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UNRAVELLING THE COMPLEXITY OF RECURRENT SPONTANEOUS ABORTION: COMPREHENSIVE INSIGHTS INTO CONTRIBUTING FACTORS AND FUTURE DIRECTIONS

***Prof. Asaad Babker**

Department of Medical Laboratory Sciences, University of Science and Technology, Omdurman, Sudan.

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***Corresponding author:**

***Prof. Asaad Babker**

Department of Medical Laboratory Sciences, University of Science and Technology, Omdurman, Sudan.

ABSTRACT

Recurrent spontaneous abortion (RSA), characterized by two or more consecutive pregnancy losses, remains a significant reproductive challenge, affecting approximately 1-3% of couples of reproductive ages. Its etiology is highly complex and multifactorial, encompassing genetic, anatomical, hormonal, immunological, infectious, environmental, and acquired thrombophilia factors. Despite considerable progress in reproductive medicine and diagnostics, over half of RSA cases remain unexplained, underscoring the intricacies of its pathogenesis. This review synthesizes current knowledge on the diverse contributors to RSA, including chromosomal abnormalities, uterine anomalies, endocrine dysfunctions, immune dysregulation, infections, and both inherited and acquired thrombophilia's. It examines the physiological mechanisms underlying pregnancy maintenance and loss, highlighting the roles of hemostatic changes, immune tolerance, and genetic predispositions. Additionally, the review identifies existing gaps in research and clinical practice, emphasizing the importance of integrated, personalized approaches for diagnosis and management. Recognizing key risk factors such as thrombophilia and chromosomal aberrations is essential for targeted interventions. Future research should prioritize elucidating gene-environmental interactions and developing innovative diagnostic and therapeutic strategies, ultimately aiming to improve pregnancy outcomes and provide comprehensive support for affected individuals and couples.

KEYWORDS: Recurrent Pregnancy Failure, Multifactorial Pregnancy Loss, Gestational Thrombosis, Genetic and Environmental Interplay, Embryonic and Uterine Factors, Hemostatic Dysregulation, Reproductive Immunopathology, Chromosomal and Coagulation Anomalies, Pregnancy Viability Factors, Obstetric Genetic Predispositions.

1. GENERAL INTRODUCTION

Spontaneous abortion and miscarriage are interchangeable terms. In the medical literature, spontaneous abortion is more commonly used, whereas in clinical practice and among the general population, the term miscarriage is preferred. Spontaneous abortion or miscarriage is defined as the involuntary termination of pregnancy before 20 weeks of gestation. Recurrent pregnancy loss (RPL), also known as recurrent miscarriages, is characterized by the consecutive loss of two or more pregnancies with the same partner and no more than one living child.[1–4] Additionally, RPL is defined as two or more consecutive pregnancy losses before twenty weeks of gestation, affecting

approximately 1-3% of couples. The American Society for Reproductive Medicine considers RPL to involve two or more prior miscarriages, while the European Society of Reproduction and Embryology defines it as three or more.[5,6] The precise frequency of miscarriages remains uncertain, as many occur before the woman is aware of her pregnancy.

There are numerous factors that may cause recurrent pregnancy loss (RPL), yet the underlying disorder often remains undetected. Although significant research has been conducted to understand the mechanisms involved, the cause of miscarriage can typically be identified in only about 50% of cases. Known causes of RPL include chromosomal and metabolic abnormalities, uterine anomalies, and immunologic factors. RPL is estimated to affect 2%–4% of couples of reproductive age.[7,8] Recurrent pregnancy loss represents one of the most challenging and frustrating areas in reproductive medicine because its etiology is frequently unknown, and there are limited evidence-based diagnostic and treatment options. Studies on the causes, evaluation, and management of RPL often exhibit methodological limitations, such as not adhering to accepted criteria for RPL, ascertainment bias, improper control selection, inconsistent cohort monitoring, failure to exclude aneuploid fetuses, and lack of stratification for key factors like the number of previous losses.[9]

Pregnancy associated with hypercoagulability establishes a foundation for hemostatic abnormalities during gestation and may be linked to pregnancy complications. Thrombophilia is a controversial issue that might be prevalent among women with unexplained recurrent pregnancy loss, with some studies reporting a prevalence as high as 65% in selected populations. The inherited forms of thrombophilia include activated protein C resistance, protein S deficiency, protein C deficiency, antithrombin III deficiency, factor II (prothrombin) mutation, and hyperhomocysteinemia.[10,11]

Epidemiologic data indicate that patients with a history of poor obstetric outcomes are at a significantly increased risk of recurrence. Inherited thrombophilic conditions are increasingly recognized as contributing to adverse pregnancy outcomes; however, paradoxically, most women carrying common mutations such as Factor V Leiden, methylene tetrahydrofolate reductase (MTHFR) gene mutations, and prothrombin gene mutation (G20210A) remain asymptomatic. Both acquired and hereditary thrombophilia have been associated with negative pregnancy results. A higher frequency of early recurrent abortion has been linked to variants such as factor V Leiden, MTHFR C677T, and prothrombin G20210A.[12–14] The suspected causes of recurrent miscarriage are diverse and include genetic, environmental, infectious, metabolic, endocrine, and anatomical factors. The most well-characterized causes are parental chromosomal abnormalities, metabolic irregularities, and structural anomalies.

2 Normal pregnancy

Pregnancy is a period of reproduction during which a woman carries one or more live offspring from implantation of a fertilized zygote in the uterus throughout gestation. Childbirth usually occurs about 38 weeks after conception; in women who have a menstrual cycle length of four weeks, this is approximately 40 weeks from the start of the last normal menstrual period. The normal menstrual cycle is 28 days long, with ovulation usually occurring on day fourteen. Implantation of the fertilized zygote occurs 7 days after conception, which is day 21 of the cycle. A normal pregnancy lasts 40 weeks (plus or minus two weeks), counted from the date of the last menstruation, which is two weeks longer than the age of the fetus. About once every 28 days, in the middle of a woman's menstrual cycle, an ovum bursts from one of her ovaries and is drawn into one of two fallopian tubes that lead to the hollow uterus. While the ovum is traveling, the spot on the ovary from which it was released, now called the corpus luteum, secretes hormones that prepare the lining of the uterus to receive a fertilized ovum. If pregnancy does not occur, the corpus luteum shrinks, and the lining of the uterus is discarded two weeks later with menstruation.[15-18]

