DYDROGESTERONE:

A Lifeline for Threatened Pregnancies

Module 1

Understanding Threatened Abortion & Role of Dydrogesterone in Pregnancy Maintenance

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Understanding Threatened Miscarriage: Clinical Evaluation and Management

Introduction

A pregnancy loss, commonly referred to as a "miscarriage," is generally defined as the failure of a pregnancy before 20 weeks of gestation. Threatened miscarriage, also known as "threatened abortion" or "threatened early pregnancy loss," is a condition characterized by vaginal bleeding and uterine cramping in a pregnancy that remains viable, typically before the 20th week of gestation. It most frequently occurs during the first trimester. The hallmark symptoms include vaginal bleeding and cramping, without passage of products of conception, and no evidence of fetal demise upon pelvic ultrasound.

Approximately 25% of pregnancies experience some form of vaginal bleeding in the first trimester, and nearly half of these cases eventually result in pregnancy loss. While the bleeding in a threatened miscarriage is usually mild to moderate, heavy bleeding akin to or exceeding menstrual flow heightens the risk of miscarriage. Alongside vaginal bleeding, intermittent cramping, lower back pain, and pelvic pressure are also common. To ensure proper management, evaluating gestational age is crucial, as clinicians must rule out other conditions, such as ectopic pregnancy, which may present with similar symptoms.

Etiology and Epidemiology

The exact cause of a threatened miscarriage is often difficult to determine. However, a variety of factors can contribute, including subchorionic hemorrhage, spontaneous miscarriage, or non-obstetric sources of bleeding. Subchorionic hemorrhage is the most common cause, occurring in 18-22% of pregnancies due to bleeding between the fetal membranes and the decidua basalis. While small subchorionic hematomas may not significantly increase the risk of miscarriage, larger hematomas measuring two-thirds or more of the gestational sac's circumference pose a higher risk of pregnancy loss.

In cases where a miscarriage is impending, fetal chromosomal abnormalities are the primary cause, with at least half of early miscarriages resulting from genetic issues. Non-obstetric causes, such as cervicitis, vaginitis, or cervical polyps, can also result in vaginal bleeding without necessarily threatening the pregnancy's viability.

Threatened miscarriage can occur in any pregnancy, regardless of maternal age, ethnicity, lifestyle, or comorbid conditions. Approximately 25% of all pregnancies present with some degree of vaginal bleeding or spotting during the first trimester. Among pregnancies with detectable fetal cardiac activity, around 11% will proceed to miscarriage.

Pathophysiology

The pathophysiology of a threatened miscarriage varies depending on its underlying cause. In cases of subchorionic hemorrhage, the bleeding occurs between the decidua basalis and the gestational sac. Non-obstetric sources of bleeding, such as cervicitis or trauma, result from cytokine-mediated inflammation or vascular permeability in the cervical and vaginal mucosa. Infection and trauma to the maternal abdomen or pelvic organs can also lead to cramping and vaginal bleeding, mimicking symptoms of a miscarriage.

History and Physical Examination

Patients with threatened miscarriages often present with symptoms of vaginal bleeding and uterine cramping. Some may not even be aware of their pregnancy and attribute the symptoms to irregular menstrual bleeding. These symptoms may also appear in abnormal pregnancies, such as ectopic or molar pregnancies, necessitating a thorough evaluation to rule out more serious complications.

A detailed medical history should be collected, including an obstetric and menstrual history, to help estimate the gestational age of the pregnancy. Bleeding can range from light spotting to heavier than normal menstrual flow, with heavier bleeding being more concerning. Patients with threatened miscarriage are typically hemodynamically stable, with less than 1% requiring a blood transfusion due to spontaneous pregnancy loss.

In addition to documenting the volume of bleeding, clinicians should assess other related symptoms such as dizziness, lightheadedness, or fainting. Determining whether the bleeding occurred after events like intercourse or a pelvic exam can also provide important clues about the underlying cause.

Pain and Cramping

The severity of cramping can vary greatly, from painless bleeding to severe menstrual-like cramps radiating to the back or thighs. Severe pain may indicate an increased likelihood of miscarriage. Clinicians should also inquire about the onset, location, and intensity of the cramping to guide their evaluation.

