

# ENDOMETRIAL VOLUME AND ENDOMETRIAL FLOW INDICES IN PREDICTING THE SUCCESS OF IVF/ICSI CYCLES

*Thesis*

Submitted for partial fulfillment  
of the Master degree in  
Obstetrics & Gynecology

By

**Mohamed Mahmoud Ahmed**

M.B., B.Ch,

Faculty of Medicine

Assiut University (2010)

Resident of obstetrics and Gynecology  
At Masr Elgededa Military Hospital

*Under Supervision of*

***Prof. Dr. Khaled Ibrahim Abdallah***

*Professor of Obstetrics and Gynecology,  
Faculty of Medicine - Ain Shams University*

***Prof. Dr. Ihab Foud Serag Eldin Allam***

*Professor of Obstetrics and Gynecology,  
Faculty of Medicine - Ain Shams University*

***Assist. Prof. Dr. Wessam Magdi Abuelghar***

*Assistant Professor of Obstetrics and Gynecology,  
Faculty of Medicine - Ain Shams University*

**FACULTY OF MEDICINE  
AIN SHAMS UNIVERSITY  
2016**



## Acknowledgment

*First and foremost, I feel always indebted to Allah; the kind and merciful, that this research came to its end with Allah's well and help.*

*I would like to express my deepest gratitude and appreciation to **prof. Dr. Khalid Ibrahim**, Professor of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University for his continuous guidance and precious encouragement. I feel great honor to work under his supervision.*

*I am also greatly indebted to **prof. Dr. Ihab Serag**, Professor of Obstetrics & Gynecology, Faculty of Medicine, Ain Shams University, whose consistent supervision, kind advice and fruitful orientation and guidance has been of great help to me in completing this work and **Assist. prof. Dr. Wessam M. Abuelghar**, Assistant Professor of Obstetrics & Gynecology, Faculty of Medicine, Ain Shams University for his endless support, continuous guidance, advice and kind supervision during all stages of the work. I have learned much from him. Many thanks to **Assist. prof. Dr. Abdelatif Elkholy**, Assistant Professor of Obstetrics & Gynecology, Faculty of Medicine, Ain Shams University for his contributions in database collection and kind guidance.*

*Many thanks to **Dr. Monira Ali Ali**, Ultrasound Special Care Unit for the fetus, Ain Shams University and **Dr. Azza Awad Abdelrazik**, Embryology Lab. Director, Assisted Reproduction Unit, Ain Shams University for their great efforts and help to finish this work.*

*I am also very grateful to all staff members and all my colleagues in the department of **Obstetrics and Gynecology**, Faculty of Medicine, Ain Shams University.*

*Finally, I would also seize the opportunity to dedicate this thesis to my **family** for their Continuous help, encouragement, support, and belief in me.*

*✍ Mohamed Mahmoud Ahmed*



بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

﴿وَأَنْزَلَ اللَّهُ عَلَيْكَ الْكِتَابَ وَالْحِكْمَةَ وَعَلَّمَكَ مَا لَمْ

تَكُنْ تَعْلَمُ وَكَانَ فَضْلُ اللَّهِ عَلَيْكَ عَظِيمًا﴾

سورة النساء آية (١١٣)

صدق الله العظيم

# Contents

Subjects	Page
• List of Abbreviations .....	4
• List of Tables .....	6
• List of Figures .....	8
• Protocol .....	11
• Introduction .....	21
• Aim of the Work .....	25
• Review of literature:	
- <i>Chapter 1:</i> Implantation and IVF/ICSI Success .....	28
- <i>Chapter 2:</i> Doppler Ultrasound and Endometrial Receptivity: .....	44
- <i>Chapter 3:</i> Endometrial Volume And Endometrial Receptivity .....	56
• Patients and Methods .....	63
• Results .....	72
• Discussion .....	100
• Summary .....	111
• Conclusion .....	116
• References .....	119
• Appendix .....	148
• Arabic Summary .....	157