2.1 Physiological and hemostatic change during pregnancy

Pregnancy is associated with normal physiological changes that assist the nurturing and survival of the fetus. Biochemical parameters reflect these adaptive changes in most organ systems and are clearly distinct from the non-pregnant state. The physiology of normal pregnancy involves major changes in the coagulation system. These changes appear to be related to the development of the uteroplacental circulation and provide a protective mechanism during delivery.[19]

Hemostasis is the complex process that maintains the balance between clotting and bleeding. It is composed of several tightly coupled biochemical reactions involving the dynamic interaction between circulating coagulation factors, the anticoagulation and fibrinolytic systems, vascular endothelium, platelets, and blood flow (Furie and Furie, 2008). Physiological changes in pregnancy affect the coagulation and fibrinolytic systems. Many of the clotting factors increase and anticoagulation factors decrease causing augmented coagulation and decreased fibrinolysis. Preexisting coagulopathy may affect the course of pregnancy, and the nature of coagulopathy may also be modified by pregnancy. Changes in coagulation affect the mode of delivery and the approach to analgesia and anesthesia in patients with hypercoagulable disorders. Different physiological changes occur during the process of pregnancy, which affect all of the woman systems; these include metabolic adaptations and hormonal changes. However, we are interested in those changes that affect the coagulation factors. It is due to secondary increase in the concentrations of pre-coagulant factors, a reduction of the naturally occurring

anticoagulant proteins and increase in fibrinogen, which characterized pregnancy with hypercoagulability.[20,21] Normal pregnancy is associated with increased concentrations of most clotting factors, decreased or unchanged concentrations of natural anticoagulants and reduced fibrinolysis. These changes are interpreted as mainly being due to increased estrogen levels. During normal pregnancy dramatic changes occur in the haemostatic system. Coagulation factors increase physiologically in pregnancy, and this is thought to be an evolutionary mechanism to prevent excessive blood loss at childbirth These physiological changes in the coagulation system may increase the risk of pregnancy failure if are associated with thrombophilia.[22]

2.3 Abnormal Pregnancy

Sometimes a pregnancy ends unhappily, but it is not technically a miscarriage. There are four main types of abnormal pregnancies. These include an early pregnancy failure, an ectopic pregnancy, a blighted ovum, and a molar pregnancy. It is important to know the signs and symptoms of abnormal pregnancies, so that you can seek our medical attention, if you believe you are at risk.

2.4 Ectopic pregnancy

It is a normal fertilized egg that gets stuck in the fallopian tube or falls into the abdominal cavity and implants there. This type of pregnancy cannot survive to term and increases risk for severe hemorrhage and possibly even death to pregnant women. When the ectopic is discovered, it is essential to surgically and immediately remove the baby. Symptoms associated with this situation include sharp, intense pain in abdomen or possibly in shoulders; a pregnancy test that is positive, then turns negative a few days later; and spotty red bleeding that continues. With rare exceptions, ectopic pregnancies are not viable. Furthermore, they are dangerous for the mother, since internal hemorrhage is a life-threatening complication. Most ectopic pregnancies (93-97%) occur in the distal Fallopian tube (so-called tubal pregnancies), but implantation can also occur in the cervix, ovaries, and abdomen.[23]

Ectopic are usually caused by scar tissue in the Fallopian tubes that could have been caused by previous surgery in the pelvic region, uterus, tubes; a pelvic infection such as Chlamydia or pelvic inflammatory disease; or endometriosis that blocks the entrance to the tubes.

2.5 A Molar Pregnancy

A Molar Pregnancy is a very rare type of pregnancy, is an abnormal form of pregnancy in which a non-viable fertilized egg implants in the uterus and will fail to come to terms with. A molar pregnancy is a gestational trophoblast disease.

The baby usually does not form, but the uterus is filled with big bubble clusters. A molar pregnancy is caused when a sperm fertilizes an empty egg (called a complete molar pregnancy) and no baby grows, or when two sperm fertilize an egg, and both the baby grows a little as well as an abnormal placenta (called a partial molar.) Even if a baby does grow, it cannot survive. The longest documented molar pregnancy which has been seen was a 24-week stillbirth. Molar pregnancies usually present with painless vaginal bleeding in the fourth to fifth month of pregnancy. The uterus may be larger than expected, or the ovaries may be enlarged. The most common symptom is vaginal bleeding, especially between the 6th and 16th weeks of pregnancy. Another symptom is bleeding that continues for a long time after delivery. Small amounts of bleeding can show up as a watery brown discharge from the vagina, there may also be more vomiting than would be expected (hyperemesis). Sometimes there is an increase in blood pressure along with protein in the urine. Blood tests will show very high levels of human chorionic gonadotropin (HCG).[24]

2.6 A stillbirth

According to the National Stillbirth Society, stillbirth is defined as the intrauterine death and subsequent delivery of a developing infant that occurs beyond 20 completed weeks of gestation. A stillbirth is technically any pregnancy that ends after the 20th week and the baby does not survive. Some babies die in utero and are discovered when the heartbeat is not found. A stillbirth occurs when a fetus dies in the uterus. A wide variety of definitions exist.[25]

2.7 An an embryonic gestation

Early pregnancy failure (also known as blighted ovum or an embryonic gestation) is a common cause of miscarriage. An embryonic gestation (also known as a blighted ovum) is a pregnancy in which the very early pregnancy appears normal on an ultrasound scan, but as the pregnancy progresses a visible embryo never develops or develops and is resorbed. A blighted ovum causes about one out of two miscarriages in the first trimester of pregnancy. A miscarriage is when a pregnancy ends on its own within the first 20 weeks. The bleeding, if that happens before the blighted ovum is found via ultrasound, is slow and brown. Your pregnancy symptoms will seem to go away. A blighted ovum is believed to be caused by an egg or sperm with poor genetic material. When the egg is fertilized, instead of creating both a sac and a baby, the part that should be a baby never grows. Some women do experience more than one blighted ovum, but most women go on to later have a baby.

