Uterine Artery and Subendometrial blood flow assessment in recurrent pregnancy loss

"Cross-sectional study"

Thesis

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Rania Al-Awadhy,

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ACAs	Anticardiolipin antibodies
ANA	Antinuclear antibodies
APA	Anti-phospholipid antibodies
APS	Antiphospholipid syndrome
APTT	Activated partial thrombin time
AR	Achrosome reaction
ATA	Anti-thyroid antibodies
b.p.m.	Beat per minute
CMV	Cytomegalo virus
CRL	Crown rump length
CTLs	Cytotoxic T cells
DES	Diethyl Stillbesterol
dRVVT	Dilute Russel's viper venom time
ET	Embryo Transfer
FSH	Follicle Stimulating Hormone
FVW	Flow velocity waveform
GnRH	Gonadotrophin releasing hormone
HCG	Human chorionic gonadotrophin
HIV	Human Immunodeficiency virus
HLA	Human leukocyte antigen
HLA	Human leukocyte antigen
HSV	Herpes simplex virus
IFN γ	Interferon gamma
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
IL-1α	Interleukin one alpha
IL-1β	Interleukin one beta
IVF	In Vitro Fertilization

KAR	killer activatory receptor
KIR	killer inhibitory receptor
LAC	Lupus anticoagulant
LDA	Low dose aspirin
LH	Luteinizing Hormone
LMP	Last menstrual period
LMW	Low molecular weight
MHC	Major histocompatibility complex
MHz	Megahertz
MSD	Mean gestational sac diameter
Muc 1	Mucin 1
NK	Natural killer
NL	Not listed
NO	Nitrous oxide
PBMCs	Peripheral blood mononuclear cells
PI	Pulsatility index
PP14	Placenta protein 14
PRL	Prolactin
RI	Resistance index
RM	Recurrent miscarriage
RPL	Recurrent pregnancy loss
S/D	Systole/Diastole
TGF	Tissue growth factor
Th	T helper cells
TNF	Tumor necrosis factor
ZP	Zona pellucida

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INTRODUCTION

Human reproduction is not considered a highly efficient biological process. Before the end of the first trimester, 30%–50% of conceptions end in spontaneous abortion. Most losses occur at the time of implantation. 15%–20% of clinical pregnancies end in spontaneous abortions **(Gupta et al., 2007).**

High-risk pregnancy is broadly defined as one in which the mother, fetus, or newborn is, or may possibly be, at increased risk of morbidity or mortality before, during, or after delivery **(Mehta and Sokol, 2007)**

Spontaneous abortion is the most common complication of pregnancy and is defined as the passage of a pregnancy prior to completion of 20 weeks gestation. It implies delivery of all or any part of the products of conception, with or without a fetus weighing less than 500gm. Recurrent abortion in its broadest definition is defined as 2 to 3 or more consecutive pregnancy losses before 20 weeks of gestation, each with a fetus weighing less than 500gm**.** Although the true incidence of spontaneous abortion is unknown, approximately 15% of clinically evident pregnancies and 60% of chemically evident pregnancies end in spontaneous abortion. Eighty percent of spontaneous abortions occur prior to 12 weeks gestation. Approximately 1% of women are habitual aborters. Prognosis for a successful subsequent pregnancy is correlated with the number of previous abortions **(Uzelac and Garmel, 2007).**

Furthermore, there is considerable debate about cause and association; as the exact pathophysiological mechanisms of the most known etiologies have not been precisely elucidated. Most women with recurrent pregnancy loss probably have several risk factors for miscarriage **(Quenby et al., 2002).**

Successful implantation depends on a close interaction between the blastocyst and the receptive endometrium **(Ng et al., 2007).** It appears that a favorable endometrial milieu is necessary for successful implantation. What determines such a favorable endometrial milieu, however, is still controversial **(Noye et al., 1995).**

Uterine receptivity is likely to be regulated by a number of factors including uterine perfusion and of 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).**

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).** Color 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).**

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).**

Abnormal uterine artery blood velocity waveforms are identified by a persistent abnormal index, a persistent diastolic notch or an abnormal

difference between the indices in the left and right uterine arteries **(Mäkikallio et al., 2007).**

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

Angiogenesis plays a critical role in various female reproductive processes such as development of a dominant follicle, formation of a corpus luteum, growth of endometrium and implantation **(Abulafia and Sherer, 2000; Smith, 2001).** Endometrial and subendometrial blood flow varies in different phases of the menstrual cycle **(Raine-Fenning et al., 2004a).** There is a significant elevation in endometrial blood flow in the middle-to-late follicular phase, followed by a substantial fall and a secondary slow luteal phase rise that was maintained until the onset of menstruation. Uterine blood flow is assumed in many studies to reflect the blood flow towards the endometrium. It is assessed by color Doppler ultrasound and is usually expressed as downstream impedance to flow because measurement of blood flow volume is difficult and inaccurate, depending on the angle of insonation, accurate measurement of vessel's diameter and tortuosity of the vessels **(Ng et al., 2006).**

In an effort to elucidate the vascular changes that occur in women with recurrent abortion, and identify women with poor uterine perfusion, **Ferreira and associates** compared uterine artery pulsatility index (PI) between women with no history of abortion and women with a history of unexplained RPL and they found that women with recurrent pregnancy loss had a significantly higher uterine artery PI **(Ferreira et al., 2007).**

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).**

Recurrent abortion is best investigated before another pregnancy occurs **(Mehta and Sokol, 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).**