Habitual abortion: causes, diagnosis, and treatment

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Abstract

Habitual abortion is defined as three or more consecutive pregnancy losses before 20 weeks of gestation and affects 1% of couples trying to conceive. It is a heterogeneous condition with a number of possible underlying causes: uterine, infectious, genetic, thrombophilic, endocrine, metabolic, immunologic, and environmental. Some of these causes are overdiagnosed because of the different methodologies employed. Over the past few years, attention has been paid to the role of infection (bacterial vaginosis and chlamydial infection) in the etiology of habitual abortion, but studies determining the role of intervention in improving pregnancy outcome are needed. Controversy surrounds the treatment of the different causes of habitual abortion. This is related to problems such as the size of the studies and the different methodologies that have been used in treatment and patient selection. To overcome this, large randomized controlled studies are necessary. Despite the various investigations, the etiology of recurrent abortions remains unknown in about half of all cases. For these individuals, psychologic support and reassurance, rather empirical treatment, are recommended.

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1. Introduction

Habitual abortion is defined as three or more consecutive pregnancy losses before 20 weeks of gestation. This condition, frustrating for both the couple involved and the physician, affects 1% of women of reproductive age.[1] The etiology remains unexplained in about 50% of cases. The known causes cover uterine, infectious, genetic, thrombophilic, endocrine, metabolic, immunologic, environmental, and unexplained factors.[2–9] In this article, the different possible causes of recurrent pregnancy loss, along with their diagnostic tools and treatment, are reviewed.

2. Uterine abnormalities

Structural anomalies of the uterus have long been recognized as a cause of obstetric complications, including habitual abortion. Approximately 15–25% of miscarriages are thought to result from mullerian fusion defects, and almost all are associated with uterine septa.[2] The proposed mechanism of habitual abortion is poor implantation dynamics, resulting from poor blood supply to the septum and the sex steroid receptor deficiency in the malformed uterus, which causes abnormal uterine contraction with subsequent fetal wastage and abortion.[10] In women with habitual abortion, hysteroscopic resection rather than uterine surgery is advocated because of the risk for post-operative adhesions and infertility in the latter.[2] Following myomectomy [12], the rate of pregnancy loss has been found to be reduced significantly following myomectomy [12]. Sudden rupture of the membranes in the second trimester followed by painless explosion of the fetus is defined as cervical incompetence. Cervical incompetence is overdiagnosed as an etiological factor involved in habitual abortion, and only one-third of cases may actually have such a diagnosis.[14] The application of cervical cerclage has been found to reduce the rate of pre-term delivery, but without a significant improvement in the fetal outcome.[14] A rare acquired condition implicated in the etiology of habitual abortion is Asherman’s syndrome. Post-traumatic intrauterine adhesions may reduce the size of the uterus.
cavity and the responsiveness to steroid hormones, leading to impaired implantation and pregnancy wastage; hysteroscopic resection of the adhesions will correct these abnormalities [15].

3. Infectious causes

The role of maternal and fetal infection in habitual abortion remains controversial. It appears that TORCH (toxoplasmosis, rubella, cytomegalovirus, and herpes) infection has no role in habitual abortion [3]. Recently, concern has been raised by certain infections such as bacterial vaginosis and infection caused by Chlamydia trachomatis [16, 17]. A significant association has been found between bacterial vaginosis detected early in pregnancy, and pre-term delivery and also late miscarriage [16]. Furthermore, significantly high titers of chlamydial antibodies were found in the sera of women with habitual abortion [17]. They postulated that an immune response to an epitope shared by a chlamydial and a fetal antigen is responsible for recurrent miscarriage. There are, however, no data available to confirm the role of intervention in improving the outcome of pregnancy.

4. Genetic causes

Both parental and embryonic chromosomal abnormalities have been implicated in the etiology of habitual abortion. The frequency of abnormal embryonic karyotypes was found to be significantly lower, and that of normal karyotypes significantly higher, with an increasing number of previous miscarriages, reaching >50% when this number reached more than six abortions [18]. The effect of maternal age in couples with habitual abortion is important as the frequency of trisomies due to non-disjunction or translocation increases with advancing age [1]. Women younger than 36 years of age with habitual abortion have been found to have a higher frequency of euploid miscarriage [6].

A parental chromosomal abnormality—most frequently a balanced reciprocal or Robertsonian translocation—is present in 6% of couples presenting with habitual abortion [19]. Parental trisomy 21 mosaicism and perereferential X-chromosome inactivation have recently been reported as etiological factors in habitual abortion, raising the question of whether all couples presenting with habitual abortion should undergo a detailed cytogenetic analysis [20, 21]. Furthermore, karyotyping of the abortus should be obtained, and counselling for the future pregnancy and prenatal diagnosis should be offered if findings are abnormal [14].