The criteria depend on the type of ultrasound exam performed. A pregnancy is an embryonic if a transvaginal ultrasound reveals a sac with a mean gestational sac diameter (MGD) greater than 25 mm and no yolk sac, or an MGD >25 mm with no embryo. Tranabdominal imaging without transvaginal scanning may be sufficient for diagnosing early pregnancy failure when an embryo whose crown–rump length is 15 mm or more has no visible cardiac activity.[26]

3. Recurrent Spontaneous abortion

Recurrent spontaneous abortion (RSA), which is also referred to as repeated pregnancy loss (RPL) and habitual abortion, is defined as three or more consecutive spontaneous miscarriages. The experience of repeated pregnancy loss is physically and emotionally traumatic to women who are trying to have children. The overall frequency of RM was estimated from 1% to 3%. The exact prevalence of RM depends on its definition. To date there is no consensus on the definition of RM about the numbers of previous miscarriages and the gestational age of RM. The American Society for Reproductive Medicine defines the numbers of previous miscarriages in RM as two or more whereas Europe Society of Reproduction and Embryology defines it as three or more.[27]

3.1 Stages and Types of Spontaneous Abortions

There are various stages and types of spontaneous abortions (threatened, inevitable, incomplete and complete abortions, missed abortion, and fetal/embryonic demise). These types are clearly defined as follows:

- Spontaneous abortion/miscarriage: A pregnancy that ends spontaneously before the fetus has reached a viable gestational age. The World Health Organization defines it as expulsion or extraction of an embryo or fetus weighing 500 g (typically corresponds to a gestational age of 22 weeks).

-Threatened abortion: Threatened abortions may progress to inevitable, spontaneous, incomplete, or complete abortions. With good medical management, most of these cases can reach full term and normal pregnancy. Bleeding through a closed cervical during the first half of pregnancy. The bleeding is often painless, although it may be accompanied by mild suprapubic pain. On examination, the uterine size is appropriate for gestational age, and the cervix is long and closed. Fetal cardiac activity can be detect-able if the gestation is sufficiently advanced.

- Inevitable abortion: When abortion is pending, there may be increased bleeding, intensely painful uterine cramps, and a dilated cervix. The gestational tissue can often be felt or visualized through the internal cervical.

- Incomplete abortion: When the fetus is passed, significant amounts of placental tissue may be retained, also called an abortion with retained products of conception (RPOC) (commonly occurs after 12 weeks' gestation). On examinations, the cervical is open, gestational tissue may be observed in the vagina/cervix, and the uterus is smaller than expected for gestational age but not well contracted. The amount of bleeding varies but can be severe enough to cause hypovolemic shock. Painful cramps are often present.

- Complete abortion: When an abortion occurs (usually before 12 weeks of gestation), and the entire contents of the uterus are expelled. More than one-third of all cases are complete abortions. If a complete abortion has occurred, the uterus is small and well contracted with a closed cervix; slight vaginal bleeding and mild cramping can be present.

- Missed abortion: Refers to in utero death of the embryo or fetus prior to the 20th week of gestation, with prolonged retention of the pregnancy (4–8 weeks). Vaginal bleeding may occur, and the cervix is usually closed.

- Septic abortion: An abortion accompanied by fever, chills, malaise, abdominal pain, vaginal bleeding, and frequently purulent discharge. Physical examination may reveal tachycardia, tachypnea, lower abdominal tenderness, and a tender uterus with dilated cervix. Infection is usually due to Staphylococcus aureus, Gram-negative bacilli, or some Gram-positive cocci. Mixed infections (anaerobic organisms and fungi) can also be encountered. The infection may spread, leading to salpingitis, generalized peritonitis, and septicemia.[28]

3.2 Incidence of recurrent Spontaneous abortion

Spontaneous abortion is the most common complication of early pregnancy, the frequency decreases with increasing gestational age. Eight to 20 percent of clinically recognized pregnancies at less than 20 weeks of gestation will undergo spontaneous abortion; 80 percent of these occur in the first 12 weeks of gestation. The overall risk of spontaneous abortion after 15 weeks is low (about 0.6 percent) for chromosomally and structurally normal fetuses, but varies according to maternal age and ethnicity.

Loss of unrecognized or subclinical pregnancies is even higher, occurring in 13 to 26 percent of all pregnancies. Early pregnancy losses are unlikely to be recognized unless daily pregnancy tests are performed. A study that compared women's bleeding following a pregnancy loss before 6 weeks of gestation with their typical menstruation found that the mean bleeding length following a pregnancy loss was 0.4 days longer than the woman's average menses and the amount of bleeding was light.[29]

3.4 Epidemiology of recurrent Spontaneous Abortion

The World Health Organization has defined spontaneous abortion as "the expulsion or extraction from its mother of an embryo or fetus weighing 500 g or less. Early spontaneous abortions are defined as those that occur before the 12th week of gestation, with late spontaneous abortions being those that occur from 12-20 weeks of pregnancy, and 500g or less .Women's experience of miscarriage is obvious and distressing, both psychologically and physiologically. The reported ratio of the number of clinically recognizable miscarriages to the number of known pregnancies in general population studies varies between 12 and 15%. The reported ratio of the number of clinically recognizable miscarriages to the

number of known pregnancies in general population studies varies between 12 and 15%.

Epidemiological studies have suggested that the condition might be multifactorial with a possible genetic predisposition and environmental factors in its pathogenesis. A better understanding of the role of various gene and gene environment interactions will enable identification of high-risk individuals and propose a genetic mechanism to explain the unknown etiology of RPL. With the completion of human genome project, it is imperative to understand the genetic basis of diseases and to identify the population and race polymorphism. Since pregnancy is a complex process and in about 50% of the RPL cases the cause is unidentified, it is essential to explore the contribution of the genetic variations in RPL.[30,31]

3.5 Etiology of Recurrent spotonus abortion

Historically, recurrent miscarriage has been attributed to either genetic, structural, infective, endocrine, immune, or unexplained causes. Thrombophilic disorders are thought to play a part in the cause of recurrent pregnancy loss, which widens the scope of investigations and management options for recurrent miscarriage. Many syndromes associated with recurrent fetal loss include anatomic anomalies, endocrine/hormonal abnormalities, genetic, chromosomal abnormalities, and blood coagulation protein/platelet defects.[32,33]

The etiology of recurrent pregnancy loss (RPL) remains unclear, but it may be related to a possible genetic predisposition together with involvement of environmental factors. The etiology of recurrent pregnancy loss is among the most studied, yet unresolved issues in modern gynecology. Among the various proposed etiological factors, abnormal parental karyotype, antiphospholipid syndrome and uterine anatomic abnormalities were reported in about 50% of the patients; however, in remaining 50%, the cause is unknown.

