Journal of Reproduction & Infertility
Volume 22, Issue no. 1
http://dx.doi.org/10.18502/jri.v22i1.4993

Original Article

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Relationship Between Polycystic Ovarian Morphology and Ectopic Pregnancy

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Abstract

Background: The purpose of the current study was to investigate the presence of polycystic ovarian morphology (PCOM) in patients with ectopic pregnancy (EP) and to find out the value of sonographic appearance of ovaries on the earlier diagnosis of EP.

Methods: In the current case-control study, thirty five patients with EP were recruited to evaluate ovarian sonographic morphology whereas 35 gestational age-matched women with healthy intrauterine pregnancy (IUP) were the controls. After ovarian sonography, ultrasound images were analyzed offline for ovarian area, ovarian volume, follicle number per cross section, and follicle distribution pattern. A questionnaire about the presence of hirsutism and menstrual irregularity prepared as well. Student's t-test or Mann-Whitney U test were used to compare continuous variables between 2 groups and categorical data were evaluated by using Chi-square or Fisher's exact test, where appropriate. Multiple logistic regression was used to find out the risk factors for EP.

Results: Mean gravidity and parity were significantly higher in the EP group compared to IUP group ($p<0.05$). PCOM was found to be significantly higher in the study group (51.4% *vs.* 20%, $p=0.006$). Logistic regression analysis showed that multiparity (OR=8.635; 95% CI, 1.653-45.104) and PCOM image on ultrasound (OR=19.081; 95% CI, 1.139-319.560) were found to be significantly associated with EP.

Conclusion: PCOM is more prevalent among women diagnosed with EP. This study demonstrates that PCOM assessed by transvaginal ultrasound may reflect EP in women with EP suspicion and may therefore serve as a clinical marker to assess EP.

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Received: Sept. 8, 2019
Accepted: Feb. 7, 2020

Keywords: Ectopic pregnancy, Estrogens, Hormones, Parity, Polycystic ovary syndrome, Progesterone.
To cite this article: Ozel S, Alkan M, Tokmak A, Oksuzoglu A, Kaya M, Aktulay A, et al. Relationship Between Polycystic Ovarian Morphology and Ectopic Pregnancy. J Reprod Infertil. 2021;22(1):32-37. http://dx.doi.org/10.18502/jri.v22i1.4993.

Introduction

Ectopic pregnancy (EP) is defined as the embryo localization outside uterine cavity. EP accounts for approximately 2% of all recognized pregnancies (1). In fact, 15% of maternal deaths during the first trimester are due to EP (2). Delay in the diagnosis of EP cases leads to restrictions in the treatment options and decreases the chance of laparoscopic and medical management (3). Therefore, early diagnosis and therapeutic intervention are potentially lifesaving and can reduce surgical morbidity by allowing elective surgery or non-surgical conservative treatment options (2). A previous study showed that the rate of EPs which resulted in complication requiring blood

transfusion, hysterectomy or sterilization, or hospitalization longer than 2 days decreased by earlier diagnosis (4). For this reason, awareness of associated risk factors with EP may lead to earlier diagnosis and management.

Polycystic ovary syndrome (PCOS) is the most common hormonal disorder affecting reproductive age women with a prevalence of 10% (5-7). The criteria for diagnosis and definition of PCOS used by clinicians and investigators are almost as heterogeneous as the syndrome itself. PCOS is characterized by a combination of oligo/amenorrhea, clinical or endocrine signs of hyperandrogenaemia and polycystic ovaries (6). Women diagnosed with PCOS have frequently difficulties to achieve pregnancy. Moreover, they are at higher risk for developing many obstetrical complications throughout pregnancy (8). The diagnosis during pregnancy cannot be made due to the hormonal changes.

Polycystic ovarian morphology (PCOM) is used for the diagnosis of PCOS in the most commonly cited classification system (7). Although no universal consensus on PCOM definition is present currently, some ultrasonographic parameters such as ovarian volume, number of follicle per ovary, and distribution pattern of follicles are used to define PCOM. The growth and development of the ovarian follicles continue during pregnancy (9). Ovarian morphology also does not significantly change during early pregnancy and the ovaries are best visible on ultrasound in the first trimester of pregnancy (10). Therefore, as a diagnostic tool, PCOM image on ultrasound may be utilized objectively during early pregnancy.

