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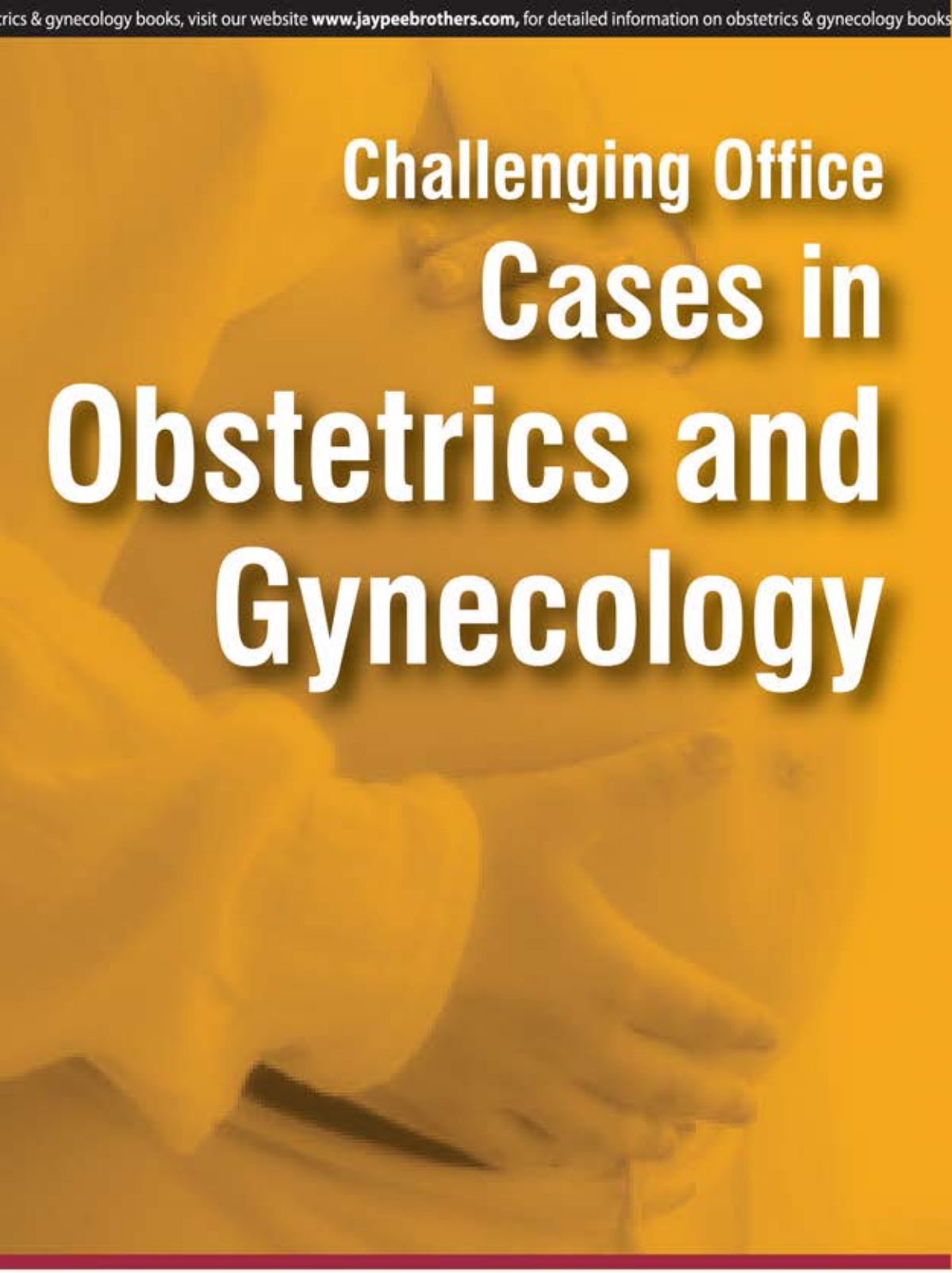
Challenging Office Cases in Obstetrics and Gynecology



Botros RMB Rizk
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Chapter
2

Office Management of Recurrent Pregnancy Loss

Sarwat Ibrahim

VIGNETTE

A 37-year-old gravida 3, para 0 woman is in your office to follow-up a diagnosis of missed abortion at eight weeks gestation. She has had two prior first trimester pregnancy losses. Your partner saw her three days ago for vaginal bleeding and diagnosed a non-viable intrauterine pregnancy by ultrasound. The patient appears to be grieving her loss and is angry at your partner. She claims the partner failed to give her any information, stating only, "You've got another miscarriage." An appointment was then made for the patient to see you today.

