

# Metformin in the Management of Clomiphene Resistant Polycystic Ovarian Syndrome

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## Abstract

**Aim:** To assess the effect of metformin on ovulation and pregnancy rates in women with clomiphene citrate resistant polycystic ovarian syndrome (PCOS).

**Methods:** A randomized placebo controlled trial which was conducted on 30 women with clomiphene citrate resistant PCOS at City Consultant Hospital, Kano, Nigeria, a specialist Hospital in a developing economy between January 2002 and December 2005. Thirty (30) women with clomiphene citrate resistant PCOS were recruited for the study. They were divided randomly into two groups of fifteen women by balloting. Their management was divided into two phases. In the first phase, one group received metformin tablets 500mg three times daily and the other was given placebo for the first three months. In the second phase, clomiphene citrate tablets were added in both groups in women who were still anovulatory at the end of the three months period. Six ovulatory cycles, a pregnancy or anovulation on maximum dose of 250mg of clomiphene citrate per day was taken as a point of termination of the study. The data obtained were recorded in tabular forms. Statistical analysis for test of significant difference was done using student t-test and Fisher exact test. A P-value of less than 0.05 was considered significant.

**Results:** Ovulation and pregnancy rates showed statistically significant difference in the two groups ( $P < 0.05$ ), with higher ovulation and pregnancy rates among the women in the metformin-clomiphene citrate group.

**Conclusion:** We recommend the sequential use of metformin and clomiphene citrate in treating women with clomiphene citrate resistant PCO.

**Keywords:** Metformin, placebo, clomiphene resistance, polycystic ovary syndrome.

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## Introduction

PCOS is the commonest cause of ovulation disorders in women of reproductive age and is a familial condition<sup>1,2</sup>. It is a common cause of anovulation, menstrual irregularities and infertility and was found to be the cause of oligomenorrhoea/amenorrhoea in 6-10% of women<sup>1-8</sup>. The cause is not fully understood<sup>9-13</sup>. There are long-term risks of developing type 2 diabetes, cardiovascular disease and cancer of the uterus and breast<sup>14-16</sup>. Women who are diagnosed as having PCOS before pregnancy have an increased risk of developing gestational diabetes<sup>15-18</sup>.

PCOS is associated with insulin resistance which is accompanied by compensatory hyperinsulinaemia.

Hyperinsulinaemia stimulates increased ovarian intra follicular androgen production<sup>3-6</sup>. Ovarian follicles that contain high levels of intra follicular androgens usually undergo premature atresia, which results in the multiple follicular cysts in the ovary and anovulation (irregular or absent menstrual periods), which characterizes this condition<sup>7</sup>. Insulin inhibits hepatic synthesis of serum hormone binding globulin (SHBG) which results in increased levels of free serum androgen<sup>8,9</sup>. The resultant hyper androgenism alters gonadotrophin secretion, with increased LH and a decreased secretion of FSH and reversal of FSH/LH ratio ( $>1$  to  $3$ ), hirsutism, menstrual irregularities, anovulation and infertility<sup>9,10,19-22</sup>. Elevated serum LH levels increase androgen

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production from the theca cells in the ovaries, which results in varying degrees of masculinization and menstrual irregularities<sup>7,13,19</sup>. The associated elevated estrogen in the absence of ovulation may have adverse effects on the uterus and breasts with increased risk of development of carcinomas<sup>15</sup>.

Clomiphene citrate is the drug of choice for anovulation complicating PCOS in women who desires to get pregnant<sup>1,6,11</sup>. Clomiphene is an oral anti-oestrogen preparation which is used to trigger ovulation<sup>11</sup>. If clomiphene alone is not effective, metformin is added to help trigger ovulation<sup>13,11,21,22</sup>. Obesity as a result of hyperinsulinaemia have been associated with clomiphene citrate resistance<sup>1,6-11</sup>. Metformin have been shown in many studies to improve the hormonal profile, ovulation and pregnancy rates, and menstrual irregularities in women with clomiphene citrate resistant PCOS, by reducing the hyperinsulinaemia and BMI, and increasing serum hormone binding globulin (SHBG) production in the liver<sup>10,16-22</sup>.

