Journal of Advances in Medicine and Medical Research

32(24): 55-62, 2020; Article no.JAMMR.64738
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Incidence of Early Pregnancy Loss in Poly Cystic Ovary Syndrome Patients With /Without Metformin Therapy: A Comparative Study

Basma S. Ibrahem[1*], Amal A. El Sokary[1], Ahmed M. Ossman[1] and Tarek M. El-Saba[1]

[1]Obstetrics and Gynecology Department, Faculty of Medicine, Tanta University, Egypt.

Authors' contributions

This work was carried out in collaboration among all authors. Author BSI designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AAES and AMO managed the analyses of the study. Author TMES managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2020/v32i2430751
Editor(s):
(1) Dr. Ashish Anand, University of Mississippi Medical Center, USA.
(2) Dr. Ravi Kumar Chittoria, Jawaharlal Institute of Postgraduate Medical Education and Research, India.
Reviewers:
(1) Consolata Kirigia, University of Embu, Kenya.
(2) Juliano Augusto Brum Scheffer, IBRRA - Instituto Brasileiro de Reprodução Assistida, Brazil.
(3) Rana Choudhary, Wockhardt Hospital, India.
Complete Peer review History: http://www.sdiarticle4.com/review-history/64738

Original Research Article

Received 25 October 2020
Accepted 31 December 2020
Published 31 December 2020

ABSTRACT

Background: The most prominent source of anovulatory infertility in the world is polycystic ovary syndrome. Getting pregnant these days has a larger risk of early maternal death than in the general population. It induces symptoms in about five and ten percent of women of reproductive age (12-45 years old). Women that are insulin tolerant are more prone to have Elevated Insulin levels, Polycystic OVARIES and Hyperandrogens. They are at risk for suboptimal reproductive activity attributable to compromising ovarian function and hormonal equilibrium. The aim of this research was to determine the prevalence of late pregnancy failure in women with Polycystic Ovary Syndrome (PCOS) taking metformin as compared to women who don't take it.
Materials and Methods: This case control-controlled study included 100 females and divided in to two groups. Each group composed of 50 patients and the patients were distributed in each group by simple Randomization method.

**Corresponding author: E-mail: basma.salah@gmail.com;*

Results: There was no significant difference between control and study group regarding todescriptive data. Association between rate of pregnancy loss and metformin treatment early pregnancy loss was significantly frequent in control group than in study group with metformin treatment. Gestational age (weeks)at which pregnancy loss occurred is significantly higher in study group than in control group. The rate of early pregnancy loss among studied groups is significantly lower than in control group.

Conclusion: Metformin therapy in pregnant women with polycystic ovary syndrome was associated with a significant reduction in the rate of early pregnancy loss. It was well tolerated by patients with a minimum of side effects. However, extended studies are required to evaluate its effect on further pregnancy complications and fetal outcomes.

Keywords: Early pregnancy loss; poly cystic ovary syndrome; metformin.

1. INTRODUCTION

Polycystic ovary syndrome is the most prevalent endocrine condition in young people [1,2]. PCO induces infertility in approximately 5 to 10 percent of women aged 12 to 45 years old, and can induce infertility in less than 5 percent of women. According to the Rotterdam criterion, a diagnosis of PCOS is made in an individual if she has two of the following three manifestations: persistent anovulation, clinical proof of hyperandrogenemia and an ultrasound image of PCOS [3,4]. carbohydrate and sugar metabolism characterized by hyperinsulinemia, insulin resistance, and reduced glucose tolerance is typical in women with PCOs, especially those with a high BMI. Since hyperinsulinemia has been seen to raise androgen levels, the hormone could play a central role in developing polycystic ovarian syndrome [5].

Metformin is an anti-type 2 diabetes drug. Metformin reduces the liver's development of glucose and increases the efficiency of the body's insulin receptors [6].

An individual who has PCOs is at high risk of an ectopic pregnancy and undesirable health conditions that may raise the miscarriage rate.

Polycystic ovarian syndrome may result in erratic menstrual cycles and diabetes through methods that can lower insulin sensitivity. Metformin can boost reproductive defects in women with PCOS by restoring ovulation, curing infertility, preventing pregnancy loss and reducing pregnancy-induced complications. Xita et al. stated that continuing metformin during pregnancy is healthy and decreases first trimester miscarriage from 64% to 5% without teratogenicity. Metformin usage may decrease risk for early pregnancy loss by decreasing estrogen concentration and improving insulin sensitivity [7] The aim of this research was to examine the occurrence of early pregnancy failure in patients suffering from polycystic ovary syndrome (PCOS) taking metformin in contrast with those not taking it.

