THE ROLE OF METFORMIN IN PREVENTION OF FIRST TRIMESTERIC MISCARRIAGE IN WOMEN WITH POLYCYSTIC OVARY SYNDROME

(Randomized Controlled Study)

Thesis

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Islam Hussein Ezzat Dabbous

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List of Abbreviations

AGA ..... Appropriate for Gestational Age

AIB1..... Amplified in breast cancer -1

AMP ..... Adenosine Monophospate

AR..... Assisted Reproduction

ASRM ..... American Society of Reproductive Medicine

BMI ..... Body Mass Index

CAH ..... Congenital Adrenal Hyperplasia

CC..... Clomiphene Citrate

DHEAS..... Dehydroepiandrostenedionesluphate

ELISA..... Enzyme Linked Immunosorbent Assay

EPL..... Early Pregnancy Loss

ESHRE ..... European Society of Human Reproduction and Embryology

FNPO..... Follicle Number Per Ovary

FSH..... Follicle Stimulating Hormone

FT ..... Free Testosterone

FTI..... Free Testosterone Index

GDM ..... Gestational Diabetes Mellitus

GnRH..... Gonadotropine Releasing Hormone

hCG ..... Human Chorionic Gonadotropin

HOMA..... Homeostasis Model Assessment

IGT ..... Impaired Glucose Tolerance

IR ..... Insulin Resistance

IVF..... In Vitro Fertilization

List of Abbreviations (Cont...)

LBR..... Live Birth Rate

LH..... Luteinizing hormone

NIH..... National Institute of Health

NIR..... Non –Insulin Resistant

OGTT ..... Oral Glucose Tolerance Test

OR …… Odds Ratio

PCO..... Polycystic Ovary

PCOS ..... Polycystic Ovary Syndrome

PE ..... Pre-eclampsia

PIH ..... Pregnancy Induced Hypertension

RCT..... Randomized Clinical Trial

RIA..... Radioimmunoassay

RPL ..... Recurrent Pregnancy Loss

SGA..... Small for Gestational Age

SHBG..... Sex Hormone Binding Globulin

W/H ratio ..... Waist / Hip ratio

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Abstract

Background:

This study aimed to evaluate the effect of Metformin on Early Pregnancy Loss (EPL) in pregnant women with Polycystic Ovary Syndrome (PCOS)

Methods:

A randomized clinical trial (Clinicaltrials.gov NCT 02498522) was conducted in Ain shams Maternity Hospital, in the period between August 201٨ and July 201٩.

One hundred and sixty six women previously diagnosed with PCOS and got pregnant with induction of ovulation in concomitance with Metformin were randomized either Metformin 500mg orally every 8 hours until the end of the 1st trimester or not receiving Metformin.

The primary outcome is to observe any significant decline in the incidence of EPL in PCOS patients after administration of Metformin through out 1st trimester.

Results

There was a significant reduction in miscarriage rate after administration of Metformin during 1st trimester. Introduction of Metformin helped pregnancy loss rate to drop to 10.8% while the rate in the group discontinued Metformin was 42.2% ($p < 0.05$). the side effects rate as Nausea, vomiting, gastric irritation and flatulence was significantly higher in the Metformin group.

Conclusion

The use of Metformin in patients with PCOS during 1st trimester reduces the incidence of early pregnancy loss (EPL)

Keywords

PCOs, Early pregnancy Loss (EPL), Metformin

Chapter I

POLYCYSTIC OVARY SYNDROME (PCOS)

Polycystic ovary syndrome (PCOS) was first reported in modern medical literature by two American scientists Stein and Leventhal who, in 1935, described seven women suffering from amenorrhea, hirsutism, and enlarged ovaries with multiple cysts "two to four times the normal size, sometimes distinctly globular", "tunica thickened, though, and fibrotic", "follicle cysts near the cortex and almost entirely confined to the cortex". "The color of the ovary was oyster gray with bluish areas where the cysts were superficial and appeared on the surface as sago-like bodies" ***(Stein IF, Leventhal ML, et al. 1935)***

Clinical Presentation and diagnosis criteria

The clinical presentation of PCOS varies widely. Women with PCOS often seek care for menstrual disturbances, clinical manifestations of hyperandrogenism, and infertility.

