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Chapter

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

Subrata Kumar Dey, Pranami Bhaumik and Mandar Bhattacharya

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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References

[1] Lejeune J, Turpin R, Gautier M. Mongolism: A chromosomal disease (trisomy). Bulletin de l Academie Nationale de Medecine. 1959;**143**:256-265

[2] Allen EG, Freeman SB, Druschel C, Hobbs CA, O'Leary LA, Romitti PA, et al. Maternal age and risk for trisomy21 assessed by the origin of chromosome nondisjunction: A report from the Atlanta and National Down Syndrome Projects. Human Genetics. 2009;**125**:41-52

[3] Hassold T, Chiu D. Maternal age specific rates of numerical chromosome abnormalities with special reference to trisomy. Human Genetics. 1985;**70**:11-17

[4] Sherman SL, Allen EG, Bean LH, Freeman SB. Epidemiology of Down syndrome. Mental Retardation and Developmental Disabilities Research Reviews. 2007;**13**:221-227

[5] Zwick ME, Salstrom JL, Langley CH. Genetic variation in rates of nondisjunction: Association of two naturally occurring polymorphisms in the chromokinesin nod with increased rates of nondisjunction in *Drosophila melanogaster*. Genetics. 1999;**152**:1605-1614

[6] Ghosh S, Feingold E, Chakraborty S, Dey SK. Telomere length is associated with types of chromosome 21 NDJ: A new insight into the maternal age effect on Down syndrome birth. Human Genetics. 2010;**127**:403-409

[7] Ghosh S, Bhaumik P, Ghosh P, Dey SK. Chromosome 21 nondisjunction and Down syndrome birth in Indian cohort: Analysis of incidence and etiology from family linkage data. Genetics Research. 2010;**92**:189-197

[8] Oliver TR, Feingold E, Yu K, Cheung V, Tinker S, Yadav-Shah M, et al. New insights into human nondisjunction of chromosome 21 in oocytes. PLOS Genetics. 2008;**4**:e1000033

[9] Ghosh S, Hong C-S, Feingold E, Ghosh P, Ghosh P, Bhaumik P, et al. Epidemiology of Down syndrome: New insight into the multidimensional interactions among genetic and environmental risk factors in the oocyte. American Journal of Epidemiology. 2011;**10**:1-8

[10] Hook EB, Cross PK. Maternal cigarette smoking, Down syndrome in live births, and infant race. American Journal of Human Genetics. 1988;**42**(30):482-489

[11] Kallen K. Downs syndrome and maternal smoking in early pregnancy. Genetic Epidemiology. 1997;**14**(1):77-84

[12] Trofor A, Man MA, Miron R. Smoking during pregnancy—A challenge to practitioners. Pneumologia. 2009;**58**(4):247-249 251

[13] Bhaumik P, Bhattacharya M, Ghosh P, Ghosh S, Kumar Dey S. Telomere length analysis in Down syndrome birth. Mechanisms of Ageing and Development. 2017;**164**:20-26

[14] Crowley PH, Gulati DK, Hayden TL, Lopez P, Dyer R. A chiasma-hormonal hypothesis relating Down's syndrome and maternal age. Nature. 1979;**280**(5721):417-418

[15] Guyton A. Textbook of Medical Physiology. 8th ed. New York: Harcourt Brace Jovanovich; 1991. pp. 826-899

[16] Moore K. The Developing Human. 4th ed. New York: Harcourt Brace Jovanovich; 1988. p. 167

[17] Eichenlaub-Ritter U, Boll I. Nocodazole sensitivity, age-related aneuploidy and alterations in the cell cycle during maturation of mouse oocytes. Cytogenetics and Cell Genetics. 1989;**52**:170-176

[18] Gaulden M. Maternal age effect: The enigma of Down syndrome and other trisomic conditions. Mutation Research. 1992;**296**:69-88

[19] Warburton D. The effect of maternal age on the frequency of trisomy: Change in meiosis or in utero selection? Progress in Clinical and Biological Research. 1989;**311**:165-181

