

**Effect of low-dose aspirin on mid-luteal phase
Uterine Artery blood flow in women with
recurrent pregnancy loss**

Thesis

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By

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم العظيم

صدق الله العظيم

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List of Contents

Title	Page No.
List of Tables	i
List of Figures	ii
List of Abbreviations	iv
Introduction	1
Aim of the Work	4
Review of Literature	
▪ Recurrent Pregnancy Loss (Miscarriage)	5
▪ Ultrasound	49
▪ Low-Dose Aspirin	67
Patients and Methods	79
Results	89
Discussion	98
Summary	107
Conclusion	110
Recommendations	111
References	112
Appendix	149
Master table	150
Arabic Summary	

List of Tables

Table No.	Title	Page No.
Table (1):	Proposed evaluation of women with recurrent miscarriage.....	32
Table (2):	Demographic characteristics of the study population	89
Table (3):	Obstetric history of the study population	90
Table (4):	Comparison of UA PI before and after treatment	92
Table (5):	Comparison of UA RI before and after treatment	94
Table (6):	Comparison of UA SD before and after treatment	96

List of Figures

Fig. No.	Title	Page No.
Figure (1):	Karyotypes of 2 women with recurrent miscarriage.	20
Figure (2):		52
Figure (3):	Anatomy of the arcuate, radial and spiral arteries during pregnancy.....	57
Figure (4):	Typical pulsed-wave Doppler waveform of the uterine artery during the luteal phase of a normal menstrual cycle.....	61
Figure (5):	Pulsed-wave waveform of the radial artery	62
Figure (6):	Doppler velocity of the spiral artery in the same patient as shown in figure 5.....	63
Figure (7):	Non-pregnant uterine artery Doppler waveform	64
Figure (8):	Normal uterine artery waveform during pregnancy.....	65
Figure (9):	Flow chart showing women participated in the study.....	81
Figure (10):	Samsung WS80A with Elite V5-9 endocavity probe transducer that used in the current study.....	87
Figure (11):	Present uterine artery Doppler indices including right RI and PI after intervention (Case No. 55).	87
Figure (12):	Present uterine artery Doppler indices including left RI and PI before intervention (Case No. 67).	88
Figure (13):	Frequency of previous abortions in the study population.....	90
Figure (14):	Number of live births in the study population.	91

List of Figures (cont...)

Fig. No.	Title	Page No.
Figure (15):	Mean uterine artery pulsatility index (UA PI) before and after low-dose aspirin. Error bars represent the 95% confidence interval (95% CI). Rt = right, Lt = left, Av = average, pre = before low-dose aspirin, post = after low-dose aspirin.....	93
Figure (16):	Mean uterine artery resistive index (UA RI) before and after low-dose aspirin. Error bars represent the 95% confidence interval (95% CI). Rt = right, Lt = left, Av = average, pre = before low-dose aspirin, post = after low-dose aspirin.....	95
Figure (17):	Mean uterine artery S/D ratio (UA SD) before and after low-dose aspirin. Error bars represent the 95% confidence interval (95% CI). Rt = right, Lt = left, Av = average, pre = before low-dose aspirin, post = after low-dose aspirin.....	97

List of Abbreviations

Abb.	Full term
<i>2-D</i>	<i>Two dimensional</i>
<i>3D US-PDA</i>	<i>Three-dimensional ultrasound and power Doppler angiography</i>
<i>ACAs</i>	<i>Anticardiolipin antibodies</i>
<i>ACAs</i>	<i>Anticardiolipin antibodies</i>
<i>ACOG</i>	<i>American college of obstetricians and gynecologist</i>
<i>AFC</i>	<i>Antral follicular count</i>
<i>ANA</i>	<i>Antinuclear antibodies</i>
<i>APA</i>	<i>Anti-phospholipid antibodies</i>
<i>APS</i>	<i>Antiphospholipid antibody syndrome</i>
<i>aPTT</i>	<i>Activated partial thromboplastin time</i>
<i>APTT</i>	<i>Activated partial thrombin time</i>
<i>AR</i>	<i>Androgen</i>
<i>ART</i>	<i>Assisted reproductive technology</i>
<i>ATA</i>	<i>Anti-thyroid antibodies</i>
<i>CBC</i>	<i>Complete blood count</i>
<i>CTLs</i>	<i>Cytotoxic T cells</i>
<i>EF</i>	<i>ESTROGEN</i>
<i>FI</i>	<i>Flow Index</i>
<i>FSH</i>	<i>Follicle Stimulating Hormone</i>
<i>FVW</i>	<i>Flow velocity waveform</i>
<i>GnRH</i>	<i>Gonadotrophin releasing hormone</i>
<i>HCG</i>	<i>Human chorionic gonadotrophin</i>
<i>Hcg</i>	<i>Human chorionic gonadotropin</i>
<i>HIV</i>	<i>Human Immunodeficiency virus</i>
<i>HLA</i>	<i>Human leukocyte antigen</i>
<i>HSG</i>	<i>Hystrosalpingography</i>
<i>HSV</i>	<i>Herpes simplex virus</i>

