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Connecting Links Between Diminished Ovarian Reserve and Recurrent Miscarriages

Xinfang Zeng[1], Yuanfang Zhu[2], Danmin Lin[1]

[1]Department of Obstetrics and Gynaecology, The First Affiliated Hospital of Jinan University, Jinan University, Guangzhou, China
[2]Department of Obstetrics and Gynaecology, Shenzhen Baoan Women's and Children's Hospital, Jinan University, Shenzhen, China

Email address:
kwwddzxf@163.com (Xinfang Zeng)

*Corresponding author: Author Name

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Abstract: For the past few years, the incidence of Recurrent Pregnancy Loss (RPL) has been on the rise, which not only plagues many couples who are preparing for pregnancy, but also has such a tremendous negative impact on the patients body and mind. Recurrent pregnancy loss is defined as two or more clinically confirmed pregnancy losses, including embryo and foetal loss, before 20-24 weeks of pregnancy. The diagnosis of early pregnancy loss is relatively straightforward, although progress in predicting and preventing recurrent pregnancy loss has been hampered by the lack of a standardized definition, uncertainty surrounding pathogenesis and a highly variable clinical presentation. The prognosis for couples with recurrent pregnancy loss is usually favourable, although the likelihood of a successful pregnancy depends on the age of the mother and the number of previous losses. Chromosomal errors, uterine anatomical defects, autoimmune diseases and endometrial dysfunction may contribute to recurrent pregnancy loss. As research continues, diminished ovarian reserve (DOR) is gaining more and more attention. Through reading related articles, this paper presents a review of the effect of diminished ovarian reserve on recurrent miscarriage, with the aim of exploring the relationship between DOR and RPL, and whether DOR has an impact on women's pregnancy outcomes.

Keywords: Diminished Ovarian Reserve, Recurrent Pregnancy Loss, Ovarian Reserve Indicators, Pregnancy Outcome

1. Introduction

As the number of births in China has continued to decline, more and more attention has been paid to the fertility rate of women of childbearing age, the delay in the age of childbearing, and the lowering of the fertility rate. In addition, the changing social structure and living habits have led to an increasing rate of abortion among women. In the last decade or so, the chances of recurrent abortion have increased significantly. For women with reduced ovarian reserve, there is a problem of insufficient number of eggs in the body and reduced quality of eggs. Although these women may be able to achieve pregnancy through Assisted Reproductive Technology (ART), the reduced quality of the eggs may affect the subsequent development of the fertilized egg, resulting in a higher risk of miscarriage. Therefore, this paper reviews the relationship between recurrent miscarriage and reduced ovarian reserve function, and provides new clinical ideas for the diagnosis and treatment of couples with recurrent miscarriage.

Ovarian reserve function refers to the ability of follicles in the ovarian cortex to grow, develop, and form fertilized eggs, and is mainly reflected in the number and quality of follicles retained in the ovaries, reflecting a woman's endocrine level and fertility potential. Reduced ovarian reserve is defined as a decrease in the number and/or quality of oocytes in the ovaries, accompanied by a decrease in anti-mullerian hormone (AMH) levels, a decrease in sinus follicle levels, and an increase in FSH, which is associated with a decrease in fertility without any emphasis on age, etiology, or menstrual changes. With research findings, decreased ovarian reserve, either in terms of decreased egg number or decreased egg quality, may interfere with the formation of a fertilized egg, leading to the occurrence of miscarriage. There is no uniform criteria for the

diagnosis of reduced ovarian reserve, nowadays the commonly applied clinical indicators for the assessment of DOR are: age, follicle stimulating hormone (FSH), anti-mullerian tubular hormone, sinus follicle count (AFC), and inhibin (INFH-B). AMH is secreted by granulosa cells in the presinusoidal and small sinusoidal follicular stages, and a study by Farzaneh et al [1] found that in premature ovarian failure patients, AMH levels can precede changes in FSH and that AMH is positively correlated with ovarian reserve. Since the values of AMH are not yet uniform, its predictive value is still a hot research topic at present.

The definition of recurrent miscarriage (RPL) has not been uniformly defined so far, and is mostly specified in relation to the economic situation and social background of the country or region. As suggested by the European Society of Human Reproduction and Embryology (ESHRE) guidelines [2], RPL is defined as two or more pregnancy losses occurring before the 24th week of pregnancy, whereas the Royal College of Obstetricians and Gynaecologists (RCOG) guidelines [3] use a more stringent criterion defining recurrent miscarriage as loss of three or more pregnancies before the 24th week of pregnancy, including biochemical pregnancies. The prevalence of RPL is low compared to spontaneous abortion, which affects approximately 1% to 3% of women trying to conceive. Despite the fact that recurrent miscarriages occur in only a minority of patients, RPL can have a significant negative impact on a woman's physical and psychological well-being and cause great emotional frustration for couples [4, 5].

