

Spontaneous abortion and age in PCOS – is the biological clock lagging?

Abstract:

BACKGROUND: The purpose of the study was to examine the prevalence of spontaneous abortion in patients with polycystic ovary syndrome (PCOS) compared with patients with tubal factor infertility. We also wanted to test the hypothesis that the miscarriage risk might not increase with age in PCOS, as PCOS patients are thought to have a greater than average ovarian reserve.

METHODS: Retrospective study of women undergoing assisted reproductive treatment at a tertiary university hospital in Oslo. We retrieved clinical records of all women with PCOS (n = 541) or tubal factor infertility (n = 1129) who conceived after assisted reproduction treatment in 1996-2010. Pregnancy outcome was divided according to fetal viability at 6 weeks' and 12 weeks' gestation, and was tabulated for age. Chi-squared test for linear trend was used. Prevalence of live birth and spontaneous abortion was also calculated according to diagnosis.

RESULTS: Prevalence of live birth was 68.8 % in the PCOS group and 69.3 % in the tubal factor group. Prevalence of spontaneous abortion between gestational weeks 6 and 12 was 10.8 % in the PCOS group and 9.6 % in the tubal factor group. The prevalence of spontaneous abortion during 6-12 weeks' gestation increased significantly with age among women with tubal factor infertility (P = 0.01), but not among women with PCOS (n = 0.55).

CONCLUSIONS: The prevalence of spontaneous abortion between gestational weeks 6 and 12 and prevalence of live birth were similar between groups. 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. Further studies are needed to examine the exact mechanisms for this.

INTRODUCTION

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 (1). 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 (2). 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 (3). Whether or not PCOS patients have an increased risk of miscarriage, is unknown (4). There is an increased prevalence of risk factors for spontaneous abortion in PCOS, particularly obesity and type 2 diabetes mellitus (5;6); 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 (7). Some studies have indicated that PCOS patients may have a sustained reproductive lifespan (8;9), 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(10). Following this, we hypothesized that they may not exhibit the age-dependent rise in miscarriage rate that normal women do. If this is indeed so, it could have

implications for selection of patients eligible for IVF, and hopefully this can spawn some new hypotheses on the aetiology of miscarriage in advanced maternal age.

MATERIALS AND METHODS

This was a retrospective study among women undergoing assisted reproduction treatment at Rikshospitalet, Oslo, during the period 1996-2010.

We retrieved clinical records of all women who conceived after any type of assisted reproduction treatment with transfer of fresh or frozen-thawed embryos or intrauterine insemination. 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.

The prevalence of spontaneous abortion was tabulated according to the following age ranges: < 30 years; 30-32 years; 33-35.5 years; > 35.5 years. Chi-squared test for linear trend was used to assess age-related increase in abortion rate in the two groups. SPSS version 16 was used for statistical analysis.

RESULTS

541 women polycystic ovary syndrome (PCOS) and 1129 with tubal factor infertility conceived one or more pregnancies after assisted reproduction treatment. The live birth rate was 68.8 % in the PCOS group and 69.3 % in the tubal factor group. The rate of abortion between 6-12 weeks' gestation was 10.8 % in the PCOS group and 9.6 % in the tubal factor group. The prevalence of spontaneous abortion during 6-12 weeks' gestation increased significantly with age among women with tubal factor infertility ($P = 0.01$), but not among women with PCOS ($n = 0.55$).

Table 1 Prevalence of spontaneous abortion between gestational weeks 6 and 12 among women with PCOS and tubal factor infertility undergoing assisted reproduction treatment

Age (years)	PCOS	TUBAL FACTOR
< 30	24/227 (10.6%)	21/289 (7.3%)
30 - 32	22/171 (12.9 %)	27/342 (7.9%)
33 - 35.5	15/144 (10.4 %)	37/371 (10.0%)
> 35.5	9/107 (8.4 %)	50/408 (12.3%)
Total	70/649 (10.8 %)	135/1410 (9.6%)

DISCUSSION

In this study we examined the age stratified miscarriage rate after assisted reproduction treatment in a group of 541 PCOS-patients compared with 1129 controls with tubal factor. We found that the miscarriage rate did not exhibit an age dependent increase in the PCOS group, whereas in the control group it did. We also found that the chance of a pregnancy ending in spontaneous abortion was similar in the two groups, as was chance of live birth.

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. Some studies have reported impressive reduction of miscarriage risk with Metformin, especially when continued through the first trimester or entire gestation (11). However, a review by Palomba et al concluded that the efficacy of Metformin in preventing abortion was uncertain (12). A Cochrane review stated that there was no significant difference in the miscarriage rate between the Metformin and placebo group (13). We searched relevant databases for prospective RCTs issued after the Cochrane review, and found a double-blind multicenter RCT by Vanky et al. It concluded that Metformin did not reduce pregnancy complications in PCOS (14). We therefore conclude that periconceptual Metformin in the PCOS group is unlikely to significantly impact our results.

