

# Physicians' Attitude toward the Use of Metformin Prior to Clomiphene Citrate in Infertile Women with PCOS in Saudi Arabia

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## Abstract

The goal of this study is to assess the different approaches gynecologists take while treating women with PCOS related infertility. Methodology: This is a quantitative cross-sectional study that involves 46 specialists and consultants from all over the kingdom of Saudi Arabia. The sample size was calculated based on the number of consultants and specialists members in the Saudi Obstetrical & Gynecology society "SOGS", we could not find any statistics on how many Ob/Gyne doctors we have in Saudi Arabia. The paper is approved by the Unit of Biomedical Ethics, King Abdulaziz University. The research team prepared an online survey of 13 questions, sent to all Consultants and Specialists in the "SOGS" during the year of 2016. The SPSS was used for the analysis. Conclusion: There is no significant difference between the different approaches of the first line of management. Comparing between Metformin and Clomiphene Citrate, Thirty Seven percent of participants preferred to start by a combination while 32% preferred to start with the former and 30.4% with the latter. Most of the doctors preferred to use Metformin for the Obese patients 76.1%, a lower percentage prefers to use it with Overweight patients 54.3%.

## Keywords

Infertility, Polycystic Ovary Syndrome, Clomiphene, Metformin

## 1. Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among reproductive age women. It affects approximately 5% to 10% of this population [1]. It is the cause of infertility in about 1/3 of couples who are receiving

treatment in infertility clinics. PCOS is diagnosed by the Rotterdam criteria (2 of 3): clinical or biochemical hyperandrogenism [2], oligo or anovulation, and polycystic ovaries on ultrasound. It's associated with heart disease, psychological diseases and other metabolic diseases like obesity, metabolic syndrome, type 2 DM, and insulin resistance with compensatory hyperinsulinemia [3] which plays a role in the pathophysiology of PCOS.

The principle treatment of infertility in PCOS is to use the ovulation induction drugs such as clomifene citrate and/or metformin. The second line treatment includes exogenous gonadotropins or laparoscopic ovarian drilling. *In vitro* fertilization is considered the third line in the treatment of infertility [4].

The goal of this study is to assess the different approaches gynecologists take while treating women with PCOS related infertility.

## 2. Methodology

This is a quantitative cross-sectional study that involves 46 specialists and consultants from all over the kingdom of Saudi Arabia. The sample size was calculated based on the number of consultants and specialists members in the Saudi Obstetrical & Gynecology society "SOGS", we could not find any statistics on how many Ob/Gyne doctors we have in Saudi Arabia. The paper is approved by the Unit of Biomedical Ethics, King Abdulaziz University. The research team prepared an online survey of 13 questions, sent to all Consultants and Specialists in the "SOGS" during the year of 2016. The SPSS was used for the analysis.

## 3. Result

Consultants and specialists participated in this study from different regions in Saudi Arabia but the upper hand was for the middle and western region (28.3%) & (26.1%) respectively. Majority of them are aged between 40 - 49 years (39.1%), most of them are females (69.6%) and consultants are the majority of the sample (73.9%). Thirty seven percent and Thirty three percent of the participants are practicing their profession in Ministry of health hospitals and teaching hospitals respectively (**Table 1**).

Almost half of the participants had (43.5%) of their patients at the clinic having PCOS related infertility, diagnosed based on a combination between the Rotterdam's & AES criteria (54.3%) (**Table 2**).

Results are almost comparable and no significant difference between the different approaches of the first line of management. Comparing between Metformin and Clomiphene Citrate, Thirty Seven percent of participants preferred to start by a combination while 32% preferred to start with the former and 30.4% with the later. Most of the doctors preferred to use Metformin for the Obese patients 76.1%, a lower percentage prefers to use it with Overweight patients 54.3%.

Fifty percent of the doctors have considered to use Letrozole as an alternative to Clomiphene Citrate while only (8.7%) did not know what Letrozole is (**Table 3**).

**Table 1.** Demographic data.

Sex	Males	14	30.4%
	Females	32	69.6%
Age	20 - 29	3	6.5%
	30 - 39	15	32.6%
	40 - 49	18	39.1%
	>=50	10	21.7%
Region	Northern	4	8.7%
	Eastern	8	17.4%
	Southern	4	8.7%
	Western	12	26.1%
	Najd	13	28.3%
Position	Consultant	34	73.9%
	Specialist	12	26.1%
Setting of practice	Teaching hospital	15	32.6%
	Ministry of health hospital	17	37%
	Private hospital	14	30.4%

**Table 2.** Percentage of PCOS patient and criteria of diagnosis.

Percentage of PCOS patients in clinic	25%	31	67.4%
	50%	10	21.7
	75%	4	8.7%
	100%	1	2.2%
Criteria for diagnosis	Rotterdam	20	43.5%
	AES	1	2.2%
	Combination	25	54.3%

**Table 3.** Approaches in managing PCOS related infertility.

First line in managing PCOS related infertility	Metformin	14	30.4%
	Clomiphene Citrate	15	32.6%
	Combination	17	37%
Patient candidate for using Metformin	Fit	9	19.6%
	Overweight	25	54.3%
	Obese	35	76.1%
	N/A	8	17.4%
Considered using Letrozol as first line management for PCOC related infertility	Yes	23	50%
	No	19	41.3%
	Don't know what Letrozol is	4	8.7%

## 4. Discussion

We conducted this study providing data on the approach different Ob/Gyne practitioner take while treating infertility in women with PCOS.

