Case Report of Ectopic Ovarian Pregnancy Following Fresh Embryo Transfer

Nivin Samara and Yaakov Bentov

Department of Obstetrics and Gynecology, TRIO Fertility Clinic, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada.

ABSTRACT

BACKGROUND: Ovarian pregnancy is a rare and challenging clinical phenomenon. Recent studies have identified assisted reproductive treatments and infertility as risk factors. However, neither a definite mechanism nor clear risk factors were identified and therefore prevention strategies are yet unavailable.

CLINICAL CASE: In this article, we present a case of ovarian pregnancy occurring following in vitro fertilization treatment and a fresh embryo transfer. The couple was diagnosed with unexplained infertility and no identifiable risk factors for extrauterine pregnancy. The diagnosis of ovarian pregnancy was made during explorative laparoscopy performed due to suspected extrauterine pregnancy. The patient had normal intra- and postoperative course.

CONCLUSION: Ovarian pregnancy is an infrequent and a challenging diagnosis. Yet, late diagnosis and lack of appropriate intervention may have long-term implications. Several mechanisms and risk factors are proposed, and their acknowledgment may improve early diagnosis and prevention of complications.

KEYWORDS: ovarian pregnancy, IVF complications, ectopic pregnancy

CITATION: Samara and Bentov. Case Report of Ectopic Ovarian Pregnancy Following Fresh Embryo Transfer. Clinical Medicine Insights: Reproductive Health 2016:10 29–32 doi:10.4137/CMHR.S40593.

TYPE: Case Report

RECEIVED: July 28, 2016. RESUBMITTED: September 21, 2016. ACCEPTED FOR PUBLICATION: September 23, 2016.

ACADEMIC EDITOR: Zeev Blumenfeld, Editor in Chief

PEER REVIEW: Two peer reviewers contributed to the peer review report. Reviewers’ reports totaled 217 words, excluding any confidential comments to the academic editor.

FUNDING: Authors disclose no external funding sources.

COMPETING INTERESTS: Authors disclose no potential conflicts of interest.

Introduction

It is well established that fertility treatments including assisted reproductive technology (ART) increase the risk of ectopic pregnancy. Ovarian pregnancy is a very rare complication of both spontaneous and ART-induced pregnancies; the estimated incidence is 0.5%–3% of all ectopic pregnancies. Ovarian pregnancy can be explained by one of the following two mechanisms: direct fertilization of an anovulated mature egg inside the ovary or retrograde embryo migration back into the ovary via the fallopian tube. Accordingly, ovarian pregnancy is classified as primary, follicular fertilization, or secondary, embryo reflux through the tube. In vitro fertilization (IVF), embryos are transferred to the uterus with ultrasound guidance. Therefore, ovarian pregnancy in IVF most likely occurs via retrograde migration of the embryo through the tube and implantation in the ovary. However, the remote possibility of fertilization of an intrafollicular anovulated egg during intercourse around the time of egg retrieval cannot be ruled out. Early detection of ovarian pregnancy is challenging, and in many cases, the diagnosis is made during an urgent surgical intervention due to acute abdominal pain or bleeding. The diagnosis is usually confirmed when choriocarcin villi are detected within the ovary.

In this case report, we describe an ovarian pregnancy occurring after a fresh embryo transfer. The patient has given her consent for publication of this report.
10,000 IU of hCG (Pregnyl®; Merck Canada Inc.) to trigger ovulation; 13 eggs were retrieved, 10 of them were mature. The eggs were fertilized with intracytoplasmic sperm injection; six blastocysts developed, of which five were frozen and a single embryo grade 4AA was transferred on day 5. Suppositories of progesterone were used for luteal support. First βhCG, two weeks later, was 329 IU and increased to 941 IU in two days. Two weeks later, the patient was admitted with acute left abdominal pain. Upon admission, she had normal vital signs and a tender abdomen. Her serum βhCG concentration on that day was 3000 IU/L. A transvaginal ultrasound demonstrated a large amount of blood and blood clots in the pelvis. No intrauterine pregnancy was observed, and a suspicious mass was seen in the left adnexa. An urgent laparoscopy was performed shortly after. After aspiration of the blood, a ruptured left ovarian ectopic pregnancy was identified. The tissue was removed from the ovary, and the edges of the ruptured follicle were confirmed to be clear. The surgeons described a normal left fallopian tube and right adnexa. The operative and postoperative course was otherwise uneventful. The patient was instructed to have serial measurements of serum βhCG concentration until it declines to zero. In a follow-up visit in our clinic, the patient was feeling well and symptom free. A frozen embryo transfer cycle was planned; it will be a medicated cycle with Estrace and intramuscular injection of progesterone expecting that the latter will achieve a more quiescent uterus. The pathological report confirmed the presence of chorionic villi in the ovary, validating the diagnosis of an ovarian ectopic pregnancy.