INTRODUCTION

Early pregnancy loss is a common problem which is described as the spontaneous loss of pregnancy before 20 weeks. Recurrent Pregnancy Loss (RPL) is defined as two or more failed clinical pregnancies before 20 weeks gestation. It is estimated that fewer than 5% of women will experience two consecutive miscarriages, and only 1% experience three or more.[1] Miscarriage is an emotionally challenging ordeal accompanied by all the feelings of bereavement.

Although epidemiological, clinical and biochemical risk factors are known for recurrent miscarriage, the etiology is usually unknown. No apparent causative factor is identified in 50–75% of couples with RPL. It is important to reassure patients with unexplained RPL that the chance for a future successful pregnancy can exceed 50–60% depending on maternal age and parity.[2,3]

EMOTIONAL SUPPORT OF PATIENTS WITH RECURRENT PREGNANCY LOSS

The patient in the vignette presented with intense feelings of sadness, despair, and anger. She expressed anger at the colleague who failed to give her the help she expected.

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It is important to spend time with the patient and acknowledge her grief and anger. Her grief could be cumulative with components including unresolved grief events from the previous losses. Her pregnancy loss is a significant event that can represent a major crisis in her life. This life crisis comprises many potential losses including, but not limited to, the loss of future hopes and dreams, loss of self-esteem, loss of the anticipated parent role, loss of being pregnant, loss of prenatal medical attention, and concern over the potential loss of the ability to create another new life.

People often discuss grief in terms of five stages, a theory which originated from psychiatrist Elisabeth Kübler-Ross's 1969 book ***On Death and Dying***. Grief after a miscarriage tends to follow these five stages.

Some women will go through all the stages; others will go through only some of them or will experience them in a different order. The stages are: denial and isolation, anger bargaining, depression, and finally acceptance. Although the pain of her miscarriage may always be with her, it will at some point become easier for her to deal with. She will be able to look back and be sad that the miscarriage happened, but these feelings of sadness will not feel nearly as overwhelming as they did in the beginning.

CAUSES OF RECURRENT PREGNANCY LOSS

Studies that focus on RPL have examined factors related to genetics, age, antiphospholipid syndrome, uterine anomalies, thrombophilias, hormonal or metabolic disorders, infection, autoimmunity, sperm quality, and lifestyle issues. Several of these issues are discussed in detail below.

Cytogenetic Abnormalities in Recurrent Pregnancy Loss

Approximately 60% of early pregnancy losses can be related to or associated with chromosomal anomalies, primarily trisomies, that are in part age related. These include polyploidy, and monosomy X.[4]

In those losses with a normal karyotype, gross morphological abnormalities in the fetus have been described in 18% of patients. The risk of sporadic miscarriage between 6 and 12 weeks of gestation in women less than 35 years of age is 9–12%. The risk increases in women over 35 years of age due to the markedly increased incidence of trisomic pregnancies.[5] In women older than 40 years of age, the sporadic miscarriage rate approaches 50%.[6] The risk of aneuploidy at each age is lower in women with RPL than in those who undergo sporadic miscarriage.

Genetic counseling is important when a structural genetic factor is identified. The likelihood of a subsequent healthy live birth depends on the chromosome(s) involved and the type of rearrangement. When one of the partners has a structural genetic abnormality, preimplantation genetic testing (PGT), amniocentesis, or chorionic villus sampling are options to detect the genetic abnormality in the offspring. If a chromosomal rearrangement is identified, genetic counselling can be helpful in providing information about

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the risk of future miscarriage or live-born offspring with an unbalanced karyotype. Genetic counseling includes discussion of these risks and also of the option for prenatal diagnosis in future pregnancies. In addition, risk to other family members is considered.

If a diagnosis of a balanced chromosomal translocation is determined, testing is recommended for siblings and parents to determine whether other family members are at risk for pregnancy loss and/or affected children.

Antiphospholipid Syndrome

The antiphospholipid syndrome is associated with recurrent pregnancy loss and arterial or venous thrombosis. The diagnostic criteria are:

1. Lupus anticoagulant present in plasma on two or more occasions at least 12 weeks apart, or
2. Anticardiolipin antibody of IgG or IgM isotype in serum or plasma present in medium or high titer, or
3. Anti-β2 glycoprotein-I antibody of IgG and/or IgM isotype in serum or plasma.

Antiphospholipid antibodies have a variety of effects on the trophoblast, including inhibition of villous cytotrophoblast differentiation and extravillous cytotrophoblast invasion into the decidua.[7] Antiphospholipid antibodies reduce the levels of annexin V and accelerate the coagulation of plasma on cultured trophoblasts and endothelial cells. The reduction of annexin V levels on vascular cells may be an important mechanism of thrombosis and pregnancy loss in the antiphospholipid-antibody syndrome.[8]

Anatomic Factors

Anatomic uterine defects are present in 15% of women evaluated for RPL. The septate uterus is the most common congenital uterine anomaly. It is associated with the highest incidence of reproductive failure such as RPL and preterm delivery. Pregnancy outcome is improved significantly after hysteroscopic metroplasty.

