Published in final edited form as:

Fertil Steril. 2010 December ; 94(7): 2507–2513. doi:10.1016/j.fertnstert.2010.02.037.

Oocyte maturation failure: a syndrome of bad eggs

Stephanie Beall, M.D., Ph.D.^a, Carol Brenner, Ph.D.^b, and James Segars, M.D.^b

^a Department of Obstetrics and Gynecology, Vanderbilt University Medical Center, Nashville, Tennessee ^b Program on Reproductive and Adult Endocrinology, NICHD, National Institutes of Health, Bethesda, Maryland

Abstract

To show that disruption of meiotic competence results in cell cycle arrest, and the production of immature oocytes that are not capable of fertilization. Through an extensive review of animal studies and clinical case reports, we define the syndrome of oocyte maturation failure as a distinct oocyte disorder, present a classification system based on clinical parameters, and discuss the potential molecular origins for the disease.

Keywords

Oocyte maturation; oocyte arrest; meiotic arrest; sterility

In vitro fertilization (IVF) provides a window into oocyte maturation and early human development. Assisted reproductive technologies involve controlled follicular development and exogenous hormone stimulation of oocyte maturation (1). Upon retrieval, oocytes are analyzed for hallmarks of maturity and classified as GV, MI, or MII based on appearance (2). These morphologic categories correlate roughly with phases of meiotic progression (Fig. 1). Oocytes that have not progressed through meiosis to MII are immature and not able to be successfully fertilized.

THE SYNDROME OF OOCYTE MATURATION FAILURE

Approximately 8.6% to 15.2% of all infertility patients produce at least one meiotically incompetent oocyte (3,4). If >25% of the oocytes were immature, then successful fertilization with clinical pregnancy was greatly reduced (3). Importantly, the occasional production of an immature oocyte is to be distinguished from a syndrome of repeated oocyte maturation failure where there is repeated production of a majority of immature oocytes. Oocyte maturation failure is occasionally absolute, meaning that no mature oocytes are produced. A handful of case reports and case series (Table 1) describe a total of 19 patients with oocyte maturation failure. The key clinical features linking these cases are: [1] primary infertility, [2] repetitive production of mostly immature oocytes, [3] inability of in vitro maturation (IVM) to stimulate maturation, and [4] fertilization failure despite intracytoplasmic sperm injection. The incidence of this syndrome is unknown.

The main clinical feature linking all these cases into a distinct syndrome is the repetitive production of immature oocytes with resulting sterility. In case reports, alterations in

Reprint requests: James Segars, M.D., Program on Reproductive and Adult Endocrinology, NICHD, National Institutes of Health, Building 10, CRC, 1E-3140, 9000 Rockville Pike, Bethesda, MD 20892 (FAX: 301-402-0884; segarsj@mail.nih.gov).

S.B. has nothing to disclose. C.B. has nothing to disclose. J.S. has nothing to disclose.

gonadotropin stimulation protocol, use of IVM or intracytoplasmic sperm injection, did not improve the outcome. Although limited in its breadth, this evidence suggests that there is a distinct disorder of oocyte maturation that results in the arrest of the oocyte at particular points of meiotic progression and subsequent sterility.

Meiotic recommencement and progression is dependent on the acquisition of meiotic competence (5,6). Before the resumption of meiosis, the oocyte undergoes a growth phase where it accumulates both mRNA and protein required for the completion of meiosis. Meiotic progression depends upon the precise control of these key regulatory proteins. This is accomplished through the regulation of protein production, phosphorylation, localization, and degradation (7–11). Any alteration in these key steps could result in maturation failure.

The cause of repetitive oocyte maturation failure in humans is not known. In animal models, alterations in key meiotic mediators, experimentally derived through the development of knockouts or through the use of inhibitors and stimulators, have produced multiple meiotic failure phenotypes (Table 2). Although these studies have provided great insight into the signaling mechanisms that control meiosis, the relationship of these mediators to human infertility remains to be explored. The remainder of this discussion will construct a framework of the clinical syndrome in humans based on the molecular understanding of oocyte maturation failure provided by animal studies.

