CASE SERIES

Does Number Matter: A Case Series of Gestational Trophoblastic Disease with Coexistent Live Pregnancies Post-multiple Embryo Transfer after *In vitro* Fertilization–intracytoplasmic Sperm Injection

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Abstract

Aim and objective: We present three cases of multiple pregnancies associated with hydatidiform mole occurring after *in vitro* fertilization (IVF)–intracytoplasmic sperm injection (ICSI).

Background: The phenomenon of molar pregnancy coexisting with higher-order pregnancies after IVF–ICSI is extremely rare as assisted reproduction techniques allow us to directly assess gametes and ICSI curtails any chances of dispermic fertilization.

Case description: Three cases are discussed each of which was managed differently according to gestational age and parity of the patient. Individualization of management along with strict follow-up is necessary in such cases.

Conclusion: A high index of suspicion must be kept for the possibility of coexistent molar pregnancy, especially in multiple conceptions occurring after IVF–ICSI. Even though rare, if diagnosed early, appropriate management can help avoid catastrophic complications and preserve future fertility.

Clinical significance: No clear guidelines exist at present regarding the management of molar pregnancies coexisting with IVF–ICSI conceptions and many factors unique to these pregnancies need to be addressed. The possibility of severe complications like massive bleeding may necessitate the termination of a precious pregnancy. The high possibility of gestational trophoblastic neoplasia and the need for long-term follow-up may delay further cycles and deny the couple a chance at their own genetic baby. Mole can recur in subsequent pregnancies and this also requires detailed patient counseling with an option for use of preimplantation genetic diagnosis techniques.

Keywords: β-hCG, Embryo transfer, Gestational trophoblastic disease, *In vitro* fertilization, Vesicular mole.

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Introduction

The field of assisted reproductive technology (ART) has seen explosive and galloping advances in recent years which have enabled more and more couples to conceive. However, along with the advances heralded by ART, certain challenges are also being encountered which are unique to *in vitro* fertilization (IVF) pregnancies. The occurrence of molar pregnancy along with a precious IVF conception is one such challenge leading to a multitude of questions regarding the etiology, the molecular–genetic mechanisms, management, and follow-up of such patients.

Gestational trophoblastic disease (GTD) consists of a wide spectrum of disorders ranging from complete or partial hydatidiform mole to the malignant disorders of invasive mole, choriocarcinoma, and placental site trophoblastic tumor.[1]

The incidence of molar pregnancies in spontaneous conception is variable ranging from 1 in 1,000 for a complete mole and 3 in 1,000 for a partial mole.[2] The coexistence of a hydatidiform mole and a live fetus is rarer still having an incidence of 1 per 20,000 to 1 per 100,000 spontaneous pregnancies.[3] Such a phenomenon in IVF pregnancies has very few sporadic cases reported as the use of micromanipulation techniques ensures monospermic fertilization during IVF–intracytoplasmic sperm injection (ICSI). A hydatidiform mole with a coexistent live fetus after IVF-ET is scarce with very few cases of twin pregnancies after IVF-ET being described in the literature.[4]

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Here, we present a case series of higher-order pregnancies resulting from IVF–ICSI complicated with the coexistent GTD. The occurrence of molar tissue along with higher-order live pregnancies in these conceptions raises several pertinent questions regarding the molecular mechanisms and morphokinetics underlying them. Furthermore, the management of such pregnancies is formidable as the crucial matter of fertility preservation in such patients may need to be considered along with regular follow-up as there is a possibility of persistent GTD. Also, the possibility of gestational trophoblastic neoplasia and recurrent GTD in subsequent pregnancies will need to be addressed.

Case Descriptions

Case 1

A 29-year-old, primigravida with IVF conception war referred to us from parent IVF center with USG suggestive of 8 weeks dichorionic diamniotic twin live pregnancy with associated vesicular mole and bleeding PV since 2 days.

She had a history of prolonged treatment for primary infertility over 9 years of married life with one failed IVF attempt. The patient conceived the present pregnancy in her second attempt of IVF which was done using donor oocytes and husband's semen as the patient's ovarian reserve was low (AMH-0.03).

The donor who provided the oocytes was a 24-year-old, Indian woman with normal hormonal parameters. Her blood group was A positive and she had a body mass index (BMI) of 24. She had two previous spontaneous conceptions resulting in healthy babies and no abortions. There was no previous or family history of molar pregnancy. She was a non-smoker and had no known comorbidities.

Ovarian stimulation of donor was done with Inj.rFSH (Recagon, Organon, India) and downregulated using Inj.Cetrorelix (Cetrolix, Intas, India) using standard antagonist protocol. The trigger for ovulation was given with Inj.rhCG (Ovitrelle, Merck Soreno, Italy). Thirty-six hours after the trigger seven mature oocytes and two immature oocytes were aspirated transvaginally.

The patient's husband was 34 years of age with blood group O positive. Semen analysis revealed a sperm count of 60 million/mL, motility 40%, and morphology 6%. Intracytoplasmic sperm injection was performed for five oocytes at the metaphase II stage. Fertilization was assessed after ICSI and four oocytes showed evidence of two pronuclei.