Surgical management of PCOS is recommended if medical treatment fails, and for women who develop ovarian hyper stimulation syndrome (OHSS), and it may be in the form of ovarian drilling or ovarian wedge resection<sup>12,13</sup>. After surgery, ovulation occurs spontaneously in 70-90% of the women, and there is no increased risk of multiple pregnancy or OHSS. It is needed to be performed only once and intensive monitoring is not required<sup>12,13</sup>. Although effective in inducing ovulation, it may be associated with complications like tubal blockage from post-operative pelvic adhesion formation and premature ovarian failure, which may account for the low pregnancy rate of 40-50%<sup>7</sup>.

In women who do not want to conceive at the time of presentation, hormone medication to suppress ovarian production of oestrogen and male hormones, or intermittent treatment with progesterone hormone to interrupt the effects of steady oestrogen exposure is a reasonable choice<sup>13</sup>. Where combined oral contraceptive pills are used to achieve this, it has the additional advantage of preventing unwanted pregnancy<sup>12,13</sup>.

Although ovulation is the real cure for PCOS, induction of ovulation is only recommended for women who want to get pregnant<sup>20</sup>. Clomiphene citrate has been found to be successful in inducing ovulation in up to 80% of the women with PCOS, with 50% of them having a baby<sup>21</sup>. Women who did not ovulate while on the maximum dose of 250mg of clomiphene citrate per day are said to be clomiphene citrate resistant<sup>15,21,22</sup>. In these women addition of metformin has been said to trigger ovulation<sup>3,5-11</sup>

It is against this background that this study was undertaken, to assess the effects of metformin, a form of medical management, on ovulation and pregnancy rates in women with clomiphene citrate resistant PCOS who are actively trying to get pregnant in our unit, so that recommendations can be made on its value in women with this condition, and on how to improve its effectiveness

## Methods

This randomized placebo-controlled study was conducted at City Consultant Hospital, Kano, Nigeria between January 2002 and December 2005. Thirty women with clomiphene resistant PCO were recruited for this study. They were divided into two groups of 15 women each by balloting. Informed consent and ethical committee approval of the institution were obtained. Clomiphene resistant PCOS was diagnosed in women who were unable to ovulate on up to 250mg of clomiphene citrate tablets per day. Insulin resistance was diagnosed when there was a hypo glycaemic response in which the 2hour insulin level was higher and the blood sugar is lower than the fasting levels. A mathematical derivation known as Homeostasis Model Assessment for Insulin Resistance (HOMA-IR), calculated from the fasting values in glucose and insulin concentrations, allowed a direct and moderately accurate measure of insulin resistance

The diagnosis of PCOS was made in the women after excluding other conditions such as diabetes mellitus, Cushing's disease, liver, kidney and thyroid problems, congenital adrenal hyper plasia or hyper prolactinoma by estimating oral glucose tolerance test, serum thyroid stimulating hormone, 17-hydroxyprogesterone, prolactin levels, liver, kidney and thyroid function tests and a dexamethasone suppression test with normal values in women with clinical and hormonal changes of PCOS. The diagnosis of PCOS in this study was based on the American Society of Reproductive Medicine (ASRM), and the European Society of Human Reproduction and Embryology (ESHRE) criteria for the diagnosis of PCOS in which two of the following criteria should be met (i) Infrequent or absent menstruation (ii) Hyper androgenism (clinical or biochemical) such as acne, hirsutism, elevated serum levels of testosterone and Luteinizing hormone (LH), raised Luteinizing hormone (LH)/Follicle stimulating hormone (FSH) ratio (>3 to 1), and (iii) Polycystic ovarian morphology on ultrasound scan - >12follicles measuring between 2 to 9mm in diameter and/or ovarian volume >10mls. The distribution of the follicles are not required and with one ovary sufficient for diagnosis.

The study was divided into two phases. In the first phase, the first group of women (cases) had oral

metformin tablets 500mg three times daily for three months, while the second group (control) had a placebo (vitamin B complex tablets) one tablet three times daily also for three months. Women who ovulated or achieved a pregnancy were excluded from the second phase.

