



# Hydatidiform molar pregnancy following assisted reproduction

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## Abstract

**Introduction** The use of assisted reproduction techniques (ART) is increasing; however, reports of molar pregnancy following ART remain scarce. Currently, the Human Fertility and Embryology Authority (HFEA) collates data on the molar pregnancies that have resulted through the use of ART. Recently, they have indicated that they will no longer collect these data.

**Aim** This paper aimed to examine the incidence of molar pregnancy amongst patients undergoing assisted reproduction.

**Methods** We contacted HFEA and placed a request under the Freedom of Information Act (2000) for the number of molar pregnancies that resulted from fresh/frozen embryo transfer since HFEA started collecting data in 1991 to February 2018. We also asked how many patients who had suffered a molar pregnancy went on to have a normal pregnancy and how many had subsequent molar pregnancies, in subsequent treatment cycles.

**Results** Between 68 and 76 molar pregnancies occurred within this period using ART ( $n = 274,655$ ). The incidence of molar pregnancy using fresh intracytoplasmic sperm injection (ICSI) (1/4302) and fresh in vitro fertilisation (IVF) (1/4333) was similar. The risk of recurrence of molar pregnancy following a previous molar was higher following ART compared to spontaneous conceptions.

**Conclusion** The use of ICSI should be protective against triploidy; however, the retrospective data suggests that molar pregnancy is not eliminated with the use of ART. It is pertinent to continue to record this data, through the gestational trophoblastic disease centres, in order to ensure no further increase in incidence, appropriate follow-up, and transparency in communication.

**Keywords** ART · HFEA · HM

## Introduction

A hydatidiform mole (HM) is a pre-malignant presentation of gestational trophoblastic disease (GTD), associated with aberrant fertilisation and reported at an incidence of 1 in 714 live births [1]. Patients with a previous HM are susceptible to

further molar pregnancies, which increase to 20% following the second molar conception [2, 3].

Hydatidiform moles are defined as complete (CHM) or partial (PHM). They are classified by their histopathological findings, clinical presentation, and the parental contribution to the molar genomes [4]. The aetiology for HM is not fully elucidated; however, its morphological presentation is derived from excessive paternally inherited chromosomes [5]. CHMs are usually diploid androgenetic in nature and comprise of paternally derived chromosomes. This results from fertilisation by a singular haploid sperm replicating to form a 46, XX (monospermic, 80% cases) or two sperms 46, XX or 46, XY (dispermic, 20% of cases) [6]. Histologically, CHMs exhibit excessive and atypical trophoblast proliferation and hydropic villi. Furthermore, they do not demonstrate any foetal or embryonic tissues.

In partial hydatidiform moles, foetal and/or embryonic tissues are present alongside villous development. Most PHM develops as androgenetic triploids (69, XXY, XXX, or XYY) [7, 8]. They result from fertilisation with two sperms (dispermy) [9].

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The aetiology of GTD is associated with several risk factors, but we are yet to fully understand the causation [10]. It is suggested HM develop due to an underlying oocyte defect. The absence of maternal chromosomes in most CHMs supports this, alongside dispermic fertilisation occurring in most PHMs and some CHMs [11].

Patients identified as susceptible to recurrent HM may elect for IVF in order to prevent abnormal conceptions. Dispermic fertilisation could be eliminated with assisted reproduction treatment (ART) involving intracytoplasmic sperm injection (ICSI). Pre-implantation genetic diagnosis (PGD) could be used to identify any evidence of triploidy due to failed meiotic division [12, 13], as well as examine polar bodies and/or blastomeres for other explanations of triploidy excluding dispermic fertilisation [13, 14].

Utilisation of ART is increasing; however, reports of HM following ART remain scarce. Currently, the Human Fertility and Embryology Authority (HFEA) collates data on the molar pregnancies that have resulted through the use of ART. Recently, following a 2-year review and consultation (The Information for Quality Programme), HFEA have indicated that they will no longer collect these data. This decision reflected the burden on clinics of reporting extensive data.

## Aim

This paper aimed to examine the incidence of molar pregnancy amongst patients undergoing assisted reproduction.

## Methods

We contacted HFEA and placed a request under the Freedom of Information Act (2000) for the number of molar pregnancies that resulted from fresh/frozen embryo transfer since HFEA started collecting data in 1991. The run date for the data was on 20 February 2018. We also asked how many patients who had suffered a molar pregnancy went on to have a normal pregnancy and how many had subsequent molar pregnancies, in subsequent treatment cycles. The HFEA does not distinguish between partial and complete molar pregnancies. The data from HFEA for the number of molar pregnancies, for the years 2015–2016, were given as a value of less than 5, in order to prevent re-identification of the patient cycle. For this reason, the data is quoted in the tables as a range. We presumed that less than 5 patients would give a range of 1 to 4 patients.