2. SUBJECTS AND METHODS

This case-controlled study included 100 pregnant women who were already diagnosed to have polycystic ovary syndrome and they were categorized into two groups, the first group included 50 women who were given metformin treatment in daily dose of 500 mg and treatment continued till 12 weeks of gestation and women in the second group (50women) serve as a control group. Who attended outpatient clinic or inpatient word of Tanta university hospitalfrom April 2018 to August 2020.Routine investigation in first trimester.

Then patients were divided into two groups:Each group composed of 50 patients and the patients were distributed in each group by simple Randomization method.The first group is composed of 50 patients (study group) take metformin 500 mg per day during the first trimester.The second group is composed of 50 patients (control group) without Metformin.U\S follow up of both groups were carried out at 8^{th} and 12^{th} week gestation.

Inclusion criteriathe patients were selected according to these criteria:Women with polycystic ovary syndrome who become pregnant, Maternal age of 18-40 years, Normal serum thyroid-stimulating hormone and prolactin levels and Singleton pregnancy .

Exclusion criteria were Other type of abnormal pregnancy. (Blighted ovum, Ectopic pregnancy, vesicular mole), Other medical disorders like D.M, thyroid, Heart disease, systemic lupus

erythematosus, rheumatoid arthritis, amyloidosis, atherosclerosis and ant phospholipid syndrome, Pregnant with any other endocrine disease, Any congenital anomaly in uterus as excluded by transvaginal ultrasound scanning (uni-cornuate or bicornuate, submucous fibroid), Pregnant women after IVF, Uses of anti-coagulant drugs, UNexplained Habitualabortion and other risk factors for miscarriage such as abnormal serum karyotyping for both parents.

All patients were subjected to: Personal history: Menstrual history, Presenthistory, Obstetric history and Surgical history: General Examination, Abdominal examination, Ultrasound examination and Routine investigation in first trimester.

2.1 Statistical Analysis

The data were carried out using SPSS V. 23. Shapiro –Wilks test, mean ± standard deviation or median and range. Categorical data were summarized as percentages. The significance for the difference between groups was determined by using two-tailed Student's t test and one way ANOVA and Post hoc tests or for quantitative data as appropriate. Also Qualitative variables were assessed by chi- square test. The probability (P) values of ≤0.05 were considered statistically significant, while P> 0.05 was considered statistically not significant and indicated NS.

3. RESULTS

There was no significant difference between control and study group regarding todescriptive data as showed in (Table 1).

According to Association between rate of pregnancy loss and metformin treatment early pregnancy loss was significantly frequent in control group than in study group with metformin treatment as shown in (Fig. 1). According to Gestational age (weeks)at which pregnancy loss occurred is significantly higher in study group than in control group as showed in (Table 2) and (Fig. 2). According to the rate of early pregnancy loss among studied groups is significantly lower than in control group as shown in (Fig. 3). A Comparison between cases with early pregnancy loss and cases continued their pregnancies regarding to demographic characteristic especially BMI there was significantly higher among early pregnancy loss cases in both study and control groups.as shown in (Table 3).

Table 1. Descriptive data of the studied groups

Variables		Cases (n=50)	Control (n=50)	P
Age (years)	Mean ± SD	24.51 ± 4.74	25.67 ± 7.45	0.354
	Range	18.0 – 40.0	19.2 – 40.0	
BMI (Kg/m^2)	Mean ± SD	27.75 ± 3.22	27.74 ± 3.32	0.687
	Range	19.0 – 32.0	19.0 – 30.0	
parity	Mean ± SD	2. 0 ± 0.7	2. 0 ± 0.9	0.587
	Range	0. 0-3.0	0. 0-3.0	
gravidity	Mean ± SD	2. 0 ± 0.1	2. 0 ± 0.2	0.987
Previous early pregnancy loss	Mean ± SD	1. 7 ± 0.4	1. 8 ± 0.7	0.347
	Range	1. 0 - 4.0	1. 0 - 4.0	

Table 2. Gestational age (weeks) at which pregnancy loss occurred among studied groups