In the second phase of the study, women in both groups were given clomiphene citrate tablets 50mg daily from day 2 to 6 of the menstrual cycle in addition to the metformin (cases) or placebo (control) that were given in the first phase. The dose of clomiphene citrate was increased by 50mg per day in the next cycle up to a maximum of 250mg per day if ovulation did not occur, but with ovulation the clomiphene citrate dose was not changed. The women kept a menstrual calendar throughout the period of study.

Before starting metformin or placebo, blood samples for hormonal assays were taken in the follicular phase of the menstrual cycle. The same was repeated at the end of three months of treatment, except for serum progesterone which was measured on day 21 and 23 of the menstrual cycle. Ovulation was presumed to have occurred if the serum progesterone level exceeded 8ng/dl on either of these days, and the collapse of an ovarian follicle that measured 20 to 23mm in diameter during follicular tracking using vaginal ultrasound scan. Pregnancy was diagnosed with serum level of  $\beta$ -subunit of Human Chorionic Gonadotropin of at least 1500miu/ml, and the finding of a gestational sac with double ring appearance on vaginal ultrasonography. Ovulation and pregnancy rates were determined by dividing the number of women, who ovulated or got pregnant during the study, by the total number of women that were involved in the study.

The outcome measures were changes in the general characteristics of the women (age and body mass index (BMI)), and hormonal profile (FSH, LH, testosterone, fasting insulin, estradiol and progesterone levels) before and after metformin or placebo treatment. Ovulation and pregnancy rates were measured after the first phase and second phase of treatment.

Treatment was terminated after six ovulatory cycles, if the woman got pregnant, or is still anovulatory despite taking 250mg per day of clomiphene citrate tablets.

The data obtained were recorded in tabular forms. The mean age, pre and post treatment changes in the BMI of the women and their hormonal levels were compared in the two groups using student's t-test, ovulation and pregnancy rates were compared using Fisher exact test.

## Results

There was no statistically significant difference in the fasting blood glucose level among the cases ( $96.5 \pm 0.5$ mg/dl vs  $96.0 \pm 0.3$ mg/dl,  $P > 0.05$ ), and the controls ( $96.6 \pm 0.8$  vs.  $97.2 \pm 0.3$ ,  $P > 0.05$ ). There was no statistically significant difference ( $P > 0.05$ ) in the mean age between the metformin and placebo groups. In the first phase of treatment (first 3 months) there was statistically significant decrease ( $P < 0.05$ ) in BMI, serum LH, and testosterone, with increase in serum estradiol and progesterone levels among the cases (metformin group). Among the control there was no statistically significant difference ( $P > 0.05$ ) in these parameters except for increase in serum estradiol. Table I

**Table 1. Changes in general characteristics and hormone during the first phase of treatment**

Variable	Metformin group		Test P-value	Placebo group		Test P-value
	Baseline	After 3 months		Baseline	After 3 months	
Age (years)	$26 \pm 0.52$	$26.2 \pm 0.5$		$26.1 \pm 0.5$	$26.2 \pm 0.3$	
BMI (Kg/m <sup>2</sup> )	$24.8 \pm 0.2$	$24.4 \pm 0.2$	$t = 5.48$ $P < 0.05$ (S)	$24.5 \pm 0.4$	$24.6 \pm 0.3$	$t = 0.78$ $P > 0.05$ (NS)
Serum FSH (miu/ml)	$6.9 \pm 0.31$	$7.1 \pm 0.28$	$t = 1.86$ $P > 0.05$ (NS)	$6.8 \pm 0.27$	$6.8 \pm 0.27$	-
Serum LH (miu/ml)	$14.8 \pm 2.11$	$11.9 \pm 1.1$	$t = 4.72$ $P < 0.05$ (S)	$13.3 \pm 0.6$	$13.1 \pm 0.7$	$t = 0.84$ $P > 0.05$ (NS)
Serum progesterone (ng/ml)	$0.7 \pm 0.4$	$0.72 \pm 0.5$	$t = 1.8$ $P < 0.05$ (S)	$0.6 \pm 0.7$	$0.6 \pm 0.7$	$t = 0.87$ $P > 0.05$ (NS)
Serum estradiol (pg/ml)	$46.1 \pm 1.4$	$58.2 \pm 1.1$	$t = 26.3$ $P < 0.05$ (S)	$58.8 \pm 2.0$	$57.4 \pm 1.8$	-
Serum testosterone (ng/dl)	$66.3 \pm 1.8$	$57.1 \pm 0.3$	$t = 19.53$ $P < 0.05$ (S)	$65.4 \pm 0.9$	$66.0 \pm 1.5$	$t = 1.33$ $P > 0.05$ (NS)

