Chapter

Impact of Biological Factors Related to Maternal Aging: Risk of Childbirth with Down Syndrome

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Abstract

Maternal aging and different biological factors play an important role in the birth of Down syndrome baby. Hormones play a crucial role for the maintenance of female sex cycle and oocyte maturation. Disparity in the level of these hormones during menstrual cycle has profound effect on female reproductive system. Hormonal imbalance also affects meiotic process and integrity of spindle structure and leads to nondisjunction of chromosome. Follicle-stimulating hormone (FSH), anti-Müllerian hormone (AMH) and luteinizing hormone (LH) play a crucial role in ovarian aging and nondisjunction of chromosomes. FSH stands as a hormonal indicator for ovarian aging, and its high level is responsible for aneuploid birth. Advanced chronological age of mother, ovarian aging, environmental factors and accelerated telomere shortening at older reproductive age are found to be risk factors for the birth of trisomy 21 Down syndrome.

Keywords: hormones, ovarian aging, nondisjunction, Down syndrome, trisomy 21, oocyte, telomere

1. Introduction

Down syndrome (DS), the most frequent live born aneuploidy in human, is predominantly caused by trisomy of chromosome 21 (Ch21), and its etiologic factors are under continuous scrutiny since its discovery by Lejeune et al. [1]. Several groups of workers have tried to explore the factors associated with nondisjunction (NDJ) of Ch21 and have identified that advanced maternal age [2, 3] and altered pattern of recombination are two strong correlates that affect proper segregation of chromosomes at oogenesis, particularly at first meiotic division (MI) [2, 4]. In elucidating the important causes of these sex bias risk factors, two hypotheses have been suggested. According to one school of thought [4], the extended phase of MI arrest in women that lasts for several years makes the oocyte more vulnerable to NDJ than spermatozoa. On the other hand, other investigators emphasized the meiotic drive of chromosomes and subsequent natural selection in asymmetric meiosis in females as the probable reasons of sex biasness of NDJ [5]. The association of advanced maternal age with DS birth is still an enigma. Although advanced maternal age is not the cause of NDJ, it is an obvious risk of DS birth. The overall maternal risk for DS birth is suggested to be multifactorial and includes both

genetic and environmental factors [2, 4, 6, 7] that impart adverse effects in either an age-dependent manner or a stochastic age-unrelated fashion [8]. In addition to genetic correlates, the genotoxic effects of smoking, chewing tobacco and oral contraceptive pills on reproductive health and fertility have also been investigated [9]. All these risk factors exacerbate age-related maternal risk for the birth of DS babies [10–12]. Telomere length is a powerful biomarker for aging. Telomere erosion at advanced reproductive age might affect the chromosomal segregation during oogenesis, and there is a strong relation between maternal aging and telomere length attrition [7, 13].

1.1 Hormonal imbalance with aging

A complex orchestrated hormonal cascade plays a very crucial role for the maintenance of female sex cycle and oocyte maturation. The brain hypothalamus releases luteinizing hormone-releasing hormone (LHRH) that triggers the anterior pituitary gland to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH and LH in turn stimulate ovary to produce estrogen (mainly estradiol) and progesterone using an complicated feedback loop. Disparities in the level of these hormones during menstrual cycle have a profound effect on female reproductive system. They are responsible for the recommencement of meiosis I in the oocyte [14], change in the follicular micro-environment around oocytes and prepare the endometrial layer of uterus for implantation of fertilized ovum [15, 16]. Maturity of oocyte, rate of meiosis and integrity of spindle are disturbed by imbalanced level of hormones and eventually lead to nondisjunction [17–19]. However, there are two major hormones FSH and anti-Müllerian hormone serve as powerful biomarkers of ovarian aging.

1.2 Follicle-stimulating hormone (FSH), aging and aneuploid birth

FSH plays a crucial role in nondisjunction. It has been documented that FSH level rises with ovarian aging [20, 21]. Moreover, women giving birth to Down syndrome (DS) child are reported to have elevated FSH level [22, 23], indicating the effect of aging on the oocyte pool. Demonstrated that higher concentration of FSH evokes chromosomal aneuploidy in murine model. They showed that the elevated FSH hampers chromosomal alignment in prometaphase and metaphase stages of meiosis I and gives rise to aneuploid oocyte. Granulosa cells of maturing follicles exclusively possess FSH receptors that are linked directly to oocyte with gap junctions [24, 25]. Thus, the effect of FSH on cumulus cells directly conducted to oocytes via secondary messenger cAMP and downstream kinase cascade [26, 27]. The spindle formation, its assembly and number of centromere in oocyte are perturbed by adverse effect of FSH both *in vivo* and *in vitro* [28]. It is also apparent that age-related reproductive failure is accelerated in transgenic FSH mice [29]. Researchers hypothesized that FSH alters the intra follicular environment that either facilitates the recruitment of an error-prone oocyte or affects cohesins and in turn reduce the pairing ability of chromosomes. Thus, chronic exposure to high FSH promotes rapid depletion of oocyte pool and accounts for trisomic pregnancies [30]. These evidences suggest that FSH stands as a hormonal indicator of ovarian aging, and its high level is responsible for aneuploid birth.