Measures	Study (N=5)	Control (N= 21)	P
Mean ± SD	11.2±1.3	8.9±1.6	
Range	8.0-14.0	6.0-14.0	0.004*
95% CI	9.8-12	8.1-9.2	
Efficacy of continuing metformin in delaying early pregnancy loss			
Items		Mean ± SD	95% CI
Pregnancy prolongation (weeks)		2.3±0.3	0.8-3.3

CI: confidence interval

Table 3. Comparison between cases with early pregnancy loss and cases continued their pregnancies regarding to demographic characteristic

Variability		Epl	Continued	P
Age (years)	Study	25.52 ± 7.71	25.51 ± 4.84	0.258
	control	25.27 ± 5.45	25.67 ± 5.55	0.877
BMI (Kg/m2)	Study	27.45 ± 4.21	25.42± 3.52	0.042*
	control	27.74 ± 4.42	25.34 ± 3.42	0.040*
parity	Study	1. 9 ± 0.7	2. 0 ± 0.2	0.385
	control	1. 9 ± 0.4	2. 0 ± 0.4	0.588
Previous early pregnancy loss	Study	1. 7 ± 0.8	1. 5 ± 0.4	0.058
	control	1. 5 ± 0.7	1. 6 ± 0.8	0.632

EPL: early pregnancy loss

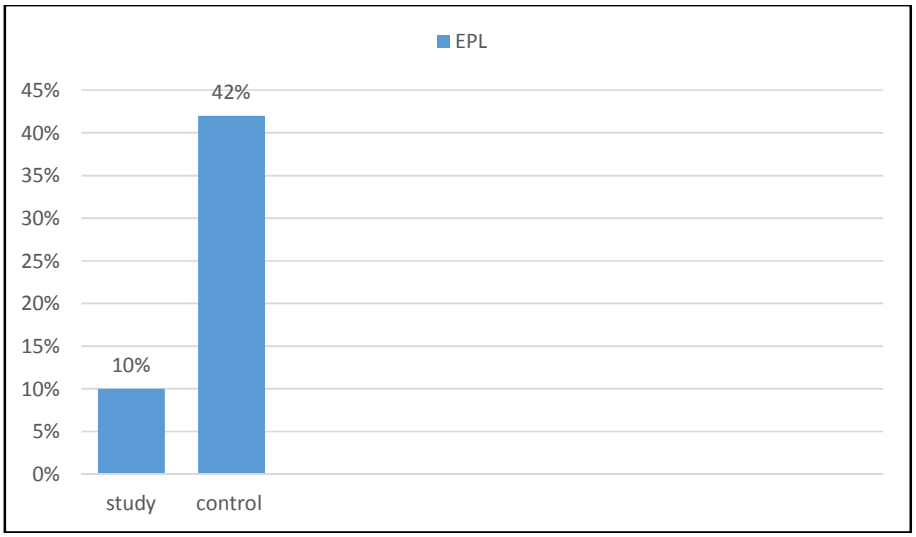

Fig. 1. Early pregnancy loss (EPL) among the studied groups

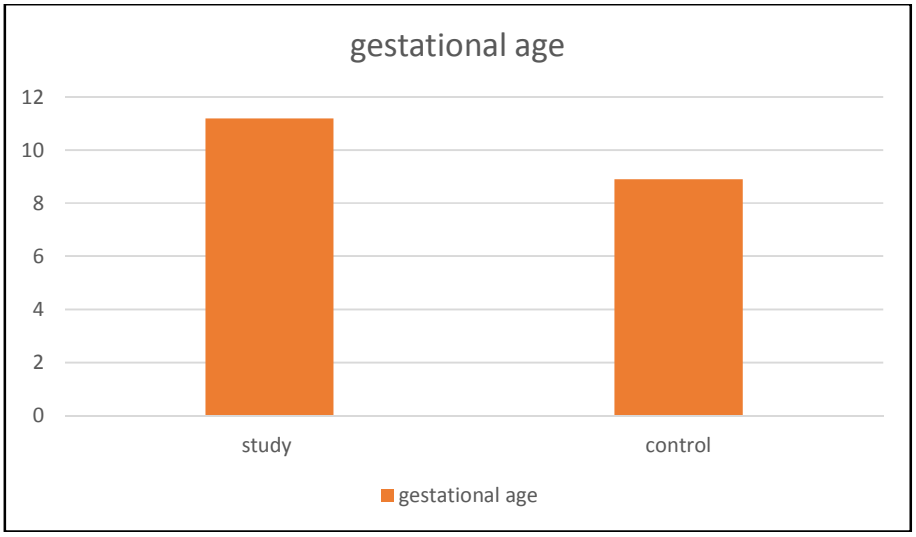

Fig. 2. Gestational age (weeks) at which pregnancy loss occurred among studied groups

