A clinical approach to recurrent pregnancy loss

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Abstract

A diagnosis of recurrent pregnancy loss can be considered after the loss of two or more pregnancies before 24 weeks' gestation. In most couples no pathological cause is identified. The outcome can be improved for women with recurrent pregnancy loss and antiphospholipid syndrome with treatment with aspirin and/or heparin. Couples with unexplained recurrent pregnancy loss have an excellent prognosis with supportive care alone and to date no pharmacological intervention has been proven to be beneficial. This review describes the causes of recurrent pregnancy loss, the clinical work-up and an evidence-based approach to management.

Keywords antiphospholipid syndrome; early pregnancy; miscarriage; recurrent pregnancy loss

Introduction

A pregnancy loss or miscarriage is the spontaneous demise of a pregnancy before the fetus reaches viability. Recurrent miscarriage was traditionally defined as three or more consecutive miscarriages. Recent guidelines have suggested this definition should be relaxed and that a diagnosis of recurrent pregnancy loss can be considered after the loss of two or more pregnancies before 24 weeks' gestation. These pregnancies should be confirmed by at least serum or urine hCG. If not visualized by ultrasound scan, only pregnancies after 6 weeks' gestation should be included. If identified as ectopic or molar pregnancies, these should also be excluded.

Pregnancy loss is a common complication of early pregnancy, occurring in up to 15% of clinically recognized pregnancies. The exact prevalence of recurrent pregnancy loss is difficult to determine but most studies estimate around 1% of couples trying to conceive. Miscarriage is an important cause of morbidity and mortality including significant emotional distress in both partners.

The observed incidence of recurrent pregnancy loss is much higher than that expected by chance alone. This suggests that there are potentially identifiable, and potentially remedial factors, which increase the chance of miscarriage. However, the causes and pathophysiology of recurrent pregnancy loss remain poorly understood. The risk of recurrent pregnancy loss increases with the maternal age and the number of successive losses. Recurrent pregnancy loss is associated with parental chromosomal anomalies, maternal thrombophilic disorders, structural or functional uterine or endometrial anomalies, maternal immune dysfunction, and endocrine abnormalities. However, in the majority of couples with recurrent pregnancy loss no cause is found.

Risks factors

Epidemiological

Maternal age at conception is a strong independent risk factor for pregnancy loss, reflecting a decline in the number and quality of the remaining oocytes. The risk of fetal loss increases steeply after the age of 30 years, rising from 11% at age 20–24 years to 93% at age 45 years and older (Tables 1 and 2). This means that many cases of recurrent pregnancy loss will be explained solely by advancing maternal age. Advanced paternal age (age 40 years and older) has also been identified as a risk factor for miscarriage although the association is less marked (OR 1.6 [1.2–2.0]).

Previous reproductive history is an independent predictor of future pregnancy outcome. The risk of a further miscarriage increases after each successive pregnancy loss, from approximately 9% after no losses, 12% after one, 20% after two, reaching 40% after three or more pregnancy losses. Women with a previous live birth are not precluded.

There is little reliable evidence on environmental risk factors and independent variables, causality and association are hard to assess. However maternal cigarette smoking and caffeine consumption (when intake exceeds more than three cups of coffee per day) are possibly associated with a dose-dependent increased risk of miscarriage. Heavy alcohol consumption has adverse effects on fertility and fetal development, though even moderate alcohol consumption of 5 or more units per week may increase the risk of sporadic miscarriage. Obesity (BMI $\geq$30 kg/m^2) is an increasingly common problem in the UK and is associated with an increase in risk of early miscarriage (OR 1.2 [1.01–1.46]) and recurrent pregnancy loss (OR 3.5 [1.03–12.01]) as well as other pregnancy complications.

Genetic factors

Developmental and genetic abnormalities are frequently found when pregnancy losses undergo detailed examination. Although not all developmental abnormalities are associated with chromosomal disorders, fetal aneuploidy is the most important cause of pregnancy loss before ten weeks' gestation. The prevalence of chromosome abnormalities in a single sporadic miscarriage is 45%, with trisomy being the most frequent abnormality seen. These mostly arise from errors in the first meiotic division of the oocyte, which is initiated prenatally and is not completed until ovulation and this risk increases with maternal age. It is important to remember however, that as the number of pregnancy losses increases, the risk of euploid pregnancy loss increases.