RSA is a heterogeneous condition, and it is unlikely that only a single pathological factor is attributed to RM. Current literature suggests that the cause of RM is only identifiable in up to 40%-50% of cases. The remaining RM cases are classified as idiopathic. Hence, this merits further research to seek other possible underlying causes of RM. To date the identifiable causes of RM have been categorized as parental, fetal, environmental and psychological factors. The etiologies of spontaneous miscarriage, as well as of recurrent miscarriage are to some degree the same and to some degree different. Some of the medical causes have a higher incidence in cases of recurrent miscarriage.[34,36]

3.6 Parental Factors

3.6.1 Chromosomal Abnormality

Parental balanced structural chromosomal rearrangement accounts for 2%-4% of RM. There are many factors that come into play when the egg and sperm unite and form that first cell. Even if both the egg and sperm come with perfect chromosomes, the first few cell divisions can see an abnormality crop up that would certainly be devastating. The main chromosomal abnormalities are autosomal trisomies, polyploidy, and monosomy X. Most trisomies show a maternal age effect, with chromosomes 16 and 22 most involved, triploidy and tetraploidy account for 30% of chromosomal abnormal abortions. Chromosomal abnormalities are less likely to occur in spontaneous abortions for women younger than age 36 with a history of recurrent abortion. The most common chromosomal rearrangement is balanced reciprocal or Robertsonian translocation which may lead to unbalanced gene translocations in the fetus, resulting in miscarriage. Other chromosomal anomalies associated with RM include chromosomal inversion, insertions and mosaicism.[37,38]

3.6.2 Maternal Factors

3.6.2.1 Ages

Paternal age also plays a part. It is well recognized that female fertility declines with advancing age, which manifests in increases in miscarriage and trisomy 21 and monosomy X of the fetus. Frequency of chromosomal anomalies in sperm appears to increase with age. Independent maternal age, paternal age of more than 40 years, carries 1:6 odds of miscarriage compared with paternal age of 25 to 29 years. It is well recognized that female fertility declines with advancing age, which manifests in increases in miscarriage and trisomy 21 and monosomy X of the fetus. RM as part of a range of reproductive failures shares common risk factors. Studies have shown that in women with RM maternal age is positively associated with the numbers of repeated miscarriages and is an important factor predicting the occurrence of miscarriage.[39,40]

3.6.2.2 Endocrinological Factors

Both estrogen and progesterone play essential roles in pregnancy. During the menstrual cycle the first half is estrogen-dominated while the second half is progesterone dominated. Estrogen and progesterone initially prepare the Endometrium for implantation by initiating a cascade of local morphological and physiological events via their respective receptors. Progesterone acts on the reproductive tract in preparation for the initiation and maintenance of pregnancy by inhibiting contraction of the uterus and the development of new follicles .Following fertilization of the oocyte, the developing embryo secretes human chorionic gonadotropin (HCG) which sustains progesterone levels. During pregnancy, fetoplacental estrogens, progestogens and adrenocorticoids are secreted into both fetal and maternal circulation. Estrogen production is mainly under the control of the fetus and is the primary signaling method by which the fetus directs essential physiologic processes that affect fetal well-being. By the 20th week of pregnancy, approximately 90% of maternal estriol excretion can be accounted for by dehydro

epiandrosterone sulfate (DHEA-S) production by the fetal adrenal gland. Estrogens affect progesterone production, uterine blood flow, mammary gland development and fetal adrenal gland function. Many endocrine disturbances have been assumed to be responsible for RSA. Higher rates of spontaneous abortions are observed among women with polycystic ovary syndrome (PCOS). This may be due to hyper androgenemia, hyper secretion of LH, or insulin resistance. High levels of androgens have been shown to interfere with normal endometrial development. They alter the production of certain growth factors and may be responsible for pregnancy failure. LH stimulates ovarian androgen synthesis; therefore, LH hyper secretion is likely to interfere with early pregnancy via hyperandrogenism.[40,41]

3.6.2.3 Anatomic Factors

Anatomic abnormalities account for 16 - 18% of RM cases. The common anatomic abnormalities include congenital uterine anomalies, uterine adhesions, uterine fibroids and polyps. These abnormalities may cause inadequate vascularity of the Endometrium where the embryos implant, resulting in placental abruption and consequently miscarriage. Among these anatomic abnormalities, congenital uterine abnormalities such as arcuate, septate or bicornuate uterus may be associated with second trimester miscarriages more than early pregnancy losses. Women with anatomic anomalies may benefit from uterine sonography and HSG in the initial diagnosis. A definitive diagnosis can be obtained by using combined laparoscopy and hysteroscopy as well as 3D sonography. Surgical resection of the uterine septum and adhesions, removal of submucous fibroids and polyps may improve subsequent pregnancy outcomes in these women.[42,43]

3.6.2.4 Immunological Factors

The implanting embryo inherits its antigens from both the mother and the father. Paternal antigens are identified as foreign by the maternal immune system. In order to prevent the rejection of pregnancy, this immune response needs to be modulated. It has been proposed that in otherwise unexplained pregnancy losses, dysregulation of the immune system could be responsible for the failure. The immunological interaction between the mother and the fetus remains a scientific enigma. In normal pregnancies, the maternal immune system does not react to spermatozoa or the embryo, even though they express antigens that are exogenous to the maternal system. Maternal-fetal tolerance has been compared to that of a semi-allogenic fetal "graft", and may be the result of a complex array of mechanisms (including HLA-G expression of trophoblast; the leukemia inhibitory factor and its receptor, indoleamine 2,3-dioxygenase; the Th1/Th2 balance; suppressor macrophages; and hormones such as progesterone, or the placental growth hormone, CD95, and its ligand and annexin II) that may be pregnancy-specific and interconnected .Immunological mechanisms are involved in successful implantation. Maternal adaptation of immunological responses to the implanting embryo is a key process in the establishment of the feto-placental unit. Miscarriage may therefore be a consequence of inappropriate humoral or cellular immunological responses towards the embryo APS belongs to the well-known risk factors of RM and has been reported in 15% of RM patients. Antibodies against anionic phospholipids such as cardiolipins, phosphatidylserine as well as cofactors such as 2-glycoproteins can be found disproportionately more of tenin RM patients as compared to healthy controls. Also, functional tests for lupus anticoagulants frequently show haemostatic changes in APS patients. The diagnosis of APS requires fulfillment of the criteria defined in the international consensus statement. There is evidence that aspirin combined with LMWH significantly increases live birth rate in RM patients with APS.[44,45]

