

# Recurrent Pregnancy Loss in Patients with Polycystic Ovary Syndrome: A Case Control Study

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## Abstract

**Objectives:** To identify different biophysical and hormonal factors that could contribute to recurrent pregnancy loss in Saudi women who have been diagnosed with polycystic ovary syndrome. **Study Design:** Case-control study. **Settings:** Infertility clinic in Dammam Maternity and Children Hospital. **Cases:** PCOS patients with recurrent pregnancy loss. **Controls:** PCOS patients without recurrent pregnancy loss. **Results:** The prevalence of recurrent abortion in PCOS patients was 31%. There was no significant difference between the cases and the controls in the age, 33.1 years versus 31.9 years, BMI, 31.4 kg/m<sup>2</sup> versus 31.6 kg/m<sup>2</sup> respectively. There was no significant difference in the successful pregnancies outcome in cases and controls, term deliveries 84% versus 90%, preterm deliveries 10% versus 5%, twin pregnancy 6% versus 5% respectively. There was no significant difference in the hormonal profile (prolactin, LH, FSH, LH/FSH ratio, TSH, progesterone, testosterone) between cases and controls. Serum estradiol level was significantly lower in the cases compared to the controls, 55.5 pg/mL versus 83.9 pg/mL respectively ( $p < 0.01$ ). **Conclusion:** PCOS patients with recurrent abortions had no significant increase in the age, BMI, preterm pregnancy, multiple gestation and ectopic pregnancy. The hormonal profile (prolactin, LH, FSH, LH/FSH ratio, TSH, progesterone, testosterone) was comparable between the cases and the controls, except for serum estradiol level, which was significantly lower in PCOS patients with recurrent abortions.

## Keywords

Polycystic Ovary, Recurrent Abortion

## 1. Introduction

Recurrent pregnancy loss classically refers to the occurrence of three or more consecutive losses of clinically recognised pregnancies prior to the 20th week of gestation. Ectopic, molar, and biochemical pregnancies are not included [1]. Approximately 15 percent of pregnant women experience sporadic loss of a clinically recognized pregnancy. About 2 percent of pregnant women experience two consecutive pregnancy losses and only 0.4 to 1 percent of them have three consecutive pregnancy losses [2].

Identified risk factors for recurrent pregnancy loss include previous pregnancy loss, advanced maternal age, uterine anomalies and adhesions, cervical insufficiency, immunological diseases such as antiphospholipid syndrome and autoimmune thyroid disease, endocrine disorders such as diabetes mellitus, polycystic ovary syndrome, and hyperprolactinemia. Although in almost fifty percent of the cases the pathophysiology remains unknown, the clinical association of recurrent pregnancy loss and polycystic ovary syndrome is more than common [2].

Polycystic ovary syndrome is an endocrine disorder that typically presents with a wide spectrum of clinical features, ranging from chronic anovulation and hyperandrogenism, to polycystic ovaries morphology on ultrasound with no menstrual or biochemical abnormality.

The incidence rate between polycystic ovary syndrome and recurrent pregnancy loss remains uncertain, due to a wide variation in different studies, ranged from 10 percent in a recent study [3], and up to 80 percent in another [4].

In addition, some studies have reported that women with polycystic ovary syndrome who either hypersecrete luteinizing hormone (LH) or who are hyperandrogenemic, are at increased risk of miscarriage following spontaneous or assisted conception [5], while other researchers disagreed [6].

The objective of this study was to identify different biophysical and hormonal factors that could contribute to recurrent pregnancy loss in Saudi women diagnosed with polycystic ovary syndrome.

## 2. Methods

This was a case-control study. It was conducted in the Maternity and Children Hospital (MCH), Dammam, Eastern Province, Saudi Arabia. This is the main maternity hospital in the Eastern Province of Saudi Arabia. The total number of deliveries is around 14,000 births each year. The hospital administration and ethics and board committee approved this study.

Saudi patients diagnosed with polycystic ovary syndrome and those who were being managed for recurrent pregnancy loss and also have polycystic ovary syndrome were evaluated.

