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PREGNANCY OUTCOMES AMONG INFERTILE PATIENTS WITH POLYCYSTIC OVARY SYNDROME TREATED WITH METFORMIN

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Summary. *The Polycystic Ovary Syndrome (PSOS) is the commonest cause of anovulatory infertility. Matformin is effective in the treatment of PCOS- related anovulation. Metformin is an oral biguanide, well established for the treatment of hyperglycemia. Preliminary evidence indicates that metformin may also be effective in decreasing the risk of early spontaneous abortion in women with PCOS. The aim of the study was to determine whether metformin would safely reduce the rate of first trimester spontaneous abortion in this women and increase the number of live birth without teratogenicity. We assessed 3 oligo-amenorrheic non-diabetic women with PCOS and previously early spontaneous abortion who conceived while taking metformin and continued it throughout pregnancy. They were prospectively assessed. Outcome measures included first trimester spontaneous abortion, normal ongoing pregnancies ≥13 weeks, live birth, birthweight and height. Results: 3 women had 3 healthy neonatuses. Conclusion: While safety during pregnancy has not been established, three women who conceived on and continued metformin through pregnancy have delivered normal babies. This study found that the abortion was reduced when metformin was used for ovulation induction before pregnancy (1 woman) and continued throughout the pregnancy (2 women): 3 month (1 woman) and during entire pregnancy (1 woman). Our data showed a decreases risk of first trimester spontaneous abortion compared with previous pregnancies in the same women not on metformin. Pregnancy outcomes did not differ in women who stopped metformin after conception and at the end of the first or third trimester pregnancy. Newborn outcomes were good in all three women, with normal growth and Apgar Score. The study found no evidence of any adverse clinical effects on the mother or the newborn when metformin is continued through first trimester and entire pregnancy. Our cases highlights the importance of PCOS diagnosis in the management women with previously first trimester spontaneous abortion.*

Key words: *PCOS, early spontneous abortion, metformin, pregnancy outcome*

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies among women of reproductive age (1). PCOS is a genetically complex endocrine disorder of women of uncertain etiology and is a common cause of anovulatory infertility, menstrual dysfunction, and hirsutism (2). PCOS appears to be associated with an increased risk of metabolic abberations, including insulin resistance and hyperinsulinism, tip 2 diabetes mellitus, dyslipidemia, cardiovascular disease, and endometrial carcinoma (3).

It is a very heterogeneous syndrome both in its clinical presentation and laboratory manifestations. The main disturbances in this syndrome are: abnormal morphology of the ovary; abnormal steroidogenesis; hiperinsulinemia, present in about 80% of obese women and 30-40% of women of normal weight with PCOS and abnormal gonadotrophin secretion. Prevalence estimates vary between 3-20%, depending on the diagnostic criteria used and the population studied (2). Anovulation, early pregnancy loss, and later pregnancy complications have all been implicated in the low fecundity of women with PCOS (1).

Its etiology is uncertain, but current theories emphasize genetic and intrauterine origins coupled with environmental factors such as diet and altered lifestyle patterns (2).

Diagnosis is not uniform for clinical trials or management and often is limited to a small number of these characteristics, such as evidence of excess androgen with irregular or absent ovulation (3).

One of the major biochemical features of PCOS is insulin resistance accompanied by compensatory hyperinsulinemia. There is increasing data that hyperinsulinemia produces the hyperandrogenism of PCOS by increasing ovarian androgen production, particularly testosterone and by decreasing the serum sex hormone binding globulin concentration (4). The high levels of androgenic hormones interfere with pituitary ovarian axis, leading to increased LH levels, anovulation, amenorrhea, recurrent pregnancy loss, and infertility (5).

Hyperinsulinemia may be a contributing factor in the higher rate of miscarriage. Hyperinsulinemia has also been associated high blood pressure and increased clot formation and appears to be a major risk factor for the development of heart disease, stroke, impaired glucose tolerance and type II diabetes (5,6).

