

Total fertilization failure with in vitro fertilization-intracytoplasmic sperm injection related to *WEE2* mutation highlights emerging importance of genetic causes of in vitro fertilization failure

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Objective: To report a unique case of total fertilization failure (TFF) after in vitro fertilization with intracytoplasmic sperm injection related to homozygous *WEE2* gene mutation and summarize the current literature and management of TFF.

Design: Case report.

Setting: Academic fertility center.

Patient(s): A 25-year-old woman and her 35-year-old partner with a history of near-complete fertilization failure after 2 cycles of in vitro fertilization/intracytoplasmic sperm injection.

Intervention(s): Consultation with medical and commercial genetic testing for *WEE2*, *PLCZ1*, and *TLE6*.

Main Outcome Measure(s): Oocyte fertilization.

Result(s): The patient was homozygous for *WEE2* pathogenic variant impacting oocyte activation and resulting in infertility.

Conclusion(s): In the setting of TFF, early consideration should be given to genetic testing to assist couples in clinical decision-making and help limit the financial and emotional burden associated with unsuccessful fertility intervention. (Fertil Steril Rep® 2022; ■: ■–■.

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Key Words: Total fertilization failure, *WEE2* gene mutation, IVF-ICSI, genetic causes of IVF failure

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Total fertilization failure (TFF) refers to the complete lack of normal fertilization of all mature oocytes in an in vitro fertilization (IVF) cycle. Normal fertiliza-

tion is considered to have occurred when a fertilized oocyte extrudes a second polar body and subsequently forms 2 pronuclei (2PN); fertilization failure is diagnosed when either or

both of these events fail to occur (1). It is an uncommon and poorly understood phenomenon historically reported to occur in approximately 5%–10% of IVF cycles with more recent data suggesting TFF in 5% of IVF and 3%–4% of intracytoplasmic sperm injection (ICSI) cycles (1, 6, 7) (2–4). In several studies, TFF has been linked to oocyte activation deficiency (OAD) related to mutations in *PLCZ1* gene in men and *TLE6*, *WEE2*, *NLRP5*, *CD20*, *TUBB8*, and *PATL2* genes in women (1, 2, 5–7). Additionally, recent

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publications reported a newly identified link between TFF/OAD and *ACTL9* mutation in men (8).

In this report, we outline the case of a 25-year-old woman with polycystic ovary syndrome and a 35-year-old man with bilateral grade I varicoceles and borderline elevated sperm deoxyribonucleic acid (DNA) fragmentation who presented with a history of near-complete fertilization failure after ICSI of 42 oocytes over 2 IVF cycles. The cause of this patient's infertility was ultimately determined to be because of a homozygous mutation of the *WEE2* gene, the function of which is essential for normal oocyte maturation and fertilization (2, 6, 9). This is a rare cause of infertility with only a handful of similar cases reported (2, 6, 9). Given the significant financial and emotional burden experienced by patients with infertility and unsuccessful treatment attempts, we present this case and review the current literature on this topic to discuss and inform clinical guidance for the management of similar cases (10, 11).

MATERIALS AND METHODS

Ethical Considerations

This study was reviewed by the University of Michigan Institutional Review Board under study ID HUM00199028 and determined to fall under "Not regulated" status because it does not fit the definition of human subject's research. Informed consent was obtained from the patient before manuscript preparation.

Subject and Clinical Findings

The patient was a 25-year-old G0P0 woman who presented with her partner for a second opinion after 2 failed IVF/ICSI cycles at an outside clinic. She and her partner are a noncon-sanguineous Middle Eastern couple and, at time of presentation, had been attempting pregnancy for 3 years. Prior fertility evaluation included hysterosalpingogram, endometrial biopsy, and laboratory evaluation. Her past medical history was significant for familial lipomatosis, polycystic ovary syndrome, endometritis treated with doxycycline, and uterine polyp resected via hysteroscopic polypectomy. Her partner was 35 years old at time of presentation and had no reported paternity. He denied issues with erections or ejaculation and had previously undergone urology evaluation, semen analysis, and sperm DNA fragmentation testing. Urology evaluation revealed bilateral grade I varicoceles, which were subsequently surgically corrected. Semen analysis was significant for abnormal morphology of 0 (normal range, >4%) with 5% morphology on repeat semen analysis, and DNA fragmentation testing revealed a DNA fragmentation index of 25% and oxidative stress adduct of 11.4 (normal range, <3.8). The couple completed 7 cycles of letrozole, including 1 cycle with intrauterine insemination without pregnancy before moving to IVF. They completed 2 IVF/ICSI cycles with an antagonist protocol. In the first cycle, 26 oocytes were retrieved, and 25 were mature and underwent ICSI. One zygote with 2PN was observed after ICSI at the initial 16-hour fertilization check; however, on later evaluation at 88 hours, it appeared to be an abnormal zygote with 3