[20] Klein NA, Battaglia DE, Fujimoto VY, Davis GS, Bremner WJ, Soules MR. Reproductive aging: Accelerated ovarian follicular development associated with a monotropic follicle-stimulating hormone rise in normal older women. The Journal of Clinical Endocrinology and Metabolism. 1996;**81**:1038-1045

[21] Santoro N, Brown JR, Adel T, Skurnick JH. Characterization of reproductive hormonal dynamics in the perimenopause. Journal of Clinical Endocrinology and Metabolism. 1996;**81**:1495-1501

[22] Nasseri A, Mukherjee T, Grifo JA, Noyes N, Krey L, Copperman AB. Elevated day 3 serum follicle stimulating hormone and/or estradiol may predict fetalaneuploidy. Fertility and Sterility. 1999;**71**(4):715-718

[23] van Montfrans JM, Dorland M, Oosterhuis GJ, van Vugt JM, Rekers-Mombarg LT, Lambalk CB. Increased concentrations of follicle-stimulating hormone in mothers of children with Down's syndrome. Lancet. 1999;**353**(9167):1853-1854

[24] Albertini DF, Anderson E. The appearance and structure of intercellular connections during the ontogeny of the rabbit ovarian follicle with particular reference to gap junctions. The Journal of Cell Biology. 1974;**63**:234-250

[25] Anderson E, Albertini DF. Gap junctions between the oocyte and companion follicle cells in the mammalian ovary. The Journal of Cell Biology. 1976;**71**:680-686

[26] Gonzalez-Robayna IJ, Falender AE, Ochsner S, Firestone GL, Richards JS. Follicle-stimulating hormone (FSH) stimulates phosphorylation and activation of protein kinase B (PKB/Akt) and serum and glucocorticoid-induced kinase (Sgk): Evidence for a kinase-independent signaling by FSH in granulosa cells. Molecular Endocrinology. 2000;**14**:1283-1300

[27] Richards JS. New signaling pathways for hormones and cyclic adenosine 39,59-monophosphate action in endocrine cells. Molecular Endocrinology. 2001;**15**:209-218

[28] Albertini DF. Cytoplasmic microtubular dynamics and chromatin organization during mammalian oogenesis and oocyte maturation. Mutation Research. 1992;**296**:57-68

[29] McTavish KJ, Jimenez M, Walters KA, Spaliviero J, Groome NP, Themmen AP, et al. Rising follicle-stimulating hormone levels with age accelerate female reproductive failure. Endocrinology. 2007;**148**:4432-4439

[30] Kline JK, Kinney AM, Levin B, Kelly AC, Ferin M, Warburton D. Trisomic pregnancy and elevated FSH: Implications for the oocyte pool hypothesis. Human Reproduction. 2011;**26**(6):1537-1550

[31] Hassold T, Hunt P. To err (meiotically) is human: The genesis of human aneuploidy. Nature Reviews. Genetics. 2001;**2**:280-291

[32] Jayaprakasan K, Campbell B, Hopkisson J, Johnson I, Raine-Fenning N. A prospective, comparative analysis of anti-Müllerian hormone, inhibin-B, and three-dimensional ultrasound determinants of ovarian reserve in the prediction of poor response to controlled ovarian stimulation. Fertility and Sterility. 2010;**93**:855-864

[33] Josso N, Picard JY, Rey R, di Clemente N. Testicular anti-Mullerian hormone: History, genetics, regulation and clinical applications. Pediatric Endocrinology Reviews. 2006;**3**:347-358

[34] Seifer DB, Maclaughlin DT. Mullerian inhibiting substance is an ovarian growth factor of emerging clinical significance. Fertility and Sterility. 2007;**88**:539-546

[35] de Vet A, Laven JS, de Jong FH, Themmen AP, Fauser BC. Antimullerian hormone serum levels: A putative marker for ovarian aging. Fertility and Sterility. 2002;**77**:357-362

[36] van Rooij IA, Broekmans FJ, Scheffer GJ, Looman CW, Habbema JD, de Jong FH, et al. Serum antimullerian hormone levels best reflect the reproductive decline with age in normal women with proven fertility: A longitudinal study. Fertility and Sterility. 2005;**83**(4):979-987