## Results

Between 68 and 76 molar pregnancies occurred within this period using ART ( $n = 274,655$ ). Between 25 and 29 molar pregnancies occurred when using fresh ICSI (Table 1). This gives an incidence of 1/3709–1/4302. The ambiguity over the numbers for the years 2015–2016 is minimal with a range of 0.004% of the total. The incidence of molar pregnancy with fresh cycle IVF was similar, with an incidence of 1/4333 (Table 2). No molar pregnancies occurred when a combination of IVF and ICSI was used, but the total number for this cohort was significantly lower than that for the others (902 total procedures). When frozen embryo transfer cycles were used, 16 to 20 molar pregnancies occurred. This gives an incidence of 1/2317 to 1/2896, suggesting molar pregnancies may be 50–100% more likely to occur with a frozen cycle. There were no molar pregnancies reported when in vitro maturation (IVM), pre-implantation genetic screening (PGS), or pre-implantation genetic diagnosis (PGD) was used, but the number of procedures was small.

We also asked HFEA for the number of women who had a molar pregnancy following licenced treatment who had previously had, or subsequently had, a normal pregnancy. They stated that 25–29 women had either had a previous normal or had a subsequent normal pregnancy. None of the patients had a subsequent molar pregnancy in the same cycle, with embryos created within the same cycle.

We asked HFEA how many women had a subsequent complete molar or partial molar pregnancy in the following fresh cycle, from a different cohort of embryos. They informed us that there were between 1 and 4 patients having a recurrence of molar pregnancy from the total cohort. This suggests that the incidence of recurrence of a molar pregnancy using ICSI could be at its highest 1/6 or at its lowest 1/29. Likewise, the data suggests that the recurrence rate of molar pregnancy for the IVF cohort could be as high as 1/7 or at its lowest 1/27. This range is quite wide, but due to the HFEA reporting of data, the ambiguity is difficult to overcome.

## Discussion

Oocyte maturation has to occur during fertilisation. During insemination, sperm migration through the zona pellucida attaches and fuses with the oolemma and enters oocyte cytoplasm, activating the egg [15]. This leads to the modification of the zona pellucida, in order to prevent polyspermy [15]. The second polar body undergoes extrusion [15]. Sperm DNA de-condenses allowing the formation of male and female pronuclei [15]. Nuclear membranes encapsulate the parental genome, resulting in the diploid zygote [15].

Triploidy does occur with natural conceptions. Ten percent of spontaneous miscarriages are attributed to triploidy [9]. A

**Table 1** Total number of pregnancies arising from fresh and frozen embryo treatment cycles and those resulting in a complete molar or partial molar pregnancy since 1991

Treatment type	Pregnancies	Molar pregnancies (%)
Fresh ICSI—own and donor eggs	107,571	25–29 <sup>1</sup> (0.023–0.027)
Fresh IVF—own and donor eggs	116,992	27 (0.023)
Fresh IVF:ICSI—own and donor eggs	902	0 (0)
Frozen cycle—own and donor eggs	46,334	16–20 <sup>1</sup> (0.035–0.043)
IVM, PGS, PGD, or unclassified	2856	0 (0)
Total	274,655	68–76 (0.025–0.028)

<sup>1</sup> Ranges are given for the molar pregnancies due to the HFEA data reporting incidences of less than 5 for the years 2015–2016

study by Zaragoza et al. reported 69% of cases were of diandric origin and 31% were attributed to a lack of extrusion of the second polar body (digynic origin) [9].

Our study, using HFEA data, shows that the incidence of molar pregnancy is considerably lower in ART pregnancies than in spontaneous conceptions. The overall incidence of molar pregnancy using fresh ICSI was similar to that for fresh IVF. The incidence of molar pregnancy with a frozen cycle is considerably (50–100%) higher than with a fresh cycle. The lack of distinction between complete and partial molar pregnancies is a weakness of the data. Nonetheless, the data support their being a partial protective effect of IVF and ICSI against molar pregnancy. It is interesting to speculate why this may be the case. Avoidance of dispermy may account for the protective effect of ICSI. With standard IVF, serial embryo observation and morphology-based selection may be relevant. We are not aware of studies examining the effect of time-lapse imaging of embryos.

Potential mechanisms for molar pregnancy following assisted conception include the inadvertent use of a diploid sperm or digynic triploidy. Triploidy following ICSI is suggested to be of digynic origin [16]. Macas et al. examined triploid zygote development in cases where ICSI was used for severe sperm abnormalities. They reported that 33% of the triploids were due to diploid sperm [17].

