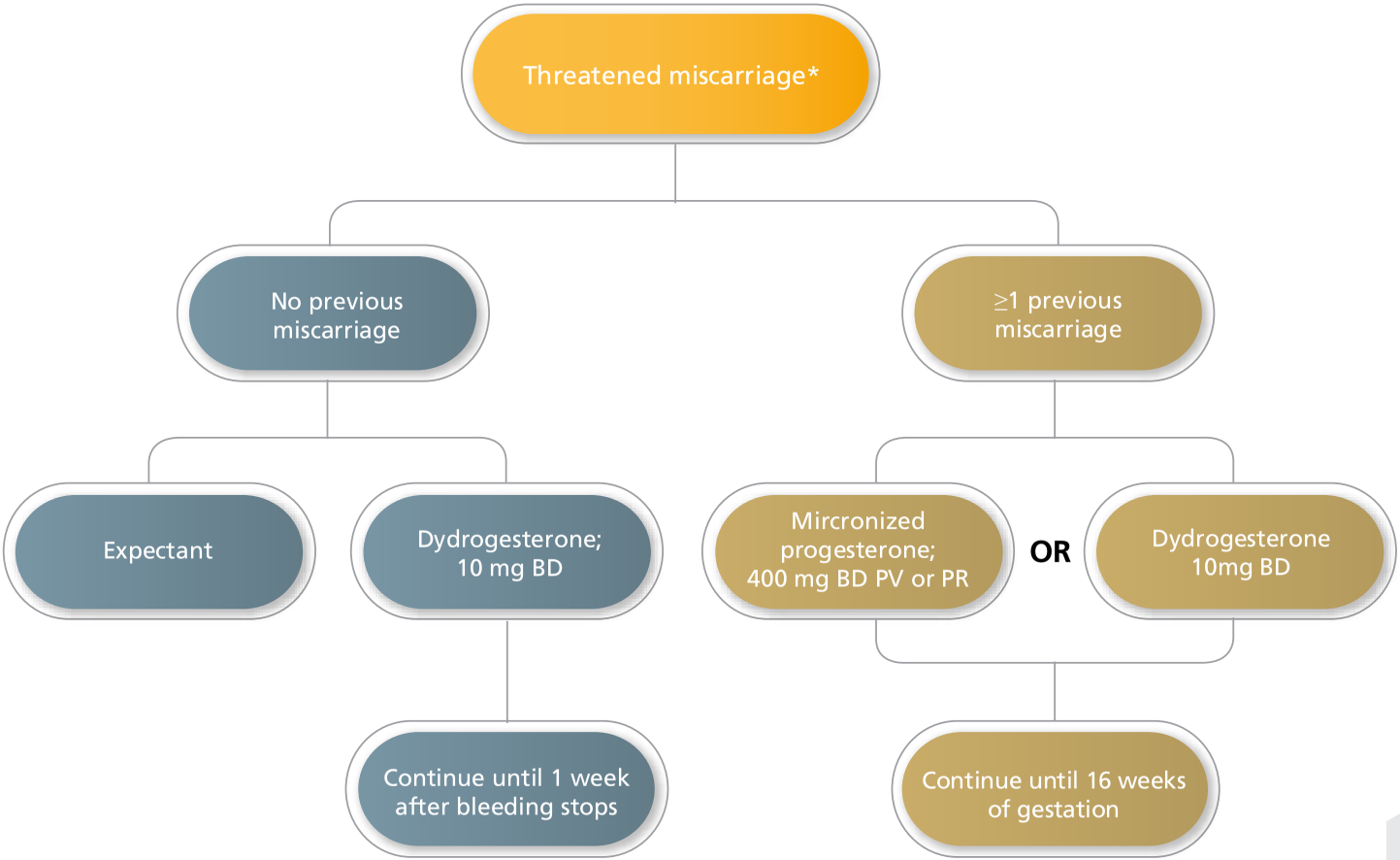


Figure 3. Clinical algorithm for threatened miscarriage
*Embryonic or fetal cardiac activity present OR Mean sac diameter <25 mm without embryonic pole OR Embryonic cardiac activity absent <7 mm crown rump length

Chapter 5: The role of progestogens for preventing miscarriage in women with recurrent pregnancy loss of unknown aetiology

