Oocyte maturation abnormalities - A systematic review of the evidence and mechanisms in a rare but difficult to manage fertility pheneomina

Oosit maturasyon anormallikleri - Nadir fakat çözümü zor fertilite fenomeninde kanıt ve mekanizmaların sistematik derlemesi

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Abstract

A small proportion of infertile women experience repeated oocyte maturation abnormalities (OMAS). OMAS include degenerated and dysmorphic oocytes, empty follicle syndrome, oocyte maturation arrest (OMA), resistant ovary syndrome and maturation defects due to primary ovarian insufficiency. Genetic factors play an important role in OMAS but still need specifications. This review documents the spectrum of OMAS and to evaluate the multiple subtypes classified as OMAS. In this review, readers will be able to understand the oocyte maturation mechanism, gene expression and their regulation that lead to different subtypes of OMAs, and it will discuss the animal and human studies related to OMAS and lastly the treatment options for OMAs. Literature searches using PubMed, MEDLINE, Embase, National Institute for Health and Care Excellence were performed to identify articles written in English focusing on Oocyte Maturation Abnormalities by looking for the following relevant keywords. A search was made with the specified keywords and included books and documents, clinical trials, animal studies, human studies, meta-analysis, randomized controlled trials, reviews, systematic reviews and options written in english. The search detected 3,953 sources published from 1961 to 2021. After title and abstract screening for study type, duplicates and relevancy, 2,914 studies were excluded. The remaining 1,039 records were assessed for eligibility by full-text reading and 886 records were then excluded. Two hundred and twenty seven full-text articles and 0 book chapters from the database were selected for inclusion. Overall, 227 articles, one unpublished and one abstract paper were included in this final review. In this review study, OMAS were classified and extensively evaluatedand possible treatment options under the light of current information, present literature and ongoing studies. Either genetic studies or in vitro maturation studies that will be handled in the future will lead more informations to be reached and may make it possible to obtain pregnancies.

Keywords: Oocyte maturation abnormalities, oocyte maturation arrest, empty follicle syndrome, in vitro maturation, oocyte maturation gene expression/pathways

Öz

İnfertil kadınların küçük bir kısmında tekrarlayan oosit matürasyon anormallikleri (OMAS) görülür. OMAS, dejenere ve dismorfik oositleri, boş folikül sendromunu, oosit olgunlaşma arrestini (OMA), rezistan over sendromunu ve primer over yetmezliğine bağlı olgunlaşma kusurlarını içerir. OMAS'de genetik faktörler önemli rol oynamaktadır ancak yine de spesifikasyonlara ihtiyaç duyulmaktadır. Bu derleme, OMAS'nin spektrumunu göstermeyi ve OMAS olarak sınıflandırılan çoklu alt türleri değerlendirmeyi amaçlamaktadır. Bu derlemede okuyucular, farklı OMA alt tiplerine yol açan oosit olgunlaşma mekanizmasını, gen ekspresyonunu ve bunların düzenlenmesini ve OMAS ile ilgili hayvan ve insan çalışmalarını ve son olarak OMA'ların tedavi seçeneklerini anlayabileceklerdir. Literatür taraması; OMAS'ye odaklanan İngilizce yazılmış makaleleri saptamak için; PubMed, MEDLINE, Embase, National Institute for Health and Care Excellence kullanılarak ve aşağıdaki ilgili anahtar kelimeleri arayarak yapıldı. Belirtilen anahtar kelimelerle arama yapılmış ve İngilizce yazılmış kitap ve makaleler, klinik deneyler, hayvan çalışmaları, insan çalışmaları, meta-analiz, randomize kontrollü araştırmalar, derlemeler, sistematik derlemeler tarandı. 1961'den 2021'e kadar yayınlanmış 3.953 kaynak tespit edildi. Çalışma türü, uygunluk ve kopya olan çalışmalar için başlık ve özet taraması yapıldı ve 2.914 çalışma hariç tutuldu. Kalan 1.039 kayıt, tam metin okuma ile uygunluk açısından değerlendirildi ve ardından 886 kayıt hariç tutuldu. Veri tabanından 227 tam metin makale ve 0 kitap bölümü dahil edilmek üzere seçildi. Son olarak, 227 makale, bir yayınlanmamış ve bir özet makale bu nihai incelemeye dahil edildi. Bu derleme çalışmasında, güncel bilgiler, mevcut literatürler ve yürütülmekte olan çalışmalar ışığında osit maturasyon anormallikleri kapsamlı olarak değerlendirilmiş, sınıflanmış ve olası tedavi seçenekleri incelenmiştir. Gelecekte yapılacak olan gerek genetik gerekse in vitro maturasyon çalışmaları, OMAS ile ilgili daha çok bilgiye ulaşılmasına imkan sağlayacak ve gebeliklerin elde edilmesi mümkün olabilecektir.

Anahtar Kelimeler: Oosit maturasyon anormallikleri, oosit maturasyon arresti, boş folikül sendromu, in vitro maturasyon, maturasyon gene ekspresyonu/yolaklar

Introduction

Oocytes undergo a passive loss beginning from approximately 24 weeks gestational age until puberty and then a transition to active loss combined with passive loss during the reproductive life[1,2]. In brief, oocytes are prone to the apoptotic processes until menopause[1,2]. Those oocytes that escape apoptosis are selected as the follicular cohort in each menstrual cycle. It is the pubertal hormonal changes that trigger the resumption of oocyte meiosis. Meiotic resumption is crucial in oocyte maturation and fertilization[3].

Intrafollicular or extrafollicular factors may interfere with the selection of the follicular cohort and can result in various oocyte pathologies including oocyte degeneration, early oocyte loss, oocyte maturation arrest and impaired embryonic development. All these pathologies are defined as oocyte maturation abnormalities (OMAS)[4].

Each one of the OMAS studied in the literature were accepted as separate pathologies, until recently. Our ongoing studies demonstrated that OMAS is often related and there may exist intercycle and intracycle variability resulting in the heterogenic presentation of OMAS. Animal studies have enlightened the mechanisms of human OMAS although, there are some differences.

Traditionally, couples with repetitive OMAS were offered oocyte donation or cytoplasmic-nuclear transfer from donor oocytes, which is unpalatable to some patients and in some societies, impermissible ethically or religiously. In the last decade, studies on the mechanisms and treatment options made it possible to overcome some forms of OMA.

In this review, we aimed to evaluate all known aspects of OMAS.

Methods

Literature searches using PubMed, MEDLINE, Embase, National Institute for Health and Care Excellence were performed to identify articles written in English focusing on the Oocyte Maturation Abnormalities by looking for the following keywords:

Oocyte maturation arrest, Oocyte Maturation failure, In vitro maturation (IVM) arrest, intrinsic oocytes maturation arrest, genetic causes of oocytes maturation arrest, meiotic arrest, meiotic resumption, empty follicle syndrome (EFS), resistant ovary syndrome (ROS), immature oocytes, degenerated oocytes, immature oocytes, zona pellucida mutation, germinal vesicle arrest, GV arrest, germinal vesicle breakdown, M1 arrest, M2 arrest, fertilization failure, fertilization arrest, mikst arrest, premature ovarian failure, premature ovarian insufficiency, somatic cell nükleer transfer, spindle transfer, pronuclear transfer, polar body transfer, DNA heteroplasmy, GV transfer, mitochondrial replacement therapy, CAPA IVM, drugs for oocytes maturation arrest, treatment of oocytes maturation arrest, in vitro activation, transvaginal ovarian injury, ovarian prp. An advanced search was made with the specified keywords by selecting the article type, books and documents, clinical trial, animal studies, meta-analysis, randomized controlled trial, review, systematic review options. The search included 3,953 studies from 1961 to 2021. After title and abstract screening for study typewith duplicates, 2,914 studies were excluded. The remaining 1,039 records were assessed for eligibility by full-text reading and 806 records were then excluded. Two hundred and twenty seven full-text papers selected from database were selected. Overall, 227 articles, one unpublished and one abstract paper were included in this final extensive review.

Literature written in English complying with our search criteria were included in this review while others, either written in languages other than English or incompliant with search criteria were excluded.

Physiology of Meiotic Arrest, Meiotic Resumption and Oocyte Maturation

Until the first LH surge at the beginning of puberty, oocytes coated with a single layer of granulosa cells remain in an arrested state at the diplotene stage of the first meiotic division

as primordial follicles[5]. This preservation of oocytes is crucial for the maintenance of the future reproductive potential. However, the apoptosis of the follicles and oocytes started at approximately 24 weeks gestation age and results in the loss of 90% of the ovarian follicular cohort by initiating puberty. Roughly, 1-2/1000 follicles have a potential to be fertilized, by having undergone maturation and ovulation. Those follicles are derived from a select follicular cohort[6].