Congenital uterine abnormalities are associated with second trimester pregnancy loss in addition to other complications, including preterm labor, fetal malpresentation, and increased rates of cesarean delivery. Although the role of uterine malformations in first-trimester RPL is debatable, assessment of uterine anatomy is recommended.

The most common uterine defects include septate, unicornuate, bicornuate, and uterus didelphys. Of these the unicornuate uterus is least common, but can result in malpresentation and fetal growth restriction. The highest rate of reproductive losses are found in bicornuate uteri (47%) compared with unicornuate uteri (17%), but both are frequently associated with second trimester loss and preterm delivery.

The clinical management of pregnancy-loss patients with Asherman syndrome/intrauterine synechiae, uterine fibroids, and uterine polyps is also

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controversial, and there is no conclusive evidence that surgical treatment reduces the risk of pregnancy loss. The general consensus is that surgical correction of significant uterine cavity defects should be considered. In the event of irreparable anatomic uterine abnormalities and RPL, In Vitro Fertilization (IVF) with transfer of embryos to an appropriately selected gestational carrier also may be a clinical consideration.[9]

The cervix is very important in the development of a pregnancy. The non-pregnant cervix is normally composed of a dense collagenous fibroconnective tissue with small amounts of smooth muscle to give it a tough texture. In pregnancy, the increased water content and vascularity in the cervix leads to a softening and a blue coloration. Throughout pregnancy the cervix and lower uterine segment change but maintain a "functionally intact" internal os. If there is painless dilatation or effacement of the cervix, usually occurring between the mid second trimester (about 20 weeks gestation) to the early third trimester (about 27-30 weeks), this is usually the result of an incompetent cervix. Pregnancy losses at progressively earlier gestational ages often reflect an incompetent cervix that gives way earlier with each subsequent pregnancy. The fetal membranes (chorionic and amniotic membranes) can sometimes be found bulging from the open cervix . Generally, 80-90% of women with cervical incompetence as their cause for recurrent pregnancy loss will deliver a viable live born following cerclage placement.

Inherited Thrombophilias; Factor V Leiden

Factor V is a coagulation factor that is normally cleaved and inactivated by activated protein C (APC). Patients with a single point mutation in the gene coding for factor V produce a mutated factor V (called Factor V Leiden) that is resistant to inactivation by ACP resulting in increased production of thrombin and a hypercoagulable state. This mutated gene is inherited as an autosomal dominant trait and is the most common cause of thrombosis and familial thrombophilia, with a prevalence of 3-5% in the general population.

Screening for inherited thrombophilias (specifically, factor V Leiden and the prothrombin gene mutations, protein C, protein S, and antithrombin deficiencies) may be clinically justified when a patient has a personal history of venous thromboembolism in RPL. An association between hereditary thrombophilias and fetal loss has been suggested.[10]

Hormonal and Metabolic Factors

As long as thyroid-stimulating hormone (TSH) levels are in the normal range, there is insufficient evidence to recommend routine thyroxine (T4) testing or screening for anti-thyroid antibodies. However, this is problematic given the lack of consensus regarding the definition of a normal upper limit of TSH.

Evidence exists that positive thyroperoxidase antibody (TPO Ab) even in euthyroid women, may increase the risk of recurrent pregnancy loss. TPO Ab constitutes a risk factor for hypothyroidism, miscarriage, impaired motor and

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mental development in the offsprings.[11] The prevalence of TPO Ab is much higher in women with a history of recurrent pregnancy loss, even those with normal thyroid function.[12]

Prolactin is commonly measured because elevated prolactin levels are associated with ovulatory dysfunction. Hyperprolactinemia may be associated with infertility through alterations in the hypothalamic- pituitary-ovarian axis, resulting in impaired folliculogenesis and oocyte maturation, and/or a short luteal phase. Lower basal serum prolactin concentrations were associated with an increased risk of miscarriage in a subsequent pregnancy in women with unexplained RPL. Normalization of prolactin levels with a dopamine agonist improved subsequent pregnancy outcomes in patients with recurrent pregnancy loss.[13]

Administration of progesterone to women with sporadic miscarriages is ineffective. However, in patients with three or more consecutive miscarriages immediately preceding their current pregnancy, empiric progestogen administration may be of some potential benefit. Progesterone is the principal factor responsible for the differentiation of proliferative endometrium to secretory, rendering the endometrium receptive to embryo implantation. In 1943, Jones first discussed the concept of insufficient luteal progesterone resulting in either infertility or early pregnancy loss. This disorder was defined as inadequate endometrium maturation resulting from a qualitative or quantitative disorder in corpus luteal function. Endometrial biopsy is the gold standard in diagnosis of luteal phase defect (LPD). Although LPD has been reported in 23-60% of women with recurrent miscarriage, as many as 31% of normally fertile women have an LPD according to the results from serial endometrial biopsy procedures. Although it is known that post-implantation failure or early nonviable pregnancy are associated with low serum progesterone levels, there is no evidence that progesterone supplementation in patients with LPD would restore the normal hormonal profile.[14]

Infection

Many organisms have been implicated in sporadic causes of miscarriage, but common causes of recurrent pregnancy loss have not been confirmed. Most patients with history of recurrent miscarriage do not benefit from extensive infection work up.