OOCYTE MATURATION FAILURE TYPE I: GV ARREST

Resumption of meiosis from the diplotene arrest is controlled by the activation of maturation-promoting factor (MPF) (Fig. 1) (12). Morphologically, reinitiation of meiosis I and entry into M phase is hallmarked by the breakdown of the germinal vesicle (GVBD). Disruption of the key signaling events leading up to MPF activation have been shown to result in the arrest of the oocyte before GVBD in animal models (Table 2). Two cases have been reported that document the presence of oocytes arrested before GVBD, and are clinically referred to as GV arrest (Table 1). Therefore, it may be that women who produce oocytes arrested at GV possess a defect in the signaling cascade responsible for the activation of MPF.

The MPF is a heterodimer composed of Cdk1 and cyclin B (13,14). The activation state of MPF is dependent on the phosphorylation state of Cdk1. Activation through dephosphorylation is mediated by *cdc25* (15–17). *Cdc25b*^{−/−} female mice are sterile with oocytes arrested in GV (18). The ovaries and oocytes appear morphologically normal. However, the oocytes isolated from *cdc25b*^{−/−} mice had low MPF activity (18). The regulation of *cdc25b* in the mouse oocyte is controlled by subcellular localization and temporal protein expression (19,20). An oscillatory pattern of *cdc25b* protein expression during meiosis, which corresponds to MPF activity, is the result of protein production and targeted protein degradation (21).

Regulation of oocyte cAMP expression has also been found to be essential for oocyte maturation (Fig. 1) (22). During oocyte maturation arrest, elevated levels of cAMP result in the inhibition of MPF (6,15,23,24). During reentry into meiosis, the reduction in cAMP permits MPF activation. Synthesis of cAMP is mediated through Gs-protein-coupled receptor 3 in the oocyte. Oocytes from mice lacking Gs-protein-coupled receptor 3 resume meiosis prematurely (25). Phosphodiesterase 3A is primarily responsible for oocyte cAMP hydrolysis. Phosphodiesterase 3A-deficient female mice are completely infertile because ovulated oocytes contained increased cAMP levels and are arrested at the GV stage (26).

Whether the block in maturation at GV observed in the case reports was because of disruption in one of the factors described above is not known because molecular analysis of

these oocytes was not performed. However, the phenotypes of the *cdc25b* and phosphodiesterase 3A knockout female mice are similar to those reported in the case reports and are candidate genes.

OOCYTE MATURATION FAILURE TYPE 2: MI ARREST

Progression through meiosis I to metaphase II arrest requires chromosome condensation, formation of the metaphase spindle, chromosome alignment along the first metaphase plate, followed by the separation and segregation of the homologous chromosomes. Completion of the first meiotic division is hallmarked by the formation of the first polar body (PBI). Oocyte arrest before the PBI formation, is morphologically classified as MI arrest. MI arrest could occur because of either a defect in the signal transduction pathway mediating meiotic progression or any abnormality in the meiotic spindle, which results in activation of the spindle assembly checkpoint (SAC). In both mouse models and case reports of MI arrest, there are generally two phenotypes observed: those with normal spindle organization and those with chromosomal aberrations.

The metaphase to anaphase transition is mediated by the Anaphase Promoting Complex/Cyclosome (APC/C) (Fig. 1) (27,28). Targeted degradation of securin by the APC/C releases separase, which cleaves cohesin and results in chromosome segregation (29). The APC/C also results in the destruction of cyclin B, leading to the inactivation of MPF and exit from meiosis I (30,31).

The key enzymes regulating metaphase I during meiosis are highly conserved and perform similar functions during metaphase II and the mitotic cell cycle. Therefore, genetic deficiency of these proteins, including APC/C and separase, results in an embryonic lethal phenotype and not MI arrest (32,33). It is possible that oocyte-specific alterations in gene or protein expression, oocyte specific compensation, or altered expression of proteins that regulate key mediators may be responsible for the clinical phenotype of MI arrest.