Fresh transfer of 4 grade I cleavage stage embryos was done on April 25, 2019. The procedure was uneventful.

Two weeks after transfer, the patient's pregnancy test was positive and β subunit of human chorionic gonadotropin (β-hCG) was 1,348. She was advised to follow up for a first-trimester scan after 2 weeks.

The patient's vitals were stable when received by us with an ultrasound report of DCDA twin live pregnancy (CRL 1–1.8 cm, CRL 2–1.9 cm) 8 weeks with an associated vesicular mole of 5.5 × 5.5 × 5 cm. β-hCG at this stage was 276,400 IU (Figs 1 and 2).

The case was discussed with the family and USG-guided suction evacuation was done. The evacuated material was sent for histopathology and it revealed molar tissue along with normal products of conception. The tissue was sent for cytogenetic analysis. This revealed the molar tissue as a complete mole coexistent with genetically normal DCDA twin pregnancy.

The post-op period was uneventful. A careful follow-up of β-hCG levels was kept post-evacuation and levels returned to baseline after a period of 3 months.

Case 2

A 40-year-old, G5P3L3A1 at 16 weeks 3 days of pregnancy was referred to our hospital from an IVF center with bleeding per vagina for 2 days with severe anemia with severe gestational hypertension.

The patient has had a history of secondary infertility for 2 years. She had previous two normal deliveries resulting in two live female babies and one cesarean section resulting in a male child who was later diagnosed with cerebral palsy. She was investigated for secondary infertility and found to have premature ovarian failure. She underwent IVF, the first cycle of which resulted in spontaneous abortion, she conceived the present pregnancy in her second attempt of IVF with donor ova.

The donor who provided the oocytes was a 25-year-old, Indian woman with normal hormonal parameters. Her blood group was B positive and she had a BMI of 22. She had two previous spontaneous conceptions and no abortions. There was no previous or family history of molar pregnancy. She was a non-smoker and had no known comorbidities.

Ovarian stimulation of donor was done with Inj.rFSH (Folisuge, Intas, India) and downregulated using Inj.Cetrorelix (Cetrolix, Intas, India) using standard antagonist protocol. The trigger for ovulation was given with Inj.rhCG (Ovitrelle, Merck Soreno, Italy). Thirty-six hours after the trigger, nine mature oocytes were aspirated transvaginally.

The patient's husband was 44 years of age with semen analysis revealing a sperm count of 32 million/mL, motility 35%,

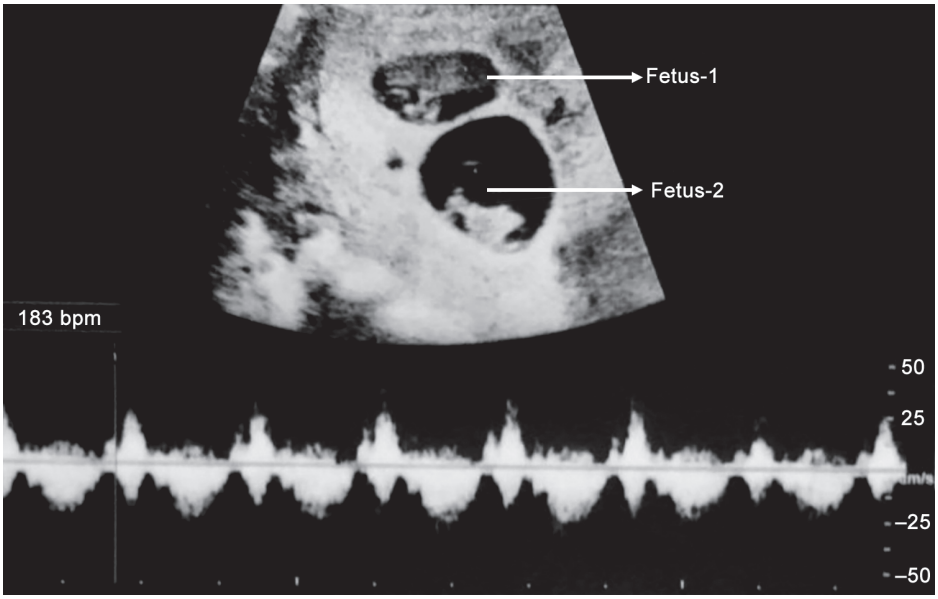

Fig. 1: Ultrasound image showing twin live intrauterine pregnancy of 8 weeks (case 1)

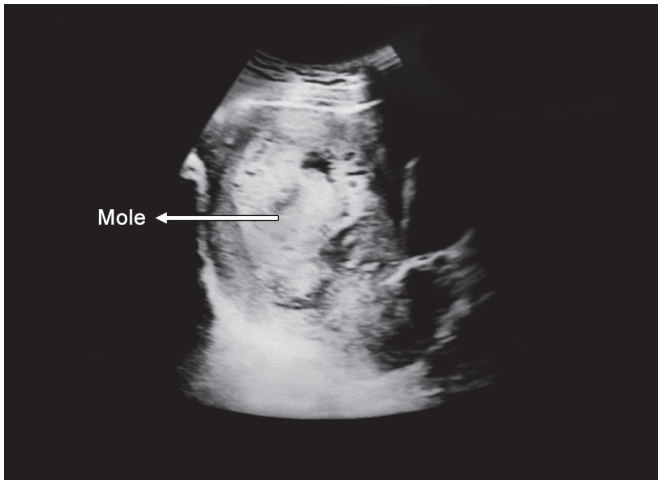

Fig. 2: Ultrasound image showing vesicular mole (case 1)