Triploid zygote formation in patients with molar pregnancy, who underwent IVF, without significant male factor, has been suggested to result from a dysfunctional oocyte.

Polyspermy can lead to diandric triploidy as a result of oocyte failure preventing multiple sperm entry. During ICSI, polyspermy is excluded; however, digynic triploidy may occur due to retaining the second polar body due to cytoplasmic incompetence [18].

Unfortunately, the data is limited identifying risk factors for triploidy formation. Triploid zygote formation has been observed to occur following rescue ICSI. Oocytes that failed fertilisation were injected the following day [19, 20]. Furthermore, if rescue ICSI was delayed, triploidy formation was increased. This suggests that ageing of the oocyte may increase the likelihood of triploid zygote formation [19, 20]. The mechanism for this is not known.

Diploid sperm is present in healthy men (0.2%) and in 1–2% in men with fertility problems [21]. Surprisingly, despite the presumed competitive disadvantage, these sperms can fertilise both spontaneously, as well as in use with ICSI. It has been reported that there may be difficulty in the visualisation of diploid sperm during ICSI [22]. Visualisation of the pronuclear stage would be unremarkable as two pronuclei would be visible in cases of PHM arising from diploid sperm in comparison to the three pronuclei that would be seen in a typical PHM resulting from two separate sperms [22]. Although diploid sperms are more common in infertile males, the incidence is relatively low as mentioned previously and should not impact on the success of ICSI in subsequent cycles.

We identified that the risk of recurrence following one previous molar pregnancy with ICSI ranges from 1/6 at its

**Table 2** Summary table of statistics for molar pregnancy in spontaneous conceptions compared to assisted reproduction

	Spontaneous conceptions in UK population	HFEA data (ART), fresh ICSI	HFEA data (ART), fresh IVF	HFEA data (ART), frozen cycle
Incidence	1/700	1/3709 to 1/4302	1/4333	1/2317 to 1/2896
Risk factors				
Extremes of age < 15 years	20-fold increase	No data on patient demographics		
> 45 years	Several hundred fold increases			
Previous molar pregnancy				
1 previous	1 in 80 (1.25%)	1 in 6, 1 in 29 (3–16%)	1 in 7, 1 in 27 (3–14%)	

highest to 1/29 at its lowest. This range is large, but the data is limited due to the small numbers and needs to protect patients being identified from it. Despite this, even at the lowest incidence of 1/29, this is still considerably higher than the risk of recurrence in spontaneous conceptions (1/80). Likewise, the risk of recurrence of molar pregnancy with IVF ranges from 1/7 at its highest to 1/27 at its lowest. We have no data for patients who suffered 2 molar pregnancies with ART. This may be as the numbers are low, as no patients suffered 2 repeat molar pregnancies. It may also be that the patients may be identifiable, or one may speculate that patients who had a molar pregnancy with ART may have been offered ART with PGD which eliminate this risk.

Recurrence of hydatidiform pregnancy may be coincidence or may be affiliated to the clinical variables and factors that lead to ART, including advanced age and poor oocyte quality. The increased incidence of recurrence could be related to the ART, alongside the patient characteristics. It may therefore be reasonable to suggest that women with previous confirmed triploid molar pregnancy to have ICSI as a treatment. Furthermore, the potential risk of recurrence if a patient has a mole through IVF/ICSI may also suggest that PGD should be considered in the next cycle, in order to prevent the recurrence.

HM is a rare disease. For this reason, there are 3 UK centres to which it is recommended that all cases be referred. These centres have good compliance and prior fertility treatment is recorded. An analysis by Bates et al. demonstrated no relationship between infertility treatment and subsequent development of HM, in a GTD centre [10]. For further research into the association into HM and ART, it appears more appropriate to record data via the specialist GTD centres rather than by HFEA reporting. Appropriate genetic analysis, demographic information, and follow-up are already carried out in these centres and may allow HFEA to reduce the burden of mandatory reporting. Future research into the underlying genetic basis of HM and causal factors in the ART process could then be carried out by linkage of the more detailed GTD databases to the HFEA register.

## Conclusion

Assisted reproductive technology has improved our understanding of human fertilisation. The use of ICSI should be protective against triploidy; however, the retrospective data suggests that molar pregnancy is not eliminated with the use of ART. However, it should be noted that the data come from infertile couples that may have biologic or genetic polymorphisms, which may predispose to abnormal fertilisation patterns. It is pertinent to continue to record this data, in order to ensure no further increase in incidence, appropriate follow-up, and transparency in communication with the couple regarding

assisted reproductive techniques. We would recommend that as GTD centres already collate the data for HM, it would be appropriate for HFEA to stop data collection. The GTD centre database may help resolve issues of data ambiguity with regard to the numbers and distinguish between partial and complete moles. It would also be beneficial to obtain more information on patient demographics and ART treatment parameters in order to uncover causal mechanisms.

