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WEE2 Mutations as a Cause of Complete Fertilization Failure (CFF) When it is the Female Factor Responsible for CFF- A Short Communication

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Abstract

Normally following in vitro fertilization(IVF), one comes across 1-4% of patients with complete fertilization failure(CFF), which usually can be overcome by shifting to intracytoplasmic sperm injection(ICSI).We have tried to explain the factors responsible for normal fertilization and earlier we had shown how calcium ionophores could be used to activate oocytes when oocyte activation was a problem. But still despite ICSI in some cases of unexplained fertility one cannot pinpoint the cause of FF. Here we have illustrated the role of WEE2 gene found essential in mammals for oocyte activation in preovulatory follicles whose mutations might explain the occurrence of CFF in women with unexplained infertility.

Keywords: CFF; IVF; ICSI; Unexplained infertility; WEE2 gene; WEE2 gene mutations

Abbreviatations: CFF: Complete Fertilization Failure; IVF: In Vitro Fertilization; ICSI: Intracytoplasmic Sperm Injection; ART: Artificial Reproductive Technology

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For fertilizaton to occur, a complex steps of processes occur like the spermatozoa binding to the zona pellucida (ZP), and must go through an acrosome reaction, then invade the ZP, fuse with the oolemma, activate the oocyte and develop pronuclei (PN) [1]. Basically, it is the development of a diploid zygote following interaction as well as fusion of the 2 haploid gametes that stimulates a cascade of processes that are necessary for the formation of a zygote and pregnancy to occur [2-5]. There are 2 parts of the fertilization i) the fusion of the gametes and ii) the activation of oocyte. Egg activation includes calcium oscillation, cortical granule exocytosis, and formation of the second polar body (2PB) and 2 pronuclei (PN) [6-8], that points that once fertilization of oocytes is finished, oocytes have finished meiosis II and would get into the interphase of mitosis [9]. As far as artificial reproductive technology [ART] is concerned complete fertilization failure by definition is all of the collected mature oocytes fail to develop PN within 15-18h of insemination [10,11]. Complete fertilization failure (CFF) is one of the reasons for female infertility. The clinical incidence of FF, particularly CFF with nonfertilized embryos is 1-4% in *in vitro* fertilization (IVF), and 1.4% in intracytoplasmic sperm injection (ICSI) [12,13].

Routinely during *in vitro* fertilization (IVF), FF occurs mainly at the time of sperm/oocyte binding as well as fusion [14-16], yet the ZP and oolemma barriers may be surpassed with the utilization of intracytoplasmic injection (ICSI) [17]. But FF following ICSI continues to remain a problem. CFF following ICSI, in case when minimum of 3 or> mature oocytes are present, takes place in 1-5% of ICSI cycles [18,19]. Genetic cause was thought of specially in cases with recurrent CFF or poor fertilization following ICSI. Earlier work demonstrated that ICSI reduced the rate of CFF with unexplained infertility, still occasional patients do present with CFF [20]. Earlier literature has pointed that the mutations of sperm activation factors gene PLCZ1, that results in great abnormal Ca^{2+} transients in oocyte, might result in FF

following ICS [21]. But the oocytes-associated factors leading to FF are mostly not found in humans. TLE6 has been correlated with the phenotype of FF [22] and recently it was documented that homozygous mutations in WEE2 in a recessive inheritance pattern were detected in 4 women with infertility presenting with CFF [23]. WEE2 is an oocytes-specific protein tyrosine kinase which phosphorylates as well as inhibits CDC2 and works as a crucial controller of meiosis at the time of prophase I and metaphase II [24] that gets encoded by the WEE2 gene. An earlier study revealed that WEE2 is expressed only in oocytes and attain s the maximum amounts in preovulatory follicles following collection at the time of folliculogenesis [25].

It seemed to be from maternal origin that remains conserved between variety of species. Different mammalian species study like in mouse, cat and pig it was shown that it was required for GV stage quietening. It is needed for metaphase II exit at the time of egg activation by phosphorylation of CDC2 to aid in PN development. Further it is needed to sustain germinal vesicle stage arrest in oocytes [26-29]. In mouse oocytes, if Wee2 was downregulating utilizing morpholino oligonucleotide it resulted in prevention of PN generation during fertilization [9].The mutations rate in WEE2 is not understood ,and if any other kind of mutation exists or is present regarding the presence of any other phenotype warrants more evaluation.

Thus Dai et al. [16] Evaluated 24 Chinese women undergoing ART, having recurrent FF or poor fertilization following ICSI. These women had a whole-exome sequencing as well as candidate mutations were confirmed by Sanger sequencing. Single cell reverse transcription was utilized to forecast the effect of missense mutations on secondary protein structure. To evaluate the protein amounts of WEE2 and phosphorylated CDC2 utilizing Immunofluorescence. Biallelic mutations in WEE2 were observed in 5/24 (20.8%) Chinese women with FF or poor fertilization. Of these subjects a novel splice-site mutation, 2 novel missense mutations as well as earlier documented frame-shift mutation were observed. Splicing mutations c.1136-2A>G of WEE2 led to changes in the reading frame and added a premature stop codon (p. Gly 379Glu fs*6/p.Asp380Leufs*39).The missense mutationsc. 585G>C (p.Lys195 Asn) and c.1228C>T (p.Arg410Trp) developed clear alterations in secondary protein structures. By immunostaining it was shown that mutated WEE2 caused a loss of phosphorylated CDC2. Slight differences were seen in phenotypes of women who carried WEE2 mutation, differing from FF to poor fertilization. Thus concluding that novel mutations in the known causative gene WEE2 were detected in 5/24 women with FF or poor fertilization, pointed to a high prevalence of WEE2 mutations in Chinese women who faced FF or poor fertilization [30].

Zhou et al. [30], tried to find if any variations in the WEE2 (WEE1 homolog 2, alias WEE1B) gene ,that has been understood to work in the generation of PN, result in FF.90 Infertile women presenting with recurrent cycles of PN generation failure going through IVF and/or ICSI therapy as well as 200 fertile controls had genomic DNA extraction from the peripheral blood .The whole exons of WEE2 were amplified utilizing polymerase chain reaction (PCR) and further Sanger Sequencing. 5 patients were isolated who were subjected to homozygous variants of WEE2: case1(belonging to a consanguineous family) with homozygous frameshift variant: c.293_294insCTGAGACACCAGCCCAACC (p.Pro98ProfsX2); Case 2 with homozygous missense variant:c.1576T>G(p.Tyr526Asp); and 3 cases with compound-hetrozygous variants: case 3: c.991 C>A (p.His331Asn) and c.1304_1307delCCAA (p.Thr 4 35 Met fsX31)case 4:c.341_342del AA (p.Lys 114Asn fsX20) and c.864G>C (from case 4 that has been documented earlier as rare single nucleotide polymorphisms(SNPs),the other 6 variants were novel and forecasted by software to be harmful. Parental genotypes of case1 and case2 pointed that the homozygous variants were inherited in an autosomal recessive way. All of the variants found were not there in the control cohort. Thus concluding that novel variants identified in WEE2, that is autosomal recessive inherited, might be associated with repeated PN generation failure and female infertility [31].

Conclusion

Earlier we had reviewed how Calcium Ionophores might be utilized for Artificially Activating Oocyte in Cases of Persistent Fertilization failure Despite ICSI [32]. Thus, concluding in cases of CFF in women despite ICSI one should try to rule out WEE2 mutation and see if Calcium Ionophores for Artificially Activating Oocyte helps in these Cases of Persistent Fertilization failure.

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