Physical Exam

A key part of managing a threatened miscarriage is conducting a physical examination. A complete pelvic exam should be performed to assess the source of bleeding, whether the cervix is dilated, and if fetal tissue is present in the vaginal vault. A pelvic exam is mandatory for any pregnant patient presenting with vaginal bleeding, as it helps to differentiate between threatened miscarriage and other potential causes such as cervical polyps, fibroids, or infection. Patients with threatened miscarriage typically have a closed cervical os, and no evidence of fetal tissue in the cervix or vagina. However, mild uterine or adnexal discomfort may be present. If significant tenderness or purulent discharge is noted, this could suggest an underlying infection, requiring immediate medical intervention.

Differential Diagnosis

A thorough pelvic exam is also necessary to rule out other causes of bleeding during pregnancy. Potential non-obstetric sources of bleeding include cervical erosions, neoplasms, and infections such as Chlamydia trachomatis or condyloma acuminata. An adnexal mass may indicate an ectopic pregnancy, ovarian cyst, or torsion, each of which may also present with abdominal pain and bleeding.

Evaluation and Diagnosis

The clinical approach to diagnosing threatened miscarriage depends on the pregnancy's gestational age. The primary goals are to establish the location and viability of the pregnancy. Ultrasound is a critical tool in diagnosing and monitoring threatened miscarriage. If fetal cardiac activity is absent, serial ultrasound exams may be necessary to differentiate between an early viable pregnancy and a potential loss.

In some cases, further testing may be required to confirm or rule out other causes of bleeding. Blood tests, including serum hCG levels, can help monitor the pregnancy's progress, while

other tests such as infection screening and cervix evaluation may also provide important diagnostic information.

Conclusion

Threatened miscarriage is a common yet complex condition that requires careful evaluation to rule out other causes of vaginal bleeding during early pregnancy. While it often resolves without further complications, it can also precede pregnancy loss, especially in cases of significant bleeding or cramping. Early diagnosis, proper management, and timely follow-up are critical to optimizing outcomes for both the patient and the pregnancy. Clinicians should maintain a comprehensive approach, considering all potential causes and conducting appropriate investigations to ensure the well-being of the patient and the developing pregnancy.

Miscarriage is often associated with significant physical and emotional distress for women. Those who experience threatened miscarriage are more likely to face pregnancy complications later on, such as antepartum hemorrhage, pre-labor rupture of membranes, preterm birth, and intrauterine growth restriction when compared to those without such complications. Additionally, the psychological toll of a miscarriage can be substantial, with women experiencing depression, anger, disturbed sleep, and even strain in marital relationships.

The introduction of ultrasound technology has improved the early diagnosis and management of miscarriage. Ultrasound allows for the rapid confirmation of fetal viability and offers important prognostic indicators such as fetal bradycardia and discrepancies between gestational age and crown-to-rump length. These advancements have led to more targeted management of threatened miscarriages, focusing on pregnancies that are more likely to be viable, particularly in the absence of chromosomal abnormalities.

The Role of Progesterone in Pregnancy Maintenance

Progesterone plays a crucial role in early pregnancy. Following implantation and the production of human chorionic gonadotropin (HCG) by the placenta, progesterone is secreted by the corpus luteum, supporting the pregnancy through several critical functions. It promotes oocyte maturation, facilitates embryo implantation, and helps maintain the placenta during early pregnancy. Insufficient progesterone levels, particularly during the luteal phase, have been linked to recurrent pregnancy loss, as progesterone also plays a role in reducing uterine contractions, regulating maternal immune responses, and improving uteroplacental circulation).

Immune Mechanisms and Pregnancy Complications

Altered immune mechanisms have been linked to complications in pregnancy, including miscarriages. For example, abnormal serum levels of interleukin 18 (IL-18), a pro-inflammatory cytokine, have been associated with recurrent miscarriage, preterm delivery, and preeclampsia. Progesterone has been shown to lower IL-18 secretion, thereby playing a protective role in pregnancy. It also supports decidualization, controls uterine contractions, and

regulates the maternal immune response to the fetus. A key mediator in this process is the progesterone-induced blocking factor (PIBF), which helps modulate the maternal immune system, preventing the rejection of the fetus. Deficiencies in progesterone can lead to complications like threatened miscarriage (TM).