\* All values are mean  $\pm$  standard deviation  
Mean age between metformin and placebo group ( $P > 0.05$ )

S = Statistically significant  
NS = Not statistically significant

In the first phase of treatment, higher ovulation and pregnancy rates occurred among those on metformin (cases) compared to those on placebo (control), but it was not enough to show statistically significant difference. In the second phase, there were statistically significant higher rates of ovulation and pregnancy among the metformin-clomiphene citrate group (cases) compared to the placebo-clomiphene citrate group (control) Table 2

shown that women who will respond to metformin will do so within three months of therapy<sup>3</sup>. There was no case of hypoglycaemia in this study following the use of metformin, probably because all the women were non diabetics, and metformin has been found not to cause hypoglycaemia in non-diabetic women<sup>20</sup>.

Metformin which is cheap, safe with no known teratogenic effects<sup>6,11</sup>, will be valuable in developing

**Table 2. Ovulation and pregnancy rates**

Variable	Ovulation	P-value Rate(%)	Pregnancy Rate(%)	P-value
Placebo n = 15	1 (6.7)	P > 0.05 (NS)	1(6.7)	P > 0.05 (NS)
Metformin N = 15	3 (20.0)		2 (13.3)	
Placebo-clomiphene citrate n = 14	2 (14.3)	P < 0.05 (S)	1 (7.1)	P < 0.05 (S)
Metformin– clomiphene citrate N = 12	10 (83.3)		6 (50.0)	

*S = statistically significant*

*NS = Not statistically significant*

## Discussion

In this study, we found that metformin-clomiphene citrate improved the ovulation and pregnancy rates compared to placebo-clomiphene citrate in women with clomiphene resistant PCOS, which was also the finding in other studies<sup>3,5,10-12</sup>. This may be because Metformin, by reducing hyperinsulinaemia and increasing SHBG, reduces the serum testosterone level<sup>6,7,8-12</sup> as seen in this study. Reduction in serum testosterone level will restore the serum gonadotrophin levels back to normal, thereby restoring normal ovarian function and hormonal profile<sup>3-5</sup>.

Obesity which has been associated with clomiphene resistance<sup>1,3,11,12</sup> was reduced among the women in the metformin group as shown by the significant reduction in the BMI among the women. This may have probably contributed to the improved ovulation and pregnancy rates in women with clomiphene resistant PCOS in this study when treated with metformin-clomiphene citrate combination, which was also the experience of other authors<sup>6,10,11</sup>. The beneficial effects of metformin on ovulation and pregnancy rates, has been associated with improvement in cervical score following increase in serum oestrogen and reduction in serum androgen levels<sup>3</sup>, which was the finding in this study

The duration of pretreatment with metformin of three months was chosen in this study, because studies have

countries like Nigeria, because it will be affordable compared with the more expensive gonadotropin drugs, and in event of a pregnancy ensuing while on treatment, it is safe even in early pregnancy<sup>6,11,12</sup>.

The gastrointestinal side effects of metformin like Stomach upset and diarrhoea<sup>21</sup> were minimized in this study by taking the drug with meals. Other side effects like, shortness of breath, severe muscle weakness or chest pain<sup>21</sup> were minimized by ensuring that all the women had normal renal function test, and were told to avoid excessive use of alcohol, and to discontinue medication 48 hours before surgery because it may predispose them to undesirable side effects<sup>20,21</sup>.

## Conclusion

Metformin pretreatment for three months, followed by metformin-clomiphene treatment were found in this study to reduce hyperinsulinaemia and increase ovulation and pregnancy rates in women with clomiphene citrate resistant PCOS. Combination of this therapy with exercise and dietary prescriptions to reduce obesity will further improve its success rate. Women who did not respond to these therapies should be treated with Human Menopausal Gonadotropin. Larger clinical trials will be needed to confirm these findings

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