PCOS is an endocrinopathy that is characterized by a reduction in all reproductive performances, including not only chronic anovulatory infertility but also increased risk of abortion and complicated pregnancy. Complications of pregnancy associated with maternal PCOS include increased prevalence of early pregnancy loss, recurrent miscarriage, gestational diabetes, pregnancy-induced hypertensive disorders, and the birth of small-for-gestational-age babies (1,2). Increased risk of early pregnancy loss or recurrent miscarriage has been attributed to obesity, hyperinsulinaemia, elevated luteinizing hormone concentrations, and endometrial dysfunction (6,7).

Effective treatment of PCOS remain controversial. For women in the reproductive age range, PCOS is a serious, common cause of infertility, because of the endocrine abnormalities which accompany elevated insulin levels (2). The medical literature suggests that the endocrinopathy in most patients with PCOS can be resolved with insulin lowering therapy (6,7). There is increasing evidence that this endocrine abnormality can be reversed by tretament with metformin (8). Metformin is an oral insulin-sensitizing agent that has been shown to reduce serum concentrations of insulin and androgens, reduce hirsutism, and improve ovulation rates (7). Women with PCOS often conceive while on metformin, and exposure during organogenesis is common. At present, metformin is classified as Class B in pregnancy, with no evidence of animal or fetal toxicity or teratogenecity (8).

In pregnancy, there are several non randomized trials that suggest that metformin may reduce the risk of first-trimester spontaneous abortions and the development of gestational diabetes mellitus in women with PCOS treated throughout pregnancy (8). With regard to congenital malformations, most retrospective studies and the published clinical experience have not demonstrated an increased risk of malformed infants among women treated with this anti-diabetes agents. Data regarding the teratogenicity of metformin or the long-term implications for the offspring are limited (9). The exact mechanisms by which metformin exert its benefitial effects on pregnancy achievement and development were not recognized. Studies in PCOS suggest that hyperinsulinemia suppresses endometrial expression of glycodelin, a protein whose circulating concentration may reflect endometrial function. Conversely, administration of metformin to women with PCOS has been shown to increase circulating glycodelin. Glycodelin is secreted by the endometrium, may inhibit the endometrial immune response to the embrio, and likely plays a critical role during implantation and in the maintenance of pregnancy (10). Moreover, both early spontaneous abortion and retarded endometrial development are associated with decreased secretion of glycodelin from secretory endometrium. However, administration of metformin to prevent miscarriage is controversial and widespread use of this drug in early pregnancy requires investigation (11,12).

The effects of metformin during pregnancy on the unborn child are not entirely known.

The Aim of the Study

To determine whether metformin, which had facilitated conception in 3 oligo-amenorrhoeic women with PCOS, would safely reduce the rate of first-trimester spontaneous abortion and increase the number of live births without teratogenicity, and without adversely affecting infants' birthweight or height.

To investigate the effect of metformin on pregnancy outcomes in the 1, 2 and 3 trimester of pregnancy in women with previously early spontaneous abortion and PCOS.

Our specific aim was to review the first 3 clinical pregnancies of women with PCOS who conceived on metformin. Two women continued metformin throughout pregnancy (first trimester - 1 woman and entire pregnancy - 1 woman).

Patients and Methods

Methods

The diagnosis of PCOS was made using revised 2003 ESHRE/ASRM consensus conference criteria (ESHRE/ASRM, 2004) (two out of three): oligomenorrhea or anovulation; clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries. Polycystic ovaries diagnosed by vaginal ultrasonography.

Exclusion criteria included:

- Serum creatinine >1.5 mg/dl
- Inclusion Criteria included:
- Women diagnosed with PCOS (ESHRE/ASRM, 2004)
- Prior and current pregnancies conceived with the same partner
- Using metformin for ovulation induction (1500-2000 mg/day)
- Conceived on metformin (1500–2000 g/day)
- Conceived on metformin (1500–2000 mg/day) cum Clomid (100–200 mg/day)
- Continued taking metformin during pregnancy (1500 mg/day)