Menstrual disturbances:

Menstrual disturbances commonly observed in PCOS include oligomenorrhea, amenorrhea, and prolonged erratic menstrual bleeding ***(Farquhar C., et al. 2007)***.

Approximately 85%–90% of women with oligomenorrhea have PCOS while 30%–40% of women with amenorrhea will have PCOS ***(Hart R, et al. 2007).***

Hyperandrogenism:

More than 80% of women presenting with symptoms of androgen excess have PCOS. Hirsutism is a common clinical presentation of hyperandrogenism occurring in up to 70% of women with PCOS**.** Hirsutism is evaluated using a modified Ferriman–Gallwey scoring system**.** ***(Azziz R, et al. 2004) (Fauser B, et al. 2012) (Ferriman D, Gallwey J. 1961)***

This tool is used to evaluate hair growth at seven sites: upper lip, chin/face, chest, back, abdomen, arms, and thighs. A score of 0 is given in the absence of terminal hair growth and a score of 4 is given for extensive growth. A total score of 8 (2 sites with extensive hair growth) or more is indicative of hirsutism. ***(Unluhizarci K, et al. 2012)***.

In addition, PCOS occurs in 50% of women with less severe distribution of unwanted hair growth. ***(Souter I, et al. 2004).***

Acne can also be a marker of hyperandrogenism but is less prevalent in PCOS and less specific than hirsutism.

Approximately 15%–30% of adult women with PCOS present with acne ***(Wijeyaratne C, et al. 2002).***

The difference in prevalence of hirsutism and acne may be attributed to the difference in expression of 5α-reductase in the sebaceous gland and the hair follicle, and resulting higher dihydrotestosterone in the hair follicle. ***(Lowenstein E. 2006).***

Some experts recommend that women presenting with acne be asked about their menstrual history and be evaluated for other signs of hyperandrogenism. ***(Lowenstein E. 2006).***

Infertility:

Infertility affects 40% of women with PCOS. ***(Teede H, et al 2010).***

PCOS is the most common cause of anovulatory infertility. Approximately 90%–95% of anovulatory women presenting to infertility clinics have PCOS. Women with PCOS have a normal number of primordial follicles and primary and secondary follicles are significantly increased. However, due to derangements in factors involved in normal follicular development, follicular growth becomes arrested as follicles reach a diameter of 4–8 mm. Because a dominant follicle does not develop, ovulation does not ensue***. (Brassard M, et al. 2008)***

In addition, spontaneous abortion occurs more frequently in PCOS with incidences ranging from 42%–73%. ***(Glueck C, et al. 2001)***

Diagnosis of PCOS:

Diagnostic criteria for PCOS have been offered by three groups: the National Institutes of Health/National Institute of Child Health and Human Disease (NIH/NICHD); ***(Zawadski JK, et al. 1992)*** the European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM***); (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group.2004)*** and the Androgen Excess and PCOS Society***. (Azziz R, et al. 2006)*** These criteria are summarized in Table 1.

Table (1): Criteria for the diagnosis of polycystic ovary syndrome.

NIH/NICHD 1992	ESHRE/ASRM (Rotterdam criteria) 2004	Androgen Excess Society 2006
Exclusion of other androgen excess or related disorders	Exclusion of other androgen excess or related disorders	Exclusion of other androgen excess or related disorders
Includes all of the following:	Includes two of the following:	Includes all of the following:
• Clinical and/or biochemical hyperandrogenism	• Clinical and/or biochemical hyperandrogenism	• Clinical and/or biochemical hyperandrogenism
• Menstrual dysfunction	• Oligo-ovulation or anovulation	• Ovarian dysfunction and/or polycystic ovaries
	• Polycystic ovaries	