Oocyte-specific alterations in transcription factors may contribute to oocyte-specific maturation failure. For example, H1foo is an oocyte-specific subtype of the linker histone H1, which contributes to gene-specific regulation of transcription (34). Knockdown of H1foo resulted in oocyte arrest at metaphase I (35). In vivo, H1foo function is mediated through methylation (34); therefore, it is possible that epigenetic modification of H1foo function may result in altered gene expression and oocyte maturation competence.

MI arrest may be mediated through either activation of the SAC because of chromosomal misalignment or through deregulated SAC signaling. Chromosomal recombination and cohesion facilitates orderly alignment and segregation of chromosomes during meiosis. Mei1 and Mlh1 mediate recombination during meiosis (36). Mei1-deficient oocytes demonstrate severe synapsis defects, unpaired and disorganized chromosomes, and MI arrest (30,37). In humans, polymorphic alleles of Mei1 have been associated with azoospermia; however, these alterations have yet to be associated with female infertility (38). Cell cycle progression requires extinction of SAC signaling, thereby permitting APC/C activation (Fig. 1) (39,40). Overexpression of one of the SAC proteins Mad2 during meiosis has been shown to potentiate SAC signaling and result in MI arrest (41).

OOCYTE MATURATION FAILURE TYPE 3: MII ARREST

The morphologic classification of MII generally denotes an oocyte that is “mature,” having arrested in metaphase II and is presumed to be capable of fertilization. However, there are subsets of women who produce oocytes with MII morphology that are not capable of embryo formation even with fertilization. This incongruence between morphologic maturity

and capacity could be attributed to either the inclusion within the morphologic classification immature oocytes arrested at any stage between PBI formation and metaphase II, which are not capable of fertilization, or oocytes arrested normally at metaphase II that do not possess the ability to complete meiosis. Fertilization defects could also produce a similar clinical phenotype. However, both the molecular etiology and the potential therapeutic interventions of these two disorders are distinct.

Arrest at metaphase II is initiated by Emi2 inhibition of APC/C, and maintained by Emi2, the Mos/MAPK pathway and the SAC (Fig. 1) (42). Oocytes deficient in Emi2 protein were not able to form a spindle complex during meiosis II and were arrested at MII (43,44). Similarly, Mos null mutants oocytes that progressed to metaphase II could not complete meiosis II after fertilization (45).

Release from metaphase II arrest is dependent upon sperm-specific phospholipase C-zeta and downstream activation of APC/C (46). The APC/C activation results in destruction of MPF and the release of separase, which is necessary for sister chromatid separation (47–50). Proteins involved in this pathway include calmodulin-dependent protein kinase II (CamKII) and protein kinase C (PKC) (Fig. 1). Inhibitors of CamKII and PKC block exit from meiosis and results in MII arrest (8,51,52). How this may translate into human infertility is not clear. In mice, age-related reduction in PKC has been described and is associated with diminished activation competence (53). It is possible that diminished PKC stores in human oocytes could result in MII arrest and age-related infertility (54).

Similar to MI arrest, the extinction of spindle assembly checkpoint signaling is required for APC/C activation and progression through the metaphase II–anaphase II transition. Factors that would result in continued activation of the SAC and therefore inhibition of APC/C could explain an MII arrest. Metaphase II differs from metaphase I in that sister chromatids separate and segregate rather than homologous chromosomes. Cohesin SMC1 beta is required for the maintenance of sister chromatid cohesion and DNA recombination (55,56). Mice deficient in SMC1 beta are sterile and female meiosis is highly error prone with oocytes arrested at MII (56,57).

OOCYTE MATURATION FAILURE TYPE 4: MIXED ARREST

Some patients produce oocytes that arrest at more than one stage of meiosis (Table 1). The key mediators responsible for cell cycle progression and arrest are highly conserved and used during mitosis and both cycles of meiosis with differentially expressed homologues to ensure specific functions. Because of this redundancy, loss of function by one homologue may be partially or completely compensated for by a related family member. If partial compensation by a related homologue occurs during meiotic progression, insufficient compensation may result in a mixed arrest phenotype.