a. first trimester
b. entire pregnancy

Subjects

Our prospective study included 3 women with PCOS and previously first trimester abortion. All women gave informed consent. All women had received the diagnosis of the PCOS, which was defined as oligoamenorrhea, hyperandrogenism and polycistic ovaries. A standardized history form was completed, with emphasis on menstrual dating and regularity, hirsutism and acne, gynecological history, medications, and family history. Two women on previously hormonal therapy were questioned regarding their menstrual cyclicity before they started the medications. The presence of acne was also recorded, although no specific scoring system was applied. Ovulatory dysfunction was surmised by a his-

tory of eight or fewer menstrual cycles in a year, or menstrual cycles less than 26 day or more than 35 day in lenght; or a midluteal progesterone level of less 16 nmol/mililiter in subjects with cycles 26–35 day in lenght. Clinical hyperandrogenism was diagnosed by the presence of hirsutism (Feriman-Gallwey score >7).

Our prospective study included 3 women with previously 2 or 3 first trimester spontaneous abortion (two or three). All women were in good health with no major medical disorders. All pregnancies (historical and current) were conceived with the same partners. All 3 women were oligomenorrhoeic. 2 women had documented clinical hyperandrogenism. Two women had greater relative ponderosity with mean BMI of 31.2 Baseline laboratory testing was performed. At pre-metformin baseline, blood was obtained for measurements of fasting serum insulin and glucose in 1 woman, and serum sex hormones in all 3 women. Screening for gestational diabetes was done between weeks 26 and 28 gestation in 2 women and resistentio insulini diagnosed (Table 1).

Table 1. PCOS patients – Clinical diagnosis

Patient	1	2	3
Polycystic ovaries	+	+	+
Hirsutism(FG)	10	11	<7
Oligo-anovulatio	+	+	+
BMI	+(31.6)	+(31.1)	(23.1)
Age(year)	29	30	26
Miscarriage (wg)	3(8,7,10)	2(8,8)	2(8,8)
Ginecological examination	normal	normal	normal
Peripheral karyotipe	normal	normal	-
Immunologic disorder	No	-	-
Trombophilic disorder	No	-	-
OGTT/insulin/basal	normal	-	-
OGTT/insulin/28wg	Resist.insul.	Resist.insul.	-
Weight gain (kg)	13	15	9

All three women with 2 (two women) or 3 (one woman) consecutive miscarriage were evaluated prospectively. Detailed history and physical examination were completed. **U**ltrasonographic, radiological and specialized procedures/tests were performed. We tested liver and kidney function before women started taking the metformin.

We used metformin because of its increased tolerability. In women without recent menses, withdrawal bleeding was induced before the initiation of medication. Preconception, metformin was started at 500 mg/day. Women gradually increased the dose until reashing the maximum dose of four tablets 500-2000 mg/day. While receiving metformin, the women with PCOS were evaluated every month. Ultrasonography for follicular and endometrial response was included. Ovulation was detected with transvaginal ultrasonography, or progesterone ≥16 nmol/per liter in second half of menstrual cycle. If woman ovulated, she continued taking the same dose of metformin.

Table 2. PCOS patients - Ante and postconception therapy

Patient	1	2	3
Anteconception	CC 100mg (2mo) M 2000mg + CC 100mg (2mo)	CC 100-200mg (6mo) M 1500mg + CC 100mg (4mo)	M 1500mg (2 mo)
Postconception			
I trimester	M (3×500 mg)	M (3×500 mg)	
II trimester	M (3×500 mg)		
III trimester	M (3×500 mg)		

M-Metformin; CC-Clomiphen citrat; mo-month

Of the 3 women on metformin, 1 woman conceived spontaneously and 2 women conceived on combined metformin+clomid. After conception, we recommended that metformin be:

- discontinued after a positive pregnancy test in 1 women;
- continued troughout pregnancy, without change in dose, to 12 weeks gestation in 1 women, or
- continued throughout the pregnancy (1 patient).

During pregnancy, women with PCOS on metformin made montly follow-up visit to our clinical centre with measurement of weight and weight gain. At each monthly visit during pregnancy, after a 5 min resiting period, seated blood pressure was obtained by a single observer and recorded, diet was reviewed, as was adherence to metformin and metformin dose.

Results

In the 3 live births height and weight were recorded. Neither weight nor height differs from the normal neonatal population. There have been no major birth defects in 3 live births as determined by pediatricians. There was no maternal hypoglycemia and lactic acidosis.

