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Endocrinological and Environmental Causes of Recurrent Miscarriage: A Review

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Review Article

Volume 1 Issue 2

Received Date: June 05, 2017

Published Date: July 04, 2017

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Abstract

Early pregnancy loss is perhaps the most common obstetric complication, occurring in over two-thirds of human conceptions. Approximately 15 – 20% of all clinically recognized pregnancies will end in a miscarriage. Approximately, 1% of all women trying to conceive have recurrent miscarriage, defined as three previous miscarriages.

Despite thorough examinations to exclude several well-known etiologic factors, the cause for recurrent spontaneous abortion can often not be found in almost 50% of cases In addition to genetic or auto-immune diseases, endocrine dysfunction and metabolic disorders have been implicated. The purpose of this review is to update potential endocrinological causes of RM including thyroid disease, diabetes mellitus, hyperprolactinemia and polycystic ovarian syndrome. Also, obesity, hyperandrogenism, luteal phase defects and environmental, occupational or personal habits, such as cigarette smoking or alcohol consumption, are assessed as potential etiologies of recurrent miscarriage.

Keywords: Recurrent miscarriage; Endocrinological etiology; Environmental etiology; Obesity; Smoking; Alcohol consumption

Introduction

Human reproduction is characterized by its inefficiency. Early pregnancy loss is perhaps the most common obstetric complication, occurring in over two-thirds of human conceptions [1]. Approximately 15 – 20% of all clinically recognized pregnancies will end in a miscarriage [2-5]. However, prospective cohort studies using sensitive and specific daily urinary hCG assays in women trying to conceive have demonstrated that only around one-third of conceptions progress to a live birth [6]. Most of the losses occur before the clinical recognition of pregnancy as implantation failures. An estimated 30% of human conceptions are lost prior to implantation and a further 30% following implantation but before the missed menstrual period, that is in the third or fourth week of gestation. These are often termed preclinical losses [2,7].

For more than 30 years, controversy has existed on the number of miscarriages required to define recurrent miscarriage (RM) and when diagnostic testing is warranted [8]. The definition ranges from two clinical miscarriages, not necessarily consecutive, according to the American Society for Reproductive Medicine (ASRM) and a joint International Committee for Monitoring Assisted Reproductive Technology and World Health Organization glossary, affecting more than 3% of couples desiring a baby to three consecutive pregnancy losses (not necessarily intra-uterine) as defined by both the European Society for Human Reproduction and Embryology and the Royal College of Obstetricians and Gynecologists and affecting 1% of couples trying to conceive [9-16]. After defining RM as the diagnosis of two or more failed clinical pregnancies, the American Society for Reproductive Medicine (ASRM) recommended that "a threshold of three or more losses should be only used for epidemiological studies while clinical evaluation may proceed following two first-trimester pregnancy losses" [9]. To address this controversy there were evaluated more than 1,000 women with RM, and, no differences were found in the frequency of abnormal diagnostic factors between women with two and those with three or more miscarriages, argued that full evaluations should be offered to women who have experienced at least two consecutive pregnancy losses [8,17]. It is estimated that fewer than 5% of women will experience two consecutive miscarriages, and only 1% experience three or more [18,19].

Compared to sporadic miscarriage the prevalence of RM is considerably lower irrespective of whether biochemical losses are included or not. Approximately 1% of all women trying to conceive have recurrent miscarriage, defined as three previous miscarriages; when recurrent miscarriage is defined as two previous miscarriages, the proportion rises to 5% [20-22]. For the purposes of determining whether evaluation for RM is appropriate, pregnancy is defined as a clinical pregnancy documented by ultrasonography or histopathological examination [2]. Ideally, a threshold of three or more losses should be used for epidemiological studies while clinical evaluation may proceed following a second miscarriage [19].

Etiology

The potential etiologies of RM can be divided into embryologically driven causes (mainly due to an abnormal embryonic karyotype) and maternally driven causes which affect the endometrium and/or placental development [24,25]. Thus, studies that focus on RM have examined factors related to age, genetics, antiphospholipid syndrome, uterine anomalies, thrombophilias, hormonal or metabolic disorders, infection, autoimmunity, sperm quality, and life-style issues (Table 1). Also, several recommendations have been published regarding the evaluation and management of RM [16].

Despite thorough examinations to exclude several well-known etiologic factors, the cause for recurrent spontaneous abortion can often not be found in almost 50% of cases [23,26]. These are termed unexplained recurrent miscarriages. In recent years, progress in the fields of cytogenetics and immunogenetics and a greater understanding of implantation and maternal-embryo interactions has offered new insights into the possible causes of this condition, and opened new avenues for research into its prevention and treatment [2]. But, in addition to genetic or auto-immune diseases, endocrine dysfunction and metabolic disorders have been implicated [27-29]. The purpose of this review is to update potential endocrinological causes of RM.

Hormonal and Metabolic Etiologies of Recurrent Miscarriage

It is generally agreed that maternal endocrine disorders (e.g., thyroid dysfunction, diabetes) should be evaluated and treated in cases of RM [30,31].