5.1 Overview

An earlier Cochrane review of all randomized or quasi-randomized controlled trials compared progestogens with placebo or no treatment, given in an attempt to prevent miscarriage.[89] The reviewers found that while there was no evidence to support the routine use of progestogen in early to mid-pregnancy, there appeared to be improved outcomes in women with a history of recurrent loss (average RR: 0.69; 95% CI: 0.51 to 0.92; 11 trials; 2359 women; moderate-quality evidence). A more recent Cochrane review then reanalysed data from trials specific to women with recurrent miscarriages and suggested that there may be a reduction in the number of miscarriages for women given progestogen supplementation compared to placebo or controls (average RR: 0.73, 95% CI: 0.54 to 1.00, 10 trials; 1684 women; moderate quality evidence).[90] A subgroup analysis comparing placebo-controlled versus non-placebo-controlled trials of women with three or more prior miscarriages compared to women with two or more miscarriages and different routes of administration showed no clear differences in rates of miscarriage. Furthermore, there was probably a slight benefit for women receiving progestogen seen in the outcome of live birth rate. It was therefore concluded that for women with unexplained recurrent miscarriages, supplementation with progestogen therapy probably reduces the rate of miscarriage in subsequent pregnancies.

One of the trials included in this most recent Cochrane Review was a randomized double-blinded trial involving 388 patients with recurrent pregnancy loss comparing 20 mg dydrogesterone daily to placebo. The trial demonstrated that the incidence of a further miscarriage was 2.4 times higher in the placebo group (RR: 2.4; 95% CI: 1.3 to 5.9), thereby supporting the use of dydrogesterone to improve pregnancy outcomes.[3]

Recommendation 5	Level of evidence *(Strength of recommendation)*
Based on clinical outcomes, we support the proposal by the American Society of Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE) to define recurrent miscarriage as two or more consecutive miscarriages.	Level 4 *(N/A)*

Recommendation 6	Level of evidence *(Strength of recommendation)*
• Consider progesterone therapy in women with unexplained recurrent miscarriages as it potentially reduces the rate of miscarriage.	Level 1 *(Strong)*
• There is some evidence that oral dydrogesterone, if initiated when fetal heart activity is confirmed, is effective.	Level 2 *(Strong)*

The Progesterone in Recurrent Miscarriages (PROMISE) in 2015 compared micronized progesterone at a dose of 400 mg twice daily to vaginal placebo capsules, from soon after a positive urinary pregnancy test (and no later than 6 weeks gestation) until 12 completed weeks, with the primary outcome being live birth after 24 weeks of gestation.[91] A total of 836 women who conceived naturally within 1 year were randomized. In an intention-to-treat analysis, the rate of live births was 65.8% (262 of 398 women) in the progesterone group and 63.3% (271 of 428 women) in the placebo group (RR: 1.04; 95% CI: 0.94 to 1.15; rate difference: 2.5 percentage points; 95% CI, –4.0 to 9.0). There were also no significant inter-group differences in the rate of adverse events including the incidence of congenital anomalies and specifically genital anomalies.

The ESHRE guideline concluded that vaginal progesterone in early pregnancy was of no benefit in women with unexplained recurrent pregnancy loss. However, it acknowledged that there was some evidence of efficacy when oral dydrogesterone was initiated at the time of confirmation of fetal heart activity.[28]

Another recent systematic review and meta-analyses included 21 randomized controlled trials that assessed a myriad of therapeutic options in recurrent pregnancy loss and concluded that treatment with progestogens starting in the luteal phase seemed effective in increasing live birth rate but not when started after conception.[92] No head-to-head randomized controlled trial (RCT) has been conducted specifically to compare the various progesterone options, doses or the modes of administration.

Recommendation 7	Level of evidence *(Strength of recommendation)*
There is no clear evidence to indicate the superiority of a particular progestogen option, dose or mode of administration.	Level 4 *(Strong)*

In May 2019, the findings of the PRISM trial, the largest controlled randomized trial of progesterone treatment of threatened miscarriages was published.[2] A sub-group analysis found that women who had had three or more previous miscarriages benefited from progesterone treatment if they presented with bleeding in early pregnancy.

