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Pregnancy outcome of polycystic ovarian syndrome cases under treatment for assisted reproduction under ultrasonic guidance

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Abstract
Aim: The purpose of the study was to examine the prevalence of spontaneous abortion in patients with polycystic ovary syndrome (PCOS) during follow-up. We also wanted to test the hypothesis that the miscarriage risk might not increase with age in PCOS.
Methods: A study of women undergoing assisted reproductive treatment at a teaching hospital was done. We retrieved clinical records of all women with PCOS (n = 62) who conceived after assisted reproduction treatment. Pregnancy outcome was divided according to fetal viability. Prevalence of live birth and spontaneous abortion was also calculated according to diagnosis.
Results: Prevalence of live birth was 61.29% in the PCOS cases. Prevalence of spontaneous abortion between gestational weeks 6 and 12 was 16.1 % in the PCOS group. The prevalence of spontaneous abortion during 6-12 weeks' gestation does not increased significantly with age among women with PCOD.
Conclusions: The prevalence of spontaneous abortion does not increase significantly with age up to 40 years in women with PCOS. This could be because of their greater ovarian reserve.

Keywords: polycystic ovarian disorder, abortion, metformin, obesity

Introduction

Polycystic ovarian syndrome is one of the most common female endocrine disorders. It is currently known to affect up to 10% of women of reproductive age and is one of the notable factors of female sub fertility [1]. The prevalence of menstrual irregularity has been addressed in several studies. PCOS is a common hyperandrogenic disorder in women of child bearing age group [2]. It is a multi-system metabolic disorder which has a major impact on quality of life and fertility [3]. The prevalence of obesity is increasing across the world particularly in the developed countries [4]. Upper - body obesity (android obesity) is common adverse health factor. There is overwhelming evidence that Upper – body obesity is major risk factor for cardiovascular disease and type 2 Diabetes Mellitus, whereas lower body obesity is not. Upper – body obesity diagnosed by measurement of waist – hip ratio (WHR), waist circumference, CT scan and MRI imaging [5]. Early stages of thyroid dysfunction may lead to subtle change in ovulation and endometrial receptivity, which may have profound effect on fertility. In adult woman, severe hypothyroidism may be associated with diminished libido and failure of ovulation, ovarian atrophy and amenorrhoea or menstrual irregularity. It is interesting to note that both PCOS and thyroid dysfunction are related [6]. Hypothyroidism is known to induce a clinical manifestation similar to PCOS [7-9]. The aims and objectives of the present work were to analyse the Problem of PCOD in women attending OPD at Teaching Hospital. The prevalence of infertility in women with PCOS varies between 70 and 80%. According to the American Society for Reproductive Medicine, the evaluation of infertility in women with PCOS or other causes of subfertility should start after six months of attempting pregnancy without success if the couple has regular sexual intercourse (2 to 3 times/week) without using contraceptive methods [10].

Infertility can have a significant psychological impact on those afflicted. Fortunately, many couples have favorable outcomes and end up conceiving without major interventions. For those who are not successful, there have been significant advancements in assisted reproductive technology (ART).Of the new methods, ultrasound has shown tremendous potential in the diagnosis and management of female infertility.

Transvaginal ultrasound is advantageous to trans abdominal because it allows for better spatial resolution and avoids the need for a full urinary bladder. Two-dimensional (2D) B-mode ultrasound depicts sagittal and transverse planes. Three-dimensional (3D) ultrasound allows for sagittal, transverse, and coronal views giving a more detailed image of the pelvic organs. The addition of color Doppler via transvaginal probes allows visualization of the miniscule intraovarian and endometrial vessels. Deviations from normal structure and function can be detected with these modern methods of imaging. There are numerous etiologies which factor into making a woman subfertile or infertile. Ovarian causes include poly- cystic ovary syndrome (PCOS), premature ovarian failure (POF), endometrioma, luteinized unruptured follicle (LUF) and luteal phase defect (LPD). Tubal factor infertility is most often associated with chronic pelvic inflammatory disease (PID). Uterine causes include submucosal fibroids, congenital Mullerian anomalies, such as septate uterus, endometrial polyps and intrauterine adhesions.

The recent advances in ultrasound technique allow for the accurate diagnosis of these disorders. For some of the seconditions, e.g. premature ovarian failure, ultrasonography has shown to be useful in formulating a treatment plan and predicting prognosis.