Progesterone as a Predictor of Miscarriage

Given the importance of progesterone in pregnancy maintenance, researchers have explored its role as a predictor of miscarriage. Several studies have suggested that low progesterone levels are strongly associated with pregnancy loss. Specifically, serum progesterone levels may help predict the risk of miscarriage during the first trimester. Multiple studies indicate that progesterone, either alone or in combination with other hormones like estrogen, HCG, and PIBF, can predict early pregnancy loss. These findings suggest that monitoring progesterone levels in early pregnancy could help identify those at risk of miscarriage and inform treatment strategies.

Progesterone Therapy for Threatened Miscarriage

Progesterone therapy has been proposed as a treatment for women experiencing TM or those with presumed progesterone deficiency. Although earlier studies yielded mixed results, more recent evidence points to the potential effectiveness of progesterone therapy, especially for women with a history of recurrent miscarriage of unknown causes. However, the inconsistency in previous studies, often due to poor trial design, has made it challenging to definitively prove the therapeutic benefits of progesterone.

A narrative review of existing literature highlights the relationship between progesterone levels and first-trimester miscarriage. Thematic analysis identified several key themes:

1. The Association between Progesterone and Pregnancy Loss: Fourteen studies identified a clear association between low progesterone levels and pregnancy loss. However, a meta-analysis by Yan et al. found no significant link between progesterone deficiency and miscarriage risk, indicating that further research is needed to clarify this relationship.

2. Progesterone as a Predictor of Miscarriage: Seven studies demonstrated that progesterone deficiency alone is a strong predictor of first-trimester miscarriage, reinforcing its importance as a biomarker in early pregnancy.

3. Progesterone Combined with Other Hormones: Some studies suggested that combining progesterone with other hormones like estrogen, HCG, or PIBF could help predict the risk of first-trimester miscarriage. This combined approach may offer a more comprehensive assessment of pregnancy risk.

4. Effectiveness of Progesterone Therapy: Five studies provided evidence supporting the effectiveness of progesterone therapy in preventing miscarriage, particularly in women with a history of one or more previous miscarriages. However, a meta-analysis and a randomized controlled trial found no significant benefit of progesterone therapy for women with TM, indicating that its use may be limited to certain subgroups.

5. Impact of Progesterone Therapy on Fetal Development: Several systematic reviews and meta-analyses concluded that progesterone therapy does not have a negative impact on fetal development. In fact, some studies suggested that progesterone may reduce the risk of low birth weight in later gestational weeks. Randomized controlled trials and cohort studies further confirmed that progesterone does not harm fetal development, supporting its use as a safe option for women at risk of miscarriage.

In conclusion, progesterone is essential for pregnancy maintenance, and its deficiency is associated with a higher risk of miscarriage. Progesterone therapy has shown promise, particularly for women with recurrent miscarriage, though its effectiveness in all cases remains to be definitively proven. Ongoing research is needed to better understand its role in miscarriage prevention and to optimize its use in clinical practice.

Dydrogesterone: A Synthetic Progestogen

Introduction to Progestogens

Progestogens encompass both the natural hormone progesterone and its synthetic variants, known as progestational agents. These hormones bind to progesterone receptors and are crucial for the establishment and maintenance of pregnancy. Progesterone is naturally secreted by the corpus luteum during the early stages of pregnancy, helping prepare the uterus for embryo implantation and preventing the rejection of the developing embryo. Progestogens are often administered to women experiencing a threatened miscarriage. Depending on the situation, they can be provided orally, through intramuscular injections, or as vaginal suppositories. However, given the diversity of progestogen types, doses, and delivery methods, there remains uncertainty about the most effective approach to manage threatened miscarriages.

Dydrogesterone: A Unique Synthetic Progestogen

One of the most commonly used synthetic progestogens is dydrogesterone, which was developed in the 1950s. Dydrogesterone is a stereoisomer of progesterone, with a unique chemical structure that makes it highly selective for progesterone receptors. This specificity enhances its progestogenic activity while minimizing its interaction with androgen, glucocorticoid, and mineralocorticoid receptors, reducing unwanted side effects commonly associated with other synthetic progestins. Dydrogesterone's chemical structure also confers higher oral bioavailability compared to natural progesterone, making it an effective treatment option for several reproductive conditions.

