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# Recurrent Spontaneous Miscarriages

THIRD EDITION

Pankaj Desai

JAYPEE

# Contents


**1. Introduction to Recurrent Spontaneous Miscarriages—An Overview** **1**

- Recurrent Spontaneous Miscarriages and Obstetric Vasculopathies *2*

**2. Ultrasonographic Features of Fetal Demise** **4**

- Terminology *4*
- Gestational Sac Features *4*
- Subchorionic Hemorrhage *6*
- Fetal Cardiac Activity *9*
- Yolk Sac *14*
- Doppler Findings *16*

**3. Anatomical Causes of Recurrent Spontaneous Miscarriages** **17**

- European Society of Human Reproduction and Embryology/European Society for Gynaecological Endoscopy Consensus on Diagnosis of Female Genital Anomalies *18*
- Congenital Uterine Anomalies *22*
- Acquired Uterine Anomalies *28*
- Cervical Incompetence *31*

**4. Immunology of Recurrent Pregnancy Miscarriage** **42**

- Hyperhomocysteinemia and Recurrent Miscarriage *43*
- Systemic Lupus Erythematosus *44*
- Leads for Obstetric Vasculopathies through Recurrent Spontaneous Abortion *44*
- Fetus as an Allograft *44*
- Partner Specificity in Miscarriages *54*
- Autoimmunity in Recurrent Pregnancy Loss *56*
- The Miracle of Paradox *67*

- Laboratory Evaluation *68*
- Treatment *69*

**5. Genetics of Recurrent Miscarriages and Other Pregnancy Losses** **77**

*Sharad Gogate*

- Etiology *77*
- Blighted Ovum and Missed Abortion *81*
- Syndromes *84*
- Chromosomal Abnormalities and Fetal Malformations *84*
- Investigative Workup for Genetic Causes of Recurrent Pregnancy Loss *85*
- Genetic Counseling *90*
- Management *91*

**6. Endocrinal Causes of Recurrent Spontaneous Miscarriages** **94**

- Diabetes and Recurrent Spontaneous Miscarriages *95*
- Thyroid Abnormalities and Recurrent Spontaneous Miscarriages *95*
- Progesterone and Recurrent Spontaneous Miscarriages *96*
- Progesterone and Human Chorionic Gonadotropins Supplementation in the Treatment of Recurrent Spontaneous Miscarriages *98*
- Luteinizing Hormone Endocrinopathy and Recurrent Spontaneous Miscarriages *103*
- Polycystic Ovarian Syndrome—Insulin Resistance and Recurrent Pregnancy Loss *106*

**7. Endometriosis and Recurrent Spontaneous Miscarriages** **115**

- Endometriosis and Pregnancy Loss—Examining the Evidence *115*
- Possible Causes of Endometriosis and Pregnancy Loss *117*

**8. Infections and Recurrent Spontaneous Miscarriages 121**
- Essentials of Laboratory Diagnosis for Proving the Association between Specific Organism and Recurrent Pregnancy Loss *123*
- Specific Infections and Recurrent Pregnancy Loss *124*

**9. Psychological Bearings of Recurrent Miscarriages 129**
- Immunology, Psychology and Recurrent Pregnancy Loss *130*
- Providing Psychological Support to Subjects with Recurrent Pregnancy Loss *131*
- Components of Support Giving that may be Helpful *132*

**10. Evidence-based Practice in Recurrent Spontaneous Miscarriages 135**
- Classification of Evidence Levels *135*
- Genetic Factors *137*
- Anatomical Factors *138*
- Cervical Weakness *139*
- Endocrinal Factors *139*
- Progesterone Supplementation *140*
- Human Chorionic Gonadotropin Supplementation *140*
- Immune Factors *141*
- Infections and Recurrent Spontaneous Abortion *142*
- Other Treatments *143*
- Allied Aspects *144*

**11. Approach to a Subject with Recurrent Spontaneous Miscarriages 148**
- The First Consultation *148*
- On Conception *152*

*Index* *155*

Chapter 4

# Immunology of Recurrent Pregnancy Miscarriage

JAYPEE BROTHERS

## INTRODUCTION

It is now well established that recurrent spontaneous miscarriages of immunological origin are one more manifestation of obstetric vasculopathies. In simplest terms, obstetric vasculopathy means disease of vessels resulting from an obstetric event. Though this is the first step to the understanding of obstetric vasculopathies, it is the simplest and most preliminary step. Immediately from here the complexity of this science begins. It is indeed this complexity that makes it very beautiful but challenging, intriguing, and therefore inviting for its keen students to decode its mysteries.