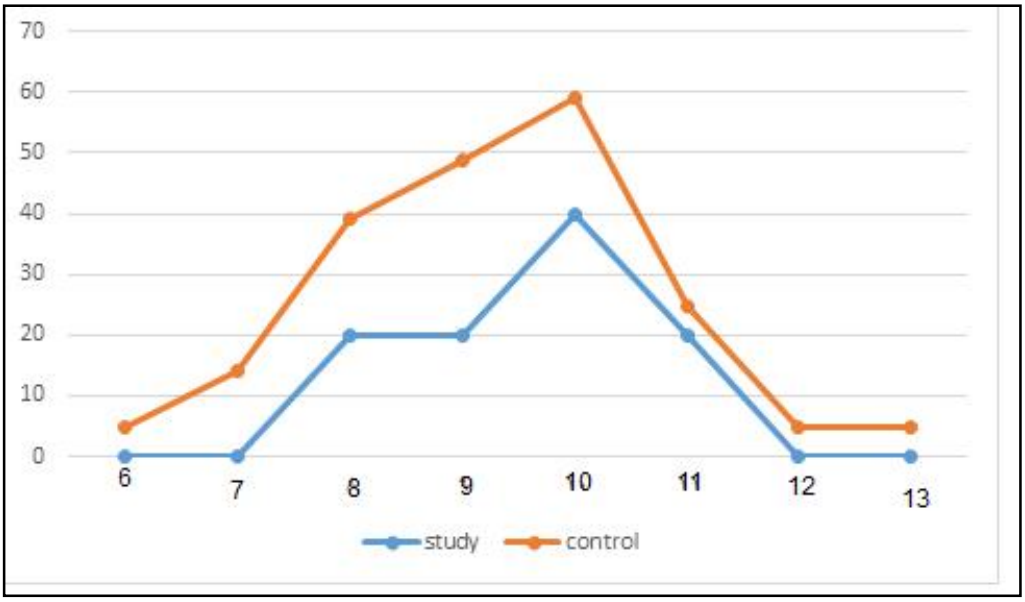

Fig. 3. Rate of pregnancy loss among studied groups

4. DISCUSSION

Polycystic ovary syndrome is a form of multiple endocrine condition, also known as Stein-Acquired syndrome, that also involves other organ systems, such as the pancreas, adrenal glands, hypothalamus, and pituitary [8].

The most prevalent source of ovulatory infertility globally is polycystic ovary syndrome. Most people with PCOS find it impossible to conceive naturally. Women with PCOS can face the possibility of early pregnancy loss as PCOS raises the risk of early pregnancy loss by 5 fold [9].

The aetiology of this disease remains unclear. Hyperinsulinemic resistance does damage to the endometrium which allows it impossible for implantation to occur. It is suspected that androgen levels are increased in men and that there is increased ovulation [10].

Treatment with metformin may improve androgen levels with restoration of menstrual periods and reduction of early pregnancy loss [11]. Research participants were pregnant women who were already confirmed with PCOS and were further split into two categories. One group got metformin medication in daily dosage of 500 mg and treatment proceeded until 12 weeks of childbirth. The other group acted as a test group and they did not receive metformin care.

The mean BMI of the studied cases was 27.7 kg/m2 and in the control group was 27.7 kg/m2 with no noticeable distinction between them.

In our research, the amount of previous abortions ranged from 1–4 while the number of previous abortions in the study conducted by Zolghadri et al. [11] was 2-7 times. Of the 56 people in the patient sample, 25 women had early pregnancy failure in their prior pregnancies and 31 women had a bad experience and none of the patients had obtained metformin in the previous pregnancies [12].

Compared to controls, the rate of early pregnancy failure in our sample was 5 (10 percent) out of 50 patients which is slightly lower than that in the analysis of Alqani et al. [9] (21 (42 percent) out of 50 patients).

Al-Biate [10] found that there were 5 (8.9%) early pregnancy deaths in the sample, while there were 18 (36%) in the control group. The gap between the two classes was important.

