Recurrent pregnancy losses, a lasting cause of infertility

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Introduction

Recurrent pregnancy losses (RPL), a lasting cause of Infertility

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Running title

RPL in infertility

Capsule

Early miscarriage occurs in approximately 12-15% of all pregnancies, an incidence that notoriously increases with age. Recurrent pregnancy loss (RPL) – ≥2-3 miscarriages – affects nearly 1-2% of women.

Abstract

Recurrent pregnancy loss (RPL) defines the occurrence of 2-3 spontaneous terminations of pregnancy before 12 weeks of gestation, a pathology that affects approximately 1% of the general population. The causes can reside in the quality of gametes – sperm and oocyte – and the resulting embryo of that of the uterus, which are congenital and acquires. Alterations of endometrial receptivity through chronic alterations due to endometriosis and/or endometritis, which are associated with an impaired action of progesterone, have also been implicated in RPLs. Finally, immunological factors and thrombophilia – congenital and acquired – have also been suspected to cause RPL.

One arbitrarily considers that miscarriages are the spontaneous terminations of pregnancy occurring before 20 weeks of gestation. Conversely, pregnancy losses that take place later are referred to as premature births, which generally have different etiologies.

Practically, miscarriages are commonly referring to spontaneous termination of pregnancies occurring before the 12th week of gestation. It is possibly the most common pathology encountered in medicine. It is generally admitted that 12-15% of all pregnancies spontaneously terminate through an early miscarriage, an incidence that is markedly influenced by age. The frequency with which miscarriages occur has been however extraordinarily stable over time. In the past decades, we have notably observed similar incidences of miscarriage in spontaneously occurring and ART-induced pregnancies. In ART however, early β-hCG measurements add the very early pregnancy arrests – before any clinical manifestation –, which are counted as biochemical pregnancies. This latter parameter is generally not recognized in non-ART conditions.

On certain occasions, miscarriages occur repetitively. By definition, one generally speaks of recurrent pregnancy losses (RPL) after 3 episodes of miscarriages, a fact encountered in approximately 1% of cases in the general population. Today however, investigations for sorting possible causes of RPL are commonly initiated after 2 miscarriages already. In infertile women, the incidence of RPL is sensibly higher. Several causes of RPL have been identified sometimes leading to practical measures to overcome recurrence. These are reviewed in the present series of articles.

The oocyte, sperm and embryos: coping with genetic causes

Klimczak et al. review the causes of RPL stemming from disorders affecting the sperm, oocyte or embryo (1). These authors emphasize that sperm anomalies likely contribute to a fraction of the high incidence of genetic disorders encountered in products of conception ending in miscarriage. Various methods of assessing sperm reproductive potential are reviewed with emphasis on sperm DNA integrity assessment and chromosomal aberrations. Options tested or in development for sperm sorting are reviewed.

Abnormalities of the oocyte – intrinsic likely present in all of a person's cohort of oocytes and functional disorders – are likely lethal to the developing conceptus. Structural rearrangements of the chromosome may be present in 12% of couples

with RPL, with 40% being identifiable by traditional karyotypes. PGTM may help in selecting the disease free embryos. Balanced translocations are found in 4-8% of couples with RPL, including in those who may have had one or more healthy children. Finally, asymmetric inactivation of the X chromosome has been found more common in women with RPL, but no specific treatment is currently available.

Uterus congenital and acquired factors

The uterine causes of miscarriages and RPL are divided in congenital – malformations – and acquired disorders. The former category amounts to various degrees of non-resorption of the septum separating the two Mullerian ducts at the time of their fusion in utero. As described by Carbonnel et al. (2), the anomaly most frequently associated with miscarriages and RPL is the septated uterus defined by a septum protruding >10 mm in the uterine cavity (2). Conversely, more and less important non resorption of the septum – double uteri and arcuated uterus (septum <10 mm) – are less prone to cause miscarriages. While a near consensus of opinion recommends surgical metroplasty in case of septate uteri with RPL, surgical abstention is generally recommended for the latter malformations – double uteri and arcuated uterus (2).

