



## EVALUATION OF CLINICAL OUTCOMES WITH METFORMIN THERAPY IN SOUTH INDIAN PCOS WOMEN

Jaganmohan Chandran<sup>1,2\*</sup>, Gunasekaran<sup>2</sup>, Ashraf Ali<sup>2</sup>, Manivannan<sup>2</sup>

<sup>1</sup> Faculty of Pharmacy, AIMST University, Semeling, Malaysia.

<sup>2</sup> Department of pharmacy, Sunrise university, Alwar, Rajasthan, India.

### ABSTRACT

**Objective:** To evaluate the clinical outcomes with metformin therapy in PCOS women.

**Design:** Retrospective observational study.

**Subject(s):** 220 South Indian women with polycystic ovary syndrome were included in the study.

**Clinical Outcome Measure(s):** Rates of spontaneous abortion, malformation and live birth.

**Result (s):** Baseline anthropometry were measured. Mean age of south indian PCOS women was  $26.2 \pm 4.78$ , and mean weight among south indian PCOS women was  $58.76 \pm 6.87$ . Before initiation of metformin therapy, 64 had abortions (56.14%), 17 had a malformation (14.91%) and 31 had a live birth (27.19%). After metformin therapy the conception rate (62.72%) and abortion rate (22.46%) and only 5.71% had malformation. Metformin showed the advantage of reducing the prevalence of abortion rate and increase the conception rate and also reduces the malformation rate.

**Conclusion (s):** Metformin therapy in women with polycystic ovary syndrome could increase the possibility of conception and reduced the abortion and malformation rate. Based on the data, metformin was not a teratogenic. It is safe for mother and baby as well, so we recommend metformin for the women with PCOS.

**Keywords:** Live birth, Metformin, Spontaneous abortion, Pregnancy, Polycystic ovary syndrome

### INTRODUCTION

Metformin is used to treat diabetes mellitus, which is approved by FDA. However, it has been increasingly used for the treatment of polycystic ovary syndrome (PCOS) as an off-label drug [1-2]. PCOS is the most common heterogeneous endocrine disorder. It is estimated that 6-15% of reproductive-aged women may have PCOS [3]. Hyperandrogenism, chronic anovulation, and oligomenorrhea are the main characteristic features of this disorder with distinct clinical phenotypes, biochemical features, and metabolic abnormalities. If untreated, lead to infertility. The pathophysiology is unclear, but insulin resistance plays a major role in PCOS [4-6]. Insulin resistance with hyperinsulinemia, deregulations of gonadotropin [decreased level of luteinizing hormone (LH) and increased follicle-stimulating hormone (FSH)] secretion [7-12]. Even if PCOS subjects become pregnant, they are more chances of early pregnancy loss, which is the distressing conditions [13-17]. The babies whose mothers are PCOS subject are high risk of neonatal complications. However, the use of

metformin therapy during pregnancy is strictly limited due to its potential teratogenic effects [18-24] Although several researchers worldwide have been reported the role of metformin therapy on PCOS continues to be controversial. However, there is a paucity of data on the clinical profiles in south indian women with PCOS. The present study was undertaken with the aim of investigating the effects of metformin therapy on clinical outcome profiles in South Indian women with PCOS.

### MATERIALS AND METHODS

The retrospective observational study was conducted in the department of Obstetrics and Gynecology (O&G) of Vaatsalya Hospital, Mandya, India between January 2013 and December 2014. A total of 310 south indian women with PCOS in the age group between 20-35 years. All the subjects either with oligomenorrhea, amenorrhea, and clinical symptoms of hyperandrogenism like hirsutism, acne, or a typical polycystic ovarian morphology by transvaginal ultrasonography at least one ovary with 10 or more follicle (which is 2-8mm in diameter), and anovulation were included in the study. Subjects consuming clomiphene citrate for ovulation induction and oral contraceptive pills (oestrogen, progesterone), undergoing laparoscopy surgery, bilateral tubal block, male factor infertility, diabetes mellitus, with the age more 35 years and less than 20

