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REVIEW

Connecting links between genetic factors defining ovarian reserve and recurrent miscarriages

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Abstract

Purpose Approximately 1–2% of the women faces three or more successive spontaneous miscarriages termed as recurrent miscarriage (RM). Many clinical factors have been attributed so far to be the potential risk factors in RM, including uterine anomalies, antiphospholipid syndrome, endocrinological abnormalities, chromosomal abnormalities, and infections. However, in spite of extensive studies, reviews, and array of causes known to be associated with RM, about 50% cases encountered by treating physicians remains unknown. The aims of this study were to evaluate recent publications and to explore oocyte-specific genetic factors that may have role in incidence of recurrent miscarriages.

Method Recent studies have identified common molecular factors contributing both in establishment of ovarian reserve and in early embryonic development. Also, studies have pointed out the relationship between the age-associated depletion of OR and increase in the risk of miscarriages, thus suggestive of an interacting biology. Here, we have gathered literature evidences in establishing connecting links between genetic factors associated with age induced or pathological OR depletion and idiopathic RM, which are the two extreme ends of female reproductive pathology.

Conclusion In light of connecting etiological link between infertility and RM as reviewed in this study, interrogating the oocyte-specific genes with suspected roles in reproductive biology, in cases of unexplained RM, may open new possibilities in widening our understanding of RM pathophysiology.

Keywords Recurrent miscarriages · Ovarian reserve · Premature ovarian insufficiency · Genetic · Factors

Introduction

Miscarriage, which is widely defined as a spontaneous loss of pregnancy before 20 weeks of gestation [1, 2], is recognized as the most common complication of pregnancy affecting 2–5% of couples [3]. About 15% of all clinically recognizable pregnancies terminates in a miscarriage [4] while preclinical miscarriages take place in approximately 60% of human conceptions and are lost very early, i.e., near or following implantation [4]. Approximately 1–2% of the women faces three or more successive spontaneous miscarriages termed as recurrent miscarriage (RM) [5–7] leaving them in a devastating and emotionally taxing situation [8, 9]. The possibility of having another miscarriage tends to increase with history of previous miscarriages [10]. Such incidence of repeated miscarriages in a women seems not to be a result of chance but is suggestive of some underlying abnormality.

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The known causes of RM

Many clinical factors have been attributed so far to be potential risk factors in RM. In 15% of the women facing RM, an anatomical abnormality could be involved, with septate uterus being most common [11]. Immunological blood clotting disorder like antiphospholipid syndrome (APS) is found associated with another 15% of RM cases causing 1st and 2nd trimester miscarriages [1, 3]. Several endocrinological abnormalities have also been implicated as etiologic factors for about 8 to 12% of RM [12]. This is due to poorly controlled

and untreatable hormonal imbalances, as in disorders like diabetes mellitus [13, 14], hypothyroidism [15, 16], and luteal phase deficiency [17] which may have deleterious effects in implantation of growing embryo. In 2–4% of RM cases, balanced chromosomal translocations in asymptomatic parents may result in generation of unbalanced translocation in conceptuses [18]. These are often negatively selected by nature and mostly end up in a miscarriage [19, 20]. Several infections have been also identified as potential cause of early miscarriage [21] with specifically, 15% of early miscarriages and 66% of late miscarriages been associated with infections [22].

The unknown cause of RM

In spite of extensive studies, reviews, and array of causes known to be associated with RM, about 50% cases encountered by treating physicians remains unexplained, idiopathic, or unknown. The challenge of identifying underlying cause in these perplexing cases is huge and urges researchers to put in efforts to know more, explore more, and relate more. There might be some related pathways that remained either unquarried or underexplored in defining their potential role in RM till date. One such entity that might affect the embryo development is the molecular factors associated with the establishment of the ovarian reserve (OR). OR is the quantity and quality of the ovarian primordial follicular pool remaining in a women's ovaries. The relationship of age-associated depletion of OR and increase in the risk of miscarriage and also role of various oocyte-specific genes in early embryonic development and in embryo implantation is suggestive of interacting biology [23, 24]. This review aims to gather evidences in establishing connecting links between genetic factors associated with age induced or pathological OR depletion and idiopathic RM, which are the two extreme ends of female reproductive pathology. This will facilitate in identifying possible candidates in the RM pathophysiology and may lead to provide possible explanation for many of the unclassified RM cases.