Obstetric vasculopathy is not the vasculopathy that occurs in the maternal vascular system. It is the vasculopathy that occurs at the fetomaternal interface. Inherited probably by the genetic propensity at the fetomaternal system, there occurs a series of changed at this interface which invites seemingly totally diverse and apparently unrelated conditions.

In early understandings, it was perceived that one condition leads to the other. But as advances in understanding increased it became obvious that this is not a cause-effect relationship but are fruits of the same pathology. In the initial years, only a few conditions were attributed to obstetric vasculopathy, viz.:

- Recurrent spontaneous miscarriages
- Intrauterine growth retardations (IUGRs)
- Preeclampsia (PE) and PE remote from term
- Accidental hemorrhage
- Chorea gravidarum.

However, with scientific research going in details of these conditions, more specifics and complexities added up. Currently, obstetric vasculopathies include:

- Recurrent spontaneous missed abortions of late 1st trimesters and 2nd trimesters.
- Accidental hemorrhage with association of IUGR or PE remote from term.
- Fetal demise of nonanomalous pregnancies with an association of any one of the earlier conditions.

With the etiopathology becoming clearer, it has become clear that the differentiation of PE remote from term from PE was unnecessary. It was, therefore, subsequently dropped.

## HYPERHOMOCYSTEINEMIA AND RECURRENT MISCARRIAGE

Hyperhomocysteinemia is a relatively newer addition in the field of understanding of recurrent spontaneous miscarriage. Homocysteine (Hcy) is a sulfur-containing amino acid produced when methionine is demethylated. The majority of Hcy undergoes transsulfuration to cysteine by cystathionine beta-synthase (CBS), of which vitamin B6 (pyridoxine) is an essential cofactor. The remainder of Hcy is remethylated by methionine synthase (MS), of which vitamin B12 (cobalamin) is an essential cofactor along with methylenetetrahydrofolate (MTHF). MTHF is generated by the enzyme MTHF reductase (MTHFR). High levels of Hcy can result from a variety of acquired factors (deficiency of vitamins B6, B12 and folic acid, high meat diet, smoking, and others) or genetic (abnormalities of methionine-Hcy metabolism). Hyperhomocysteinemia is associated with premature atherosclerosis and venous thromboembolism, so called "cholesterol of XXI age". Results of many studies suggest that hyperhomocysteinemia, homozygous state for MTHFR gene mutation, and folate deficiency are probably risk factors for recurrent fetal loss, intrauterine fetal death, thromboembolic disease in pregnancy, neural tube defects and congenital cardiac malformation at infants, and other placental conditions (PE, placental abruption, and IUGR). The plasma Hcy values can be modulated by vitamins, vitamin B6, and folic acid in particular.[1]

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## SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) associated pregnancies are an individual class. They have a magnified manifestation of vasculopathy thereby enabling a closer look at this miraculous but mysterious phenomenon. It needs to be clarified here that all obstetric vasculopathies are not SLE but SLE does produce obstetric vasculopathy. Also, immunology and its disturbances have a significant role to play in obstetric vasculopathy. These aspects will be handled in details in the following pages of this chapter.

## LEADS FOR OBSTETRIC VASCULOPATHIES THROUGH RECURRENT SPONTANEOUS ABORTION

There are explainable and unexplainable causes of recurrent spontaneous abortion (RSA). The classic example of explainable causes includes the anatomical defects of the genital tract, both congenital and acquired. However, the most intriguing and therefore the most challenging among all causes remain immunological causes. They are very complicated to understand and a test to treat. Nevertheless, they prove very vital leads to the understanding of obstetric vasculopathy.