## *List of Abbreviations*

<b>AFC</b>	: Antral follicular count
<b>ART</b>	: Assisted reproductive technology
<b>CG</b>	: chorionic gonadotrophin
<b>CT</b>	: Cytotrophoblast
<b>ECM</b>	: extracellular matrix
<b>ET</b>	: endometrial thickness
<b>EV</b>	: endometrial volume
<b>EVT</b>	: extravillous trophoblast
<b>FI</b>	: Flow Index
<b>FSH</b>	: Follicle stimulation hormone
<b>Hcg</b>	: Human chorionic gonadotropin
<b>HSG</b>	: Hystrosalpingography
<b>ICSI</b>	: Intracytoplasmic sperm injection
<b>IGFBP-1</b>	: insulin-like growth factor binding protein-1
<b>IVF</b>	: In vitro fertilization
<b>IVFET</b>	: In vitro fertilization- embryo transfer
<b>PCOS</b>	: polycystic ovarian syndrome
<b>PI</b>	: Pulsatility index

<b>PL</b>	⋮	placental lactogen
<b>PSV</b>	⋮	Peak systolic velocity
<b>RBC</b>	⋮	Red blood cell
<b>RI</b>	⋮	Resistant Index
<b>SD</b>	⋮	Standard deviation
<b>ST</b>	⋮	Syncytiotrophoblast
<b>TSH</b>	⋮	Thyroid stimulating hormone
<b>SIS</b>	⋮	Saline infusion Sonohysterography
<b>uNK</b>	⋮	Uterine natural killer
<b>US</b>	⋮	Ultrasound
<b>VEGF</b>	⋮	Vascular endometrial growth factor
<b>VFI</b>	⋮	Vascularization flow index
<b>VI</b>	⋮	Vascularization Index
<b>VOCAL</b>	⋮	Virtual Organ Computer-aided Analysis
<b>2-D</b>	⋮	Two dimensional
<b>3D US- PDA</b>	⋮	Three-dimensional ultrasound and power Doppler angiography
<b>4D</b>	⋮	Four dimensional

## *List of Tables*

<b>Table No.</b>	<b>Title</b>	<b>Page</b>
<b>Table (1)</b>	Patients' characteristics of the studied sample	74
<b>Table (2)</b>	Type of infertility in the studied sample	75
<b>Table (3)</b>	Etiology of infertility of the studied sample	76
<b>Table (4)</b>	Three-dimensional ultrasound and power Doppler angiography parameters of the studied sample	77
<b>Table (5)</b>	Outcome measures of the studied sample	78
<b>Table(6)</b>	Outcome of current ICSI procedure in the studied sample	79
<b>Table (7)</b>	Comparison between non pregnant and pregnant cases as regards patients' characteristics	80
<b>Table (8)</b>	Comparison between non pregnant and pregnant cases as regards past history	81
<b>Table (9)</b>	Comparison between non pregnant and pregnant cases as regards duration, type, and etiology infertility	82
<b>Table (10)</b>	Comparison between non pregnant and pregnant cases as regards ultrasound and HSG work-up	83
<b>Table (11)</b>	Comparison between non pregnant and pregnant cases as regards laparoscopy and hysteroscopy work-up	84

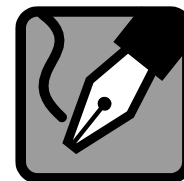
<b>Table (12)</b>	Comparison between non pregnant and pregnant cases as regards hormonal profile	85
<b>Table (13)</b>	Comparison between non pregnant and pregnant cases as regards Current ICSI procedure	87
<b>Table (14)</b>	Comparison between non pregnant and pregnant cases as regards Three-dimensional ultrasound and power Doppler angiography parameters	88
<b>Table (15)</b>	Receiver-operating characteristic (ROC) curve analysis for prediction of pregnancy using the endometrial volume, VI, FI, or VFI	92
<b>Table (16)</b>	Comparison of the receiver-operating characteristic (ROC) curves for prediction of clinical pregnancy using the endometrial volume, VI, FI, or VFI	97
<b>Table (17)</b>	Summary of studies of endometrial blood flow by 3D transvaginal power Doppler ultrasound	109
<b>Table (18)</b>	Summary of data published about the role of Endometrial Volume in predicting outcome in IVF program	110