List of Abbreviations (cont...)

Abb.	Full term
ICSI	<i>Intracytoplasmic sperm injection</i>
IFN γ	<i>Interferon gamma</i>
IgA	<i>immunoglobulin A</i>
IgG	<i>Immunoglobulin G</i>
IgM	<i>Immunoglobulin M</i>
IL.....	<i>Interleukin</i>
IL-1 α	<i>Interleukin one alpha</i>
IL-1 β	<i>Interleukin one beta</i>
IPI	<i>Inter pregnancy Interval</i>
IVF	<i>In-vitro fertilisation</i>
IVIg	<i>Intravenous infusion of immunoglobulins</i>
KAR.....	<i>killer activatory receptor</i>
KIR.....	<i>killer inhibitory receptor</i>
LAC.....	<i>Lupus anticoagulant</i>
LDA.....	<i>Low dose aspirin</i>
LH.....	<i>Luteinizing Hormone</i>
LMP	<i>Last menstrual period</i>
LMW	<i>Low molecular weight</i>
LMWH	<i>low molecular weight heparin</i>
LPD	<i>Luteal phase defect</i>
LT	<i>Left</i>
MHC	<i>Major histocompatibility complex</i>
MPL	<i>IgM phospholipid</i>
MTHFR	<i>Methylenetetrahydrofolate reductase</i>
NK.....	<i>Natural killer</i>
NO.....	<i>Nitrous oxide</i>
PAI	<i>Plasminogen activator inhibitor</i>
PCOS	<i>Polycystic ovary syndrome</i>
PI.....	<i>Pulsatility index</i>

List of Abbreviations (cont...)

Abb.	Full term
<i>pNK</i>	<i>Peripheral NK cells</i>
<i>PR</i>	<i>Progesteron</i>
<i>PRL</i>	<i>Prolactin</i>
<i>PSV</i>	<i>Peak systolic velocity</i>
<i>PT</i>	<i>Prothrombin time</i>
<i>RBC</i>	<i>Red blood cell</i>
<i>RCOG</i>	<i>Royal College for Obstetricians and Gynaecologists</i>
<i>RI</i>	<i>Resistance index</i>
<i>RM</i>	<i>Recurrent miscarriage</i>
<i>RPL</i>	<i>Recurrent pregnancy loss</i>
<i>RR</i>	<i>Relative risk</i>
<i>RT</i>	<i>Right</i>
<i>S/D</i>	<i>Systole / Diastole</i>
<i>SA</i>	<i>spontaneous abortion</i>
<i>SD</i>	<i>Standard deviation</i>
<i>ST</i>	<i>Syncytiotrophoblast</i>
<i>TGF</i>	<i>Tissue growth factor</i>
<i>Th</i>	<i>T helper cells</i>
<i>TNF</i>	<i>Tumor necrosis factor</i>
<i>TSH</i>	<i>Thyroid stimulating hormone</i>
<i>UA</i>	<i>uterine artery</i>
<i>uNK</i>	<i>Uterine natural killer</i>
<i>US</i>	<i>Ultrasound</i>
<i>USPSTF</i>	<i>U.S Preventive Services Task</i>
<i>VEGF</i>	<i>Vascular endometrial growth factor</i>
<i>VFI</i>	<i>Vascularization flow index</i>
<i>VI</i>	<i>Vascularization Index</i>
<i>VOCAL</i>	<i>Virtual Organ Computerized Aided Analysis</i>

INTRODUCTION

Recurrent pregnancy loss is defined as two or more consecutive pregnancy losses prior to completion of 20 weeks gestation. It is a common and frustrating pregnancy complication, which affects 1% to 5% of reproductive women worldwide (*Shahine and Lathi, 2015*).