In 2–5% of couples with recurrent pregnancy loss one partner carries a balanced structural chromosomal anomaly. This is either a balanced reciprocal translocation in which there is an exchange of two terminal segments from different chromosomes, or a Robertsonian translocation, in which there is centric fusion

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Miscarriage rates by maternal age at conception

Age (years)	Miscarriage rate
20–24	11%
25–29	12%
30–34	15%
35–39	25%
40–44	51%
≥45	93%

Table 1

Predicted percentage success rate of subsequent pregnancy according to age and miscarriage history (adapted from Brigham et al. 1999)

Age (years)	Number of previous miscarriages			
	2	3	4	5
20	92%	9%%	88%	85%
25	89%	86%	82%	79%
30	84%	80%	76%	71%
35	77%	73%	68%	62%
40	69%	64%	58%	52%
45	60%	54%	48%	42%

Table 2

of two acrocentric chromosomes. Carriers of these translocations are phenotypically normal but 50–70% of their gametes and therefore embryos are unbalanced, because of abnormal segregation at meiosis. The risk of subsequent pregnancy loss is dependent on the type of rearrangement and whether it is carried by the female or the male partner.

Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is an important treatable cause of recurrent pregnancy loss. APS is an acquired autoimmune disorder associated with vascular thrombotic events and pregnancy failure. The disease can occur as a discrete entity (primary APS) or in association with other autoimmune disease, usually systemic lupus erythematosus (SLE). Antiphospholipid antibodies are a family of around 20 antibodies that are directed against phospholipid binding plasma proteins and include lupus anticoagulant, anticardiolipin antibodies, and anti-β_2 glycoprotein-I antibodies.

Antiphospholipid antibodies are present in 15% of women with recurrent miscarriage. These women have a potential 90% risk of further fetal loss if left untreated. The pathophysiological mechanisms by which antiphospholipid antibodies cause pregnancy morbidity include inhibition of trophoblastic function and differentiation, activation of complement pathways causing inflammation-mediated placental injury, and in later pregnancy thrombosis of the uteroplacental vasculature.

Inherited thrombophilias

Inherited thrombophilias (factor V Leiden, activated protein C resistance, prothrombin gene mutation, and protein S deficiency) are associated with venous thromboembolism and may also increase the risk of recurrent miscarriage. The presumed mechanism for these effects is thrombosis of the uteroplacental circulation.

Methylenetetrahydrofolate reductase (MTHFR) mutations are gene polymorphisms that have historically been classified as hereditary thrombophilia factor but are no longer routinely assessed.

In a meta-analysis Factor V Leiden was associated with early recurrent fetal loss (OR 2.01), as was activated protein C resistance (3.48), and prothrombin gene mutation (OR 2.56). Protein S deficiency was also associated with recurrent fetal loss (OR 14.72) whereas MTHFR mutations, protein C and antithrombin deficiencies were not significantly associated with fetal loss.

Anatomical factors

Congenital uterine anomalies (uterine septate and bicornuate uterus) are found in between 1.8% and 37.6% of women with recurrent pregnancy loss and the reproductive implications remain unclear. Women with untreated uterine anomalies are reported to experience high rates of miscarriage and preterm delivery though no reliable data are available.

Uterine fibroids are present in 30% of women, but their impact on reproductive outcome is controversial. It has been postulated that uterine fibroids have a mechanical or space-occupying effect that impedes embryonic implantation. The expression of *HOXA10*, a gene that controls differentiation and is involved with implantation has been shown to be lower in uteri with fibroids than in those without. This suggests that fibroids affect endometrial receptivity through a molecular mechanism of action that has global endometrial consequences.

The findings of a recent large American cohort study however, do not support the hypothesis that fibroids cause miscarriage.

Cervical weakness is a recognized cause of second trimester miscarriage but the incidence is unknown as there is no objective test that can identify women with cervical weakness in the non-pregnant situation. The diagnosis is mainly a clinical one based on a history of second-trimester miscarriage preceded by spontaneous rupture of membranes or painless cervical dilatation.

Endometrial factors

There is an increasing amount of research into the role of the endometrium in recurrent miscarriage. Decidualization is the changes to the endometrial glands, stroma and cellular composition induced by progesterone that supports implantation of the embryo. It has been suggested that there may be disorders or decidualization in some women with recurrent miscarriage. The endometrium interacts with the embryo and seems to favour implantation of normally developing embryos. One current theory suggests that in some cases of recurrent miscarriage the endometrium allows abnormally developing embryos, which will ultimately miscarry, to implant. This is supported by the observation that time to conception is markedly reduced in some women with recurrent miscarriage.

Progesterone, secreted mainly by the corpus luteum, induces secretory changes in the endometrium which are essential for implantation of the embryo. It has been suggested that some cases of miscarriage might be due to inadequate secretion of

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