Several mouse models exist where immature oocytes are observed at more than one stage of meiotic progression. The proteins associated with mixed oocyte maturation failure include Mlh3 and Ubb. Both of these two proteins are members of protein family with multiple different homologues expressed during oocyte maturation. Mlh3 belongs to a family that includes Mlh1, Pms1, and Pms2. During meiosis, Mlh3 functions in the maintenance of chiasmata. Mlh3 knockout mice are sterile, with oocytes arrested at MI and MII (58). Ubiquitin is encoded by four Ub genes: Uba52, Uba80, Ubb, and Ubc. Mice deficient in Ubb are infertile, with oocytes arrested at GV and MI (59). In response to the loss of Ubb, transcription of both Uba52 and Uba80 increases in an attempt to compensate (59). However, this compensation is not sufficient to permit meiotic maturation. The role of compensatory mechanisms in the generation of the mixed oocyte maturation failure

phenotype are not known. Future experiments with mice deficient in more than one homologue will be required to answer this question.

DISCUSSION

The process whereby the oocyte acquires meiotic competence involves the transcription and translation of key regulatory enzymes and signaling molecules. The complex interplay between these factors, and the determination of arrest versus progression, relies on a delicate balance between production and targeted degradation of signaling. Ultimately, what is observed in maturation arrest is that dysfunction on the molecular level results in the incapacity of the oocyte to progress through meiosis either because of errors in signaling or aberrations in chromosomal/spindle formation.

CLINICAL PERSPECTIVE

In 1978, Drs. Edwards and Steptoe astonished the world by announcing that the first IVF baby, Louise Brown, was born. Currently, the International Committee for Monitoring Assisted Reproductive Technologies (ICMART) estimates that annually 1 million assisted reproductive technology procedures are performed, and approximately 200,000 babies born (ICMART report presented at the conference of the European Society of Human Reproduction and Embryology in Prague, Czech Republic, June 21, 2006). We estimate that approximately 0.1% to 1% of women may have defective oocyte maturation, whether absolute or qualitative. The descriptive classification and framework provided here serve to highlight the serious nature of the syndrome of oocyte maturation failure. Levrin (60) reported that five of the eight patients with oocyte maturation failure underwent a donor–oocyte cycle with husband's sperm, with four patients achieving pregnancy. At present, use of donor oocytes is the only option available for women with oocyte maturation failure if the defect is profound.

FUTURE DIRECTIONS

The clinical criteria used to assess gamete potential are subjective and based primarily on morphologic characteristics. Here we propose a classification scheme for the clinical syndrome of oocyte maturation failure and identify key molecular candidates based on existing animal models. In so doing, a scaffold has been created on which to expand knowledge. This classification scheme can be used to associate the clinical situation to the research on pathophysiologic mechanism.

Further research is needed to define whether alterations in these proteins are involved in the production of immature human oocytes. There is great promise for the production of a molecular tool to classify gamete potential. The diagnosis of the syndrome of oocyte maturation failure could save a couple from the financial and emotional hardship of multiple failed cycles. Counseling could then be geared toward donor egg or adoption. In addition, through understanding the mechanism of oocyte maturation in humans it is possible that IVM protocols could be developed to provide the signaling machinery necessary for oocyte maturation competence. This technology could be used not only to treat patients afflicted with oocyte maturation failure but also to mature primordial follicles ex vivo.

Care must be taken so that understanding the molecular mechanisms involved in this syndrome precede attempted therapeutic intervention. Because many of the animal models and cases presented implicate processes responsible for proper alignment and segregation of the chromosomes, any attempt to bypass the checkpoints evolution has provided to protect our species could result in increased aneuploidy.

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FIGURE 1.

