International Journal of Trend in Scientific Research and Development (IJTSRD)
Volume 8 Issue 6, Nov-Dec 2024 Available Online: www.ijtsrd.com e-ISSN: 2456 – 6470

Advanced Maternal Age Impact on Oocyte Morphology, Its Effects on Fertilization Potential and Embryo Development

Dr. Devuni Vageeshwari

Student, Asia Pacific Institute of Embryology, Mysuru, Karnataka, India

ABSTRACT

Advanced maternal age is defined as age above 35 in females. Advanced maternal age is progressively recognized as a serious societal and clinical issue, as women are more choose to delay in pregnancy planning until their late 30s or early 40s. Advanced maternal age is linked with poor ovarian reserve and diminished oocyte quality, leading to complications in fertility. Numerous social factors like higher education, career accomplishments, and ineffective state support for families following this trend. The possibility of successful pregnancy highly depends on the age at which women starts her conception planning, with maternal age being a crucial factor in assisted reproductive technologies like IVF.

Over time, the oocytes and embryos lose integrity of aging women that are related to energy production as well as cell cycle regulation which can result in a higher frequency for chromosomal aneuploidy. Most of these chromosomal abnormalities result from errors during oogenesis, especially in meiosis I. Moreover, the aging process also affects mitochondrial function and telomere integrity that are crucial for both oocyte quality and developmental competence as well.

Healthcare Providers should proactively counsel women on their fertility preservation options, specifically oocyte vitrification as a counterbalance to age-related declines in reproductive potential. Not just for medical reasons like cancer treatment, but also your own personal family planning choices. In conclusion, the issue of fertility with AMA is a complex one and will require more than just measures to prolong the reproductive years.

KEYWORDS: *Advanced maternal age, poor ovarian reserve, reproduction, oocyte quality, delayed fertility, chromosomal aneuploidy, telomere integrity, fertility preservation, assisted reproductive technologies*

How to cite this paper: Dr. Devuni Vageeshwari "Advanced Maternal Age Impact on Oocyte Morphology, Its Effects on Fertilization Potential and Embryo Development" Published in International Journal of Trend in Scientific Research and Development (ijtsrd), ISSN: 2456-6470, Volume-8 | Issue-6, December 2024, pp.302-308, URL: www.ijtsrd.com/papers/ijtsrd70484.pdf

IJTSRD70484

INTRODUCTION

Background: Advanced maternal age (AMA) is a significant social and clinical scenario. Today, more and more women want to give birth later in their reproductive cycle usually by late third- early fourth decade of life. It is known that advanced maternal age, which refers to the mother of > 35 years old, has a negative impact on ovarian reserve and oocyte quality. The older infertile female has been the most challenging patient that fertility practitioners have encountered having grown up in a culture context of waiting to begin child bearing due to working. For women, it is not all the time that they are fertile. There are reasons like raising the educational level and feminizing of the labor market, professional ambitions, proper contraception use or lack of active State family support (no public preschools from 6 months to retirement), also misplaced hope that infecundity will be supported in gynecological child-bearing age infertility treatment through IVF and the like. Greater chances of successful reproductive are associated with the extent of time at which women initiate conception attempts, and this is increasing across countries 1. IVF prognosis is second only to the health of both parents According to Oxford University, a woman's age is one of IVF's checkpoints after her medical examination 2. More accurately,

advanced maternal age is irrelevant the answer when assessing fertilization rate 3, and an intermediate effect on embryo development to blastocyst stage but markedly elevates the rate of aneuploid blastocysts 4, 5. As women progress in their age along with a decrease in the Ovarian reserve, there is an increase in the incompetency of the oocytes and embryos.6,7 This relates to the pathological changes seen in some processes such as energy metabolism, cell cycle checkpoints, epigenetic processes, and also meiotic missegregation. After birth and until follicle recruitment and ovulation, oocytes are said to be held in a state of prolonged the prophase I of meiosis and only mature during ovulation. During this period oocytes are prone to the effects of age as this undermined the genetic kvality, and subsequently the chances of reproductive success.8

OLDER AGE AND LOW OOCYTE MORPHOLOGY

Maternal age is the most absolute factor that is responsible for embryonic Mosaics 9, 10, 11. Over 90 percent of samples deficient in embryonic balance receive this deficiency from mothers which is majorly due to chromosomal misbiogenesis during oogenesis. The biosynthetic meiosis i operates with over 70 percent error ratios making it most prevalent however, they may sometimes be replaced in meiosis II. In females as approximately homologous chromosomes exchanged in the primary oocyte during the development stage, which formed bivalent during the meiotic prophase I. This particular structural bivalent is kept for years as the primary oocytes are in the G2/M transition stagnation phase also called dictyate till menarche, when egg maturation resumes, and then disseminated.

