Controversies in Obstetrics & Gynecology

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CHAPTER

4 Recurrent Miscarriage: The Role of Supplementation of Progesterone

Renu Tanwar, Neha Varun

INTRODUCTION

Recurrent miscarriage (RM) affects 0.5 to 1 percent of couples.[1] The pathophysiology of recurrent miscarriage is complex. The suggested causes include anatomical, genetic and molecular abnormalities, endocrine disorders, thrombophilias and antiphospholipid syndrome. In approximately 50 percent of the cases neither of the above can be identified.[1]

Definition: Recurrent miscarriage or early pregnancy loss (RPL) according to newer guidelines from the American Society of Reproductive Medicine defined as the loss of two or more pregnancies.[2]

Risk: The risk of miscarriage in subsequent pregnancies is 30 percent after 2 losses, compared with 33 percent after 3 losses among patients without a history of a livebirth.[3]

Etiology: Etiology is often unknown. Only in 50 percent of the cases the cause can be determined.[3] *Etiological categories (Fig. 4.1)*:[4]

- Parental chromosomal anomalies (4%)
- Uterine
  - Congenital or acquired anomalies (most common septate)
  - Leiomyoma
  - Endometrial polyp
  - Asherman's syndrome, endometrial fibrosis
  - Primary endometrial defect
  - Cervical insufficiency
- Immunologic [antiphospholipid antibodies (APAs)]

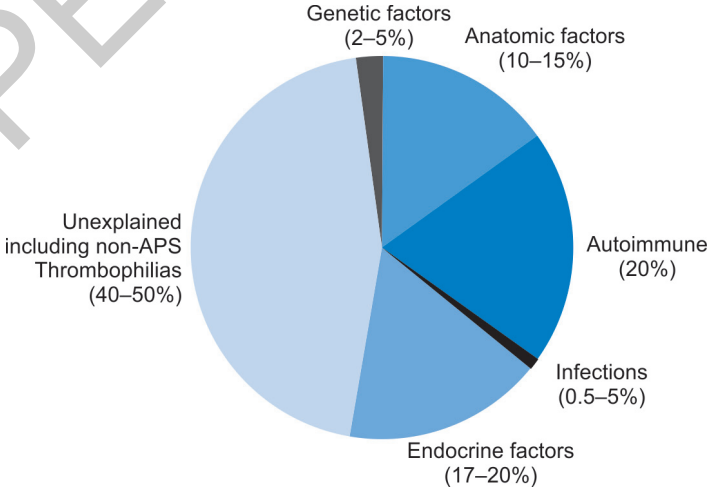


Fig. 4.1 Etiologies of recurrent miscarriage

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- Endocrine diabetes mellitus (DM), thyroid disorder, hyperprolactinemia, hypersecretion of LH, polycystic ovaries, systemic lupus erythematosus (SLE) and luteal phase deficiency (LPD)
- Heritable thrombophilia
- Environmental (Environmental chemicals—PCP, selenium and stress)
- Hematological abnormality (Impaired fibrinolytic activity, essential thrombocytopenia)
- Nutritional factors (Alcohol, coffee consumption, smoking)
- Miscellaneous (Male factor, decreased ovarian reserve, infection and celiac disease).

Prognosis: Prognosis for successful future pregnancy is good. Livebirth rates after normal and abnormal diagnostic evaluations are 77 and 71 percent, respectively. Emotional support is important and enhances success.

UNEXPLAINED RECURRENT MISCARRIAGE

Fifty percent of recurrent miscarriage (RM) remains unexplained. Prognosis is still good. More than 50 percent livebirth seen even without intervention.

Management

Specific treatment is according to the etiology.

- Lifestyle modification
  - Eliminating use of tobacco, alcohol, and caffeine and reduction in body mass index (BMI) (for obese women).
- Progesterone
  - Widely used
  - Orally or vaginally or intramuscular
- Human menopausal gonadotropin
  - Correcting LPD or creating thicker endometrium
  - Clinical experience supports the efficacy[4]
- IVF +/- PGD
  - Mixed results
  - Promising.

ROLE OF PROGESTERONE IN RECURRENT MISCARRIAGE

The role of progesterone in preparing the uterus for the implantation of the embryo and its role in maintaining the pregnancy have been known for a long time. Inadequate secretion of progesterone in early pregnancy has been linked to the etiology of miscarriage and progesterone supplementation has been used as a treatment for recurrent miscarriages.

Progesterone[5]

Progesterone is a 21 carbon compound formed from steroid precursors in the ovary, testis, adrenal gland, placenta and glial cells of CNS. Progesterone is secreted during early pregnancy from the ovary by corpus luteum.

Natural progesterone has its main progestional action, antiandrogenic and antimineralocorticoid effects. Natural progesterones are rapidly metabolized and have poor bioavailability when administered by oral route. Bioavailability is ten times more with intramuscular administration than oral route.