Sohrabvand et al. [12] reported that metformin usage before conception decreases the risk of abortion from 20% to 4% and that continuity of care for the first 8 weeks of pregnancy further reduces the rate of abortion from 40% to 8% and that findings are followed by our results as the effectiveness of continuing metformin in delaying early pregnancy failure in the current study

indicates pregnancy prolongation to 2.3±0.3 weeks.

In a meta-analysis by Zeng et al. [13] it was observed that a highly substantial decrease in abortion rate occurred with metformin treatment in early pregnancy with P<0.001 and that findings agree with the present research as early pregnancy loss was significantly greater in control group than in sample group with metformin treatment with P = 0.004.

In Zolghadri et al. [11], the abortion incidence decreased after metformin therapy in women without PCOS relative to the placebo community (15% vs. 55%; OR 2.4, 95% CI 0.35–4.4, P¼0.02) and while the abortion rate decreased after metformin therapy in women with PCOS, the P value was not statistically important (25% vs. 66%; P=0.42).

Women of insulin resistance are at risk for PCOS and hyperandrogenism [14]. They are often at risk of suboptimal hormonal milieu that may affect pregnancy and implantation [15]. For this disorder, a medication could be helpful in restoring ovulation, avoiding early pregnancy failure, and likely enhancing insulin tolerance. This medication has been seen to be effective in the first trimester of pregnancy considering the conventional response that all oral hypoglycemic agents are contraindicated in pregnancy [16].

The Glueck et al. [16-19] research, found that women with PCOS and abnormal glucose resistance had a higher risk of early abortions. It has been shown that metformin in the treatment of pregnancy may reduce the amount of early pregnancy losses. Zolghadri et al. [11] reported that treating PCOS with metformin had a favourable effect on reducing pregnancy and abortion rates [19].

The findings may mean metformin reduces the rate of early pregnancy death. Treatment may boost the damaged glucose tolerance in patients with a diabetic state. Studies show insulin tolerance can be a major risk factor for early pregnancy failure in women with PCOS. Investigators found that hyperinsulinemia decreases endometrial activity and the preimplantation climate by reducing glycodelin and IGF- binding protein 1. Glycodelin may be active in inhibiting the immune reaction to the embryo [20]. The treatment impact of metformin on the irregular GTT can also be clarified by a process of inhibiting this pathway. It has been noted that plasma plasminogen activator inhibitor 1 concentrations are increased in insulin resistance, including PCOS [21]. Increased plasminogen activator inhibitor 1 (PAI-1) is an independent risk factor for miscarriage in PCOS [22]. It has been documented that metformin therapy reduces circulating plasminogen activator inhibitor 1 in women with PCOS. It may be a potential mechanism in women without PCOS. Metformin is a type B medicine, meaning no teratogenic results have been shown in animal research [23].

Metformin has a beneficial purpose irrespective of its hypoglycemic action but arises by the impact on lipid, inflammation, hemostasis, endothelial cells, and platelet function. Few of the other modes of action include diabetes, insulin resistance, and leptin resistance. In comparison, the reduction of the hyper androgenization of the embryo is important. There is also an impact on the immune system through the molecule, which appears to promote the adhesion phase [24].

BMI was substantially higher among cases in both research and control groups in the present study, which is in accordance with a report by Al- [10]; Hussein et al. [24]. The adverse effects might be induced by high insulin resistance, which is correlated with high BMI.

Controversies concern whether metformin can be stopped and how frequently metformin should be utilised. Some experts reported that there are concerns that stopping metformin during pregnancy could damage the embryo. And if there is evidence that metformin is not teratogenic [24].

5. CONCLUSION

Metformin therapy in pregnant women with polycystic ovary syndrome was associated with a significant reduction in the rate of early pregnancy loss. It was well tolerated by patients with a minimum of side effects. However, extended studies are required to evaluate its effect on further pregnancy complications and fetal outcomes.