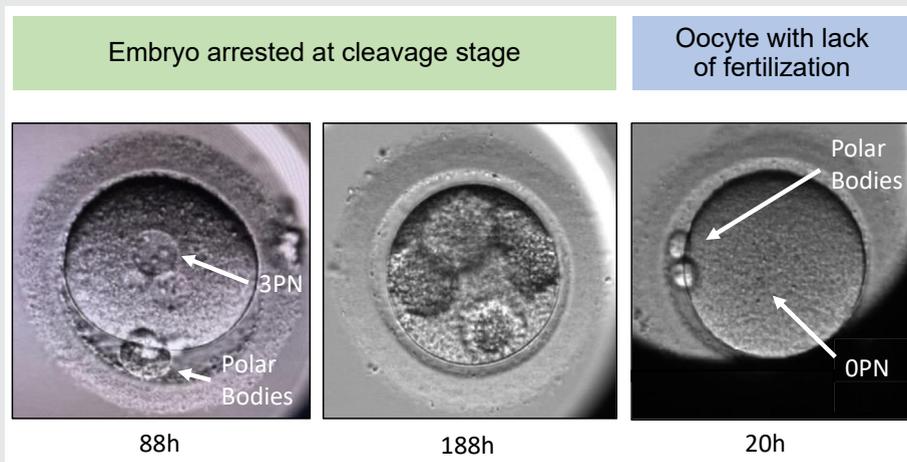
pronuclei observed. The embryo ultimately arrested at the 6-cell stage (Fig. 1). The remainder of the oocytes did not have evidence of normal fertilization with the lack of pronuclei formation (Fig. 1), raising concern for an OAD. The couple then underwent a second cycle, at which time 17 oocytes were retrieved. All oocytes were mature and underwent ICSI. Calcium ionophore was used for oocyte activation in this cycle. No normal fertilization occurred. On embryoscope evaluation, most of her oocytes in both cycles were observed to have extruded a second polar body after ICSI, although they did not ultimately demonstrate normal fertilization and zygote formation as evidenced by the lack of development of 2PN. Given the unique features of the case and low incidence of complete fertilization failure, we recommended consultation and testing through medical genetics (1, 2, 4, 9).

Medical genetic consultation was completed with recommendation for analysis of *WEE2* and *TLE6* in our female patient and *PLCZ1* for her partner. *WEE2* mutation is associated with oocyte maturation defects (OOMDs) resulting in fertilization failure, and *TLE6* mutation is associated with fertilization failure and preimplantation embryonic lethality (2, 6, 7). *PLCZ1* mutation in men is associated with OAD (1). Embryoscopic evaluation has allowed further characterization of these defects. Normal extrusion of the second polar body without formation of 2PN has been reported to characterize both the *WEE2* and *TLE6* mutations, whereas the *PLCZ1* mutations are associated with the lack of the second polar body and lack of 2PN (1, 5). Of note, reports of the connection between *ACTL9* mutation and OAD were published after this evaluation was completed (8). All genetic testing was completed through a Clinical Laboratory Improvement Amendments–certified commercial laboratory. Chromosome analysis was previously completed for our male patient during early fertility workup with normal male chromosomal complement, 46,XY (26/30 cells). Three cells were identified as aneuploid, and 1 was identified to have an inversion of chromosome 14, designated 46,XY,inv(14)(q11.2q32.3). Per laboratory interpretation, these results were felt to represent random chromosomal loss and culture artifact, respectively. Chromosome analysis for our female patient was not recommended during initial genetic evaluation given no observed family history of infertility, recurrent pregnancy loss, stillbirth, birth defects, intellectual disability, or developmental delay.

RESULTS

WEE2 sequencing and deletion/duplication analysis identified a homozygous, pathogenic variant, designated c.224_227del (p.Glu75Valfs*6). The identified variant results in a deletion of 4 base pairs in exon 1 of the *WEE2* gene, causing frameshift and generation of a premature stop codon, to ultimately encode a truncated *WEE2* protein. The *WEE2* c.224_227del variant has been previously reported in the medical literature in 2 patients with primary infertility related to complete fertilization failure and has been demonstrated during functional studies to lead to abnormal phosphorylation of *WEE2* (9). *TLE6* sequencing and deletion/duplication analysis was negative with no variants reported. Her partner

FIGURE 1



Comparison of oocyte with the lack of fertilization and 1 embryo with evidence of abnormal fertilization and cleavage ultimately arresting at the cleavage stage. PN = pronuclei.