Recommendation 8	Level of evidence *(Strength of recommendation)*
Consider initiating progesterone in women with one or more previous miscarriages if they presented with bleeding in early pregnancy.[21]	Level 2 *(Conditional)*

5.2 Key Messages

- Progestogen should be considered in women with unexplained recurrent miscarriage as it potentially reduces the rate of miscarriage.
- There is some evidence that oral dydrogesterone, if initiated when fetal heart activity is confirmed is effective.
- Vaginal progesterone is unlikely to be of benefit in women with unexplained recurrent pregnancy loss in women without bleeding in early pregnancy.
- There is no clear evidence to indicate the superiority of a particular progestogen option, dose or mode of administration.

Chapter 6: The role of prophylactic use of progestogens to prevent pregnancy loss

6.1 Introduction

Historically, progesterone has been used to prevent miscarriages and PTB, especially in women perceived to be at risk. Although a pregnancy at 'high risk' of miscarriage or PTB has not been explicitly defined, the literature identifies various risk factors such as conception via assisted reproductive techniques (ART), history of recurrent pregnancy loss, previous preterm deliveries and multiple pregnancy. Patient-related risk factors such as advanced maternal age, uterine anomalies and previous cervical surgery have also been identified.[93],[94],[95]

Conversely, a 'low-risk' pregnancy would be defined as a natural conception with no known risk factors. There would be a large proportion of pregnancies that fall in the grey area between these two distinct groups and in such cases, clinical judgement is imperative.

6.2 Luteal Phase Support

The most recent Practice Committee of ASRM in 2015 reaffirms the use of progesterone supplementation for luteal phase support in patients undergoing ART procedures.[96] A Cochrane review by van der Linden reported that progesterone given during the luteal phase was associated with higher rates of live birth or ongoing pregnancy compared with placebo or no treatment.[97] The evidence was not conclusive due to the high risk of bias in most domains of the 94 randomized controlled trials that were analysed. Barbosa and colleagues also supported the routine use of luteal support in IVF cycles that utilized either the gonadotrophin-releasing hormone analogue (GnRHa) or antagonist protocol.[98]

6.2.1 Route Of Administration

Nine different progesterone regimens were compared in the Cochrane review above, namely IM versus oral, IM versus vaginal/rectal, vaginal/rectal versus oral, low-dose versus high-dose vaginal, short versus long protocol, micronized versus synthetic, vaginal ring versus gel, subcutaneous versus vaginal gel and vaginal versus rectal. The summary of this review indicated no difference in the routes of administration. Interestingly there was a higher live birth rate when GnRHa was added to the progesterone during the ART cycles.[97]

6.2.2 Dosing

van der Linden also included the dosage of vaginal progesterone in the review. Five studies compared a low dose (≤100 mg) with a high dose (≥100 mg) and reported no difference in live birth or ongoing pregnancy rate (Odds ratio [OR]: 0.97; 95% CI: 0.84 to 1.11; 3720 women).

6.2.3 Types Of Progestogens

While micronized vaginal progesterone has conventionally been regarded as the preferred option for luteal support, two recent double-blinded randomized control trials (Oral Dydrogesterone versus Micronized Vaginal Progesterone for Luteal Support in IVF [LOTUS I] & Oral Dydrogesterone versus Intravaginal Micronized Progesterone Gel for Luteal Phase Support in IVF [LOTUS II]) showed no difference in live birth rate (34.4% [170/494] versus 32.5% [159/489] between oral dydrogesterone and vaginal progesterone (micronized or vaginal gel).[4],[5]

6.2.4 Timing Of Initiation Of Progestogens

One RCT comparing starting luteal phase support with progesterone on the day of oocyte retrieval, versus the day after oocyte retrieval reported no significant difference in live birth rate (46.6% [48/103] versus 45.7% [43/94]).[99] On the other hand, three RCTs which compared starting progesterone on the evening of oocyte retrieval with starting on the evening of embryo transfer reported no significant difference in clinical pregnancy rate.[100],[101],[102]

6.2.5 Duration Of Progestogen Prophylaxis

A meta-analysis of six RCTs found comparable live birth rate (RR: 0.95; 95% CI: 0.86 to 1.05; 369 women) and ongoing pregnancy rate (RR: 0.97; 95% CI: 0.90 to 1.05; 1066 women) when stopping progesterone for luteal phase support at the time of pregnancy test or continuing it longer until 6 to 7 weeks of gestation.[103]

