EFFECT OF METFORMIN TREATMENT ON ENDOMETRIAL VASCULAR INDICES IN ANOVULATORY OBESE WOMEN WITH POLYCYSTIC OVARIAN SYNDROME USING THREE-DIMENSIONAL POWER DOPPLER ULTRASONOGRAPHY

THESIS

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بسم الله الرحمن الرحيم

"يُؤْتِي الْحِكْمَةَ مَنْ يَشَاءُ وَمَنْ يُؤْتَ
الْحِكْمَةَ فَقَدْ أُوتِيَ خَيْراً كَثِيراً وَمَا يَذَّكَّرُ إِلاَّ
أُولُو الْأَلْبَابِ"

صدق الله العظيم

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Abstract

Introduction: Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders, affecting 5–10% of women of reproductive age. Its diagnosis is confirmed by the presence of two of the following three disorders: oligomenorrhea or amenorrhea, signs of hyperandrogenism (eg, hirsutism, acne, and alopecia) or elevated levels of total or free testosterone, and polycystic ovaries on sonography Metformin has been shown to be an effective treatment for anovulatory PCOS patients, not only in terms of menstrual cyclicity but also of fertility. Several randomized controlled trials have shown that PCOS women who resumed ovulation after metformin treatment exhibited a surprisingly high reproductive potential with lower rates of early miscarriage. which may be due to a beneficial action of the drug on endometrial development/receptivity to blastocyst implantation and/or on the quality of the oocytes/embryos

Objective: The aim of the study is to assess the effect of metformin on the endometrial vascular indices in anovulatory obese PCOS women using three-dimensional power Doppler sonography (3DPDUS).

Method: A prospective study will be set to determine the beneficial effects of metformin on PCOS patients Total number of participants included in the study 40, will be divided into two groups. Twenty anovulatory obese PCOS patients will be compared with another 20 healthy volunteers who are age- and body mass index-matched).

Results: In the current study, metformin therapy leads to significant increase of endometrial thickness and volume and had no significant effect on uterine RI and PI. On the endometrial level, endometrial and subendometrial VI, FI and VFI increased significantly after metformin treatment

Conclusion: In summary, short-term administration of metformin in PCOS women resulted in enhancement of the endometrial thickness and volume and endometrial and subendometrial vascular indices on 3DPDUS. This may be one of the possible mechanisms by which metformin improves the reproductive outcome in PCOS patients.

Key words metformin.endometrial vascular indices,power doppler

Contents

List of Abbreviations

17 HP	17 hydroxy progesterone enzyme
21-OH	21 hydroxy progesterone enzyme
2D	Two dimensional
3D	Three dimensional
A4	Androstenedione
ACTH	Adrenocorticotrophin Hormone
AI	Aromatase Inhibitors
ASRM	American Society for Reproductive Medicine
AUC	Area Under Curve
BMI	Body Mass Index
Camp	Cyclic Adenosine Mono-Phosphate
CC	Clomiphene Citrate
DHEA	Dehydroepiandrosterone
DHEAS	Dehydroepiandiosterone Sulfate
DHT	Dihydrotestosterone
DM	Diabetes Mellitus
E1	Estrone
E2	Estradiol
ESHRE	European Society for Human Reproduction and Embryology
FI	Flow Index
FSH	Follicular Stimulating Hormone
GnRH	Gonadotrophin Releasing Hormone
hCG	human Chorionic Gonadotrophin
HDL	High Density Lipoproteins

hMG	**human menopausal Gonadotrophins**
ICSI	**Intra-Cytoplasmic Sperm Injection**
IVF	**In Vitro fertilization**
IVM	**In Vitro Maturation**
LDL	**Low Density lipoprotein**
LH	**Luteinizing Hormone**
LOD	**Laparoscopic Ovarian Diathermy**
mFG	**Modified Ferriman and Gallway score**
MG	**Mean Grayness**
mRNA	**Messenger Ribonucleic Acid**
NIH	**National Institute of Health**
OGTT	**Oral Glucose tolerance Test**
OHSS	**Ovarian Hyper stimulation Syndrome**
OS	**Ovarian Stroma**
OV	**Ovarian Volume**
P4	**Progesterone**
PCO	**Polycystic Ovary**
PCOS	**Polycystic Ovarian Syndrome**
PPCOS	**Pregnancy in Polycystic Ovarian Syndrome**
RCT	**Randomized Controlled Trial**
rFSH	**recombinant Fol1icular Stimulating Hormone**
SHBH	**Sex Hormone Binding Globulin**
T	**Testosterone**
TA	**Transabdominal**
TSH	**Thyroid Stimulating Hormone**
TV US	**Transvaginal Ultrasound**

