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EC GYNAECOLOGY
Review Article

Polycystic Ovary Syndrome and Early Pregnancy Loss: A Review Article

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Received: December 18, 2017; **Published:** January 10, 2018

Abstract

Polycystic Ovary Syndrome (PCOS) is one of the most common endocrinopathies, affecting 5 - 10% of women of reproductive age. Whether PCOS is implicated in the aetiology of early pregnancy loss (EPL) or not, has long been debated and results so far have been conflicting. In this article we will review the current evidence regarding the prevalence of EPL in women with PCOS as well as the possible pathophysiologic mechanisms involved. Finally, we will review the current evidence regarding the potential link between PCOS and recurrent EPL.

Keywords: *Polycystic Ovary Syndrome (PCOS); Early Pregnancy Loss (EPL)*

Introduction

Polycystic Ovary Syndrome (PCOS) is one of the most common endocrinopathies, affecting 5 - 10% of women of reproductive age [1]. PCOS is diagnosed using the Rotterdam criteria [2] which require the presence of 2 out of the following 3 criteria: a. oligo- and/or anovulation, b. clinical or biochemical hyperandrogenism, c. polycystic ovaries (≥ 12 follicles measuring 2 - 9 mm and/or ovarian volume ≥ 10 ml) and exclusion of other endocrine disorders with similar clinical picture. Early pregnancy loss occurs in 15 - 20% of pregnancies. Whether PCOS is implicated in the aetiology of early pregnancy loss or not has long been debated and results so far have been conflicting. In this review we attempt to shed light in the current evidence regarding the relationship of PCOS and miscarriages as well as recurrent pregnancy loss.

Methodology

We searched PubMed using the following terms, Polycystic Ovary Syndrome, polycystic ovarian morphology, miscarriage, early pregnancy loss, recurrent pregnancy loss, 1st trimester loss. We identified 11 original studies and one meta-analysis related to our subject. Studies using languages other than English were excluded.

Polycystic Ovary Syndrome and Early Pregnancy Loss

Prevalence

Two studies have demonstrated that early pregnancy loss is more prevalent among women with PCOS. A population based retrospective cohort study from Australia demonstrated higher rates of admissions for miscarriage in women with PCOS. They looked at the health records of 2566 PCOS patients and 25660 controls and they found out that admission rates for miscarriage management were 11.1% and 6.1% for PCOS patients and controls respectively [3]. Another Australian longitudinal cohort study showed increased miscarriage rates in women with PCOS in a multivariable regression model. More specific, reported miscarriage rates in PCOS patients were 20% where as in

controls the reported rates were 14.9%, a difference which was statistically significant [4]. However when use of fertility treatment was included in the model (ovulation induction and/or IVF), PCOS was no longer related to pregnancy loss. Fertility treatment and BMI in the overweight and obese groups were independently associated with pregnancy loss.

Several other studies have also demonstrated increased miscarriage rates in PCOS patients following IVF treatment. Li found increased early pregnancy loss rates in PCOS patients following IVF treatment compared to controls. Interestingly, isolated PCOM was not associated with increased miscarriage rates [5]. Wang in 2001 found that miscarriage rates are increased in PCOS (25% vs 18% in controls) but when logistic regression was used to adjust for BMI the association was only marginally significant [6]. Increased early pregnancy loss rates following IVF treatment were reported by other authors in the past such as Ludwig in 1999 [7], Balen and Homburg in 1993 [8,9] (Table 1).

Author	Year	Results
Hart., *et al.*	2015	11.1% vs 6.1% admissions for miscarriage
Joham., *et al.*	2014	20% vs 14.9% (P = 0.003) reported miscarriage rates
Li., *et al.*	2014	34% vs 17% miscarriage rates following IVF (P = 0.025)
Wang., *et al.*	2001	25% vs 18% miscarriage rates following IVF (P < 0.001)
Ludwig., *et al.*	1999	41% vs 21% following IVF (P < 0.05)
Balen., *et al.*	1993	36% vs 24% following IVF (P < 0.05)
Homburg., *et al.*	1993	37% vs 25% following IVF (P < 0.05)