Table 3. PCOS - Pregnancy outcome

Patient	1	2	3
Infant-Gender	female	male	male
Birth weight (g)	3000	3600	3400
Birth height (cm)	50	56	55
Apgar score 1/5min	9/10	9/10	9/10
Birth defects	no	no	no
Week gestation	39	41	40

Discussion

In this study of 3 women, we concluded that Metformin reduces the endocrinopathy of PCOS, allowing resumption of normal menses in previously amenorrheic women with PCOS. All three women resumed spontaneous menses following treatment and showed presumptive evidence of ovulation with metformin alone or with CC. One woman conceived on Metformin; one woman concaived with M+CC and remained on metformin during first trimester, and one woman concaived

on M + CC and remained on Metformin during entire pregnancy. All 3 women were followed with standard obstetrical high risk pregnancy protocol.

There were no congenital defects in the 3 live births of women who conceived on and remained on Metformin. The 3 infants' lenght, weight, and physical examination at birth were within normal limits. Before Metformin, all three women had 7 previous pregnancies, with 7 first trimester misscariage. In all 3 women with PCOS who conceived on and remained on Metformin, there were 3 live healthy babies.

PCOS is associated with poorer pregnancy outcome. Early pregnancy loss is a major complication of pregnancy in women with PCOS (6). It is estimated that 30-50% of pregnancies in women with PCOS end with spontaneous abortion or recurrent miscarriage during the first trimester (12). In most cases no apparent cause can be identified but, in addition to defects in the developing embryo, adverse alterations in endometrial function may play a role (10).

Metformin alone or metformin plus clomid will restore regular ovulatory menstrual cycles to a majority of previously infertile oligoamenorrhoeic women with PCOS, many of whom will conceive. After conception, metformin significantly reduces the otherwise high rate of spontaneous abortion which characterizes PCOS. In our study metformin use during pregnancy was not associated with increased development of major birth defects. Because metformin has beneficial effects on risk factors for the high rate of first trimester spontaneous abortion in PCOS (hyperinsulinaemia, insulin resistance, hyperandrogenemia, obesity, and high level of plasminogen activator inhibitor activity -PAI-Fx), metformin therapy was safely associated with a significant reduction in early pregnancy loss (12,13).

The current report can also be assessed by comparing antecedent pregnancies that occurred in the absence of metformin and the current pregnancies on metformin in the same women. Pregnancy outcomes did not difer in women who stopped metformin at the end of the first trimester versus those who continued it throughout. However, a major benefit of continuing metformin beyond the first trimester and throughout pregnancy in women with PCOS is a sharp reduction in gestational diabetes (14).

In the our mini study, reduction in the rate of first trimester miscarriage was achieved without evident teratogenicity, intrauterine growth retardation, maternal or neonatal side-effects, and adverse effects on birthweight and height. Currently available data suggest that metformin improves pregnancy outcome by decreasing early spontaneous miscarriages in women with PCOS (11). Evidence in support of a reduction in miscarriage rates can be found in two retrospective analyses which showed that metformin reduced first trimester spontaneous miscarriages in women with PCOS. (15). Metformin therapy has also been shown to reduce the risk of gestational diabetes in women with PCOS.(16) Whether women with PCOS should remain on metformin during pregnancy is a more difficult controversial question.

Metformin is a common treatment for women who have insulin resistance manifesting as type 2 diabetes or polycystic ovarian syndrome. With an increasing number of these patients conceiving, it is expected that the use of metformin in and around the time of pregnancy will increase. The use of metformin in early pregnancy for reducing the risk of miscarriage should be avoided outside of the context of properly designed prospective randomized trials. Safety in early pregnancy appears to be reassuring, but not completely proven.

Metformin therapy throughout pregnancy in women with PCOS reduces the rate of first trimester of spontaneous abortion seen among same women. Although metformin is known to cross the placenta, there is, as yet, no evidence of teratogenicity (11). So far, evidence for safety of continued therapy throughout gestation is insufficient, and existing papers are limited in design and might mask for fetal toxic outcomes due to metformin therapy. Prior to a recommendation of sustained metformin therapy throughout pregnancy, randomized placebo-controlled double-blinded clinical trials are awaited with interest, so that present assumptions on efficiency can be clarified, in order to assure efficient and safe management of pregnant polycystic ovary syndrome patients (16).