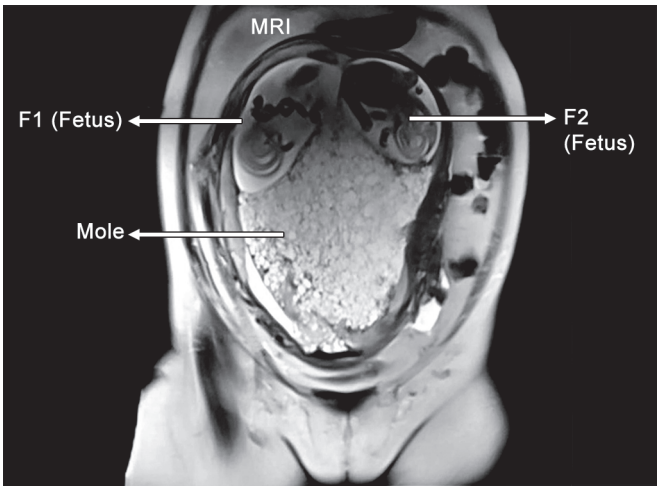

Fig. 3: MRI image showing huge vesicular mole with 16 weeks twin live pregnancy (case 2)

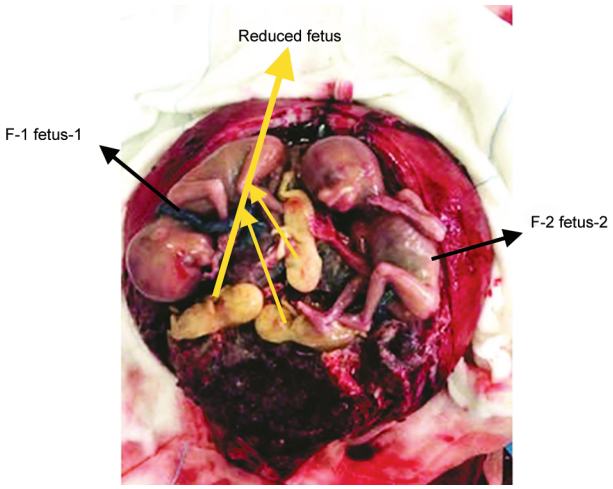

Fig. 4: Hysterectomy specimen showing huge vesicular mole with twin pregnancy with three reduced fetuses (case 2)

and morphology 8% normal forms. Intracytoplasmic sperm injection was performed for nine oocytes at the metaphase II stage. Fertilization was assessed after ICSI and six oocytes showed evidence of two pronuclei.

On April 13, 2018, 6 day 3 grade I cleavage stage embryos were transferred. On day 15 post-transfer, pregnancy was confirmed and the initial serum β-hCG level was 4,128.

The patient underwent a confirmatory scan at 7 weeks which showed five live fetuses and one blighted ovum and was advised selective fetal reduction. At 10 weeks, selective reduction of three fetuses was done under USG guidance. The patient was lost to follow-up afterward and reported directly at 16 weeks 3 days with a history of bleeding after which she was referred to us.

On examination, her pulse was 120 bpm, BP-190/120, and she had severe pallor (h/o three blood transfusions received before referral). Her uterus was 34 weeks in size with difficulty locating the fetal heart.

She was investigated and Hb was 8 g%, TLC-16,800, TSH-0.96 IU/mL. The blood group was B positive. β-hCG was more than 260,000 mIU/mL. Urine protein was 4+. CXR-Blunting of right costophrenic angle s/o pleural effusion. Hypoalbuminemia (1.7 g/dL) and hypocalcemia (7.8 mg/dL) were present.

On USG, twin live intrauterine pregnancy of 16 weeks 6 days with three reduced fetuses and a 13.4 × 6.8 cm large echogenic, multiple cystic areas with high vascularity on Doppler was seen in a lower uterine segment covering the internal os. MRI abdomen was done which confirmed the findings of ultrasound. There were no lesions seen in the liver or chest associated with the molar pregnancy (Fig. 3).

While under evaluation, the patient complained of the second episode of severe bleeding PV and was taken up for emergency exploratory laparotomy and proceed. Blood and blood products arranged.

The intra-op lower segment of the uterus was highly vascular with dilated veins and multiple sinuses. The decision for hysterectomy with fetuses *in situ* with bilateral salpingectomy was taken after detailed discussion, counseling, and consent (Fig. 4).

The specimen was sent for histopathology and was consistent with a partial molar pregnancy.

