Effect of amlodipine on blood flow of preovulatory follicle in Polycystic ovarian patients: A Randomized Controlled Trial

Thesis

Submitted for partial fulfillment of Master Degree in obstetrics and gynecology

By

Doaa Abdelmageed Saleh Hassan

Specialist in National Research Centre, *M.B.,B.CH. (2008)*

Under supervision of

Prof. Dr. / Khaled Kamal Ali

Professor of obstetrics and gynecology

Faculty of Medicine, Ain Shams University

Prof. Dr. / Osama Mahmoud Azmy

Professor of obstetrics and gynecology

National Research Centre

Dr. / Adel Shafik Salah El Din

Lecturer in obstetrics and gynecology

Faculty of Medicine, Ain Shams University

Faculty of Medicine

Ain Shams University,2013

Acknowledgement

*First and foremost, I feel always indebted to **Allah**, the most kind and most merciful.*

*I am deeply grateful to **Prof. Dr. Khalid Kamal Ali**, Professor of Obstetrics and gynecology, faculty of medicine, Ain Shams University, for continuous help and valuable advice and support.*

*I would like also to express the deepest thanks, appreciation and gratefulness **Prof. Dr. Osama Mahmoud Azmy**, Professor of Obstetrics and gynecology, National Research Centre, for his cooperation and advice whenever needed and for his kind help guidance and supervision.*

*I also like to express my deepest gratitude and utmost appreciation to **Dr. Adel Shafeik Salah El Din,** Lecturer in Obstetrics and gynecology, Facualty of medicine, Ain Shams University, Who was patient and considerate, saving no time and effort helping me with this work.*

*I would like to express my deep appreciation to **Dr. Mamdouh Abd El Aziz Papeirs**, Assistant Professor of Obstetrics and gynecology, National Research Centre, for his guidance and supervision.*

I would like to thank all Staff and employees of the Special Care Centre of the fetus of for their cooperation with the cases and their effort to finish this work.

*I would like to express my gratitude to **every patient** contributed in this study, and was keen for her follow up visits, without them this work wouldn't have come to light.*

*I would like also to express my best regards and thanks to **my family** specially **my husband** and **my mother** who supported and helped me during working on this research.*

List of Abbreviations

Abb.	Description
ACE	Angiotensen converting enzyme
ART	Assisted Reproductive Technology
AV node	Atrioventricular node
BMI	Body mass index
BPM	Beat Per Minute
CCBs	Calcium channel blockers
CC	Clomiphene citrate
cGMP	Cyclic Guanisine monophosphate
CYP	Cytochrome
DHEA-S	Dehydroepiandrosterone-sulfate
eNO	Endothelial Nitric oxide synthetase
FDA	Food and drug administration
FSH	Follicle stimulating hormone
I-alpha-I	Intrafollicullar inter alpha trypsin inhibitor
KHZ	Kilo Hertz
IR	Insulin Resistance
IVF	In Vitro Fertilization
LH	Luteinizing hormone
LOD	Laparoscopic ovarian diathermy
MHZ	Mega Hertz
NE	Nor epinephrine
NIH	National Institutes of Health
NO	Nitric oxide
OGTT	Oral Glucose Tolerance Test

OHSS	Ovarian hyperstimulation syndrome
P	Progesteron
PCOS	Polycystic ovary syndrome
PDE5	Phosphodiesterse type 5
PI	Pulsatility index
PSV	Peak systolic velocity
PZT	Lead Zicronate Titnate
SA node	Sinoatrial node
T1/2	Half life
2D and 3D	Two dimensional and three dimensional

List of Figures

List of Tables

Contents

Aim of the work

The aim of the work *is to study the effect of the vasodilator calcium channel blocker, amlodipine, on the vessels supplying preovulatory follicle as compared to placebo control, in order to increase the blood supply to the preovulatory follicle and thus improve ovulatory outcome.*

Introduction

Infertility is the failure to conceive following twelve months of unprotected intercourse. Approximately 8-12% of couples experience some form of infertility problem. On a worldwide scale, this means that 50-80 million people suffer from infertility. ***(WHO, 2012).***

This study will be directed to PCO infertile female population. Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies in women of fertile age. ***(Vrbikova and Hainer ,2009)***. . It has been shown that 21–23% of the normal female population has PCO on ultrasound scan ***(Farquhar* et al., *1994*).**

In each menstrual cycle, the dominant follicle that ovulates originates from a primordial follicle that was recruited almost one year earlier. In preantral or Class 1, the development of a primordial to a full-grown secondary follicle requires about 290 days or about 10 regular menstrual cycles. The antral phase is typically divided into four stages: the small (Class 2, 3, 4, 5), medium (Class 6), large (Class 7), and preovulatory (Class 8) Graafian follicle stages. After antrum formation occurs at the Class 3 stage (~0.4mm in diameter), the rate of follicular growth accelerates. The time interval between antrum formation and the development of a 20 mm preovulatory follicle is about 60 days or about 2 menstrual cycles. A dominant follicle is selected from a cohort of class 5 follicles at the end of the luteal phase of the cycle . About 15 to 20 days are therefore required for a dominant follicle to grow to the preovulatory stage, ***(Williams and Erickson, 2012)***, i.e. In second phase (gonadotrophin dependent phase), it takes about 80 days for mature graafian follicle to develop.

Several vascular components appear to be critical to vascular regulation of the ovary. The ovarian resistance arteries, which in many species anastomose with major vessels of the uterus, may help regulate ovarian flow magnitude and ovarian capillary pressure. ***(Heap,et al., 1985).*** Ovarian arterioles that reside in stromal tissue may modulate flow distribution to the follicles and corpora lutea. Follicular and luteal capillaries, which undergo a dramatic change in number and distribution throughout the estrous cycle ***(Forsman and McCormack,1992)***, clearly affect the capacity for exchange in these ovarian compartments.

Primordial or smaller preantral follicles do not have any special vascular supply of their own and derive their blood supply from stromal blood vessels ***(Findaly, 1986)***. Subsequent growth of primary follicles leads to development of a vascular network with increased follicular blood flow. Thus the stromal blood flow velocity in an inactive or quiescent ovary may reflect the baseline blood flow perfusion.

High-resolution ultrasonographic machines with color-, power-, and spectral-Doppler modes have brought a powerful dimension to the evaluation of the preovulatory follicle during recent years. Power Doppler imaging permits the accurate localization of vessels. Transvaginal Doppler offers a closer look at blood flow within the reproductive organs. ***(Bork, 1996).*** Power Doppler is better suited to the study of the ovarian stromal vascularity, as it is more sensitive to lower velocities and essentially angle-independent ***(Guerriero, et al., 1999).*** Thus, peak systolic blood flow velocity wave-forms could be detected, and optimal flow velocity wave-forms could be selected. Then pulsitality index and resistance index could be calculated in each selected Doppler wave.

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Serum calcium concentration is not affected by amlodipine. ***(NORVASC, Pfizer Laboratories Div Pfizer Inc, 2011)***. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect., it is long acting drug with $\mathbf{t}\ \frac{1}{2}$ 35-45 hour**.** ***(Drug information reference, 2003).*** It has wide safety margin, it is also used in treatment of some cases of pediatric hypertension. Adult dose for treatment of peripheral vascular resistance is from 5-10mg / day. ***(Palamaras and Kyriakis, 2005).***