Although there are multiple studies that have investigated risk factors for EP (2, 11), there are limited studies evaluating the association between polycystic ovaries and EP. In a study by Wang et al. (12), it has been suggested that women with PCOS receiving *in vitro* fertilization (IVF) treatment have increased relative risk of EP. It is also uncertain to what extent PCOS itself influences pregnancy outcomes. The aim of this study was to explore the relationship of PCOM, as a part of PCOS, and EP which would assist early diagnosis and awareness.

Methods

Settings and study design: This case-control study was performed in a six-month period at the Zekai Tahir Burak Women's Health Education and Research Hospital between July 2016 and December 2016. The study protocol was approved by the local ethic committee. Women were informed about the study and those who participated provided written consent prior to transvaginal sonography.

Study samples: After selecting women meeting the inclusion criteria with confirmed EP, healthy pregnant women who applied for the first antenatal visit in the same gestational age as the index case were chosen as control group. Failure to visualize an intrauterine gestational sac or/and identified EP by ultrasonography combined with a level of the β-subunit of human chorionic gonadotropin (β-hCG) >1300 *mlU/ml* were the diagnostic criteria of EP. The study group consisted of 35 pregnant women whose EP was histopathologically confirmed as Arias Stella reaction in endometrial biopsy or/and pregnancy material extracted during surgery.

Patients with multiple pregnancies, patients carrying high risk factors for EP (History of EP, pelvic inflammatory disease, pelvic surgery, and IUD use) who conceived with IVF treatment, and who did not want to participate in the study were excluded. Other systemic diseases which can be associated with PCOM were also excluded from the study such as obesity [Body mass index (BMI) >30 kg/m^2], insulin resistance or diabetes mellitus, hypothyroidism, Cushing's disease, hyperprolactinemia, and late onset congenital adrenal hyperplasia. BMI was calculated as weight in kilograms divided by height in meters squared. Gestational ages were calculated according to the last menstrual period or measurement of crown–rump length.

Ultrasonographic evaluation: All our patients were examined by targeted transvaginal ultrasonography by the same radiologist with a Voluson 730 Expert ultrasound machine (GE Medical Systems, Kretztechnik GmbH & OHG, Zipf, Austria) equipped with a 3.5–5 *MHz* curvilinear transvaginal transducer. The sonographer who performed the ultrasound scans of women was blinded as to whether the pregnancy was ectopic or intrauterine before to confirm or exclude the diagnosis PCOM in pregnant women. Ultrasound images of ovaries were analyzed offline for ovarian area, ovarian volume, follicle number per cross section, and follicle distribution pattern. PCOM was defined by more than 12 peripheral follicular cysts in one plane between 2-8 *mm* in diameter and an increased ovarian volume of >10 cm^3 in one ovary. Ferriman–Gallwey scoring system was used to

assess hirsutism. A score of 8 or more was representative of clinical hirsutism. Oligomenorrhea was considered as menstrual cycles longer than 45 days, whereas amenorrhea was defined as the absence of a menstrual period for three consecutive months before the current pregnancy.

Statistical analysis: Data analysis was performed using SPSS, version 22.0 (SPSS Inc., Chicago, IL, United States). The Kolmogorov-Smirnov test was used to test whether continuous variables were normally distributed. Continuous variables were shown as mean±standard deviation (SD). Categorical variables were expressed as number (Percentages). Mean differences between study and control groups were compared using Student's t-test; the Mann-Whitney U test was used for comparisons of the median values. Differences between categorical data were evaluated using the Chi-square test. Multivariate logistic regression using enter method was conducted to find out the risk factors of EP. A $p<0.05$ was considered statistically significant.

Power analysis for two different proportions was conducted in G*Power software (G-power v3.1.9.2, Universitat Kiel, Kiel, Germany) to determine a sufficient sample size using an alpha of 0.05 and a power of 0.80. The proportions were set as 0.2 and 0.5 for each group with an allocation ratio of 1. Based on the aforementioned assumptions, the sufficient sample size was found to be 35 for each group.

Ethical consideration: Research involving human participants and/or animals. The study was approved by the ethical committee of the institution and was performed according to the standards of the Helsinki Declaration on human experimentation. Informed consent was obtained from all patients for being included in the study.