[37] Fanchin R, Schonauer LM, Righini C, Frydman N, Frydman R, Taieb J. Serum anti-Müllerian hormone dynamics during controlled ovarian hyperstimulation. Human Reproduction. 2003;**18**:328-332

[38] Hehenkamp WJ, Looman CW, Themmen AP, de Jong FH, Te Velde ER, Broekmans FJ. Anti-Mullerian hormone levels in the spontaneous menstrual cycle do not show substantial fluctuation. The Journal of Clinical Endocrinology and Metabolism. 2006;**91**:4057-4063

[39] La Marca A, De Leo V, Giulini S, Orvieto R, Malmusi S, Giannella L, et al. Anti-Mullerian hormone in premenopausal women and after spontaneous or surgically induced menopause. Journal of the Society for Gynecologic Investigation. 2005;**12**:545-548

[40] La Marca A, Giulini S, Orvieto R, De Leo V, Volpe A. Anti-Mullerian hormone concentrations in maternal serum during pregnancy. Human Reproduction. 2005;**20**:1569-1572

[41] Somunkiran A, Yavuz T, Yucel O, Ozdemir I. Anti-Mullerian hormone levels during hormonal contraception in women with polycystic ovary syndrome. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2007;**134**:196-201

[42] La Marca A, Stabile G, Artenisio AC, Volpe A. Serum anti-Mullerian hormone throughout the human menstrual cycle. Human Reproduction. 2006;**21**:3103-3107

[43] Streuli I, Fraisse T, Pillet C, Ibecheole V, Bischof P, de Ziegler D. Serum antimullerian hormone levels remain stable throughout the menstrual cycle and after oral or vaginal administration of synthetic sex steroids. Fertility and Sterility. 2008;**90**:395-400

[44] Tsepelidis S, Devreker F, Demeestere I, Flahaut A, Gervy C, Englert Y. Stable serum levels of anti-Mullerian hormone during the menstrual cycle: A prospective study in normo-ovulatory women. Human Reproduction. 2007;**22**:1837-1840

[45] Plante BJ, Beamon C, Schmitt CL, Moldenhauer JS, Steiner AZ. Maternal antimullerian hormone levels do not predict fetal aneuploidy. Journal of Assisted Reproduction and Genetics. 2010;**27**:409-414

[46] Shim SH, Ha HI, Jung YW, Shim SS, Cho YK, Kim JY, et al. Maternal antimullerian hormone as a predictor of fetal aneuploidy occurring in an earlypregnancy loss. Obstetrics & Gynecology Science. 2015;**58**(6):494-500

[47] Fragouli E, Alfarawati S, Spath K, Jaroudi S, Sarasa J, Enciso M, et al. The origin and impact of embryonic aneuploidy. Human Genetics. 2013;**132**:1-13

[48] Handyside AH. Molecular origin of female meiotic aneuploidies. Biochimica et Biophysica Acta. 2012;**1822**:1913-1920

[49] Pellestor F, Andreo B, Anahory T, Hamamah S. The occurrence of aneuploidy in human: Lessons from the cytogenetic studies of human oocytes. European Journal of Medical Genetics. 2006;**49**:103-116

[50] Kuliev A, Zlatopolsky Z, Kirillova I, Spivakova J, Cieslak Janzen J. Meiosis errors in over 20,000 oocytes studied in the practice of preimplantation aneuploidy testing. Reproductive Biomedicine Online. 2011;**22**:2-8

[51] Battaglia DE, Goodwin P, Klein NA, Soules MR. Fertilization and early embryology: Influence of maternal age on meiotic spindle assembly oocytes from naturally cycling women. Human Reproduction. 1996;**11**:2217-2222

[52] Coticchio G, Guglielmo MC, Dal Canto M, Fadini R, Mignini Renzini M, De Ponti E, et al. Mechanistic foundations of the metaphase II spindle of human oocytes matured in vivo and in vitro. Human Reproduction. 2013;**28**:3271-3282