Table 1: *Studies demonstrating increased miscarriage rates in PCOS patients.*

Liu in 2014, studied 564 cycles from PCOS patients vs 7494 cycles from non – PCOS patients and found a statistically significant increase in biochemical pregnancy loss rates among PCOS patients but clinical miscarriage rates did not differ between controls and women with PCOS [10]. Hudecova in 2009, did not find any association between early pregnancy loss and PCOS after long term follow up of an unselected population of 91 PCOS patients and 87 healthy controls [11]. A meta-analysis which included 9 studies of PCOS patients undergoing IVF between 1992 and 2004 was performed in 2006. They compared reproductive outcomes between 458 PCOS patients and 694 healthy controls but failed to demonstrate increased miscarriage rates in the PCOS group [12]. Winter in 2002, found increased miscarriage rates in 120 PCOS patients following IVF treatment but the difference compared to 1076 controls was not significant (26% vs 18%) [13]. The joint ESHRE/ASRM consensus in 2012 stated that miscarriage rates are not increased in natural conceptions in women with PCOS, independent of obesity. Miscarriage rates after fertility treatment, mirror those found in other infertile populations [14] (Table 2).

Author	Year	Result
Liu., *et al.*	2014	Increased biochemical pregnancies but no difference in clinical miscarriage rates following IVF
Hudecova., *et al.*	2009	No difference in miscarriage rates after natural conception
Boomsma., *et al.*	2006	No difference in miscarriage rates following IVF
Winter., *et al.*	2002	Not statistically significant increase in miscarriage rates following IVF

Table 2: *Studies that failed to demonstrate increased miscarriage rates in PCOS patients.*

Aetiology

Obesity

Obesity is common in PCOS with estimated prevalence between 50 - 70% [1,15]. It is generally accepted that obesity has a central role in the pathophysiology of PCOS, as even mild weight loss results in improvement in symptoms of anovulation and hyperandrogenism [16-

18]. Obesity has also been associated with increased risk of early pregnancy loss in patients undergoing fertility treatment [19]. According to a 2008 meta-analysis, BMI > 25 is associated with significantly higher odds of miscarriage regardless of method of conception [20]. It remains controversial, if PCOS is an independent factor for increased rates of early pregnancy loss as according to Wang., et al. [6] when logistic regression was applied to adjust for BMI the association was only marginally significant. On the other hand treatment of obesity based on a 6 month lifestyle intervention program has shown that a mean weight loss of 10 kg resulted in significant reduction of early pregnancy losses [21].

Hyperinsulinaemia- Insulin Resistance

The association of hyperinsulinemia with PCOS was first introduced in 1980 [22]. Insulin resistance (IR) is a common feature amongst PCOS patients with estimated prevalence between 64 - 79% [23-25]. Furthermore, among PCOS women, IR is more common in the obese patients and when comparing normal weight PCOS to non-PCOS, IR is more common in PCOS [23,26]. According to Tian (2007) IR is an independent risk factor for early pregnancy loss after infertility treatment [27]. Hyperinsulinemia is also associated with obesity and high circulating levels of plasminogen activator inhibitor-1 [28]. Both these factors are implicated in the aetiology of early pregnancy loss [19,28].

LH Hypersecretion

LH hypersecretion due to inherent dysfunction of Hypothalamic-Pituitary axis is well described and common among patients with PCOS. Elevated LH levels in the early follicular phase have been associated with increased miscarriage rates in both natural [29] and ovulation induction cycles [30,31]. It has also been demonstrated that in PCOS patients, the use of GnRH agonist in order to decrease LH levels in ovulation induction or IVF cycles is associated with significant reduction in miscarriage rates [8,9]. The association between elevated LH levels frequently seen in PCOS and increased miscarriage rates is also highlighted by the effect of laparoscopic ovarian diathermy (LOD) in the reproductive outcome of such patients. LOD reduces LH and it has been found that PCOS patients who underwent LOD demonstrate decreased miscarriage rates [32].

Plasminogen Activator Inhibitor-1 (PAI-1)

PAI-1 is a glycoprotein partly secreted by the adipose tissue [33], which inhibits fibrinolysis through inhibition of plasmin biosynthesis [34]. Elevated levels of PAI-1 have also been associated with increased cardiovascular risk [35]. High levels of PAI-1 are common in PCOS [36-40] and correlate with increased miscarriage rates and various obstetric complications [28]. Other investigators believe that increased PAI-1 levels seen in PCOS are due to obesity and insulin resistance and that its role in the pathogenesis of the syndrome in not significant [41].

Endometrial Dysfunction

It has been suggested by various authors that PCOS demonstrates endometrial dysfunction which impairs endometrial receptivity resulting in increased chances of early pregnancy loss. This impairment is indicated by the reduced endometrial blood flow observed in PCOS most probably due to hyperinsulinemia and insulin resistance as well as other parameters such as decreased glycodelin and Insulin like growth factor binding protein -1 (IGFBP-1) [42] and increased endothelin-1 (ET-1) [43]. Metformin administration and correction of insulin resistance resulted in improvement of endometrial blood flow parameters [44].