Her postoperative period was uneventful and she was discharged on day 5 of surgery. Strict follow-up of β-hCG levels was kept on an OPD basis and levels reached a nadir after 3 weeks.

Case 3

A 43-year-old, primi at 21 weeks 2 days gestation with quadruplet pregnancy was referred to us from IVF center with USG suggestive of two live and one dead fetus along with a complete molar pregnancy with a 5 cm fibroid on the anterior wall for further management.

The patient was married for 18 years, a case of primary infertility because of low ovarian reserve and AMH of 0.01.

The donor who provided the oocytes was a 25-year-old, Indian woman with normal hormonal parameters. Her blood group was A positive and she had a BMI of 22. She had two previous spontaneous conceptions resulting in healthy babies and no abortions. There was no previous or family history of molar pregnancy. She was a non-smoker and had no known comorbidities.

Ovarian stimulation of donor was done with Inj.rFSH (Gonal F, Merck Serono, Italy) and downregulated using Inj.Cetrorelix (Cetrotide, Merck Soreno, Italy) 0.25 mg/day using standard antagonist protocol. The trigger for ovulation was given with Inj. rhCG (Ovitrelle, Merck Soreno, Italy). Thirty-six hours after the trigger, seven mature oocytes were aspirated transvaginally.

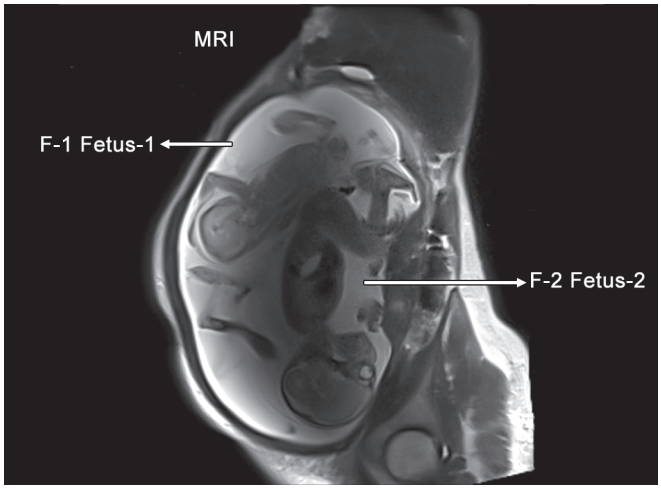

Fig. 5: MRI image showing two of the three live fetuses (case 3)

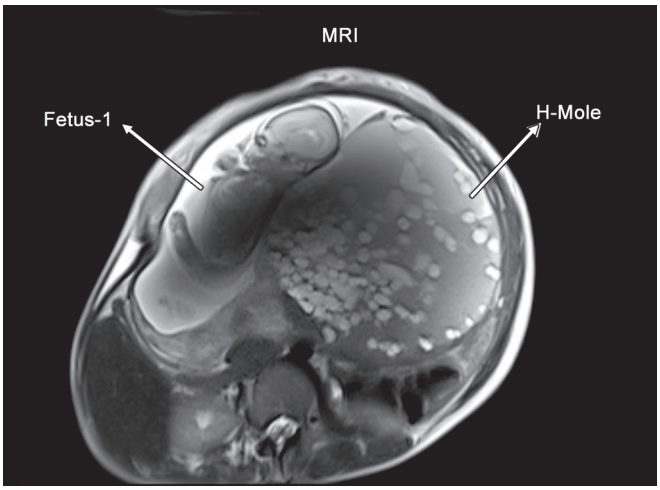

Fig. 6: MRI image showing huge vesicular mole with one live fetus (case 3)

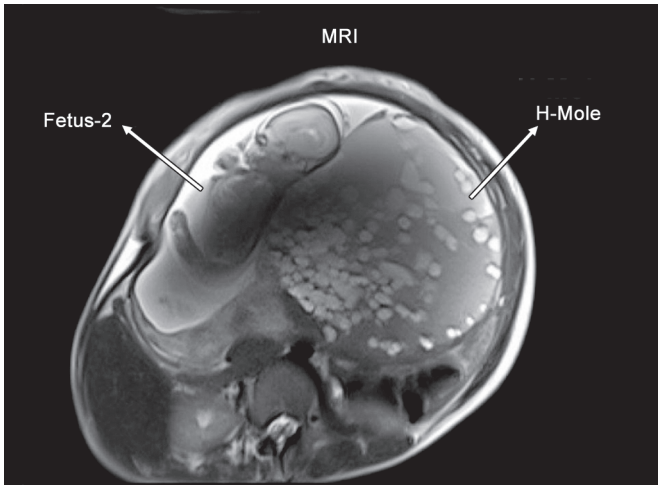

Fig. 7: MRI image showing huge vesicular mole with second live fetus (case 3)