While there are certain consistencies between the criteria offered by the different groups, important differences exist. Each issuing group considers PCOS a diagnosis of exclusion, and other diagnoses, such as congenital adrenal hyperplasia, nonclassic adrenal hyperplasia, Cushing syndrome, androgen-secreting tumor, idiopathic hyperandrogenism, idiopathic hirsutism, hyperprolactinemia, and thyroid disorders must be excluded. Because 20%–30% of otherwise normal women have evidence of multiple cysts on their ovaries**,** the presence of polycystic ovaries (PCO) alone was not considered sufficient by any group. The NIH/NICHD and the Androgen Excess Society require that patients have signs or symptoms of hyperandrogenism such as hirsutism, or hyperandrogenemia, defined as elevated free testosterone, reduced SHBG (sex hormone-binding globulin), elevated free testosterone index, or elevated dehydroepiandrosterone sulfate**.** ***(Zawadski JK, et al. 1992. Azziz R, et al 2006)***

However, ESHRE/ASRM (Rotterdam) criteria allows for the diagnosis of PCOS without the presence of hyper-androgenemia or clinical hyperandrogenism. Women with ovulatory dysfunction and the presence of polycystic ovaries are considered to have PCOS by the Rotterdam criteria. Another key difference between the criteria is how oligomenorrhea or amenorrhea are viewed. The Rotterdam criteria did not require

irregular menses or ovulatory dysfunction for diagnosis citing that women with regular menstrual cycles could be considered to have PCOS in the presence of PCO and hyperandrogenemia or hyperandrogenism Subclinical ovulatory dysfunction can occur in women with regular menstrual bleeding**.** However, NIH/NICHD excludes the diagnosis of PCOS in women with regular menses and subclinical ovulatory dysfunction. ***(Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group.2004) (Azziz R, et al 2006)***

The diagnosis of PCOS using the Rotterdam and AES criteria depends on the use of a reliable method to describe polycystic ovarian morphology. The criteria for polycystic ovarian morphology proposed by the Rotterdam consensus group includes the presence of 12 or more follicles measuring between 2 and 9 mm in diameter and/or an increased ovarian volume of greater than 10 cm^3. This presentation in one ovary sufficiently defines the polycystic ovary**.** ***(Rotterdam ESHRE/ ASRM-Sponsored PCOS Consensus Workshop Group.2004)***

However, since that time, significant advancements in ultrasound image technology have been made, improving resolution and allowing for the detection of smaller follicles**.** ***(Lujan ME, et al. 2013)***

This has prompted calls for revising the criteria used to define polycystic ovarian morphology. Allemand et al used three-dimensional transvaginal ultrasound to measure the mean follicle number per ovary (FNPO) and the maximum number of follicles in a single sonographic plane in ten patients with diagnosed PCOS and 29 normoandrogenic ovulatory controls. ***(Allemand MC, et al. 2006)***

Using two-dimensional transvaginal ultrasound, Dewailly et al measured the total number of all follicles that were less than 10 mm in diameter throughout the ovary and also measured the ovarian volume. A mean FNPO of ≥20.1 identified PCO with 100% specificity and 70% sensitivity. A maximum number of follicles in a single sonographic plane of ten identified PCO with 100% specificity and 90% sensitivity. Ovarian volume, measured by two-dimensional transvaginal ultrasound, of ≥13.0 cm^3 predicted PCO with a specificity of 100% and a sensitivity of 50%. ***(Dewailly D, et al. 2011)***

A threshold follicle number of 19 had a sensitivity for predicting PCO of 81% and a specificity of 92%. Ovarian volume of 7 cm^3 predicted PCO with a sensitivity of 87% and a specificity of 89%. Lujan et al measured FNPO, follicle counts in a single cross section, and ovarian volume in images that were digitally archived for offline analysis. In their analysis, a FNPO threshold of 26 follicles had a sensitivity of 85% and specificity