Biological ovarian age and risk of miscarriages

Recent decades have witnessed an increase in the mean maternal age at the time of childbirth in developed countries [25]. Advanced maternal age has long been linked with increasing incidence of RM. For example, miscarriage risk of 9 to 12% is found in a women ≤ 35 years, but this risk upsurges to 75% in women with age > 40 [26]. The ovaries of a women exhibit accelerated aging in comparison to other biological system and therefore result in deterioration of OR both in number and quality of the oocytes. In fact, an exponential relationship has been observed between maternal age and presence of chromosomal abnormality in oocytes, with about 40–60% of oocytes from women of 40 years being aneuploids [27, 28]. Subsequently, such oocytes after fertilization translate into compromised quality embryos. Recently, Quenby et al. suggested that RM is a failure of nature's quality control that allows poor quality embryos to implant inappropriately, present as clinical pregnancy, and then undergo miscarriages [29]. This is evident from the fact that about 40–50% of miscarriages in the first trimester are result of chromosomal abnormalities in the conceptuses [30, 31].

Also, it was observed that assisted reproductive technology (ART) methods often fail for older women using their own oocytes, while donor oocytes from younger women can be successfully used in these women [32]. Reports depicting the potential of postmenopausal women to act as a successful surrogate have also been identified previously [33–36]. Similarly, with the help of ART, cases where postmenopausal women have given birth to healthy offspring have become quite common. These findings establish that parameters associated with decreased fertility appear to be present majorly within oocyte itself rather than the uterine environment. Therefore, understanding the genetic factors affecting the oocyte quality and quantity and further in embryo development is important to define its role in compromised fertility.

Apart from age-related physiologic depletion of OR in women of more than 40 years of age, a premature reduction of OR (pathological OR depletion) has also been identified in a subset of women suffering with diminished ovarian reserve (DOR). DOR is defined as reduced capacity of the ovaries to produce oocytes and is characterized by an abnormal OR testing with decreased antral follicle count (AFC < 5) on ultrasound, reduced anti-müllerian hormone (AMH < 0.5–1 ng/mL), or higher levels of follicle stimulating hormone (FSH > 10 IU/L on cycle days 2 to 4) [37, 38]. Toukhy et al. in 2002 enrolled 762 women with DOR and classified them in three different age groups of young, intermediate, and old. The miscarriage rate was found to be similarly high in all these three groups. The results of this study depicted that it is not the chronological age which is important; instead, it is the biological age of the ovary that dictates the pregnancy outcome and also, that the young age of a women does not protect her against the adverse effect of reduced OR [39]. In some women, a severe form of DOR can be present called as premature ovarian insufficiency (POI), characterized by 4 months of amenorrhea and day 3 FSH to be > 40 IU/L. Once the diagnosis of POI is reached, the women's reproductive potential is completely exhausted and women enter an early age menopause before 40 years. As quantity and quality of the oocytes and thereby the reproductive potential of a women go on depleting [40] and ultimately come to an end at natural menopause, thus it is likely that a diagnosis of POI (complete cessation of fertility) may be preceded by RM due to compromised oocyte quality with an augmented meiotic nondisjunction and subsequent generation of aneuploidy of embryos, which is one of the main causes of spontaneous

miscarriages [41–44]. In fact, a study by Santos et al., in 2015, observed that the oocyte in women with elevated FSH (prone to POI) is of worst quality in comparison to age-matched control women. Here, the author concluded that these oocytes of compromised quality are indicative of ovarian aging and may negatively affect the oocyte development into viable embryos leading to frequent miscarriages. Another recent study reported that percentage of women with elevated FSH was higher in the women undergoing RM, as compared to age-matched control women, and thereby recommended the association of DOR and RM [45]. The association of oocyte quality and RM in both physiological (normal aging) and pathological depletion of OR (DOR or POI) cases suggest that they may share common etiological pathways. Exploring the molecular pathways related to physiological aging and the pathologic disorders of oocyte quality would give researchers and clinicians the ability to improve fertility and pregnancy outcomes for many women.

