Effect of metformin on pregnancy outcomes in women with PCOS

Asma A. Swadi[1], Saba M.Swadi[2]

الخلاصة

أجريت هذه الدراسة على مجموعه من النساء المصابات بمتلازمة تكيس المبايض واللاتي تعرضن الى حالة فقدان حمل متكرر(اجهاض متكرر).

82 امراه مصابه بمتلازمة تكيس المبايض وغير مصابات بداء السكري تم تقسيمهم الى مجموعتين (المجموعه1)وعددها 38 اعطيت عقار الميتفورمين لمدة 3 اشهر قبل الحمل وتم ايقافه عند حدوث الحمل مباشرة. اما (المجموعه2) وعددها 45 اعطيت عقار الميتفورمين لمدة 3 اشهر قبل الحمل واستمرت باخذ العقار 4 اشهر بعد حدوث الحمل.

النتائج:الجموعه الاولى كانت نسبة الاجهاض المتكرر فيها = 83.78% مقارنة بالمجموعه الثانيه التي استمرت باخذ العقار 4 اشهر بعد حدوث الحمل حيث اصبحت نسبة الاجهاض= 15.5% .

نستنتج بان استمرار استخدام عقار الميتفورمين لمدة 4 اشهر بعد الحمل يقلل من نسبة الاجهاض المتكرر وبشكل ملحوظ(p=0.001) .

Abstract

Background: Recurrent pregnancy loss (RPL) classically refers to the occurrence of three or more consecutive losses of clinically recognized pregnancies prior to the 20th week of gestation (ectopic, molar, and biochemical pregnancies are not included). we hypothesized that metformin owing to its metabolic, endocrine effect may reduce the incidence of first trimester miscarriage in PCOS women.

Materials and Methods: We examined the records of all 82 nondiabetic women with the polycystic ovary syndrome who became pregnant while being seen in the out patients Clinic of the maternity teaching hospital and private clinic in AL-Qadisyiah city between January 2011 and march 2014, and who did receive metformin 3 months pre-conception (group1; n = 37) in contrast to second group who became pregnant while taking metformin and continued taking metformin at a dose of 1000–2000 mg daily throughout the first 20 weeks of gestation(group2; n = 45).

Results: both groups were similar with respect to all background characteristics (age, BMI, parity, RBS, blood urea and serum creatinin).rates of early pregnancy loss in group1(82.5%) compared with (79.7%) in group2.after administration of metformin; pregnancy loss was(83.7%,15.5%) in group1 and group2 respectively (P value = 0.001).

Conclusion: administration of metformin in the first 20 weeks of pregnancy to women with PCOS was associated with a marked and significant reduction in the rate of early pregnancy loss.

KeyWords: PCOS , BMI,

[1]Department of Pharmacology and Therapeutics, College of Medicine.
[2]Department of Gynecology and Obstetric, College of Medicine.

Introduction

Recurrent pregnancy loss (RPL) classically refers to the occurrence of three or more consecutive losses of clinically recognized pregnancies prior to the 20th week of gestation (ectopic, molar, and biochemical pregnancies are not included). However, many investigators use variations of this definition. As an example, some include occult early pregnancy failures diagnosed by sensitive human chorionic gonadotropin tests in the definition and others initiate evaluation and treatment of couples after two consecutive losses[1]. Spontaneous pregnancy loss is a surprisingly common occurrence. Whereas approximately 15% of all clinically recognized pregnancies result in spontaneous loss, However, epidemiologic studies have revealed that 1% to 2% of women experience recurrent pregnancy loss[2,3] Approximately 2% to 4% of RPL is associated with a parental balanced structural chromosome rearrangement, Anatomic abnormalities account for 10% to 15% of cases of RPL and are generally thought to cause miscarriage by interrupting the vasculature of the endometrium, prompting abnormal and inadequate placentation[4]. Certain infections, including Listeria monocytogenes, Toxoplasma gondii, rubella, herpes simplex virus (HSV), measles, cytomegalovirus, and coxsackieviruses, are known or suspected to play a role in sporadic spontaneous pregnancy loss. However, the role of infectious agents in recurrent loss is less clear, with a proposed incidence of 0.5%to 5%[5].