## FETUS AS AN ALLOGRAFT

It is well understood that the fetus is immunologically a very dynamic structure. It bears an expression of maternal as well as paternal antigens on itself. Any foreign protein that enters a human body generates a series of immunological reactions in the host. These are the responses that ultimately destroy the entrant to protect the host. On these very lines, the fetus is also a graft, albeit an allograft that is transplanted into the mother's body. It has in itself an expression of maternal and paternal alloantigens. The fetus, therefore, behaves as a transplanted graft. It has been a big challenge for all transplant scientists to understand how does the fetus quiescence the host reaction and generates a peaceful acceptance. This phenomenon is the key to any graft acceptance.

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There is no reason why the fetus also should not be treated as a graft. Attempts are bound to be made by the maternal immune system to reject it. The paternal alloantigens are foreign to the maternal immune system. They generate the graft-host reaction. The maternal antigens are not alien to the mother. They are her own. Therefore, the mother accepts those antigens. But the paternal antigens have no business to expect such a warm welcome and tolerance by the mother's system.

Now that it has been understood that the fetus is an allograft which too has an expression of antigens, the question that arises is why does the fetus escape from the rejection phenomenon? Not only does the fetus not get rejected but it is also made to thrive and is nourished. On one side are the protective mechanisms in the mother that readily reject any foreign graft and on the other are the maternal system that tolerates, accepts, nourishes, and ensures that the fetal allograft thrives. What provides this privileged status to the fetus? How does this miracle occur? The antigens that have been found to have a significant bearing on this entire phenomenon are the antigens of the major histocompatibility complex (MHC). These antibodies have been documented to bind the cells of the fetus and the trophoblast.

## What Protects the Fetus?

Due to ethical constraints, most of the understanding of human pregnancy and the immunological response comes from studies in mice. Mice too have a hemochorial pregnancy and are therefore providing valuable insight into the understanding of human pregnancy tolerance.

### *Small Size*

The small size of the embryo does help in protecting it. The effector cells from the maternal system that may have strayed into the fallopian tube or the peritoneal pelvic fluid fail to detect this small embryo. Also, due to this small size, there is no interaction between the maternal lymphatic systems and the embryo. This small size also prevents the detection of the embryo while it transits from

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the fallopian tube to the uterus. Hill (1987) demonstrated that if for whatever reason, the macrophage effector cell system does get activated; it effectively releases destructive cytokines like tumor necrosis factor-alpha (TNF-α) and granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-1, interleukin-6, and others.[2] It can lead to implantation failure following embryo damage. The fact that these inflammatory substances do play a critical role in protection–destruction interplay of the fetal allograft has been demonstrated in another study in which it was found that for the first time that allograft inflammatory factor-1 (AIF-1) was expressed in uterus. The expression level was associated with the population size of macrophage and varied during the estrous cycle and the pregnancy period. The augmented expression of AIF-1 with concomitant expressions of TNF-α and nitric oxide synthase 2 (NOS2) messenger ribonucleic acid (mRNA) in poly (I:C) injected mice suggests a correlation between AIF-1 production and fetal resorption.[3]

## *Zona Pellucida*

The shield provided by the zona pellucida plays a treasured role in the failure of the maternal protective system while the embryo is in its phase of transit migration. It is not precisely understood as to whether the zona provides a physical barrier to the detection by the maternal protective systems only or also makes the embryo hypoantigenic. The role of zona in protecting the conceptus is confined to the transit. It is proved by it getting shed off just before implantation. It is not required once the embryo reaches the uterus. One study has shown that the zona pellucida thickness has a significant influence on in vivo fertilization and implantation processes, but not on birth.[4]

## *Paralysis of Maternal Protector Systems and Pregnancy*

In the days when hysterosalpingography and Rubin's tubal insufflation tests were still attractive for tubal patency testing, clinicians know that there used to be successful pregnancies just after performing these tests. This phenomenon was more consistently observed after hysterosalpingography and is attributed to the transient paralysis

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or ablation of maternal macrophage effectors systems. This is the explanation to how the fetal embryo gets protected in transit. However, the bigger challenge lies in protecting, implanting, and bringing about a thriving growth of the conceptus.