Key molecular events during meiotic progression. Oocyte meiosis initiates during in utero development when the female germ cell progresses through prophase I and arrests at the diplotene stage before birth. During this time, the chromosomes condense, cohesion between sister chromatids is established and synaptonemal complexes form between homologous chromosomes. The cohesin proteins form the molecular glue between sister chromatids and proteins involved in double-strand break repair in addition to meiosis, specific SCP1, 2, and 3 are essential for recombination and synaptonemal complex formation. During the reproductive phase of life, reinitiation of meiosis occurs in response to hormonal stimulation just before ovulation. The teeter-totter between oocyte arrest and progression depends on alternating levels of the key mediators: MPF and APC/C. This is regulated by multiple signaling cascades as illustrated above. LH, through a mechanism not yet elucidated, stimulates PDE3 resulting in decreased cAMP levels within the oocyte. Simultaneously, cdc25 is activated. The combination of these two events results in activation of MPF, which drives meiotic progression. Exit out of prophase I and entry into M phase of meiosis I is hallmarked by the GVBD and the formation of the meiotic spindle. Following formation of the spindle apparatus homologous chromosome pairs align along the meiotic equatorial plate. When the chromosomes are all properly aligned, the SAC signal is extinguished, resulting in APC/C activation. The APC/C is a ubiquitin ligase that targets securin for degradation allowing the release of the active form of separase, which cleaves Rec 8, therefore releasing the cohesin glue along chromosome arms resulting in separation homologous chromosomes. Sister chromatids do not separate at this point in meiosis because Rec8 at the centromere is protected by shugosin during metaphase I. Following the separation of the sister chromosomes, Emi2, through its inhibition of APC/C maintains MPF function, therefore allowing progression of meiosis II through to metaphase II arrest. The oocyte remains arrested at this stage until it is fertilized. Upon sperm penetration, a rise in intracellular calcium concentration leads to CamKII activation and subsequent inhibition of Emi2. This chain of events leads to the activation of APC/C. In a process similar to the metaphase I-anaphase I transition, APC/C activation results in destruction of MPF and the release of separase. Centromeric Rad8 is no longer protected by shugosin, therefore allowing cleavage of cohesin at the centromere and sister chromatid separation. Meiosis is complete following reformation of the nuclear envelope, uncoiling of chromosomes and second polar body formation. At this point the gamete transitions from meiotic cell division to mitotic, thus permitting embryonic development.

TABLE 1

Case reports describing infertility patients with the syndrome of oocyte maturation failure.

OMF type	No. of patients	Country	Results	Reference
I	1	Israel	GV arrest	60
II	1	Germany	MI arrest	61
	1	UK	MI arrest. Initially GV then with IVM progressed to and arrested at MI. Oocytes remained arrested at MI despite incubation in gonadotropin.	62
	2	Australia	MI arrest, underwent IVM and ICSI without further maturation or fertilization	63
	1	France	MI arrest. Unsuccessful IVM. Patient with a family history significant for three of four sisters with infertility.	64
	1	Canada	MI arrest. Unsuccessful IVM. Ultrastructural analysis demonstrated irregular chromatin condensation, disrupted spindle formation, and distorted and/or stunted microvilli protruding to the perivitelline space	65
	3	Israel	MI arrest. Failed IVM.	60
III	1	Israel	MII arrest	60
IV	3	Israel	Mixed arrest (one GV + MI, one GV + MII, one MI + MII)	60
	3	Israel	One patient with GV + MI arrest, failed IVM. Two patients (sisters) with mixed MI and MII arrest, fertilized with pronuclei observed but no polar bodies. All had an abnormal chromosomal number.	66
	2	USA	One patient with GV + MI arrest. IVM with progression to MII in 3/16 oocytes. ICSI performed without fertilization. Ultrastructural analysis demonstrated chromosomal aberrations and disrupted spindle formation. One patient underwent four cycles with between 40% and 100% immature oocytes retrieved. Mixed GV (8%) + MI (65%) arrest with MII (22%). IVM performed without success. ICSI performed on MII with fertilization (total four embryos and two transfers) without pregnancy.	67

Note: IVM = in vitro maturation; ICSI = intracytoplasmic sperm injection.