Spontaneous abortion and PCOS

It was previously believed that PCO morphology was associated with increased risk of spontaneous abortion. A much-cited study by Sagle et al (15) 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 (16;17). 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 (4). 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 (18;19). 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 (20). 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 (21). In the IVF-population, Wang et al found no independent effect of PCOS on miscarriage rate (22). This is in line with the findings of the present study.

Spontaneous abortion and age

The aetiologies of spontaneous abortion are traditionally divided into maternal and foetal. It is generally accepted that the main part of the increment in abortion rate with age is caused by an increase in foetal aetiologies, i.e. aneuploidies. This conclusion is drawn from studies on oocyte donations, where miscarriage rates in older recipients of ova from younger women are significantly reduced (23). Karyotyping human oocytes obtained from IVF patients does also show increasing aneuploidy rates with age. Pellestor et al found a very strong correlation between the rate of

aneuploidy and maternal age in a sample of more than 3000 oocytes (24;25). It is also supported by the observation that the steep rise in miscarriage rate in women of 35 is coinciding with a similar steep rise in the probability of a live born baby having trisomy 21, Down syndrome.

Ovarian reserve

The risk of an aneuploid conceptus and miscarriage is thought to be 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 (26). 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 (27-29). 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 (30). 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 (31-33). The ovarian reserve is hard to study in humans, as it is necessary to remove the ovary to accurately count the primordial follicles. However, excellent studies have been made in another single ovulating species, the cow. The bovine model offers unique advantages where research on humans falls short as it permits twice daily sonography, daily blood draws, oophorectomy and randomized IVF treatment, and in contrast to rodents, cows are single ovulating. Research on AFC in the bovine has shown that despite high variability between individuals, AFC-count is very highly repeatable within the same animal (34). AFC in the bovine is also highly positively associated with ovary size and the total number of morphologically healthy oocytes (35). Further, AFC count in the bovine is inversely correlated with serum FSH concentrations, as is also the case in humans (36;37). In a very interesting study, ovaries were removed from cattle with high vs. low AFC and examined for biomarkers for follicular differentiation and oocyte quality. Animals with high AFC had significantly higher mRNA for an enzyme involved in androgen synthesis (CYP17A1), higher capacity of theca cells to produce androstendione in response to LH, higher intrafollicular androstendione and higher circulating testosterone (38). This is suggestive of cattle with high AFC having an endocrinological profile not unlike that of women with very high AFC, i.e. PCOS patients. Intrafollicular concentration of estradiol was significantly higher in the ovaries from the low AFC-group, as was mRNA for (CYP19A1) aromatase in granulosa cells and estrogen receptors in cumulus cells (39). FSH is a positive regulator of these parameters in cows, and also in rats, and as lower AFC is associated with higher FSH, this could be the underlying mechanism (39-41). Higher physiological concentrations of estradiol has been shown to cause metaphase I block and chromosome aberrations in bovine oocytes matured in vitro (42). In humans, polymorphisms in the aromatase coding gene (CYP19A1) have been associated with ovary size, AFC, unexplained infertility and endometriosis in a promising report (43). Epistasis between CYP19A1 and FSH-receptor polymorphisms is associated with premature ovarian failure (44). Of particular relevance to the topic of spontaneous abortion, was that cattle with low AFC also had an altered corpus luteum function, reduced capacity to produce progesterone and poor endometrial growth (45). Contrary, in ovaries from cattle with high AFC there was significantly more mRNA for AMH (39). This is not surprising, as AMH is another measure of ovarian reserve, and is indeed correlated with AFC in both cows and humans (35;37). AMH is produced by growing pre-antral and early antral follicles, and in humans it is strongly associated with IVF-outcomes and age at

menopause (31;46;47). In PCOS levels of AMH fall when patients are treated with Metformin. This shows that the markers of ovarian reserve are modifiable. This is also evident from parabiotic studies in mice, where animals are joined so that they share a circulatory system. When young females were joined with young males, follicle atresia was significantly increased. When young females were joined with aging males, they exhibited a significant increase in the number of primordial follicles (48). The rejuvenating effect of androgens on reproductive function has been reported in humans supplemented with DHEA. DHEA has been shown to improve ovarian function and increase the chance of pregnancy, reduce miscarriage rates and aneuploidy as assessed by preimplantation genetic screening (49-51). As the PCOS women have naturally higher levels of DHEA, this could contribute to their favourable miscarriage rates found in our study.

Concluding remarks

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. There is still work to do in this field, as of “... so far, we have not learned how to reprogram a woman’s biological clock, nor to turn off her desire to nurture her children” as Dorothy Warburton, pioneer in human genetics, put it (52).

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