The principle infertility treatment initially includes preconception guidelines and the use of drugs to induce mono- or bifollicular ovulation. Other therapeutic modalities may also be employed, such as exogenous gonadotropins or laparoscopic ovarian drilling, which are considered to be second-line treatments, or *in vitro* fertilization (IVF), which is a third-line treatment [11] Thus, the choice of the most appropriate treatment depends on the patient's age, presence of other factors associated with infertility, experience and duration of previous treatments and the level of anxiety of the couple. The aim of the study was to determine the prevalence of PCOD cases in a study population and the outcome of Pregnancy after Assisted Reproduction in these cases who attended the OPD of a teaching hospital and were willing to participate in the current study after Proper consent

Materials and Methods

A total of 62 patients with suspected PCOS had been recruited from the Gynaecology and Endocrinology clinics. The diagnosis of PCOS was based on the association of one clinical criterion [hirsutism (as assessed by a modified Ferriman and Gallwey score of >8) or menstrual disturbances (i.e. oligomenorrhoea or amenorrhoea or cycle length either <25 days or >35 days and/or ovulatory disturbances as assessed by basal body temperature chart and/or serum progesterone level <3 ng/ml in luteal phase)], with either one biological criterion (serum LH levels >6.5 UI/l, and/or testosterone levels >0.7 ng/ml, and/or and rostenedione levels >2.2 ng/ml), or an ovarian area >5.5 cm^2 unilaterally or bilaterally at ultrasound. Women fulfilling the inclusion criteria (oligo/hypomenorrhea, infertility, weight gain, hyperandrogenism) were enrolled. Ultrasound pelvis was obtained in all women. Presence of eight or more multiple follicles in both or one ovary without presence of mature follicle was the cut off number for positive ultrasound. We retrieved clinical records of all women who conceived after any type of assisted reproduction treatment. Pregnancy was defined as serum β-hCG> 20 U/l on day 12 after embryo transfer. Pregnancy outcome was further divided according to fetal viability at 6 weeks' and 12 weeks' gestation on routine ultrasound scans. Ultrasound examination was performed between cycle days 2 and 7.Ultrasound measurements were taken in real time, according to a standardized protocol. The highest possible magnification available was used to examine the ovaries. After the longest medial axis of the ovary had been determined, the length and thickness were measured and the area was calculated using a manual or automatic ellipse to outline the ovary as described previously. Several follicles were measured in two planes of the ovary in order to estimate the size and their position. All follicles of <9 mm, but >2 mm, were counted. The diameter of several follicles was measured from the mean of two diameters (longitudinal and anteroposterior), then the number of follicles measuring >5 mm or ≤5 mm was established by scanning each ovary from the inner margin to the outer margin in longitudinal cross-section. Patients in whom transvaginal ultrasonography was inappropriate (virgin or refusing patients) were excluded from the analysis, as well as those in whom no follicle was seen in either the right or the left ovary and/or in whom the ovarian area was below the lower normal limit, i.e. 2.5 cm^2. Patients with at least one follicle <9 mm in diameter at ultrasound, or a serum estradiol level >80 pg/ml, were also excluded from the study so as not to confound the data with the presence of a dominant follicle.

Results

Among the Women who attended OPD and show willingness to be a part of Clinical Study after taking Proper Consent,62 women were diagnosed to have PCOD as per the laid criteria.Out of 62 women with polycystic ovary syndrome (PCOS) who are on treatment for assisted reproduction, 38 conceived after 1 year,12 cases went missed abortion. Among abortion cases, 10 out of 12 were aborted in between 6-8 weeks.1 was aborted at 15th week & 1 was blighted.

Table 1: Shows total number of pcod woman participated in a study

Total Number Of Women Diagnosed With Pcod	62

Table 2: shows total percentage of pcod woman who conceived after 1 year of treatment

Total number of patients diagnosed with pcod	Total number of patients conceived after assisted reproduction
62	38 (61.29%)

Table 3: Showing percentage of abortion cases in pcod women after 1 year treatment

Total Number of Patients Diagnosed With Pcod	Total number of patients underwent abortion even after assisted reproduction
62	12 (19.35%)

Table 4: Shows the number of abortion cases during 6-8 weeks of gestation

Total Number of Patients Diagnosed With Pcod	Total number of patients underwent abortion even after assisted reproduction	Total number of patients underwent abortion even after assisted reproduction during 6-8 weeks of gestation
62	12	10

Discussion

In this study we examined the Pregnancy outcome of PCOD Cases after assisted reproduction treatment in a group of 62 PCOS Cases. We found that the percentage of live birth is 61.29%. The miscarriage rate did not exhibit an age dependent increase in the PCOS cases. A Cochrane review has concluded that metformin is an effective first-line treatment for anovulation in women with PCOS [12]. In fact, the increase in ovulation rate is independent of weight loss [13]. Suggesting that the benefit lies in correcting the primary dysfunction, namely reduced insulin sensitivity. However, diet and exercise are also effective first-line treatments in obese women with PCOS [14, 15]. Mediated by correcting their reduced insulin sensitivity [16]. With or without treatment, the majority of