## *List of Figures*

<b>Fig. No.</b>	<b>Title</b>	<b>Page</b>
<b>Fig. (1)</b>	(a) Trilaminar endometrium as seen at the end of the follicular phase. (b) luteal endometrium as seen at about the time that implantation would normally occur	35
<b>Fig. (2)</b>	Three-dimensional power Doppler angiography of the uterine blood supply.	37
<b>Fig. (3)</b>	Intra-subject variation in endometrial blood flow measurement	38
<b>Fig. (4)</b>	Schematic representation of the pulse echo system in the pregnant abdomen	51
<b>Fig. (5)</b>	The 'Histogram'	52
<b>Fig. (6)</b>	Determination of the subendometrial area volume by using the "shell" facility	54
<b>Fig. (7)</b>	The techniques of Endometrial volume calculation	58
<b>Fig. (8)</b>	Three-dimensional 'wire' models of the endometrium	59
<b>Fig. (9)</b>	Longitudinal ultrasound images demonstrate the endometrial pattern	60
<b>Fig. (10)</b>	Schematic characterization of endometrial vascular indices	68
<b>Fig. (11)</b>	Patient number (16, 24) 3D US-PDA showing Technique used for calculating Endometrial Volume and three	69

	angiographic Power Doppler indices.	
<b>Fig. (12)</b>	Diagram showing flow of participants through the study	73
<b>Fig. (13)</b>	Showing type of infertility in the studied sample	75
<b>Fig. (14)</b>	Distribution of cohort according to etiology of infertility	76
<b>Fig. (15)</b>	Showing Outcome of current ICSI procedure in the studied sample	79
<b>Fig. (16)</b>	Endometrial volume in patients with positive or negative clinical pregnancy.	88
<b>Fig. (17)</b>	VI in patients with positive or negative clinical pregnancy.	89
<b>Fig. (18)</b>	FI in patients with positive or negative clinical pregnancy	90
<b>Fig. (19)</b>	VFI in patients with positive or negative clinical pregnancy	91
<b>Fig. (20)</b>	Receiver-operating characteristic (ROC) curve for prediction of clinical pregnancy using the endometrial volume	93
<b>Fig. (21)</b>	Receiver-operating characteristic (ROC) curve for prediction of clinical pregnancy using the VI.	94
<b>Fig. (22)</b>	Receiver-operating characteristic (ROC) curve for prediction of clinical pregnancy using the FI	95
<b>Fig. (23)</b>	Receiver-operating characteristic (ROC) curve for prediction of clinical pregnancy using the VFI	96

<b>Fig. (24)</b>	Comparison of the receiver-operating characteristic (ROC) curves for prediction of clinical pregnancy using the endometrial volume, VI, FI, or VFI.	98
------------------	---	----



---

# *Protocol*

---

# ENDOMETRIAL VOLUME AND ENDOMETRIAL FLOW INDICES IN PREDICTING THE SUCCESS OF IVF/ICSI CYCLES

*Protocol of Thesis*

Submitted for partial fulfillment  
of the Master degree in  
Obstetrics & Gynecology

By

**Mohamed Mahmoud Ahmed**  
M.B., B.Ch, Faculty of Medicine  
Assiut University (2010)  
Resident of obstetrics and Gynecology  
At Masr Elgededa Military Hospital

*Under Supervision of*

***Prof. Dr. Khalid Ibrahim Abdullah***

*Professor of Obstetrics and Gynecology,  
Faculty of Medicine - Ain Shams University*

***Prof. Dr. Ihab Foud Serag Eldin Allam***

*Professor of Obstetrics and Gynecology,  
Faculty of Medicine - Ain Shams University*

***Assist. Prof. Dr. Wessam Magdi Abuelghar***

*Assistant Professor of Obstetrics and Gynecology,  
Faculty of Medicine - Ain Shams University*