Results

A total of 70 pregnant women were included in this study. There were 35 patients in both EP (Study) and healthy pregnancy (Control) group. The mean maternal age was 30.6±5.2 and 28.4±5.3 years in the study and control groups, respectively (P=0.082). No significant differences were observed between the groups in terms of BMI, gestational age and number of previous EP and miscarriage (Table 1). Mean gravidity and parity were significantly higher in the study group compared to control group (p=0.001 and p<0.001, respectively). Number of smokers and women with comorbid disease (Hypertension) was also similar. PCOM was found to be significantly higher in the study group (51.4% *vs*. 20%, p=0.006). Hirsutism scores and history of oligomenorrhea did not statistically differ among the groups. Table 2 summarizes the outcomes of the logistic regression analysis. According to the analysis, multiparity (OR=8.635; 95% CI, 1.653-45.104; p=0.011) and PCOM image on ultrasound (OR=19.081; 95% CI, 1.139-319.560; p=0.040) were found to be significantly associated with EP.

Discussion

In the present study, an attempt was made to investigate the presence of PCOM in patients with EP and to find out the value of sonographic ap-

Table 1. Comparison of demographics and clinical characteristics

Variable	Study group (n:35)	Control group (n:35)	p-value
Maternal age (years) mean±SD	29.6±5.2	28.4±5.3	0.082 *
Body mass index (kg/m^2) mean±SD	26.5±3.5	25.9±3.6	0.684 *
Gravidity median (IQR)	3 (2)	2 (2)	<0.001 **
Parity median (IQR)	1 (1)	0 (1)	<0.001 **
No. of miscarriage median (IQR)	0 (1)	0 (1)	0.136 **
Gestational age (week) median (IQR)	6.0 (2)	6.0 (2)	0.628 **
Hirsutism score >8 *n* (%)	4 (11.4)	4 (11.4)	1.000 ***
Oligo-amenorrhea *n* (%)	7 (20)	7 (20)	1.000 ***
Smoker *n (%)*	10 (28.6)	5 (14.3)	0.145 ***
Comorbidity *n (%)*	2 (5.7)	1 (2.9)	0.550 ***
PCOM on TVUS *n (%)*	18 (51.4)	7 (20)	<0.006 ***

EP: Ectopic Pregnancy, PCOM: Polycystic Ovarian Morphology. TVUS: Transvaginal Ultrasound, SD: Standard Deviation, IQR: Interquartile Range. Data are expressed as mean±SD, median (IQR) and number (Percentage). * Student's t test, ** Mann Whitney-U test, *** Chi-square or Fisher's exact test. A p<0.05 is considered statistically significant

Table 2. Logistic regression analysis of risk factors for EP

Variable	Wald	p	Odds ratio	95% CI
Age (years)	1.201	0.273	0.914	0.778-1.074
BMI (kg/m^2)	0.282	0.595	0.952	0.793-1.143
Gestational week	0.955	0.328	1.220	0.819-1.817
Multiparity	6.533	0.011	8.635	1.653-45.104
Smoking	0.693	0.405	1.940	0.407-9.245
Co-morbidity	0.006	0.936	0.893	0.058-13.819
PCOS history	1.545	0.214	0.162	0.009-2.853
PCOM on TVUS	4.205	0.040	19.081	1.139-319.560

EP: Ectopic Pregnancy, BMI: Body Mass Index, PCOS: Polycystic Ovary Syndrome, PCOM: Polycystic Ovarian Morphology, TVUS: Transvaginal Ultrasound. A $p<0.05$ is considered statistically significant

pearance of ovaries on the diagnosis of EP. Although association of PCOM and EP has apparently not been explored until now, significant difference was found between study and control groups in the rate of sonographic polycystic ovary appearance. In fact, 51.4% of the study and 20% of the control group had ovaries with polycystic sonographic appearance. Our results showed that PCOM is more prevalent in women diagnosed with EP.

PCOS is a common reproductive disorder associated with many characteristic features, including hyperandrogenaemia, menstrual irregularity, and polycystic ovaries on ultrasonography. PCOM has been documented in 16–25% of normal women and ovulatory women with PCOM may be at the mildest end of the spectrum of PCOS (13). However, it is unknown whether women with PCOM and ovulatory cycles are at risk for the development of PCOS. There was no difference between the study and control groups in terms of hirsutism and menstrual irregularities in our study. Since the clinical and biochemical findings of the hyperandrogenism could not be evaluated in our pregnant women for the diagnosis of PCOS, our patients were checked only in terms of PCOM.