3.7 Infections

Infective causes of recurrent miscarriage remain speculative. For any infective agent to be implicated, it must be capable of persisting in the genital tract undetected and must cause few maternal symptoms. The pathogenetic mechanisms of these infections are unique. Because of their relatively low virulence, the organisms involved seldom lead to fetal death beyond the earliest stages of embryogenesis. Since the fetus is essentially a graft of foreign tissue in the uterus, the placenta constitutes a protective immunologic barrier that shields the fetus from the mother's humoral and cell-mediated immune responses. This makes the fetus especially susceptible to infection during the first trimester. A number of microorganisms have been suggested to be associated with spontaneous miscarriage, including Chlamydia trachomatis, Listeria monocytogenes, Toxoplasma gondii, rubella, and herpes simplex virus (HSV). Bacterial vaginosis (BV) seems to be associated with premature rupture of membranes resulting in mid trimester loss and preterm labor more than early pregnancy losses. Repeated second-trimester fetal losses following cervical dilatation or rupture of membranes can be attributed in many cases to bacterial infections, as well as early preterm delivery. These patients should be screened for bacterial vaginal infections and treated if treatment is carried out 20 weeks before gestation, it succeeds in preventing pre-term delivery.[46,47]

3.7.1 Toxoplasmosis

Toxoplasmosis is caused by a protozoan parasite called Toxoplasma gondii with long-term living in the humans and animal bodies. One third of the general population is approximately infected by Parasite. The seroprevalence studies indicate that toxoplasmosis is one of the most common human infections in many parts of the world. Three different ways of Toxoplasma infection induction are: eating the cysts in not fully cooked contaminated meats, using water or food contaminated with oocytes excreted from the feces of cats and transmission from mother, who has been contaminated by the previous

ways, to fetus Although toxoplasmosis is often benign in the women, disease transmission through the placenta can lead to serious consequences such as abortion, still birth, different degrees of mental or physical retardation, hydrocephaly and blindness. reported that the seroprevalence of Toxoplasma gondii antibodies in pregnant women varies from the 6.1 to 75.2 percent based on the geographical region.[48,49]

3.7.2 Cytomegalovirus (CMV)

The human cytomegalovirus (CMV) or human herpes virus 5 is one of the major causes of congenital infections. Its clinical manifestations range from asymptomatic forms (90% of cases) to severe fetal damage and, in rare cases, death due to abortion. Furthermore, 10%–15% of the children who are asymptomatic at birth may develop late sequelae, especially hearing defects, after a period of months or even years Latency following a primary infection (first contact with the virus) may be punctuated by periodic reactivations that give rise to recurrent infections, and in utero transmission may occur during either primary or recurrent infections. Recurrent infections may be due to reinjection with a new strain or to reactivation, but it is likely that most recurrent infections are due to reinjection. The risk of congenital infection is much higher during primary infection.[50,51]

3.7.3 Rubella

Rubella is a common, normally mild disease that mainly affects children aged 2–12 years. Rubella in pregnancy may cause abortion, stillbirth and congenital anomalies, or congenital rubella syndrome (CRS. Prior to the introduction of rubella vaccine in 1969, the disease was distributed evenly throughout the world. In temperate regions, the incidence was usually highest in late winter and early spring. Minor epidemics occurred every 6–9 years, with major epidemics occurring at intervals ranging from 10 to 30 years.[52,53]

3.7.4 Thrombophilia's

Thrombophilia can be defined as a predisposition to form clots inappropriately. Thrombotic events are increasingly recognized as a significant source of mortality and morbidity. The predisposition to form clots can arise from genetic factors, acquired changes in the clotting mechanism, or, more commonly, an interaction between genetic and acquired factors. A successful pregnancy requires a well-developed placenta and sufficient placental function to sustain adequate fetomaternal microcirculation and the normal coagulation pathway is pivotal for the pregnancy outcomes. Also, any kind of disorder in coagulation pathway may cause thrombophilia that may be the reason for placental insufficiency and PL. Recently, it has become clear that prothrombotic changes are associated with a substantial proportion of these fetal losses. Therefore, the role of thrombophilia in RPL has generated a great deal of interest. This heterogeneous group of disorders results in increased venues and arterial thrombosis. Although some thrombophilia states in RPL may be acquired such as antiphospholipid antibody syndrome (APAS). Pregnancy may be compromised by prothrombotic disorders leading to subsequent miscarriages. The term thrombophilia refers to inherited or acquired conditions that predispose individuals to thromboembolic events.[54,55]

4. Inherited thrombophilia

Inherited thrombophilia is the leading cause of maternal Thromboembolism and are associated with an increased risk of certain adverse recurrent miscarriage including second- and third-trimester fetal loss, abruptions, and severe intrauterine growth restriction, and early onset, severe preeclampsia. Inherited thrombophilia is the leading cause of maternal thrombo embolism and are associated with an increased risk of certain adverse recurrent miscarriage including second and third trimester fetal loss, abruptions, severe intrauterine growth restriction, and early-onset, severe preeclampsia. Current information suggests that all patients with a history of prior venous thrombotic events and those with these characteristic adverse pregnancy events should be evaluated for thrombophilia Current information suggests that all patients with a history of prior venous thrombotic events and those with these characteristic adverse pregnancy events should be evaluated for thrombophilia. The most common inherited thrombophilic disorders are deficiencies of antithrombin III, protein C and protein S, Factor V Leiden mutation, methylene tetrahydrofolate reductase (MTHFR) and prothrombin gene mutation (G20210A). The most common cause of hyper homocysteimia rarer thrombophilias includes autosomal-dominant deficiencies of antithrombin, protein C (PC), and protein S (PS).[56,57]

4.1 Prothrombin gene mutation (G20210 mutation)

Prothrombin is a protein in the blood that is required for the blood to clot. It is also called factor II. It is a vitamin K-dependent protein which is synthesized in the liver and circulates with a half-life of approximately three to five days. Vitamin K acts as a cofactor for posttranslational gamma-carboxylation of prothrombin which is required for functional activity. Blood clots are composed of a combination of blood platelets and a meshwork of the blood clotting protein fibrin. Prothrombin is a blood clotting protein that is needed to form fibrin. If somebody has too little prothrombin, he or she has a bleeding tendency.[58,59]

Prothrombin gene (G20210A) mutation is associated with an increased risk of thrombosis, and it is the most identifiable risk factor for venous thrombosis and is in fact the second most common genetic defect for inherited thrombosis, with Factor V Leiden being the most common. It is an autosomal dominant disorder, with Heterozygotes being at a 3- to 11-fold greater risk for thrombosis in both men and women and for all age groups. Although homozygosity is rare, inheritance of

two 20210A alleles would increase the risk for developing thrombosis.[60,61]