Patients attending the infertility clinic in the outpatient department of the afore-mentioned maternity were enrolled. The exclusion criteria were non-Saudi women, single women with PCOS, married nulliparous women, women with

uterine anomalies, antiphospholipid syndrome (APS), or women with chronic diseases that could contribute to pregnancy loss.

The patients were identified by searching the medical records database for the diagnosis of PCOS, body measurements, parity and pregnancy outcome, and hormonal levels.

### 2.1. Data Collection

Data was collected from the medical records on a specifically designed Excel 2011 workbook (Microsoft Inc.).

Information was retrieved for the following variables: age, height, weight, body mass index, parity and pregnancy outcome, history of ectopic and molar pregnancy, and hormonal levels including prolactin, luteinizing hormone (LH), follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), estradiol (E2), progesterone, and testosterone.

### 2.2. Data Analysis

These variables for patients diagnosed with PCOS with recurrent pregnancy loss were compared with a control group of women with PCOS without recurrent pregnancy loss.

Statistical analysis was carried out using Excel 2011 and social science statistics website. The mean, median, mode, standard deviation, and range, were measured. For the continuous data, student t-test was used to compare the means. A p-value of less than 0.05 was considered significant.

## 3. Results

A total of 148 women were identified as PCOS. Forty-six women (31%) had a history of recurrent abortions, and 102 women (69%) were diagnosed as PCOS but without history of recurrent abortion.

**Table 1** shows the demographic data of 46 patients with PCOS with recurrent abortions and 102 controls.

Women with PCOS with recurrent abortions were slightly older than the controls, with a mean age of 33.1 years (21 - 50) compared to 31.9 years (21 - 47), but the result was not statistically significant (p-value > 0.05).

Height and weight were measured to calculate the body mass index (BMI). Mean height was 1.57 cm for the cases, and 1.56 cm for the controls, and the mean weight was 78.4 kg for the cases, and 77.9 kg for the controls. There was no significant difference in the BMI between the cases and the controls, 31.4 kg/m<sup>2</sup> (16.8 - 47.1) and 31.6 kg/m<sup>2</sup> (17.0 - 49.1) respectively (p-value > 0.05).

**Table 2(a)** compares the parity and pregnancy outcome in both cases and controls. A total number of 211 pregnancies were identified in the cases, and 198 pregnancies were identified in the controls.

A total 26/211 term deliveries (12%) were identified in the cases, compared to 102/198 term deliveries (51%) in the control (p-value < 0.05).

**Table 1.** Demographic data mean (Range).

	CASES		CONTROL		p-value
<b>Number (n)</b>	46		102		-
<b>Age (years)</b>	33.1	(21 - 50)	31.9	(21 - 47)	NS
<b>Height (m)</b>	1.57		1.56		-
<b>Weight (kg)</b>	78.4		77.9		-
<b>BMI (kg/m<sup>2</sup>)</b>	31.4	(16.8 - 47.1)	31.6	(17.0 - 49.1)	NS

**Table 2.** (a) Parity and outcome number (Percentage); (b) Successful pregnancy number (Percentage).

(a)					
	CASES (n)	%	CONTROL (n)	%	p-value
<b>Term</b>	26	-12.3	102	-51.5	<0.05
<b>Preterm</b>	3	-1.4	6	-3	NS
<b>Twin</b>	2	-0.9	6	-3	NS
<b>Abortion</b>	174	-82.4	77	-38.8	<0.001
<b>Ectopic</b>	3	-1.4	7	-3.5	NS
<b>Molar</b>	3	-1.4	0	0	-
<b>Total</b>	<b>211</b>	<b>100%</b>	<b>198</b>	<b>100%</b>	<b>409</b>

  

(b)				
	CASES (n)	%	CONTROL (n)	%
<b>Term</b>	26	-84	102	-90
<b>Preterm</b>	3	-10	6	-5
<b>Twin</b>	2	-6	6	-5
<b>Total</b>	<b>31</b>	<b>100%</b>	<b>114</b>	<b>100%</b>

There was no significant increase in preterm deliveries in either cases or controls, 1.4% (3/211) and 3% (6/198) respectively, and there was no significant difference either (p-value > 0.05).