Weiner. Fertilization failure due to WEE2 mutation. *Fertil Steril Rep* 2022.

underwent *PLCZ1* sequencing and deletion/duplication analysis, and this was also negative. After extensive counseling, the couple ultimately decided to proceed with donor oocyte IVF using the male partner's sperm. The couple completed 1 cycle of IVF using donor oocytes with a normal fertilization rate (89%). She underwent 1 single embryo transfer, which was successful. She was discharged to her general obstetrician at 10 weeks' gestation with a viable singleton pregnancy.

DISCUSSION

Genetic Etiologies

The WEE2 protein belongs to a kinase family involved in oocyte maturation and is highly conserved across numerous mammalian species (2, 6, 12). It has an important role both in arrest of development of oocytes before puberty and subsequently during fertilization by allowing the oocyte to proceed through the cell cycle. The loss of WEE2 protein causes OOMD type 5, typically resulting in primary infertility. For patients undergoing fertility treatments, WEE2-related OOMD type 5 may present as extrusion of a second polar body after ICSI but ultimately arrest in meiosis II after fertilization failure and lack of zygote formation, indicated by the lack of development of 2PN (2, 5, 6, 9, 13).

Clinical Management

In vitro fertilization is a common treatment for infertility but is physically, emotionally, and financially taxing. The frequent monitoring, daily injections, and invasive procedures required can result in a demanding and stressful process for patients even when treatment is successful (10). This effect is exacerbated when IVF cycles are not successful. Indeed, unsuccessful cycles are associated with increased rates of anxiety and depression, which can continue to persist even at 6

months after the treatment (11). Additionally, IVF is often financially burdensome, and families may take out loans to accommodate additional cycles or prematurely end treatment if they cannot afford to continue (10).

The rate of unsuccessful IVF cycles related to TFF has decreased in recent reports to 5% of conventional IVF cycles and 3%–4.3% of IVF-ICSI cycles, possibly related to an improvement in techniques and technology (3, 4). Kinzer et al. (3) report that several of the couples they studied with a cycle characterized by TFF had previous and subsequent cycles with normal fertilization after ICSI. This suggests that in some cases, the TFF could be related to characteristics of an individual IVF cycle, such as lower oocyte yield and perhaps differences in ovarian response (2). Shinar et al. (4) noted that for patients aged <40 years with at least 5 metaphase II oocytes retrieved, the rate of TFF was estimated at 0.7%. Before applying their exclusion criteria on the basis of age and number of oocytes, they report that the total rate of TFF was 4.3% for all couples, suggesting that TFF is much less common in cycles involving younger women who produce higher numbers of eggs. Additionally, they point out that of these young couples with TFF who attempted IVF again, 70% demonstrated normal fertilization for some oocytes. However, the overall fertilization rate after ICSI was only 20%, a much lower rate than their average fertilization after ICSI, which they report as 80% (4). These data would suggest that TFF in a young couple with at least 5 metaphase II oocytes retrieved is more worrisome and additional autologous cycles are less likely to be successful.

An IVF cycle resulting in TFF can leave a couple with a difficult decision between attempting additional autologous cycles with a potentially lower chance of success vs. consideration of IVF with donor gametes. These couples may be good candidates for referral to medical genetics for further investigation into underlying genetic causes for their TFF.

TABLE 1

Known gene mutations related to oocyte activation deficiency and OOMDs.