Recommendation 9	Level of evidence *(Strength of recommendation)*
• Progesterone prophylaxis is recommended to support the luteal phase in patients undergoing IVF.	Level 2 *(Strong)*
• Progesterone prophylaxis should be started either on the day of, or the day after oocyte retrieval.	Level 2 *(Strong)*
• There is no clear evidence to indicate the superiority of a particular progestogen option, dose or mode of administration.	Level 1 *(Strong)*

6.3 Prophylaxis In Women With Previous Preterm Birth

PTB complicates between 7-12% of all births yet accounts for more than 85% of all perinatal morbidity and mortality. Its aetiology is multifactorial and pathophysiological mechanisms include intrauterine infection, cervical insufficiency and increased uterine stretch/distension in the cases of multiple pregnancies.[104] PTB can broadly be classified as spontaneous or medically-indicated ("iatrogenic"). A previous PTB is the strongest predictor for a subsequent PTB.[105] However, approximately 20% of preterm deliveries are due to various maternal or fetal indications such as severe preeclampsia or fetal growth restriction. The term medically-indicated PTB has been proposed to describe this subgroup. Clearly, progesterone has no role in these women.

Cervical shortening is a known risk factor for PTB in both low and high risk populations.[106] The relative risk of preterm birth was estimated at 6 if <26mm (10th centile), 9 <22mm (5th centile),

14 if <13mm (1st centile).[104] The majority of studies on cervical length were performed in mid-trimester, coinciding with morphology screening, using thresholds of below 20 mm or 25 mm for intervention and these cut-offs remain the most frequently used in clinical practice.[105] The ability of clinicians to identify women at high risk of preterm birth has improved due to the introduction of transvaginal cervical length measurements and the expanding use of biochemical markers such as cervicovaginal fetal fibronectin testing.[107],[108]

A meta-analysis in 2005 found singleton women with history of spontaneous preterm birth (PTB), including preterm labour and premature rupture of membranes, who received 250 mg intramuscular 17-α-hydroxy-progesterone caproate (17P) weekly, had lower rates of recurrent PTB (29.3% versus 40.9%; OR: 0.45; 95% CI: 0.22 to 0.93). In addition, subjects allocated to receive 17P had lower rates of birth weight less than 2500g. No differences in rates of hospital admissions for threatened preterm labour or perinatal mortality were noted for subjects receiving progestational agents in general or for those receiving only 17P specifically.[109]

Hassan et. al. demonstrated that in a cohort of 458 women, the progesterone group had a lower rate of preterm birth before 33 weeks compared to placebo. Vaginal progesterone was also associated with a significant reduction in the rate of preterm birth before 28 weeks and 35 weeks, respiratory distress syndrome and birth weight <1500 g.[110]

A subsequent literature review of all randomized trials between 2003 and 2017 reaffirmed that only two modes of progesterone administration were effective, weekly intramuscular injections of 17P and daily administration of vaginal progesterone suppository of 100-200 mg in preventing further PTB, in singleton pregnancies with previous PTB.[108] The purported efficacy of IM 17P and the American College of Obstetricians and Gynecologists (ACOG) recommendation is largely based on data from Meis et al, although the recent trial, 17P to Prevent Recurrent Preterm Birth in Singleton Gestations (PROLONG) has brought us back to the drawing board.[8],[111] This trial which recruited four times more women, including women outside of the United States, showed that 17P did not reduce the risk of preterm labour. Of note, the racial and social demographics in the PROLONG study appear to reflect women of a lower risk group.

The safety of progesterone in pregnancy is supported by several epidemiological studies and clinical trials, although a recent meta-analysis has suggested an increased risk of gestational diabetes with 17P.[112],[113],[114] This risk has not been demonstrated with vaginal progesterone.[114]

For a brief period, questions were raised on the efficacy of progesterone after the publication of the Vaginal Progesterone Prophylaxis for Preterm Birth (OPPTIMUM) trial in the Lancet in 2016. The results of that trial showed that vaginal progesterone did not significantly reduce the risk of preterm birth or perinatal morbidity and mortality in the entire population, or in the subgroup of women with a cervical length ≤25 mm. Needless to say, this created significant confusion amongst clinicians and international obstetric societies. A closer look at OPPTIMUM however, revealed that this study had a very broad inclusion criteria, where more than a quarter of women did not even have a short cervix. Furthermore, there were methodological concerns about the interval between diagnosis, randomization and starting progesterone in high risk women.