## Compliance with ethical standards

**Conflict of interest** The authors declare that there are no conflicts of interest.

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## References

1. The management of gestational trophoblastic disease. Green top guideline number 38. Royal College of Obstetricians. 2010.
2. Berkowitz RS, Bernstein MR, Laborde O, Goldstein DP. Subsequent pregnancy experience in patients with gestational trophoblastic disease. New England Trophoblastic Disease Center, 1965–1992. *J Reprod Med.* 1994;39:228–32.
3. Berkowitz RS, Im SS, Bernstein MR, Goldstein DP. Gestational trophoblastic disease. Subsequent pregnancy outcome, including repeat molar pregnancy. *J Reprod Med.* 1998;43:81–6.
4. Berkowitz RS, Goldstein DP. Clinical practice. Molar pregnancy. *N Engl J Med.* 2009;360:1639–45.
5. Slim R, Mehio A. The genetics of hydatidiform moles: new lights on an ancient disease. *Clin Genet.* 2007;71:25–34.
6. Fluker MR, Yuzpe AA. Partial hydatidiform mole following transfer of a cryopreserved-thawed blastocyst. *Fertil Steril.* 2000;74(4):828–9.
7. Golubovsky MD. Postzygotic diploidization of triploids as a source of unusual cases of mosaicism, chimerism and twinning. *Hum Reprod.* 2003;18:236–42.
8. Hoffner L, Surti U. The genetics of gestational trophoblastic disease: a rare complication of pregnancy. *Cancer Genet.* 2012;205:63–77.
9. Zaragoza MV, Surti U, Redline RW, Millie E, Chakravarti A, Hassold TJ. Parental origin and phenotype of triploidy in spontaneous abortions: predominance of diandry and association with the partial hydatidiform mole. *Am J Hum Genet.* 2000;66:1807–20.
10. Bates M, Everard J, Wall L, Horsman JM, Hancock BW. Is there a relationship between treatment for infertility and gestational trophoblastic disease? *Hum Reprod.* 2004;19:365–7.
11. Fallahian M. Familial gestational trophoblastic disease. *Placenta.* 2003;24:797–9.
12. Edwards R, Crow J, Dale S, Macnamee M, Hartshome G, Brinsden P. Pre-implantation diagnosis and recurrent hydatidiform mole. *Lancet.* 1990;335:1030–1.
13. Reubinoff BE, Lewin A, Verner M, Safran A, Schenker JG, Abeliovich D. Intra-cytoplasmic sperm injection combined with pre-implantation genetic diagnosis for the prevention of recurrent gestational trophoblastic disease. *Hum Reprod.* 1997;12:805–8.
14. Rosenbusch B, Schneider M, Sterzik K. The chromosomal constitution of multi-pronuclear zygotes resulting from in-vitro fertilization. *Hum Reprod.* 1997;12:2257–62.

15. Georgadaki K, Khoury N, Spandidos DA, Zoumpourlis V. The molecular basis of fertilization (review). *Int J Mol Med*. 2016;38(4):979–86.
16. Grossmann M, Calafell JM, Brandy N, Vanrell JA, Rubio C, Pellicer A, et al. Origin of tri-pronucleate zygotes after intracytoplasmic sperm injection. *Hum Reprod*. 1997;12:2762–5.
17. Macas E, Imthum B, Keller PJ. Increased incidence of numerical chromosome abnormalities in spermatozoa injected into human oocytes by ICSI. *Hum Reprod*. 2001;16:115–20.
18. Rosen M, Shen S, Dobson AT, Fujimoto VY, McCulloch CE, Cedars MI. Triploidy formation after intracytoplasmic sperm injection may be a surrogate marker for implantation. *Fertil Steril*. 2006;85(2):384–90.
19. Nagy ZP, Staessen C, Liu J, Joris H, Devroey P, Van Steirteghem AC. Prospective, auto-controlled study on reinsemination of failed-fertilized oocytes by intracytoplasmic sperm injection. *Fertil Steril*. 1995;64:1130–5.
20. Chen C, Kattera S. Rescue ICSI of oocytes that failed to extrude the second polar body 6 h post-insemination in conventional IVF. *Hum Reprod*. 2003;18:2118–21.
21. Egozcue S, Blanco J, Vidal F, Egozcue J. Diploid sperm and the origin of triploidy. *Hum Reprod*. 2002;17:5–7.
22. Rosenbusch BE. Mechanisms giving rise to triploid zygotes during assisted reproduction. *Fertil Steril*. 2008;90:49–55.