Phenotype	Gene	Protein product	Source	OMIM ID
Inability to exit MII, fertilization failure	<i>WEE2</i> (OOMD5)	WEE2 (protein tyrosine kinase)	Female	#617996
Fertilization failure, early embryonic arrest	<i>TLE6</i> (PREMBL2)	SCMC protein	Female	#616814
Fertilization failure, abnormal fertilization, MI arrest, early embryonic arrest, implantation failure	<i>TUBB8</i> (OOMD2)	Tubulin (major constituent of microtubules)	Female	#616780
Fertilization failure, GV/MI/early embryonic arrest	<i>PATL2</i> (OOMD4)	RNA binding protein acting as a translation repressor	Female	#617743
Fertilization failure, thin ZP, defective sperm binding, enlarged perivitelline space	<i>ZP2</i> (OOMD6)	Zona pellucida glycoprotein 2	Female	#618353
Fertilization failure, oocyte maturation arrest, early embryonic arrest	<i>CDC20</i>	Cell division cycle protein 20, regulatory protein for cell cycle/microtubule dependent processes	Female	*603618
Fertilization failure, early embryonic arrest	<i>NLRP5</i>	NALP family, SCMC protein	Female	*609658
Oocyte lacks ZP	<i>ZP1</i> (OOMD1)	Zona pellucida glycoprotein 1	Female	#615774
Degeneration of oocyte and "empty follicle syndrome"	<i>ZP3</i> (OOMD3)	Zona pellucida glycoprotein 3	Female	#617712
Oocyte death before or after fertilization	<i>PANX1</i> (OOMD7)	Innexin family, structural component of gap junctions	Female	#618550
Failure of zygotic cleavage after fertilization	<i>BTG4</i> (OOMD8)	BTG/Tob family, antiproliferative, G1 arrest in the cell cycle	Female	#619009
Oocyte MI arrest, abnormal zygotic cleavage	<i>TRIP13</i> (OOMD9)	Thyroid hormone receptor interactor 13, hormone-dependent transcription factor	Female	#619011
Abnormal fertilization (multiple or absent PN), embryonic arrest, implantation failure	<i>REC114</i> (OOMD10)	Meiotic recombination protein	Female	#619176
Early embryonic lethality	<i>PADI6</i> (PREMBL2)	SCMC protein	Female	#617234
Early embryonic arrest	<i>NLRP2</i>	SCME protein	Female	*609364
Fertilization failure	<i>PLCZ1</i> (SPGF53)	Phosphoinositide-specific phospholipase C family	Male	#617214
Fertilization failure	<i>ACTL9</i> (SPGF53)	Testis-specific actin-like protein, formation of the perinuclear theca	Male	#619258

Note: MI = metaphase I oocyte; OOMD = oocyte maturation defect; PREMBL = preimplantation embryonic lethality; SCMC = subcortical maternal complex; ZP = zona pellucida. (Compiled from Sang et al. (5), Dai et al. (8), Zhang et al. (12), the Online Mendelian Inheritance in Man Catalog at OMIM.org, and The Human Gene Database at Genecards.org.)

Weiner. Fertilization failure due to *WEE2* mutation. *Fertil Steril Rep* 2022.

Additional factors that may raise concern for an underlying genetic contribution include the presence of a family history of infertility or prior unsuccessful IVF, as well as consanguinity within families given that most genes currently associated with TFF, OOMDs, and early embryonic arrest are inherited in an autosomal recessive manner.

The process by which the gamete and later embryonic genomes drive fertilization and early embryo development is incredibly complex, and although research is ongoing, still relatively little is known about clinical applications of genetic testing in the setting of IVF/ICSI failure (3, 9). Until very recently, it was assumed that because oocyte activation was precipitated by sperm proteins, most TFF was related to a defect in the sperm that prevented oocyte activation from occurring (14). If a couple chooses to proceed with donor gametes after TFF, it was historically thought that the appropriate choice would be the use of donor sperm, especially if there is a

known underlying male factor on the basis of semen analysis, as in this case (14). However, sperm factors, like *PLCZ1* and *ACTL9*, appear to explain only a portion of this TFF/OAD (1, 8). Artificial oocyte activation with either a chemical or mechanical approach can overcome most sperm and even some oocyte-related activation defects related to an oocyte cytosolic factor and is, therefore, still considered a reasonable first-line treatment for couples with fertilization failure (14). It was only recently suggested that there are oocyte factors that can contribute to TFF/OAD that are not overcome with oocyte activation protocols (14). Sang et al. (5) recently reviewed the major oocyte factors that are thought to play a role in fertilization failure and early embryonic lethality. A list of genes cataloged in the Online Mendelian Inheritance in Man database for their association with TFF/OAD, and with OOMDs and early embryonic arrest, is provided in Table 1.

Given the significant financial and emotional burden associated with each unsuccessful cycle, a single episode of TFF, especially in a young couple with a reasonable number of oocytes retrieved, should prompt review of management and consideration of possible factors for both male and female partners. Evolving research and published case reports now implicate a number of human genes associated with female-specific defects in oocyte maturation, oocyte activation, TFF, and early embryonic arrest, in addition to the expanding list of male-specific gene mutations related to TFF/OAD. This suggests that joint genetic evaluation be considered for couples presenting with recurrent IVF/ICSI failure.