Although during this prolonged period of dormancy, the stability of bivalent structure may be compromised, which can lead to the development of univalents or cleaving of sister chromatids during meiosis I. Both these phenomena are attributed to increase in maternal age and decrease in recombination rates.

Nonetheless, the precise mechanisms that account for these correlations are not known. This brings about the complicated interaction of the maternal age and chromosomal stability with reproductive outcomes. Knowing such mechanisms is important in managing reproductive factors associated with advanced maternal age as well as enhancing ART techniques. 12,13.

MITOCHONDRIAL DYSFUNCTION

They are self-replicative with their own genome (mtDNA) and form the fundamental contribution of the maternal contribution to development embryonic. 14. Mitochondria play important roles in many signaling pathways, including calcium (Ca2+) signaling and intracellular redox potential regulation. These functions are especially important for processes such as fertilization and early development. 15. Apparently, aging negatively affects mitochondria in oocytes; a number of researchers described mitochondrial swelling, vacuolization and rearrangement of the cristae in the oocytes of older women, that is AMA advanced maternal age. 16,17. Older oocytes contain more decreases in ATP production and metabolic activity. Those factors could be involved into the functions disorders in meiotic spindle formation, cell cycle control and chromosome alignment and segregation, embryo development and finally, implantation. 18,19. Longer periods of quiescence, for instance, would increase the chances of mtDNA mutations. The cumulative concentration of mtDNA also appears to be lower in oocytes derived from older women, consequently decreasing the competency of the oocytes as well as the corresponding embryos. Such decreases in mtDNA might interfere with the developmental capacity of the reproductive cells engaged.20,21. In humans, the synthesis of mitochondria occurs physiologically only during the developmental stage at the level of the blastocyst.22,23. The oxidative phosphorylation-related stress, which develops during the initial stages of embryonic development, is typically counteracted by the induction of mitochondrial biogenesis. In older women, however, the reduced numbers and dysfunctional existing mitochondria in oocytes may provoke an earlier, compensatory induction of mitochondrial biogenesis. An early induction leads to defects in proper embryo development, which predisposes embryos to failure of development early on. Understanding these dynamics is important to address fertility challenges associated with advanced maternal age. 24,25. Mitochondria are contained within granulosa cells (GCs) that embrace the oocyte during early stages of oogenesis. During these events, these GCs are crucial in developing oocyte competence that directly affects the quality and functionality of the oocyte as it matures. 26,27. AMA granulosa cells showed higher contents of mtDNA deletions and damaged mitochondria. 28, 29. The content of mtDNA in GCs has been linked with the quality of embryos and inversely related with low ovarian reserve. This may indicate that mtDNA in GCs is highly important for the reproductive ability and outcomes concerning embryo development.30. Age could therefore compromise the integrity and shape of mtDNA as well as the mitochondria and disturbs the follicle microenvironment. These changes might result in impaired communication between the

oocyte and GCs surrounding it. Subsequent oocyte development and reproduction would be affected; therefore, understanding the nature of their relationship will begin to solve fertility problems that are characterized by aging. 31, 32.

SHORTENING OF THE TELOMERES

Telomeres attach the chromosomes to the nuclear membrane, assisting in the homologous pairing and initiation of synapsis to form chiasmata. Chiasmata physically are the site for recombination. Since it is indispensable for proper chromosome segregation and a failure in this might result in n-on-disjunction with genetic implications, proper telomere function is crucial for Genetic stability during cell division. 33,34. Telomere shortening associated with aging may occur in dividing and non-dividing cells and has been linked to many diseases, including diabetes, cardiovascular disease, and cancer. This attrition of telomere length is thought to play a part in cellular aging and dysfunction that makes an aging person more susceptible to these diseases. Understanding more about this process is important in understanding the implications of aging on health. 35,36. Telomeres in oocytes commence to shrink during fetal oogenesis and remain in this stage within the adult ovary. Diminished telomerase activity and oxidative and genotoxic stress most likely dictate this shortening, apart from delayed release of female gametes from a cycle arrest and their subsequent reduced health and functionality as women age. Understanding this process holds great importance for the management of fertility problems associated with aging. 37,38,39. Studies indicate that telomeres from women who failed an IVF cycle or suffer from multiple recurrent miscarriage are shorter. This indicates that the length of telomeres is associated with a poor reproductive outcome, 40. Similarly, fragmented or aneuploid embryos arise as a product of oocytes, 41, 42.