Those follicles should be in a dormant state until puberty to survive and reach reproductive potential[7]. In estrous cycles of most animal species and in menstrual cycles of humans, maturation promoting factor (MPF) is a crucial cytoplasmic factor that initiates meiotic resumption. MPF induces germinal vesicle breakdown and promotes the subsequent maturation processes in response to the LH surge[8-10]. Without the introduction of LH analogs or an endogenous LH surge, mature oocytes would be collected at IVF cycles. Mechanisms and pathways of meiotic arrest and resumption are depicted in Figure 1.

High levels of cGMP and cAMP and low levels of PDE 3A enzyme within the oocyte are *sine qua non-oocyte* in meiotic arrest[5,9] cAMP is produced in the oocyte but cGMP is produced in the somatic cells surrounding oocytes and through Nppc/Npr2 system diffuses into the oocyte. MPF is inhibited by the increased cGMP and cAMP and eventually oocytes remained in an arrested state. Until the release of oocytes with surrounding cumulus

Figure 1. Orchestration of maintenance of meiotic arrest and resumption

cells, there are strong bounds between mural granulosa cells and oocytes. This interaction is bidirectional and interruption of this communication result in spontaneous meiotic resumption in mammals[9,11]. This bidirectional communication is orchestrated by oocyte itself[5,12,13]. LH exerts its action on the resumption of meiosis. Mural granulosa cells carry LHR while cumulus cells and oocytes are lack LHR[14,15]. Thus LH exerts its action on COC indirectly. The LH peak stimulates the expression of endothelin-1, leptin, epidermal growth factor-like ligands, and insulin like-3 transcript in the process of meiotic resumption[5]. Key role in meiotic resumption is the decline in the concentration of cAMP in the oocyte cytoplasm[16]. Nppc/Npr2 pathway is present in granulosa cells[17]. This pathway is strongly expressed in mural granulosa cells and almost not expressed in cumulus cells and oocytes[18,19] Nppr/Npr2 pathway plays important role in follicular competence, formation of healthy cumulus oophorus and maintenance of oocyte meiotic arrest[20]. Human intrafollicular C- type natriuretic peptide (CNP) expression, along with Nppc/Npr2 precursors was determined in human follicular fluid and follicles having mature oocytes were found to have less FF CNP and less Nppc/Npr2 m RNA expresssion[21]. LH, cAMP and Nppc/Npr2 pathway related cGMP are key factors for oocyte meiotic arrest and oocyte meiotic resumption. LH related meiotic resumption happens either using gap junction-related processes or by non-gap junction-related process. In gap junction related process, mural granulosa cell to oocyte cGMP transport is blocked by the closure of gap junctions, thus intracytoplasmic cGMP and cAMP concentrations decrease which increases PDEA3 enzyme concentrations and initiates meiotic resumption[22]. For EGFR to exert its action on maintaining oocyte maturation arrest in zebrafish, Pgrmc1 signaling was reported essential[23]. In non-gap junction process, LH induced EGFR directly inhibits Nppc/Npr2 pathway and decreases cGMP levels[24-26]. FSH stimulation elevates cAMP in mural granulosa cells and make gap junctions more permeable and changes the intracellular distribution of connexin43 (Cx43). This in turn maintain cAMP levels in a certain threshold[27-29]. Additionally, G protein, its Gs protein-coupled receptor (GPR3) was found to play an important role in maintenance of oocyte meiotic arrest by the maintenance of basal cAMP concentrations[30]. Spontaneous meiotic resumption was reported in GPR3 knockout mice[30-32].

Up regulation of GPR3 in Xenopus oocyte resulted in increased intracytoplasmic cAMP levels and inhibition of meiotic resumption process[33]. Lincoln et al.[34] studied the role of Cdc25b phosphatase in meiotic resumption in mice. They used Cdc25b knockout female mice and reported that they were sterile and that the oocytes remained arrested at prophase with very limited MPF activity. Cytosolic malate dehydrogenase (Mor2) injected mouse oocytes demonstrated significant decreases in oocyte maturation[35].

Mor2 mRNA levels were signficantly decreased in immature oocytes. Mor2 has been reported as an essential component
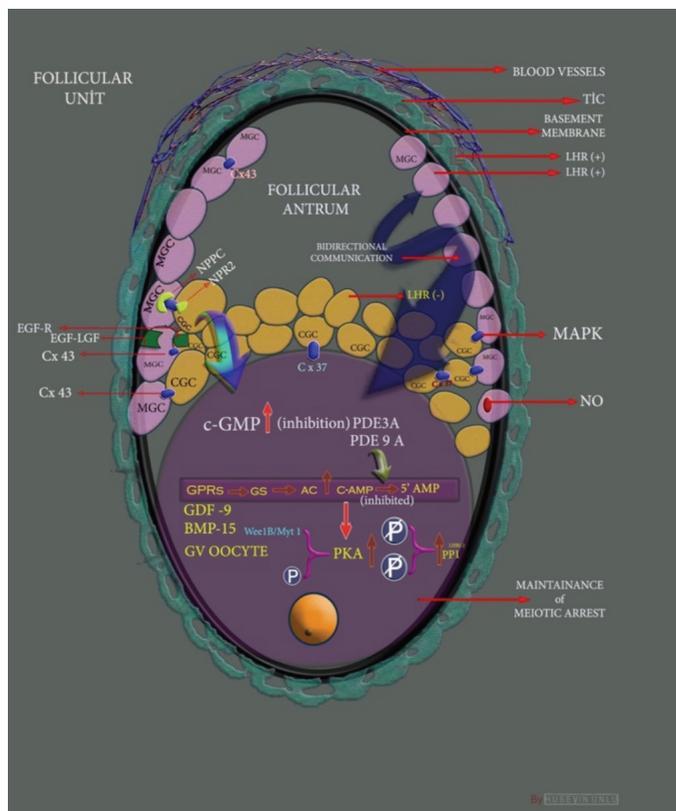
of oocyte maturation and embryo development in the mouse and microinjection of Mor2 mRNA decreases the IVM of mouse oocytes[35]. Mor2 mRNA is highly expressed in MII stage mouse oocytes during maturation cytoplasmic maturation.The disruption of Mor2 mRNA results in inability of the mouse oocyte to use the malate-aspartate shuttle that is crucial for regulating the balance between cytoplasmic and mitochondrial metabolism.

Ovarian follicles, with their mural granulosa cells, cumulus cells and the oocyte is a unit with bidirectional communications. All these communications are orchestrated by the oocyte itself. Theca cells provide structural support for follicles together with synthesis of androgens that are used as susbtrates for aromatase enzyme activity[9]. Since cGMP levels do not change in concentration during meiotic resumption in theca cells, it can be stated that theca cells are not involved in the meiotic resumption, which is energy intensive. This may be attributed to the absence of gap junction between theca and granulosa cells[9].

Oocyte-specific Genes and Their Expression and Regulation During Oocyte Maturation

The oocyte exhibits an unusual pattern of gene expression regulation, with separate transcription and translation profiles. Whereas some oocyte RNA are translated for cellular metabolism, others are deadenylated and stored in cytoplasm. In most mammalian species RNA content of the fully grown oocyte is estimated to be 0.3-0.5 ng (mouse, human)[36]. After maturation and fertilization, the transition from the maternal to embryonic control of genome expression occur gradually.

mRNA deadenylase shortens the poly(a) tail of mRNA via deadenylation and this event slows down or prevent mRNA translation.Thus regulation of posttranscriptional gene expression is ensured.

Oocyte maturation is related to reproductive potential and understanding the gene regulation of human oocyte maturation is important for understanding oocyte physiology and to advance IVM technology, determination of upregulated and downregulated genes, during oocyte maturation can help identify markers of competent oocytes. To examine how the genes are regulated at different maturation stages of human oocytes, Yu et al.[37] evaluated genes at three human oocyte maturation stages (GV, MI, MII) within the same individual. Single-cell mRNA sequencing and single-cell whole genome bisulfite sequencing was performed (WGBS). They also focused on the possible role of non-CpG methylation and the DNA methylome in oocyte maturation. DNA methylation plays important roles in gene expression, regulation and chromatin structure/modifications. They demonstrated that when comprising MII and MI oocytes, 1,077 genes were upregulated in mature oocytes (MII) and 3,758 were downregulated[37].