1.3 Anti-Müllerian hormone (AMH), ovarian reserve and aneuploid birth

Anti-Müllerian hormone (AMH) or Müllerian inhibiting substance (MIS) is a homodimeric glycoprotein and belongs to transforming growth factor-β (TGF-β)

superfamily. Synthesis of AMH occurs in ovarian granulosa cells. Several studies exhibit its prime role as a useful biomarker for ovarian reserve [31–34]. Gradual aging affirms a decline in the level of serum AMH. This hormone is proved to be a superior predictor of ovarian reserve than chronological age [35, 36]. The quality of an embryo depends upon both the quantity and quality of ovarian reserve which diminished with age. AMH, however, is essential for the maintenance of both the number and functional quality of oocyte pool. Moreover, AMH is a stable marker and not influenced by pregnancy, oral contraceptives and antagonist of gonadotropin-releasing hormone [37–41]. The undetectable level of AMH after 3–5 days of bilateral ovariectomy suggests that the origin of the circulating AMH is chiefly ovarian [39, 40]. AMH is an exclusive endocrine parameter to presume the ovarian function as it is evident from several studies that AMH level remains mostly unchanged throughout menstrual cycle unlike other gonadotropins and steroids [38, 42–44]. The association between serum AMH and fetal aneuploidy is a topic of debate. Seifer and Maclaughlin found lack of association of maternal AMH and Down syndrome conceptions [34]. This finding was again supported by Plante et al. who suggested that AMH decreases with age, and the dose level did not vary in cases of aneuploid and euploid pregnancies [45]; whereas Shim et al. demonstrated a significant association of circulating AMH with fetal aneuploidy in early pregnancies [46].

2. Alteration of sister chromatid cohesion: aging effect

A growing body of evidence suggests that aneuploid fetus formation speeds up as maternal age crosses 35 years. Moreover, a 10-fold increase in aneuploid conception is apparent after 38 years and involves aneuploidy of multiple chromosomes [47–49]. In older women, the probability of erroneous separation of sister centromere increases in anaphase-II [47, 48, 50]. Extensive loss of centromeric cohesion and subsequent instability of spindle are reported in oocytes arrested in MII from aged women [51–53]. Cohesin protein between two sister chromatids depletes with aging and gives rise to nondisjunction error [54]. Studies reveal that in MII oocytes of older mice [55, 56] and women [57], sister chromatids having incompletely separated distantly placed centromeres face problem in biorientation and result in spindle instability.

3. Telomere theory of ovarian aging

The telomeres are the nucleotide repeat sequence TTAGGG insulating the terminal ends of eukaryotic chromosomes, protecting them from getting fused with adjacent chromosomes [58]. In each cell division, telomere corrodes and restored by a unique reverse transcriptase called telomerase [59]. Gradual depletion of telomere length with age marked it as an impressive biomarker of aging [60]. Ovarian aging confirms a positive correlation between shorter telomere length and decreased reproductive lifespan [61]. The role of telomere biology in reproduction is supported by numerous opinions. Telomere theory of reproductive senescence states that prolonged exposure to reactive oxygen species (ROS) hastens the erosion of telomere in older women [62]. Telomerase is imperative for oocyte development and parthenogenesis. Telomerase is found in early antral follicle, preovulatory follicle and ovulated oocyte, but its expression diminishes at the time of oocyte maturation [63, 64]. After fertilization, telomerase activity ensures remodeling of telomere length (TL) essential for faithful embryonic development.

A conversed correlation exists amid the activity of telomerase and ovarian aging [65]. In occult ovarian insufficiency, telomerase inactivation and erosion of telomere are evident [66]. Researchers showed that telomere-deficient mice are infertile [67, 68]. Ovarian and uterine malformation and inadequacy of steroid hormone are apparent in mice lacking telomerase [68]. Oocytes having shorter telomere undergo aberrant fertilization and bizarre pattern of embryonic cleavage [69]. Age-related abrasion of telomere may in turn responsible for age-related aneuploidy. Mania et al. [70] exhibited that the aneuploid cells derived from disorganized cleavage-stage embryos have shorter telomeres than euploid cells in mother with older reproductive age or with recurrent history of miscarriage. Telomere shortening is also associated with aneuploidy in malignant cells [71]. Dorland et al. did not find any significant difference in telomere length between mothers of Down syndrome babies and euploid children [72]. However, Ghosh et al. and Bhaumik et al. demonstrated that the older mothers of Down syndrome child have shorter telomere than control [7, 13]. The author suggested that there is a perceptive connection between the constituents of telomere maintenance machinery and chromosome segregation system at molecular level. Moreover, this speculation is supported by several studies stating that disturbed telomere protection is responsible for chromosomal missegregation [73, 74]. Again, in yeast *Saccharomyces cerevisiae*, the improper chromosome separation was noticed due to mutant telomere sequence [75]. Thus, telomere biology has a great impact on the reproductive success particularly in nondisjunction.

