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The Main Causes of Recurrent Spontaneous Miscarriages

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Abstract **Review Article**

Summary: Repeated spontaneous miscarriages are defined as at least three consecutive episodes of spontaneous miscarriage, less than 14 weeks of amenorrhea, with the same partner, in a patient under 40 years of age. 80% of these patients have an identifiable cause justifying an etiological approach. A guided history and clinical examination are necessary. An etiological assessment is to be carried out: a pelvic ultrasound and a hormonal assessment in the woman, as well as a karyotype of the two members of the couple. The other examinations are requested as a second intention. The main causes are balanced chromosomal abnormalities of the parents, sperm DNA fragmentation, congenital malformations and lesions of the uterine cavity, anti-phospholipid syndrome, unbalanced diabetes, dysthyroidism and luteal insufficiency. In the event of an identified cause, certain therapeutic or preventive measures must be discussed in order to limit the risk of recurrence.

Keywords: Recurrent spontaneous miscarriage, genetics, hormone, uterus, thrombophilia.

INTRODUCTION

Recurrent spontaneous miscarriages (RSM) are defined as at least three consecutive episodes of spontaneous miscarriage (SM), less than 14 weeks of amenorrhea, with the same partner, in a patient under 40 years of age. The proportion of women affected by RSM is estimated at 1.5% [1].

The retained cause of RSM can be permanent and unique, it can also be more complex to highlight and correspond to an association of predisposing factors. But in about 20% of women undergoing RSM, the etiological assessment would come back negative, leaving the doctor and the couple without an answer [1]. The main etiological classes are:

I. Genetic Causes

1) Chromosomal abnormalities

The karyotype of the miscarriage product allows the diagnosis of an embryonic chromosomal abnormality in 60% of early sporadic abortions. It is useful for differentiating between a sporadic chromosomal abnormality (acquired de novo) and a repetition of the same abnormality. Most of these abnormalities detected are accidental, and the parents have normal karyotypes and are therefore not responsible in principle for RSM. However, since the incidence of certain meiotic aneuploidies increases with maternal age, the repetition of these RSM would then appear simply by chance [2].

In the case of RSM, the karyotype of the couple is fundamental because it makes it possible to discover balanced constitutional chromosomal abnormalities in the parents (Robertsonian translocations, reciprocal translocations, chromosomal inversions), or the presence of a Turner syndrome, especially in mosaic (45,X/46,XX). In this context, the rate of chromosomal abnormalities in one of the parents is 5% [3]. Genetic counseling should explain the chromosomal abnormality and sometimes consider preimplantation diagnosis if there is a risk of having a child with a serious illness.

2) Sperm DNA fragmentation

It can be caused by an increase in oxidizing substances secondary to age, infection or environmental factors: toxic substances, heat, etc. Sometimes it results in an oligo-astheno-teratospermia. When oocytes cannot correct these sperm abnormalities through their own repair system, this can result in RSM. The pregnancy rate can be improved after treatment or diet rich in antioxidants [4].

II. Uterine abnormalities

1) Synechiae

Synechiae are present in about 1.5% of patients with a history of surgery and in 7 to 22% of patients with RSM. They are confirmed by hysteroscopy. Endoscopic treatment appears to improve pregnancy rates [5]. A control hysteroscopy must be performed one month after the operation to detect recurrences.

2) Endocavity Polyps

They alter the embryo implantation process and are found in 0.5 to 5% of women with RSM. The gold standard diagnostic test is hysteroscopy. Its surgical resection, especially for the ostial locations, improves the pregnancy rate [6].

3) Submucosal leiomyomas

These are frequent lesions responsible for both RSM and infertility. Their diagnosis is made by ultrasound. Their surgical treatment is better than embolization in improving pregnancy rates [7].

4) Adenomyosis

It decreases the implantation rate and increases the SM rate [8].

5) Uterine malformations

Even if they are most often responsible for abortion in the second trimester of pregnancy, they are found in 15 to 20% of cases of RSM. Their diagnosis is confirmed by hysteroscopy, 3D ultrasound or MRI.