Dydrogesterone has been widely used to treat various menstrual disorders, including premenstrual syndrome, irregular menstrual cycles, endometriosis, and both threatened and habitual miscarriages. It has also been used in postmenopausal hormone therapy. A key advantage of dydrogesterone is its safety profile. While other progestins may pose risks in pregnancy due to receptor cross-activation, dydrogesterone is considered safe for use during pregnancy. Along with bioidentical progesterone and 17-hydroxy-progesterone caproate, it is one of the few progestins considered sufficiently safe for the developing fetus.

Pharmacokinetics and Mechanism of Action

Dydrogesterone stands out due to its minimal effect on gonadotropin release, which means it does not significantly interfere with follicular growth, ovulation, or corpus luteum function. This characteristic makes it particularly suitable for fertility treatments, where maintaining normal ovarian function is essential. Clinical doses ranging from 5 to 30 mg do not suppress ovulation, a critical aspect in its use for controlled ovarian stimulation (COS).

Compared to natural progesterone, dydrogesterone has better oral bioavailability, with around 28% being absorbed when taken orally. It also has a half-life of 5-7 hours, while its active metabolite, 20α-hydroxydydrogesterone, has a half-life of 14-17 hours. The drug is primarily converted to its active form through enzymatic processes, which allow for effective prereceptor regulation of its activity.

Global Availability and Market Withdrawal

Despite its extensive use, dydrogesterone is no longer available in certain markets like the United States, United Kingdom, and Australia, primarily due to commercial reasons. It was first introduced in the U.S. in 1961 but was withdrawn in 1997 as the indications for which it was originally marketed became less commercially viable. Similarly, the drug was pulled from the UK and Australian markets due to low sales and a lack of new, financially promising indications. Nevertheless, dydrogesterone remains licensed for use in over 100 countries, including many European nations, where it is still used to support pregnancy.

Dydrogesterone in IVF and Luteal Phase Support

Dydrogesterone plays a crucial role in supporting endogenous progesterone production by the corpus luteum and placenta, particularly in assisted reproductive technologies (ART) such as **in vitro fertilization (IVF)**. The luteal phase, the second half of the menstrual cycle following ovulation, is a critical period for embryo implantation and the establishment of pregnancy. During this phase, progesterone levels must be sufficient to prepare the endometrium for embryo attachment and to maintain early pregnancy.

Luteal Phase Defect and IVF

In the context of **controlled ovarian stimulation (COS)**, a common procedure in IVF, multiple follicles are stimulated to mature simultaneously, which often disrupts the natural progesterone production from the corpus luteum. This phenomenon, known as **luteal phase defect (LPD)**, is an iatrogenic (treatment-induced) issue that may compromise pregnancy outcomes if left unaddressed. LPD in COS cycles is marked by inadequate progesterone levels, which may prevent proper endometrial development and, consequently, embryo implantation.

Though the concept of LPD as an independent cause of infertility remains debated, its occurrence in COS cycles is widely acknowledged. Therefore, **luteal phase support (LPS)** is routinely provided during IVF treatments to enhance pregnancy success rates. Progestogens, including dydrogesterone, are essential in supporting this phase, compensating for the disrupted natural progesterone production caused by the ovarian stimulation process.

Dydrogesterone as an Alternative to Micronized Vaginal Progesterone (MVP)

Dydrogesterone, a synthetic progestogen, has emerged as an effective alternative to **micronized vaginal progesterone (MVP)**, which has traditionally been used for luteal phase support in IVF. MVP, delivered either as vaginal suppositories or gel, is known to be effective in maintaining appropriate progesterone levels during the luteal phase. However, it can be inconvenient for patients due to its mode of administration and potential side effects, such as vaginal irritation or discharge.