UER	**Ultrasound Examination Route**
US	**United states**
VEGF	**Vascular endothelial growth NCAII**
	Vascularization flow index
VFI	**Vascularization index**
VI	**Virtual organ computer-aided Analysis**
VOCAL	**Wan**
W	**Waist to Hip Ratio**
WAIR	

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders, affecting 5–10% of women of reproductive age. Its diagnosis is confirmed by the presence of two of the following three disorders: oligomenorrhea or amenorrhea, signs of hyperandrogenism (eg, hirsutism, acne, and alopecia) or elevated levels of total or free testosterone, and polycystic ovaries on sonography (US).

PCOS is not only the most common reproductive disorder, but also a plurimetabolic syndrome. Obesity, insulin resistance, and resultant hyperinsulinemia are cardinal features of PCOS with a greater risk of developing diabetes mellitus (DM), hypertension, and dyslipidemia

Recognition of insulin resistance as a principal factor in the pathogenesis of PCOS has led to the use of insulin sensitizers for its treatment. The most extensively studied insulin sensitizer is metformin—an oral antihyperglycemic agent used initially in the treatment of type 2 DM.

Metformin has been shown to be an effective treatment for anovulatory PCOS patients, not only in terms of menstrual cyclicity but also of fertility. Several randomized controlled trials have shown that PCOS women who resumed ovulation after metformin treatment exhibited a surprisingly high reproductive potential with lower rates of early miscarriage which may be due to a beneficial action of the

drug on endometrial development/receptivity to blastocyst implantation and/or on the quality of the oocytes/embryos.

Successful implantation depends on a close dialogue between the blastocyst and the receptive endometrium. Endometrial receptivity can be evaluated by histologic evaluation of an endometrial biopsy, endometrial proteins in uterine flushing, or, more commonly, US examination of the endometrium.

Various US parameters have been used to assess endometrial receptivity including endometrial thickness, pattern, and volume, as well as Doppler study of the uterine arteries and endometrial blood flow. However, Doppler indices may not be representative of the downstream endometrial and subendometrial blood flow. and three-dimensional Doppler US (3DPDUS) may be a more appropriate tool to assess these vascular beds, as it allows reliable and objective assessment through quantification of power Doppler data.

AIM OF THE WORK

This work aimed at evaluating the role of metformin on the endometrial vascular indices in anovulatory obese PCOS women using three-dimensional power Doppler sonography (3DPDUS).

POLYCYSTIC OVARY SYNDROME

(A) Historical Background:

In 1935, Stein and Leventhall first defined a disorder, which would eventually become known as the polycystic ovary (or ovarian) syndrome (PCOS). These gynecologists described 7 women suffering from infertility and amenorrhea and determined, upon surgical exploration, that these women had enlarged ovaries with several superficial cystic structures. Stein and Leventhall performed ovarian wedge resections on these patients, in the belief that they were removing obstructions or cysts from the ovary, which would allow for normal ovarian function to resume. After the surgery, all women resumed their cyclic menses and 5 conceived **(Stein, 1945).**

In 1945, Stein published a follow-up report in which he added excessive male-pattern hair growth and in contrast to what is known today, obesity to the list of symptoms, and noted that the disorder was overall quite rare. The disorder remains a fertile ground for academic debate and research investigation **(Trivax and Azziz, 2007).**

(B) Defining Pcos:

Basics:

PCOS is a functional disorder of unclear etiology, and, as such, is a diagnosis of exclusion, with other androgen excess and ovulatory disorders of clearly defined etiologies excluded. Androgen