The most common malformations that cause SM are hypoplastic uteri and septate uteri. The frequency of uterine septa is 1% in infertile patients and 3% in those with RSM [9]. Endoscopic surgical treatment improves implantation but increases the risk of synechiae and uterine rupture in pregnancy.

III. Thrombophilia

1) Antiphospholipid Syndrome (APS)

The diagnosis of APS is based on a panel of clinical criteria such as venous thrombosis, and biological criteria such as the presence of anti-b2 glycoprotein-1 antibodies. Positive lupus anticoagulants and anticardiolipin antibodies are found in 15% of women with RSM [10]. The standard treatment consists of a combination of aspirin and low molecular weight heparin. On the other hand, in unexplained RSM, there is no benefit in prescribing these treatments to prevent a recurrence [11].

2) Hyperhomocysteinemia

It is linked to the homozygous mutation of the methylene tetrahydrofolate reductase gene. The homocysteine assay may be incorrect if folic acid is taken during pregnancy. Its presence justifies treatment with vitamins B6 and B9 during pregnancy [1].

IV. Endocrine causes

1) Unbalanced diabetes

Its screening by fasting blood glucose associated with glycated hemoglobin (HbA1c) is therefore necessary in case of RSM. The balance of diabetes allows the prevention of recurrences [12].

2) Dysthyroidism

Hyperthyroidism is associated with an increased risk of SM. Autoimmune hypothyroidism (Hashimoto's disease) through antithyroid antibodies (anti-TPO and anti-thyroglobulin). In this case, levothyroxine is recommended to achieve a serum thyroid stimulating hormone (TSH) level below 2.5 mIU/l [13].

3) Luteal insufficiency

A defect in the function of the corpus luteum leads to a deficit in the production of progesterone. It is not only associated with implantation failure, but also with an increased risk of miscarriage.

Progestogen supplementation is the most commonly used treatment. But it would seem that it is not effective in preventing the risk of RSM [14].

4) The "non-classical" form of 21-hydroxylase deficiency

Unlike the classic form, this form appears in adulthood and is responsible for oligomenorrhea with normal or subnormal fertility, and with a 25.2% risk of SM [15]. The diagnosis is confirmed in the presence of a high level of 17-OH Progesterone and sometimes following the synacthen test. Preventive treatment with hydrocortisone is instituted to prevent recurrence. Genetic counseling is necessary in the event of a diagnosis in the patient so that screening of the spouse is offered to prevent a classic form in the child.

5) Hyperprolactinemia

Hyperprolactinemia can alter folliculogenesis, oocyte maturation or cause a shortening of the luteal phase. The use of a dopaminergic agonist to normalize blood prolactin levels improves the pregnancy rate in patients with RSM [16].

V. Immunological disorders

Alterations in the *FOXP3* gene suppress the regulatory function of Treg cells necessary for immune tolerance in pregnancy and could, through this, be involved in RSM. Natural Killer lymphocytes would be involved in the immunotolerance mechanisms of the semi-allogeneic transplant that is pregnancy. In patients who undergo RSM, this regulation would be lost, resulting in an excessive response of TH17 lymphocytes and extensive local inflammation [17].

VI. Potentiating environmental factors

We especially cite obesity, tobacco and drugs, alcohol consumption, pesticides and vitamin deficiencies (B9 and B12) [1].

CONCLUSION

When a doctor is faced with a case of repeated spontaneous miscarriages, he must adopt an orderly etiological diagnostic approach through an oriented anamnesis and clinical examination. An etiological assessment must be carried out a hormonal assessment: prolactin, TSH, anti-TPO and anti-TG antibodies if hypothyroidism, fasting blood glucose ± HbA1c, coupled with a pelvic ultrasound. We also perform an APS assessment, a dosage of vitamins B9 and B12, a homocysteine dosage, a hysteroscopy, a 3D ultrasound or pelvic MRI if we are moving towards a uterine malformation, as well as a karyotype of the two couple members.

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