The prevalence of hypothyroidism with or without underlying thyroid autoimmunity is significant among women in fertile age. There is evidence that thyroid dysfunction and thyroid autoimmunity is associated with infertility and pregnancy loss both in the situation where the woman is euthyroid with thyroid antibodies and in a thyroid antibody negative woman with an elevated level of thyroid stimulating hormone (TSH) [31]. As long as thyroid-stimulating hormone (TSH) levels are in the normal range, there is insufficient evidence to recommend routine thyroxine (T4) testing or screening for anti-thyroid antibodies [32]. According to a recent meta-analysis of 38 studies, the presence of antibodies against thyroperoxidase (TPO-Ab) increased the risk of sporadic miscarriage with an odds ratio of 3.73 (95% CI 1.8 to 7.6) as well as RM (OR 2.3, 95% CI 1.5 to 3.5) [33]. However, this is problematic given the lack of consensus regarding the definition of a normal upper limit of TSH. Whereas TSH values of 4.0–5.0 mIU/L were once considered normal, a consensus is emerging that TSH values above 2.5 mIU/L are outside the normal range. In a large prospective study including pregnant thyroid antibody negative women, a TSH level within the normal

range but higher than 2.5 mIU/L in the first trimester, nearly doubled the risk of a miscarriage [34]. However, the true significance of thyroid dysfunction and the value of its correction in improving outcomes in RM remains unclear [35].

The prevalence of diabetes mellitus in women who suffer recurrent miscarriage is similar to that reported in the general population [36]. Current evidence shows that well-controlled diabetes is not a risk factor for RM. However, uncontrolled diabetes is associated with increased pregnancy loss thus, attention should first be given to optimal metabolic control of diabetic women during the preconceptional period [37,38].

Prolactin is commonly measured because elevated prolactin levels are associated with ovulatory dysfunction. Hyperprolactinemia may be associated with recurrent pregnancy loss through alterations in the hypothalamic-pituitary-ovarian axis, resulting in impaired folliculogenesis and oocyte maturation, and/or a short luteal phase. Normalization of prolactin levels with a dopamine agonist improved subsequent pregnancy outcomes in patients with recurrent pregnancy loss [39]. Patients (n 1/4 64) with 2 or more pregnancy losses and hyperprolactinemia were treated with bromocriptine in their next pregnancy. Treatment resulted in an 85.7% live-born rate, whereas the untreated cohort had a 52.4% live-born outcome [39].

The role of other hormonal abnormalities remains controversial. Polycystic ovarian syndrome (PCOS) is a common endocrine disorder of reproductive-age women. PCOS may be associated with ovulatory disorder and miscarriage when fertility is desired. It has been estimated that 40% of pregnancies in women with PCOS will result in spontaneous loss [38]. However, using strict criteria the prevalence of PCOS among women with RM is estimated to be 8.3% to 10% [40]. Polycystic ovary syndrome (PCOS) has been linked to an increased risk of miscarriage but the exact mechanism remains unclear. Polycystic ovarian morphology, elevated serum luteinizing hormone levels or elevated serum testosterone levels, although markers of PCOS, do not predict an increased risk of future pregnancy loss among ovulatory women with a history of recurrent miscarriage who conceive spontaneously [22].

The mechanisms behind an increased miscarriage risk in women with PCOS remains partly unclear. The current view is that the main cause may be the associated obesity, as well as insulin resistance, hyperinsulinemia and hyperandrogenemia.

Retrospective evidence suggests that obesity increases the risk of miscarriage [41]. Obese women with RM have a higher frequency of euploid miscarriage compared with non-obese women. Obesity is associated with many endocrine disorders, such as diabetes, hypothyroidism, and PCOS, which, theoretically, could result in an increased risk of euploid miscarriage due to suboptimal implantation related to endocrine changes.

It is thought that obesity acts on female reproductive function through hyperinsulinemia and, consequently, through its effect on androgen production. Some authors have argued that insulin resistance is a key factor in explaining the association between obesity, PCOS and recurrent miscarriages [42]. The prevalence of insulin resistance is increased in women with recurrent miscarriage compared with matched fertile controls. An elevated free androgen index appears to be a prognostic factor for a subsequent miscarriage in women with recurrent miscarriage [40]. Metformin treatment of PCOS patients decreases insulin resistance, thus improving ovulation cycles and, therefore, conception rates in infertile women but it is uncertain whether it decreases the rate of miscarriage in PCOS patients as no proper RCT has been conducted [37].

Boots and Stephenson completed a systematic review evaluating whether obesity increases the rate of miscarriage in spontaneously conceived pregnancies [43]. Overall, 3,800 obese, 3,792 overweight, and 17,146 normal weight women were included in the pooled analysis. The percentages of women with RM were 16.6%, 11.8%, and 10.7%, respectively. The odds of having RM were increased for obese women (odds ratio [OR] 1.31, 95% CI 1.18–1.46) and overweight women (OR 1.11, 95% CI 1.00– 1.24), when compared with women with normal BMI.