CONSENT AND ETHICAL APPROVAL

As per international standard or university standard guideline participant consent and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Umland EM, Weinstein LC, Buchanan EM. Menstruation-related disorders. In: DiPiro JT, Talbert RL, Yee GC, et al., editors. Pharmacotherapy: A Pathophysiologic Approach. 8th ed. New York: McGraw-Hill. 2011;1393.
2. Lin LH, Baracat MC, Gustavo AR et al. Androgen receptor gene polymorphism and polycystic ovary syndrome. Int J Gynaecol Obstet. 2013;120:115–118.
3. Aubuchon M, Legro RS. Polycystic ovary syndrome: Current infertility management. Clin Obstet Gynecol. 2011; 54(4):675–684.
4. American congress of obstetricians and gynecologists. ACOG practice bulletin no. 108: Polycystic ovary syndrome. Obstet Gynecol. 2010;114(4):936–949.
5. Sidelnikov VM. Preparation and manage ment of pregnancy in women with recur rent pregnancy loss. Int J Gynaecol Obs tet. 2011;9-76.
6. McFarland C. Treating polycystic ovary syndrome and infertility. Am J Matern Child Nurs. 2012;37(2):116–121.
7. Xita N, Georgiou I, Tsatsoulis A. The genetic basis of polycystic ovary syn drome. Eur J Endocrinol. 2002;147:717–725.
8. 114-Macut D, Bjekić-Macut J, Doknića M. Insulin and the polycystic ovary syndrome. Diabetes Research and Clinical Practice. 2017;130:163-170.
9. Alqani V, Mohammed A, Meziel M. The role of metformin in reducing rate of abortion in women with polycystic ovary syndrome (PCOS). Int J Res Pharm Sci. 2017;8:41-414.
10. Al-Biate M. Effect of metformin on early pregnancy loss in women with polycystic ovary syndrome. Taiwanese Journal of Obstetrics & Gynecology 54. 2015;266-269
11. Zolghadri J, Tavana Z, Kazerooni T et al. Relationship between abnormal glucose tolerance test and history of previous recurrent miscarriages and beneficial effect of metformin in these patients: a prospective clinical study. Fertility and Sterility. 2008;90:3.
12. Sohrabvand F, Shariat M, Bagehri B, et al. effect of metformin on miscarriage in pregnant patient with polycystic ovary syndrome. West Indian Med. 2009;58: 433-6.
13. Zeng H, Zhang Y, Tian F et al. Effect of metformin on pregnancy outcomes in women with polycystic ovary syndrome. Meta-analysis, Medicine.2016;95:4526.
14. Jakubowicz DJ, Iuorno MJ, Salmon J. Effects of metformin on early pregnancy loss in the polycystic ovary syndrome. J Clinic Endocrinol. 2002;87:524–9.
15. Jakubowicz DJ, Seppalam, Jakubowicz S. Metformin increases luteal phase, serum glycodelin and insulin-like growth factor-binding protein-1 concentrations and enhances uterine vascularity and enhances uterine blood follow in the polycystic ovary syndrome. J Clin Endocrinol Metab. 2001;86:1126–33.
16. Glueck CJ, Wang P, Goldenberg N, Smith LS. Pregnancy outcome among women with polycystic ovary syndrome treated with metformin. Hum Reprod 2002;17: 2858–64.
17. Glueck CJ, Sherif G, Awadella MO, Harvey PH. Polycystic ovary syndrome, infertility, familial thrombophilia, familial hypo fibrinolysis. 2000;74:394–7.
18. Glueck CJ, Harvey PH. Dancameron. Continuing metformin throughout preg nancy in women with polycystic ovary syndrome appears to safely reduce first trimester spontaneous abortion, a pilot study. FertilSteril. 2001;75:46–52.
19. Glueck CJ, Wang P, Fontine RN, Sieve L, Smith LS. Plasminogen activator inhibitor activity: an independent risk factor for the high miscarriage rate during pregnancy in women with polycystic ovary syndrome. Metabolism 1999;48:1589–95.
20. Atiomo WU, Bates SA, Condon JE, Shaw S, West JN, Prentice AG. The plas mino gen activator system in women with policy stic ovary syndrome. FertilSteril. 1998; 69:236–41.
21. Motta AB. Dehydroepiandrosterone to induce murine models for the study of polycystic ovary. J Steroid Biochem Mol Biol. 2010;119:105e11.
22. Okamoto N, Uchida A, Takakura K, Kariya Y, Kanzaki Y, Riittinen L, et al. Suppression by human placental protein 14 of natural killer cell activity. Am J Reprod Immunol. 1991;26:137e42.

23. Giudice LC, Mark SP, Irwin JC. Paracrine actions of insulin-like growth factors and IGF binding protein-1 in non-pregnant human endometrium and at the decidual-trophoblast interface. J Reprod Immunol 1998;39:133e48.

24. Hussein I, Abdelshafy A, Awwad H. The role of metformin for prevention of first trimesteric miscarriage in women with poly cystic ovary syndrome: A rando mized controlled trial. 2019;10(1):2090-7625.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/64738