Successful implantation depends on close interaction between the blastocyst and the receptive endometrium. It appears that a favorable endometrial milieu is necessary for successful implantation (*Ng et al., 2007*).

Uterine receptivity is likely to be regulated by number of factors including uterine perfusion and its great importance in achieving a normal pregnancy. Studies suggest that uterine artery perfusion may regulate endometrial receptivity, and that poor uterine perfusion could be one of the causes of unexplained abortions and, probably of faulty implantation (*Habara et al., 2002*).

An unsupportive endometrium, leading to abnormal implantation, is considered a vital factor contributing to recurrent pregnancy loss (*Mahajan, 2015*).

Assessment of uterine blood flow has become potentially valuable for evaluating the functional capacity of the endometrium during the implantation window after the

introduction of Doppler methods to clinical practice (*Pietropolli et al., 2015*).

The Doppler ultrasound provides a unique tool with which to examine the blood supply towards the whole endometrium and the subendometrial region (*Wu et al., 2003*). Colored Doppler is used in obstetrical ultrasound as a complementary tool to grayscale imaging to gain information about the presence, direction and velocity of blood flow (*Benson, 2006*).

Increased uterine artery vascular resistance and decreased uterine blood flow have been used as predictors of high-risk pregnancies, which also may be the likely causes of recurrent pregnancy loss (*El-Mashad et al., 2011*).

Among potential uterine predictors for implantation measurable by ultrasonography are endometrial thickness and volume, endometrial pattern as well as blood flow in the uterine and subendometrial arteries (*Schild et al., 2000*).

Before pregnancy, blood flow of the uterine artery demonstrates high resistance to absent or reversed diastolic flow (*Park, 2006*).

The pulsatility index of uterine artery has been known to diminish progressively during the luteal phase during which implantation occurs (*Habara et al., 2002*).

Decreased uterine blood flow is considered a causative factor in recurrent pregnancy loss (*Koo et al., 2015*).

Previous studies provided evidence that low-dose aspirin as a common anticoagulant can produce a vasodilatory effect (*Lazzarin et al., 2009*).

Supplementation with low-dose aspirin has been widely reported to be effective in improving uterine blood flow and pregnancy outcomes in patients with impaired uterine vascularization who had undergone assisted reproductive technologies (*Wada et al., 1994*).

Therefore, it has been considered that measurement of uterine artery pulsatility index in the mid luteal phase of spontaneous cycles might isolate patients with recurrent pregnancy loss associated with impaired uterine circulation (*Habara et al., 2002*).

Lazzarin and co-workers evaluated the relationship between uterine artery blood flow and subendometrial blood flow using Doppler ultrasonography in patients with recurrent pregnancy loss and they have postulated that endometrial and subendometrial vascularity are significantly reduced in women with unexplained subfertility during the mid-late follicular phase (*Lazzarin et al., 2007*).

Access to prenatal care, early detection of the disorder, careful monitoring and appropriate management are crucial elements in the prevention of pregnancy-related complications (*Wagner, 2004*).

AIM OF THE WORK

The objective of this study is to assess the efficacy of low-dose aspirin on uterine artery blood flow which can be used as a treatment modality in recurrent pregnancy loss cases before getting pregnant.

Chapter 1

RECURRENT PREGNANCY LOSS (MISCARRIAGE)

Definition:

The generally accepted definition of abortion is discontinuation of pregnancy with fetus or embryo weigh 500gm or less, according to the world health organization (*Kolte et al., 2014*).

The classic term recurrent miscarriage is defined as the loss of 3 or more consecutive pregnancies with or without previous live births, and this condition affects about 1% to 3% of women (*Danny and Holly, 2009; Jaslow et al., 2010*).

However, there is no consensus regarding the definition of recurrent miscarriage and many clinicians define recurrent miscarriage as two or more losses before the fetus has reached viability (*Zidi-Jrah et al., 2016*). The number of miscarriages has been a debate, according to the Royal College of Obstetricians and Gynecologists, the definition is three or more consecutive losses (*Jauniaux et al., 2006*). While according to the American Society for Reproductive Medicine, the definition is two or three consecutive losses (*Pfeifer et al., 2012*).

The definition variation from three consecutive losses to two consecutive losses made an increase in the scale of the