COHESIN FUNCTION DISRUPTION

Age-related factors influencing telomeres of an advanced maternal aging may also lead to similar impairments of cohesin activity, thereby compromising the stability and segregation of chromosomes during mitosis.43 Cohesins are protein rings that condense sister chromatids following DNA replication, holding them together for a longer duration and thus guarding their bivalent structure during long intervals of quiescence. These proteins hold the chromatids together until anaphase, when they are released to initiate sister chromatid separation. The function is critical to ensuring proper chromosome segregation in cell division and to maintaining genomic integrity, and demonstrates an important function of cohesins in genome stability44. Loss of cohesion between sister chromatids near the centromeres could be another cause of aging-related chromosomal missegregation. This deficiency disrupts appropriate chromosome segregation in mitosis and meiosis, leading to an elevated possibility of genetic aberrations. Appreciation of this age-related loss of cohesin function is important for managing potential effects on reproductive health and general genomic integrity.

SPINDLE INSTABILITY

The meiotic spindle plays a critical role in the segregation of homologous chromosomes and sister chromatids to ensure accurate segregation during cell division. Normally in young oocytes, the spindle is compact and correctly oriented relative to the oolemma, and each pole is attached to a ring of centrosome proteins. The spindle, however, of patients with AMA may have structural defects at up to 80% of the oocytes: elongation or even shrinkage. Moreover, these typical oocytes lack fewer microtubular foci at the cortex. Such structural abnormalities can disrupt normal spindle function; hence, the overall risks of chromosomal missegregation are increased, which can contribute to infertility. Appreciation of these differences in spindle morphology in young and aged oocytes is very important for continued reproductive success for the advanced maternal age woman. 45,46 Abnormal spindle assembly appears to enhance the risk of aneuploidy in older women. These defects can also be due to reduced mitochondrial function leading to reduced ATP production which is associated with advanced maternal age.47.

OOCYTE CRYOPRESERVATION FOR MEDICAL AND NON-MEDICAL CANDIDATES

All women, not only those undergoing cancer treatment, should be properly counseled on the various methods available to retain their fertility.

In the last decade, oocyte preservation has really gained momentous breakthroughs, especially with the advent of vitrification-a rapid cryopreservation technique that does not form ice crystals as opposed to the slow freezing. This advancement has boosted the survival rate significantly, and thus established a new gold standard in fertility preservation. It then becomes a proactive approach for women to protect their options for reproductive purposes in the future. All these options and the advantages of vitrification would empower women to make sound decisions about their fertility, especially in the context of health concerns, lifestyle choices, or age-related factors. Therefore, education on fertility preservation techniques is of utmost importance for all women so

they are not misguided with a decision that may affect them long-term in their reproductive health. 48. Clinicians should support oocyte vitrification, or egg banking, for medical reasons like cancer or endometriosis to save fertility. This method also helps conquer the aging process that comes with a decrease in the number of eggs and quality of eggs that are available. This is an acceptable method to be used for non-medical purposes, "social freezing." It encourages healthcare providers to help women make informed decisions about their reproductive health and future family planning despite their health and personal scenarios. This strategy maximizes the chances for women to conceive as late as possible in life. 49, 50.

ADVANCED MATERNAL AGE IMPACT ON FERTILIZATION POTENTIAL

As a woman advances in age, the number and quality of her oocytes significantly decline.

This decline may impact fertility and the ability to conceive normally, and significant efforts should be directed toward knowing more about age-related changes in reproductive health.51, 52. With age, the development of chromosomal aneuploidy is much more possible and associated with decreased fertilization rate, embryonic development, and implantation and pregnancy success. This correlation also brings out the relevance of age in terms of reproductive outcomes and the complexity entailed to achieve successful pregnancy.53,54.