Uterine fibromas and endometrial polyps constitute the bulk of the acquired anatomical anomalies together with intra-uterine adhesions. Uterine fibroids are classified according to their anatomical position in relation to the uterine cavity and uterine wall. Today the classification of the international federation of gynecologists (FIGO) is preferred over the descriptive localization that was used before. Fibroids classified as FIGO 0-2 protrude inside the uterine cavity. Common sense and widely accepted medical practices recommend surgical removal of such fibroids even if guidelines, such as those proposed by ESHRE, remain elusive about such indications. As underscored by Carbonnel et al., clear benefit from removing endometrial polyps is lacking despite a general practice that calls for endoscopic removal of such protruding structures (2).

Intra-uterine adhesions and scar tissue is a lingering problems encountered in women who had uterine procedures and or infections. As discussed by Carbonnel et al. in this issue of views and reviews, the management is a lingering problems and matter of debates (2). In unmanageable cases – alterations beyond hope for repair – certain are proposing the use of stem cells and even at times, possible uterine transplantation or gestational surrogacy.

The endometrium: Endometriosis, inflammation and chronic endometritis

Embryo implantation – the necessary step of the initiation of pregnancy – requires a proper development of the embryo itself and an adequate receptivity of the endometrium. Embryo quality – notably, its euploidy status – stems from oocyte and sperm quality as discussed by Klimczak et al. (1) in an article of this series. An impairment of endometrial quality may affect implantation and placentation. This may affect proper embryo development and result in miscarriage and in certain circumstances, RPL, as reviewed by Pirtea et al. (3).

Endometriosis has been demonstrated to affect the eutopic endometrium. Inflammation caused by endometriosis ultimately impairs the normal endometrial response to progesterone. As addressed by Pirtea et al. in a dedicated article of this series (3), endometriosis-led changes alter the endometrial response to progesterone and notably, a proper predecidual transformation of the endometrium. Endometriosis has indeed been associated with increased miscarriage risk possibly, leading to RPL.

The mechanisms causing the endometrial alterations in case of endometriosis are linked to a prevailing inflammation in the eutopic endometrium. A variant of endometriosis – adenomyosis – is also susceptible to induce the same consequences and notably, RPL. This is primarily the case for internal adenomyosis.

Still another circumstance associated with endometrial inflammation is chronic endometritis (CE) found in 10-15% of infertile women and 40% of those suffering from endometriosis. Cicinelli's team conduct a systematic review of the incidence of miscarriages and RPL in case of CE in the same article of this series (3). Cicinelli et al. also assess the beneficial effects of specific treatment (3). This team emphasizes the difficulty in making the diagnosis of CE – thereby explaining some discrepancy in results – and emphasizes the need to perform both endometrial biopsies and hysteroscopy. The core message on the role of CE on RPL conveyed by Cicinelli's team is that it can be diagnosed and effectively treated thereby reducing if not preventing the risk of recurrence (3).

Immunological, thrombophilia and hormonal causes of RPL

The development of pregnancy implies an immune-tolerance for the development of the 'non-self' embryo. In this issue of Views and Reviews, Diana

Alecsandru et al. review the immunological mechanisms that permit a normal development of the embryo and the possible impairments that may lead to miscarriages and RPL (4). Likewise, Alecsandru et al. review the metabolic – including diabetes mellitus – and autoimmune disorder that me be associated with RPL (4). In the same article Klimczak and Franasiak review the alterations of hemostasis – thrombophilias – that may lead to miscarriages and RPLs (4). Reminding us that pregnancy itself is a prothrombotic state, these authors explain that therefore thrombophilias may increase the risk of complication.

It is debated whether inherited thrombophilias are associated with RPLs, with a majority of publication indicating that this is not the case (4). Conversely acquired thrombophilias may cause RPLs such as notably, the antiphospholipid antibody syndrome encountered in 5%-20% of cases with RPLs (4).

References

1. Klimczak et al. FS 2020 in press
2. Carbonnel et al. FS 2020 in press
3. Pirtea et al. FS 2020 in press
4. Alecsandru et a. FS 2020 in press