Address for correspondence:

Jaganmohan Chandran,

Faculty of Pharmacy,

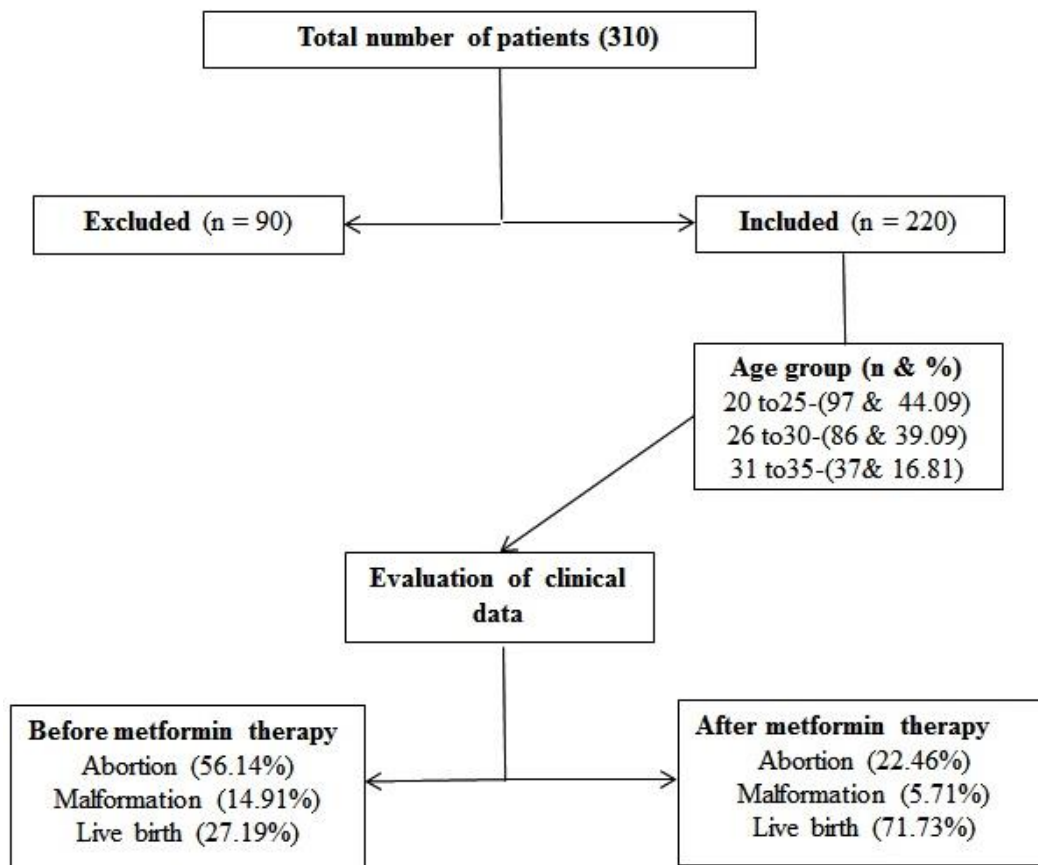
AIMST University, Semeling, Kedah

Malaysia 08100

*Jaganmohan, : Evaluation of clinical outcomes with metformin therapy in south indian pcos women*

years, subject unable to follow up were excluded from the study. This study was approved by the Internal Review Boards of Vaatsalya Hospital, Mandya, India. Baseline demographic data, complete obstetric history, menstrual pattern, the presence of acne and hirsutism were noted. Our study determines the clinical outcome before and after metformin therapy in women with PCOS. Totally 310 south indian women diagnosed with PCOS in the age group of 20 to 35 years were selected and reviewed and 220 South India with

PCOS were included in our study and the remaining was excluded from the study. All the subjects' data were retrieved from the medical record department and entered into a computer database and analysis was performed using SPSS 20.0. Descriptive statistics were used to summarize the baseline characteristics. Results were reported as mean  $\pm$  standard deviation for the quantitative variables and percentages for the categorical parameters. Figure 1 flow chart for the clinical outcome assessment of participants.