[53] Volarcik K, Sheean L, Goldfarb J, Woods L, Abdul-Karim FW, Hunt P. The meiotic competence of in-vitro matured human oocytes is influenced by donor age: Evidence that folliculogenesis is compromised in the reproductively aged ovary. Human Reproduction. 1998;**13**:154-160

[54] Angell RR. Predivision in human oocytes at meiosis-I—A mechanism for trisomy formation in man. Human Genetics. 1991;**86**:383-387

[55] Chiang T, Duncan FE, Schindler K, Schultz RM, Lampson MA. Evidence that weakened centromere cohesion is a leading cause of age-related aneuploidy in oocytes. Current Biology. 2010;**20**:1522-1528

[56] Yun Y, Lane SIR, Jones KT. Premature dyad separation in meiosis II is the major segregation error with maternal age in mouse oocytes. Development. 2014;**141**:199-208

[57] Duncan FE, Hornick JE, Lampson MA, Schultz RM, Shea LD, Woodruff TK. Chromosome cohesion decreases in human eggs with advanced maternal age. Aging Cell. 2012;**11**:1121-1124

[58] Allshire RC, Dempster M, Hastie ND. Human telomere contains at least three types of G-rich repeats distributed non-randomly. Nucleic Acids Research. 1989;**17**:4611-4627

[59] Shampay J, Blackburn EH. Generation of telomere-length heterogeneity in *Saccharomyces cerevisiae*. Proceedings of the National Academy of Sciences of the United States of America. 1988;**85**:534-538

[60] Aviv A. The epidemiology of human telomeres: Faults and promises. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2008;**63**:979-983

[61] Aydos SE, Elhan AH, Tükün A. Is telomere length one of the determinants of reproductive life span? Archives of Gynecology and Obstetrics. 2005;**272**:113-116

[62] Keefe DL, Marquard K, Liu L. The telomere theory of reproductive senescence in women. Current Opinion in Obstetrics and Gynecology. 2006;**18**:280-285

[63] Betts DH, King WA. Telomerase activity and telomere detection during early bovine development. Developmental Genetics. 1999;**25**:397-403

[64] Eisenhauer KM, Gerstein RM, Chiu CP, Conti M, Hsueh AJ. Telomerase activity in female and male rat germ cells undergoing meiosis and in early embryos. Biology of Reproduction. 1997;**56**:1120-1125

[65] Kinugawa C, Murakami T, Okamura K, Yajima A. Telomerase activity in normal ovaries and premature ovarian failure. The Tohoku Journal of Experimental Medicine. 2000;**190**:231-238

[66] Liu JP, Li H. Telomerase in the ovary. Reproduction. 2010;**140**:215-222

[67] Herrera E, Samper E, Blasco MA. Telomere shortening in mTRK/K embryos is associated with failure to close the neural tube. EMBO Journal. 1999;**18**:1172-1181

[68] Lee HW, Blasco MA, Gottlieb GJ, Horner JW II, Greider CW, De Pinho RA. Essential role of mouse telomerase in highly proliferative organs. Nature. 1998;**392**:569-574

[69] Liu L, Blasco M, Trimarchi J, Keefe D. An essential role for functional telomeres in mouse germ cells during fertilization and early development. Developmental Biology. 2002;**249**:74-84

[70] Mania A, Mantzouratou A, Delhanty JD, Baio G, Serhal P, Sengupta SB. Telomere length in human blastocysts. Reproductive Biomedicine Online. 2014;**28**:624-637

[71] Plentz RR, Schlegelberger B, Flemming P, Gebel M, Kreipe H, Manns MP, et al. Telomere shortening correlates with increasing aneuploidy of chromosome 8 in human hepatocellular carcinoma. Hepatology. 2005;**42**:522-526

[72] Dorland M, van Montfrans JM, van Kooij RJ, Lambalk CB, te Velde ER. Normal telomere lengths in young mothers of children with Down's syndrome. Lancet. 1998;**352**:961-962

[73] Sabatier L, Ricoul M, Pottier G, Murnane JP. The loss of a single telomere can result in instability of multiple chromosomes in a human tumor cell line. Molecular Cancer Research. 2005;**3**:139-150

