Causes of Recurrent of Abortion

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Abstract:
Reoccurrence of Spontaneous abortion (RSA) in pregnant women is frequently encountered complications with no apparent cause. Multiple environmental and genetic factors had been studied that included; hereditary factors, hematologic and immunologic factors, endocrine factors and lifestyle factors. The key aspects of chromosomal abnormalities in RSA women were reviewed. The central theme of the hematologic and immunologic factors focused on studies that associated RSA to infection, clot formation, pro-inflammatory and anti-inflammatory cytokines as well as their genes polymorphism. The factors that underlie hormonal abnormalities and occupational hazards as they pertain to RSA were also reviewed. To conclude genes polymorphisms of inflammatory and anti-inflammatory cytokines seem promising to establish causal molecular relations with RSA.

Key Words: Abortion, RSA, Pregnancy Loss, Cytokines, Genes Polymorphisms

Abbreviations: RSA - Reoccurrence of Spontaneous abortion

Introduction:

Miscarriage, also known as spontaneous abortion and pregnancy loss, is the natural death of a fetus. Spontaneous abortion in healthy pregnant women is a frequently encountered complication, often with no apparent cause (8). Reoccurrence of spontaneous abortion (RSA) can be defined as" three or more consecutive pregnancy losses before the 20th week of gestation" (1). Frequently, abortions occur spontaneously and there are no specific factor can be associated separately. Numerous factors have been implicated as causative factors in the etiology of spontaneous abortion. This revie whig lights the main findings of the RSA relevant studies under the headings of four sections namely: (i) hereditary factors, (ii) Hematologic and immunologic factors, (iii) endocrine factors sand (IV) life style factors.

I. Hereditary Factors:

A) Chromosomal Abnormality:

Both parental and embryonic chromosomal abnormalities have been indicated as a causative factor for reoccurrences of spontaneous abortion (RSA) (16). Chromosomal abnormalities can be caused by different number or a structural abnormality in a segment in the chromosomes and that can be detected on a karyotype. The frequency of abnormal embryonic karyotypes was found to be significantly lower, compared with normal karyotypes, leading to more than >50%
abortions (17, 18). Translocation of chromosomes had been reported in advancing age couples with RSA (18). Although women younger than 36 years old with RSA are genetically normal, they have a higher frequency of euploid miscarriage (19). Robertsonian translocation which is caused by breaks near the centromeres of two acrocentric chromosomes leading to the formation of large metacentric chromosome and small chromosome. If the small chromosome is lost, hence the karyotype leaves only 45 chromosomes (23). Furthermore parental trisomy 21 mosaicism and preferential X-chromosome inactivation have recently been reported as causative factor for RSA (20).

B] Congenital abnormalities of the uterus factor:

**Uterus Septum Defects:**

Anatomical abnormalities of the uterus have long been recognized as a cause of pregnancy loss (2, 7). Uterus septum defects are responsible for about 15–25% of miscarriages (3). Frequently, septum defects are associated with poor blood supply leading to poor implantation. In addition defects in the septum diminish the chance for sufficient receptors that are necessary for the action for sex steroid hormones, hence, abnormal uterine contraction with subsequent fetal wastage and abortion (4, 5, and 29). Surgical corrections may be necessary, however, elective excision of septum still would be difficult to justify. Furthermore comparisons between different surgical protocols are limited by population frame errors in the population being studied and differences in diagnostic methods as well as criteria used to differentiate between various types of uterine structural abnormalities (29). There have been two techniques used to assess the structural defects of the uterus; hysterosalpingography and hysteroscopy. However the reliability of both techniques have not been well established with regard to the evaluation of uterine cavity, subseptate, arcuate, and bicornuate uterus(7, 29).

**Uterus Tissue Changes:**

Fibrotic uterus had been reported as about 1–4% of pregnancies (6). It has been suggested that uterine fibrosis impairs implantation and/or calcium dynamics in the myometrial myocytes, resulting in abnormal uterine contracture state (8). Cervical incompetence had been studied extensively as an etiological factor involved in RSA, and only one-third of cases may actually have such a diagnosis (9). A rare acquired condition implicated in the etiology of RSA is Asherman’s syndrome (10) (11). Asherman's syndrome is being diagnosed with increasing frequency of pregnancy loss.