Most of the available literature suggests that pregnancies obtained with natural conception or assisted reproductive techniques in patients with PCOS have an increased risk of complications such as miscarriage, preeclampsia, preterm labor, gestational diabetes, meconium aspiration, and delivering large baby (8). However, it is uncertain to what extent the medical condition itself influences pregnancy and neonatal outcomes. Although there are studies evaluating pregnancy outcomes in patients with PCOS (14), no study exists yet to prove an association between PCOS and EP in natural conceptions.

Changes in serum sex steroid hormone levels may cause malfunction in tubal motility. In a previous experimental study, it was shown that in the presence of low serum progesterone levels, tuba uterinas worsened ovum transfer electrophysiologically (15). It has also been claimed that this worsening may be related to the higher incidence of EP in patients with luteal phase defects. Horne et al. (16) demonstrated that expression of sex steroid hormone receptors (Both progesterone and estrogen receptors) in fallopian tubes in women with EP altered compared with normal fallopian tubes.

Insulin resistance appears to play a pivotal role in the PCOS pathophysiology. Insulin like growth factors (IGFs) have been suggested to be involved in androgen production in theca cells in synergy with luteinizing hormone which probably contribute to the occurrence of hyperandrogenism in PCOS along with elevated levels of insulin (17). Tubal epithelial cells secrete IGF-1 which helps normal embryo implantation (18). Estrogen-responsive areas exist in the regulatory regions of the IGF-1 gene suggesting that estrogens regulate IGF-1 by a direct transcriptional mechanism (19). Eventually, IGF-1 is responsive to the cyclic changes of estradiol. Current evidence also suggests that the morphology and the functional integrity of the fallopian tubes is estrogen dependent (18).

In a more recent study conducted on IVF patients, it was suggested that women with PCOS had a lower threshold value for hyperphysiological estradiol levels that triggered EP formation (12). Collectively, all those studies indicate the

importance of serum hormone levels in the development of EP. Since PCOS is the most common hormonal and endocrine disorder seen in reproductive age women, it is not surprising that there is such a relationship with EP.

There are several defined risk factors for the development of EP. Some of them are easy to understand when considered pathophysiologically. Previous pelvic surgery, pelvic infections, and history of EP may cause anatomical distortion of the fallopian tubes. IVF, IUD, infertility, smoking, and advanced maternal age may cause functional tubal damage. On the other hand, parity is expected to increase with increasing maternal age. However, there is no exact consensus about the relation of parity and EP in the literature. A study conducted by Sindos et al. (20) proposed a statistically significant positive association between EP and parity. Conversely, Majhi et al. (21) showed increased risk of EP in primigravida which conflicts with the results of our study. The groups were matched in terms of age and many well known causes of EP were excluded; but the final analysis still showed that multiparity with PCOM is the most significant risk factor related to EP.

Nine percent of all pregnancy-related deaths are due to EP (8). It is a life threatening condition. Although early diagnosis and treatment are life-saving, it is more important to know the risk factors and take necessary precautions accordingly. Polycystic appearance of ovaries creates doubt about EP which may lead to earlier diagnosis. Early diagnosis of cases is important in choosing a less invasive treatment method. Fortunately, there was no maternal death due to EP in our hospital for 5 years.

To our knowledge, our study is the first to evaluate the relationship between PCOM and EP. The main limitation of our study was that PCOS was not clearly diagnosed because patients were included in the study after conception. Therefore, only the possible association of EP with PCOM was evaluated. Moreover, serum hormone levels such as estradiol and progesterone were not assessed. Some of the strengths of our study are its prospective nature and all ultrasound evaluations were performed by the same experienced radiologist.

Conclusion

In conclusion, this study indicated that PCOM was associated with an increased risk of EP after constitutional conceptions. Women with PCOM have increased relative risk of EP and in the suspicion of EP, morphology of ovaries can guide and help early diagnosis, thereby reducing morbidity in patients. Further studies with more patients are needed to reveal the definitive relationship between PCOS and EP.

Acknowledgement

We thank all the women who participated in our study.

Conflict of Interest

The authors report no conflict of interest regarding publication of this paper.

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