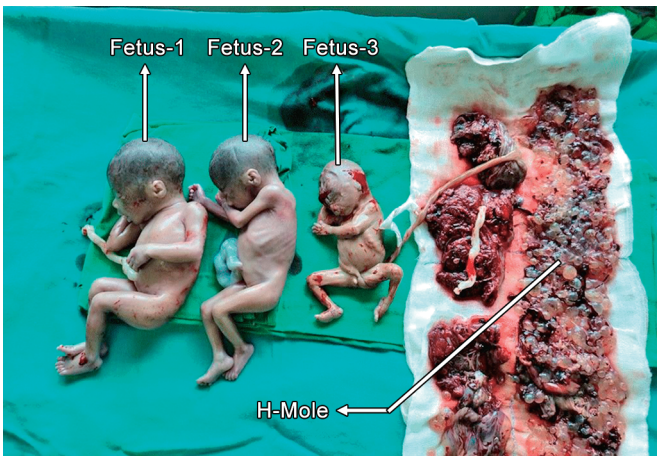

Fig. 8: Postoperative image of triplet babies along with molar tissue

The patient's husband was 46 years of age with blood group O positive. Semen analysis revealed a sperm count of 41 million/mL, 50% motility, and 14% normal morphology. Intracytoplasmic sperm injection was performed for six oocytes at the metaphase II stage. Fertilization was assessed after ICSI and five oocytes showed evidence of two pronuclei.

Five grade A cleavage stage embryos were transferred on day 5 under ultrasound guidance.

Triplet pregnancy was confirmed at a first-trimester scan done at 6 weeks. β-hCG level at that time was 5,189. Post-initial testing, the patient was lost to follow-up. She reported back at 21 weeks where a repeat scan was done which revealed triplet pregnancy with a large molar component.

On admission, her vitals were stable. Her per abdomen examination correlated with 34–36 weeks of pregnancy and two fetal hearts were localized. On per vaginum examination os was closed, uneffaced and Bishops score was poor. Her β-hCG on admission was 294,000. Blood group A+, Hb-10.3, TSH-N, CXR-WNL.

USG (Obs) was s/o triplet intrauterine pregnancy of 23 weeks with two live fetuses and one fetal demise (18 weeks) with an associated intrauterine mole of 20.9 × 15.5 cm.

MRI was done to rule out invasion and showed e/o of 21.8 × 14.2 × 12.7 cm large heterogeneous mass with numerous cystic areas on T1 and T2 images. Moderate B/L hydronephrosis due to ureteric compression by gravid uterus (Figs 5 to 7).

The case was discussed with the family and after appropriate counseling and consent, the patient was planned for exploratory laparotomy with adequate blood arranged. Hysterotomy followed by delivery of triplets and evacuation of molar tissue was done under general anesthesia. An additional finding of a 5 cm fibroid on the anterolateral wall of the uterus was noted. Intra-op there was approximately 1,200 mL of blood loss which was replaced. Fortunately, with the help of uterotonics, the uterus could be conserved and the patient did not require a hysterectomy (Fig. 8).

Histopathology was consistent with complete molar pregnancy.

Her postoperative period was uneventful. β-hCG levels were followed up and reached negative levels at 4 weeks postoperative.

Discussion

The GTD consists of a spectrum of interrelated conditions originating from the placenta. Histologically distinct disease entities encompassed by this general terminology include complete and partial hydatidiform moles, invasive moles, gestational

choriocarcinomas, and placental site trophoblastic tumors. Hydatidiform moles are divisible into complete moles and partial moles which have distinct cytogenetic, pathologic, and clinical characteristics. Both these entities occur due to hydropic changes and proliferation of the trophoblast and are potential premalignant conditions that can progress to malignant trophoblastic disease and hence require prompt recognition, management, and follow-up.[1]

In vitro fertilization has helped many couples to achieve successful pregnancies. These pregnancies are unique as they allow us to analyze embryogenesis and transfer only healthy embryos to ensure a good outcome. The existence of molar pregnancies, in IVF conceptions, despite direct evaluation and use of micromanipulation techniques, is, therefore, unusual.

The etiological factors predisposing to molar pregnancies are many and varied. It is known that paternal age, maternal genetic anomalies, blood group, oral contraceptives, maternal age, and environmental factors; in particular, vitamin A and folate deficiency can predispose to molar pregnancy.[5] However, the relationship of molar pregnancy occurring in pregnancies conceived as a result of *in vitro* fertilization has not yet been fully explored.

The incidence of molar pregnancies in spontaneous conception is uncommon, and the presence of molar tissue with assisted reproduction is even scarce with very few cases reported in the literature.[2–4] We report a case series of live, higher-order pregnancies, coexisting with the GTD, occurring after assisted contraception, and analyze the possible causes of abnormal embryogenesis in these conceptions, leading to the formation of molar tissue.

All three cases were retrospectively analyzed and since all cases utilized donor oocytes for conception, data regarding oocyte donors were collected.