Polycystic Ovary Syndrome and Recurrent Pregnancy Loss

Recurrent miscarriage is defined as loss of 3 or more consecutive pregnancies and it affects approximately 1% of couples trying to conceive [45]. It has been suggested that many risk factors are implicated in the pathogenesis of recurrent miscarriages such as advanced maternal age [46], previous miscarriages [47], antiphospholipid syndrome [48], chromosomal abnormalities [49,50], congenital uterine malformations [51], inherited thrombophilic defects [52], immunological factors [53] and finally endocrine factors [54] (Table 3).

Advanced Maternal Age	
Previous Miscarriages	
Antiphospholipid Syndrome	
Genetic factors	• Balanced reciprocal or Robertsonian translocations • Chromosomal abnormalities
Anatomical factors	• Congenital Uterine malformations • Cervical weakness
Endocrine factors	• Insulin resistance/DM • Thyroid disease • PCOS
Immunological factors	• Uterine NK cells • Cytokines • Bacterial vaginosis infection
Inherited thrombophilic defects	• Activated protein S resistance • Factor V Leiden deficiency • Protein C and S deficiency • Antithrombin III deficiency • Prothrombin gene mutation • Hyperhomocystinemia

Table 3: *Risk Factors for Recurrent Pregnancy Loss.*

PCOS has been linked to increased risk of recurrent miscarriage although the exact mechanism remains unclear. Recently it has been suggested that this link is mainly due to hyperandrogenaemia and insulin resistance. The prevalence of IR is increased in women with RMs compared with matched fertile controls [55]. An elevated free androgen index appears to be a prognostic factor for a subsequent miscarriage in women with RMs [56].

The prevalence of polycystic ovarian morphology amongst patients with recurrent miscarriages varies according to different authors. Rai., *et al*. studied 2199 women with RMs and found that the prevalence of PCOM was 40.7%. The presence of PCOM is not predictive for pregnancy loss [57]. In contrast, Cocksedge., *et al*. in their study of 300 patients with RMs found that the prevalence of PCOM and PCOS was 12% and 10% respectively [58]. The reported prevalence of PCOS among patients with RMs is also quite variable ranging between 10 - 25% [58-60]. Finally, Banu., *et al*. in their cross sectional case control study, investigated the prevalence of RMs in 100 infertile patients (50 PCOS and 50 non-PCOS) and they found that this was elevated in the PCOS group (40% vs 12%). The authors conclude that the most probable explanation for this is high testosterone and insulin resistance seen in PCOS patients [61].

Discussion

Our review suggests that the evidence regarding the association of PCOS with early pregnancy losses is conflicting. Several studies have demonstrated an increased rate of early pregnancy losses in PCOS patients both in natural conceptions and after fertility treatment. Other authors believe that PCOS per se is not a risk factor for early pregnancy loss and that the main factors affecting this risk is increased

BMI and fertility treatment, both of them commonly found in the PCOS population. In addition the joint ESHRE/ASRM consensus states that miscarriage rates are not increased in natural conceptions independent of obesity and that early pregnancy loss rates after fertility treatment in PCOS patients are similar with other infertile populations. Our experience indicates that PCOS patients have higher miscarriage rates compared to other infertile groups. We believe that the combination of adverse metabolic, hormonal and endometrial parameters frequently found in PCOS patients are all implicated in the increased rates of first trimester losses observed in the syndrome. A strong causative relationship though still remains largely unconfirmed from the current evidence.

A relationship between PCOS and recurrent miscarriages is not established according to our review. In the past it was believed that PCOS could possibly be a risk factor for RMs but according to more recent studies the prevalence of both PCOS and PCOM in patients with RMs is no different than in the general population. We agree with many authors that insulin resistance is probably the key endocrine risk factor in the pathogenesis of RMs rather than PCOS.

Conclusion

PCOS is a common endocrine disorder frequently seen in women seeking fertility advice and treatment. The association between PCOS and early pregnancy loss has been described by various authors in the past and in more recent studies. Other authors argue that PCOS is not an independent risk factor for early pregnancy loss and it is fertility treatment and BMI that make the difference. The association between PCOS and recurrent miscarriage not as strong as it was believed in the past with recent studies confirming that the prevalence of PCOS in patients with recurrent miscarriages is similar to the prevalence seen in the general population.

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Volume 7 Issue 2 February 2018