There was no significant increase in the rate of twin pregnancy in cases and controls, 0.9% (2/211) and 3% (6/198) respectively. There was no significant difference either (p-value > 0.05).

A total of 174/211 abortions (82%) were identified in the cases, compared to 77/198 abortions (38%) in the controls, and it was very highly significant (p-value < 0.001).

The overall prevalence of ectopic pregnancy among cases and controls was 2.4% (10/409). The rate of ectopic pregnancies in the cases and the controls was 1.4% (3/211) and 3.5% (7/198) per total parity respectively. There was no significant difference (p-value > 0.05). Three episodes of molar pregnancy were iden-

tified in a single patient in the cases group only.

**Table 2(b)** is a subdivision of **Table 2(a)** to assess the outcome of successful pregnancy. 84% (26/31) of the cases and 90% (102/114) of the controls had term pregnancies. The incidence of preterm delivery was double in the cases compared to control, 10% (3/31) versus 5% (6/114) respectively. The rate of twin pregnancy was similar between the cases and the controls where it was 6% (2/31) versus 5% (6/114) in the cases compared to the controls.

**Table 3** compares the mean hormonal level between the cases and the controls.

There was no significant difference in the mean prolactin level between the cases and the controls, 16.7 (4.68 - 75.4) and 17.7 (0.76 - 297) respectively (p-value > 0.05).

Luteinizing hormone (LH) level was 7.18 (1.06 - 75.4) in the cases compared to 6.93 (1.29 - 26.2) in the controls. The result was not statistically significant (p-value > 0.05).

Follicle-stimulating hormone (FSH) level was 6.54 (0.75 - 16.2) in the cases, compared to 6.24 (2.7 - 23.5) in the controls. The result was not statistically significant (p-value > 0.05). In addition, there was no significant difference in the LH/FSH ratio between the cases and the controls, 1.29 and 1.17 respectively (p-value > 0.05).

There was no significant difference in the mean thyroid-stimulating hormone (TSH) level between the cases 2.57 (0.86 - 6.25), and the controls 2.48 (0.46 - 14.4) (p-value > 0.05).

The mean estradiol (E2) level was slightly lower in the cases compared to the controls, 55.5 (13.1 - 224) and 83.9 (0.83 - 482) respectively. The difference was statistically significant (p-value < 0.01). Pearson correlation coefficient for estradiol (R-value) was -0.188.

Mean progesterone level was 11.04 (0.1 - 25.3) in the cases, compared to 9.50 (0.1 - 35.8) in the controls. The difference was not statistically significant (p-value > 0.05).

**Table 3.** Hormonal levels mean (Range).

	CASES (mean)		CONTROL (mean)		p-value
<b>Prolactin (ng/mL)</b>	16.7	(4.68 - 75.4)	17.7	(0.76 - 297)	NS
<b>LH (IU/L)</b>	7.18	(1.06 - 28.2)	6.93	(1.29 - 26.2)	NS
<b>FSH (IU/L)</b>	6.54	(0.75 - 16.2)	6.24	(2.7 - 23.5)	NS
<b>LH/FSH Ratio</b>	1.29	(0.145 - 6.86)	1.17	(0.247 - 4.93)	NS
<b>TSH (<math>\mu</math>IU/L)</b>	2.57	(0.86 - 6.25)	2.48	(0.46 - 14.4)	NS
<b>Estradiol (pg/mL)</b>	55.5	(13.1 - 224)	83.9	(0.83 - 482)	<0.01
<b>Progesterone (ng/mL)</b>	11.04	(0.1 - 25.3)	9.5	(0.1 - 35.8)	NS
<b>Testosterone (ng/dL)</b>	6.22	(0.23 - 58.9)	8.5	(0.08 - 126.4)	NS

The mean testosterone level was slightly lower in the cases compared to the controls, 6.22 (0.23 - 58.9) and 8.50 (0.08 - 126.4), but the difference was not statistically significant (p-value > 0.05).