Given the lack of prospective studies linking any infectious agent to recurrent early pregnancy loss, any use of antibiotics is not supported by the evidence.[15]

Psychological Factors

Women with sporadic and recurrent miscarriage show high levels of pregnancy-related fear and state anxiety. It seems that early pregnancy-related fear correlates significantly with complications during pregnancy and

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delivery.[16] A possible psychological etiology for recurrent pregnancy loss was suggested by a published trial with expanded data in a later publication.[17]

Alloimmune Factors

Miscarriage may occur when the maternal immune response to antigen of placental or fetal tissue is abnormal. Human leukocyte antigen (HLA) has been reported as such an alloimmune response inducer. HLA sharing is a condition in which the normal process that allow the creation of maternal blocking antibodies in pregnancy is decreased.[18]

A meta-analysis of trials on paternal white blood cell immunization concluded that immunization had no beneficial effect.[19]

Treatment with intravenous immunoglobulin (IVIG) has also been proposed for unexplained pregnancy loss. However, several trials and meta-analyses concluded that IVIG is ineffective for primary recurrent pregnancy loss, thus this treatment is not recommended.[20]

Sperm DNA Fragmentation

There is a documented link between DNA damage in sperm and miscarriage. A recent meta-analysis including 16 studies found a highly significant increase in miscarriage rate in couples where the male partner had elevated levels of sperm DNA damage compared to those where the male partner had low levels of sperm DNA damage.[21]

Lifestyle, Environmental and Occupational Factors

Cigarette smoking has been suggested to have an adverse effect on trophoblastic function and is linked to an increased risk of sporadic pregnancy loss. Obesity has also been shown to be associated with an increased risk of RPL in women who conceive naturally.[22] Other lifestyle habits such as cocaine use, alcohol consumption (3 to 5 drinks per week), and increased caffeine consumption (>3 cups of coffee, have been associated with risk of miscarriage).

Ongoing Research

A. T helper 17 (TH17) cells have been shown to be important in host defense against extracellular infectious agents, autoimmune disease and chronic inflammatory diseases. Recently, TH17 cells have also been shown to participate in successful pregnancy, as well as in the pathogenesis of diseases of pregnancy, such as recurrent spontaneous abortion and pre-eclampsia.[23]
B. Additional areas for future testing include sperm, semen and related factors necessary for successful fertilization. Determination of conditions for production of growth factors necessary for implantation in the uterus is

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also under study. Finally, the determination of conditions necessary for the vascularization of the placenta and growing fetus by activated natural killer (NK) cells is being evaluated. These areas are novel but understanding their role in pregnancy may lead to insight into the treatment of pregnancies with complicating factors.[24]

SUMMARY OF MEDICAL EVALUATION

Recurrent pregnancy loss is defined as 2 or more consecutive pregnancy losses before 20 weeks gestation. There is strong evidence for testing of thyroid diseases, autoimmune disorders, thrombophilias, diabetes, prolactinomas and uterine malformations.

Health care providers need to encourage patients to talk about their feelings, acknowledge their grief, and assist in helping them cope with the loss.

FINAL THOUGHTS

Recurrent miscarriage is a difficult emotional battle for many women. Health care providers need to spend extra time with the affected couples to understand their feelings following pregnancy loss, so as to find out solutions for their grief reaction. Providers need to be empathic, sensitive and supportive of couples faced with this loss. There is a need for greater awareness among health care providers about the emotional and psychological reactions following RPL.

Physicians should work with patients to develop good strategies to cope with their grief and anger. For the patient in the vignette, it would be appropriate to acknowledge her feelings, educate her about possible causes of recurrent miscarriage, and start the clinical work up to identify possible causes of her RPL.

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Challenging Office Cases in Obstetrics and Gynecology

The care of Office Obstetrics and Gynecology patients can be quite challenging at times. This book, *Challenging Office Cases in Obstetrics and Gynecology*, describes 30 complex topics which may be difficult to manage due to its rarity. It also offers literature review and concrete suggestions for management options. It will help the practitioners improve care to women patients in the office setting.



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