**Figure-1: flow chart for the clinical outcome assessment of participants**

**Table 1: Baseline Demographic details of the subjects**

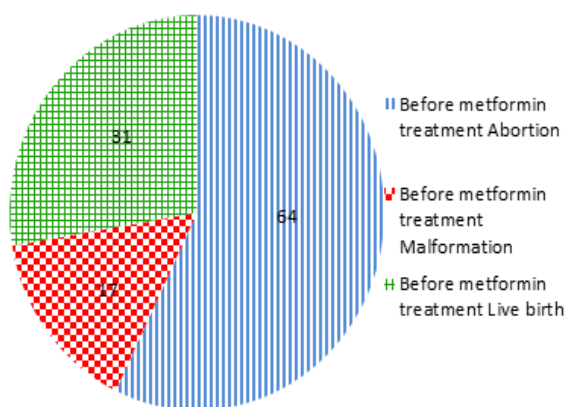
Demographic details	Number (Mean $\pm$ SD)
Number of subjects enrolled	310
Number of subjects participated	220
Age (in years)	26.73 $\pm$ 4.98
20-25	97(44.09)
26-30	86(39.09)
31-35	37(16.81)
Weight (in kg)	58.76 $\pm$ 6.87

**RESULTS:**

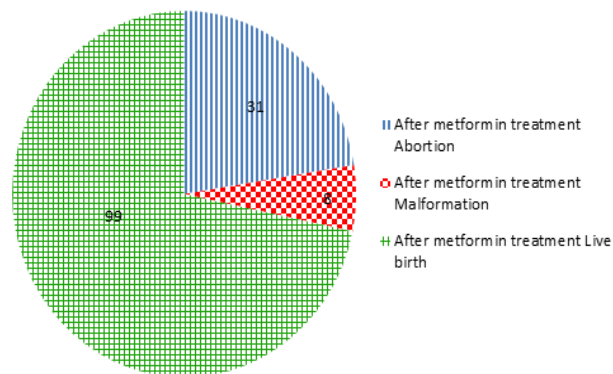
A total of 320 South Indian women with symptoms of PCOS were enrolled in our study, After a set exclusion criteria, 90 subjects not fulfill and excluded from study remaining 220 South Indian were taken into the account with the mean age of South Indian PCOS women was 26.73 ±4.98 years. 44.09% (97) subjects were in the age group of 20-25 years and 39.09% (86),16.18% (37) subjects were in the age groups of 26-30 and 31-35 years, respectively. The average weight of the subject was 58.76 ± 6.87kg. The participants’ demographic data were listed in Table 1.

Before initiation of metformin therapy, the conception rate and miscarriage rate and live birth rate were measured. Figure 2 shows Before metformin therapy 64 (56%) subjects were experienced abortion, about 15% (seventeen) subjects experienced teratogenicity (Malformation) and a paltry thirty three (27%) subjects had normal live birth.

**Figure-2: Before metformin therapy the summary of clinical data**



metformin therapy significantly increases the number of conceptions from one hundred and fourteen 52% to one hundred and thirty eight (62%). Figure 3 shows the clinical outcomes after metformin therapy, After metformin therapy the total no of subjects increased the conception rate to 62% and drastically decreased the abortion rate thirty one (22%) and only (6%) eight subjects had malformation, only thirty three subjects were give normal birth before treatment, Metformin significantly increase the conception rate, from 21% thirty one to 71% ninety nine subjects give a normal live birth of these PCOS women.



**Figure-3: Summary of clinical data after metformin treatment**

**DISCUSSION**

PCOS is the heterogeneous endocrine disorder. It is the mostly cause anovulatory infertility, those who have PCOS have difficulty in conceiving in the reproductive age. Even if PCOS women become pregnant, still they have risk of spontaneous abortion, and malformation in neonates. The results of our study show that metformin therapy is markedly reduced spontaneous abortions and malformation rate.