Genetic factors involved in launch of OR and their putative role in RM

The OR decreases constantly, from fetal life, when it is established, until the menopause. The fetal number of oocytes is approximately 7 million during mid-gestation, 1 to 2 million at birth which further drops down to only 0.3–0.5 million at puberty [46–48]. A women can ovulate about 500 times in her lifetime, and a majority of oocytes undergo atresia; thus, perimenopausal women's ovaries are left with only approximately 1000 oocytes of compromised quality [49, 50]. The overall process of OR establishment, pubertal OR activation, and age-dependent or pathological depletion of OR is largely influenced by genetic parameters. An alteration in the genes underlying these processes may lead to a spectrum of impaired ovarian function including POI. Till date, several causative mutations in various oocyte-specific genes have been implicated in POI rendering women infertile [51, 52].

Researchers have noted that there is an elevated risk of miscarriages in infertile women and vise versa [53–55]. Also, following infertility treatment, a high frequency of miscarriages has been reported [56]. These findings point out that both infertility and miscarriages lie within the spectrum of human reproductive failure that is inclusive of inability to conceive, inability to maintain pregnancy, or post-conception pregnancy loss. Some of the earlier studies have also shown common etiopathogenic pathways underlying these two extreme ends of reproductive failure spectrum [57, 58]. As POI is associated with infertility [59–61], thus factors contributing to development of POI may have implication in RM owing to proven links between infertility and the later.

Mutation in several genes has been validated by functional studies to be implicated in POI (for example *BMP15*, *GDF9*, *FSHR*, *LHCGR*, *FOXL2*, *FIGLA*, *NR5A1*, *NOBOX*, *NANOS3*, and *STAG3*) [51, 62–72]. Several mutations in folliculogenesis growth factors like *BMP15* and *GDF9* gene have been reported in POI women with either primary or secondary amenorrhea [65, 66, 73–84]. The influence of level of these factors (*GDF9* and *BMP15*) in the follicular fluid, on the quality of the embryo, has been studied formerly. It was observed that a high mature *GDF9* level in follicular fluid was positively correlated with embryo quality [85]. Similarly, role of *BMP15* in determining oocyte quality and developmental potential has also been previously recognized with a finding that a high *BMP15* level in follicular fluid is associated with best grade embryo morphology [85, 86]. Also, augmented levels of *GDF9* and *BMP15* mRNA in cumulus granulosa cells are found to correlate with oocyte maturation, fertilization, embryo quality, and pregnancy outcome in humans [87]. All these findings suggest that the intra-ovarian *BMP*/*GDF* system is of great importance in regulating a spectrum of ovarian functions from establishment of OR to generation of a competent oocyte for embryo development and thus may have roles in problems of infertility/subfertility and miscarriages both.