#### 4. Discussion

The association between PCOS and recurrent pregnancy loss has been studied in many literatures since a couple of decades. Most researchers studied PCOS patients and compared them to normal controls. In our study, we divided the women who have been diagnosed with PCOS into two groups, PCOS with recurrent abortions and PCOS without recurrent abortions. The prevalence of recurrent abortions varied widely in different literatures. In an old historic study by Sagle *et al.*, they reported that 80% of PCOS women had recurrent pregnancy loss [4], whereas more recent studies reported a prevalence of 30 to 40 percent [6]. Homburg *et al.* studied the prevalence of recurrent pregnancy loss among PCOS and non-PCOS patients who underwent ovulation induction. He reported a prevalence of 33% among PCOS patients, compared to 10% in non-PCOS women [6]. Rai *et al.* and Banu *et al.* also reported a prevalence of recurrent abortion of 40% among women with PCOS compared to normal controls [7] [8].

In our study, we found the prevalence of recurrent pregnancy loss among women diagnosed with PCOS to be 31%, which is close to most reports.

Maternal age is an important factor for the prediction of possible pregnancy loss. Unfortunately, we could not find many reports comparing maternal age in two groups of PCOS with and without recurrent pregnancy loss. Most reports studied the prevalence of pregnancy loss in association with advanced maternal age. Literatures reported that the risk increases significantly after 35 years of age. In a large Scandinavian study by Andersen *et al.*, they found that women older than 35 years of age had 25 percent risk of spontaneous abortion [9]. McClure *et al.* studied the association of serum estradiol level, maternal age, and pregnancy outcome in PCOS patients. They found that increased maternal age was associated with lower serum estradiol level, which in turn, was significantly associated with recurrent miscarriage [10]. In our study, the mean maternal age was below 35 years for both cases and controls. In addition, we did not find any significant difference in the mean age between cases and controls, 33.1 years versus 31.9 years respectively.

Obesity has been conclusively associated with an increased prevalence of miscarriage, and obesity is obviously more common in PCOS patients than in normal controls [6]. Wang *et al.* found that a higher rate of spontaneous miscarriage in PCOS patients was due to higher prevalence of obesity [11]. In addition, Boots *et al.* found that obese women are more prone to have euploid miscarriage compared to non-obese controls [12]. Obesity is a common finding in Saudi women due to dietary habits and personal lifestyle. When Fakhoury *et al.* compared PCOS patients to normal controls in Saudi women; they found both groups to have BMI above 25 kg/m<sup>2</sup> [13]. Similar to Fakhoury *et al.*, we found that both groups of PCOS cases and controls having a BMI above 30 kg/m<sup>2</sup>. On the other

hand, there was no significant difference in the BMI between both groups where it was 31.4 kg/m<sup>2</sup> among cases, and 31.6 kg/m<sup>2</sup> among controls.

Many researchers have studied adverse obstetric outcome in PCOS patients, apart from pregnancy loss. In a recent meta-analysis by Qin *et al.*, they found that PCOS patients had higher incidence of pregnancy induced hypertension, gestational diabetes, preterm delivery, and Caesarean section [14]. In addition, Naver *et al.* reported a doubled incidence of preterm delivery and pre-eclampsia in hyper-androgenic women with PCOS compared to normo-androgenic PCOS [15]. In our study, most of the cases and controls who delivered, had a term pregnancy, 84 percent versus 90 percent, respectively. On the other hand, similar to what was observed by Naver *et al.*, the rate of preterm deliveries among the cases was twice as much as the controls, 10 percent versus 5 percent, respectively. Multiple gestation is a possible complication of induction of ovulation as a treatment of the anovulatory cycles in PCOS patients. Nahuis *et al.* reported an incidence of twin pregnancy in PCOS patients in a randomised trial as 5 percent after being treated by laparoscopic electrocautery, and 8 percent after receiving recombinant-FSH [16]. In addition, Zhao *et al.* studied the pregnancy outcome after in vitro maturation of immature oocytes, and found a significant increase in multiple gestation up to 30 percent, low birth weight, and preterm deliveries [17]. In our study, we did not find a significant increase in the rate of twin pregnancy in either cases or controls. Similar to what was observed by Nahuis *et al.*, the rate of twin pregnancy, out of the successful deliveries, was comparable between cases and controls, 6 versus 5 percent respectively. There are few reports studied the incidence of ectopic pregnancy in PCOS patients. Wang *et al.* studied the incidence of ectopic pregnancy after in vitro fertilization in PCOS patients, and reported a threefold increase in the incidence of ectopic pregnancy in PCOS patients compared to normal controls specially after fresh embryo transfer [18]. In our study, the overall prevalence of ectopic pregnancy among cases and controls was 2.4 percent, which is slightly higher than general population, twenty per thousand [19]. In addition, the cases had slightly higher incidence of ectopic pregnancy than the controls, 8 percent versus 6 percent. There were 3 incidents of molar pregnancy in a single patient in the cases group.