In general the upregulated genes or pathways play significant roles in RNA degradation, splicing and transport, the cell cycle, ubiquitin-mediated proteolysis and oocyte meiosis. The downregulated pathways were primarily the metabolic pathways, such as TCA (tricarboxylic acide) cycle and oxidative phosphorylation[37] these data matches with the results of other studies[38-41].

TET proteins play an important role in the regulation of DNA-methylation as related to the regulation of gene expression during early zygote formation, embryogenesis, and neuronal differentiation[42-45].

TET3 is significantly upregulated in MII oocytes compared to MI oocytes. Both TET3 and TET2 genes are expressed in all stages of oocyte maturation (GV, MI and MII) and they are important in removing methylation in the genome of zygotes because of fertilization.

The downregulated pathways mostly involve the alternative glucose metabolic pathways which is required during the oocyte cytoplasmic maturation stage. A group of signal transduction (WNT) pathways have been implicated in ovarian development, oogenesis, and early embryonal development[46,47].

Zheng et al.[48] demonstrated an overall downregulation of genes encoding important components of the WNT signaling pathway during preimplantation development.

Chermuta et al.[49] analysed more than twenty genes involved in the cellular response to hormone stimuli during the oocyte maturation process. Ten of these genes (*ID2, FOS, CYR61, BTG2, AR, ESR1, CCND2, TACR3, TGFBR3,* and *EGR*) were downregulated by the IVM conditions.

Insulin-Like Growth Factor I Receptor; IGF1R

Insulin stimulates glucose uptake by regulating the transporter activities at both the transcriptional and post-translational levels. IGF1R mRNA is abundant in oocytes and early stage embryos, but decreased dramatically upon the formation of early blastocysts. The INSR, IRS1 and IRS2 mRNAs were expressed in oocytes and throughout preimplantation development. The gene for the catalytic subunit of PI3K, PIK3CA, displayed a maternal expression pattern, with its mRNA abundance decreasing by the morula stage. Similar to PIK3CA, the AKT1/AKT2 cDNA probe revealed down-regulation in morula and blastocyst stages, although the overall amount of transcript was low. Oocyte-specific gene expressions are presented in Table 1. Meta-analysis have found that genes involved in oocyte maturation are highly conserved in flies (drosophila) and distantly related vertebrates including the mouse. Among them, BMP15 and GDF9, which plays an important role in bidirectional communication between the oocytes and the granulosa cells, in vertebrate species[36]. This could be explained by the fact that, recombinant GDF9 (oocyte-derived growth differentiation factor-9) inhibits KITL mRNA expression in mouse preantral granulosa cells[64], whereas BMP15 (bone morphogenetic protein-15) promotes KITL expression in monolayers of granulosa cells from rat early antral follicles[65].

Other important conserved genes that play a role in the quality of IVM oocytes are: GREM1, HAS2, COX2/PTGS2, EGFR,

Table 1. Oocyte-specific gene expressions (upregulation or downregulation) during maturation

	GV	MI	MII	Reference
DAZL	+	+	+	Yu et al. 2020[37]
BMP15	++	++	++	Yu et al. 2020[37]
GDF9	++	++	++	Yu et al. 2020[37]
RBBP7	+	+	+++++	Yu et al. 2020[37]
PTTG1	+	+	+++	Yu et al. 2020[37]; Assou et al. 2006[50]
50TUBB9	+	++	++++	Huang et al. 2017[51]; Feng et al. 2016[52]
PTTG3	+	+	+	Assou et al. 2006[50]
AURKC	+	+	+	Assou et al. 2006[50]
TET2	+	+	+	Wossidlo et al. 2011[44]; Gu et al. 2011[45]
TET3	+	+	+++	Wossidlo et al. 2011[44]; Gu et al. 2011[45]
DNMT3B	+	+	+++	Yu et al. 2020[37]
DNMT3A	+++	+++	+	Yu et al. 2020[37]
ECAT1	+++++	++	+	Liu et al. 2016[53]; Parry et al. 2011[54]
AR	++++++	++	-	Gleicher et al. 2011[55]
TMEFF2	++++++	++	+	Markholt et al. 2012[56]; Yu et al. 2020[37]
TEs	+	+	+	Guo et al. 2014[57]; Georgiou et al. 2009[58]; Smith et al. 2014[59]
LİNE1	+	+	+	Smith et al. 2014[59]; Luo et al. 2016[60]
MPF	+++	++	++	Assou et al. 2006[50]
CDC25A-CDC25B-CDC25C	++	++	++	Assou et al. 2006[50]
CDC1-CDC2	++	++	++	Assou et al. 2006[50]
CCNB1-CCNB2	++	++	++	Assou et al. 2006[50]
BUB1-BUBR1	++	++	++	Assou et al. 2006[50]
MAD2-MAD2L1	++	++	++	Assou et al. 2006[50]
CENP-A - CENP-E	++	++	++	Assou et al. 2006[50]
APC/C	+	+	+	Assou et al. 2006[50]
CDC20	+	+	+	Assou et al. 2006[50]
STAG3	+	+	+	Assou et al. 2006[50]
ZP1-ZP2-ZP3-ZP4	++	++	++	Assou et al. 2006[50]
BMP6	+	+	+	Assou et al. 2006[50]
FGFR2 (HDAC9,DNMT1, DNMT3B,H1FOO)	+	+	+	Assou et al. 2006[50]
CENPH	+	+	+	Assou et al. 2006[50]
ANAPC1, ANAPC10	+	+	+	Assou et al. 2006[50]
FBXO5	+	+	+	Assou et al. 2006[50]
Emi 1	+	+	++	Assou et al. 2006[50]
MOS	+	+	+	Assou et al. 2006[50]
SOCS7	+	++	+++++	Krebs and Hilton, 2000[61]; Assou et al. 2006[50]
Oogenesins	+	+	+	Dalbies-Tran et al. 2020[36]
Nlrp	+	+	+	Dalbies-Tran et al. 2020[36]
Khdc 1	+	+	+	Dalbies-Tran et al. 2020[36]
Ooep	+	+	+	Dalbies-Tran et al. 2020[36]
Nlrp5	+	+	++	Tong et al. 2000[62]
Nlrp14	+	+	++	Hamatani et al. 2004[63]

cAMP, CDC42, GDF-9, PTX3, ACSL, CYP19A1, BMP15, Caspase 9 and FAS[66].

The large number of oocyte-specific genes and the complex gene regulation that are involved in oocyte maturation, makes it difficult to plan the clinical use of genetic tests. Therefore, it is necessary to perform gene sequence analysis, as well as carrying out gene expression tests and evaluating methylation patterns. Thanks to NGS platforms, it is possible to perform extended panels or WES (Whole Exome Sequence) analysis. However, the important problem with these techniques is that some variations detected are not classified sufficiently. In the future, as more cases are reported and new studies are done, a clearer interpretation of the variations of unknown significance of these genes will emerge.

What does any of the apragrtaphs in the above section have to do with OMAS. Either tie it in or remouve it.

Definitions of Oocyte Maturation Abnormalities and Early Descriptions

Rudak et al.[67] reported four cases with OMAS including GV arrest, MI arrest and EFS,

Levran et al.[68] reported on OMAS in eight women with unexplained infertility including one patient with GV arrest, four with MI arrest and three women with MII arrest. OMAS was first used as a term in the literature by Hourvitz et al.[69], and included patients with EFS together with OMA in their series of seven women with repeated IVF failures. They achieved pregnancies in two women with genuine EFS (G-EFS) by IVM but failed to manage other causes of OMA.

Three months after Hourvitz publication, Beall et al.[4] published the first classification of oocyte maturation failure. They classified OMA into four types (Type I; GV arrest, Type II; MI arrest, Type III; MII arrest and Type IV; Mixed arrest).

Their publication was based on animal studies and several human case reports. Galvão et al.[70] studied 28 cases (9 cases with ROS and 19 cases with oocyte maturation arrest) with OMAS. The nine women with ROS underwent 24 IVM cycles. The IVM resulted in 5 healthy livebirths. The nineteen women with OMA underwent 25 IVM cycles. However, none of the 24 cycles resulted in fertilized 2PN oocytes after ICSI. In one patient a high quality embryo was transferred, but failed to result in a pregnacy? In this study, ROS was presented as one of the causes of OMAS.