Donors in all three cases were of Asian ethnicity and belonged to low-socioeconomic strata according to the Kuppuswamy scale.[6] It is known that the incidence of molar pregnancy varies with ethnicity and is more common in areas of South-East Asia, India, and Africa.[7]

Also, increased maternal age has been shown to have a clear association with increased risk of hydatidiform mole.[8,9] Both in low and high incidence areas molar pregnancies are more common in women <20 or >40 years of age.[7] Age of all three donors was between 21 years and 25 years. As per Savage et al., the overall risk of molar pregnancy in this age group is <1:500.[10]

Findings from various animal studies show that diet can reset the genetic imprint and a diet deficient in vitamin A and folates may be responsible for the production of an immature oocyte, prevents meiosis II to be carried out correctly, and cause consequent development of molar pregnancy.[11,12] BMI of all three donors was in the normal range of 18.5–24.9 with no evidence of malnutrition. There were no clinical features of vitamin A or folate deficiency even though laboratory estimations were not done.

There has been an association of increased incidence of molar pregnancies in mothers with A positive blood group married to men with O positive blood group. This factor was present in two of our cases. The maternal blood group II which was present in case 2 was, however, actually deemed protective for GTD.[7]

Two donors used copper-based IUCD for contraception and the third used barrier contraception. History of usage of IUCD has also been known to increase the incidence of GTD as per Vecchia et al.[7] This was attributed to the inflammatory changes induced in the endometrium by these devices. Since in our case, the oocyte donors only provided the ova and embryos were transferred to mothers with no history of contraceptive use, this does not qualify as a possible contributory cause for the development of molar pregnancy.

All donors were multipara with no history of abortions or voluntary terminations of pregnancies. None of them had any previous history of molar pregnancies or had any family history of the same.

There was no history of smoking in any of the donors. All routine investigations of the donors were within normal limits.

All three donors were downregulated using Inj.Cetrorelix as per conventional antagonist protocol. Ovarian stimulation was started on day 2 with recombinant FSH. Dose adjustment was done according to transvaginal follicular monitoring. For downregulation, Inj.Cetrorelix 0.25 mg was added once follicles reached 13–14 mm. Once follicles reached 18 mm, a trigger was given using recombinant human chorionic gonadotropins (hCG). Association between drugs used for ovulation induction such as clomiphene and gonadotropins and their association with hydatidiform mole has been reported before by Petignat et al.[13] It was estimated that when stimulated by clomiphene 11% of patients presented with molar pregnancies vs 3.8% seen in patients stimulated with gonadotropins. It was also observed that in 26.9% of patients stimulated by gonadotropins multiple pregnancies with molar tissue were seen. Oocytes were aspirated after giving trigger using recombinant hCG. It was postulated by Flam et al. that due to increased incidence of aspiration of immature oocytes after ovarian stimulation,[14] it was possible that some immature oocytes with impaired genetic material when subjected to embryo formation, may give rise to molar tissue.

The semen analysis of partners was evaluated in all three cases and was found to be normal as per WHO 2010 criteria.[15] It has been theorized that low-quality sperm also might contribute to the phenomenon of irregular cleavage.[16] Since complete moles are paternal in origin, hence the role of paternal age and sperm morphology may have a role in the pathogenesis of molar tissue in IVF pregnancies. Tests for genetic evaluation of sperms such as sperm DNA fragmentation may be of value in such cases.

Cytogenetic studies have shown us that complete moles have a 46 XX chromosomal makeup and are completely androgenetic in origin. Partial moles on the other hand are triploids containing two sets of paternal and one set of maternal chromosomes. The proposed mechanisms for the extra set of haploid chromosomes in partial moles include (i) dispermy, (ii) failure of first or second paternal meiotic divisions, and (iii) failure of first or second maternal meiotic divisions. Out of these, the commonest mechanism is dispermy.[17] Intracytoplasmic sperm injection was done in all three cases. Since partial moles arise out of dispermic fertilization, couples undergoing ICSI are actually at reduced risk of the same. Edwards et al. postulated that defective oocyte meiosis with complete exclusion of the second meiotic spindle, followed by duplication of androgenic chromosomes was the mechanism most leading to the formation of a complete mole.[18] While complete moles are possible, partial moles seen with ICSI pregnancies are difficult to explain.

Detailed embryologist notes regarding the development of embryos were compared. Parameters such as formation and documentation of two pronuclei, embryo morphology, timing and symmetry of cleavage, presence or absence of fragmentation were noted. In all three cases, we analyzed all the embryos that were found to have developed zygotes having two pronuclei and two polar bodies. The transfer of embryos at the blastocyst stage ensures that only the healthiest embryos are transferred, however, embryos were transferred at the cleavage stage in all three cases.

It is not clear which molecular mechanisms may have contributed to lead to morphologically normal-appearing embryos to form molar tissue. However, the disruption of the meiotic spindle and loss of maternal chromosomes after oocyte handling or due to fragmentation and degeneration of oocytes may be a probable cause.[19]

The number of embryos transferred in each was evaluated. In all three cases, no. of embryos transferred were 4, 6, and 5, respectively. The goal of *in vitro* fertilization is to optimize the number of embryos to transfer to maximize the live birth rate while minimizing the risk of multiple gestations. American Society for Reproductive Medicine (SART/ASRM) guidelines on the number of embryos to transfer reflect a trend toward transferring fewer embryos, with the most recent SART/ASRM guidelines recommending the transfer of one to two embryos in patients <35 years of age having a good prognosis.[20] However, various factors influence the number of embryos actually transferred at ground levels. As per our research, these may include ART providers' experience, institute preferences, patient wishes, and nonavailability of cryopreservation facilities at many centers. Ambiguity and absence of a uniform code of guidelines governing ART in India may also be a reason for the above. Transfer of multiple embryos not only increases chances of higher-order pregnancies and the maternal and fetal morbidity associated with it but the association of molar tissue along with higher-order pregnancies can present a whole new set of challenges for the clinician. Decisions regarding the fate of a precious pregnancy along with the risk of morbidity caused by the coexisting mole and the risk of persistent trophoblastic disease or recurrent molar pregnancy may need to be individualized and carefully balanced.