As previously known, polycystic ovary syndrome is an endocrine disorder that typically present with a wide spectrum of clinical features. Many literatures have studied the association between different endocrinopathies and recurrent miscarriage that present in PCOS and non-PCOS patient. Most researchers studied the effect of hyperprolactinemia, subclinical hypothyroidism, abnormal luteinizing and follicle stimulating hormones, abnormal progesterone level, and hyperandrogenism. In our study we measured these hormones, and compared them between the cases and the controls.

Many researchers have noticed the association between hyperprolactinemia and early pregnancy loss. In a randomized controlled trial by Hirahara *et al.*, they evaluated the effect of isolated hyperprolactinemia in the pathogenesis of recurrent spontaneous abortion. They found that restoration of normal prolactin



level with bromocriptine was associated with a significant improvement in the pregnancy outcome, and concluded that appropriate circulating levels of prolactin may play an important role in maintaining early pregnancy, especially in cases of hyperprolactinemic recurrent miscarriage [20]. On the other hand, Li *et al.* found that even low basal serum prolactin level was associated with early pregnancy loss [21]. In our study, the mean serum prolactin level was comparable between the cases and the control, 16.7 ng/mL versus 17.7 ng/mL respectively, and it was within normal limits.

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) plays a critical role in the hormonal secretion, ovulation, and endometrial integrity. There is a controversy between literatures regarding the association between abnormal gonadotropin levels and pregnancy outcome.

It was previously thought that elevated level of luteinizing hormone in PCOS patient was associated with recurrent miscarriage [5]. However, many researchers found no significant association between serum LH concentration and recurrent miscarriage [10] [22] [23]. In a randomized control trial by Clifford *et al.*, they suppressed pituitary LH release and observed its effect on patients with recurrent pregnancy loss. They concluded that pre-pregnancy suppression of high luteinizing hormone concentrations in ovulatory women with recurrent miscarriage and hypersecretion of luteinizing hormone does not improve the outcome of pregnancy [24]. On the other hand, some literatures found a significant association between elevated day 3 FSH level in women with recurrent unexplained miscarriage [25] [26]. In addition, Fakhoury *et al.* reported an elevated level of LH/FSH ratio in PCOS patients compared to normal controls [13]. In our study, we found no significant difference between the cases and the controls regarding mean LH, FSH levels, and LH/FSH ratio, 7.18 IU/L versus 6.93 IU/L, 6.54 IU/L versus 6.24 IU/L, 1.29 versus 1.17 respectively.