**Discussion**

Ovarian pregnancy is a rare diagnosis. Its incidence is reported to be 0.5%–3% of all extrauterine pregnancies (1:3000–1:7000 of all pregnancies). Some reports suggest that the apparent increase in the incidence of ovarian pregnancy is the result of improved diagnostic tools. Presumably, some of the ovarian pregnancies are mistakenly diagnosed as tubal pregnancies and treated conservatively or medically without a final confirmation of the exact location. Due to the scarcity of ovarian pregnancies, it is hard to demonstrate a causal relationship between ART and the occurrence of ovarian pregnancy. One study among IVF patients showed a higher frequency of ovarian pregnancy comprising 4.5%–6% of extrauterine pregnancies and 0.35% of all clinical pregnancies. However, there may be a detection bias since IVF pregnancies are usually monitored earlier and more carefully than natural pregnancies; and therefore, short-lived IVF-induced ovarian pregnancies have a higher likelihood of being detected.

The ovarian pregnancy case presented here is a result of fresh embryo transfer of single embryo. The most likely explanation to its occurrence is a retrograde migration of the blastocyst through the tube and implantation into the ovary, possibly through one of the aspiration needle puncture sites. The transfer itself was reported to be easy and uneventful.

Ovarian pregnancy presents with similar symptoms to tubal pregnancy symptoms, namely, delayed menses, vaginal bleeding, and abdominal pain; however, asymptomatic ovarian pregnancies were also described. As with other extrauterine pregnancies, an empty uterus and rising serum βhCG should raise suspicion; however, preoperative diagnosis is not common as the sonographic appearance might mimic a corpus luteum, a hemorrhagic ovarian cyst, or a tubal pregnancy. Koo et al did, however, report about seven cases of confirmed preoperative diagnosis. In 1868, Otto Spiegelberg, a German gynecologist established the diagnostic criteria for ovarian pregnancy. These criteria are based on intraoperative findings: (1) intact fallopian tube on the ipsilateral side, (2) the gestational sac is in the same position as the ovary, (3) the ovary is connected to the uterus by the utero-ovarian ligament, and (4) the ovarian tissue is present in the wall of the gestational sac.

Ovarian pregnancy is more common in fertile women; however, no other clear risk factors for ovarian pregnancy were reported. Nonetheless, several publications reported an increased rate of ovarian pregnancies that was associated with certain clinical conditions. Choi et al suggested that spontaneous ovarian pregnancies were related to the concurrent use of intrauterine device. A possible association was suggested between pelvic inflammation reaction secondary to a pelvic inflammatory disease or surgical intervention and ovarian pregnancy. It should be noted that a high concentration of estradiol, as reported in this case report, may promote pelvic inflammation. Factors associated with extrauterine pregnancy in IVF are tubal infertility, fresh embryo transfer compared to frozen, cleavage stage compared to blastocyst stage embryos, and large number of transferred embryos. As mentioned earlier, several authors described an increased risk of ovarian pregnancy among fertile patients undergoing ovulation induction treatment as well as IVF treatment. Apart from the aforementioned risk factors, possible explanations for the increased risk of ovarian pregnancy are injection of a high volume of transfer media and the patient in a tilted position. Oliveira et al described a possible association between blastocyst transfer and intraovarian implantation, as they had no cases of ovarian pregnancies following transfer of embryos on days 2 and 3. Surprisingly, several cases of ovarian pregnancies were described following in vitro fertilization-embryo transfer (IVF-ET) in patients who had previously undergone bilateral salpingectomy. The exact mechanism for these is unclear but should encourage further evaluation of other potential pathophysiological mechanisms for the formation of ovarian pregnancies following fresh and frozen embryo transfer. An interesting proposed mechanism was described by Shan et al. According to this suggestion, the cause for ovarian pregnancy is pelvic inflammation that involves the ovary. Consequently, the inflammation of the ovary may affect the process of detachment of the cumulus-oocyte complex and...
prevent the release of the ovulated oocyte, leading to fertilization of the mature oocyte by the sperm arriving through the fallopian tube inside the ruptured follicle. Despite its uncommon occurrence, perhaps ovarian stimulation and the resulting high estradiol concentration as well as the oocyte retrieval induce an inflammatory process in the ovary, which affects the oocyte release. Combined with intercourse close to the time of oocyte retrieval may lead to spillage of sperm via the tubes through the puncture site of the ovarian follicle, leading to intrafollicular fertilization.