3.1 Ovarian aging: genetic background

There is an enigma about the factors influencing the age at menopause in women. Certain lifestyle factors like parity, use of oral contraceptive pills and smoking habits are reported to be pertinent with the age of natural menopause [76]. However, discrepancy in menopausal age cannot be fully interpreted by these factors [77]. Growing body of research indicate that "menopausal age" is a complex genetic trait regulated by genetic factors. This notion is supported by the associations between menopausal age of mother-daughter pairs and sister pairs [78–80]. Premature ovarian failure (POF) is considered as a study model of ovarian aging. Researches revealed that several genetic variations are associated with POF [81, 82]. Variations in genes encoding sex hormones (FSH, FSHR, LH, LHR), enzymes (CYP17, CYP19) and those responsible for follicular recruitment (BMP15, GDF9, and GPR3) regulate the durability of oocyte pool and in turn adjust the span of reproductive life [83]. POF patients are also reported to carry mutations in genes (NANOS, GDF9, NOBOX, LDX8, etc.) expressed in the course of oogenesis [84]. Gene copy number variations (CNVs) are also linked to POF manifestation [85–88]. Gene involved in maturation of primary follicles, apoptosis of follicles, fetal ovarian development or vascularization in ovary are the suitable candidates for studying genetic background of POF [89–92]. Menopausal age is also associated with the presence of mutant allele factor V Leiden or E2 allele of apolipoprotein E [93–95]. Gene-driven compromised microcirculation around oocyte pool is considered as a prime cause of early menopause [96]. Studies pointed out that polymorphisms in genes playing role in steroidogenic pathways like 5-α-reductase type 2 [97] and CYP1B1 [98] also regulate menopausal age. However, polymorphism in folate pathway genes like MTHFR or MTRR is also associated with POF phenotype [99, 100] as well as with trisomy 21 conception [101–104]. Genome-wide association studies identified powerful association between menopausal age and variations in chromosome numbers 20, 19, 5, 6 and 13 [105, 106].

4. Molecular factors associated with maternal age

Advanced chronological age of mother is probably the oldest known factor associated with Down syndrome birth. Risk of having a trisomy 21 baby significantly increases as mother ages. This advanced chronological aging was first postulated in the year of 1933 [107]. Advanced maternal age-specific Down syndrome birth has been studied in almost all the population. One interesting point that came up from these studies is that maternal age varies with the type of nondisjunction. Ages of MII error mother are on the right side to that of MI mothers. Therefore, chronological aging has a direct impact on not only the origin of the disease as well as disease subgroups. Some studies proposed halting of meiosis during oogenesis exert a negative impact on the oocytes. Female oocytes unlike male sperm undergo several checkpoints halting during maturation as meiosis I occur only during puberty and meiosis II after fertilization. This prolonged inertness of oocyte might make it vulnerable to aging-related deterioration. Accumulation of stress factors over time may disrupt the proper chromosomal segregation machinery inducing nondisjunction. Cohesion proteins were expressed during intrauterine condition and must remain active till the completion of meiosis. During this period (~50 years), any disruption in cohesin machinery will result in nondisjunction [108]. Separase cleaves cohesin to release the bound chromatids. Shugoshin-mediated cohesin protection therefore plays a major role in premature separation of sister chromatids (PSSC) [109, 110]. In mice model, age-specific loosening of SMC1beta is observed resulting in abnormal chromosomal segregation [111]. Percentage of premature sister chromatid separation increases in a six-month SMC1b−/− old mother compared to a 1-month-old mother. Age-specific cohesion loosening is also present in *Drosophila* [112]. However, whether age-dependent deterioration or replacement of cohesin is affected by progressive maternal age is still up for debate [113]. Not only cohesin proteins, mitotic proteins associated with spindle assembly are also affected by aging process. Oocytes from older mice have significantly lower expression of MCAK mRNA with altered AURKB [114]. MAD, BUB and TTK are also proposed to decline with progressive aging [115–119]. However, there are alternate studies where it has been proposed that SAC components have similar effect on both old and young oocytes [120]. Therefore, initial cohesion loosening may not recruit MCAK to centromere, properly disrupting normal microtubule depolymerization process [121].