C] Early developmental abnormalities factor:

Implantation failure is early important factors contribute to reoccurrence of spontaneous abortion (RSA). In mammals, a fertilized ovum adheres to the endometrial epithelium (6). After the trophoblast invasion into uterine stromal cells (implantation), direct contact between the trophoblast and the maternal vessel is established. Once the placenta is formed, the embryo receives nourishment through it and continues to develop normally in the uterus (6, 25).

(ii) Hematologic and Immunologic Factors

A] Blood Clot Factor:

The formation of a clot, also known as thrombophilia, in the blood vessels of the uterus is associated with recurrences of spontaneous abortion (RSA). Inherited thrombophilia is rare and has a family history of relatives with excessive blood clotting. Whereas acquired thrombophilia common and is known as antiphospholipid syndrome, in which antiphospholipids antibodies are directed against the phospholipids (21, 22 and 23). Anti-phospholipid antibodies, had been reported at a rate of 10–20% of women, with RSA compared to 2–5% in women, without a previous history of abortion [23]. It was reported that, anti-phospholipid antibodies may impair trophoblastic invasion and hormonal production, leading to an early and late pregnancy loss (24). It was show that pregnant women with antiphospholipid syndrome (APS) and high positive antiphospholipid antibody are at high risk for pregnancy loss (25). In addition reduction and/or blocking of placental blood flow, secondary to localized thrombosis, would also lead to recurrent spontaneous abortion.

B] Infectious factor:

Infectious microbes in the female organ may be considered as causative factor for reoccurrence of spontaneous abortion (RSA). Some bacterial cause vaginosis, and that was detected during the early pregnancy (14). These findings were supported by the presence of chlamydial

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antibodies was reported in women with recurrent spontaneous abortion (12, 15). However the presence of antibodies cannot establish causative relations. On the other hand, however, it had been reported that first-trimester trophoblast cells are known to express TLR1 and TLR2 indicating viral infection (13). Toll-like receptors (TLRs) are evolved with distinctive specificity for particular pathogen-associated molecular patterns. Placenta transcripts for TLRs 1-10 have been reported, however, some concerns had been raised by certain infections such as bacterial vaginosis (BV) which is characterized by excess of virginal discharge and infection caused by Chlamydia trachomatis (13).

C] Pregnancy and immune mediation factor:

During pregnancy, the maternal immune system is confronted by placental antigens and the recognition of paternally derived fetal and placental antigens. The maternal immune response is suppressed during normal pregnancy in attempt to avoid rejection of the semi-allogenic concepts. Although the exact mechanism by which RSA is linked to allo-immunity is not clear, Lim et al., (1996) have postulated three mechanisms by which allo-immunity could be responsible for RSA: (i) human leukocyte antigen (HLA) sharing, (ii) a deficiency of blocking antibodies, and (iii) a mechanism involving immune mediators and suppressor cells (35, 37). If the problem arises from HLA-sharing, maternal recognition of the fetus is impaired because they share some polymorphic genes. Under this condition, the fetus is unable to block maternal antibodies, hence, will subsequently be aborted (39). Some studies have confirmed the hypothesis of increased HLA-sharing among women with RSA (40, 42). Therefore it is reasonable to assume that the production of blocking antibodies by the mother is necessary to prevent spontaneous abortion. Considerable evidence has accumulated indicating that cytokines play a very important role in the maintenance of pregnancy by modulating the immune system.

During pregnancy, the immune system plays an important role to ensure normal pregnancy development (41). Successful pregnancy, without complications, requires strict temporal regulation of maternal immune response to accommodate the growing fetus. For example, early implantation is facilitated by inflammatory processes so that vascular remodeling and placental invasion develop normally as such to prevent rejection of the fetus (42, 44). In support of this, corruptions of varieties of immune pathways have been implicated in the pathophysiology of RSA. Immune tolerance of the fetal-placental unit and placental angiogenesis are mandatory for a successful pregnancy outcome (6, 43). Successful pregnancy depends upon a discrete balance between the cytokines of Th1 and Th2 that are involved in fetal growth and development (2). TNF-α, IL-1β, and IL-6 are some of the fundamental cytokines in early pregnancy (2). These participates in blastocyst implantation and, adversely, in first-trimester losses (2). As pregnancy develops, high TNF-α concentration have been related to the development of preeclampsia, reduced IL-10 levels, and preterm birth (2, 45). Placental mechanisms are also involved in the regulation of the immunologic response in pregnancy (46).