4.2 Factor V Leiden mutation

Factor V is one of the essential clotting factors in the coagulation cascade. Its active form, factor Va, acts as a cofactor allowing factor X to stimulate the conversion of prothrombin to thrombin. Thrombin is then able to cleave fibrinogen to fibrin and a fibrin clot is formed. Activated protein C is a natural anticoagulant. It limits the extent of clotting by destroying factor V and reducing further thrombin formation. Factor V Leiden (FVL) mutation (named after the Dutch university where it was discovered) is a point mutation in the gene for clotting factor V. It has autosomal dominant inheritance and is the most common cause of inherited thrombophilia. The mutation of Factor V Leiden causes acquired protein C resistance, resulting in thrombophilia both in veins and spiral arteries of the placenta. This may lead to placenta abruption and consequently results in miscarriage heterozygotes having a three to five times increased risk of thrombosis. Women with this mutation are two to three times more likely to have multiple (recurrent) miscarriages or a pregnancy loss during the second or third trimester. Some research suggests that the factor V Leiden mutation may also increase the risk of other complications during pregnancy, including pregnancy-induced high blood pressure (preeclampsia), slow fetal growth, and early separation of the placenta from the uterine wall (placental abruption). However, the association between the factor V Leiden mutation and these complications has not been confirmed. Most women with factor V Leiden thrombophilia have normal pregnancies and Homozygotes are much less common but have a much higher thrombotic risk, around eight times increased risk.[62,63]

4.3 Methylene tetrahydrofolate reductase deficiencies

Methylene tetrahydrofolate reductase (MTHFR) is one of the main regulatory enzymes in the metabolism of homocysteine that catalyses the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate Methylene tetrahydrofolate reductase (MTHFR) is a rare genetic defect that leads to complications in pregnancy. MTHFR gene produces an enzyme called methylene tetrahydrofolate reductase and mutation in the gene inhibits the production of this enzyme, resulting in hyperhomocystinemia, which is an elevated level of an enzyme homocysteine found in blood plasma. When the body is deficient in methylene trahydrofolate reductase, its ability to absorb folate, such as folic acid, is inhibited. Folic acid and B9 are both essential to the development and health of the fetus. Because of a mother with MTHFR' inability to efficiently metabolize folic acid and vitamin B9, the disorder has been linked to a variety of pregnancy complications such as congenital malformations. Elevated levels of homocysteine have been associated with placental disease, preeclampsia and RPL.[64,65]

4.4 Factor XII

Factor XII (Hageman factor) is an important protease that plays a major role in the initiation of the intrinsic pathway of blood coagulation and fibrinolysis and kinin formation. Although congenital factor XII deficiency (up to 50% normal) is not associated with a clinical bleeding tendency, it can be identified on a routine coagulation test, such as a prolonged activated partial thromboplastin time This deficiency is a rare autosomal recessive disorder. It is still unclear whether factor XII deficiency causes any disorders during pregnancy.[66]

4.5 Protein C and Protein S deficiencies

Protein C inactivates factor Va and VIIIa involved in the anticoagulant process and this function is enhanced in the presence of protein S. Protein C deficiency results from a decrease in protein C antigen or the activity of protein C also Protein C is a 62-kD, vitamin K-dependent glycoprotein synthesized in the liver. It circulates in the blood as an inactive zymogene at a concentration of 4 μg/ml. Its activation into the serine-protease like enzyme, activated protein C (aPC), is catalyzed by thrombin when it is bound to the endothelial proteoglycan thrombomodulin (Dahlback , 2008) Protein S is a vitamin K-dependent, single-chain glycoprotein, which is synthesized in the liver and vascular endothelium, and acts mainly as a cofactor to aPC in the inactivation of FVIIa and FVa. Protein S is the principle cofactor of activated protein C, and deficiency states mimic protein C deficiency with increased fibrin formation Protein. Bind directly to inhibit factors Va, VIIIa, and Xa. Proteins exist in two distinct forms in plasma the free form accounts for 35 to 40% of total protein S, whereas the remainder is found in a form bound to C4b binding protein. Only the free protein S can serve as a cofactor for protein. The plasma level of protein S depends upon age, sex, lipid levels, estrogen, oral anticoagulant usage and the presence of acute thrombosis. In the plasma, around 60% of circulating protein S is bound to C4b binding protein, and only free protein S can function as a cofactor to aPC. Heritable protein S deficiency is transmitted as an autosomal trait.[67,68]

4.6 Antithrombin III deficiencies

Antithrombin is a potent inhibitor of the reactions of the coagulation cascade. Although the name, antithrombin, implies that it works only on thrombin, it actually serves to inhibit virtually all of the coagulation enzymes to at least some extent. The primary enzymes it inhibits are factor Xa, factor IXa and thrombin (factor IIa). It also has inhibitory actions on factor XIIa, factor XIa and the complex of factor VIIa and tissue factors. Its ability to limit coagulation through multiple interactions makes it one of the primary natural anticoagulant proteins. Its numerous interactions are depicted on the above figure.[69]

4.7 Plasminogen Activator Inhibitor 1 (PAI1)

Plasminogen activator inhibitor-1 is the principal inhibitor of tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA), the activators of plasminogen and hence fibrinolysis. Plasminogen activator inhibitor 1 (PAI-1) inhibits plasminogen activators (u-PA and t-PA) by forming stable complexes endocytosed via a low-density lipoprotein receptor super family member-dependent mechanism. PAI-1 circulates actively in plasma and latently in platelets but is also secreted and deposited into the matrix by several cells, where it participates in tissue repair processes. Endothelial PAI-1 expression is modulated by a 4G/5G polymorphism in the PAI-1 promoter, which is 675 bp upstream from the start site of transcription. Angiotensin II plasma levels also influence PAI-1 expression. Homozygosity for the 4G allele of the PAI-1 gene increases the risk for pregnancies, predisposing to prematurity, intrauterine growth retardation, miscarriage and stillbirth.[70]

5. Acquired thrombophilia

Acquired thrombophilias are hypercoagulable states secondary to various aetiologies. In particular, during pregnancy the risks are exaggerated due to the underlying physiological changes. The most common acquired thrombophilia associated with RM is the antiphospholipid syndrome (APS). Antiphospholipid antibodies are auto antibodies against negatively charged phospholipids. APS is categorized as primary (where it occurs in isolation) and secondary.[71]