In habitual abortion with a normal karyotype, a substantial role may exist for molecular mutations. Recurrent abortions have been found significantly to be associated with mutations in G1691A factor V (Leiden), G20210A prothrombin, and C677T methylenetetrahydrofolate reductase, and coagulation factor XII genetic polymorphism [22, 23]. These mutations in the coagulation proteins can lead to habitual abortion by the development of microthrombi at the feto-maternal interface, with subsequent pregnancy wastage.

5. Thrombophilia

Acquired and hereditary thrombophilic conditions have been described in association with adverse pregnancy outcome, including habitual abortion. The proposed mechanism responsible for pregnancy loss is attributed to thrombosis in the utero-placental vasculature [7, 24]. The most common acquired thrombophilia is the anti-phospholipid syndrome, in which anti-phospholipid antibodies are directed against phospholipids, resulting in the various manifestations of this syndrome. The most commonly detected sub-groups of these antibodies are lupus anticoagulant, anti-cardiolipin, and anti-h2 glycoprotein I antibodies [24]. Anti-phospholipid antibodies have been found in 10–20% of women with habitual abortion compared to 2–5% in women without a previous history of abortion [25]. Habitual abortion may occur as a result of poor placental perfusion caused by localized thrombosis. Furthermore, anti-phospholipid antibodies may also impair trophoblastic invasion and hormonal production, leading to an early and late pregnancy loss [25].

Various modalities of treatment have been described to treat women with anti-phospholipid syndrome suffering from habitual abortion, including aspirin, prednisolone, heparin, and immunoglobulin infusion. In a recent meta-analysis of 10 randomized controlled trials, the combination therapy of heparin and aspirin was association with a significantly better outcome than aspirin alone or in combination with prednisolone [26].

Numerous hereditary thrombophilic conditions have been described as contributing significantly to habitual abortion; these include anti-thrombin III deficiency, protein S and C deficiencies, and the molecular mutations mentioned above. In a recent study, activated protein C resistance was found to be the most common thrombophilic defect documented in 39% of women with habitual abortion [7].

6. Endocrine causes

Habitual abortion has also been linked to underlying abnormal endocrine disorders. An endocrine factor, for example a luteal phase defect, insulin-dependent diabetes mellitus, thyroid disorder, or a hypersecretion of luteinizing hormone (LH), is responsible for 20% of cases of habitual abortion [4]. Luteal phase insufficiency, defined as the inadequate secretion of progesterone by the corpus luteum in the secretory phase of the menstrual cycle and early pregnancy, is reported as a cause of habitual abortion in 20–60% of women with the condition [27]. This wide range of incidence is related to the different methodologies used to diagnose the luteal phase deficiency. Sub-normal levels of progesterone
lead to an underdeveloped endometrium unable to maintain implantation and embryo growth [15]. Endometrial dysfunction caused by progesterone deficiency may be manifested by a disturbance in endometrial protein secretion. The concentrations of placental protein 14 and mucin-1 in uterine flushings were both significantly reduced in women with habitual abortion compared to normal controls [15]. Luteal phase insufficiency has traditionally been treated with exogenous progesterone or human chronic gonadotropin supplementation after conception. Results from controlled randomized trials have, however, failed to support the efficacy of these treatments in improving outcome [27,28].

The hypersecretion of LH in women with polycystic ovary syndrome is considered to be a marker of habitual abortion. High levels of LH were found in 27-41% of women with habitual abortion who had polycystic ovaries on ultrasound imaging [29]. It has been postulated that elevated levels of LH are responsible for habitual abortion by adversely affecting oocyte quality or the endometrium, either directly or indirectly, by producing elevated levels of androgens and estrogens [29]. More recent studies have failed to confirm the relationship between elevated LH level and habitual abortion [30,31]. In these studies, women with an elevated serum LH concentration showed no significant difference in future pregnancy outcome when compared to those with normal concentrations. In a prospective, randomized, placebo-controlled study, Clifford et al. [32] reported no improvement in the live birth rate after suppressing high endogenous LH secretion with gonadotropin-releasing hormone agonists.

It has recently been suggested that hyperinsulinemia and insulin resistance in women with polycystic ovary syndrome augment the LH-driven production of androgens from the ovarian theca cells [33]. The amelioration of insulin resistance has been achieved after treatment with metformin (an insulin sensitizer). In a prospective, randomized, placebo-controlled study, we found a significant reduction in the concentrations of LH and androgens after treatment with metformin, as well as a low miscarriage rate compared to the placebo group [34].