ADVANCED MATERNAL AGE AND ITS EFFECT ON EMBRYO DEVELOPMENT

This trend makes it challenging for the fertility specialist as they see an increase in patients who are greater than 35 years which is a defined age above which a patient is branded advanced maternal age or AMA 55. Women over 35 have a sharp increase in the rates of aneuploid embryos which shoot from a baseline of 30% to as high as 90% by their late 40s, before menopause. 56, 57. Several mechanisms have been implicated in the pathogenesis of this problem, including dysfunctional cohesins 58, weakened stringency of the spindle-assembly checkpoint (SAC)59, 60, telomere shortening61, 62, and impaired mitochondrial metabolic activity63, 64. All of them contribute directly or indirectly to proper chromosome segregation, an important factor for the influence on embryo competence at the moment of development. Their impact at this stage can considerably influence the results of reproduction. 65.

CONCLUSION

This means that educating the public on how aging and lifestyle choices affect fertility can help to reduce infertility rates in the future.

Lifestyle factors demand a multi-disciplinary approach to infertility. Advanced maternal age makes the mother vulnerable to consequences aside from the impairments of oocyte competence. It rather increases the rate of ectopic pregnancies, increases chances of developing preeclampsia, increases the rate of caesarean delivery, increases rates of preterm deliveries, and lowers birth weights. Such information should make counselling evidence based so that the patients, more so those above 35, are well informed of their chances of conception. Aged 35 should be the minimum barrier to defining AMA and 45 the maximum for IVF with one's own eggs.

REFERENCES

[1] Schmidt L, Sobotka T, Bentzen JG, Nyboe Andersen A, ESHRE reproduction and Society Task force. “Demographic and Medical Consequences of delaying Parenthood”. Human Reproduction update (2012) 18:29-43. Doi:10.1093/humupd/dmr040.

[2] Nelson SM, Lawer DA. Predicting live birth, preterm delivery, and low birth weight in infants born from in vitro fertilisation: a prospective study of 144, 018 treatment cycles. PLoS Med(2011) 8:e1000386.

[3] Grondahl ML, Christiansen SL, Kesmodel US, I, Agerholm E, Lemmen JG, Lundstorm P, et al. Effect of women’s age on embryo morphology, cleavage rate and competence – a Multicenter cohort study. PLos One(2017)12:e0172456.10.1371/journal.pone.0172456.

[4] Mazzilli R, Cimadomo D, Vaiarelli A, Capalbo A, Dovere L, Alviggi E, et al. Effect of the male factor on the clinical outcome of intracytoplasmic sperm injection combined with preimplantation aneuploidy testing: observational longitudinal cohort study of 1,219 consecutive cycles.FertilSteril(2017)108(6):961-72.e3.

[5] Franasiak JM, Forman EJ, Hong KH, Werner MD, Upham KM, Treff NR, et al. The nature of aneuploidy with increasing age of female partner :a review of 15, 169 consecutive trophectoderm biopsies evaluated with comprehensive chromosomal screening. Fertil Steril(2014)101.656-63.e1.10.1016/j.fertnstert.2013.11.004.

[6] Capalbo A, Hoffmann ER, Cimadomo D, Maria Ubaldi F, Rienzi L. Human female meiosis revised: new insights into the mechanisms of chromosome segregation and aneuploidies from advanced genomics and time-lapse imaging.

Hum Reprod Update(2017)23(6):706-22.10.1093/humupd/dmx026.

[7] Santonocito M, Guglielmino MR, Vento M, Ragusa M, Barbagallo D, Borzi P, et al. The apoptotic transcriptome of the human MII oocyte: characterization and age-related changes. *Apoptosis* (2013) 18:201–11. 10.1007/s10495-012-0783-5

[8] Nagaoka SI, Hassold TJ, Hunt PA. Human aneuploidy: mechanisms and new insights into an age-old problem. *Nat Rev Genet* (2012) 13:493–504. 10.1038/nrg3245.

[9] Heffner LJ. Advanced maternal age – how old is too old? *N Engl J Med* (2004) 351:1927–9. 10.1056/NEJMp048087.

[10] Hassold T, Hunt P. To err (meiotically) is human: the genesis of human aneuploidy. *Nat Rev Genet* (2001) 2:280–91. 10.1038/35066065

[11] Hassold T, Hall H, Hunt P. The origin of human aneuploidy: where we have been, where we are going. *Hum Mol Genet* (2007) 16 Spec No. 2:R203–8. 10.1093/hmg/ddm243.

