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Case Report and Review of the Literature

Malignant Ovarian Dysgerminoma Following Ovulation Induction in Patients with Polycystic Ovarian Syndrome: A Literature Review and Two Case Reports

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ABSTRACT

Background: The relation of ovarian induction drugs to development of ovarian cancer is still unclear. Polycystic ovary syndrome (PCOS) is a complex endocrine disorder that has been reported as a risk factor for ovarian cancer in some studies.

Case presentation: We report two cases with polycystic ovarian syndrome who developed a malignant ovarian dysgerminoma following use of ovulation induction drugs. One of them was diagnosed during fifth month of pregnancy by intracytoplasmic injection (ICSI). Both cases were treated with conservative surgery.

Conclusion: We reported 2 cases of ovarian dysgerminoma in patients with PCOS following ovarian stimulation. A large multicenter observational study is recommended to investigate a possible association.

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Background

There is increasing use of fertility medications for ovulation induction and ovarian stimulation for in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) in the treatment of female infertility. The relation of assisted reproduction to development of ovarian cancer is still unclear. It is well-known that uninterrupted ovulation causing repeated ovarian epithelial surface damage and repair underlies the 'incessant ovulation theory' [1]. Use of fertility medications could increase ovarian cancer risk by promoting polyfollicular ovulation and ovulation trauma [1]. An alternate mechanism underlying the relationship between fertility treatment and ovarian cancer is the 'elevated gonadotropin' theory, which postulates that elevated gonadotropin levels resulting from fertility medications stimulate the ovarian epithelium and may induce malignant changes [2]. Two studies found an association between fertility medication use and ovarian cancer [3, 4]. While most recent studies and systematic reviews show no overall association between fertility medication use and

invasive ovarian cancer when using a subfertile control group or the general population [5].

Furthermore, in a Cochrane database systematic review, Rizzuto *et al.* found no convincing evidence of an increase in the risk of invasive ovarian tumors with fertility drug treatment but there may be an increased risk of borderline ovarian tumors in subfertile women treated with in-vitro fertilization (IVF) [6]. The review was updated in 2019 and concluded that some studies added a supporting evidence to suggest that infertility drugs may increase the risk of ovarian cancer slightly in subfertile women treated with infertility drugs when compared to the general population or to subfertile women not treated. The risk is slightly higher in nulliparous than in multiparous women treated with infertility drugs [7]. Polycystic ovary syndrome (PCOS) is a complex endocrine disorder characterized by oligo-ovulation, hyperandrogenism, and certain ultrasound criteria [8]. PCOS has been reported as a risk factor for ovarian cancer in multiple studies [9, 10]. However, some studies have reported a reduced risk of ovarian cancer among women with oligomenorrhea [1, 10].

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We report two cases with polycystic ovarian syndrome who developed a malignant ovarian dysgerminoma following ovulation induction. One of them was diagnosed during fifth month of pregnancy by ICSI. To the best of our knowledge; this association was not described before.

Case Presentations

Case I

A 23 years old female complained of primary infertility for 5 years because of polycystic ovarian syndrome (PCOS). Her husband had normal semen analysis and other fertility factors were normal. The couple decided to start an assisted reproduction trial on June 2018. Prior to the trial; the ovaries were seen by transvaginal ultrasound with polycystic criteria with no abnormal cystic or solid masses. To avoid ovarian hyperstimulation; the ovaries were stimulated using an antagonist protocol and triggering was done using LHRH analogue (Decapeptyl 0.1 mg ampoules subcutaneous injection). Ovum pick up was performed on 03/07/ 2018 and during oocyte retrieval ovaries were normal with no solid masses. Forty oocytes were retrieved, 32 were M2 grade that were fertilized by intracytoplasmic sperm injection (ICSI) technique resulted in 24 embryos of grade A. All embryos were cryopreserved at day-3 by verification. After thawing, 2 good-quality embryos were transferred to uterus 2 months later (on 01/09/2018).