There is also the possibility of these cases being diagnosed late. The detection of a fetal heartbeat during early pregnancy can cause the coexistent mole to be overlooked. Also, the overall sensitivity and positive predictive value for the grayscale ultrasound diagnosis of a hydatidiform mole are 44% and 48%, respectively. For partial moles, the respective values are 20 and 22% and for complete moles, they are 95% and 40%.[21] The rise in β-hCG may be attributed to multiple pregnancies. Hence, the diagnosis may be missed and these cases detected at an advanced gestation with increased risk of morbidity.

These pregnancies are difficult to manage as they are associated with hyperthyroidism, vaginal bleeding, atonicity, and risk of embolism and subsequent neoplasia. All three pregnancies needed termination. In cases 1 and 3, patients and relatives did not want to continue a pregnancy after being explained regarding the risks. Whereas in case 2, pt presented with profuse bleeding and required a life-saving hysterectomy. Preoperative workup of these cases include careful pelvic ultrasound (MRI occasionally), detailed pre-anesthetic checkup, complete blood counts, blood grouping with Rh typing and cross match, thyroid profile, serum electrolytes, LFT, KFT, chest X-ray or CT chest scan, ECG, and echo. During surgery, a wide bore cannula and cross-matched blood should be available. General anesthesia instead of regional is preferred. Inadvertent fluid overload should be avoided. Peroperative surgical challenges are the risk of perforation at the time of the suction evacuation of the uterus. Hemorrhage during an evacuation may be life-threatening at times. Detailed counseling of the patient and relatives is necessary as the possibility of a life-saving hysterectomy following torrential bleeding is a very real possibility. Moreover, the release of molar tissue could trigger the coagulation cascade. Thromboembolism leading to acute respiratory distress may be fatal. Chances increase with increasing size of uterus (>16 weeks). In our two cases, the uterus was term size. Sometimes, as seen in case 2, hysterectomy with fetuses *in situ* may be the only option for the surgeon. In patients who desire future fertility, this may be a difficult decision to make. While doing the hysterectomy of a huge uterus like in our case, it is advisable to follow:

- The no-touch technique, i.e., minimal manipulation of the uterus while applying hemostatic clamps.
- Small bits of the pedicle to be secured in the clamp step by step to avoid the release of molar tissue in circulation.
- Harmonic/bipolar cautery or electrocautery with simultaneous suturing can be used as a replacement of sutures alone as they give the additional benefit of the plug at the pedicle which decreases further chances of dissemination of molar tissue.
- Preoperative, internal iliac artery catheterization can be done which can be converted to embolization in case of hemorrhage occur during surgery.

In some cases, like case 3, it may be possible to remove the fetuses and molar tissue *via* hysterotomy and preserve the uterus. Whether or not to do a repeat embryo transfer/IVF cycle in such patients is a dilemma for the clinician. Berkowitz et al. in a study have reported a higher propensity for a patient with one episode of GTD (complete or partial mole) to develop a molar disease of either type in an ensuing pregnancy.[22] Poor regulation of the polar body and pronucleus formation in fertilized oocytes may be the reason for a recurrent hydatidiform mole in such patients. Preimplantation genetic diagnosis should be offered to such patients to avoid the possibility of recurrent molar pregnancy if a repeat IVF cycle is desired.

The limitation of the above case reporting is that since the incidence of occurrence of molar pregnancy in IVF conceptions is low, only a retrospective analysis of the characteristics of donors, techniques used during the process of ovarian stimulation, grading, and quality of embryos could be done. Hence, the results must be interpreted within the context and limitations of the same.

Conclusion

It is estimated that as many as 15% of couples worldwide suffer from infertility.[23] While the advances in recent fertility treatments have been a major step forward in the direction of helping such couples achieve conception, it is also imperative that techniques involving the handling of genetic material be evaluated for their safety toward the mother and guidelines developed which can standardize these procedures with respect to evidence-based data available.