Hyperprolactinemia without evidence of corpus luteum dysfunction has recently been described as a causative factor in habitual abortion [35]. The authors suggested that a high level of prolactin might cause recurrent miscarriage by endometrial alteration of the extracellular matrix or by some immunologic mechanism. In a randomized controlled trial, they found a significant improvement in pregnancy outcome after treatment with bromocriptine.

The association between thyroid disorders and habitual abortion is controversial. In recent years, concern has arisen over thyroid auto-immunity. A significant association between the presence of thyroid antibodies in euthyroid women and the risk for habitual abortion has been reported [36]. The mechanism involved in thyroid auto-immunity and habitual abortion is unclear, but activation of the immune system, particularly T cells, has been suggested.

Previous reports failed to identify an association between diabetes and habitual abortion [37]. A significant correlation has, however, been reported between an increased spontaneous abortion rate and increasing concentrations of first-trimester hemoglobin A1c [38]. Maternal hyperglycemia has been linked to an increased rate of malformation that may be incompatible with embryonic or fetal life, leading to miscarriage. Furthermore, an increased risk for habitual abortion seems to be related to abnormal placentation resulting from increased atherosclerosis or fibrin deposition in women with diabetes [39]. There is a recent evidence that well-controlled insulin-dependent diabetes mellitus is not associated with habitual abortion [40].

7. Metabolic causes

Hyperhomocysteinemia, as a consequence of folate and Vitamin B12 deficiency, is a risk factor that predisposes to thrombophilic events and is linked to habitual abortion [5]. A 1-month treatment with high-dose folic acid (15 mg per day) and Vitamin B6 (750 mg per day) in women with hyperhomocysteinemia and habitual abortion proved effective in normalizing their homocysteine level, with a significant improvement in fetal outcome [41].

Celiac disease is a relatively frequent disease, with an incidence of 0.5%. It is a digestive disease resulting from gluten intolerance that damages the small intestine and interferes with the absorption of nutrients from food. Celiac disease may be atypical or silent. The association of the disease with recurrent abortion has recently been reported [42]. The efficacy of a gluten-free diet during pregnancy on decreasing the miscarriage rate remains to be investigated.

8. Immunologic causes

During pregnancy, the maternal immune system confronts the conceptus with a host-defense reaction based on the recognition of paternally derived fetal and placental antigens. To avoid rejection of the semi-allogenic conceptus, the maternal immune response is suppressed during normal pregnancy [43]. The mechanism by which habitual abortion is linked to allo-immunity is not clear. Lim et al. [43] have postulated three mechanisms by which allo-immunity could be responsible for habitual abortion: human leukocyte antigen (HLA) sharing, a deficiency of blocking antibodies, and a mechanism involving immune mediators and suppressor cells.

If the problem arises from HLA-sharing, maternal recognition of the fetus is impaired because they share some polymorphic genes. Such a fetus is therefore unable to induce maternal blocking antibodies and will subsequently be aborted [44]. Some studies, although not the majority, have confirmed the hypothesis of increased HLA-sharing among women with habitual abortion [8]. It has been suggested that
the production of blocking antibodies by the mother is necessary to prevent pregnancy wastage [45]. More recent studies indicate that these antibodies have no predictive value with respect to pregnancy outcome [8].

In recent years, attention has focused on an immune mediator and suppressor cell mechanism. Increased cytotoxic activity arising from activation of natural killer cells, leukocytes, lymphocytes, and macrophages has been found in women with habitual abortion [46]. Macrophages are capable of producing cytokines of the T-helper 1 (Th1) type: interleukin-2 (IL-2), tumour necrosis factor-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 trophoblast. 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 [47].

On the basis of these hypotheses, various immunomodulatory therapies could be employed to inhibit natural killer cell cytotoxicity, enhance the formation of blocking antibodies, or promote a Th1–2 cytokine shifting. Such therapies include allogenic lymphocyte immunotherapy and intravenous immunoglobulin (IVIG). The efficacy of both treatments in the prevention of habitual abortion of the euploid embryo is, however, controversial. This may be related to a number of scientific problems, for example different treatment methodologies, patient selection, and small-size studies that result in an underestimation of the actual results in the general population, with high false-positive and false-negative rates.