Dydrogesterone, by contrast, is formulated for **oral administration**, making it a more convenient option for patients undergoing IVF. It offers similar clinical outcomes with higher patient comfort and compliance due to its ease of use. Studies have demonstrated that oral dydrogesterone is just as effective as MVP for luteal phase support, ensuring optimal conditions for embryo implantation and pregnancy maintenance.

One of the largest investigations into the efficacy of dydrogesterone for LPS in IVF treatments was conducted through the **Lotus I and Lotus II clinical trials**. These large-scale, multicenter, Phase III trials involved over 2000 patients undergoing fresh IVF cycles. The studies aimed to establish whether oral dydrogesterone could offer comparable results to MVP in terms of pregnancy outcomes. The trials concluded that dydrogesterone was **non-inferior** to MVP, as

evidenced by similar **pregnancy rates at 12 weeks gestation**, which is a key marker for the success of IVF treatment.

The findings from the Lotus studies provide robust, clinically significant evidence supporting the use of oral dydrogesterone for luteal phase support in IVF. The **non-inferiority** results indicate that dydrogesterone performs as well as MVP, while offering the added benefit of improved patient experience through oral administration.

Comparative Efficacy and Meta-Analyses

Several studies have been conducted to compare the efficacy of oral dydrogesterone and MVP in the context of luteal phase support for IVF. These studies generally aim to determine whether dydrogesterone can offer comparable pregnancy outcomes, such as **live birth rates**, **ongoing pregnancy rates**, and **clinical pregnancy rates**.

In 2015, a **Cochrane systematic review and meta-analysis** compared dydrogesterone with MVP for luteal phase support in fresh IVF cycles. This review, which analyzed data from multiple studies, found no significant differences in **live birth rates** or **ongoing pregnancy rates** between the two treatments, confirming that both dydrogesterone and MVP are effective for luteal phase support. However, the review did suggest that dydrogesterone might be associated with a higher **clinical pregnancy rate** than MVP based on data from four studies involving a total of 2388 patients. The higher clinical pregnancy rate indicates that dydrogesterone may lead to a greater number of confirmed pregnancies based on early signs of success, such as the detection of a fetal heartbeat.

Following the publication of the **Lotus I and Lotus II trials**, further analyses were conducted to better understand the implications of dydrogesterone use in IVF. Notably, meta-analyses using **individual participant data (IPD)** provided even more detailed insights into the efficacy and safety of dydrogesterone. Unlike traditional meta-analyses, which rely on aggregate study-level data, IPD meta-analyses use raw patient-level data from each eligible study. This approach has several advantages, including more consistent analysis of data across studies, the ability to adjust for confounding variables, and the potential for **subgroup analyses**. By analyzing patient data at the individual level, IPD meta-analyses can provide more precise estimates of treatment effects, which is especially important in assessing outcomes like pregnancy rates and live births.

In the case of dydrogesterone, IPD meta-analyses have reinforced the conclusions drawn from aggregate data. These analyses highlight the treatment's efficacy and safety in luteal phase

support, offering reassurance to clinicians and patients alike. Furthermore, combining IPD data with traditional aggregate data in meta-analyses allows for more comprehensive comparisons and helps overcome potential limitations of either approach when used alone.

Conclusion

Dydrogesterone has become a central agent in luteal phase support for IVF, offering a viable alternative to micronized vaginal progesterone. Its **oral formulation**, coupled with its comparable efficacy to MVP, makes it a patient-friendly option without compromising treatment success. Studies, including the large-scale Lotus I and II trials, have established that dydrogesterone is **non-inferior** to MVP in achieving pregnancy outcomes, further strengthening its role in fertility treatments.

Comparative studies and meta-analyses, particularly those utilizing individual participant data, have provided further confirmation of dydrogesterone's effectiveness and safety. As a result, dydrogesterone is now routinely used in many IVF protocols worldwide, ensuring that patients receive adequate luteal phase support for optimal pregnancy outcomes. The growing body of evidence positions dydrogesterone as a reliable and convenient option for women undergoing IVF, enhancing the success rates of assisted reproductive technologies while improving the overall patient experience.