## Hypoimmunogenic Embryo

The mechanisms of protection of embryo from getting destroyed by the maternal protective systems also include its hypoimmunogenicity. The embryo is always flat in creating an immune reaction. As it has been stated in previous pages, there are different types of antigens expressing on its surface. These include products of the MHC or major histocompatibility complex (H) such as human leukocyte antigen (HLA) and non-MHC or minor histocompatibility (h) gene complexes. It is interesting to note that expression of (H) is shut off before implantation. This process is an important change in the embryo to render it hypoantigenic.[5]

It seems the hormone leptin, which is primarily produced by adipose tissue, is a critical permissive factor for multiple reproductive events (in the mouse), including implantation. Throughout development, leptin patterning suggests that it is a component of the subcortical maternal complex with as yet unknown significance in preimplantation development.[6]

## Fetus as a Unique Allograft

A question arises in the investigators mind as to why does the fetus not get rejected. It is extremely complicated but fascinating phenomenon. The conceptus has two mechanisms of immunologically active strata. One is the fetus itself, and the other is the trophoblast. The fetal tissue is immunologically susceptible to recognition and rejection by the mother. This rejection would occur if there is a direct interaction between the fetal surface and the maternal lymphomyeloid cells. In animal experiments, it has been found that if the fetal tissue is directly injected into the thigh of mice, there is an immediate rejection of this tissue.[7] Direct contact between the maternal lymphocytes and fetal cells can also occur if

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there is an intrauterine transfusion accidentally or spontaneously. This contact leads to fetal rejection.

Entry of maternal cells in fetal circulation and entry of fetal cells into the maternal system is rare. But the maternal system has a significant advantage. It has a very competent effector system, and the intruding fetal cells are quickly and efficiently eliminated from the maternal protective system. If in any instance there is a failure of any of these systems graft-versus-host (GVH) diseases get manifested.

On the flip side, the phenomenon of fetal microchimerism has been found to have interesting bearings. Fetal cells can persist in a wide range of woman's tissues following a pregnancy or a miscarriage, and she becomes a chimera. Fetal cells have been found in the maternal circulation, and they were shown to persist for the entire life in humans, thus demonstrating long-term engraftment and survival capabilities. Microchimerism is a subject of much interest for a number of reasons. Studies of fetal microchimerism during pregnancy may offer explanations for complications of pregnancy, such as PE, as well as insights into the pathogenesis of autoimmune diseases which usually ameliorate during pregnancy. The impact of the persistence of allogeneic cells of fetal origin and the maternal immunological response to them on the mother's health is still not clear. On the beneficial side, it has been proposed that genetically dissimilar fetal microchimerism protects against some cancers, that fetal microchimerism can afford the mother new mechanisms of protection to some diseases, that fetal microchimerism can enlarge the immunological range of the mother improving her defense against the aggressor. Fetal cells are often present at sites of maternal injury and may have an active role in the repair of maternal tissues.[8]

Now let us see a very intriguing phenomenon. The estimated instance of the passage of maternal lymphocytes is believed to be rare but at 1 in 50 to 1 in 100 embryos. We have seen that if at any instance such an exchange if at all it occurs, the fetus gets rejected. Thus, the estimated spontaneous resorption rate (in mice) and miscarriage rate in humans should be around 1–2% (1 in 50 to 1 in 100). But in actual clinical practice, this rate is much higher. Thus,

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there is some more to explain than mere lymphocytes of the mother playing havoc.

This is where the second strata of immunological activity beyond the conceptus steps and this layer is the stratum of trophoblasts. It is well established since the mid-1980s that the trophoblasts are very specialized forms of tissues as regards genetic expression is concerned. There are two groups: One that is found primarily at the fetomaternal interface between the fetoplacental capillaries and maternal blood (fetal interface), the second is at the maternal interface in contact with the decidua.