It is an essential hormone for the establishment and maintenance of pregnancy by inducing secretary changes in the lining of the uterus, which are important for implantation of the fertilized ovum. Progesterone enhances uterine quiescence and suppresses uterine contractions.

During the last few decades, synthetic derivatives of testosterone or 17-hydroxy progesterone have been the orally active agents. These are called progestational agents, gestagens, progestogens or progestins.

Uses

- In recurrent miscarriages.
- Prevention of preterm birth [6]
- Luteal support in assisted reproductive technology (ART) cycles such as *in vitro* fertilization (IVF)

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- To control persistent anovulatory bleeding
- Used to prepare uterine lining in infertility therapy
- To support early pregnancy
- Used in nonpregnant women for withdrawal bleed.
- Treatment of multiple sclerosis
- Progesterone also has a role in skin elasticity and bone strength, in respiration, in nerve tissue and in female sexuality, and the presence of progesterone receptors in certain muscle and fat tissue may hint at a role in sexually dimorphic proportions of those[7]
- Hidradenitis suppurative.

Various Types of Progesterone

- Natural
  - Progesterone
  - Micronized progesterone
- Synthetic
  - Structurally related to progesterone
    - i. Pregnane derivatives
      - a. Acetylated
        1. Medroxyprogesterone acetate
        2. Megestrol acetate
      - b. Nonacetylated
        1. Dydrogesterone
    - ii. Nonpregnane derivatives
      - a. Demegestone
      - b. Promegestone
      - c. Nomegestrol acetate
  - Structurally related to testosterone
    - i. Ethinylated
      - a. Estrane derivatives
        1. Norethindrone
        2. Norethynodrel
        3. Lynestrenol
        4. Norethindrone acetate
        5. Ethynodiol diacetate
      - b. Gonane derivative
        1. Levonorgestrel
        2. Desogestrel
        3. Gestodene
        4. Norgestimate
    - ii. Nonethinylated
      - a. Dienogest

Different routes of progesterone use are depicted in Table 4.1.

Advantages of Oral Micronized Progesterone

- No adverse effect on the lipid profile.
- It can have mild diuretic effect.
- Only disadvantage is its shorter duration of action. Therefore frequent administration is required.
- Although bioavailability is enhanced with micronization but it is still less than that after vaginal administration.

Advantages of Vaginal Route of Progesterone

- No pain of injection.
- Avoidance of first pass hepatic metabolism.
- Rapid absorption via vaginal epithelium.
- Relatively higher and sustained plasma concentration.
- Uterine first pass effect leading to local endometrial effect.
- Lack of adverse effect.

Table 4.1 Different routes of progesterone use

	Vaginal micronized progesterone	*Oral route*	*Intramuscular route*
1. Plasma concentration			
a. Peak	Within 3 hours	Within 2 hours	Same as vaginal route
b. Duration	>48 hours	6 hours	Same as vaginal route
2. Endometrium	• Favorably receptive • Homogeneous in phase with day of cycle	• Poorest receptive • Heterogeneous and inadequate	• Less receptive • Slight delay in maturation

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Role of Progesterone Deficiency in the Etiology of Recurrent Miscarriages

- Insufficient progesterone secretion and delayed endometrial development at the time of implantation or during early pregnancy may occur naturally or due to luteal phase defect and has been implicated as a cause of sporadic and recurrent miscarriages.[8-10]
- Several studies reported lower than normal serum progesterone concentrations in RM patients with delayed endometrium, compared those with normal endometrium.[1]
- If plasma progesterone levels are normal, the endometrium can, still be progesterone deficient due to receptor abnormalities.[1]
- Mutations of the progesterone receptor gene could also contribute to impaired reproductive function and consequently to early abortions.
- Some studies reported on a polymorphism within the coding sequence of the human progesterone receptor gene that occurs at a significantly higher frequency in patients with RM than in controls.
- Progesterone deficiency leads to increased levels of proinflammatory interleukin 8 (IL-8), cyclo-oxygenase-2, and monocyte chemoattractant protein-1 which destabilize the endometrium.[11]
- Successful pregnancy is associated with the downregulation of proinflammatory T helper cell type 1 (Th-1) cytokines and upregulation of anti-inflammatory T helper cell type 2 (Th-2) cytokines. A 34-kDa protein, progesterone-induced blocking factor (PIBF) prevents inflammatory reactions by blocking Th-1 cytokines and natural killer cells degranulation and increasing asymmetric nontoxic blocking antibodies.[12,13]
- An inappropriate endometrial development can thus develop on the basis of progesterone receptor defects in the presence of sufficient progesterone concentrations.
- These findings support the existence of absolute or relative progesterone deficiency as a biologically significant entity in recurrent first-trimester spontaneous miscarriage. In the former cases progesterone supplementation should potentially be successful. Women suffering from relative progesterone deficiency will probably not benefit from this treatment.[1]