[74] Stewénius Y, Gorunova L, Jonson T, Larsson N, Höglund M, Mandahl N, et al. Structural and numerical chromosome changes in colon cancer develop through telomere-mediated anaphase bridges, not through mitotic multipolarity. Proceedings of the National Academy of Sciences of the United States of America. 2005;**102**:5541-5546

[75] Lin J, Smith DL, Blackburn EH. Mutant telomere sequences lead to impaired chromosome separation and a unique checkpoint response. Molecular Biology of the Cell. 2004;**15**(4):1623-1634

[76] van Noord PA, Dubas JS, Dorland M, Boersma H, te Velde E. Age at natural menopause in a population-based screening cohort: The role of menarche, fecundity, and lifestyle factors. Fertility and Sterility. 1997;**68**:95-102

[77] van Asselt KM, Kok HS. Age at menopause. A genetic epidemiological study [academic thesis]. The Netherlands: Utrecht; 2003

[78] Murabito JM, Yang Q, Fox C, Wilson PW, Cupples LA. Heritability of age at natural menopause in the Framingham Heart Study. The Journal of Clinical Endocrinology and Metabolism. 2005;**90**:3427-3430

[79] Torgerson DJ, Thomas RE, Reid DM. Mothers and daughters menopausal ages: Is there a link? European Journal of Obstetrics, Gynecology, and Reproductive Biology. 1997;**74**:63-66

[80] van Asselt KM, Kok HS, Pearson PL, Dubas JS, Peeters PH, Te Velde ER, et al. Heritability of menopausal age in mothers and daughters. Fertility and Sterility. 2004;**82**:1348-1351

[81] Laissue P, Vinci G, Veitia RA, Fellous M. Recent advances in the study of genes involved in non-syndromic premature ovarian failure. Molecular and Cellular Endocrinology. 2008;**282**:101-111

[82] Laissue P, Lakhal B, Benayoun BA, Dipietromaria A, Braham R, Elghezal H, et al. Functional evidence implicating FOXL2 in non syndromic premature ovarian failure and in the regulation of the transcription factor OSR2. Journal of Medical Genetics. 2009;**46**(7):455-457

[83] Kok HS, van Asselt KM, van der Schouw YT, Peeters PH, Wijmenga C. Genetic studies to identify genes underlying menopausal age. Human Reproduction Update. 2005;**11**:483-493

[84] Skillern A, Rajkovic A. Recent developments in identifying genetic determinants of premature ovarian failure. Sexual Development. 2008;**2**:228-243

[85] Knauff EA, Wijmenga C, van't Slot R, Franke L, Fauser BC. Genome wide high density SNP-CGH reveals several new deletion copy number variants on the X chromosome in POF patients. Reproductive Sciences. 2009;**15**:601

[86] McCarroll SA. Extending genome-wide association studies to copy-number variation. Human Molecular Genetics. 2008;**17**:R135-R142

[87] Rodriguez-Revenga L, Mila M, Rosenberg C, Lamb A, Lee C. Structural variation in the human genome: The impact of copy number variants on clinical diagnosis. Genetics in Medicine. 2007;**9**:600-606

[88] Wang K, Li M, Hadley D, Liu R, Glessner J, Grant SF, et al. Penn CNV: An integrated hidden Markov model designed for high-resolution copy number variation detection in whole-genome SNP genotyping data. Genome Research. 2007;**17**:1665-1674

[89] Di Pasquale E, Rossetti R, Marozzi A, Bodega B, Borgato S, Cavallo L, et al. Identification of new variants of human BMP15 gene in a large cohort of women with premature ovarian failure. The Journal of Clinical Endocrinology and Metabolism. 2006;**91**:1976-1979

[90] Dixit H, Rao LK, Padmalatha VV, Kanakavalli M, Deenadayal M, Gupta N, et al. Missense mutations in the BMP15 gene are associated with ovarian failure. Human Genetics. 2006;**119**:408-415

[91] Laissue P, Christin-Maitre S, Touraine P, Kuttenn F, Ritvos O, Aittomaki K, et al. Mutations and sequence variants in GDF9 and BMP15 in patients with premature ovarian failure. European Journal of Endocrinology. 2006;**154**:739-744