Threatened Miscarriage

Threatened miscarriage (TM) is characterized by vaginal bleeding, with or without abdominal pain, but no cervical dilation during the first 20 weeks of pregnancy. Research indicates that vaginal bleeding occurs in about 20% of recognized pregnancies before 20 weeks, with approximately half of these cases leading to miscarriage. First-trimester bleeding may also be linked to placental issues, and TM has been associated with complications such as placental abruption, preterm birth, preeclampsia, gestational hypertension, and fetal growth restriction. While chromosomal abnormalities account for around half of all miscarriages, other risk factors include advanced maternal age, smoking, maternal health conditions, infections, abnormal body mass index, and low levels of progesterone and human chorionic gonadotropin (hCG).

Once a viable intrauterine pregnancy is confirmed through serum hCG levels and ultrasound, common treatments include bed rest and luteal support using hCG or progestogens. However, Cochrane Reviews suggest that there is insufficient evidence to support bed rest or hCG supplementation for preventing miscarriage. On the other hand, a more recent review found that progestogens may be effective in treating TM, although the evidence is limited.

Dydrogesterone vs. Standard Care or Placebo

Three controlled studies compared dydrogesterone, either alone or in combination with standard supportive care (such as bed rest, folic acid, or multivitamins), to standard care alone. One study found that significantly more women receiving dydrogesterone continued their pregnancies beyond 20 weeks compared to those receiving only bed rest and folic acid. In this study, the miscarriage rate was 4.1% in the dydrogesterone group compared to 13.8% in the control group. Another study showed that adding dydrogesterone to a regimen of bed rest, iron, folic acid, and multivitamins led to a significant reduction in miscarriage rates (17.5% vs. 25.0%). No significant differences were observed between the groups for outcomes such as preterm labor, preeclampsia, intrauterine growth restriction (IUGR), or congenital abnormalities. In a larger study, dydrogesterone was also found to significantly reduce miscarriage rates compared to bed rest alone (12.5% vs. 28.4%). There were no differences between the groups in terms of preterm labor, pregnancy-induced hypertension, or cesarean section rates, and no intrauterine or congenital abnormalities were reported.

Dydrogesterone was also compared to placebo in two older studies, both of which reported lower miscarriage rates in the dydrogesterone group. In one study, 19.4% of women in the dydrogesterone group miscarried or had stillbirths, compared to 28.4% in the placebo group. In another study, no miscarriages were reported in the dydrogesterone group, while 22.2% of women in the placebo group miscarried.

A meta-analysis of five randomized studies revealed that dydrogesterone was associated with a significant 53% reduction in the odds of miscarriage. A subgroup analysis of three more recent studies showed a 58% reduction in the odds of miscarriage.

Dydrogesterone vs. Vaginal Micronized Progesterone

Dydrogesterone has been compared to vaginal micronized progesterone in two studies for the treatment of TM. One study examined the effects of both drugs on uteroplacental blood flow, as early vascular changes may predispose mothers to complications such as IUGR and pregnancy-induced hypertension. In this study, 8.3% of women receiving oral dydrogesterone miscarried, compared to 13.8% of those receiving vaginal progesterone, although the differences were not statistically significant. In another study, the miscarriage rates were 8.1% in the dydrogesterone group and 7.9% in the vaginal micronized progesterone group, with no significant differences between the two treatments.

Overall, prospective studies show that dydrogesterone is consistently more effective than standard care or placebo and tends to be more effective than vaginal micronized progesterone in managing TM. Based on clinical evidence, dydrogesterone, and in some cases progestogens in general, are recommended by various medical societies for treating TM.

Recurrent Miscarriage

Recurrent miscarriage (RM) is defined as the loss of two or three consecutive pregnancies before 24 weeks of gestation. It is estimated that approximately 5% of couples trying to conceive experience two consecutive miscarriages, while 2-3% experience three or more consecutive losses. Diagnosing the underlying cause of RM is particularly challenging, as no clear cause is identified in about half of the cases. Known etiological factors include chromosomal abnormalities, immune dysfunction, endocrine disorders, thrombophilic conditions, and structural uterine anomalies. Treatment options, apart from supportive care, include pharmacological interventions such as anticoagulants (e.g., aspirin and heparins for women with antiphospholipid syndrome or inherited thrombophilias) and progestogens. This

section focuses on the role of dydrogesterone in the treatment of RM, based on findings from four prospective controlled studies, a meta-analysis, and an additional non-randomized clinical study.

