Relationship between Anti-Müllerian Hormone level in women with polycystic ovary syndrome and response to ovulation induction with clomiphene citrate

Thesis Submitted for Partial Fulfillment
of Master Degree in Obstetrics and Gynecology

Presented by
Mohammed Mostafa Ahmed Mostafa
M.B., B.Ch. (2007)
Faculty of Medicine – Cairo University

Under Supervision of

Prof. Dr. Osama Saleh El-Kady
Professor of Obstetrics and Gynecology
Ain-Shams University

Dr. Mohamed Samir Sweed
Lecturer of Obstetrics and Gynecology
Ain-Shams University

Faculty of Medicine
Ain Shams University
Cairo-2014

Acknowledgement

First of all, I thank ALLAH,

Then, I would like to express my great thankfulness and appreciation to ***Prof. Dr. Osama Saleh El-Kady,*** *Professor of Obstetrics & Gynecology, Faculty of Medicine, Ain-Shams University, for his help, encouragement, patience and support throughout this work.*

I also would like to show my gratitude and thankfulness to ***Dr. Mohamed Samir Sweed,*** *Lecturer of Obstetrics and Gynecology, Faculty of Medicine, Ain-Shams University, for his effective scientific supervision and precious assistance*.

Last but not least, I thank all ***my family*** *for their patience, support and understanding.*

List of Contents

List of Abbreviations

ACTH	Adrenocorticotropic hormone
ACVR1	Activin A receptor, type I
AE-PCOS Society	Androgen Excess and Polycystic Ovary Syndrome Society
AES	Androgen Excess Society
AFC	Antral follicle count
Alk	Activin receptor-like kinase
AMH	Anti-Müllerian hormone
AMHR2	Anti-Müllerian hormone specific type 2 receptor
ANOV	Anovulation
ART	Assisted Reproductive Techniques
ASRM	American Society for Reproductive Medicine
AUC	Area under the curve
B	Regression coefficient
BMI	Body mass index
BMPR	Bone morphogenetic protein receptor
BMPs	Bone morphogenetic proteins
BSA	Bovine serum albumin
CAH	Congenital adrenal hyperplasia
CC	Clomiphene Citrate
CI	Confidence Interval
CL	Corpus luteum
CNS	Central nervous system
DF	Degree of freedom
DHEA-S	Dehydroepiandrosterone sulfate
DHT	Di-hydro-testosterone

DNA	Deoxyribonucleic acid
E_1	Estrone
E_2	Estradiol
ELISA	Enzyme-linked immunosorbent assay
ESHRE	European Society of Human Reproduction and Embryology
FSH	Follicle-stimulating hormone
GH	Growth hormone
GnRH	Gonadotropin-releasing hormone
GnRH-A	Gonadotrophin - releasing hormone analogue
HA	Hyperandrogenism
HCG	Human chorionic gonadotropin
HMG	Human menopausal gonadotropin
HRP	Horseradish peroxidase
IBM	International Business Machines Corporation
ICSI	Intra-cytoplasmic sperm injection
IGF-1	Insulin-like growth factor-1
IGFBP-1	Insulin - like growth factor-binding protein-1
IgG	Immunoglobulin G
IGT	Impaired glucose tolerance
IR	Insulin resistance
IV	Intravenous
IVF	In Vitro Fertilization
IVM	In Vitro Maturation
J	Youden index
LH	Luteinizing hormone
LOD	Laparoscopic Ovarian Drilling

MHPG	3-Methoxy-4-hydroxyphenylglycol
MIS	Müllerian-inhibiting substance
MS	Metabolic syndrome
N	Number
NIDDM	Non - insulin - dependent diabetes mellitus
NIH	National Institutes of Health
OGTT	Oral glucose tolerance test
OHSS	Ovarian hyperstimulation syndrome
OR	Odds ratio
PCO	Polycystic ovaries
PCOD	Polycystic ovary disease
PCOM	Polycystic ovary morphology
PCOS	Polycystic ovary syndrome
PI	Pulsatility index
P-value	Probability value
RI	Resistance index
ROC	Receiver operating characteristic
R-Smads	Receptor - regulated small mothers against decapentaplegic proteins
SC	Subcutaneous
S/D	Systolic/Diastolic
SD	Standard deviation
SE	Standard error
SHBG	Sex hormone-binding globulin
SMADs	Small mothers against decapentaplegic proteins
SPSS	Statistical Package for the Social Sciences
TGF-β	Transforming growth factor-beta
TMB	Tetramethylbenzidine
TSH	Thyroid-stimulating hormone
U/S	Ultrasound

