

Can we use in vitro fertilization with preimplantation genetic testing to avoid molar pregnancies?

Molar pregnancy is a rare but serious complication of conception. If it occurs in conjunction with fertility treatment, it is particularly disruptive, because the female partner must wait for a significant amount of time before attempting conception again to rule out persistent gestational trophoblastic disease (GTD). First described by Hippocrates in ancient Greece as “dropsy of the uterus,” the hydatidiform mole is the result of abnormal fertilization of the oocyte. Because in vitro fertilization (IVF) allows the observation of fertilization as well as early embryonic development, it is tempting to speculate that IVF, particularly if combined with preimplantation genetic testing (PGT), may be used to detect the abnormal fertilization, so that molar pregnancy can be avoided.

A complete molar pregnancy most commonly has a 46,XX karyotype, but all the chromosomes are of paternal origin. This is because of the reduplication of the paternal chromosomes with the simultaneous loss of the maternal chromosomes. In addition, the 46,XY karyotype occurs, albeit more rarely, and is thought to be because of polyspermy (which can be avoided by intracytoplasmic sperm injection). If the maternal DNA is not lost, a partial mole may develop, which is triploid with a 1:2 maternal to paternal DNA content. Because of the excessive expression of paternal genes, which exert a higher control over placental growth, enhanced trophoblastic proliferation is observed, and represents one of the hallmarks of molar gestations.

If the molar pregnancy has an abnormal genetic content, can we not avoid it through the use of PGT? In order to avoid molar gestations after IVF, the genetic analysis of the trophoblast biopsy must include determination of the ploidy and the parental origin of the DNA. In this issue of the journal, Zhou et al. present a case of a complete molar pregnancy that occurred after the transfer of a single euploid blastocyst. The embryo was initially monopronuclear; however, subsequent development to the blastocyst stage was normal. Preimplantation genetic testing demonstrated a 46,XX karyotype. The accompanying editorial by Martin and Slim expounds on this subject and outlines a potential PGT strategy. The bottom line is that a complete molar pregnancy may be avoided by detection of uniparental disomy using PGT.

The remaining question is whether fertility treatment is associated with an increased risk of molar pregnancy. To date, only a few estimates are available in the literature. Martin and Slim cite a 1998 study, which reported a 0.3%–0.5%

incidence of molar pregnancy after assisted reproductive technology (1), considerably higher than the control incidence of 0.08% in naturally conceived pregnancies. However, a 2019 summary of data collected by the Human Fertility and Embryology Authority showed that between 1991 and 2018, fresh IVF was associated with a relatively low incidence of molar pregnancy (1/4,300 or 0.02%) (2). The Society for Assisted Reproductive Technology registry does not collect data about molar gestations; however, a 2004 case control study of 231 consecutive women receiving chemotherapy for persistent GTD in England found no association between GTD and infertility treatment (3). Thus, more recent reports provide some reassurance that fertility treatment and IVF do not increase the risk of molar pregnancy.

Another feature of molar pregnancy is its tendency to recur. The risk of recurrence after one molar pregnancy is about 1%–2%, but after two molar pregnancies, the risk increases to 15%–17% (4). Avoiding a molar gestation in this clinical situation would be a clear indication for IVF with PGT and may present a strong argument for IVF insurance coverage.

The case report by Zhou et al. clearly asks the question, “Can IVF with PGT be used to avoid molar pregnancies?” The answer is a qualified YES, with the caveat that the genetic testing must include an analysis of ploidy status and parental origin of the DNA. It appears also that we can add molar pregnancy to the list of conditions that may be avoided by the use of IVF with PGT.

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