Our group published a classification system combined with a series of the highest number of OMA cases at that point listed in the litterature which we termed the Hatirnaz and Dahan Classfication[71]. In that study FSH-hCG primed follicular phase IVM cycles were performed in all patients. In the Hatirnaz and Dahan classification system, GV arrest is accepted as OMA Type I, MI arrest is accepted as OMA Type II, MII arrest is accepted as OMA Type III, GV, MI arrest is accepted as OMA Type IV and Mixed Arrest (GV, MI and and MII) is accepted as Type V. Type IV arrest (GV-MI arrest) was added as a subtype of OMA since such patients were noted to occur. In this classification

and that Beall cases of ROS, G-EFS, and degenerated oocytes were excluded. IVM cycle outcomes were compared with their previous IVF cycle outcomes. Though an improved outcomes in term of the collection of MII oocytes and embryo development was observed, no pregnancy were achieved in this study group. Studies of *in vitro* activation of ovarian tissue in premature ovarian failure cases[72,73] lead to the idea of using transvaginal ovarian needle injury (TVOI)[74] in cases with OMAS. Our group perfomred a study on the comination of transvaginal ovarian needle injury together with dual stimulation IVM (letrozole priming and hCG triggering) and obtained the first succesful pregnancies and livebirths in women with type II and type V OMAS (Hatirnaz et al, 2020ASRM and Hatirnaz et al, 2021ESHRE abstracts).

Upon investigating patients with OMAs we noted that there were inter-cycle variability in their previous IVF attemts (ranginfrom 2-11 IVF cycles with different cycle managements). We also confront intracycle variability of cases during Duostim IVM (luteal phase stimulaton and follicular phase stimulation). Intracycle distribution of in vitro matured oocytes in DuoStim IVM cycles are presented in Table 2.

Types of Oocyte Maturation Abnormalities

Issues remain related to the two classification systems of OMA. Both classification systems described so far used oocyte maturation arrest by excluding other factors that cause OMAS[71,4].

Curently we are investingating whole genome exomic testing for women with OMAS to evaluate the underlying genetic pathologies. Potential etiopathogenesis of OMAS subtypes are depicted in Figure 2.

Gene expressions related to OMAS in animal and human species are presented in Table 3.

a. Dysmorphic and/or Degenerated Oocytes

Oocyte dysmorphism in assisted reproduction is not uncommon and can be observed either extracytoplasmic or intracytoplasmic manner. Indented oocytes may be persistent in some cases (Soussa et al., 2013) or may be seen as part of the apoptosis/degeneration process in follicular waves. One rare form of dysmorphic/degenerated oocytes is necroptosis[75,76].

b. Empty Follicle Syndrome (EFS)

Coulam et al.[77] reported on four women with five IVF attempts without retrieved oocytes and described this entity as EFS. Awadalla et al.[78] accepted EFS as technical failure rather than a syndrome which was felt to be related to stimulation error causing defects in final maturation resulting in an oocyte that cannot repsond to the hCG surge. Zreik et al.[79] studied 200 cycles of 35 women with EFS (single cycle with EFS n=27 and more than one IVF cycle with EFS n=8). They reported the incidence of EFS was 1.8% and the recurrence rate was 24% in 34-39 year old patients and 57% in women over 40 years of age, suggesting that EFS may be associated with decreased

Table 2. Intracycle variability of in vitro matured oocytes of OMAS cases (Data from ongoing, unpublished study by Hatirnaz S et al)

		Luteal phase stimulation and follicular phase stimulation oocytes of duostim IVM									
		Numb. Oocyte	Dys Deg	GV	MI	MII	IVM (Fertilized by ICSI)	PN	Embryo Develop.	Freezing	Type of OMAS
Case 1	Follicular	11	0	0	5	6	4	0	4	2	MI arrest
	Luteal	12	0	0	7	5	3	0	2	2	
Case 2	Follicular	9	4	1	4	0	0		0	0	Mixed arrest
	Luteal	9	0	4	2	2	2	0		0	
Case 3	Follicular	8	0	2	3	3	2	0	2	0	Mixed arrest
	Luteal	5	0	2	1	1	0	0		0	
Case4	Follicular	4	0	0	4	0	0	0	0	0	MI arrest
	Luteal	5	0	0	5	0	0	0		0	
Case 5	Follicular	12	0	0	11	1	0	0	0	0	EFS-OMA
	Luteal	7	0	4	3	0	0	0		0	
Case 6	Follicular	2	1	1	0	0	0	0	0	0	GV arrest
	Luteal	2	0	1	1	0	0	0		0	
Case 7	Follicular	2	0	1	1	0	0	0	0	0	GV arrest
	Luteal	2	0	1	1	0	0	0		0	
Case 8	Follicular	4	0	0	4	0	0	0	0	0	MI arrest
	Luteal	4	0	0	4	0	0	0		0	
Case 9	Follicular	2	0	0	0	2	2	0	2	0	Mixed arrest
	Luteal	5	0	3	0	2	1	1			
Case 10	Follicular	3	0	1	0	2	2	1	1	0	Mixed arrest
	Luteal	1	0	0	0	1	0	0		0	
Case 11	Follicular	8	0	3	0	5	3	1	2	0	Mixed arrest
	Luteal	3	0	1	0	2	2	2		0	
Case 12	Follicular	2	2	0	0	0	0	0	0	0	MI arrest
	Luteal	3	0	0	3	0	0	0		0	
Case 13	Follicular	7	0	1	0	6	2	2	2	0	Mixed arrest
	Luteal	7	0	4	0	3	2	0		2	
Case 14	Follicular	5	0	2	1	2	2	2	0	0	Mixed arrest
	Luteal	8	0	5	0	3	1	1		0	
Case 15	Follicular	4	0	2	2	0	0	0	0	0	Mixed arrest
	Luteal	3	0	0	3	0	0	0		0	
Case 16	Follicular	2	0	1	0	1	1	1	0	0	Mixed arrest
	Luteal	2	0	1	1	0	0	0		0	
Case 17	Follicular	2	0	1	0	1	1	1	0	0	GV-MI arrest
	Luteal	4	4	0	0	0	0	0		0	
Case 18	Follicular		2	2	1	0	0	2	0	0	Mixed arrest
	Luteal	9	2	4	1	2	0	2		0	
IVM: In vitro maturation, OMAS: Oocyte maturation abnormalities, EFS: Empty follicle syndrome											

ovarian reserve, oocyte potential, errors in stimulation or hCG triggering. Possibly as women age the number of LH receptors on the follicles decrease, resulting in a deminished responce to the LH surge (or hCG trigger) and an increase in EFS. However, Uygur et al.[80] reported a case of recurrent EFS in a young woman with normal ovarian reserve and hypothesized about altered folliculogenesis or early oocyte atresia as the cause of EFS in this case. Whether it is a technical artifact or G-EFS was discussed by Bastillo[81] in her review in 2003. She associated EFS with problems of oocyte aspiration without flushing and other problems of aspiration or as a result of a premature LH surge. However, reports of some recurrent cases arguies against the hypothesis of technical failures at the oocyte collection in all cases. Clearly, the cause of EFS is multifactorial. hCG dosing, inappropriate administration and bioavailability of hCG should also be investigated as causes of false EFS (F-EFS) cases.

Van Heusden et al.[82] sent a letter to the editor disucsing EFS and claimed that EFS was virtually nonexistent and not evidence based due to lack of metaanalysis However, Vutyavanich et al.[83] reported a case of G-EFS where they were able to identify immature oocytes in the filtrate of follicular aspirates which wer initialy missed by the embryologist. The prevalence of EFS

Figure 2. Schematic representation of etiopathogenetic mechanisms of OMAS

was studied by Mesen et al.[84] and found to occur in 0.016% of collection. They found 11 cases (2 G-EFS and 9 F-EFS) in 12 359 IVF cycles between 2004-2009 at there center. The estimated incidence of EFS ranges from 0.016-7% in the literature[85-87].

Baum et al.[86] reported in their study that EFS is more prevalent in older aged women with prolonged infertility and diminished ovarian reserve Yakovi et al.[88] was prospectively studied EFS in 95 women with between 2011 and 2015 and found four G-EFS cases with advanced maternal age (4.2%).

They concluded that G-EFS complicates infertile women with a low number of mature oocytes stimulated in their IVF cycles and classified it as two form of EFS. F-EFS related to hCG bioavailability and G-EFS[89,90].

EFS can be seen alone or a part of oocyte degeneration or maturation arrest In our OMAS series of patients, there are cases which were three times diagnosed as G-EFS. However, in their subsequent round of IVF with double dose HCG trigger, oocytes were retrieved and a pregnancy was obtained.

EFS can also be secondary to agonist triggering in antagonist IVF cycles. Deep luteolysis and a lack of repponce with an LH surge are causes of EFS[91].

Castillo et al.[92] retrospectively studied the incidence of 2034 donation cycles and 1433 IVF cycles EFS and reported EFS rate were 3.5% and 3.1% respectively.