Pregnancy was confirmed and continued with one normal fetus. The course of pregnancy was normal till the twenty-second week where a solid right ovarian mass 5X5 cm accidentally discovered during routine ultrasound scanning with no ascites and other abdominal organs were normal (Figure 1). Lactate dehydrogenase was found to be high (2400 mg/ml) raising the possibility of germ cell tumors of the ovary. The patient and her husband were informed about the condition and counseled about options of treatment and prognosis, but they chose to continue pregnancy till fetal maturity.



Figure 1: Transvaginal ultrasound picture of case 1 at 22 weeks of pregnancy showing a solid ovarian mass on one side of the gravid uterus.

At completed 37 weeks, an elective caesarean section was performed during which a staging laparotomy was done. The tumor was confined to right ovary with intact capsule measuring 11X9 cm (Figure 1). Liver, omentum, and intestine were free. No iliac or para-aortic lymph node enlargement. The neonate was a healthy female. A fertility-sparing right salpingo-oophorectomy with omental biopsy was performed (Figure 2).

Post-operative histopathology revealed ovarian dysgerminoma with focal infiltration of the capsule (Figure 3) with negative peritoneal cytology and free omental biopsy (stage Ic2). Immunohistochemical staining with CD 117 monoclonal antibody revealed diffuse positive membranous and cytoplasmic reaction (Figure 4). According to tumor board recommendations the patient was advised to receive 4 courses of BEP (Bleomycine, Etopozide, Cisplatinum) chemotherapy as an adjuvant treatment. Her post-operative follow-up by CT scans and tumor markers at 3, 6, and 12 months was normal.



Figure 2: Right ovarian solid mass 11X9 CM with fallopian tube (Case 1).

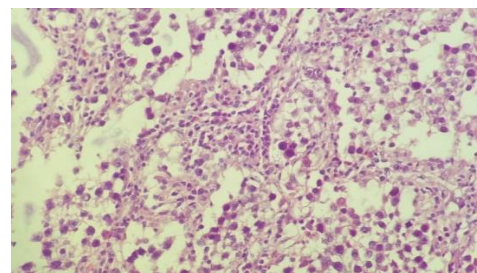


Figure 3: Hematoxyline and Eosin picture (H&EX400) shows sheets of large cells with vesicular nuclei and mitotic activity separated by fibrous strands with lymphocytes (Case 1).

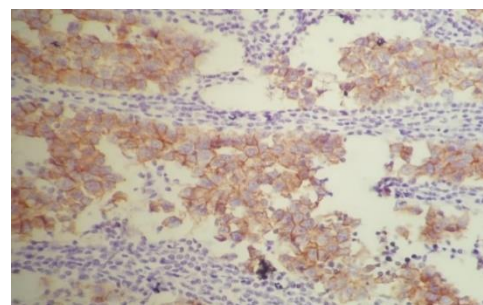


Figure 4: Immunohistochemical staining with CD 117 revealed diffuse positive membranous and cytoplasmic reaction (X 400) (Case 1).

Case II

A lady aged 25 years old, presented by primary infertility 3 years because of chronic anovulation diagnosed as PCOS based on chronic anovulation, ultrasound picture, and hyperandrogenism. Other fertility factors were normal. History of ovarian stimulation with clomiphene citrate and gonadotrophins for 8 months with poor response. The case was referred to our center for laparoscopic ovarian drilling. During routine ultrasound examination; left ovary showed a heterogenous ovarian mass 8X6 cm with a solid area more than 1 cm but no ascites and free pelvic and abdominal structures. Serum CA125 level was in normal range (12 IU/ml). After counseling of the couple; laparoscopy was performed (on

26/09/2006) during which the left ovarian mass could not be removed for fear of rupture of the capsule and spillage to pelvic cavity.

The case was shifted immediately to laparotomy for surgical staging. The tumor was limited to left ovary with intact capsule and free pelvic and abdominal organs. Intra-operative frozen section was done, and ovarian dysgerminoma was suspected. Left salpingo-oophorectomy, biopsies from other ovary, omental biopsy, peritoneal washing were done. The histopathological examination revealed left ovarian dysgerminoma, free other ovary, other biopsies and fluid cytology were free. The case was diagnosed as stage IA ovarian dysgerminoma and subsequently no further adjuvant treatment was given. During follow up with CT scans and tumors markers; the patient was going well with no evidence of tumor recurrence. One year later; the patient lost to follow up and her reproductive outcome was not known.