Because a fetus is not genetically identical to its mother, it is reasonable to infer that there are immunologic events that must occur to allow the mother to carry the fetus throughout gestation without rejection. One specific autoimmune disorder, APS, requires particular attention as it has been clearly linked with many poor obstetric outcomes, including RPL[6,7].Half of patients will remain without a definitive diagnosis[8].

Studies have found evidence of PCOS in at least 40% of women with RPL[9].

Polycystic ovary syndrome is characterised by anovulation, infertility, and hyperandrogenism, with clinical manifestations of irregular menstrual cycles, hirsutism, and acne. And it affects 5–10% of women of reproductive age [10].

In addition to poor conception rates, pregnancy loss rates are high (30,50%) during the first trimester. We hypothesized that hyperinsulinemic insulin resistance contributes to early pregnancy loss in the syndrome, and that decreasing hyperinsulinemic insulin resistance with metformin during pregnancy would reduce the rate of early pregnancy loss[11]. Hyperinsulinemic insulin resistance is also a key feature of the polycystic ovary syndrome, and evidence suggests that hyperinsulinemia plays a pathogenic role in the disorder by increasing circulating ovarian androgen concentrations and impeding ovulation[12,13].

Metfomin (a Biguanide) is the most commonly prescribed oral antidiabetic drug in the world, which primarily helps by lowering blood glucose levels and

preventing insulin resistance by virtue of its hepatoselective insulin-sensitizer action. It is regarded as the first-line treatment in type 2 diabetes mellitus (DM). It primarily reduces hepatic gluconeogenesis, i.e., decreases hepatic glucose production and increases insulin action in muscle and fat .Recently, benefits in the macrovascular complications of diabetes have been attributed to it. It also finds place in the treatment of many clinical conditions other than type 2 DM (polycystic ovarian syndrome, obesity, fatty liver disease, heart failure and hypertention). This makes metformin offer many advantage over the currently available other oral anti diabetic drugs.

Metformin has proven successful in treating some of the symptoms of Polycystic Ovary Syndrome (PCOS), the most common form of female infertility in which women fail to ovulate. [14,15].

Materials and Methods

Study subjects

We examined the records of all 82 nondiabetic women with the polycystic ovary syndrome who became pregnant while being seen in the out patients Clinic of the maternity teaching hospital and private clinic in AL-Qadisyiah city between January 2011 and march 2014, and who did receive metformin 3 months pre-conception (group1; n = 38) in contrast to second group who became pregnant while taking metformin and continued taking metformin at a dose of 1000–2000 mg daily throughout the first 20 weeks of gestation (group2; n = 45). Polycystic ovary syndrome was defined by the presence of oligomenorrhea (8 or fewer menstrual periods in the last year) and hyperandrogenemia (elevated serum total or free T concentration). Ultrasonography of the ovaries revealed polycystic ovaries in all women, as defined by an ovarian volume more than 9 ml, the presence of 10 or more cysts of 2- to 8-mm diameter, and increased density of stroma[16]. All women had normal serum TSH, PRL, and 17α-hydroxyprogesterone concentrations. None of the women had diabetes mellitus, as determined by random [17].

All women had normal uterine anatomy, demonstrated by ultrasonography and tested negative for the antiphospholipid syndrome.

It was the standard of care for this practice to assess all women who miscarried in the study for blood urea and serum creatinin to exclude renal impairment which is contraindicated to use metformin[18].

Diagnosis of pregnancy:

Pregnancy was determined by plasma β-human CG (β-hCG) more than 50 IU/liter and by detection of a gestational sac in the uterine cavity, by ultrasonography.

Once pregnancy was confirmed, the first group stopped metformin while the second group continue to take metfomin till 20 weeks of gestation.

Miscarriage determined whenever the women had symptoms suggestive of miscarriage (*e.g.* vaginal bleeding, abdominal pain) or ultrasonographic evaluation suggested a poor prognosis for pregnancy outcome.

Statistical analysis:

Two software programs were used for the analysis of data. These were SPSS version 16 and Microsoft Office Excel 2010. Numeric variable were expressed as mean standard deviation and standard error. Nominal variables were expressed as number and percentage. Independent sample student T test was used to compare between 2 groups. chi-square test was used to compare frequency distribution between 2 groups. P-value would be considered significant if it was less than or equal to 0.05.

Results

With regard to previous pregnancy outcomes, 28 of the 45 women in the group 2 had a history of at least 1 prior pregnancy, whereas 16 women were nulliparous. None of the women had received metformin during these previous pregnancies. Among the 28 women in the group 2 with a history of prior pregnancy, there were a total of 84 pregnancies, which resulted in 17 live births and 67 miscarriages, yielding a miscarriage rate of 79.7%.