Though statistically insignificant, EFS can be observed in agonist trigger cycles. Deepika et al.[93] studied 271 women affected by polycystic ovary syndrome (PCOS) with agonist triggering in GnRH-antagonist IVF cycles and found a 3.3% incidence of EFS.

In case studies dual trigger with GnRH analog and hCG triggering in GnRH-antagonist cycles with healthy livebirths were reported[94,95]. Blazquez et al.[96] studied 12.483 oocyte donation cycles and found 0.59% EFS cases in their study group and they found no difference in the gonadotropin stimulaton and triggering et al first achieved two livebirths by IVM in two women suffering from G-EFS[69]. Al-hussaini et al.[97] reported repeated immature oocyte retrieval in IVF cycles but failed to mature them *in vitro*[97]. In conclusion, EFS can be cathegorised as a subtype of OMAS and oocyte retrieval, oocyte maturation, clinical pregnancy and livebirths are possible following IVM in women suffering from EFS.

c. Oocyte maturation arrest (OMA)

c.1. GV Arrest (Type I OMA)

Meiotic resumption depends on meiotic competence and acquires some key steps including protein production, localization, phosphorilation and degradation[98,99]. Knockout mice studies and inhibitory drug use in animal studies enlighten meiotic arrest and resumptiom mechanisms but their impact on human OMA and resumption yet to be clarified. Other factors related with GV arrest were listed in Table 3.
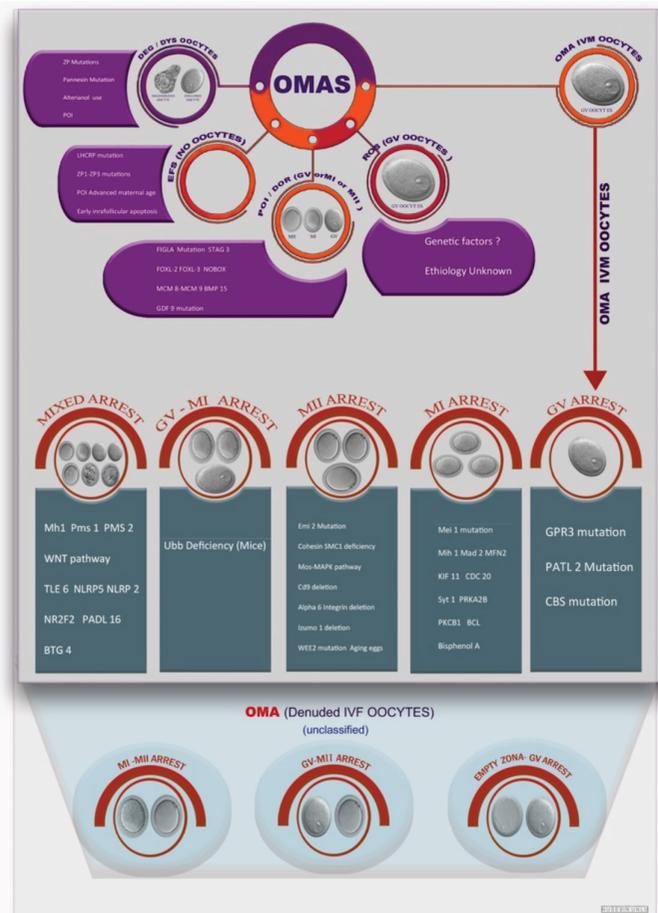
Table 3. Gene expressions (up regulation or down regulation) related to subtypes of OMAS in animal and human species

	Dys Deg	EFS	POI DOR	GV Arrest	MI Arrest	MII Arrest	GV-MI Arrest	Mixed Arrest	Ref
ZP1	+++	++	NA	NA	NA	NA	NA	NA	Chen et al.[100], Zhang et al., 2017[100];Cao et al, 2020[101]; Xu et al., 2020[102]; Sun, 2019[103]; Yang et al., 2017[104]; Luo et al., 2020[105]; Okutman et al., 2025[106]
ZP2	+++	++	NA	NA	NA	NA	NA	NA	Yang et al., 2017[104]; Luo et al., 2020[105]
ZP3	++	++	+/-	+/-	+/-	+/-	+/-	NA	Chen et al., Zhang et al., 2017[100,107]; Zhang et al., 2020[107]
ZP4	+	+	+/-	+/-	+/-	+/-	+/-	NA	
PNX1	++	+	NA	NA	NA	NA	NA	NA	Sang et al., 2019[108]
LHCGR	NA	+++	NA	NA	NA	NA	NA	NA	Chen et al., 2018[109];Yuan et al., 2017[110]
GPR3	NA	NA	NA	++	NA	NA	NA	NA	Mehlman, 2005[31]
PDE3A	NA	NA	NA	++	NA	NA	NA	NA	Masciarelli et al., 2004[111]
PATL2	NA	NA	NA	++	NA	NA	NA	NA	Maddirevula et al., 2017[112]; Chen et al., Zhang et al., 2017[100,107]; Huang et al., 2018[113]; Wu et al., 2019[114]
CBS	NA	NA	NA	++	NA	NA	NA	NA	Liang et al., 2007[11]
Mad2	NA	NA	NA	NA	+++++	NA	NA	NA	Madgwick and Jones., 2007[115]
MFN2	NA	NA	NA	NA	+++++	NA	NA	NA	Wang et al., 2020[116]
KIF11	NA	NA	NA	NA	+++	NA	NA	NA	Wan et al., 2018[117];Santella et al., 2018[118]
CDC20	NA	NA	NA	NA	++	+/-	+/-	NA	Yang et al., 2014[119];Sang et al., 2018[108]
Syt1	NA	NA	NA	NA	-----	NA	NA	NA	Zhu et al., 2012[120]; Zhang et al., 2010[121]
PRKAR2B	NA	NA	NA	NA	-----	NA	NA	NA	Yoon et al., 2018[122]
PKCB1	NA	NA	NA	NA	------	NA	NA	NA	Yi et al., 2009[123]
Bcl2110	NA	NA	NA	Overinjection	++++	NA*	NA	NA	Yoon et al., 2009[124]
TUBB8	NA	NA	NA	NA	++++++++	NA	NA	NA	Feng et al., 2016[52]; Feng et al., 2016[125]; Chen, Li et al., 2019[126]; Huang et al., 2017[51]; Wang et al., 2018[127]; Xiang et al., 2018[128]; Chen et al., 2019[126]
TRIP13	NA	NA	NA	NA	++	NA	NA	NA	Li and Schimenti., 2007[129]; Zhang et al., 2020[130]
Emi2	NA	NA	NA	NA	NA	++	NA	NA	Araki et al., 1996[131]
APC/C-PKC	NA	NA	NA	NA	NA	++	NA	NA	Lorca et al., 1993[132]
CamKII	NA	NA	NA	NA	NA	++	NA	NA	Lorca et al., 1993[132]
SMC1	NA	NA	NA	NA	NA	++	NA	NA	Hodges et al., 2005[133];Revenkova et al., 2004[134]
MOS-MAPK	NA	NA	NA	NA	NA	++	NA	NA	Inoue et al., 2007[135]
Erp1	NA	NA	NA	NA	NA	++	NA	NA	Inoue et al., 2007[135]
P90Rsk	NA	NA	NA	NA	NA	++	NA	NA	Maller et al., 2002[136]
CD9	NA	NA	NA	NA	NA	++	NA	NA	Kaji et al., 2000[137]; Bianchi et al., 2014[138]; Inoue and Sagata, 2005[139]
A6 Integrin	NA	NA	NA	NA	NA	++	NA	NA	
Izumo1	NA	NA	NA	NA	NA	++	NA	NA	