[92] Schmidt D, Ovitt CE, Anlag K, Fehsenfeld S, Gredsted L, Treier AC, et al. The murine winged-helix transcription factor Foxl2 is required for granulosa cell

differentiation and ovary maintenance. Development. 2004;**131**:933-942

[93] Kok HS, van Asselt KM, van der Schouw YT, van der Tweel I, Peeters PH, Wilson PW, et al. Heart disease risk determines menopausal age rather than the reverse. Journal of the American College of Cardiology. 2006;**47**:1976-1983

[94] Koochmeshgi J, Hosseini-Mazinani SM, Morteza Seifati S, Hosein-Pur-Nobari N, Teimoori-Toolabi L. Apolipoprotein E genotype and age at menopause. Annals of the New York Academy of Sciences. 2004;**1019**:564-567

[95] Pripp U, Eriksson-Berg M, Orth-Gome'r K, Schenck-Gustafsson K, Landgren BM. Does body mass index, smoking, lipoprotein levels, surgically induced menopause, hormone replacement therapy, years since menopause, or age affect hemostasis in postmenopausal women? Gender Medicine. 2005;**2**:88-95

[96] Huber A, Grimm C, Huber JC, Schneeberger C, Leodolter S, Reinthaller A, et al. A common polymorphism within the steroid 5-α-reductase type 2 gene and timing of menopause in Caucasian women. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2006;**125**:221-225

[97] Hefler LA, Grimm C, Heinze G, Schneeberger C, Mueller MW, Muendlein A, et al. Estrogen-metabolizing gene polymorphisms and age at natural menopause in Caucasian women. Human Reproduction. 2005;**20**:1422-1427

[98] Weel AE, Uitterlinden AG, Westendorp IC, Burger H, Schuit SC, Hofman A, et al. Estrogen receptor polymorphism predicts the onset of natural and surgical menopause. The Journal of Clinical Endocrinology and Metabolism. 1999;**84**:3146-3150

[99] Hou N, Chen S, Chen F, Jiang M, Zhang J, Yang Y, et al. Association between premature ovarian failure, polymorphisms in MTHFR and MTRRgenes and serum homocysteine concentration. Reproductive Biomedicine Online. 2016;**32**(4):407-413

[100] Rah H, Jeon YJ, Choi Y, Shim SH, Yoon TK, Choi DH, et al. Association of methylenetetrahydrofolate reductase (MTHFR 677C>T) and thymidylatesynthase (TSER and TS 1494del6) polymorphisms with premature ovarian failure in Korean women. Menopause. 2012;**19**(11):1260-1266

[101] Dutta S, Das AB, Mukhopadhyay K. Risk of Down syndrome conferred by MTHFR C677T polymorphism: Ethnic variations. Indian Journal of Human Genetics. 2007;**13**(2):76-77

[102] James SJ, Pogribna M, Pofribny IP, Melnyk S, Hine RJ, Gibson JB, et al. Abnormal folate metaboloism and mutation in the methylenetetrahydrofolate reductase gene may be maternal risk factors for Down syndrome. American Journal of Clinical Nutrition. 1999;**70**:495-501

[103] Martínez-Frías ML, Bermejo E, Rodríguez-Pinilla E, Prieto D, Prieto L. MTHFR 677C-T polymorphism is not excluded as maternal risk for Down syndrome among Turkish women. American Journal of Medical Genetics. Part A. 2005;**134**(4):461-462

[104] Meguid NA, Dardir AA, Khass M, Hossieny LE, Ezzat A, El Awady MK. MTHFR genetic polymorphism as a risk factor in Egyptian mothers with Down syndrome children. Disease Markers. 2008;**24**(1):19-26

[105] He C, Kraft P, Chen C, Buring JE, Pare G, Hankinson SE, et al. Genome-wide association studies identify loci associated with age at menarche and age at natural menopause. Nature Genetics. 2009;**41**:724-728