Fetal trophoblasts are substantially dependent on paternal genetic material for their survival and development. However, if there is only paternal genetic material pathological pregnancies like gestational trophoblastic diseases develop. It means that the maternal genetic expression on the trophoblast helps in creating a balance. It is well known that there is an uncontrolled growth of trophoblastic tissue in hydatidiform mole. This uncontrolled growth is checked by the expression of maternal genetic material on trophoblast which brings about a healthy fetal growth and development.

It is fascinating to note that in the absence of maternal genetic expression the trophoblasts have a field day. This paradox is worth understanding. The maternal immune system is derived from the mother and therefore should not give any resistance to growth or survival of its own material. However, the paternal contribution is alien to the maternal effector system. The latter is supposed to react and protect the maternal system by eliminating any foreign genetic material. Nevertheless, at the fetomaternal interface, a complete reversal of this phenomenon occurs. Instead of removing the tissue with paternal genetic expression (alien to the mother), it brings about a growth of these trophoblasts.

A complete foreign or alien genetic material seems to promote trophoblastic growth. Only paternal genetic expression, however, brings about uncontrolled growth as is seen in hydatidiform mole. It appears that such an uncontrolled growth is prevented by the maternal genetic material. Thus, at the level of the trophoblast, an entirely paradoxical situation develops. Foreign genetic material promotes growth and genetic material from the host check

JAYPEE BROTHERS

this growth or may even hamper this growth. It seems that the trophoblast has a privileged status. This privileged status is given to the syncytiotrophoblasts.

An important characteristic of most trophoblasts is their capacity to resist rejection by the host antigen specific effectors mechanism. This privileged status of the trophoblast is the key to the survival and growth of a partly foreign genetic material on the conceptus in an alien environment (the maternal environment).

The early invasion of the trophoblast into the maternal spiral arterioles and their resistance to maternal elimination systems are the keys to healthy pregnancy outcome. As a corollary to this, any impendence or failure to this invasion can lead to complete rejection of fetal tissue. This phenomenon is seen in miscarriages. In subjects in whom the trophoblasts partially resist maternal rejection, manifestations of other obstetric vasculopathies result. Thus, pregnancy-induced hypertension (PIH) and IUGR are a result of partial rejection by the host.

Hence, it gets well established that paternal genetic expression is the key to the survival of fetal tissue. It is the paternal genetic material which is the growth driver in the trophoblast and subsequently in the fetus. The trophoblasts are extremely resistant to maternal rejection due to a paternal genetic expression which is a privileged status. This resistance is intrinsic.

The entire spectrum of healthy fetal growth and development along with resistance to rejection gets explained. At one end of the spectrum is a total failure of trophoblast to resist the maternal rejection systems. It results in a miscarriage. At the middle of the spectrum is an array of obstetric vasculopathies where there is a partial rejection or partial activation of maternal effectors systems not killing the conceptus but producing diseased states. On the other extreme of the spectrum is a hydatidiform mole. In this, there is only paternal genetic expression and no maternal expression. It gives a field day to the trophoblasts leading to their uncontrolled growth. Therefore, there is a strong genetic platform for the immunological basis for obstetric vasculopathies. These will be revisited in the pages to follow.

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## Suppressor Mechanisms in Protection

In this section, we shall see one more unique and unusual phenomenon that takes place at the level of the decidua which plays a significant role in the successful nidation and then a proper growth of the fetus. At this stage, it will be worthwhile noting that all these protective mechanisms act partly in tandem with each other and partially independent to achieve the ultimate goal of a successful pregnancy outcome. Scrupulous understanding of these mechanisms will play a pivotal role in our understanding of the processes involved in causation, and management of obstetric vasculopathies.

Just before implantation, workers like Brierley and Clark and Daya et al. have shown that unique populations of cells develop in the uterine lining. These are the suppressor cells. They are unique in ways more than one. They are developed under the hormonal influence and not under the influence of antigens. They are locally generated, confining themselves to the uterine lining, and not all across the mother's body. They are relatively large cells resembling the structure and function of T cells.[9,10] To understand the role of suppressor T cells, one has to know the concepts of DTH or delayed type of hypersensitivity reaction. If DTH is generated before the time, it can prove lethal to the process of successful implantation. However, the same process of DTH is necessary later to maintain a proper growth of the conceptus postimplantation.

