A Study of Endometrial Perfusion in Unexplained Infertility

Thesis

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List of Abbreviations

ADM : Adrenomedullin

AFC : Antral follicle count

AMH : Anti-müllerian hormone

ASRM : American Society of Reproductive Medicine

CC : Clomiphene citrate

CCCT : Clomiphene citrate challenge test

eNOS : Endothelial nitric oxide synthase

FI : Flow index

HyCoSy : Hysterosalpingo-contrast sonography

ICI : Intracervical insemination of sperm

IUI : Intrauterine insemination

IVF : In vitro fertilization

LH : Luteinizing hormone

NIH : National Institutes of Health

NK : Natural killer

NSFG : National Survey of Family Growth

OA : Ovarian artery

PECAM-1 : Platelet endothelial cell adhesion molecule

PI : Pulsatility index

RI : Resistance index

S/D : Systolic/diastolic

SEBF : Sub-endometrial blood flow

TGF : Transforming growth factor

UtA : Uterine artery

VFI : Vascularisation-FI

VI : Vascularisation index

WHO : World Health Organization

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Introduction

Infertility in itself represents a wide spectrum of disorders explaining the inability to conceive. Series of investigations are required to depict the potential cause of infertility, yet there exist a small percentage (10 -25%) of couples in which no obvious cause is delineated. these groups of patients are classified as ‘unexplained infertility **(Rain-Fenning et al., 2004).**

A number of studies showed that poor uterine and ovarian blood flow can be an important - often undiagnosed factor - in infertility, miscarriage and IVF failure; research shows that poor blood flow may be at the root of 'unexplained infertility' too. however, most women with a diagnosis of 'unexplained' will never be offered the diagnostic test for uterine blood flow impairment and will never be offered treatment, instead they will retain their frustrating non-specific diagnosis of ‘unexplained’ **(Edi-Osagie et al., 2004).**

Ultrasonography has an increasingly important role in the evaluation and treatment of infertility patients, being an efficient and cost-effective modality for studying the female reproductive organs and for monitoring functional changes during spontaneous and induced cycles **(Goldberg et al., 1991).**

During spontaneous menstrual cycles endometrial volume increased significantly during the follicular phase, reaching a plateau around the time of ovulation and remaining relatively stable throughout the luteal phase **(Rain-Fenning et al., 2004).**

Uterine arterial resistance changes might reflect receptivity of endometrium, so color Doppler signals are measured at the uterine arteries and their ascending branches located in the outer third of the myometrium **(Steer et al., 1994).**

Uterine spiral artery perfusion has been found to improve during the luteal phase, which coincides with the implantation window **(Battaglia et al., 1990).**

Impedance of uterine and spiral arteries blood flow change periodically during the normal ovulatory menstrual cycle. Endometrial receptivity is regulated by many factors including uterine perfusion. Several studies have shown that uterine receptivity is decreased when the uterine artery impedance has been increased during the mid-luteal phase, Abnormal uterine perfusion may be a contributing factor to etiopathology of infertility especially in couples with unexplained infertility. Transvaginal Doppler pulsed ultrasound is an important tool for examining the female

reproductive system and is a non-invasive method to assess the uterine perfusion **(Rain-Fenning et al., 2004).**

It is interesting that the lowest impedance at spiral artery blood flow has been detected just at the time at mid-luteal phase, during which endometrium has been transformed from proliferative phase to secretory phase. At this specific time period blood supply of uterus is rich and implantation is most likely to occur **(Gong et al., 2005).**

In addition to this it was reported that impedance of spiral artery blood flow in women with unexplained infertility was significantly higher than that of the fertile counterparts similarly suggested that decreased uterine perfusion might be a cause of unexplained infertility **(Steer et al., 1994).**

Aim of the Work

The aim of this study is to evaluate the uterine perfusion, particularly the endometrial blood flow in women with unexplained infertility.

Research question:

In women with unexplained infertility, does endometrial perfusion differ from that of fertile ones?

Research Hypothesis:

In women with unexplained infertility, endometrial perfusion may be unlike that of fertile women.

Chapter (1)

Unexplained Infertility

Introduction:

Infertility is a common condition with important psychologic, economic, demographic, and medical implications. Demand for infertility services has grown substantially even though the prevalence of infertility has been stable. This phenomenon may be due to entry of the "baby boom" generation into the reproductive age group during a period of highly publicized technologic advances, and unparalleled publicity given to fertility issues in the lay press **(Kuohung et al., 2013**).

It is relatively simple to identify the cause of infertility in women with ovulatory disorders or tubal disease, and in men with semen abnormalities. These categories account for the source of infertility in approximately 75 percent of couples. Infertility in the remaining 25 percent of couples is due to endometriosis (8 percent) or miscellaneous factors (e.g., cervical factor, immunological factor, uterine synechiae) (2 percent) or is unexplained (15 percent) (**Collins et al., 1992; Guzick et al., 1994).**

Definition:

Infertility is a unique medical condition because it involves a couple, rather than a single individual. It is defined as failure of a couple to conceive after 12 months of regular intercourse without use of contraception in women less than 35 years of age; and after six months of regular intercourse without use of contraception in women 35 years and older (**Practice Committee of the American Society for Reproductive Medicine, Fertil Steril, 2008)**.

Unexplained infertility refers to the absence of a definable cause for a couple's failure to achieve pregnancy after 12 months of attempting conception despite a thorough evaluation, or after six months in women 35 and older (**Practice Committee of the American Society for Reproductive Medicine, 2008).**

Authorities vary in their concept of what constitutes a thorough evaluation, and these opinions have evolved over time. Currently, a thorough evaluation typically includes documentation of:

- Ovulation
- Tubal patency
- Normal uterine cavity
- Normal semen analysis

- Adequate ovarian oocyte reserve **(Practice Committee of the American Society for Reproductive Medicine, Fertil Steril, 2008).**

Prevalence of infertility:

The National Survey of Family Growth (NSFG) interviewed 15, 303 married women aged 15 to 44 to estimate the prevalence of infertility in the United States. Married women were considered infertile if they reported they had not conceived over the past 12 months and were sexually active and not using contraception or surgically sterilized from 1982 to 2002, the percentage of married women meeting these criteria for infertility fell from 8.5 to 7.4 % then fell to 6% in the 2006-2010 survey **(Stephen et al., 2013)**.

In contrast, the estimated percent of married women with impaired fecundity increased from 11% in 1982 to 15% in 2002 then fell to 12% in 2006_2010. Impaired fecundity was defined as a 36-month interval of unprotected sexual activity without conception or the woman's perception that it was physically impossible or difficult for her to conceive or her husband to father a child (does not include surgically sterile individuals) **(National Public Health Action Plan, 2014).**