[12] Angell RR. Meiosis I in human oocytes. *Cytogenet Cell Genet* (1995) 69:266–72. 10.1159/000133977

[13] Kong A, Barnard J, Gudbjartsson DF, Thorleifsson G, Jonsdottir G, Sigurdardottir S, et al. Recombination rate and reproductive success in humans. *Nat Genet* (2004) 36:1203–6. 10.1038/ng1445

[14] Hutchison CA, III, Newbold JE, Potter SS, Edgell MH. Maternal inheritance of mammalian mitochondrial DNA. *Nature* (1974) 251:536–8. 10.1038/251536a0

[15] Dumollard R, Duchen M, Carroll J. The role of mitochondrial function in the oocyte and embryo. *Curr Top Dev Biol* (2007) 77:21–49. 10.1016/S0070-2153(06)77002-8

[16] Muller-Hocker J, Schafer S, Weis S, Munscher C, Strowitzki T. Morphological-cytochemical and molecular genetic analyses of mitochondria in isolated human oocytes in the reproductive age. *Mol Hum Reprod* (1996) 2:951–8. 10.1093/molehr/2.12.951

[17] Van Blerkom J. Mitochondrial function in the human oocyte and embryo and their role in developmental competence. *Mitochondrion* (2011) 11:797–813. 10.1016/j.mito.2010.09.012

[18] Van Blerkom J. Mitochondrial function in the human oocyte and embryo and their role in developmental competence. *Mitochondrion* (2011) 11:797–813. 10.1016/j.mito.2010.09.012

[19] Eichenlaub-Ritter U. Oocyte ageing and its cellular basis. *Int J Dev Biol* (2012) 56:841–52. 10.1387/ijdb.120141ue

[20] Duran HE, Simsek-Duran F, Oehninger SC, Jones HW, Jr, Castora FJ. The association of reproductive senescence with mitochondrial quantity, function, and DNA integrity in human oocytes at different stages of maturation. *Fertil Steril* (2011) 96:384–8. 10.1016/j.fertnstert.2011.05.056

[21] Murakoshi Y, Sueoka K, Takahashi K, Sato S, Sakurai T, Tajima H, et al. Embryo developmental capability and pregnancy outcome are related to the mitochondrial DNA copy number and ooplasmic volume. *J Assist Reprod Genet* (2013) 30:1367–75. 10.1007/s10815-013-0062-6

[22] Van Blerkom J. Mitochondrial function in the human oocyte and embryo and their role in developmental competence. *Mitochondrion* (2011) 11:797–813. 10.1016/j.mito.2010.09.012

[23] Sathananthan AH, Trounson AO. Mitochondrial morphology during preimplantational human embryogenesis. *Hum Reprod* (2000) 15(Suppl 2):148–59. 10.1093/humrep/15.suppl_2.148

[24] May-Panloup P, Boucret L, Chao de la Barca JM, Desquiret-Dumas V, Ferre-L'Hotellier V, Moriniere C, et al. Ovarian ageing: the role of mitochondria in oocytes and follicles. *Hum Reprod Update* (2016) 22:725–43. 10.1093/humupd/dmw028

[25] Diez-Juan A, Rubio C, Marin C, Martinez S, Al-Asmar N, Riboldi M, et al. Mitochondrial DNA content as a viability score in human euploid embryos: less is better. *Fertil Steril* (2015) 104:534–41.e1. 10.1016/j.fertnstert.2015.05.022

[26] Buccione R, Schroeder AC, Eppig JJ. Interactions between somatic cells and germ cells throughout mammalian oogenesis. *Biol Reprod* (1990) 43:543–7. 10.1095/biolreprod43.4.543

[27] Gilchrist RB, Lane M, Thompson JG. Oocyte-secreted factors: regulators of cumulus cell

function and oocyte quality. *Hum Reprod Update* (2008) 14:159–77. 10.1093/humupd/dmm040

[28] Seifer DB, DeJesus V, Hubbard K. Mitochondrial deletions in luteinized granulosa cells as a function of age in women undergoing in vitro fertilization. *Fertil Steril* (2002) 78:1046–8. 10.1016/S0015-0282(02)04214-0

[29] Tatone C, Carbone MC, Falone S, Aimola P, Giardinelli A, Caserta D, et al. Age-dependent changes in the expression of superoxide dismutases and catalase are associated with ultrastructural modifications in human granulosa cells. *Mol Hum Reprod* (2006) 12:655–60. 10.1093/molehr/gal080