[106] Stolk L, Zhai G, van Meurs JB, Verbiest MM, Visser JA, Estrada K, et al. Loci at chromosomes 13, 19 and 20 influence age at natural menopause. Nature Genetics. 2009;**41**:645-647

[107] Penrose LS. The relative effect of paternal and maternal age in mongolism. Journal of Genetics. 1933;**27**:219-224

[108] Chiang T, Schultz RM, Lampson MA. Age-dependent susceptibility of chromosomecohesion to premature separase activation in mouse oocytes. Biology of Reproduction. 2011;**85**(6):1279-1283. DOI: 10.1095/biolreprod.111.094094. Epub 2011 Aug 24. PubMedPMID: 21865557; PubMed Central PMCID: PMC3223255

[109] Kitajima TS, Sakuno T, Ishiguro K, Iemura S, Natsume T, Kawashima SA, et al. Shugoshin collaborates with protein phosphatase 2A to protect cohesin. Nature. 2006;**441**(7089):46-52. Epub 2006 Mar 15. PubMed PMID: 16541025

[110] Riedel CG, Katis VL, Katou Y, Mori S, Itoh T, Helmhart W, et al. Protein phosphatase 2A protects centromeric sister chromatid cohesion during meiosis I. Nature. 2006;**441**(7089):53-61. Epub 2006 Mar 15. PubMed PMID: 16541024

[111] Hodges CA, Revenkova E, Jessberger R, Hassold TJ, Hunt PA. SMC1beta-deficientfemale mice provide evidence that cohesins are a missing link in age-related nondisjunction. Nature Genetics. 2005;**37**(12):1351-1355. Epub 2005 Oct 30. PubMed PMID: 16258540

[112] Miyazaki WY, Orr Weaver TL. Sister chromatid misbehavior in Drosophila ord mutants. Genetics. 1992;**132**(1047):1061. PMID: 1459426

[113] Gilliland WD, Hawley RS. Cohesin and the maternal age effect. Cell. 2005;**123**(3):371-373. PubMed PMID: 16269329

[114] Pan H, Ma P, Zhu W, Schultz RM. Age-associated increase in aneuploidy and changes in gene expression in mouse eggs. Developmental Biology. 2008;**316**(2):397-407. DOI: 10.1016/j.ydbio.2008.01.048. Epub 2008 Feb 15. PubMed PMID: 18342300; PubMed Central PMCID: PMC2374949

[115] Brunet S, Pahlavan G, Taylor S, Maro B. Functionality of the spindle checkpoint during the first meiotic division of mammalian oocytes. Reproduction. 2003;**126**:443-450

[116] Hached K, Xie SZ, Buffin E, Cladiere D, Rachez C, Sacras M, et al. Mps1 at kinetochores is essential for female mouse meiosis I. Development. 2011;**138**:2261-2271

[117] Lane SI, Chang HY, Jennings PC, Jones KT. The Aurora kinase inhibitorZM447439 accelerates first meiosis in mouse oocytes by overriding the spindle assembly checkpoint. Reproduction. 2010;**140**:521-530

[118] Niault T, Hached K, Sotillo R, Sorger PK, Maro B, Benezra R, et al. Changing Mad2 levels affects chromosome segregation and spindle assembly checkpoint control in female mouse meiosis I. PLoS One. 2007;**e1165**:2

[119] Wassmann K, Niault T, Maro B. Metaphase I arrest upon activation of the Mad2-dependent spindle checkpoint in mouse oocytes. Current Biology. 2003;**13**:1596-1608

[120] Duncan FE, Chiang T, Schultz RM, Lampson MA. Evidence that adefective spindle assembly checkpoint is not the primary cause of maternalage-associated aneuploidy in mouse eggs. Biology of Reproduction. 2009;**81**:768-776

[121] Eichenlaub-Ritter U, Staubach N, Trapphoff T. Chromosomal and cytoplasmic context determines predisposition to maternal age-related aneuploidy: Brief overview and update on MCAK in mammalian oocytes. Biochemical Society Transactions. 2010;**38**(6):1681-1686. DOI: 10.1042/BST0381681. PubMed PMID: 21118147