Thyroid hormones are essential for the normal fetal metabolism and growth. Hypothyroidism was thought to be associated with recurrent early pregnancy loss. In a study by Jacob involved one thousand women, he reported that even mild thyroid dysfunction could greatly increase the risk of serious problems. Women with mild thyroid dysfunction had double the risk of miscarriage, premature labor, and low birth weight as compared to normal controls [27]. In our study, there was no significant difference in the thyroid-stimulating hormone (TSH) level between cases and controls, and there was no suspicion of subclinical hypothyroidism. There was a controversy in literatures regarding the association of serum estradiol level and current pregnancy loss. Gurbuz *et al.* and Trout & Seifer reported an elevation of serum estradiol level in women with recurrent pregnancy loss [25] [26]. On the other hand, McClure *et al.* found that PCOS patients with recurrent pregnancy loss had lower serum estradiol level [10]. Evrim *et al.* when studied the association of LH level and thyroid volume in PCOS patients, also reported a low normal serum estradiol level in PCOS patients in comparison to normal controls [28]. Similar to McClure *et al.* and Evrim *et al.*, in our study we found that PCOS patients with recurrent abortion



having lower normal serum estradiol level compared to PCOS without recurrent abortion, and it was statistically significant. In addition, serum estradiol level was negatively correlated with the incidence of pregnancy loss.

The association between serum progesterone and recurrent pregnancy loss was studied in few literatures, last was by Yan *et al.* who found mid-luteal serum progesterone measurement does not predict the outcome of a subsequent pregnancy in women with unexplained recurrent miscarriage [29].

Some literatures found positive correlation between hyperandrogenemia and recurrent abortion. Banu *et al.*, Tulppala *et al.*, and Okon *et al.*, have found that elevated serum testosterone and other androgen level was associated with recurrent pregnancy loss in PCOS and non-PCOS patients [8] [23] [30]. On the other hand, Nardo *et al.* and Lathi *et al.* found no relation between serum testosterone level and recurrent miscarriage in PCOS and non-PCOS patients [22] [31]. In our study, serum testosterone level was higher in the control group compared to the cases, and the difference was not statistically significant.

Some researchers studied the effect of serum estradiol and pregnancy outcome in non-PCOS cases such as normal women, *in-vitro* fertilisation cases (IVF), and women undergoing intra-cytoplasmic sperm injection (ICSI). In three different studies by Check *et al.*, Takeuchi *et al.*, and Aksoy *et al.*, serum estradiol level was measured in women with history of missed abortion or an embryonic pregnancy and compared to normal controls. All of these studies found that women with history of missed abortion had lower serum estradiol level compared to normal controls [32] [33] [34].

Other researchers found that women with recurrent abortion had significantly lower serum progesterone level compared to normal controls [33] [34]. In our study, we found no significant difference in the serum progesterone level between cases and controls.

One of the most important manifestations of PCOS is hyperandrogenism, and many literatures studied the relationship of increased androgens in PCOS patients and pregnancy outcome. Fujimoto *et al.* and Joo *et al.* focused on the effect of serum estradiol level and pregnancy outcome in IVF cases. Fujimoto *et al.* found that higher serum estradiol level was associated with better pregnancy outcome, while Joo *et al.* found a concentration-dependent effect between serum estradiol and pregnancy outcome [35] [36]. There are two studies by Rehman *et al.* studied the relationship between obesity, serum estradiol level, and pregnancy outcome in ICSI cases. They found that lower serum estradiol level had adverse effect on pregnancy outcome, and high peak estradiol with maintenance of optimal levels in mid-luteal phase is required for implantation of fertilized ovum and accomplishment of clinical pregnancy [37] [38]. Carranza-Lira *et al.* and Salazar and Calzada measured serum estradiol and progesterone levels in women with recurrent miscarriages in addition to endometrial receptors for estrogen and progesterone. They found that both estrogen and progesterone receptors were at their lowest level in the cytosol and nuclear compartment in women with recurrent miscarriage compared to normal controls [39] [40].

The limitations in our study was the sample size, where we had 46 cases and 102 controls over the period studied. Also, dehydroepiandrosterone (DHEA) was not routinely measured in either cases or controls.

## 5. Conclusion

PCOS patients with recurrent abortions had no significant increase in the age, BMI, preterm pregnancy, multiple gestation and ectopic pregnancy. The hormonal profile (prolactin, LH, FSH, LH/FSH ratio, TSH, progesterone, testosterone) was comparable between the cases and the controls, except for serum estradiol level, which was significantly lower in PCOS patients with recurrent abortions.

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