Several studies have indicated a possible relationship between supraphysiologic levels of estradiol in ART cycles and ectopic pregnancy. In their study, Wang et al found a higher prevalence of ectopic pregnancy following fresh embryo transfer compared to frozen embryo transfer, a subanalysis of the results showed more ectopic pregnancies among patients with peak serum estradiol concentration exceeding 4085 pg/mL (15,000 pmol/L). The peak serum estradiol for the patient presented in this case report did exceed this threshold (19,584 pmol/L).

A possible mechanism for the effect of high estradiol concentration is provided by the following observations: it has been described that elevated estradiol leads to alteration in the normal physiologic function of the fallopian tube, increasing the likelihood for extraterine implantation. These effects include impaired protein secretion, ciliary motion frequency, embryonic motility, and implantation. We can assume that the impact of high estradiol on the normal function of the tube can lead to nontubal ectopic pregnancy such as ovarian pregnancy in certain patients. Another hypothesis that attempts to explain ovarian pregnancies post bilateral salpingectomy states that during embryo transfer an incidental puncture of the uterus occurs, and the embryo descents through the microscopic tract, resulting in ovarian pregnancy. A case report by Hsu et al described a cornual fistula in patients who had previous salpingectomy. No abnormal findings during surgery and no history of any uterine manipulation were reported in our case.

Since imaging and serum βhCG measurements are of limited contribution to the diagnosis of ovarian pregnancy, the American Society for Reproductive Medicine recommends on a surgical intervention in any case of suspected ovarian pregnancy. Surgical intervention may begin as explorative laparoscopy for suspected extraterine pregnancy. The surgical treatment for ovarian pregnancy may include salpingo-oophorectomy, oophorectomy, wedge resection, and removal of gestational product. Conservative surgery is widely accepted today. As long as the patient is stable, the aim should be to attempt to keep as much ovarian tissue as possible and avoid compromising ovarian reserve. Medical intervention with IM methotrexate (MTX) injection is a reasonable option in hemodynamically stable patients with preoperative diagnosis of ovarian pregnancy. It should be noted that unlike treatment with MTX for tubal pregnancy, the use of MTX to treat ovarian pregnancy is not as well established. Kudo et al and Shamma and Schwartz described a successful treatment for ovarian pregnancies with systemic MTX, while Mittal et al showed promising results with an intragestational sac MTX injection. In stable patients with decreasing levels of βhCG, expectant management with no intervention can also be considered. The risk for recurrence is very low, as only one case of recurrent ovarian pregnancy had been described thus far.

Conclusion

We present a case of ovarian pregnancy following a fresh embryo blastocyst transfer that was managed surgically by removal of the gestational sac from the ovary while preserving the ovary. Ovarian pregnancy is a challenging diagnosis; however, clinicians should be aware of the possible risk of ovarian pregnancy in ART treatment. It should be actively pursued in high-risk patients in order to prevent complications.