[30] Ogino M, Tsubamoto H, Sakata K, Oohama N, Hayakawa H, Kojima T, et al. Mitochondrial DNA copy number in cumulus cells is a strong predictor of obtaining good-quality embryos after IVF. *J Assist Reprod Genet* (2016) 33:367–71. 10.1007/s10815-015-0621-0

[31] Muller-Hocker J, Schafer S, Weis S, Munscher C, Strowitzki T. Morphological-cytochemical and molecular genetic analyses of mitochondria in isolated human oocytes in the reproductive age. *Mol Hum Reprod* (1996) 2:951–8. 10.1093/molehr/2.12.951

[32] Van Blerkom J. Mitochondrial function in the human oocyte and embryo and their role in developmental competence. *Mitochondrion* (2011) 11:797–813. 10.1016/j.mito.2010.09.012

[33] Bass HW, Riera-Lizarazu O, Ananiev EV, Bordoli SJ, Rines HW, Phillips RL, et al. Evidence for the coincident initiation of homolog pairing and synapsis during the telomere-clustering (bouquet) stage of meiotic prophase. *J Cell Sci* (2000) 113(Pt 6):1033–42.

[34] Scherthan H. Telomere attachment and clustering during meiosis. *Cell Mol Life Sci* (2007) 64:117–24. 10.1007/s00018-006-6463-2

[35] Martinez-Delgado B, Yanowsky K, Inglada-Perez L, Domingo S, Urioste M, Osorio A, et al. Genetic anticipation is associated with telomere shortening in hereditary breast cancer. *PLoS Genet* (2011) 7:e1002182. 10.1371/journal.pgen.1002182

[36] Calado RT, Young NS. Telomere diseases. *N Engl J Med* (2009) 361:2353–65. 10.1056/NEJMra0903373

[37] Kalmbach KH, Fontes Antunes DM, Dracxler RC, Knier TW, Seth-Smith ML, Wang F, et al. Telomeres and human reproduction. *Fertil Steril* (2013) 99:23–9. 10.1016/j.fertnstert.2012.11.039

[38] Keefe DL, Marquard K, Liu L. The telomere theory of reproductive senescence in women. *Curr Opin Obstet Gynecol* (2006) 18:280–5. 10.1097/01.gco.0000193019.05686.49

[39] Keefe DL. Telomeres, reproductive aging, and genomic instability during early development. *Reprod Sci* (2016) 23:1612–5. 10.1177/1933719116676397

[40] Mania A, Mantzouratou A, Delhanty JD, Baio G, Serhal P, Sengupta SB. Telomere length in human blastocysts. *Reprod Biomed Online* (2014) 28:624–37.

[41] Keefe DL, Franco S, Liu L, Trimarchi J, Cao B, Weitzen S, et al. Telomere length predicts embryo fragmentation after in vitro fertilization in women – toward a telomere theory of reproductive aging in women. *Am J Obstet Gynecol* (2005) 192:1256–60; discussion 60–1. 10.1016/j.ajog.2005.01.036

[42] Treff NR, Su J, Taylor D, Scott RT, Jr. Telomere DNA deficiency is associated with development of human embryonic aneuploidy. *PLoS Genet* (2011) 7:e1002161. 10.1371/journal.pgen.1002161

[43] Cheng JM, Liu YX. Age-related loss of cohesion: causes and effects. *Int J Mol Sci* (2017) 18. 10.3390/ijms18071578.

[44] Cheng JM, Liu YX. Age-related loss of cohesion: causes and effects. *Int J Mol Sci* (2017) 18. 10.3390/ijms18071578

[45] Bennabi I, Terret ME, Verlhac MH. Meiotic spindle assembly and chromosome segregation in oocytes. *J Cell Biol* (2016) 215:611–9. 10.1083/jcb.201607062

[46] Battaglia DE, Goodwin P, Klein NA, Soules MR. Influence of maternal age on meiotic spindle assembly in oocytes from naturally cycling women. *Hum Reprod* (1996) 11:2217–22. 10.1093/oxfordjournals.humrep.a019080

[47] Battaglia DE, Goodwin P, Klein NA, Soules MR. Influence of maternal age on meiotic

spindle assembly in oocytes from naturally cycling women. *Hum Reprod* (1996) 11:2217–22. 10.1093/oxfordjournals.humrep.a019080