The number of pregnancy is considered as one of the parameter to diagnose PCOS and the number of pregnancy will decrease in women with PCOS. Before the start of metformin treatment only forty one subjects had regular menses and the remaining one hundred and seventy nine subjects had irregular menses. Metformin therapy has significantly restored normal of menses in one hundred eighty subjects which was evident from their conception. A similar effect was seen in the study by velazquez et al [14] in which 27% of patients resumed normal measures and there became pregnant. HC Zisser [1] also observed that 27% of the study participants were resumed with normal measures and there become pregnant after metformin therapy. Our study results shows metformin significant reduction in the abortion rate. Metformin’s efficacy in the reduction of early pregnancy loss in polycystic ovary syndrome (PCOS) patients was also indicated by Daniel AJ et al [22]

In our study, there were very less fetal outcomes noted in PCOS women, only 5% of the subject had malformations. Our results compare with Glueck et al, [8] in their study suggested that continuing metformin throughout pregnancy in women with

PCOS is safety and reduces first trimester miscarriage from 64% to 5% without teratogenicity. Gilbert et al [11] also believed there was no evidence of an increased risk of major malformations when metformin was taken during pregnancy. Continuing metformin throughout the pregnancy achieves 65% live births compare with other groups. Glueck et al[10] in an another study found that metformin therapy throughout pregnancy in women with PCOS reduces chances of abortion and increase the live birth.

## CONCLUSION

Insulin sensitizing agent metformin shows the ability to reduce the abortion rate, malformation and drastically increase the conception rate. Metformin may be a better therapeutic option for PCOS based on outcomes of clinical parameters. Administration of metformin in pregnant women with PCOS throughout pregnancy was associated with a marked and significant reduction in the rate of early pregnancy loss and achieving in live birth. Based on the study data metformin not a teratogenic. Hence it is safe for mother and baby as well, so we recommend metformin for the women with PCOS.

---

**ABBREVIATIONS USED:** FDA - Food and Drug Administration, PCOS - Poly cystic ovary syndrome, O&G - Obstetrics and Gynecology LH - Luteinizing hormone, FSH - Follicle stimulating hormone, SPSS - Statistical Package for the Social Sciences.