Author Contributions

Analyzed the data: NS. Wrote the first draft of the manuscript: NS and YB. Agree with manuscript results and conclusions: NS and YB. Jointly developed the structure and arguments for the paper: NS and YB. Made critical revisions and approved final version: NS and YB. All authors reviewed and approved of the final manuscript.

REFERENCES

1. Marcus SF, Brinsden PR. Analysis of the incidence and risk factors associated with ectopic pregnancy following in-vitro fertilization and embryo transfer. Hum Reprod. 1995;10(1):199–203.
2. Raziel A, Schachter M, Mordechai E, Friedler S, Panoski M, Ron-El R. Ovarian pregnancy–a 12-year experience of 10 cases in one institution. Eur J Obstet Gynecol Reprod Biol. 2004;114(1):92–96.
3. Boronow RC, Mcelin TW, West RH, Buckingham JC. Ovarian pregnancy; report of four cases and a thirteen-year survey of the English literature. Am J Obstet Gynecol. 1965;91:1095–1106.
4. Marcus SF, Brinsden PR. Primary ovarian pregnancy after in vitro fertilization and embryo transfer: report of seven cases. Fertil Steril. 1993;60(1):167–169.
5. Grimes HG, Noul RA, Gallagher JC. Ovarian pregnancy: a series of 24 cases. Obstet Gynecol. 1983;61(2):174–180.
6. Gaudain MR, Coulter KL, Robins AM, Verghese A, Hanretty KP. Is the incidence of ovarian ectopic pregnancy increasing? Eur J Obstet Gynecol Reprod Biol. 1996;70(2):141–143.
7. Bougher J, Coste J, Fernandez H, Pouly JL, Job-Spiira N. Sites of ectopic pregnancy; a 10 year population-based study of 1800 cases. Hum Reprod. 2002;17(12):3224–3230.
8. Choi HJ, Im KS, Jung HJ, Lim KT, Mok JE, Kwon YS. Clinical analysis of ovarian pregnancy: a report of 49 cases. J Obstet Gynecol Reprod Biol. 2011;158(1):87–89.
9. Andrade AG, Rocha S, Manques CO, et al. Ovarian ectopic pregnancy in adolescence. Clin Case Rep. 2015;3(11):912–915.
10. Koo YJ, Choi HJ, Im KS, Jung HJ, Kwon YS. Pregnancy outcomes after surgical treatment of ovarian pregnancy. Int J Gynaecol Obstet. 2011;114(2):97–100.
11. Kashima K, Yahata T, Yamaguchi M, Fujita K, Tanaka K. Ovarian pregnancy resulting from cryopreserved blastocyst transfer. J Obstet Gynaecol Res. 2013;39(1):375–377.
12. Huang B, Hu D, Qian K, et al. Is frozen embryo transfer cycle associated with a significantly lower incidence of ectopic pregnancy? An analysis of more than 30,000 cycles. Fertil Steril. 2014;102(3):1345–1349.
13. Shapiro BS, Daneshmand ST, De Leon L, Garner FC, Aguirre M, Hudson C. Frozen-thawed embryo transfer is associated with a significantly reduced incidence of ectopic pregnancy. Fertil Steril. 2012;98(6):1490–1494.
14. Ishihara O, Kuwahara A, Saitoh H. Frozen-thawed blastocyst transfer reduces ectopic pregnancy risk: an analysis of single embryo transfer cycles in Japan. *Fertil Steril.* 2011;95(6):1966–1969.

15. Bu Z, Xiong Y, Wang K, Sun Y. Risk factors for ectopic pregnancy in assisted reproductive technology: a 6-year, single-center study. *Fertil Steril.* 2016;106(1): 90–94.

16. Acharya KS, Acharya CR, Provost MP, et al. Ectopic pregnancy rate increases with the number of retrieved oocytes in autologous in vitro fertilization with non-tubal infertility but not donor/recipient cycles: an analysis of 109,140 clinical pregnancies from the Society for Assisted Reproductive Technology registry. *Fertil Steril.* 2015;104(4):873–878.

17. Fernandez H, Coste J, Job-Spira N. Controlled ovarian hyperstimulation as a risk factor for ectopic pregnancy. *Obstet Gynecol.* 1991;78(4):656–659.