Table 3. Continued

	Dys Deg	EFS	POI DOR	GV Arrest	MI Arrest	MII Arrest	GV-MI Arrest	Mixed Arrest	Ref
WEE2 CDC2	NA	NA	NA	NA	NA	+++	NA	NA	Dai et al., 2019[140]; Sang et al., 2018[141]; Han and Conti, 2006[142]
WEE1B	NA	NA	NA	NA	NA	++	NA	NA	Kim et al., 2015[143];Zielinska et al., 2019[144]
Ubb Mlh1	NA	NA	NA	NA	NA	NA	++	NA	Ryu et al., 2008[145]; Lipkin et al., 2002[146]
Pms1	NA	NA	NA	NA	NA	NA	NA	++	Lipkin et al., 2002[146]
Pms2	NA	NA	NA	NA	NA	NA	NA	++	Lipkin et al.,2002[146]
BTG4	NA	NA	NA	NA	NA	NA	NA	++	Zheng et al., 2020[147]
WNT	NA	NA	NA	NA	NA	NA	NA	++	Paonessa et al., 2021[148];Assou et al., 2011[149]
NR2F2	NA	NA	NA	NA	NA	NA	NA	++	Paonessa et al., 2021[148]; Zhang et al., 2009[150]
TLE6	NA	NA	NA	NA	NA	NA	NA	++	Wang et al., 2018[151]; Mu et al., 2019[152]; Wang et al., 2018[151]
NLRP5	NA	NA	NA	NA	NA	NA	NA	++	
NLRP2	NA	NA	NA	NA	NA	NA	NA	++	
PAD16	NA	NA	NA	NA	NA	NA	NA	++	
FIGLA	NA	NA	++	NA	NA	NA	NA	NA	Zhao et al., 2008[153]
FOXL2 FOXO3	NA	NA	++	NA	NA	NA	NA	NA	Chatterjee et al., 2007[154];Wang et al., 2010[155]
MCM8	NA	NA	++	NA	NA	NA	NA	NA	Tenenbaum-Rakover et al., 2015[156];Al Asiri et al., 2015[157]
MCM9	NA	NA	++	NA	NA	NA	NA	NA	Wood-Trageser et al., 2014[158]; Fauchereau et al., 2016[159]
STAG3	NA	++ (Hatirnaz et al., ongoing study)	++	NA	NA	NA	NA	NA	Caburet et al., 2014[160]; Le Quesne Stabej et al., 2016[161]; He et al., 2018[162]
NOBOX	NA	NA	++	NA	NA	NA	NA	NA	Bouilly et al., 2011[163];Bouilly et al., 2015[164]
FSHR	NA	NA	++	NA	NA	NA	NA	NA	Masui and Markert, 1971[165]; Doherty et al., 2002[166]; Meduri et al., 2003[167]; Nakamura et al., 2008[168]
GDF9	NA	NA	++	NA	NA	NA	NA		Dixit et al., 2005[169]; França et al., 2018[170]
BMP15	NA	NA	++	NA	NA	NA	NA	NA	Di Pasquela et al., 2006[171], Di Pasquela et al., 2004[172]

c.2. MI Arrest (Type II OMA)

MI to MII transition is different from GV to MI transition wherein chromosomal condensation, spindle formation and chromosomal alignment on the equatorial plate happens before segregation of homologous chromosomes. Morphologically the transition of MI to MII can be noted with extrusion of the first polar body (PBI). Any factors blocking this transition to MII could cause MI arrest. If MI arrest is present alone, it is called Type II OMA by the Hatirnaz and Dahan classification system. MI arrest is observed in the absense of Mei1 and Mlh1 in mices, both have role in recombination during completion of meiosis[173]. The role of Mei1 in female infertility is not clear[174]. Meiotic spindle formation is crucial step in MI to MII transition. Other factors related with MI arrest are listed in Table 3.

Bisphenol A (BPA), a well known plastic material also used in laboratory materials was shown to damage spindle configuration and chromosomal alignment at the MI stage. BPA resulted in MI arrest in high doses in mouse oocytes[175].

Dietylstilbestrol (DES) leads to oocyte meiotic dysfunction and oocyte maturation arrest by impairing spindle formation and chromosomal malalignment in mouse oocytes[176].

A widely used chemotherapeutic drug, doxorubicin (DOX) was shown to arrest oocyte maturation by reducing PBI extrusion and by triggering early oocyte apoptosis[177].

c.3. MII Arrest (Type III OMA)

MII oocytes are accepted as mature morphologically and presumed to be fertilizizable. Fertilization is a complex process involving the transition from meiosis to mitosis and from oocyte to zygote. This process includes sperm egg binding, the release of corticle granules (also a measure of oocte maturation), Polar body II (PBII) extrusion and pronuclear formation[178]. However, normal aprearing MII oocytes may fail to form viable embryos and may present with fertilization failure, whcih could be caused by imaturity of the MII oocyte. Oocyte maturation is a continuous process and after the extrusion of the first polar body (PB1), should be completed in order for the oocyte to be capable of fertilization. This unique pathology is quite uncommon and presents as mixed OMAs and presents with fertilization failure (FF). The main difference between FF and MII arrest is that FF can be overcome in repeated cycles or ICSI while MII arrest is persistent. More collected data is needed to clearly differantiate this abnormality from FF. MII imuaturity is normaly present before fertilization and this is thought to be regulated by cytostatin factor (CSF). MII maturation arrest may be caused by dysregulation in levels of cyclin B. Meng et al.[179] studied the role of Cyclin B (Ccnb3) on MII arrest in mouse oocytes and found that gradual decreases in Ccnb3 levels is required for meiotic maturation to ocur.

Ccnb3 participates in the separation of homologous chromosomes during the first meiotic process by forming a complex with Cyclin dependent kinase (CDK1).

In mammals, MPF play an important role in oocyte maturation[180]. MPF concentration increases during oocyte maturation and reaches maximum level at MII stage and than mature oocyte is arrested at this phase. This arrest stage is exclusive for oocytes and is regulated by the cytostatic factor (CSF). This factor stabilizes the MPF, keeps chromosomes condensed, therefore, allows avoiding a second round of DNA replication during transition from MI to MII[181,182].

For the successful in vivo or in vitro fertilization, both oocyte and sperm cells need to have some essential elements. For example phospholipase C zeta protein in the sperm cell is essential for the reactivation of the oocyte arrested at MII stage through the induction of intracellular calcium oscillation.

However the oocyte activation failure is not the only reason of the fertilization failure. Sperm nuclear descondensation failure and premature chromosome condensation (PCC) have been showed as reasonable events in fertilization failure studies (Sedo CA, 2015). Of course both nuclear and cytoplasmic maturation of the oocyte have important effects on the fertilization rate. Other factors related with MII arrest are listed in Table 3.

c.4. GV and MI Arrest (Type IV OMA) May Also Include Some MIIs

In this subset of OMA, oocytes mature to the MI and GV stages and were found to be arrested during the meiotic resumption process. Beall et al.[4] included this group in mixed arrest OMA. However, in the Hatirnaz and Dahan system we classified this as a seperate group from Mixed OMA where GV, and MI oocytes were observed together[71]. Rarely, imature MII oocytes are also noted in this group, which fail fertilization with ICSI. Many studies in animal models revealed that mixed oocyte maturation arrest are related to MutL homolog 3 (Mlh3) and Ubiquitin b (Ubb) proteins[145,146].

Mlh3 plays a dual role in DNA mismatch repair and meiosis. Mlh3–/–oocytes fail to complete meiosis I after fertilization[146]. Deficiencies of Ubb, a member of the ubiquitin family results in infertility and GV and MI arrest in mices[145]. Ubb geneis essential for postnatal gonadal maturations and fertility. Ubb_/_ oocytes do not proceed beyond metaphase I. Loss of one Ubb family member may be compensated by the expression of other Ubb family members (Uba 52, Uba80 though this compensation is not enough to sucessfully compete the meiotic resumption)[145].

c.5. Mixed Arrest (Type V OMA)

This is the most commonly encountered subtype of OMA and has the highest chance of ET and clinical pregnancy[71] arnt rates of pregnacy rare how wer they achieved you need to disucss this. In this subtype, only a small proportion of collected oocytes (rougly less than 25%) are MII and most others are immature, either GV or MI in repeated cycles. Mhl3 belongs to a family including Mlh1, Pms1 and Pms2. Deficiency of Mhl in mice result in MI and MII arrest[146].

In this subtype of OMA, compensatory mechanisms hypothetised to play a role in maturing oocytes but their maturation rate and clinical significance are not well known. Zygotic cleavage failure (ZCF) is also commonly seen in this subtype. Homozygous mutations in BTG4 (B cell translocation gene 4) is reported to cause ZCF[147].

MII oocytes complete their maturation mostly improperly thus embryonic development may be arrested at the PN stage or at the cleavage stage. Most developed embryos are observed as bad quality embryos. Embryos can be transferred in this subtype. Early embryonic arrest is common in OMA type V. In this subtype MII oocytes are immature and FF, PN arrest and bad quality nembryo development are the consequences of treatment. Letrozol IVM together with TVOI improved the maturation and fertilization and pregnancy was achieved. This is the form where zygotic cleavage failure can happen and sperm related factors may also have impact but all case with previous attemts had failed to achieve pregnancy and in most of the case fertilization and cleavage of embryos.