5.1 Acquired hyperhomocystinemia

Hyperhomocystinemia has been underlined as an emerging risk factor for several diseases such as arterial and/or venous thrombosis. Hyperhomocystinemia may be acquired secondary to dietary and lifestyle factors such as a reduced intake of folate, vitamin B6 or vitamin B12, excessive caffeine consumption and excessive coffee intake. The acquired form of hyperhomocystinemia may also result from certain medical conditions such as hypothyroidism or renal impairment. Inherited and acquired conditions have been involved to explain pathophysilogy as gene polymorphism. The Homocysteine Lowering Trial Collaboration has suggested that endothelial dysfunction, alteration of platelet reactivity and disruption of prostacyclin pathways, may be some of the mechanisms responsible for the reported venous thrombosis risk as well as theoretical risk of pregnancy loss. A meta-analysis of ten studies concluded that acquired hyperhomocystinemia is a risk factor for recurrent pregnancy loss.[72]

5.2 Acquired activated protein C resistance

APCR is the most prevalent risk factor for thrombosis. The presence of the factor V Leiden mutation produces a protein that is intrinsically resistant to activated protein C, causing the pathological phenotype. The pathophysilogy underlying APCR not caused by the FVL mutation is still not completely understood. In different studies, it has been suggested that acquired factors might be the cause of APCR in the absence of FV Leiden. Several coagulation factors can affect the activated partial thromboplastin time (aPTT). Previous literature suggested a possible positive correlation between levels of factors V, VIII and IX and acquired APCR. Protein S and protein C, levels can (or may) affect acquired APCR.[73]

5.6 antiphospholipid syndromes

Antiphospholipid syndrome is the most important treatable cause of recurrent miscarriage. Anti-Phospholipid antibodies are a family of about 20 antibodies that are directed against phospholipid binding plasma proteins. Evidence for pregnancy loss having a thrombotic basis is based mostly in the association between anti-phospholipid (aPL) antibodies and RPL.[74]

They include lupus anticoagulants and anti-cardiolipin antibodies. Antiphospholipid syndrome was originally defined as the association between antiphospholipid antibodies and recurrent miscarriage, thrombosis, or thrombocytopenia, anti-phospholipid antibody syndrome is characterized by the presence of aPL, anti-lupus coagulant, anti-cardiolipin, and/or anti-beta-2-glycoprotein I antibodies that bind to negatively charged phospholipids on the membranes of endothelial cells, monocytes, and platelets.[75]

5.7 Disseminated intravascular coagulation (DIC)

Disseminated intravascular coagulation (DIC) is a serious disorder of hemostasis characterized by systemic activation of blood clotting, resulting in widespread fibrin deposition (stage I). This process eventually leads to the depletion of platelets and coagulation factors, culminating in severe bleeding (stage III). In obstetrics, common causes of DIC include amniotic fluid embolism, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), pre-eclampsia/eclampsia, placental abruption, and septic abortion. Although the exact mechanisms triggering DIC are not fully understood, placental insufficiency and utero-placental hypoperfusion are believed to play key roles. Typical laboratory findings in DIC include prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), low platelet counts, elevated fibrin degradation products such as D-dimer, and decreased plasma levels of coagulation inhibitors like antithrombin III (ATIII).[76]

6. Fetal Factors

Chromosomal anomaly is the commonest fetal cause of RM. Aneuploidy is the most prevalent chromosomal abnormalities of abortuses in RM Evidence from preimplantation genetic diagnosis (PGD) has shown that women with RM had a higher incidence of chromosomally abnormal embryos after Aneuploidy screening than those without RM.[77]

6.1 Fetal-blocking antibodies

Fetal blocking antibodies function to shield the developing baby from the mother's immune system, which might otherwise recognize the father's genetic material as foreign and mount an attack. When sperm fertilizes the egg, it introduces foreign material, including histocompatibility locus antigens (HLA). The sperm's HLA interacts with the mother's HLA, which under normal circumstances would trigger an immune response against the developing fetus. This interaction helps stimulate the mother's immune system to protect the baby. However, in some cases, the father's genetic material is too similar to the mother's, resulting in a weak or inadequate immune response. Consequently, the mother's immune system may fail to defend the fetus effectively, leading to early miscarriage—often before 12 weeks. This type of immune-related pregnancy loss is commonly suspected after multiple miscarriages occurring around the same pregnancy stage.[78]

6.2 Umbilical cord abnormalities

The umbilical cord is a slender, tube-like structure that connects the developing fetus to the placenta. It begins to form approximately five weeks after conception. Inside the umbilical cord are three blood vessels: two arteries and one vein. The vein transports oxygen-rich blood and nutrients from the placenta to the fetus, while the two arteries carry waste products from the fetus back to the placenta, where waste is transferred to the mother's bloodstream and eliminated by her kidneys. Various abnormalities can affect the umbilical cord; these include an excessively long or short cord, improper attachment to the placenta, or the cord becoming knotted or compressed. Such abnormalities may lead to complications during pregnancy, labor, or delivery. In some instances, cord problems can impact both mother and baby. The most common umbilical cord issues and their potential effects on mother and fetus are outlined in.[79]

7. Environmental Factors

Environmental factors such as heavy metals, organic solvents, and ionizing radiation are established teratogens, and exposure to these agents can contribute to pregnancy loss. Alcohol and cocaine are also confirmed teratogens, whereas caffeine and smoking are considered suspected teratogens; however, their teratogenic effects remain controversial. Both caffeine consumption and smoking have been associated with an increased risk of miscarriage. Recent research indicates that women who are homozygous for CYP1A2 -1F alleles, an enzyme involved in caffeine metabolism, have a higher risk of recurrent miscarriage, with a dose-dependent relationship to daily caffeine intake. Additionally, other studies have shown that women exposed to environmental tobacco smoke face a heightened risk of spontaneous miscarriage, especially when combined with caffeine and alcohol consumption.[80]

8. Stress factor

Pregnancy is a unique and pivotal period for a woman and her family, marked by numerous physical, emotional, and life changes. Stressful stimuli can activate a series of physiological adaptive responses. These changes often add additional pressures to pregnant women, who already manage many demands both at home and at work. However, when physical or emotional stress becomes excessive, it can pose risks to the health of the pregnant woman. The primary systems involved in responding to stress include the hypothalamo-pituitary-adrenal (HPA) axis and the sympathoadrenal system. Stress influences the secretion of parvocellular neurons (PVN) in the hypothalamus, leading to the release of neuropeptides such as corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP). Recently, greater attention has been given to the impact of psychological stress on recurrent miscarriage (RM), with studies suggesting that stress may contribute to RM through interactions within the maternal neuro-endocrine-immune network. Stress, defined as pressure or tension, is considered a psychological, physiological, and behavioral response in a transaction between the individual and their environment termed as a person-environment fit. In this context, the external stimulus is viewed as a stressor, and the psychological response as stress. While stress can sometimes be beneficial, activating the fight-or-flight response and helping adapt to threatening situations, it can also be harmful when prolonged or excessive. Chronic or intense stress may lead to adverse physical effects, including impaired cognition, abnormal metabolism, weakened immune function, and reproductive issues. Two types of stress are recognized: acute stress and chronic stress.[81,82]