Putting aside chronological aging effect on meiotic machinery, separate model proposes genetic aging as the origin of aneuploidy. Using telomere length as marker, older Down syndrome bearing mother showed rapid telomere attrition than their younger counterpart. Therefore, only older mother experiences this genetic aging. However, we need to keep in mind that peripheral telomere length might not be an actual interpreter of oocytes telomere length. This hypothesis proposes a separate theory about the origin of aneuploidy which was proposed in the year of 1989. Ovarian follicles are formed during intrauterine period in female fetuses. Once puberty is reached, usually one follicle becomes antral follicle and after maturation, ovulates. Total number of follicles and selectable follicles go down as females' age. There may be couple of thousands of follicles present at the age around 40, only two to three selectable follicles present in both the ovaries [122, 123]. Therefore, as women age, the chance of suboptimal follicle ovulation increases [19, 124].

4.1 Recombination pattern and frequency of association with maternal age

Maternal nondisjunction is a multifactorial phenomenon. One major factor that contributes to NDJ is altered recombination pattern during meiosis [125].

Chiasmata is the physical connection where two non-sister chromatids exchange genetic materials in first meiotic division. They stabilize sister chromatids, ensure proper chromosomal spindle attachments and segregation [126]. However, absence of chiasma leads to a situation where chromosomes freely move around, increasing the possibility of aneuploidy. Not only is the absence of chiasma, placement of chiasma is equally important. Achismate condition gives rise to MI meiotic errors. Single telomeric chiasma is an important risk factor for MI type meiotic error as well. Pericentromeric chiasma formation, on the other hand, increases MII meiotic error risk. A broad array of studies conducted with several model organisms such as *Drosophila* [127–129], yeast [130, 131] and *Caenorhabditis elegans* [132] support this fact. In the light of chromosome 21 specific nondisjunction, absence of chiasma formation is a major cause of recombination frequency reduction [133]. Low percentage of detectable crossovers in Ch21 NDJ has been observed across different population [4, 134]. About 57% reductions in linkage map length were reported in Indian population [30.8 cM compared to 72.1 cM CEPH] [6]. Association between advanced chronological age and recombination frequency reduction is well known [135]. 21q-specific recombination analysis showed lower percentage of recombination in older mothers (aged 35 or higher) compared to younger mother [135]. Therefore, absence of recombination could be an age-dependent factor. Studies conducted on Indian population revealed 80% of younger mothers are achismate and had MI NDJ [134]. STR analysis of trisomy 21 families showed high number of single telomeric exchanges in MI NDJ mothers and higher number of single centromeric exchange in MII NDJ mothers. A hypothesis proposed by Ghosh et al. stated that telomeric chiasma as maternal age-independent risk, whereas pericentromeric chiasma is age dependent. How pericentromeric chiasma is affected by maternal age is debatable. Two possible models have been proposed. In the first model, pericentromeric chromosomal exchange may trigger different configurations which increase susceptibility to age-related risk. In the second model, pericentromeric exchange may allow proper segregation in MI but not in MII [8]. As previously mentioned, age-related degradation of cohesion machinery may be a reason behind abnormal chiasma formation. Unlike pericentromeric exchanges, telomeric exchanges give rise to MI type NDJ. The proper reason behind it is not clear. One reason might be the lower amount of cohesion complex in distal region. In Indian cohort, the single chiasma formation was scored at near telomeric 5.1 Mb region [134]. Therefore, single telomeric chiasma can up the risk of NDJ of Ch21 irrespective of maternal age. Lack of biorientation of homologs due to low cohesion protein can give rise to single telomeric chiasma error [127]. Number of studies conducted on different chromosomes showed linear relationship between maternal age and chiasma frequency [136–138]. Multiple chiasmas may increase bivalent stability during MI; therefore, NDJ might not occur.

5. Conclusion

Down syndrome birth is attributable to multiple maternal risk factors that include both genetic and environmental challenges, but there is limited understanding of the complicated interactions among these factors. Along with aging-induced hormonal imbalance, environmental factors such as cigarette smoking, oral contraceptive pills, consumption of alcohol, and use of smokeless chewing tobacco interact with molecular components of the oocyte which ultimately increase the risk of chromosome 21 nondisjunction and subsequently of giving birth to a child with Down syndrome. Age-related abrasion of telomere may in turn be responsible

for age-related meiotic abnormalities, subsequent aneuploidy and birth of DS babies in genetically older mother. This "genetic aging" is probably the background cause of all age-related degenerative changes and malfunctions in the ovary.

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