List of Tables

List of Figures

Relationship between Anti-Müllerian Hormone level in women with polycystic ovary syndrome and response to ovulation induction with clomiphene citrate

Thesis Submitted for Partial Fulfillment
of Master Degree in Obstetrics and Gynecology

Presented by

Mohammed Mostafa Ahmed Mostafa
M.B., B.Ch. (2007)
Faculty of Medicine – Cairo University

Under Supervision of

Prof. Dr. Osama Saleh El-Kady
Professor of Obstetrics and Gynecology
Ain Shams University

Dr. Mohamed Samir Sweed
Lecturer of Obstetrics and Gynecology
Ain Shams University

Faculty of Medicine
Ain Shams University
Cairo-2013

Introduction

Infertility is defined as one year of unprotected coitus without conception. It affects approximately 10-15% of couples in the reproductive age group which makes it an important component of the practices of many physicians ***(Barbieri, 2000).***

Infertility is a common problem, approximately one sixth of marriages are involuntarily childless. Studies of populations of patients with infertility indicates that approximately 10-25% have unexplained infertility, 20-30% ovulatory dysfunction, 20-25% tubal damage, 10-50% sperm dysfunction, 5-10% endometriosis, 5% cervical mucus problems, and 5% coital dysfunction ***(Jacobs and Balen, 2003).***

Ovulatory dysfunction is observed in approximately 15% of all infertile couples and 40% of all infertile women ***(ASRM, 2002).*** Causes of ovulatory dysfunction include hypothyroidism, hyperprolactinemia, polycystic ovary disease, eating disorders, obesity, extremes of weight loss or exercise, and advancing maternal age ***(Greene and O'Keane, 2000).***

The definition of polycystic ovary syndrome (PCOS) has evolved over the past several years ***(Rosenfield, 2007).*** PCOS was originally described in 1935 by Stein and Leventhal who reported a group of women with amenorrhea and polycystic ovaries, of whom some were hirsute and/or obese ***(Stein and Leventhal, 1935).***

In 1990, a National Institutes of Health (NIH) consensus conference defined PCOS as a combination of hyperandrogenism, menstrual dysfunction (oligo and/or anovulation), and exclusion of known disorders such as congenital adrenal hyperplasia (CAH) leading to the above ***(Zadawski and Duanif, 1992).*** This definition was broadened at the 2003 Rotterdam consensus workshop. The revised definition included two of the following three criteria, with exclusion of other medical conditions: oligomenorrhea and/or anovulation; signs of either clinical or biochemical hyperandrogenism; and polycystic ovaries by ultrasound ***(Revised 2003 consensus on diagnostic criteria and long-term health risks related to PCOS, 2004).***

The Rotterdam criteria expanded previous definitions by including in the PCOS spectrum women with hirsutism, but regular menses, as well as inclusion of polycystic

ovarian morphology. The 2006 Androgen Excess Society (AES) Task Force on the Phenotype of PCOS, however, narrowed the definition to exclude women who did not have androgen excess. The criteria include hyperandrogenism (hirsutism and/or hyperandrogenemia); ovarian dysfunction (oligo and/or anovulation and/or polycystic ovarian morphology on ultrasound); and exclusion of other disorders ***(Azziz et al., 2006).***

Current estimates suggest that PCOS affects 5-10% of reproductive age women ***(Jeffrey and Coffler, 2007).*** In comparison, 'polycystic ovaries' alone are estimated to be present in 21-23% of this same population ***(Stankiewicz and Norman, 2006).***

The Anti-Müllerian hormone (AMH), which is also known as Müllerian-inhibiting substance (MIS), is a member of the transforming growth factor-beta (TGF-β) superfamily, which includes more than 35 structurally related peptides, including activins, inhibins, bone morphogenic proteins (BMPs) and growth differentiation factors ***(Itman et al., 2006).*** Many of these are involved in the reproductive function of both sexes ***(Knight and Glister, 2006).*** AMH binds to dimeric receptors comprised of the AMH-specific type 2 receptor