

# 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

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**CORRESPONDENCE:** nivin5ss@yahoo.com

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## Introduction

It is well established that fertility treatments including assisted reproductive technology (ART) increase the risk of ectopic pregnancy.<sup>1</sup> 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.<sup>1,2</sup> 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.<sup>3</sup> In 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.<sup>4</sup> 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 chorionic 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.

## Case Report

The couple, a 33-year-old female patient and her 33-year-old male partner both with unremarkable medical history, underwent fertility investigation for primary infertility for more than one year. Her day 3 serum follicle stimulating hormone (FSH) was 11 IU, estradiol (E2) 177 pmol/L, anti-Müllerian hormone 1.6 ng/mL, and the rest of the hormonal measurements were normal. The patient had a sonohystero-gram that demonstrated an intramural fibroid with a diameter of 2 cm that did not interfere with uterine cavity and patent tubes with normal spillage. Her partner had a normal sperm analysis. The couple had three cycles of ovarian stimulation with good response (letrozole followed by recombinant FSH) combined with intrauterine insemination; however, no pregnancy was achieved. A decision was made to proceed with IVF treatment.

Her IVF treatment cycle was done using an antagonist protocol. On day 3 of the cycle, the patient began injections of 300 IU of recombinant FSH daily (Puregon®; Merck Canada Inc.). Ganirelix 250 µg (Orgalutran®; Merck Canada Inc.) was started on day 7 of stimulation and was combined with a 100 IU of human chorionic gonadotropins (hCGs; Pregnyl®; Merck Canada Inc.). All the medications were continued until the induction day. Peak serum 17-β-estradiol concentration was 19,584 pmol/L on the day on which she was given



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  $\beta$ hCG, 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  $\beta$ hCG 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  $\beta$ hCG 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).<sup>2,4–6</sup> Some reports suggest that the apparent increase in the incidence of ovarian pregnancy is the result of improved diagnostic tools.<sup>6,7</sup> 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.<sup>8</sup> 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.<sup>1</sup> 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.<sup>9</sup> As with other extrauterine pregnancies, an empty uterus and rising serum  $\beta$ hCG 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<sup>10</sup> 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.<sup>8</sup>

Ovarian pregnancy is more common in fertile women;<sup>6</sup> 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<sup>8</sup> 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.<sup>11</sup> 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,<sup>12–14</sup> cleavage stage compared to blastocyst stage embryos, and large number of transferred embryos.<sup>15</sup> Interestingly, several studies had reported an increased ectopic pregnancy rate following ovarian stimulation only.<sup>15,16</sup> As mentioned earlier, several authors described an increased risk of ovarian pregnancy among fertile patients undergoing ovulation induction treatment<sup>17</sup> as well as IVF treatment.<sup>18–21</sup> 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.<sup>19</sup> Oliveira et al<sup>18</sup> 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.<sup>22</sup> An interesting proposed mechanism was described by Shan et al.<sup>23</sup> 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.<sup>22,23</sup> 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.<sup>15</sup> In their study, Wang et al<sup>24</sup> 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).<sup>24</sup> 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 extrauterine implantation.<sup>25</sup> These effects include impaired protein secretion,<sup>26</sup> ciliary motion frequency,<sup>27</sup> embryonic motility,<sup>28</sup> and implantation.<sup>29</sup> 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 descends through the microscopic tract, resulting in ovarian pregnancy.<sup>30</sup> A case report by Hsu et al<sup>31</sup> described a corneal 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  $\beta$ hCG 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.<sup>32</sup> Surgical intervention may begin as explorative laparoscopy for suspected extrauterine 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<sup>33</sup> and Shamma and Schwartz<sup>34</sup> described a successful treatment for ovarian pregnancies with systemic MTX, while Mittal et al<sup>35</sup> showed promising results with an intragestational sac MTX injection. In stable patients with decreasing levels of  $\beta$ hCG, 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.<sup>9</sup>

## 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. Contributed to the writing 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.

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