Different retrospective studies have suggested a relationship of obesity and miscarriage, either sporadic or recurrent [44]. Furthermore, in 2010, Landres, et al. [45] reported a significant increase in euploid (46,XX or 46,XY) miscarriages in overweight or obese women (BMI R25 kg/m2) compared with women of normal weight (BMI <25 kg/m2), in a retrospective case-control study of 204 miscarriages from an infertility practice. More recently, Boots et al showed in a powerful study that obese women with recurrent miscarriage were also more likely to have euploid miscarriages and, therefore, are at an increased risk of subsequent miscarriages [41].

Conceptually, delayed or late implantation may increase pregnancy losses [46]. A shortened luteal phase

has been associated with pregnancy loss but the assessment and interpretation of a putative luteal phase defect is problematic [47]. The use of histologic and biochemical end-points as diagnostic criteria for endometrial dating are unreliable and not reproducible utilizing the traditional histological criteria or other biochemical approaches. Therefore, routine endometrial biopsy for dating is not recommended, although continued research on the emerging molecular markers of endometrial development should be encouraged [3].

Administration of progesterone to women with sporadic miscarriages is ineffective [48]. However, in patients with three or more consecutive miscarriages immediately preceding their current pregnancy, empiric progestogen administration may be of some potential benefit [49].

Environmental, Occupational or Personal Habits

The evidence on the effect of environmental risk factors is based mainly on data studying women with sporadic rather than RM. The results are conflicting and biased by difficulties in controlling for confounding factors and the inaccuracy of data on exposure and the measurement of toxin dose.

Maternal cigarette smoking and caffeine consumption have been associated with an increased risk of spontaneous miscarriage in a dose-dependent manner. Smoking-related complications in late pregnancy are substantial and well documented. However, current evidence is insufficient to confirm the association with miscarriage [2].

Nevertheless, cigarette smoking has been suggested to have an adverse effect on trophoblastic function and a link to an increased risk of sporadic pregnancy loss has been suggested [50]. A recent review reports an increased risk of pregnancy loss among smokers whereas a large prospective study including 24.608 pregnancies could not demonstrate an association between smoking and miscarriage [51-52].

Other life-style habits such as cocaine use, alcohol consumption (3 to 5 drinks per week), and increased caffeine consumption (>3 cups of coffee), have been associated with risk of miscarriage. Heavy alcohol consumption is toxic to the embryo and the fetus. Even moderate consumption of five or more units per week may increase the risk of sporadic miscarriage [2,16,19].

Etiology		Screening	Management	Controversial evidence	Not recommended
Genetic abnormalities	Embryonic chromosomal abnormalities	Genetic analysis of products of conception	Preimplantational genetic screening		
	Parental balanced reciprocal translocations	Parental karyotype	Preimplantational genetic screening		
	Sperm DNA fragmentation				
Thrombotic disorders	Hereditary thrombophilia	Thrombotic tests		Heparin, LDA	
	Antiphospholipid syndrome		LAC, ACA IgG & IgM antibody		
Alloimmunity			None	Uterine NK cells, cytokine profiles	Circulating NK cells HLA typing

Uterine anatomic abnormalities	Congenital uterine malformations	MRI 3D-ultrasound	Hysteroscopy: septal resection		
	Adquired anatomic disorders	MRI 3D-ultrasound	Hysteroscopy	Treatment of myomas	Cervical incompetence
Hormonal/metabolic etiology	Hypotidoidism, hyperprolactinemia, diabetes mellitus polycystic ovarian syndrome	TSH, PRL, Hb A1C	Levothyroxine	Insulin resistance	Luteal phase progesterone
Environmental, occupational, personal habits.		Anamnesis	Alcohol cessation	Weight loss	

Table 1: Possible causes of Recurrent Miscarriage (RM).
LDA: low.dose aspirin.
LAC: lupus antiocoagulant.ACA: anticardiolipin antibodies.

Possible Etiologies of Recurrent Miscarriages

1. Genetic abnormalities
   - Embryonic chromosomal abnormalities
   - Parental balanced reciprocal translocations
2. Thrombotic disorders
   - Thrombophilia
   - Adquired thrombophilic conditions: antiphospholipid syndrome
   - Alloimmunity
3. Uterine anatomic abnormalities
   - Congenital uterine malformations
   - Adquired anatomic disorders
4. Hormonal/metabolic etiology
   - Hypotiroidism
   - Diabetes mellitus
   - Hyperprolactinemia
   - PCOS
   - Lutelphasedeffect
   - Obesity
5. Environnmental, occupational, personal habits.

Summary and clinical implications

The loss of pregnancy at any stage can be a devastating experience and particular sensitivity is required in assessing and counselling couples with RM.

Recurrent miscarriage (RM) represents a clinical challenge for physicians not only because there are multiple possible etiologies, but also because the diagnostic testing is costly and time consuming.

In addition to genetic or auto-immune diseases, endocrine dysfunction, metabolic disorders and environmental risk factors may play an important role in the etiology of RM.

Thus, diagnosis and management of some endocrinological disorders, including obesity, as well as the modification of some life-style habits may be beneficial in this challenging problem.

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