Dydrogesterone vs. Standard Supportive Care or Placebo

Studies have demonstrated that dydrogesterone is associated with lower miscarriage rates when compared to standard care or placebo. In one study involving women with proven progesterone deficiency, those who received dydrogesterone and supportive care had a significantly lower miscarriage rate (33.3%) compared to those who received supportive care alone (92.3%). Another study compared dydrogesterone and human chorionic gonadotropin (hCG) alongside standard care to standard care alone, finding that significantly fewer women miscarried in the dydrogesterone group (13.4%) compared to the control group (29.2%). Other studies comparing dydrogesterone to placebo yielded mixed results, with one showing no difference between the groups, while another found a significantly lower miscarriage rate in the dydrogesterone group (6.9%) compared to placebo (16.8%).

A Cochrane Systematic Review analyzed the use of progestogens, including dydrogesterone, in preventing miscarriage. Although no significant differences in rates of preterm birth, neonatal death, or fetal anomalies were observed between progestogen and placebo/no treatment groups, a subgroup analysis showed a significant reduction in miscarriage rates in women with RM who received progestogen therapy. A meta-analysis of dydrogesterone studies later reported a 71% reduction in miscarriage odds when compared to standard care.

Dydrogesterone vs. Vaginal Micronized Progesterone

Dydrogesterone has also been compared to vaginal micronized progesterone in women with a history of RM. One study suggested that dydrogesterone may be more effective than vaginal progesterone in preventing miscarriage, although the differences were not statistically significant. Both treatments improved endometrial blood flow parameters, with dydrogesterone showing a more significant effect on uteroplacental blood flow compared to vaginal progesterone. Another recent trial comparing vaginal micronized progesterone to placebo in women with a history of RM found no significant difference in live birth rates between the two groups, nor in secondary outcomes such as miscarriage rates, stillbirth, or neonatal outcomes.

The differences in findings between studies comparing dydrogesterone and vaginal progesterone may be explained by several factors. First, dydrogesterone and micronized

progesterone differ in their structure, pharmacokinetic properties, and binding characteristics, with dydrogesterone exhibiting better bioavailability and progestogenic effects. Moreover, dydrogesterone has a longer half-life compared to vaginal progesterone. Additionally, dydrogesterone has been shown to have a more pronounced effect on uteroplacental blood flow, potentially contributing to better pregnancy outcomes in RM.

Differences in study inclusion criteria, particularly regarding maternal age and pregnancy stage, may also account for the varying results. One study included women under 35 years of age at 4-8 weeks of gestation, while another study enrolled women up to 39 years of age earlier in pregnancy. Maternal age is a known factor influencing chromosomal abnormalities, which are associated with RM. Furthermore, the studies varied in treatment duration, with one study extending dydrogesterone treatment up to 20 weeks, compared to 12 weeks in another trial.

Overall, dydrogesterone has been shown to improve several pregnancy outcomes in women with a history of RM, including reducing miscarriage rates, increasing gestational age, and improving birth weight. As a result, dydrogesterone is recommended by clinical guidelines for the prevention of RM.

Abstracts

Efficacy of dydrogesterone on treating recurrent miscarriage and its influence on immune factors: a systematic review and meta-analysis

Background: This study aimed to explore the clinical efficacy of dydrogesterone in treating recurrent spontaneous abortion (RSA), analyze the influence of dydrogesterone on cellular immune factors, and provide evidence for clinical medication.

Methods: We used the China National Knowledge Infrastructure (CNKI) platform, Wanfang Data resource, PubMed, Web of Science, and Embase database to conduct a literature search to screen clinical studies published between 2005 and 2021 concerning dydrogesterone treatment for RSA. Stata 16.0 was used for meta-analysis and sensitivity analysis, and Begg's funnel chart was used to test publication bias.