It has been thought for many years that maternal tolerance to alloantigen can be explained by the predominance of Th2 immunity over Th1 immunity, hence, protecting the fetus from maternal “attack” (2). However Th1 predominance was in cases of recurrent and spontaneous miscarriages and preeclampsia (47) and the predominance of Th2 immunity was also reported in cases of recurrent abortions (48). Clearly the Th1/Th2 paradigm had become insufficient evidence to explain the mechanism that prevents the rejection of the fetal allograft.

D] Cytokines factor:

Many cytokines are involved in implantation and any abnormality in these cytokines may influence continuation of normal pregnancy (6, 49). Although the immunosuppressant of maternal lymphocytes in the uterus are necessary to accept embryos as semi-allograft, recent findings, however, revealed that maternal lymphocytes in the decidua were activated and secreted many cytokines factor that prevents the rejection of the fetal allograft. In support of this, pregnant women who miscarry have higher plasma levels of pro-inflammatory cytokines, while levels of anti-inflammatory cytokines are lower compared to those who maintain their pregnancy (8, 51). Trophoblast activated peripheral blood mononuclear cells from women with a history of recurrences of spontaneous abortion (RSA) produce more pro-inflammatory cytokines but less anti-
inflammatory cytokines than women without a
tory of RSA. It was reported that trophoblastic
vasion into the uterus is regulated by cytokine-1
(II-1) and transforming growth factor (TGF- β),
which regulates the functions of matrix metallic-
proteases (MMP) (6, 25, 52).
Macrophages are capable of producing cytokines
of the T-helper 1 (Th1) type: interleukin-2 (IL-2),
tumors necrosis factor-α (TNF-α), and interferon-
γ. These cytokines are produced in increased
amounts at the maternal—fetal interface. They are
considered deleterious to the pregnancy by direct
embryotoxic activity or by damaging the placental
trophoblasts. Conversely, high concentrations of
the anti-inflammatory cytokines IL-4, -6,-10, and
-13 (Th2 type) are beneficial to the developing
embryo by enhancing placental growth and
function (53).
Ev
Evidence exists that inter individual variation in
the inflammatory cytokine response may affect
the risk of unexplained recurrent pregnancy loss
(RPL). Enhanced uterine expression of pro-
inflammatory cytokines such as tumor necrosis
factor (TNF), interferon-gamma (IFN-γ), IL-1β,
and IL-6 is associated with embryo loss(27).
Anti-inflammatory cytokines such as IL-10 appear
to protect against inflammation-induced
miscarriage (54). The TNF-α and IFN-γ are
classified among the cytokines that are
particularly detrimental to the survival of the
fetus, while IL-4, IL-6 and IL-10 promote
embryonic development When anti-TNF-α agents
or antibodies were administered, fetal
reabsorption rates and embryonic apoptosis were
reduced in a murine model of immunologically
mediated miscarriages (2, 37, 55, 56). The
interaction between pro- and anti-inflammatory
cytokines seems to be the key factor throughout
successful pregnancy, thus, it is fundamental to
promote normal pregnancy outcomes. In other
words the balance between inflammatory and anti-
inflammatory cytokines promotes normal
pregnancy. On the hand however, the loss of
elevated levels of pro-inflammatory cytokines and
C-reactive protein (CRP), and decreased amounts
of anti-inflammatory cytokines were reported to
be associated with the occurrence of pre-
eclampsia (PE) and premature labor (12).