---

## REFERENCES

- [1] HC Zisser. Polycystic Ovary Syndrome and Pregnancy: Is Metformin the Magic Bullet? *Diabetes Spectrum*. 20(2):85-9(2007).
- [2] Rackow, B.W.,. Polycystic ovary syndrome in adolescents. *Current Opinion in Obstetrics and Gynecology*. 24(5): 281-287 (2012).
- [3] A Hsu Roe, A Dokras. The diagnosis of Polycystic Ovary Syndrome in Adolescents. *Reviews in Obstetrics and Gynecology* 4:45-5 (2011).
- [4] SM Sirmans, KA Pate. Epidemiology, diagnosis, and management of polycystic ovary syndrome. *Clin Epidemiol*. 6(12):1-13 (2013).
- [5] A Ben-Haroush, Y Yogevev, B Fisch. Insulin resistance and metformin in polycystic ovary syndrome. *European Journal of Obstetrics & Gynecology and Reproductive Biology*.115(2):125-33 (2004).
- [6] Antonio La Marca, Alfredo Carducci Artensio, Gaspare Stabile, Annibale Volpe. Metformin treatment of PCOS during adolescence and the reproductive period. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 12:3-7(2015).
- [7] Kelly CJ, Gordon D. The effect of metformin on hirsutism in polycystic ovary syndrome. *Eur J Endocrinol*.147(2):217-2 (2002).
- [8] Glueck, C.J., Wang, P., Fontaine, R., Tracy, T. Sieve-Smith, L. Metformin to restore normal menses in oligo-amenorrheic teenage girls with polycystic ovary syndrome. *Journal of adolescent health*, 29(3):160-169 (2001).
- [9] Vincenzo De Leo. Effects of metformin on gonadotropin induced ovulation in women with polycystic ovary syndrome. *Fertility and Sterility*. 72(2).282-285 (1999).
- [10] Glueck, C.J., Phillips, H., Cameron, D., Sieve-Smith, L. and Wang, P.,. Continuing metformin throughout pregnancy in women with polycystic ovary syndrome appears to safely reduce first-trimester spontaneous abortion: a pilot study. *Fertility and sterility*. 75(1): 46-52 (2001).
- [11] Gilbert C, Valois M, Koren G. Pregnancy outcome after first-trimester exposure to metformin: a meta-analysis. *Fertility and sterility*. 86:658-63 (2006).
- [12] Aruna, J., Mittal, S., Kumar, S., Misra, R., Dadhwal, V. and Vimala, N. Metformin therapy in women with polycystic ovary syndrome. *International Journal of Gynecology & Obstetrics*, 87(3):237-241 (2004).
- [13] Beta Kolodziejczyk, Antoni J, Duleba, Robert. Z, Spaczynski, LeszetPawelezyk. Metformin therapy on hormonal and clinical indices in polycystic ovary syndrome. *Fertility & Sterility*, 73: 114-54 (2000).
- [14] Velazquez, E.M., Mendoza, S., Hamer, T., Sosa, F. and Glueck, C.J. Metformin therapy in polycystic ovary syndrome reduces hyperinsulinemia, insulin resistance, hyperandrogenemia, and systolic blood pressure, while facilitating normal menses and pregnancy. *Metabolism-Clinical and Experimental*, 43(5): 647-654. (1994).

*Jaganmohan, : Evaluation of clinical outcomes with metformin therapy in south indian pcos women*

- [15] Lord JM, Flight. HK, Norman. RJ.. Metformin in polycystic ovary syndrome: Systemic review and Meta analysis. *The Journal of British Medical Journal*. 327(7421): 951-955(2003)
- [16] A.S Mawahib, Al-Biate. Effect of metformin on early pregnancy loss in women with polycystic ovary syndrome. *Taiwanese Journal of Obstetrics & Gynecology*. 54: 266-269 (2015).
- [17] C Jaganmohan, R Mani Vannan, Ashraf Ali, S Parasuraman. Evaluation of Clinical Efficacy of Metformin Therapy in Polycystic Ovary Syndrome. *Journal of Young Pharmacist*. 9(2):277-9 (2017).
- [18] A.S Mawahib, Al-Biate. Effect of metformin on early pregnancy loss in women with polycystic ovary syndrome. *Taiwanese Journal of Obstetrics & Gynecology*. 54.266-269(2015).
- [20] Stefano Palomba, Angela Falbo. Metformin hydrochloride and recurrent miscarriage in a woman with polycystic ovary syndrome. *Fertility and Sterility*. 1511:85(5)(2006).
- [21] C Jaganmohan, Mani Vannan, Ashraf Ali, Evaluation of fertility potential of metformin in Poly Cystic Ovary Syndrome patients. *International conference of pharmaceutical Science and Medicines, Bangkok, Thailand*. June. (2017).
- [22] Daniela J. Jakbowicz, Maria J, Luorona, Salomon Jakubowicz, Katherine A, Roberts, John E. Nestler. Effects of metformin on early pregnancy loss in polycystic ovary syndrome. *The Journal of American Family Physician*, 68(4): 697-704 (2003)
- [23] Ahmed Badawy and Abubaker Elnashar. Treatment options for polycystic ovary syndrome. *Int J Women Health*.3: 25-35 (2011).
- [24] Nestler J E. Should patients with polycystic ovarian syndrome be treated with metformin: an enthusiastic endorsement. *Human Reproduction*. 17(8): 1950(2002).