In the group 1, 21 of the 38 women had a history of at least 1 prior pregnancy, whereas 17 women were nulliparous. Among the 21 women in the group 1 with a history of prior pregnancy, there were a total of 63 pregnancies, which resulted in 11 live births and 52 miscarriages, yielding a miscarriage rate of 82.5%.

Table 1 describes the baseline characteristics and variables for both groups, which did not differ with respect to age, gravida, parity, body mass index,random blood sugar, blood urea and serum creatinin.

Table (1) describes the baseline characteristics and variables for both groups

	Group (2) n=45			Group (1) n=38				
Parameter	**Mean**	**SD**	**SE**	**Mean**	**SD**	**SE**	**P**	**Significance**
Age	30.60	3.80	0.57	28.57	5.06	0.83	0.080	NotSignificant
Para	0.73	0.84	0.12	1.00	1.15	0.19	0.23	Not significant
Gravida	5.00	2.10	0.31	4.68	2.48	0.41	0.523	Not significant
Abortion	4.27	1.80	0.27	3.70	2.15	0.35	0.199	Not significant
BMI	24.93	4.86	0.73	25.14	4.71	0.77	0.85	Not significant
R.B.S	133.20	12.28	1.83	135.68	11.58	1.90	0.354	Not significant
bl.urea	27.76	4.93	0.73	27.54	4.93	0.81	0.845	Not significant
S.creatinin	0.85	0.26	0.04	0.76	0.24	0.04	0.132	Not significant

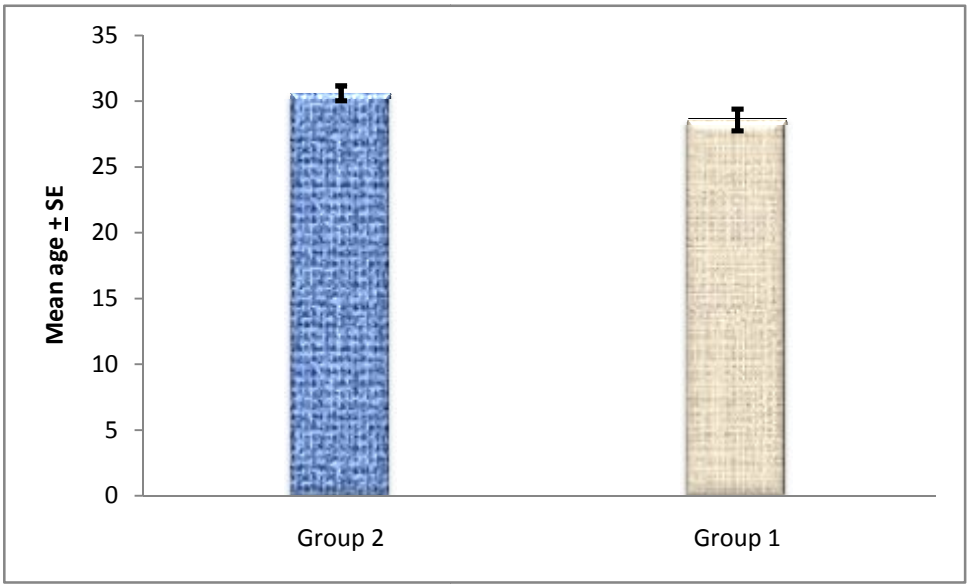

Figure 1 describes the baseline characteristic and variable for both groups, which does not differ with respect to age.

Table 2 and figure 2 show the differences of pregnancy outcomes in both groups, in group1 the number of term pregnancy was 6(16.22%) and number of miscarriage was31(83.78%), while in group 2 the number of term pregnancy was 38(84.44%) and number of miscarriage was7(15.56%).

Table 2:Show the differences of pregnancy outcomes in both groups.