Once a high-quality oocyte is generated, the next important primary process required for successful reproduction is the transformation of this terminally differentiated oocyte to a pluripotent embryo after fertilization. Before the massive activation of zygotic genes, the early embryo development solely relies on the maternal transcripts and proteins that have accumulated during the course of folliculogenesis and oogenesis [88–91]. The genes encoding these transcripts and proteins are called as maternal effect genes (MEG) and are fundamental for early cleavage events post-fertilization [92, 93]. The maternal effect proteins can interact together to form a large multiprotein complex known as sub-cortical maternal complex (SCMC), which are uniquely expressed in oocytes and in early embryos. Studies conducted on mice model with mutations in genes encoding these maternally provided proteins and multi-component complexes showed impaired early embryonic development and hence leads to RM [94–100]. In a recent publication, the authors have identified human SCMC homologous genes (*NLRP5*, *OOEP*, *TLE6*, and *KHDC3L*) to be specifically expressed in the oocytes of human fetal ovaries and concluded that the human SCMC and its regulators may too have similar central role in early embryonic development. Investigating these oocyte-specific genes can thus provide answer for many unresolved RM cases [101]. In this context, various oocyte-specific transcription factors like *FIGLA*, *NOBOX*, *SOHLH1*, and *SOHLH2* have been found to regulate the expression of important MEG like *PADI6*, *KHDC3L*, *NLRP* gene family, *Pou5f1* [97, 102–109]. The same oocyte-specific transcriptional factors have been identified to have established role in controlling the expression of genes involved follicular development also [105–108, 110–112]. Furthermore, mutations in genes encoding these transcription factors are found to be associated with POI [52, 62, 68,

113–119]. This suggests an interconnected pathway between various facets of reproduction, viz. folliculogenesis and establishment of OR, pathogenic depletion of OR and RM.

Another important ovarian transcription factor is *FOXO3* which plays a key role in appropriate maintenance of the ovarian functioning, belongs to the *FOXO* (Forkhead box O) family of transcription factors, it acts as a key regulator for follicle activation or quiescence [Hopkins et al. 2014]. Constitutive activation of this protein blocks primordial follicle growth and thus induces infertility [120]. Other member of this family, *FOXO*1a, regulates the cell cycle progression [121]. A number of studies have described potential POI-causing variants both in *FOXO*3A and *FOXO*1A [122, 123]. *FOXL2*, which also belongs to fork head family, is also identified to function as the central transcription factor of the ovary and is essential for follicular maturation and maintenance of ovarian identity [124]. Heterozygous mutations in *FOXL2* have been identified in 90% cases of BPES (Blepharophimosis, ptosis, epicanthus inversus syndrome) [125–127], an autosomal dominant syndrome with complex eyelid malformations either associated with POI (type I BPES) or not (type II). *FOXL2* mutation has also been reported in isolated form of POI [128, 129].

Evidences have proved the role of these *FOX* factors in regulating the development and differentiation of endometrial cells during pregnancy also. This process is called as endometrial decidulization, and it is indispensable for the placental formation as it helps in maintaining the proper microenvironment for the implantation and growth of the embryo. An impaired decidualization of endometrium disables embryo-maternal recognition and selection upon implantation, which causes RM [130–133]. For instance, *FOXO1* protein is recognized to have a critical role in regulation of progesterone-dependent endometrial decidulization and protection of the feto-maternal interface against oxidative damage during pregnancy [134–137]. Similarly, another forkhead protein implicated in POI, i.e., *FOXL2*, has been recently shown to be strongly expressed in the uterine tissue of human, mice, and bovine besides its early expression in the ovarian follicles and granulosa cells [138–140]. Studies have also shown that *FOXL2* controls the expression profile of the endometrial genes and plays a pivotal role in regulating uterus receptivity and embryo implantation [141, 142]. Owing to high level of expressivity and functionality of these FOX proteins in the uterine tissue, in addition to ovaries, speculates that mutation in these genes may have significant implication in RM alongside with their putative role in POI.

Conclusion

In summary, it is understood that the clinical miscarriages result either when a poor quality oocyte develops into poor quality embryo which subsequently fails to implant properly, or when a high-quality embryo gets implanted in a hostile uterine environment which does not support the embryo growth. As there are evidences, the oocyte quality, embryogenesis, and also the uterine microenvironment are governed by various oocyte-specific genes, while most of these genes are also implicated in POI, thus a connecting etiological link between infertility and RM could be thought of. Interrogating the oocyte-specific genes with suspected roles in reproductive biology, in cases of unexplained RM, may open new possibilities in widening our understanding of RM pathophysiology.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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