2. The Causes of RM

Many clinical factors have been attributed so far to be potential risk factors in RM. Anatomical abnormalities may be involved in 15% of women facing RM, with uterine septum being the most common [6]. Immune coagulation disorders, such as antiphospholipid syndrome (APS), have been found to be associated with another 15 % of RM cases, which result in early and mid-pregnancy miscarriages. A number of endocrine abnormalities are also thought to contribute to the etiology of about 8 to 12% of RM [7]. In 2-4% of RM cases, balanced chromosomal translocations in asymptomatic parents may lead to unbalanced translocations in fertilized eggs [8]. These are usually negatively selected by nature and mostly end in miscarriage. A number of infections have also been identified as potential causes of early miscarriage [9], specifically, 15% of early miscarriages and 66% of late miscarriages are associated with infection [10].

Despite a plethora of research, reviews, and causes linked to RM, approximately 50% of cases that treating physicians come across are still unidentified, idiopathic, or unexplained. It is extremely difficult to determine the fundamental reason of these puzzling occurrences, which motivates academics to work hard to learn more, investigate more, and connect more. Some associated pathways may yet be unidentified or understudied in terms of their potential contribution to RM today. The molecular elements linked to the formation of the ovarian reserve (OR) are one such item that may have an impact on embryo development. Therefore relevant research is currently underway. Age-related OR depletion is linked to an increased risk of miscarriage, and different oocyte-specific genes play roles in early embryonic development and embryo implantation, all of which point to interacting biology. Thus a clear understanding of the correlation between recurrent miscarriage and ovarian reserve will help to identify possible candidates in the pathophysiology of RM and may provide possible explanations for many unclassified cases of RM.

3. Indicators of Ovarian Reserve and Recurrent Miscarriage

3.1. Age and RM

As we age, the follicles continue to deplete with each menstrual cycle and begin to decrease in number, while the reproductive organs begin to shrink and age. Thus for older women, there seems to be a natural high risk of recurrent miscarriage. As ovarian reserve function begins to diminish, a woman's ability to conceive decreases and the risk of spontaneous abortion, stillbirths, and live births increase. Canadian Society of Obstetricians and Gynaecologists guidelines state that the spontaneous abortion rate for pregnant women between the ages of 35 and 45 years old is approximately 40 percent, and the rate for women over the age of 45 years old is between 60 and 65 percent. The main reason for the higher rate of spontaneous abortion and lower delivery rate at older ages is the increased incidence of chromosomal aneuploidy. Several studies in recent years have found that the risk of chromosomal aneuploidy in the embryo increases with the age of the mother, and the chance of recurrent miscarriage increases [11, 12]. In addition, the detection rate of chromosomal abnormalities in embryos is as high as 78% in women older than 35 years of age [13]. However, it has also been pointed out that ovarian age is not exactly the same as actual age, and that a woman's mental age, family history, living environment, and economic level are all related to it. Therefore, age can only be used as a rough indicator to assess recurrent miscarriage and should be evaluated in conjunction with other indicators.

3.2. AMH and RM

AMH, also known as Mullerian inhibiting substance (MIS), is a biologically active substance secreted by the granulosa cells of the ovary and was first discovered in the 1940's. AMH is secreted mainly by the pre-sinus follicle and the small sinus follicle, and is unaffected by the menstrual cycle, and is often used as a predictor of ovarian reserve. In women, plasma AMH levels are secreted at low levels from birth, rising gradually during puberty, peaking at about age 25, and then declining with age to become undetectable before menopause [14, 15].

Recent studies have found that patients with recurrent miscarriage have lower levels of anti-Müllerian hormone than

normal women. Lyttle SB [16] and others, in a prospective cohort study, found that the risk of miscarriage decreases with increasing AMH, and the results remained unchanged, even after adjusting for confounders such as mother's age, ethnicity, history of recurrent miscarriages, and after obesity. It was also noted that the miscarriage rate in women with severely reduced ovarian reserve function (AMH ≤ 0. 4 ng /mL) was more than twice as high as the miscarriage rate in women with AMH ≥ 1 ng /mL. Similarly, the findings of Atasever et al. [17] observed that 71 patients with unexplained REM had significantly lower AMH levels (2.9 ± 1.7 ng/mL) than 70 healthy control women (3.6 ± 1.7 ng/mL) seeking contraception (41 patients). These results all suggest that AMH levels may be lower in patients with recurrent miscarriage than in women with non-recurrent miscarriage. However, there are some studies suggesting that there is no statistically significant difference between AMH levels in patients with recurrent miscarriage and normal women [18, 19]. Whether there is a difference in AMH levels in patients with recurrent miscarriage is more controversial up to now and more prospective cohort studies are needed to determine this.