Role of Progesterone Therapy in the Management of Recurrent Miscarriage

- For more than five decades, progesterone has been administered orally, intramuscularly and vaginally in an attempt to prevent miscarriage in early-to-mid pregnancy.
- In Cochrane review (2008) randomized or quasi-randomized controlled trials comparing progestogens with placebo or no treatment given in an effort to prevent miscarriage were included. In a subgroup analysis of three trials involving women who had recurrent miscarriages (three or more consecutive miscarriages), progestogen treatment showed a statistically significant decrease in miscarriage rate compared to placebo or no treatment (95% CI 0.20 to 0.70). There seems to be evidence of benefit of progesterone use in women with a history of recurrent miscarriage. Treatment for these women may be warranted given the reduced rates of miscarriage in the treatment group and the finding of no statistically significant difference between treatment and control groups in rates of adverse effects suffered by either mother or baby in the available evidence.[14]
- Progesterone supplementation reduces the risk of repeat miscarriage and the scientific basis for its use may be related in part to its role in the regulation of inflammatory mediators in pregnancy.[15]
- In one study, women with at least three unexplained recurrent miscarriages were included in the study. They were divided into three groups according to their initial and 48-hour repeat progesterone levels. Natural progesterone vaginal pessaries 400 mg 12-hourly were offered until 12 weeks gestation for women with inadequate endogenous progesterone secretion. Overall livebirth and miscarriage rates were 63 percent and

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36 percent, respectively. When analyzed by the number of previous miscarriages there was a reduction in the miscarriage rate following progesterone supplementation in women with four previous miscarriages when compared with historical data. It was concluded that progesterone supplementation may have beneficial effects in women with otherwise unexplained recurrent miscarriages.[16]

- No statistically significant differences were found between the route of administration of progestogen (oral, intramuscular or vaginal). No side effects of progesterone were reported.[1]
- In one study (not included in the meta-analysis) oral dydrogesterone and intramuscular human chorionic gonadotropin were given. Miscarriages were significantly less common in the dydrogesterone group than in the control group. There were no differences between the groups with respect to pregnancy complications or congenital abnormalities.[1]

  In this study 180 women with a history of recurrent, unexplained spontaneous miscarriage were randomized to receive oral dydrogesterone, intramuscular human chorionic gonadotropin or no additional treatment. Miscarriages were significantly ($p = 0.05$) less common in the dydrogesterone group (13.4%) than in the control group (29%); there were no statistically significant differences between the hCG group and the control group. This study was however neither placebo-controlled, nor blinded.
- In a subgroup analysis of trials in Green Top Guidelines involving women with recurrent miscarriage, progesterone treatment offered a statistically significant decrease in miscarriage rate compared with placebo or no treatment (OR 0.38, 95% CI 0.2–0.7).[17]
- In a review of progesterone therapy for recurrent miscarriage covering the period of 1987 to 2007, it was concluded that progesterone is given as a treatment of recurrent miscarriages. Standardized laboratory protocols for identifying potential targets of progestogen treatment as well as implementation of well-designed randomized studies are needed to establish the usefulness of progesterone supplementation in the treatment of recurrent miscarriage.[1]

CONCLUSION

- Considering that progesterone has important immunomodulatory functions by decreasing proinflammatory and increasing anti-inflammatory cytokines in early pregnancy, progesterone's role in maintaining early pregnancy is crucial.
- Progesterone supplementation reduces the subsequent miscarriage rate in patients with unexplained recurrent miscarriages in comparison with historical data.
- It is concluded that progesterone supplementation may improve the pregnancy outcome in selected groups of unexplained recurrent miscarriages.

CURRENT TRIALS

- Two randomized controlled trials of progesterone supplementation for recurrent miscarriage are awaited.
  - 20 mg oral dydrogesterone versus placebo for recurrent miscarriage (clinical trial number: NCT00193674)
  - Cyclogest vaginal pessaries versus placebo (PROMISE study ISRCTN 92644181).
- These studies may provide clearer evidence for the role of progesterone in recurrent miscarriage management.

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Controversies in Obstetrics & Gynecology

This book is an authoritative contributed volume containing vast knowledge and experience of the eminent faculties. The contributors are associated with India's prestigious medical institution, and hence, their presentations are the fine synthesis of practical and theoretical knowledge with the excellence in an ethical approach.

It covers almost all controversial issues in Obstetrics and Gynecology from the point of view of postgraduate examinations (MD/MS/DGO/DNB). It also contains commonly asked theory examination questions on recent topics of present scenario.

This volume has been brought out with the coordinated efforts of three professors (Latika Sahu, Devender Kumar, Usha Manaktala) of Maulana Azad Medical College and Lok Nayak Hospital, New Delhi, India. The editors hope that this will be the useful guide for the postgraduates in solving the controversial issues on 20 different topics in Obstetrics and Gynecology.

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