Other factors related with mixed arrest are listed in Table 3.

d. Premature Ovarian Failure (POF)/Premature Ovarian Insufficiency (POI)

The spectrum of OMAS frequently manifested in IVF cycles of women with POI[183]. POI is characterized by oligo/amenorrea and high serum gonadotropin levels, POI affects 1-3% of women before the age of 40[183]. POI is a heterogenous disorder both phenotypically and genetically[184]. Novel candidate genes were reported in POI[185,186]. More than one genetic variation was reported in one woman with POI[187].

Menstrual Dynamics in women with POI is abnormal and there is a failure of development of regular follicular waves in POI cases[188]. Both follicle recruitment and follicular apoptosis frequencies are diminished in POI. Oocyte collected in POI may range from EFS, dysmorphic/degenerated oocytes to MII oocytes which can be normaly functioning (ongoing study). Other factors related with POI are listed in Table 3.

e. Resistant ovary syndrome (ROS)

ROS is a rare entity where there is ovarian resistance to both endogenous or exogenous gonadotropins, elevated FSH and LH are observed, although AMH levels and antral follicle counts are in the normal range[70].

Persistent immature oocytes are often obtained in cases with ROS. Thus ROS is evaluated as part of the OMAS spectrum. The etiology of this condition is uncertain but immunological and genetic factors[70] may have role in occurence.FSHR mutations play role in the pathogenesis of ROS.Heterozygous mutation of FSHR: c.182T>A (p.Ile61Asn) and c.2062C>A (p.Pro688Thr) was found pathogenic for ROS in the siblings of a chinese family[189]. IVM is the selected mode of treatment to overcome this clinical entity. Livebirths of babies from IVM of ROS was reported[190-192].

f. Unclassified

f.1. Empty Zona-GV Arrest

f.2. GV-MII Arrest

f.3. MI and MII Arrest

So far we had two cases with this subtype and both cases were seen long after our classification system was published. In the first case, three IVF attempts were performed. Collected oocytes in the first attempt consisted of 16 MI and 1 MII with 1 fertilization and ETof day 3 8 cell grade II embryo without pregnancy. In the second IVF attempt 4 MI oocytes whcih failed in-vitro maturation were obtained. In the third IVF attempt 16 MI oocytes and1 MII oocyte was retrieved and the MII developed into an embryo and was vitrified at the cleavage stage for pooling. Due to financial reasons, the frozen-thawed ET was performed without a pregnancy occuring. This patient stoped care.

The second case had four previous IVF cycles. The patient had 6 MI and 1MII oocyte in her first IVF cycle with fertilization of the MII, 8 cell grade I ET was performed on day 3 of embryo development and a pregnancy with a biochemical loss occured. Whole genome exomic analysis performed and TUBB8 (c.535G>A) mutation was determined in her genetic testing. This mutation is related with MI arrest in OMAS. Her second attempt yielded 6 MI and 1 MII oocyes with fertilization failure with ICSI. The third IVF attemt yielded 4 MI and 4 MII oocytes, three 2PN fertilization developed and only one 7 cell grade III embryo transfer was performed without a pregnancy. The fourth IVF attempt resulted in the collection of 6 MI and 1 MII oocytes with fertilization but ET cancelled due to arrested embryos only whihc had degenerated by day 3.

Treatment Modalities of Oocyte Maturation Abnormalities

Treatment options other than oocyte donation for OMAS are below;

1. Organelle Transfer

Until recently, the only recommended treatment for women with OMAS was oocyte donation (OD). In the last two decades, the use of somatic cell nuclear transfer, pronuclear transfer and polar body transfer have been used and succesful pregnancies and livebirths have been reported both in humans and animal species[193].

Pronuclear transfer of oocytes from OMAS patient to subzonal area of enucleated donor oocytes resulted in blastocyst development and healthy livebirth which is the demonstration of the role of oocyte cytoplasm on embryogenesis and implantation[193]. Nuclear genetic codes were matching with mother but mitochondrial DNA were coming from donor oocytes. The use of this tehchnique may be beneficial in women with mitochondrial DNA related diseases However the application of this method is ethically questioned.

Germinal vesicle transfer is the removal of germinal vesicle from GV oocyte and reimplantation of GV into the subzonal perivitelline area of donor oocyte[194]. GV transfer gives opportunity to investigate the interrelation of nucleus and cytoplasm in the oocyte maturation process. GV removal from the cytoplasm is a less invasive procedure as compared to chromosomal removal from mature oocytes and GV transferred mouse oocytes have reached blastocyst stage[195]. GV transfer into discarded human oocytes revealed normal PBI extrusion and MII transition[196]. However GV transfer carries the risk of mitochondrial DNA heteroplasmy[197]. Moffa et al.[198] reported the use of GV transfer between fresh and frozen mouse oocytes and GV transfer from frozen immature oocytes produced chromosomally normal oocytes. Nuclear transfer in primates were studied and challenged because of molecular requirements and for nonhuman primates, nuclear transfer was reported unsuccesfully[199].

There is only one rhesus monkey birth after embryonic cell nuclear transfer[200].

Pronuclear transfer embryos of nonhuman primates had more spindle defects and had higher aneuploidy rate[201]. GV transfer can be a unique option for women having meiotically arrested oocytes or ovarian resistance to gonadotropins[194].

For all above mentioned treatments, the availability of IVM setup in IVF laboratories is mandatory.

IVM for OMAS

Until the most recent commitee opinion from the ASRM[202]. the use of IVM in humans has drasticaly declined because of the previous ASRM opinion that IVM is experimental in the era of agonist triggering for PCOS[203]. Tremendous efforts have been devoted to the development of culture media for better clinical outcomes in IVF. However, there has been much less effort put into the development and advancement of IVM culture medias. Capacitation IVM(CAPA IVM) Recently, a novel approach, CAPA IVM was introduced with favorable oocyte maturation in IVM cycles[204-206]. In this treatment, immature oocytes with cumulus complexes were put in a prematuration culture medium including C type natriuretic peptide for up to 24 hours before standart IVM culture media use. CAPA IVM was studied in minimally stimulated mice and results showed that both cumulus function and oocyte quality were improved[207]. In a clinical trial conducted by Vuong et al.[208], 40 women with CAPA IVM were compared with 40 women with standart IVM and they reported significantly higher clinical pregnancy rates (63.2%, 38.5%, respectively). Although this is an interesting result in a small study, the role of CAPA IVM in OMAs is unclear and not studied yet. There is no evidence of the use of CAPA IVM in women with OMAS.

Coenzyme Q10 supplementation in IVM culture media was shown to increase maturation rates in human oocytes and decrased aneuploidy rates in the oocytes of elderly women[209]. There is no evidence of teh use of Coenzyne Q10 as a supplement in IVM cultur media for the maturation of oocytes from women with OMAS.

A more advanced IVM culture media in the future may improve oocyte maturation in IVM cycles. The addition of autocrine and paracrine factors were reported to significantly influence the embryonic development in animal models[73] of IVM. While brain derived neurotropic factor, colony stimulating factor (CSF), granulocyte macrophage CSF, epidermal growth factor, artemin and insulin-like growth factor increased the blastocyst rate 2.5 fold, growth hormone increased the blastocyst rate two folds[73]. Whether to use these add ons in IVM culture media for OMA has yet to be clarified and studies are needed.

Putrescine supplementation in IVM culture media of elderly mouse oocytes yielded better quality blastocyst development[210,211]. LH induces a temporary rise of ornithine decarboxylase (ODC) activity and its enzymatic product, putrescine in mamalian ovaries during the ovulation and the implantation period[212]. Periovulatory rise of putrescine in mouse ovaries resulted in more blastocyst development, less embryonic loss and more livebirths[210]. Human use of putrescine may improve periovulatory diminished ODC activity and targets oocyte maturation[213]. Putrescine use, if alloved for human studies may help to improve oocyte maturation in IVM cycles and may be beneficial for OMAS in future.

IVM cycles have demonstrated promising results in women with G-EFS and ROS[69,70].

FSH-hCG priming IVM FSH-hCG priming IVM in women with intrinsic OMA resulted in a slight improvement in maturation however, no pregnancy was achieved in these cases[214]. Letrozole priming IVM was reported to have favorable outcomes in PCOS and cancerphobic women[214,215] without maturation arrest. The use of letrozole for OMA has been investigated by our group.

Letrozole is an aromatase inhibitor, which increases androgen levels in the ovary and triggers endogenous FSH secretion. Hte increased intra follicular androgen levels will also increase FSh receptors and ltalamtely LH receptors. By this mechanism, letrozole stimulates follicular and oocyte development[216]. Letrozole primed IVM was performed by our group in 25 women with OMAS and the first two healthy livebirths were achieved by this treatment modality (Hatirnaz et al., Ongoing study).