women with PCOS will get pregnant and present to antenatal clinics for care. It is well established that fecundity declines with maternal age, particularly past the age of 35 years. This is partly due to reduced fertility and partly due to a steep rise in miscarriage rate [17]. A large, Danish register study on more than 1.2 million pregnancies, found age to be a strong, independent risk factor for spontaneous abortion, reporting that 20 % of pregnancies end in SA at maternal age of 35 years, compared to 40 % of pregnancies at maternal age of 40 years [18]. IVF has come a long way in helping couples conceive, but unfortunately, miscarriage rate after IVF is similar to that in natural cycles. In the 2008 US National Summary of ART Success Rates, the miscarriage rate after IVF was below 14 % among women younger than 35, 30% at age 40 and 55% at age 44 [19]. Whether or not PCOS patients have an increased risk of miscarriage, is unknown [20]. There is an increased prevalence of risk factors for spontaneous abortion in PCOS, particularly obesity and type 2 diabetes mellitus [21, 22]; however, PCOS women are also thought to have a greater ovarian reserve, which could possibly exert a protective effect. Advances have been made in what a greater ovarian reserve implies on the molecular level [23]. Some studies have indicated that PCOS patients may have a sustained reproductive lifespan [24, 25], and a longitudinal prospective cohort study by Tehrani *et al* concluded that the reproductive life span of PCOS women extended on average 2 years beyond that of normo-ovulatory women [26]. Following this, we hypothesized that they may not exhibit the age-dependent rise in miscarriage rate that normal women do. It was previously believed that PCO morphology was associated with increased risk of spontaneous abortion. A much-cited study by Sagle *et al* [27] from 1988 found polycystic ovaries in 82% of their sample of women attending a recurrent miscarriage clinic. However, their study population was quite small, 56 cases and 11 voluntary parous controls. Their finding was not replicated in two following studies, and PCO morphology did not predict subsequent pregnancy outcome [28, 29]. There is limited research on miscarriage risk in PCOS, and new research in this area is much needed, as stated in a review of the literature from 2008. Here it is concluded that the prevalence of PCOS in recurrent miscarriage remains completely uncertain. Several studies have investigated the prevalence of PCOS in women attending recurrent miscarriage clinics, and found the prevalence to be similar to the prevalence of the background population [30, 31]. Outside of the hospital setting Koivunen *et al* did a cohort study on 4535 women. They found that women with self-reported oligo-amenorrhea and / or hirsutism did not have an increased risk of spontaneous abortion compared with asymptomatic women [32]. A long term follow-up of unselected PCOS-patients by Hudecova *et al*, found no significant difference in miscarriage rate between PCOS-patients and healthy controls [33]. In the IVF-population, Wang *et al* found no independent effect of PCOS on miscarriage rate [34]. This is in line with the findings of the present study.

The risk of an miscarriage is thought to be a dependent on the ovarian reserve, i.e. the number of follicles present in a woman's ovaries at a given time. The prevailing concept assumes that the ovaries are endowed with a certain number of follicles in fetal life, a number which starts to decline even before the female leaves the womb. The rate of decline was previously thought to be biphasic, but this notion has been replaced by a power function, which is more biologically plausible [35]. Tests have been developed to depict the ovarian reserve, as fertility is thought to be a function of this, and there is considerable variation between individuals at the same chronological age. One such test is antral follicle count (AFC). Antral follicles are fluid-filled follicles, 2mm-10 mm, which can be visualized using Transvaginal sonography. The number of antral follicles visible is correlated with the number of resting primordial follicles, and a lower count is associated with infertility [36-38]. AFC is the sum of antral follicles in both ovaries, the 50th percentile of healthy women with regular cycles has been reported to be nine [39]. In relation to this, it is of pivotal importance to take into account that a PCO diagnosis (more than 12 follicles of 2 mm -9 mm in one ovary) translates to a very high AFC. PCO is present in about 75 % of patients with a clinical diagnosis of PCOS, and this is indicative of a greater ovarian reserve [40-42].

Conclusion

What becomes eminent is that PCOS patients have a very large ovarian reserve, and this might be a protective factor in spontaneous abortion. What is more, it is evident that what is described as various measures of "ovarian reserve" or indicators of "ovarian age", are indeed also measures of the ovarian microenvironment. The ovarian microenvironment is not static; it is a delicate interaction between the various cell types of the ovary and the systemic circulation. There is a lot of promising research aiming to decipher this very complex interaction. However, PCOS patients are often excluded from research on ovarian reserve. Perhaps they should rather be included as representing one extreme of the continuum of ovarian reserve. If we could better understand what goes on in the PCOS ovary, perhaps we could implement this knowledge in helping patients on the other end of the continuum; those with diminished ovarian reserve.

Limitations of the study

A possible confounder in our study could be that some of the PCOS-patients received 1500 mg Metformin per day until pregnancy was confirmed. Metformin treatment was then discontinued. But finally we conclude that periconceptual Metformin in the PCOS group is unlikely to significantly impact our results.

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