The National Institute for Health and Care Excellence (NICE) in the UK suggests a cut-off of 25 mm be used for intervention, with vaginal progesterone again being the first line for women with no prior PTB but a short cervix of <25 mm. However, in women with prior PTB, it recommends either

vaginal progesterone or cervical cerclage. Cervical cerclage was recommended as a first line in women deemed to be at the highest risk; those with a short cervix of <25 mm and either a history of preterm prelabour rupture of membranes (PPROM) or cervical surgery.[117]

In addition, OPPTIMUM did in fact find a reduction in neonatal brain injury and neonatal death but these were not given sufficient emphasis compared to the composite primary outcome, which was non-significant.[113]

Romero et. al. then performed a meta-analysis using individual patient data, including five high quality trials and OPPTIMUM to resolve this controversy. A total of 974 women (498 allocated to vaginal progesterone, 476 allocated to placebo) with a cervical length ≤25 mm was included and it was found that vaginal progesterone was associated with a significant reduction in the risk of PTB <33 weeks of gestation. Moreover, vaginal progesterone significantly decreased the risk of respiratory distress syndrome, composite neonatal morbidity and mortality, birthweight <1500 and <2500g and admission to the neonatal intensive care unit.[7]

Conde- Agudelo et. al. showed that vaginal progesterone was as effective as performing a cervical cerclage in women who could be considered at the highest risk of preterm birth.[115] The authors made an indirect comparison meta-analysis in a cohort of women with singleton pregnancy, previous spontaneous PTB and a short cervix. Five trials that compared vaginal progesterone versus placebo (265 women) and another five that compared cerclage versus no cerclage (504 women) were included. Vaginal progesterone, compared to placebo, significantly reduced the risk of PTB <35 and <32 weeks of gestation, composite perinatal morbidity/mortality, neonatal sepsis, composite neonatal morbidity, and admission to the neonatal intensive care unit. Cerclage, compared to no cerclage, significantly decreased the risk of PTB <37, <32, and <28 weeks of gestation, composite perinatal morbidity/mortality, and birthweight <1500 g. Vaginal progesterone and cerclage were found to be comparable in terms of the reduction of PTB and adverse perinatal outcomes.

Recommendation 10	**Level of evidence** *(Strength of recommendation)*
Vaginal progesterone should be considered in asymptomatic women with a short cervix, regardless of history of prior preterm births (PTB). The reviewers recognized that cervical shortening would only be detected in women who are screened. Management in women without risk factors would therefore depend on the individual unit's screening policy for the detection of cervical shortening.	Level 1 *(Strong)*

6.3.1 From Evidence To Recommendations

The Society for Maternal-Fetal Medicine (SMFM) in North America recommends that women with singleton pregnancies, no prior PTB and short cervical length (CL) of 20 mm at 24 weeks receive vaginal progesterone. In singleton pregnancies with prior PTB 20+0 to 36+6 weeks, 17P given intramuscularly weekly, preferably starting at 16-20 weeks until 36 weeks, is recommended. On the other hand, in women with prior PTB, if the transvaginal ultrasound CL shortens to 25 mm at 24 weeks, cervical cerclage may be offered.[116]

However, subsequent to the release of both guidelines above, further meta-analysis have suggested that progesterone provides the most consistent benefit in prevention of preterm labour, compared to cervical cerclage. This was effect was seen in both women with or without prior PTB, therefore giving rise to our recommendation above.[115],[118],[119]

6.4 Prophylaxis In Multiple Pregnancies

Evidence from an updated individual patient meta-analysis by Romero et al. showed that progesterone supplementation prolonged gestation and improved perinatal outcomes in women with twin pregnancies and a short cervix.[9] This contradicts earlier clinical trials which did not take into consideration the cervical length when starting progesterone.[74],[120] Further studies are required in this area as the outcome of the meta-analysis was significantly influenced by a single study.