	MTF till conception(group1)		MTF 4th month (group2)	
Outcome	No.	%	No.	%
Term	6	16.22	38	84.44
Abortion	31	83.78	7	15.56
Total	37	100.00	45	100.00
P	<0.001	Significant		

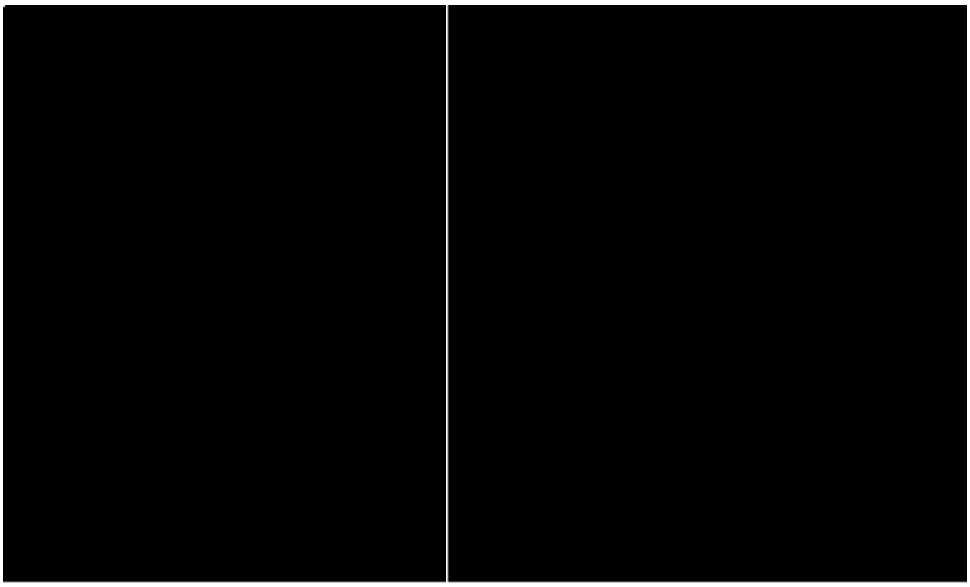

Figure 2: Show the differences of pregnancy outcomes in both groups.

Table 3 show the number and percentage of congenital anomalies at term in both groups, in group1 the number of congenital anomalies at term was 0 while in group 2 the number of congenital anomalies at term was 2 (Not significant).

Table 3 Show the number and percentage of congenital anomalies at term in both groups.

	MTF till conception(group 1)		MTF 4th month(group 2)	
Congenital abnormality	No.	%	No.	%
No	45	100	36	94.74
Yes	0	0	2	5.26
Total	45	100	38	100.00
P*	1.000	Not significant		

Discussion and conclusion

Polycystic ovarian syndrome is the most common cause of anovulation and female infertility. Not only these women are infertile but also more likely to have pregnancy complications, like recurrent miscarriage[19].

Various studies have shown that women with PCOS have increased chances of miscarriage in the first trimester [20].

When women with polycystic ovary syndrome finally achieve pregnancy (often after a long, arduous, and expensive course of fertility treatments), they are faced with the distressing prospect of a substantially increased risk for

miscarriage during the first trimester[21]. The various reasons cited for this increased occurrence miscarriage are increased LH levels, hyperandrogenism and hyperinsulinemia[22]. Hyperinsulinemia adversely affects the pre-implantation environment by decreasing the expression of glycodelin and IGF-binding protein-1 which may play a role in inhibiting the endometrial immune response of the embryo, and seems to facilitate adhesion processes at the feto-maternal interface[23] Excess insulin appears to increase production of androgen. High androgen levels can lead to ovulation abnormality. Elevated androgen levels and insulin resistance decrease oocyte quality and embryo viability[24].

Metformin, an insulin sensitizing agent, is known to restore regular ovulatory menstrual cycle in majority of these oligomenorrheic women many of whom thereafter conceive naturally[19]. Beside that, its also shown to improve the pregnancy outcomes in these women by reducing the incidence of recurrent miscarriage[20]. The exact mechanism by which metformin prevents miscarriage is not known but many possibilities are suggested: Decreasing androgen, decreasing insulin levels or by improving oocytes quality[25].In the index study, the incidence of recurrent miscarriage among these PCOS women was(79.7%) which decreased dramatically after using metformin in the first 20 weeks of gestation(15.5%) and these results in agreement with Palomba S[1], Falbo A et al and Thatcher and Jackson [26,27].

Metformin use during pregnancy does not appear to be linked to teratogenicity or developmental disorders among exposed children studied during their first 18 months of life[28].

We concluded that administration of metformin in the first 20 weeks of pregnancy to women with PCOS was associated with a marked and significant reduction in the rate of early pregnancy loss.

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