Results: Only 13 studies, which included a total of 2,454 RSA patients, met the study inclusion criteria. The experimental group was treated with dydrogesterone, and the control group was treated with progesterone, human chorionic gonadotropin (hCG), placebo, or active immunization. Meta-analysis showed that the pregnancy success rate of the experimental group was higher than the control group, and the adverse reaction rate was lower than the control group. In addition, subgroup analysis also revealed that the experimental group had a higher pregnancy success rate than the control group and a lower adverse reaction rate. Levels of progesterone and hCG in the experimental group were dramatically higher than the control group after treatment. The experimental group also had higher levels of interleukin 4 (IL-4) and interleukin 10 (IL-10) than the control group, while levels of interferon-gamma (IFN-γ) were lower.

Discussion: Dydrogesterone, a safe and effective synthetic progesterone drug, had a significant clinical effect on RSA and effectively improved hormone levels and related cellular immune factors in RSA patients.

Real-world evaluation of safety and effectiveness of dydrogesterone in the management of threatened abortion

Background: Threatened abortion is a relatively common complication during pregnancy. Inadequate production of endogenous progesterone is implicated as a risk factor for miscarriages. Thus, supplementation of external progesterone can be used as a preventive strategy in these women. Dydrogesterone a stereoisomer of progesterone has a good safety and tolerability profile and is known to effectively prevent pregnancy loss in women with threatened miscarriage, however, real-world data safety and effectiveness analysis of dydrogesterone in Indian patients was lacking. Therefore, this real-world retrospective analysis of the case reports was done to evaluate the safety, effectiveness, compliance, and tolerability of oral dydrogesterone in the treatment of women with threatened abortion.

Methods: Data was collected from 194 obstetricians and gynaecologists in India, on the use of oral dydrogesterone in women presenting with threatened abortion in the first trimester of pregnancy.

Results: Completed case report forms of patients who met the eligibility criteria (n = 617) were considered for the analysis. The main presenting symptom was vaginal bleeding/spotting with an additional symptom of abdominal cramp/pelvic pain/low back pain in 364 (69.07%) patients. Miscarriage was reported in 45 (7.29%) patients and 23 (3.98%) patients needed surgical intervention before 20 weeks of gestation with dydrogesterone treatment. The median time for relief of symptoms from the start of dydrogesterone tablets was 3.32 days for low back pain, 3.9 days for abdominal pain, and 4.37 days for the establishment of hemostasis. Treatment with dydrogesterone was found to be well-tolerated and adverse events were reported in 3.72% of the patients.

Conclusions: This retrospective analysis suggests that dydrogesterone is safe and effective in reducing the incidence of pregnancy loss in women with threatened abortion.

References

- Mouri MI, Hall H, Rupp TJ. Threatened Miscarriage. [Updated 2024 Feb 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430747/
- Wahabi HA, Fayed AA, Esmaeil SA, Bahkali KH. Progestogen for treating threatened miscarriage. *Cochrane Database Syst Rev*. 2018;8(8):CD005943.
- Bataa M, Abdelmessih E, Hanna F. Exploring Progesterone Deficiency in First-Trimester Miscarriage and the Impact of Hormone Therapy on Foetal Development: A Scoping Review. *Children (Basel)*. 2024;11(4):422.
- Griesinger G, Blockeel C, Kahler E, et al. Dydrogesterone as an oral alternative to vaginal progesterone for IVF luteal phase support: A systematic review and individual participant data meta-analysis. *PLoS One*. 2020;15(11):e0241044.
- Griesinger G, Blockeel C, Tournaye H. Oral dydrogesterone for luteal phase support in fresh in vitro fertilization cycles: a new standard?. *Fertil Steril*. 2018;109(5):756-62.
- Mirza FG, Patki A, Pexman-Fieth C. Dydrogesterone use in early pregnancy. *Gynecol Endocrinol*. 2016;32(2):97-106.
- Guo H, Lu Q. Efficacy of dydrogesterone on treating recurrent miscarriage and its influence on immune factors: a systematic review and meta-analysis. *Ann Palliat Med*. 2021;10(10):10971-985.
- Nagarkatti, Rajendra & Mehra, Dolly & Mandal, et al. (2022). Real-world evaluation of safety and effectiveness of dydrogesterone in the management of threatened abortion. International Journal of Reproduction, Contraception, Obstetrics and Gynecology. 11. 10.18203/2320-1770.ijrcog20221833.

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