DuoStim IVM was selected for almost all cases to obtain more oocytes and to have more embryos to transfer. Duostim IVM also enabled us to evaluate the oocytes yielded in follicular and luteal phase and to determine the intracycle variability of oocytes. The clinical and laboratory outcomes of treatment modalities used and attempted in OMAS cases are depicted in Table 4.

In vitro activation of primordial follicles (IVA). Patients with diminished ovarian reserve and with POI commonly present with OMAS. Therefore, IVA by disrupting the hipposignaling pathway and Akt stimulation may be an option for treatment. The hypothesis of this approach was inspired from ovarian tissue injuries (wedge resection or drilling) in women with PCOS[73,217]. Grafting and reimplantation of ovarian cortical slices produced rapid follicle development and Kawamura et al.[72] reported first livebirth with this method in an women with POI. Drug free IVA of diminished ovarian reserve patients was studied by Kawamura et al.[72] and 9 out of 11 women with DOR responded well to the IVA with 68.7% fertilization and 56.9% high quality embryo development repoorted with one livebirth and two ongoing pregnancies occuring. IVA has not been studied in women with OMAS and there is no evidence fort he efficacy of IVA in OMAS.

Transvaginal ovarian needle injury (TVOI) may have similar action with drug free IVA on the ovaries and need to be evaluated in women with POI or DOR. TVOI was studied in women with PCOS[74] but not studied alone in cases with OMAS. In our ongoing study, we use TVOI as to trigger the primordial follicle pool and follicular and oocyte activation but in our protocol TVOI is added to Duostim IVM and we can not prove that TVOI alone is a good option for OMAS. An interesting finding is that laparoscopic ovarian tissue stripping, a similarly damaging procedure may overcome ROS[218] in one study.

There are various causes and mechanisms of fertilization failure. Some of these have been shown to benefit from piezoelectric application.

Piezoelectricty was introduced to be a valuable option in patients with fertilization failure[140]. The electromagnetic field created by applying electric current increases the number of pores and calcium conductivity in the cell membrane by enabling the movement of proteins. This situation increases the calcium concentration in the cell[219].

This high concentration of calcium triggers oocyte fertilization. Fertilization and pregnancies have been reported especially in cases of unspecified fertilization failure cases or in cases with spermatogenic disorders (structural disorders such as globozoospermia)[220,221].

There is currently no evidence of the use of piezoelectricity in women with OMAS but it could be studied to trigger cytoplasmic maturation in OMAS.

Immature oocyte vitrification before IVM was found slightly increased high quality embryo rates[222]. Immature oocyte vitrificiation can be used to store oocytes for future studies and for future treatment modalited developed. Similar experiment was performed by Molina et al.[223] and they reported promising outcomes. The rationale behind this is the rapid transmembrane ionic changes which may trigger cytoplasmic maturation and thus can be used in women suffering from OMAS. There is currently no evidence for the use of vitrification of oocytes from OMAS.We tried this in two cases after their permission and vitrified and thaved the immature oocytes but failed to mature oocytes by this modality.

Before concluding the review, we would like to present some future perspectives related to OMAS:

1. Bypassing OMAS and offering OD as the firstline treatment should be rethought by the clinicians.

2. Although promising results reported, organele transfers have some limitations, either ethical or genetical.

3. Succesfull treatment of EFS and ROS and some OMAS by IVM is possible with clinical pregnancies and healthy livebirths.

4. A new classfication system of OMAS including degenerated oocytes, dysmorphic oocytes, G-EFS, POI and ROS should be considered in future.

5. EFS is neither a syndrome nor empty and this pathology should be redefined and included into OMAS as subtype which will clear the confusions.

6. Type V OMA (Mixed arrest) has genetic roots with bodily compensatory mechanisms and can be managed by TVOI DuoStim IVM with letrozole priming.

7. For those women with genetic factors, future studies may reveal production of defective proteins and adding these proteins in IVM culture media may overcome arrested meiotic resumption, especially MI arrest.

8. Thorough investigation of OMAS in fact has great impact on the understanding of meiotic resumption and oocyte maturation and understanding the mechanisms may postpone menopouse and may open a new field of contraception. Besides, these developments may control the abnormal apoptotic process that led to OMAS.

Table 4. Clinical and laboratory outcomes of treatment modalities of OMA subtypes

	OMA / Dysmorphic Degenerated	OMA /G-EFS	OMA Type I(GV)	OMA Type II(MI)	OMA Type III(MII)	OMA Type IV(GV-MI)	OMA Type V(Mixt)	OMA / POI	OMA / ROS
FSH-hCG IVM	+/-	+	+/-	-	-	+/-	+	+/-	+
Duostim IVM*	+	+	+/-	+/-	?	+/-	+++	+/-	+
CAPA IVM	?	+	?	?	?	?	++?	?	+
Spindle transfer	-	-	-	+	?	+/-	-	-	-
Nuclear transfer	-	-	+	+	?	+/-	-	-	-
PB I transfer	-	-	-	+	?	+/-	-	-	-
PB II transfer	-	-		+	?		-	-	-
Coenzyme Q 10	?	?	?	?	?	?	++?	?	?
Putrescine	?	?	?	?	?	?	?	?	?
Oocyte maturation	+/-	+	+/-	+/-**	-	+/-	+	+/-	+
Fertilization by ICSI	+/-	+	+/-	+/-	-	+/-	+	+/-	+
Embryonic development	+/-	+	+/-	+/-	-	+/-	+	+/-	+
Embryo transfer	+/-	+	+/-	+/-	-	+/-	+	+/-	+
Pregnancy	None	+	-	+/-	-	-	+	+	+
Livebirth	None	+	-	+/-	-	-	+	+	+
Embryo freezing	-	+	-	+	-	-	+	+	+
IVM: In vitro maturation, OMAS: Oocyte maturation abnormalities, ROS: Resistant ovary syndrome, POI: Premature ovarian insufficiency									

9. Clinical protocols using physiological mechanisms, ovarian tissue trauma by TVOI or drug free IVA and mechanisms of action of letrozole (local androgenic effect, endocrine and paracrine effect and endogenous FSH release) together with advanced in vitro culture media should be studied. A study of TVOI DuoStim IVM with letrozole priming conducted by our group is ongoing and preliminary results are promising.

10. Add on's for IVM culture media including CAPA IVM, Coenzyme Q-10 and putrescine should be studied in OMAS both in human and animal species.

11. Since immature oocyte freezing is reliable, women with OMAS should be offered for oocyte freezing because of future developments may overcome their pathologies. Some oocytes, with the written permission of patients should be frozen for electronmicroscopic evaluations.

Conclusion

Complete oocyte maturation has many steps including follicular and granulosa maturation, zona pellucida maturation, nuclear maturation, cytoplasmic maturation, genetic maturation and epigenetic maturation. Among these processes, cytoplasmic maturation is the most important step. Until last decade, animal studies led the human OMAS but datas on human OMAS accumulated and factors related to human OMAS become much clear though there are a lot to be done. Present data shows that OMAS are a spectrum and there are intercycle and intracycle variabilities which may be attributed to changing dynamics of apoptosis. Some genetic pathologies have certain impact on meiotic resumption while other genetic factors may be compensated by the other genes of the same family. In this review study, OMAS were classified and extensively evaluatedand possible treatment options under the light of cuurent information, present literature and ongoing studies. Either genetic studies or IVM studies that will be handled in the future will led more informations to be reached and may make it possible to obtain pregnancies.

Ethics

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: Ş.H., E.S.H., A.E.K., K.H., C.S.Ç., Ö.S., N.D.G., C.D., V.B., S.T., M.D., Design: Ş.H., E.S.H., A.E.K., K.H., C.S.Ç., Ö.S., N.D.G., C.D., V.B., S.T., M.D., Data Collection or Processing: Ş.H., E.S.H., A.E.K., K.H., C.S.Ç., Ö.S., N.D.G., C.D., V.B., S.T., M.D., Analysis or Interpretation: Ş.H., E.S.H., A.E.K., K.H., C.S.Ç., Ö.S., N.D.G., C.D., V.B., S.T., M.D., Literature Search: Ş.H., E.S.H., A.E.K., K.H., C.S.Ç., Ö.S., N.D.G., C.D., V.B., S.T., M.D., Writing: Ş.H., E.S.H., A.E.K., K.H., C.S.Ç., Ö.S., N.D.G., C.D., V.B., S.T., M.D.

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