**FACULTY OF MEDICINE  
AIN SHAMS UNIVERSITY  
2014**

## INTRODUCTION

Assisted reproductive techniques (ART) are used widely to treat fertility problems, which affect approximately 7–15% of women of reproductive age (**Thoma et al., 2013**). Although there have been several improvements in techniques during the last three decades (**Martins et al., 2011 ; Phillips et al., 2013**) clinical pregnancy and live-birth rates remain at approximately 30–40% and 20–30%, respectively (**Sunkara et al., 2011 ; Gunby et al., 2011**) according to results from the Canadian ART Register in 2007. Increasing these rates is desirable for couples undergoing ART, as treatment failure is a source of psychological distress (**Pasch et al., 2012**) and the most common cause of drop-out before achieving pregnancy (**Verberg et al., 2008**). The success of in vitro fertilization and embryo transfer (IVF-ET) cycles depends mainly on embryo quality and uterine receptivity (**Barker et al., 2009**). Endometrial receptivity is regulated by many factors including endometrial perfusion (**Ng et al., 2006**).

Several studies have demonstrated the existence of a correlation between endometrial characteristics and pregnancy rate in IVF/ICSI patients (**Noyes et al., 1995; Richter et al., 2007; Al-Ghamdi et al., 2008**).

Factors affecting the growth of endometrium are still not well understood, but recently many researchers have focused on the angiogenesis and vascularization within the endometrium and found that a poor uterine receptivity in women with thin endometrium may be due to the impairment of blood flow impedance through the endometrium (**Sher and Fisch: 2000; Ng et al., 2007; Ho et al., 2009; Takasaki et al., 2010**).

Some studies have suggested a minimal thickness for a successful pregnancy to occur, while others have reported adverse effects of increased endometrial thickness above which pregnancy is unlikely to occur (**Zenke et al., 2004; Rashidi et al 2005; Schild et al., 2001**). In contrast, others have failed to demonstrate a relationship between endometrial thickness, pattern, and pregnancy and implantation rates (**Laasch et al., 2004; Garcia-Velasco et al., 2003; Dietterich et al., 2002; Yuval et al., 1999; Sundstrom et al 1998**).

Biopsy of the endometrium cannot be considered during the treatment, and this has encouraged the development and use of ultrasonography and Doppler-like non-invasive methods to evaluate ovarian response to the stimulation and uterine receptivity (**Ebrard-Charra *et al.*, 2005**).

The advantages of ultrasonography include its non-invasiveness, repeatability, real-time monitoring and predictability (**Wang *et al.*, 2010**).

Furthermore, numerous other studies on uterine blood flow have led to conflicting conclusions (**Yang *et al.*, 1999; Schild *et al.*, 2001; Basir *et al.*, 2002a, b; Chien *et al.*, 2004**).

**Merce. (2002)** postulated that endometrial blood flow reflects properly the uterine receptivity because the endometrium is the site where embryonic implantation takes place. Similarly ( **Chien *et al.*, 2002**) reported the absence of Color Doppler mapping at the endometrial and sub endometrial levels is related to a significant decrease in the implantation rate , whereas the pregnancy rate increases when vessels can be depicted reaching the sub endometrial halo and the endometrium.

**Raine-Fenning *et al.* (2004)** found during the study of implantation window that after an increase in several ultrasonographic parameters three days before ovulation, decreases in the vascular index (VI) and the sub-endometrial vascular flow index (VFI), respectively. These observations suggest that there is specific vascular regulation during the cycle that correlates with endometrial development of a receptive state.

**L'ed'ee *et al.* (2007)** assume that the use of Three-dimensional ultrasound and power Doppler angiography (3D US-PDA) a non-invasive technology to assess blood flow, could provide information regarding the local angiogenic processes occurring in the endometrium which are essential for implantation and gestation.

**Merce *et al.* (2008)** results show a statistically significant increase in endometrial indexes of vascularization, flow, and vascularization flow indexes on the day of HCG administration in the pregnant group.

**Ng *et al.* (2006)** didn't prove the 3D Power Doppler indexes to be good predictors after (FSH) stimulation or on oocyte retrieval day. The difference between results in the studies may be due to the difference in the time of indexes measurement.