A trial involving 134 healthy women with triplet pregnancies on the other hand, showed that the rate of fetal loss or preterm birth <35 weeks was similar between women assigned to receive 17P and placebo from 16 to 21 weeks through 35 weeks of gestation.[121] Similarly, another placebo-controlled, randomized trial of prophylactic 17P supplementation in 81 cases of triplet pregnancy also found no benefit, as well as a possible increase in mid-trimester pregnancy loss.[122]

Recommendation 11	Level of evidence *(Strength of recommendation)*
Vaginal progesterone prophylaxis should be offered to women with twin pregnancies and a short cervix. However, this benefit cannot be extrapolated to higher order pregnancies at the time of writing.	Level 1 *(Strong)*

6.5 Progestogens In The Treatment Of Preterm Labour

The previous sections have described the use of progesterone in prevention of preterm labour, in a subset of asymptomatic women with short cervix (prophylaxis). This should be distinguished from its application in symptomatic women with preterm labour (treatment), where progesterone has been used for tocolysis or maintenance after successful tocolysis. It is also imperative that we remain cognizant of the route and type of progesterone used in each recommendation, in addition to the specific population it is used for (e.g. singleton vs multiple pregnancy).

Progesterone has a concentration-dependent relaxant effect on spontaneous myometrial contractile activity and is thought to modulate potassium channel activity, allowing direct inhibition of contractions. In addition, progesterone may also act by sensitizing the uterus to tocolytics.[123]

6.5.1 Progestogens for tocolysis

The goals of tocolysis has remained unchanged over the years; to allow time for in-utero transfer and completion of antenatal steroids and magnesium sulphate for neuroprotection.

One randomized trial involving only 57 women in the 1980s, compared 400 mg of oral progesterone vs. placebo. The results showed that oral progesterone significantly reduced uterine activity (defined by frequency of uterine contractions), although the rate of decline was slower than that achieved with beta mimetics.[124]

Two trials examined the use of 17P as a primary tocolytic agent compared to either placebo or nifedipine and bed rest. Neither trial reported on preterm birth less than 37 weeks or latency until delivery as outcomes. Both 17P and nifedipine resulted in reduced uterine activity, although this effect was achieved earlier with nifedipine.[125],[126]

Perhaps more relevant to our setting, one local trial investigated the use of progesterone as an adjunct to primary tocolysis with nifedipine. 112 women were randomized to a single injection of 17P or placebo, in addition to nifedipine.[127] There was a trend towards fewer deliveries within 48 hours and 7 days with 17P, although this was not significant and the trial terminated early due to slow enrolment. There was also no difference in the rates of PTB less than 37 weeks and latency to delivery. We did not identify any trials reporting the use of vaginal progesterone as the primary tocolytic agent.

6.5.2 Progestogens For Maintenance After Tocolysis

A meta-analysis of five randomized trials included 426 women with a singleton gestation who received 17P maintenance tocolysis. Women who received 17P for arrested preterm labour had a similar rate of PTB <37 weeks (42% vs 51%; relative risk [RR], 0.78; 95% confidence intervals [CI], 0.50-1.22) and PTB <34 weeks (25% vs 34%; RR, 0.60; 95% CI, 0.28-1.12) compared to controls.[128]

However, women who received 17P had significantly later gestational age at delivery (mean difference, 2.28 weeks; 95% CI, 1.46-13.51), longer latency (mean difference, 8.36 days; 95% CI, 3.20-13.51), and higher birthweight (mean difference, 224.30 g; 95% CI, 70.81-377.74) as compared to controls. Although women on 17P were randomized about half a week later in terms of gestation age at the point of randomization, they delivered about 2 weeks later compared to controls. Other secondary outcomes including incidences of recurrent preterm labour, neonatal death, admission to neonatal intensive care unit, neonatal respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular haemorrhage, necrotizing enterocolitis, and neonatal sepsis were similar in both groups.