Now let us see why these suppressor T cells get generated in the uterine lining. Firstly, they have a capacity to keep the maternal macrophages at bay. Secondly, they delay the generation of DTH preventing its occurrence in first 4 days. If DTH occurs as early as the first day of implantation, it will sense an allergen-like antigen in the implanting conceptus. This premature sensing will bring about changes to cause its rejection. It also includes activating macrophages. Whether the suppressor T cells can keep the macrophages at bay individually or through the delay in generation of DTH is not known.

By the fifth postimplantation day, these large T-cell suppressors get replaced by smaller suppressor cell population. This replacement is necessary as the new population of cells has a different role to

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play besides protecting the conceptus. They also have a function to generate potent immunological molecule RGF-B which promotes new blood vessel formation and growth. These are early steps being taken to generate a healthy growth of the conceptus.

Before we go further into the depth of understanding the role of these new suppressor cells, we need to revise some basic facts. The conceptus is half alien to the mother. Therefore, the tendency of the maternal protecting systems to reject and eliminate it is understandable. Through a series of complicated but amazing mechanisms, the conceptus protects itself from getting eliminated. At the same time, the maternal protective systems help the conceptus to successfully implant and then nidate and grow.

To understand this complex phenomenon a little more easily, one can draw a parallel in something that is occurring in the world, so naturally. Every large and thriving country has a problem of illegal migrants. India too has such a problem. Simplistically put, the conceptus is such an illegal migrant. Illegal immigrants devise different mechanisms by which sneak in through the Indian borders. To avoid detection, it may sneak in at night or through porous areas on the Indian borders. Once within the territory of India, politicians who may have been bribed or may have same political ulterior motives generate mechanisms by which this migrant gets some foothold either at some shanty dwelling or as a guest of some host without getting detected. Soon the politician becomes his protector and generates illegal housing, ration benefits and subsequently even gets him a voting right. The migrant under the patronage of his protector soon starts getting accepted in his new country. He starts growing in acceptance, starts his own business, or gets some other employment. As time passes, he grows so much in stature that even becomes an accepted leader thereby influencing the entire host mechanism in its favor.

The fetus also behaves similarly. As pregnancy advances, it grows in size and maturity and changes the whole maternal physiology in such a way that it may even endanger the mother's life to ensure its survival. This newly generated smaller suppressor cell crop can suppress destruction of the embryo by releasing a potent immune suppressive molecule like transforming growth factor-beta (TGF-β).

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This molecule seems to be inhibitive to natural killer (NK) cells and suppresses the plethora of destructive cytokines like interleukin-3 (IL-3). Thus, this TGF-β appears to have a potent capacity to block nearly all maternal effectors systems.[11,12]

It seems that TGF-β and TNF-α has a point to point antagonizing mechanism as regards to their effects on immune mechanisms.[13] While one protects and prepares for the growth and development of the conceptus, the other is a potent protector of the mother. TNF-α is all out to destroy any immunologically alien molecule, in this case, the conceptus. It gets neutralized by TGF-β.

From a bird's eye view, it seems the general opinion is that the fundamental protective mechanism must be located locally on the contact plate, between the maternal and fetal tissues. Immunologic investigations proved the presence of specific systems which block the function of antipaternal maternal antibodies, as well as the formation of cytotoxic maternal T-cells to paternal antigens. The system preventing rejection of graft during pregnancy is operating at the level of maternal and fetal tissues. The protective mechanisms are coded by genes of MHC region, locus HLA-G.

## Protective Mechanisms in the Placenta

The placenta protects itself against antibody-mediated damage. High levels of complement regulatory proteins (CD46, CD55, and CD59) are produced in response to the synthesis of complement fixing maternal antibodies to paternal antigens. Regulation of the placental HLA expression as a defensive reaction of the fetoplacental unit to the influence of protective cytotoxic T lymphocytes (CTLs) is the most important protective mechanisms of the placenta.