Although genetic evaluation for TFF shows promise as an intriguing and exciting new diagnostic tool, there are still some considerations and limitations to the technology in its current iteration. As illustrated in [Tables 1](#), there is a significant overlap in the phenotypes among the published genes, which suggests that curated, validated multigene panels would be the ideal way to evaluate these couples. Although there are some “infertility gene panels” in development, as summarized by Okutman et al. (15), they are not yet validated to a point where they would be broadly clinically applicable. The current lack of laboratory-curated multigene panels often constrains genetic workup to a single gene approach, which can be costly and time-consuming and may impact the diagnostic yield if the most appropriate genes are not selected for analysis. Although a single gene approach to testing in this couple did yield a clinically relevant positive result, the targeted selection of genes may prove more challenging as the number of genes associated with human fertility expands and as genetic workup for couples with IVF failure becomes more mainstream. In addition to the aforementioned challenges, pathogenic variants in many of the Online Mendelian Inheritance in Man genes cataloged for TFF/OAD, OOMDs, and early embryonic arrest have been identified in only a small number of families with few variants comprehensively characterized in the medical literature. Without a more robust understanding of observed variation within these genes and the functional relevance of newly identified variants, any clinical testing pursued is anticipated to have a high rate of inconclusive results or variants of uncertain significance (VUS). The return of a VUS result can complicate patient decision-making because we are unable to provide conclusive information on the contribution of the VUS to the couples' infertility and, therefore, are unable to predict the success rate of future IVF cycles. Additionally, the lack of consensus guidelines surrounding the use of genetic testing in the workup for couples with recurrent IVF failure may limit insurance reimbursement. This may result in high up-front cost for couples, consequently limiting access, especially given the significant cost of IVF itself. Given these considerations, couples pursuing genetic evaluation for recurrent IVF failure should receive appropriate counseling regarding potential benefits, risks, and limitations.

The patient we present here is homozygous for the *WEE2* pathogenic variant, c.224_227del, associated with autosomal recessive OOMD type 5. Diagnosis in this patient prompted genetic counseling on alternative options for family planning as well as on implications for other family

members of reproductive age. Identification of other affected female relatives through cascade genetic testing would allow for appropriate counseling on family planning options (e.g., adoption and use of donor egg) and would spare them the financial and emotional burden of infertility workup and multiple rounds of unsuccessful IVF. From published studies, the effect of *WEE2* mutation on fertility appears to be limited to the oocyte given the gene's specific function in its maturation. However, studies involving men with homozygous or compound heterozygous *WEE2* mutations have not been completed to date to confirm no underlying effects on health or fertility. *WEE2* mutations are uncommon and have not been widely studied, and there is not a known estimate of carrier status in the general population. Zhang et al. (12) suggested a rate of 40% among couples with TFF on the basis of a study of 25 couples, 10 of whom were affected by *WEE2* mutation. However, this study is limited by small sample size and may have been affected by ascertainment bias because we do not regularly test all patients with TFF for *WEE2* mutation. Although normal fertilization and live birth are possible after TFF, with some studies estimating the delivery rates as high as 36% per patient, 23% per embryo transfer, and 18% per cycle in subsequent cycles, there is limited information about outcomes and possible future treatment options for fertilization failure related to *WEE2* mutation (7). Research on this area is ongoing, and in 2018, Sang et al. (9) reported restoration of normal fertilization by injecting *WEE2* complementary DNA into oocytes from women with infertility related to *WEE2* mutation. The embryos were successfully cultured to the blastocyst stage in a research setting (5). Although this is an exciting and promising research, this study was limited to a small number of oocytes in a research protocol, and clinical trials have not been completed.

After 2 IVF-ICSI cycles complicated by TFF, the recommendation for our couple was initially to consider another cycle with split fertilization using half partner and half donor sperm given the concern for an underlying issue with sperm. After medical genetic consultation with the results of a homozygous *WEE2* mutation in the female patient suggesting that the TFF was related to an intrinsic OOMD, we were able to recommend donor oocyte IVF, which would have a higher chance of success than another attempt at autologous IVF. The couple was ultimately relieved with this result because donor sperm was not in line with their wishes for family building, whereas donor oocyte was an acceptable option for them. The genetic testing in this case helped guide the shared clinical decision-making process by illuminating a previously unrecognized oocyte deficiency.

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