[48] Practice Committees of American Society for Reproductive Medicine, Society for Assisted Reproductive Technology. Mature oocyte cryopreservation: a guideline. *Fertil Steril.* (2013) 99:37–43. 10.1016/j.fertnstert.2012.09.028

[49] Martinez F. Update on fertility preservation from the Barcelona International Society for Fertility Preservation-ESHRE-ASRM 2015 expert meeting: indications, results and future perspectives. *Hum Reprod.* (2017) 32:1802–11. 10.1093/humrep/dex218

[50] Stoop DF, van der Veen F, Deneyer M, Nekkebroeck J, Tournaye H. Oocyte banking for anticipated gamete exhaustion (AGE) is a preventive intervention, neither social nor nonmedical. *Reprod Biomed Online* (2014) 28:548–51. 10.1016/j.rbmo.2014.01.007

[51] Fitzgerald C, Zimon AE, Jones EE. Aging and reproductive potential in women. *Yale J Biol Med.* (1998) 71:367–81.

[52] Lim AS, Tsakok MF. Age-related decline in fertility: a link to degenerative oocytes? *Fertil Steril*. (1997) 68:265–71. doi: 10.1016/S0015-0282(97)81513-0

[53] Klein J, Sauer MV. Assessing fertility in women of advanced reproductive age. *Am J Obstet Gynecol.* (2001) 185:758–70. doi: 10.1067/mob.2001.114689

[54] Munné S, Chen S, Colls P, Garrisi J, Zheng X, Cekleniak N, et al. Maternal age, morphology, development and chromosome abnormalities in over 6000 cleavage-stage embryos. *Reprod Biomed Online*. (2007) 14:628–34. doi: 10.1016/S1472-6483(10)61057-7

[55] Goossens V, Harton G, Moutou C, Traeger-Synodinos J, Van Rij M, Harper J, et al.. ESHRE PGD Consortium data collection IX: cycles from January to December 2006 with pregnancy follow-up to October 2007. *Hum Reprod.* (2009) 24:1786–810. 10.1093/humrep/dep059

[56] . Capalbo A, Hoffmann ER, Cimadomo D, Maria Ubaldi F, Rienzi L. Human female meiosis revised: new insights into the mechanisms of chromosome segregation and aneuploidies from advanced genomics and time-lapse imaging. *Hum Reprod Update* (2017) 23:706–22. 10.1093/humupd/dmx026

[57] Franasiak JM, Forman EJ, Hong KH, Werner MD, Upham KM, Treff NR, et al.. The nature of aneuploidy with increasing age of the female partner: a review of 15,169 consecutive trophectoderm biopsies evaluated with comprehensive chromosomal screening. *Fertil Steril.* (2014) 101:656–63.e1. 10.1016/j.fertnstert.2013.11.004

[58] Cheng JM, Liu YX. Age-related loss of cohesion: causes and effects. Int J Mol Sci. (2017) 18:E1578. 10.3390/ijms18071578

[59] Eichenlaub-Ritter U. Oocyte ageing and its cellular basis. Int J Dev Biol. (2012) 56:841–52. 10.1387/ijdb.120141ue

[60] Nagaoka SI, Hodges CA, Albertini DF, Hunt PA. Oocyte-specific differences in cell-cycle control create an innate susceptibility to meiotic errors. Curr Biol. (2011) 21:651–7. 10.1016/j.cub.2011.03.003

[61] Keefe DL. Telomeres, reproductive aging, and genomic instability during early development. Reprod Sci. (2016) 23:1612–5. 10.1177/1933719116676397

[62] de Lange T. How telomeres solve the end-protection problem. Science (2009) 326:948–52. 10.1126/science.1170633

[63] Van Blerkom J. Mitochondrial function in the human oocyte and embryo and their role in developmental competence. Mitochondrion (2011) 11:797–813. 10.1016/j.mito.2010.09.012

[64] Eichenlaub-Ritter U. Oocyte ageing and its cellular basis. Int J Dev Biol. (2012) 56:841–52. 10.1387/ijdb.120141ue

[65] Cimadomo D, Fabozzi G, Vaiarelli A, Ubaldi N, Ubaldi FM, Rienzi L. Impact of maternal age on oocyte and embryo competence. Front Endocrinol. (2018) 9:327. 10.3389/fendo.2018.00327