## Protective Mechanisms Shared by the Placenta and Uterus

Protective mechanisms common both for placenta and uterus are as follows: Expressions of Fas ligand, prevention of infiltration of activated immune cells, regulation of immunosuppression which prevents the proliferation of immune cells, and high natural immunity (Na cells and macrophages) of the decidua.[14]

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## PARTNER SPECIFICITY IN MISCARRIAGES

In the early 90s, there was a trend to classify women who abort as primary aborters and secondary aborters. Primary aborters were those mothers who aborted all her pregnancies and never had a successful outcome. On the other hand, secondary aborters were those who at some time or the other have had at least one successful outcome. By successful outcome, it was meant as a live birth. Interestingly primary miscarriages seemed to be partner specific and secondary aborters, aborted irrespective of the partner. Though this classification did not become clinically popular, it raised some interesting questions.

It is possible that partner specific miscarriages could have a genetic basis, but nonpartner specific miscarriages have an explanation beyond the faulty genetic material. Currently, it is accepted that majority of miscarriages result from immunological problems. This issue can be simply worded as failure to prevent rejection. It is fascinating to note that 25% of mothers threaten a miscarriage, but only 10% actually abort. It means that while the maternal system is all out to reject it (threatened abortion), the fetal system protects itself from the rejection onslaught and successful outcome results. If fetal heart activity can be detected in the 1st trimester more than 90%, conceptuses gestate successfully. Thus, the onus of initial survival of the fetus against the maternal onslaught is not on the shoulders of the mother but in the fetus itself.

Also, the clinical phenomenon of threatened miscarriage is merely a clinical expression of the ongoing conflict between the fetal system to survive and the maternal system to destroy. As it has been hinted in some of the preceding pages cytokines have a vital role to play in this process. It is well known that there are a set of protective cytokines and destructive cytokines. This activity occurs throughout the maternal vascular channels. As a result of this, there is an injury and rupture of the vascular system resulting in threatened miscarriage clinically.

However, it is not necessary that the destructive cytokines should win or lose. The war may go on any side. If the destructive cytokines win, the mother aborts. If protective cytokines win, it results in

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# Recurrent Spontaneous Miscarriages

This third edition of the highly popular and fast-seller *Recurrent Spontaneous Miscarriages* has come out in a short span of time. It shows the popularity of the book and its clinical usefulness. This new edition has many nuances and latest references incorporated within. Aspects of obstetric vasculopathies in reference to recurrent miscarriages have been specifically handled. Special attention has been given to recent advances in genetics, endocrinology, immunology and ultrasonography in approach to a subject with recurrent miscarriages. Frequently asked questions regarding the use of heparin, progesterone, HCG and other supplements have been refreshed in the light of latest literature. Literature review has been stretched to include references upto the end of 2017. Evidence-based practice in recurrent miscarriages with practical tips to the management of these cases has been continuously kept in mind while preparing this new edition. Profusely illustrated with pictures, tables and laced extensively with clinical case studies this book will make the students and clinicians best equipped to approach the enigma of recurrent miscarriages in the most modern way.



**Pankaj Desai** MD FICOG FICMCH is one of the best known academicians and educators in Obstetrics and Gynecology in India. All his eleven books published till date, have proved to be bestsellers, one of which was awarded the best book award, in the subject, in India. A prolific writer, he has contributed 39 chapters to different textbooks internationally and nationally. His outstanding academic contributions in the subject have been acknowledged and honored with 7 gold medals and 57 orations. An extremely popular teacher that he is, he has delivered 677 guest lectures in different parts of India and the world at the time of this book going for print. He has published 100 research papers in peer-reviewed journals till date, 9 of which have been awarded best research paper prizes. His website www.drpankajdesai.com has become an extremely popular portal for students and practitioners of the subject seeking references and up-to-date knowledge. It has invited nearly 187000 hits by the time of this publication. His blogs on different academic and non-academic aspects being published on the net as Dr Pankaj Desai's blogs have also become very popular inviting more than 63000 reads as of now. His webinars conducted periodically on the net invite thousands of logins all throughout the world.

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