References

1. Soper JT, Mutch DG, Schink JC. American College of Obstetricians and Gynecologists. Diagnosis and treatment of gestational trophoblastic disease: ACOG practice bulletin no. 53. Gynecol Oncol 2004;93(3):575–585. DOI: 10.1016/j.ygyno.2004.05.013.
2. Seckl MJ, Sebire NJ, Berkowitz RS. Gestational trophoblastic disease. Lancet 2010;376(9742):717–729. DOI: 10.1016/S0140-6736(10)60280-2.
3. Jinno M, Ubukata Y, Hanyu I, et al. Pregnancy: hydatidiform mole with a surviving coexistent fetus following in-vitro fertilization. Hum Reprod 1994;9(9):1770–1772. DOI: 10.1093/oxfordjournals.humrep.a138792.
4. Cheng PJ, Chang FH, Liang CC, et al. A twin pregnancy with a hydatidiform mole and an alive, coexistent baby after in

vitro fertilization and embryo transfer. J Assist Reprod Genet 1995;12(6):389–392. DOI: 10.1007/BF02215731.
5. Candelier JJ. The hydatidiform mole. Cell Adh Migr 2016;10(1-2):226–235. DOI: 10.1080/19336918.2015.1093275.
6. Wani RT. Socioeconomic status scales-modified Kuppuswamy and Udai Pareekh's scale updated for 2019. J Family Med Prim Care 2019;8(6):1846. DOI: 10.4103/jfmpc.jfmpc_288_19.
7. Vecchia CL, Franceschi S, Parazzini F, et al. Risk factors for gestational trophoblastic disease in Italy. Am J Epidemiol 1985;121(3):457–464. DOI: 10.1093/oxfordjournals.aje.a114018.
8. Savage P, Williams J, Wong SL, et al. The demographics of molar pregnancies in England and Wales from 2000–2009. J Reproduct Med 2010;55:341–345.
9. Sebire NJ, Foskett M, Fisher RA, et al. Risk of partial and complete hydatidiform molar pregnancy in relation to maternal age. Br J Obstet Gynaecol 2002;109(1):99–102. DOI: 10.1111/j.1471-0528.2002.t01-1-01037.x.
10. Savage PM, Sita-Lumsden A, Dickson S, et al. The relationship of maternal age to molar pregnancy incidence, risks for chemotherapy and subsequent pregnancy outcome. J Obstet Gynaecol 2013;33(4):406–411. DOI: 10.3109/01443615.2013.771159.
11. Clagett-Dame M, Knutson D. Vitamin A in reproduction and development. Nutrients 2011;3(4):385–428. DOI: 10.3390/nu3040385.
12. Yokobayashi S, Liang CY, Kohler H, et al. PRC1 coordinates timing of sexual differentiation of female primordial germ cells. Nature 2013;495(7440):236–240. DOI: 10.1038/nature11918.
13. Petignat P, Vassilakos P, Campana A. Are fertility drugs a risk factor for persistent trophoblastic tumour? Hum Reprod 2002;17(6):1610–1615. DOI: 10.1093/humrep/17.6.1610.
14. Flam F, Lundstrom V, Lindstedt J, et al. Choriocarcinoma of the fallopian tube associated with induced superovulation in an IVF program; a case report. Eur J Obstet Gynecol Reproduct Biol 1989;33(2):183–186. DOI: 10.1016/0028-2243(89)90212-8.
15. Cooper TG, Noonan E, von Eckardstein S, et al. World health organization reference values for human semen characteristics. Hum Reprod Update 2010;16(3):231–245. DOI: 10.1093/humupd/dmp048.
16. Rubio I, Kuhlmann R, Agerholm I, et al. Limited implantation success of direct-cleaved human zygotes: a time-lapse study. Fertil Steril 2012;98(6):1458–1463. DOI: 10.1016/j.fertnstert.2012.07.1135.
17. Lubna P, Toth TL, Leykin L, et al. High incidence of triploidy in in-vitro fertilized oocytes from a patient with a previous history of recurrent gestational trophoblastic disease. Hum Reprod 1996;11(7):1529–1532. DOI: 10.1093/oxfordjournals.humrep.a019432.
18. Edwards R, Crow J, Dale S, et al. Preimplantation diagnosis and recurrent hydatidiform mole. Lancet 1990;335(8696):1030–1031. DOI: 10.1016/0140-6736(90)91089-S.
19. Harada I, Tsutsumi O, Takai Y, et al. DNA polymorphism analysis of a case of complete hydatidiform mole coexisting with a fetus. Hum Reprod 1997;12(11):2563–2566. DOI: 10.1093/humrep/12.11.2563.
20. Practice Committee of the American Society for Reproductive Medicine. Guidance on the limits to the number of embryos to transfer: a committee opinion. Fertil Steril 2017;107(4):901. DOI: 10.1016/j.fertnstert.2017.02.107.
21. Kirk E, Papageorghiou AT, Condous G, et al. The accuracy of first trimester ultrasound in the diagnosis of hydatidiform mole. Ultrasound Obstet Gynecol 2007;29(1):70–75. DOI: 10.1002/uog.3875.
22. Berkowitz RS, Bernstein MR, Laborde O, et al. Subsequent pregnancy experience in patients with gestational trophoblastic disease. J Reprod Med 1994;39(3):228–232. DOI: 10.1097/00006254-199408000-00015.
23. Agarwal A, Mulgund A, Hamada A, et al. A unique view on male infertility around the globe. Reprod Biol Endocrinol 2015;13(1):37. DOI: 10.1186/s12958-015-0032-1.