There is no significant difference between the different approaches of the first line of management. Comparing between Metformin and Clomiphene Citrate, thirty seven percent of participants preferred to start by a combination while 32% preferred to start with the former and 30.4% with the latter. Most of the doctors preferred to use Metformin for the obese patients 76.1%, a lower percentage preferred to use it with overweight patients 54.3%.

Fifty percent of the doctors have considered to use Letrozole as an alternative to Clomiphene Citrate while only (8.7%) did not know what Letrozole is.

- In June 2006, Effect of clomifene citrate plus metformin and clomifene citrate plus placebo on induction of ovulation in women with newly diagnosed polycystic ovary syndrome: randomised double blind clinical trial Etelka by Moll, Patrick M M Bossuyt, Johanna C Korevaar, Cornelis B Lambalk, Fulco van der Veen [5], Based on the results of this trial, they cannot exclude the possibility that addition of metformin may lead to an increase in the ovulation rate of up to 5%, though whether such a small difference is clinically relevant is doubtful. Though metformin seems to be a relatively safe medication, it is associated with a high incidence of side effects. They conclude that metformin should not be added to clomifene citrate as primary method for induction of ovulation in women with polycystic ovary syndrome.
- In Sep. 2010 Letrozole versus combined metformin and clomiphene citrate for ovulation induction in clomiphene resistant women with polycystic ovary syndrome: a randomized controlled trial. Conducted by Hatem Abu Hashim, M.D., M.R.C.O.G., Tarek Shokeir, M.D., and Ahmed Badawy, M.D., Ph.D. [6]. Their findings suggest that letrozole and combined metformin-CC are equally effective for inducing ovulation and achieving pregnancy in patients with CC-resistant PCOS. Letrozole is well tolerated and represents an acceptable alternative if CC-resistant PCOS patients cannot tolerate long-term metformin pretreatment.
- In July 30, 2012 Misso ML, Costello MF, Garrubba M, Wong J, Hart R, Rombauts L, Melder AM, Norman RJ, Teede HJ [7], this study showed there is insufficient evidence to establish a difference between metformin and clomiphene citrate in terms of ovulation, pregnancy, live birth, miscarriage and multiple pregnancy rates in women with PCOS and a BMI < 32 kg/m [2].
- In 2014 Jun., Ovulation induction with clomiphene citrate and metformin in women with polycystic ovary syndrome study conducted by Leanza V, Coco L, Grasso F, Leanza G, Zarbo G, Palumbo M. [8]. The aim of this paper was to evaluate effects of a Clomiphene citrate alone versus a combined treatment (Metformin and Clomiphene citrate), Combined treatment was found to be more effective (53.5) in improving pregnancy rate compared to monotherapy (28.5%).

## References

- [1] Morin-Papunen, L., Rantala, A.S., Unkila-Kallio, L., Tiitinen, A., Hippeläinen, M., Perheentupa, A., Tinkanen, H., Bloigu, R., Puukka, K., Ruokonen, A. and Tapanainen, J.S. (2012) Metformin Improves Pregnancy and Live-Birth Rates in Women with Polycystic Ovary Syndrome (PCOS): A Multicenter, Double-Blind, Placebo-Controlled Randomized Trial. *The Journal of Clinical Endocrinology & Metabolism*, **97**, 1492-1500. <https://doi.org/10.1210/jc.2011-3061>
- [2] Balen, A.H. and Rutherford, A.J. (2007) Managing Anovulatory Infertility and Polycystic Ovary Syndrome. *BMJ*, **335**, 663. <https://doi.org/10.1136/bmj.39335.462303.80>
- [3] Nestler, J.E., Jakubowicz, D.J., Evans, W.S., M.D. and Pasquali, R. (1998) Effect of Metformin on Spontaneous and Clomiphene-Induced Ovulation in the Polycystic Ovary Syndrome. *The New England Journal of Medicine*, **338**, 1876-1880. <https://doi.org/10.1056/NEJM199806253382603>
- [4] Melo, A.S., Ferriani, R.A. and Navarro, P.A. (2015) Treatment of Infertility in Women with Polycystic Ovary Syndrome.
- [5] Moll, E., Bossuyt, P.M., Korevaar, J.C., Lambalk, C.B. and van der Veen, F. (2006) Effect of Clomifene Citrate plus Metformin and Clomifene Citrate plus Placebo on Induction of Ovulation in Women with Newly Diagnosed Polycystic Ovary Syndrome: Randomised Double Blind Clinical Trial. *BMJ*, **332**, 1485.
- [6] Hashim, H.A., Shokeir, T. and Badawy, A. (2010) Letrozole versus Combined Metformin and Clomiphene Citrate for Ovulation Induction in Clomiphene Resistant Women with Polycystic Ovary Syndrome: A Randomized Controlled Trial.
- [7] Misso, M.L., Costello, M.F., Garrubba, M., Wong, J., Hart, R., Rombauts, L., Melder, A.M., Norman, R.J. and Teede, H.J. (2013) Metformin versus Clomiphene Citrate for Infertility in Non-Obese Women with Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis. *Human Reproduction Update*, **19**, 2-11. <https://doi.org/10.1093/humupd/dms036>
- [8] Leanza, V., Coco, L., Grasso, F., Leanza, G., Zarbo, G. and Palumbo, M. (2014) Ovulation Induction with Clomiphene Citrate and Metformin in Women with Polycystic Ovary Syndrome.