[122] Gougeon A, Ecochard R, Thalabard JC. Age-related changes of the population of human ovarian follicles: Increase in the disappearance rate of non-growing andearly-growing follicles in aging women. Biology of Reproduction. 1994;**50**(3):653-663. PubMed PMID: 8167237

[123] Gougeon A. Ovarian follicular growth in humans: Ovarian ageing and population of growing follicles. Maturitas. 1998;**30**(2):137-142. Review. PubMed PMID: 9871908

[124] Hansen KR, Knowlton NS, Thyer AC, Charleston JS, Soules MR, Klein NA. A newmodel of reproductive aging: The decline in ovarian non-growing follicle number from birth to menopause. Human Reproduction. 2008;**23**(3):699-708. doi: 10.1093/humrep/dem408. Epub 2008 Jan 11. PubMed PMID: 18192670

[125] Warren AC, Chakravarti A, Wong C, Slaugenhaupt SA, Halloran SL, Watkins PC, et al. Evidence for reduced recombination on the nondisjoined chromosomes 21 in Down syndrome. Science. 1987;**237**:652-654

[126] Carpenter AT. Chiasma function. Cell. 1994;**77**:957-962

[127] Koehler KE, Hawley RS, Sherman S, Hassold T. Recombination and nondisjunctionin humans and flies. Human Molecular Genetics. 1996;**5**:1495-1504

[128] Moore DP, Miyazaki WY, Tomkiel JE, Orr-Weaver TL. Double or nothing: A *Drosophila* mutation affecting meiotic chromosome segregation in both females and males. Genetics. 1994;**136**:953-964

[129] Rasooly RS, New CM, Zhang P, Hawley RS, Baker BS. The lethal(1) TW-6cs mutationof *Drosophila melanogaster* is a dominant antimorphic allele of nod and is associated with a single base change in the putative ATP-binding domain. Genetics. 1991;**129**:409-422

[130] Krawchuk MD, Wahls WP. Centromere mapping functions for aneuploid meioticproducts: Analysis of rec8, rec10 and rec11 mutants of the fission yeast *Schizosaccharomyces pombe*. Genetics. 1999;**153**:49-55

[131] Sears DD, Hegemann JH, Shero JH, Hieter P. Cis-acting determinants affectingcentromere function, sister-chromatid cohesion and reciprocal recombinationduring meiosis in *Saccharomyces cerevisiae*. Genetics. 1995;**139**:1159-1173

[132] Zetka MC, Rose AM. Mutant rec-1 eliminates the meiotic pattern of crossing over in *Caenorhabditis elegans*. Genetics. 1995;**141**:1339-1349

[133] Lamb NE, Sherman SL, Hassold TJ. Effect of meiotic recombination on theproduction of aneuploid gametes in humans. Cytogenetic and Genome Research. 2005;**111**:250-255

[134] Ghosh S, Feingold E, Dey SK. Etiology of Down syndrome: Evidence for consistent association among altered meiotic recombination, nondisjunction

and maternal age across populations. American Journal of Medical Genetics. 2009;**149A**:1415-1420

[135] Sherman SL, Petersen MB, Freeman SB, Hersey J, Pettay D, Taft L, et al. Non-disjunction of chromosome 21 in maternal meiosis I: Evidence for a maternal age-dependent mechanism involving reducedrecombination. Human Molecular Genetics. 1994;**3**:1529-1535

[136] Bugge M, Collins A, Petersen MB, Fisher J, Brandt C, Hertz JM, et al. Non-disjunction of chromosome 18. Human Molecular Genetics. 1998;7:661-669

[137] Robinson WP, Kuchinka BD, Bernasconi F, Petersen MB, Schulze A, Brondum-Nielsen K, et al. Maternal meiosis I non-disjunction ofchromosome 15: Dependence of the maternal age effect on level of recombination. Human Molecular Genetics. 1998;7:1011-1019

[138] Thomas NS, Ennis S, Sharp AJ, Durkie M, Hassold TJ, Collins AR, et al. Maternalsex chromosome non-disjunction: Evidence for X chromosome-specific risk factors. Human Molecular Genetics. 2001;**10**:243-250