3.3. Other Ovarian Reserve Indicators and RM

Sinus follicle count (AFC) is one of the factors used to detect ovarian reserve. Sinus follicles are precursors to mature follicles, and when the pre-sinus follicle develops, the granulosa cells slowly produce follicular fluid and further form a follicular cavity. Early follicular stage, i.e. day 3-5 of the menstrual cycle after ultrasonography, the underlying sinus follicle with a diameter of 2-10mm is visible. In recent years, domestic and international studies have generally concluded that AFC has a predictive value for ovarian responsiveness and its reserve function. Hendriks et al. [20] applied ROC curves to compare the ability of AFC and FSH to predict ovarian responsiveness and showed that AFC was a better predictor of poor ovarian response than FSH, and concluded that AFC is the preferred predictor of ovarian hyporesponsiveness. This shows that AFC is a good predictor of follicle number. In terms of recurrent miscarriage, Atasever et al. [17] and Yildirim et al. [21] reported an association between DOR as defined by AFC ≤ 7 in RPL and non-RPL women and at a later stage through a meta-analysis by Bunnewelld [22], the pooled data of 313 women showed that women with RPL as compared to non-RPL women had a higher rate of DOR.

FSH is also another factor that responds to ovarian reserve, which is secreted by the follicle-stimulating hormone cells of the pituitary gland and is collectively known as gonadotropins along with luteinising hormone. Early follicular FSH represents basal FSH, which is usually checked on the 2nd-3rd day of menstruation. Foreign studies have shown that basal FSH rises with age and that an elevated basal FSH suggests a decline in ovarian reserve. This is because follicular dysplasia promotes follicular development by compensatory elevation of gonadotropins through feedback regulation of the hypothalamic-pituitary-ovarian axis. Thus, it can be said that FSH reflects ovarian reserve to some extent. In patients older than or equal to 35 years of age, elevated baseline levels of FSH are positively associated with the risk of pregnancy loss, and this risk increases with age. Recent studies have suggested that there is no uniformity in FSH levels between women with and without RPL. Some findings suggest that there is no statistically significant difference between the two [21-23], but at the same time, some studies have shown that FSH levels are higher in the RPL group than in the non-RPL group [17], while other studies suggest that FSH levels are lower in the RPL group than in the non-RPL group [19]. There may be several reasons for these differences in results, firstly, different ethnicity. Second the definition of recurrent miscarriage is different. Third, different methods of FSH testing.

Oestrogen fluctuates continuously and cyclically with the menstrual cycle, and in the early stages of diminished ovarian reserve, oestrogen can rise before FSH. However, oestrogen levels are susceptible to ovarian-related diseases, medications, and psychological states. At present, there is no strong evidence that higher luteinising hormone and lower oestrogen are associated with recurrent miscarriage.

4. DOR and Pregnancy Outcome

Whether reduced ovarian reserve affects subsequent pregnancy outcomes in women with recurrent miscarriages remains highly controversial. Some studies have found that patients with recurrent miscarriages who have reduced ovarian reserve have a lower rate of live births than normal women of childbearing age. However, some studies have also found that reduced ovarian reserve function may be a factor in recurrent early miscarriage but is not decisive for further miscarriages [24]. These studies were designed through small as well as retrospective studies and thus the predictive values of these studies were low. More in-depth studies are necessary to better determine the effect of reduced ovarian reserve on pregnancy outcomes in patients with recurrent miscarriage.

5. Conclusion

As the childbearing age continues to lengthen in China, an increasing proportion of the many women preparing for pregnancy are experiencing DOR. For patients with recurrent miscarriage, if conception is still not possible after adjusting menstruation and promoting ovulation, assisted reproductive technology can be used to shorten the time to reach pregnancy if necessary. However, it should be noted that the older the patient is, the less responsive the ovaries may be to artificial ovulation, and the chance of miscarriage increases after implantation of the embryo. Even after successful conception, whether reduced ovarian reserve affects the outcome of subsequent pregnancies is controversial and requires further study.

ORCID

Xinfang Zeng: 0009-0003-7852-3469

Conflicts of Interest

The authors declare no conflicts of interest.

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