A meta-analysis of 441 singleton pregnancies across five randomized trials found that women who received vaginal progesterone for arrested preterm labour had a significantly lower rate of preterm birth <37 weeks (42% vs 58%; RR, 0.71; 95% CI, 0.57-0.90; 3 trials, 298 women), longer latency to delivery (mean difference 13.80 days; 95% CI, 3.97-23.63; 4 trials, 368 women), later gestational age at delivery (mean difference 1.29 weeks; 95% CI, 0.43-2.15; 4 trials, 368 women), lower rate of recurrent preterm labour (24% vs 46%; RR, 0.51; 95% CI, 0.31-0.84; 2 trials, 122 women), and lower rate of neonatal sepsis (2% vs 7%; RR, 0.34; 95% CI, 0.12-0.98; 4 trials, 368 women).[129] In spite of this, the authors were cautious in their recommendations as the trials were generally of poor quality and lacked blinding. Following this, the 4P trial, a multicentre, double-blinded and placebo-controlled trial involving 29 centres, randomized 385 women between 24+0 to 33+6 weeks who presented with preterm labour to receive either 200mg of vaginal progesterone or placebo. In this trial, maintenance vaginal progesterone was started within 48 hours of tocolysis. Primary outcome was delivery before 37 weeks gestation while secondary outcomes were delivery before 32 and 34 weeks, adverse effects, duration of tocolysis, re-admissions for preterm labour, length of hospital stay, and neonatal morbidity and mortality. There were no differences in the incidence of PTB or neonatal outcomes with maintenance vaginal progesterone following tocolysis.[130]

Of note, the trial involved women from Switzerland and Argentina (largely Caucasian and Hispanic populations), beta-mimetics were the primary agents used for tocolysis in more than three quarters of women, with only one in eight women using calcium channel blocker. There were also concerns regarding the methodology of monitoring the compliance of patients involved in the study. The trial was also ended prematurely based on results of the intermediate analysis.

Recommendation 12	Level of evidence *(Strength of recommendation)*
There is insufficient evidence for progesterone to be used in the treatment of preterm labour, either as a tocolytic or for maintenance after tocolysis.	Level 1 *(Strong)*

6.6 Monitoring Of Serum Progesterone

Progesterone is a critical hormone in early pregnancy. There is now emerging evidence that serum progesterone levels are associated with an increased likelihood of threatened miscarriage. Serum progesterone concentrations have been shown to increase in a linear fashion with gestational age from 5 to 13 weeks in women with normal pregnancies while those with spontaneous miscarriage showed a marginal and non-significant increase in serum progesterone.[54] This study highlighted the pivotal role of progesterone in supporting an early pregnancy, with lower serum progesterone associated with threatened miscarriage and a subsequent complete miscarriage at 16 weeks gestation. A few older smaller studies showed that low serum progesterone is associated with poor pregnancy outcomes.[131],[132] The evidence however is still inadequate to advocate the routine use of serum progesterone levels to determine the management or prognosis of a pregnancy.

Recommendation 13	Level of evidence *(Strength of recommendation)*
There is currently no role for serum progesterone monitoring before or after starting progesterone.	Level 2 *(Strong)*

6.7 Key Messages

- The prophylactic use of progestogens is beneficial in reducing pregnancy loss in women who are undergoing ART, when given to support the luteal phase and should be started after the oocyte retrieval until at least the pregnancy test.
- Vaginal progesterone should be considered in asymptomatic women with a short cervix, regardless of history of prior PTB. The reviewers however recognize that cervical shortening would be detected in women with a prior history of PTB undergoing surveillance while its detection in women without risk factors would depend on the individual unit's screening policy.
- There appears to be evidence of benefit in progesterone prophylaxis in women with twin pregnancies and a short cervix. However, this benefit cannot be extrapolated to higher order pregnancies at the time of writing.
- There is currently no role for serum progesterone monitoring before or after starting progesterone.

Appendix I: Levels of evidence (Modified from the Scottish Intercollegiate Guidelines Network)

Levels of evidence	Study type
1	• Meta-analysis • Systematic reviews of randomized controlled trials
2	• Single randomized trial • Large non-randomized trial(s) • Case control/cohort studies
3	Non-analytic studies (e.g. Case reports/case series)
4	Expert opinion

Appendix II: Formulation of Recommendations (Adopted from the European Society of Human Reproduction and Embryology's Manual for development of recommendations for good practice)

Target group	Strong recommendations	Conditional (weak) recommendations
Patients	Most people in the situation would want the recommended course of action and only a small proportion would not	The majority of people in the situation would want the recommended course of action but many would not
Clinicians	Most patients should receive the recommended course of action	Recognize that different choices will be appropriate for different patients and that greater effort must be made with helping each patient to arrive at a management decision consistent with her values and preferences. Decision aids and shared decision making are particularly useful.
Policy makers	Non-analytic studies (e.g. Case reports/case series)	Policy making will require substantial debate and involvement of many stakeholders.

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