9. Alcohol and smoking

Drinking alcohol during pregnancy can lead to physical and mental birth defects. According to the Centers for Disease Control and Prevention, each year between 1,300 and 8,000 babies in the United States are born with fetal alcohol syndrome (FAS), which encompasses a range of physical and mental abnormalities. Alcohol consumption during pregnancy increases the risk of miscarriage, low birth weight, and stillbirth. Heavy drinkers are two to four times more likely to experience a miscarriage between the fourth and sixth months of pregnancy compared to nondrinkers. This represents significant public health concern because, in addition to the harmful effects of smoking on a woman's health, smoking during pregnancy can cause serious health issues in the newborn. Smoking has been linked to various pregnancy complications, and early in pregnancy, it appears to increase the risk of ectopic pregnancy.[83,84]

10. Signs and Symptoms of miscarriage

The following are considered the main signs

- Strong cramps that breathe in a huffy way followed by quick bleeding.
- Heavy bleeding that soaks in a few hours or less.

- Passage of tissue, resembling large thick blood clots in the earliest weeks up to pinkish/grayish material, with or without cramps or pain.

Other possible signs include

- Vaginal bleeding: The bleeding associated with spontaneous abortion ranges from scant brown spotting to heavy vaginal bleeding. The volume or pattern of bleeding does not predict spontaneous abortion. Vaginal bleeding is common in the first trimester, occurring in 20 to 40 percent of pregnant women even heavy, prolonged bleeding can be associated with a normal outcome. As an example, in a prospective study of over 4000 pregnant women, 12 percent of women with first trimester vaginal bleeding had a miscarriage, but miscarriage also occurred in 13 percent of women without bleeding.[85,86]

11. Future Directions of Recurrent Spontaneous Abortion

Recurrent spontaneous abortion (RSA) remains one of the most challenging areas within reproductive medicine. Despite significant advances in genetics, immunology, and obstetric diagnostics, a substantial proportion of cases continue to be idiopathic, underscoring the need for future research to unravel its intricate aetiology and improve clinical outcomes. Moving forward, several promising avenues hold the potential to transform our understanding and management of RSA, enhancing personalized care and increasing the likelihood of successful pregnancies.[87]

11.1 Advancement in Genetic Research and Personalized Medicine

One of the key future directions involves deepening our understanding of genetic contributions to RSA. High-throughput sequencing technologies, such as whole-genome sequencing (WGS) and whole-exome sequencing (WES), offer unprecedented opportunities to identify rare genetic variants, structural chromosomal abnormalities, and epigenetic modifications associated with pregnancy loss. These approaches can help discover novel genetic markers and pathways involved in embryo viability and placental development. Personalized medicine, driven by genetic profiling, is poised to revolutionize RSA management, enabling clinicians to tailor interventions based on individual genetic susceptibilities. For example, identifying specific thrombophilia gene mutations or immune-related polymorphisms may allow for targeted therapies that improve pregnancy outcomes.[88]

11.2 Elucidating Gene-Environment Interactions

Understanding how environmental factors interact with genetic predispositions is crucial in RSA. Future research should focus on large-scale, multi-omics studies integrating genomics, epigenomics, proteomics, and metabolomics. Such comprehensive approaches can reveal how exposure to environmental toxins, lifestyle choices, nutritional status, and infections influence gene expression and pregnancy viability. Unravelling these interactions may lead to preventive strategies, including lifestyle modifications and targeted nutritional supplementation, thereby reducing the risk of recurrent pregnancy loss in susceptible populations.[89]

11.3 Innovative Immunological Therapies

Immune dysregulation is a well-recognized factor in RSA, yet therapies targeting immune mechanisms remain largely empirical. Future directions should emphasize the development of precise immunomodulatory treatments based on robust immunological profiling. Advances in immunogenetics and immune cell characterization could facilitate the design of personalized immunotherapy regimens, such as use of biologics that modulate specific cytokine pathways or immune checkpoints. Additionally, emerging concepts like maternal-foetal immune tolerance and microbiome influences are gaining attention, offering novel targets for intervention to promote immune acceptance and reduce miscarriage risk.[90]

11.4 Refined Diagnostic Technologies

Improving diagnostic accuracy is fundamental in RSA research and clinical practice. Emerging technologies such as advanced ultrasonography, 3D imaging, and minimally invasive biopsy techniques can enhance detection of uterine anatomical anomalies, placental insufficiency, and subtle immunological disturbances. Furthermore, integrating biomarkers like circulating cell-free fetal DNA, microRNAs, proteomic profiles, and immune signatures could provide real-time insights into pregnancy health. Such innovations can facilitate early risk stratification and enable timely, targeted interventions.[91]

11.5 Development of Novel Therapeutic Strategies

Current treatments for RSA often have limited efficacy and are based on broad immunosuppressive or anticoagulant approaches. The future lies in developing targeted therapies that correct specific pathophysiological derangements. Gene editing technologies, such as CRISPR-Cas9, may eventually permit correction of genetic mutations implicated in RSA. Regenerative medicine and stem cell therapy also hold promise in repairing uterine damage or supporting placental development. Moreover, advancements in placental bioengineering and tissue scaffolding could contribute to more effective management of structural uterine abnormalities.[92]

11.6 Psychosocial Support and Ethical Considerations

As research progresses, the importance of holistic care, including psychological support, cannot be overstated. The emotional toll of RSA necessitates integrating mental health services into treatment paradigms. Future research should explore the psychosocial dimensions of recurrent pregnancy loss and design supportive interventions tailored to patients' needs. Ethical considerations surrounding novel genetic and

reproductive technologies must also be addressed, ensuring that advances are implemented responsibly and equitably.[93]

12. CONCLUSION

The future of RSA research and management is promising, driven by technological innovations, personalized medicine approaches, and a deeper understanding of complex physiological and immunological interactions. Multidisciplinary collaborations combining genetics, immunology, bioengineering, and psychosocial sciences are essential to unravel the multifaceted nature of RSA. Ultimately, these efforts aim to develop more accurate diagnostics, targeted therapies, and comprehensive care models that will significantly improve pregnancy outcomes and emotional well-being for women experiencing recurrent pregnancy loss. Continued investment and research in these domains will be critical in transforming RSA from an often-enigmatic condition into a manageable and preventable reproductive challenge.

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