TABLE 2

Alterations of key meiotic mediators lead to oocyte maturation failure in animal models.

OMF Type	Protein	Species	Function	Genotype or alteration	Phenotype	Reference
I	Cdc25b	Mouse	Phosphatase. Activation by dephosphorylation of CDK1, a component of MPF	Cdc25b ^{-/-}	GV arrest. Infertile. Morphologically normal	18
	Pde3a	Mouse	Oocyte cAMP hydrolysis	Pde3a ^{-/-}	GV arrest. Infertile. Failed to undergo spontaneous maturation in vitro. Meiotic maturation restored by inhibiting PKA.	26
II	MPF	<i>Xenopus</i>	Resumption of meiosis	CDK Inhibitor	GV arrest	68
	CDC25a	Mouse	Activate cyclin-dependent kinases	1) Overexpression 2) RNAi	1) MI Arrest. Spindle defects and aberrant chromosomal congression 2) Mixed GV (36%) and MI (54%) arrest	69
	H1foo	Mouse	Localized in oocyte nucleus, believed to play role in control of gene expression throughout oocyte maturation	Antisense morpholino oligonucleotides	MI arrest, normal chromatin condensation, and spindle organization	35
	Mei1	Mouse	Recombination	Mei1 ^{-/-}	MI arrest, impaired synaptonemal complex formation, aberrant chromosome congression, asynchronous, and unequal segregation	37
	Cks2	Mouse	Cdk1 interacting protein possibly required for entry into anaphase	Cks2 ^{-/-}	MI arrest with normal synaptonemal complex and spindle formation	70
III	Mlh1	Mouse	DNA mismatch repair during replication and promotion of recombination	Mlh1 ^{-/-}	MI arrest. Spindle defects, aberrant chromosomal congression, decreased recombination events	71, 72
	Mad2	Mouse	Spindle assembly checkpoint	Overexpression	MI arrest	41
	Lfng	Mouse	Modulator of Notch signaling to downstream transcription factors in granulosa cells	Lfng ^{-/-}	MI arrest. Only 5% MII progression. Infertile. Aberrant follicles. Can ovulate when induced but incapable of completing meiotic maturation and fertilization.	73
	Emi2	Mouse	Inhibitor of APC/C during meiosis II	Antisense morpholino oligonucleotide and siRNA	MI arrest. Failure of metaphase spindle formation, chromatin decondensed inside a nucleus.	43, 44
	Smc1 beta	Mouse	Sister chromatid cohesion and DNA recombination	Smc1 beta ^{-/-}	MI arrest, fertilization failure	57
	PKC	Mouse	Protein kinase involved in oocyte activation	Inhibitor	MI arrest	74

OMF Type	Protein	Species	Function	Genotype or alteration	Phenotype	Reference
IV	CamKII	Mouse	Calcium induced kinase necessary for APC/C activation	Inhibitor	MII arrest	75
	Mos	Mouse	Activation of MAPK	Mos ^{-/-}	MI arrest. Abnormal chromosome condensation and spindle formation, interphase following meiosis I, and parthenogenesis	45, 76, 77
	Mlh3	Mouse	Replication and promotion of recombination	Mlh3 ^{-/-}	MI and MII arrest. Spindle defects, aberrant chromosomal congression, decreased recombination events	58
	Ubb	Mouse	Targeted protein degradation by the proteasome, membrane trafficking, and transcriptional regulation	Ubb ^{-/-}	Mixed GV and MI arrest with spindle defects and abnormal chromosomal alignment	59
	Cortex	<i>Drosophila</i>	Meiosis specific activator of APC/C	Cortex ^{Δ65} , Cortex ^{ΔW55}	MI and MII arrest, aberrant chromosome segregation in meiosis I	78, 79
	Unknown	LT, LTXBO strain—mice	Unknown	Unknown	MI and MII arrest, parthenogenetic activation. Abnormalities of chromatin, microtubule, and centrosome configuration.	80, 81