Two multi-centre meta-analyses [48,49] have investigated women receiving lymphocyte immunotherapy; the first showed a 10% absolute improvement in take-home baby rate, while the second showed no statistically significant improvement. This type of treatment should be balanced against the potential risks of transfusion, mainly those of allergy and viral infection [4]. IVIG seems to be more advantageous because it is well tolerated and the potential risks associated with lymphocyte immunotherapy are rare. In a meta-analysis of three placebo-controlled trials of IVIG in the treatment of habitual abortion, a significant improvement in pregnancy outcome was reported for the treated group compared to controls receiving placebo [8].

The natural immunosuppressive effect of progesterone has recently been studied. In vitro studies have shown that progesterone specifically blocks Th1 immunity to the trophoblast, which has a deleterious effect on the developing embryo [50].

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical causes and diagnosis of habitual abortion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>Uterine anomalies</td>
<td>Hysterosalpingography</td>
</tr>
<tr>
<td></td>
<td>Hysteroscopy</td>
</tr>
<tr>
<td></td>
<td>Laparoscopy</td>
</tr>
<tr>
<td></td>
<td>Ultrasonography</td>
</tr>
<tr>
<td>Infection</td>
<td>Endocervical and posterior vaginal fornix swabs</td>
</tr>
<tr>
<td></td>
<td>Anti-chlamydial antibody titer</td>
</tr>
<tr>
<td>Genetic</td>
<td>Parental karyotype</td>
</tr>
<tr>
<td></td>
<td>Fetal karyotype</td>
</tr>
<tr>
<td></td>
<td>Quantitative X-chromosome inactivation</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>Protein C measurement</td>
</tr>
<tr>
<td></td>
<td>Protein S measurement</td>
</tr>
<tr>
<td></td>
<td>Anti-thrombin III measurement</td>
</tr>
<tr>
<td></td>
<td>Genetic analysis for molecular mutations</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Endometrial biopsy</td>
</tr>
<tr>
<td></td>
<td>Luteal phase progesterone level</td>
</tr>
<tr>
<td></td>
<td>Luteaming hormone, follicle-stimulating hormone, prolactin, and androgen levels</td>
</tr>
<tr>
<td></td>
<td>Thyroid-stimulating hormone</td>
</tr>
<tr>
<td></td>
<td>Hemoglobin A1c level, fasting glucose concentration, glucose tolerance test</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Serum homocystine</td>
</tr>
<tr>
<td></td>
<td>Small bowel biopsy</td>
</tr>
<tr>
<td></td>
<td>Antibodies to gluten</td>
</tr>
<tr>
<td>Immunologic</td>
<td>Anti-cardiolipin antibodies (IgG, IgM, IgA)</td>
</tr>
<tr>
<td></td>
<td>Lupus anticiplglant</td>
</tr>
<tr>
<td></td>
<td>Cytokine levels</td>
</tr>
<tr>
<td></td>
<td>Human leukocyte antigen typing</td>
</tr>
<tr>
<td>Environmental</td>
<td>History</td>
</tr>
<tr>
<td>Unexplained</td>
<td>All investigations</td>
</tr>
</tbody>
</table>
9. Environmental causes

The lifestyle of pregnant women appears to affect the rate of habitual abortion as smoking, alcohol, and heavy coffee consumption can adversely affect fetal development. The risk for recurrent abortion increases linearly with the number of cigarettes smoked and number of drinks, of either alcohol or coffee, taken; education and an avoidance of these substances will decrease this risk [9].

10. Unexplained factors

Despite thorough investigations according to various clinical protocols, the underlying cause of habitual abortion remains unexplained in about half of all cases. In this category, psychotherapy rather than empiric treatment is needed. A ‘tender loving care’ type of psychotherapy in a present or a subsequent pregnancy appears to improve pregnancy outcome significantly [1]. Causes of and various investigations for recurrent miscarriage are summarized in Table 1.

11. Practice points

- The etiology of habitual abortion remains unexplained in about 50% of cases.
- Cervical incompetence and hormonal abnormalities are overdiagnosed as causes of habitual abortion because of the different methodologies employed.
- Large randomized controlled studies and international investigations are needed to determine the role of chlamydial infection and bacterial vaginosis in habitual abortion.
- In diabetes and thyroid disease, auto-immunity related to the underlying disease, rather than organ dysfunction, may be responsible for recurrent abortion.
- In recurrent first- and second-trimester abortions of eutrophic fetuses, searching for acquired or hereditary thrombophilia is recommended.
- The importance of auto-immunity in the etiology of habitual abortion is increasing, and the role of progesterone as a natural immunosuppressant needed to be investigated in a randomized controlled trials.

References