E) Cytokines genes factor (INSERT REF (7) :)
Research efforts have focused on single
nucleotide polymorphisms (SNP) in candidate
cytokine genes. These SNP generally occur in the
promoter region where they putatively act as
transcriptional regulators. Several SNPs in
different cytokine gene have been reported to be
associated with infectious and inflammatory
conditions, including the risk of prelabour rupture
of the amniotic membranes and preterm labor
(12). Numerous studies have shown that
polymorphism in cytokine genes are associated
with susceptibility to certain inflammatory and
infectious disease (56). Polymorphisms in the
promoter regions, exons or introns of certain
cytokine genes, influence the level of cytokine
production and result in high, intermediate or low
levels of cytokines (25).
The genetic contribution of pro-inflammatory and
anti-inflammatory cytokines gene polymorphisms
has been reported in women with RSA so far. It is
often difficult to understand the scope of genetic
contributions, especially in immune regulation
during a pregnancy, because several cytokines are
involved and each cytokine may have multiple
polymorphisms. The relevance of gene
polymorphisms in the development of unexplained recurrent spontaneous abortion is still
unclear. Cytokines, antigenic mediators, and
hormones are involved in all stages of
reproduction and pregnancy outcome. Impaired
production and/or unbalanced ratios of these
mediators have been implicated in the
pathogenesis of unexplained recurrent
spontaneous abortion (RSA). Functional
polymorphism influence gene activity and
therefore can interfere with the expression of
drivers. Several studies have been carried out
to evaluate the relationship between cytokines,
angiogenic drivers, and hormones gene
polymorphisms and unexplained recurrent
spontaneous abortion. The results of these studies
are mostly contradictory, and few significant
associations have been identified (1). Up to
present time, the evidence is insufficient to
support the evaluation of cytokines, angiogenic
drivers, and hormones gene polymorphism in
routine workup in all cases of recurrent pregnancy
loss, and many of these genetic tests have not yet
implemented the major obstetric guidelines.

(iii) Endocrine Factors:
Hormonal-disturbance-related disorders had been
reported to be associated with recurrent
spontaneous abortion (RSA). For example a luteal
phase defect, insulin-dependent diabetes mellitus,
thyroid disorder, and over secretion of luteinizing

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hormone (LH), are all responsible for about 20% of cases of RSA (26, 27). Inadequate secretion of progesterone was reported as a cause of RSA in 20–60% in pregnant women (27). Sub-normal levels of progesterone lead to an underdeveloped endometrium, hence, uterus becomes unable to maintain implantation and embryo growth (26). Furthermore hyper–pro-lactinemia had been reported as a causative factor in spontaneous abortion (28). Clearly prolactin plays a role in the pathogenesis of antiphospholipid syndrome, especially antiphospholipid syndrome-related reproductive failure (29). In addition the association between the presence of thyroid antibodies in euthyroid women and the risk for RSA has been reported (30, 46). Overt hyperthyroidism and hypothyroidism is associated with RSA (31). Anti-thyroid auto antibodies are associated with miscarriage (RM) and could be an expression of a more general maternal immune system abnormality leading to RM. Anti-thyroid auto antibodies (ATA) could have a role in RM irrespective of thyroid hormone status (31, 32). Previous reports found association between diabetes and RSA. Maternal hyperglycemia increases the rate of malformation that may be incompatible with embryonic or fetal life, leading to miscarriage. Furthermore, an increased risk for RSA was reported to be associated with abnormal placenta resulting from increased atherosclerosis or fibrin deposition in pregnant women with diabetes (33). It was reported that insulin resistance in patients with RSA was more likely to have insulin resistance (34).

Sex steroid hormones, including estrogen and progesterone, have been regarded as important substances to maintain pregnancy. Additionally the regulation of ovarian cycle requires some cytokines, IL-1β, IL-6 and TNF-α, that essential function during growth and development of ovarian follicle (2, 44).

(iv) Lifestyle Factors:

The harmful effects of occupational exposures on pregnant women had reported to indirectly expose fetus to occupational hazards (11). Clearly, maternal exposure to occupational and/or environmental insults might have significant negative implications on pregnancy outcome. The available data on heavy metal toxicity such as lead, mercury; industrial pollutants such as dioxin, organic solvents, radiations; and some other component of lifestyle-associated factors such as tobacco smoking (active and passive) and excessive maternal intake of alcohol had adverse effect on pregnancy outcome. There are substantial scientific evidences that are supported by the fact that working women have a higher risk of RSA compared with nonworking women as they are more likely to be exposed to environmental insults (36).

Implications for research:

Together, the single factor causality relationship with RSA cannot be established; hence, any of the factors reviewed in sections (i- IV) remain the confounding stage rather than single factors causality relationship. This implies that RSA is caused by multiple environmental and genetic factors mixed with cultural and ethnic factors. While genes polymorphisms of inflammatory and cytokines seem promising to establish causal molecular relations with RSA, still further research are needed specific to IL-17 and IL 23 genes polymorphisms in RSA women.

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