18. Oliveira FG, Abdelmassih V, Costa AL, Balmaceda JP, Abdelmassih S, Abdelmassih R. Rare association of ovarian implantation site for patients with heterotropic and with primary ectopic pregnancies after ICSI and blastocyst transfer. *Hum Reprod.* 2001;16(10):2227–2229.

19. Arabekoglu CS, Berkner B, Dunder I. Ovarian ectopic pregnancy after intracytoplasmic sperm injection. *Eur J Obstet Gynecol Reprod Biol.* 2004;112(1):104–106.

20. Dursun P, Gultekin M, Zeyneloglu HB. Ovarian ectopic pregnancy after ICSI-ET: a case report and literature review. *Arch Gynecol Obstet.* 2008;278(2):191–193.

21. Priya S, Kamala S, Gunjan S. Two interesting cases of ovarian pregnancy after in vitro fertilization-embryo transfer and its successful laparoscopic management. *Fertil Steril.* 2009;92(1):e17–e19.

22. Feit H, Leibovitz Z, Kerner R, Keidar R, Sagiv R. Ovarian pregnancy following in vitro fertilization in a woman after bilateral salpingectomy: a case report and review of the literature. *J Minim Invasive Gynecol.* 2015;22(4):675–677.

23. Shan N, Dong D, Deng W, Fu Y. Unusual ectopic pregnancies: a retrospective analysis of 65 cases. *J Obstet Gynaecol Res.* 2014;40(1):147–154.

24. Wang J, Wei Y, Diao F, et al. The association between polycystic ovary syndrome and ectopic pregnancy after in vitro fertilization and embryo transfer. *Am J Obstet Gynecol.* 2013;209(2):e1–9.

25. Shao R, Deng Y, Zou S, et al. The role of estrogen in the pathophysiology of tubal ectopic pregnancy. *Am J Transl Res.* 2012;4(3):269–278.

26. Shao R, Egecioglu E, Weijdegej B, et al. Dynamic regulation of estrogen receptor-alpha isoform expression in the mouse fallopian tube: mechanistic insight into estrogen-dependent production and secretion of insulin-like growth factors. *Am J Physiol Endocrinol Metab.* 2007;293(5):E1430–E1442.

27. Nakahari T, Nishimura A, Shimamoto C, et al. The regulation of ciliary beat frequency by ovarian steroids in the guinea pig Fallopian tube: interactions between oestradiol and progesterone. *Biomed Res.* 2011;32(5):321–328.

28. Parazzini F. Oestrogens and progesterone concentrations and risk of ectopic pregnancy: an epidemiological point of view. *Hum Reprod.* 1996;11(2):234–238.

29. Wang H, Dey SK. Roadmap to embryo implantation: clues from mouse models. *Nat Rev Genet.* 2006;7(3):185–199.

30. Fisch B, Peled Y, Kaplan B, Zehavi S, Neri A. Abdominal pregnancy following in vitro fertilization in a patient with previous bilateral salpingectomy. *Obstet Gynecol.* 1996;88(4 pt 2):642–643.

31. Hsu CC, Yang TT, Hsu CT. Ovarian pregnancy resulting from cornual fistulae in a woman who had undergone bilateral salpingectomy. *Fertil Steril.* 2005;83(1):205–207.

32. Practice Committee of American Society for Reproductive Medicine. Medical treatment of ectopic pregnancy. *Fertil Steril.* 2006;86(suppl 1):S96–S102.

33. Kudo M, Tanaka T, Fujimoto S. [A successful treatment of left ovarian pregnancy with methotrexate]. *Nihon Sanka Fujinka Gakkai Zasshi.* 1988;40(6):811–813.

34. Shamma FN, Schwartz LB. Primary ovarian pregnancy successfully treated with methotrexate. *Am J Obstet Gynecol.* 1992;167(5):1307–1308.

35. Mittal S, Dallttwal V, Bnatural P. Successful medical management of ovarian pregnancy. *Int J Gynaecol Obstet.* 2003;80(3):309–310.