Recent data suggest sparing effects of continued metformin therapy throughout pregnancy on early pregnancy loss and gestational diabetes mellitus, but its impact on hypertensive complications to pregnancy appears less evident (14).

Conclusion

The report showing the efficacy of metformin, given before and during pregnancy in women with PCOS and previously early spontaneous abortion. Our mini study found that the recurrent early abortion was reduced when metformin was used for ovulation induction before pregnancy (3 woman) and continued throughout the pregnancy (2 women). We presented data on the use metformin throughout one and three trimesters in 2 women with PCOS and previously first trimester abortion. Pregnancy outcome did not differ in women who stopped metformin at the end of the first trimester, versus woman who continued it throughout. Whether metformin's beneficial effects on pregnancy outcome are primarily realized during the first trimester need to be examined. The our data showed a decreased risk of first-trimester spontaneous abortions compared with previous pregnancies in the same women not on metformin, and suggest that metformin may be safe in pregnant PCOS women. There was no increase in infant birth weight compared with gestational-age and sex-matched norms.

On the basis of the limited data available today, there is no evidence of an increased risk for major malformations when metformin is taken during the first trimester of pregnancy. Large studies are needed to corroborate these preliminary results.

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ISHOD TRUDNOĆE KOD INFERTILNIH PACIJENTKINJA SA SINDROMOM POLICISTIČNIH OVARIJUMA LEČENIH METFORMINOM

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Kratak sadržaj: *Sindrom policisticnih ovarijuma je čest uzrok anovulatornog infertiliteta. Metformin je efikasan u tretmanu anovulacije povezane sa sindromom policističnih ovarijuma. Metformin je oralni bigvanid, dobro afirmisan u tretmanu hiperglikemije. Preliminarni podaci indiciraju da metformin može biti takodje efikasan i u sniženju rizika od ranih spontanih pobačaja kod žena sa sindromom policističnih ovarijuma. Cilj studije bio je da proceni da li metformin može sigurno da redukuje stopu pobačaja u prvom tromesečju trudnoće u ovih žena i da poveća broj živo rođenih bez anomalija. Tri oligo-amenoroične nedijabetične žene sa sindromom policističnih ovarijuma i prethodnim ranim spontanim pobačajima začele su na metforminu i nastavile su da ga koriste tokom trudnoće. Praćene su prospektivno. Procena ishoda uključivala je spontane abortuse u prvom tromesečju, normalne trudnoće u toku starije od 13 nedelja, živo rodjene, težinu i dužinu na rođenju. Tri žene rodile su tri zdrava neonatusa. Iako sigurnost metformina za vreme trudnoće još nije dobro ispitana, tri žene koje su začele na metforminu i nastavile da ga koriste tokom trudnoće rodile su zdrave bebe. Ova studija je našla da do redukcije stope pobačaja dolazi kada se metformin koristi za indukciju ovulacije pre trudnoće i nastavlja tokom trudnoće (3 meseca, ili tokom cele trudnoće). Naši podaci ukazuju na sniženje rizika od spontanih pobačaja u prvom tromesecju trudnoće, u komparaciji sa prethodnim trudnoćama u istih žena, kada nisu bile na terapiji metforminom. Ishod trudnoće nije se razlikovao kod žene koja je stopirala metformin nakon ovulacije, na kraju prvog, ili trećeg tromesečja trudnoće. Studija nije našla dokaze za nepovoljne kliničke efekte na majku ili fetus kada je metformin nastavljen tokom prvog tromesečja ili čitave trudnoće. Naši slučajevi ukazuju na značaj PCOS dijagnoze u vodjenju žena sa prethodnim spontanim pobačajima u prvom tromesečju trudnoće.*

Ključne reči: *sindrom policističnih ovarijuma, rani spontani pobačaji, metformin, ishod trudnoće*