Discussion

Since introduction of in vitro fertilization in 1981 by Steptoe and Edward thousands of infertile couples could have children but ovaries of these women were subjected to ovarian stimulation over variable periods of time. There is a debate if the ovarian stimulating drugs increase risk of ovarian cancer or not. Some studies supported its role while others did not [3-7]. Moreover, progesterone, that usually used after ovarian stimulation as “luteal support” was reported to increase the risk for serous borderline ovarian tumors (RR 1.82; 95% CI 1.03-3.24), and among women treated with ≥ 4 cycles of progesterone (RR 2.63; 95% CI 1.04-6.64) [11]. On the other hand, other associated factors with infertility as anovulation, endometriosis, and nulliparity may increase risk of cancer. Factors suppressing ovulation, including pregnancy and oral contraceptive use, were inversely associated with the risk of all histologic types [12].

Yin *et al.*, studied 14,764 women had been diagnosed with PCOS; 182 developed a primary cancer 1 year or more after PCOS diagnosis [13]. The fully adjusted HR was 1.15; 95% CI, 1.00-1.33. The risks for specific cancers also were increased, compared with women without PCOS, including endometrial (hazard ratio, 2.62), ovarian (HR, 2.16), endocrine (HR, 1.92), pancreatic (HR, 3.4), kidney (HR, 3.0), and skeletal and hematopoietic (HR, 1.69) cancers. However, the study did not report the histopathologic types of the diagnosed cases of ovarian cancer and did not clarify if these women had received ovulation induction drugs. Besides the biological factors in PCOS, ovarian stimulation usually results in polyfollicular development with possibility of more ovulation traumas which is the basic part of pathogenesis of ovarian carcinoma according to “incessant ovulation theory” [1]. However, this is applied more for epithelial ovarian tumors.

In the first case, although rare, malignant ovarian tumors with pregnancy represent a real challenge. The reported incidence is 0.42 per 1000 pregnancies mainly borderline tumors followed by epithelial tumors [14]. However, diagnosis of ovarian mass was late at 22 weeks of pregnancy as the mass may mimic luteoma of pregnancy and corpus luteum hematoma. The diagnosis was supported by elevated LDH which agreed with other authors [15]. To the best of our knowledge, no published studies to report the association between ovarian stimulating drugs and malignant germ-cell tumors in women with PCOS. In case 2,

ovarian tumor was diagnosed during routine transvaginal ultrasound before laparoscopic ovarian drilling for treatment of PCOS. The updated Cochrane review concluded increased incidence of ovarian cancer after fertility drugs but did not report specific increase in incidence of dysgerminoma [7]. Both cases were diagnosed at stage 1 (Ic and Ia respectively), Thomas and colleagues reported that approximately 65% of patients with ovarian dysgerminoma present with stage IA disease with a cure rate approaching 100%, and fertility is usually preserved [16].

Conclusion

We reported 2 cases of ovarian dysgerminoma in patients with PCOS following ovarian stimulation. A large multicenter observational study is recommended to investigate a possible association.

Abbreviations

IVF: In-vitro Fertilization
ICSI: Intracytoplasmic Sperm Injection
PCOS: Polycystic Ovarian Syndrome
GCT: Germ-Cell Tumor
LDH: Lactate Dehydrogenase

Acknowledgment

Not applicable.

Ethics Approval and Consent to Participate

The case presentations are anonymous, and no IRB approval is needed for publication of case reports in our institution. Figures are anonymous and do not point to patient personal information.

Consent

A written consent for publication was obtained from “case 1” and a verbal consent from “case 2” as she is travelling abroad nowadays.

Availability of Data and Material

The data and figures are included in the manuscript.

Competing Interests

None.

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None.

Author Contributions

RH and NA: Collection of clinical data, management of the cases, and editing the manuscript.
AA and KZ: Histopathological diagnosis and preparation of histopathology pictures.

Conflicts of Interest

None.

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