

EFFECT OF SILDENAFIL CITRATE ON UTERINE ARTERY  
BLOOD FLOW IN PATIENTS WITH UNEXPLAINED  
RECURRENT MISCARRIAGES: A RANDOMIZED CLINICAL  
TRIAL

Thesis

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# List of Abbreviations

Abb.	Full term
<b>ACL</b>	: Anticardiolipin antibodies
<b>APAS</b>	: Antiphospholipid antibody syndrome
<b>APS</b>	: Antiphospholipid syndrome
<b>ARDS</b>	: Adult respiratory distress syndrome
<b>AUC</b>	: Area under the curve
<b>BV</b>	: Bacterial vaginosis
<b>CAT</b>	: Catalase
<b>cGMP</b>	: Cyclic guanosine monophosphate
<b>CMV</b>	: Cytomegalovirus
<b>D&amp;C</b>	: Dilatation and curettage
<b>DNA</b>	: Deoxyribonucleic acid
<b>ED</b>	: Erectile dysfunction
<b>EDRF</b>	: Endothelium-derived relaxing factor
<b>eNOS</b>	: Endothelial nitric oxide synthase
<b>ET</b>	: Endometrial thickness
<b>EU</b>	: European union
<b>FDA</b>	: Federal drug administration
<b>FIEI</b>	: Female intervention efficacy index
<b>FSAD</b>	: Female sexual arousal disorder
<b>FSAD</b>	: Female sexual arousal disorder

<b>FSFI</b>	: Female sexual function index
<b>FSH</b>	: Follicle stimulating hormone
<b>GP</b>	: Glycoprotein
<b>GSH-S-T</b>	: Glutathione S-transferase
<b>HCG</b>	: Human chorionic gonadotropin
<b>HIV</b>	: Human immunodeficiency virus
<b>HLA</b>	: Histocompatibility leukocyte antigen
<b>HSDD</b>	: Hypoactive sexual desire disorder
<b>HSG</b>	: Hysterosalpingogram
<b>IFN-<math>\gamma</math></b>	: Interferon-gamma
<b>Ig</b>	: Immunoglobulin
<b>IL</b>	: Interleukin
<b>INR</b>	: International normalized ratio
<b>ISMO</b>	: Isosorbide mononitrate
<b>IUFD</b>	: Intrauterine fetal demise
<b>IUGR</b>	: Intrauterine growth restriction
<b>IVF</b>	: In vitro fertilization
<b>IVIg</b>	: Intravenous immunoglobulins
<b>LAs</b>	: Lupus anticoagulants
<b>LH</b>	: Luteinizing hormone
<b>LMWH</b>	: Low-molecular-weight heparin
<b>LPD</b>	: Luteal phase deficiency
<b>MDA</b>	: Malondialdehyde
<b>MRHD</b>	: Maximum recommended human dose
<b>MRI</b>	: Magnetic resonance imaging

<b>MTD</b>	: Maximum tolerated dose
<b>MTHFR</b>	: Methylene tetrahydrofolate reductase
<b>NADH</b>	: Nicotinamide adenine dinucleotide
<b>NAION</b>	: Non-arteritic anterior ischemic optic neuropathy
<b>NANC</b>	: Non-adrenergic, non-cholinergic
<b>NK</b>	: Natural killer
<b>NO</b>	: Nitric oxide
<b>NO-cGMP</b>	: Nitric oxide-cyclic guanosine monophosphate pathway
<b>OD</b>	: Optical density
<b>PCOS</b>	: Polycystic ovary syndrome
<b>PDE<sup>o</sup></b>	: Phosphodiesterase type <sup>o</sup>
<b>PGD</b>	: Preimplantation genetic diagnosis
<b>PI</b>	: Pulsatility index
<b>PIH</b>	: Pregnancy-induced hypertension
<b>PT</b>	: Prothrombin time
<b>RCOG</b>	: Royal college of obstetricians and gynecologists
<b>RI</b>	: Resistance index
<b>RPL</b>	: Recurrent pregnancy loss
<b>S/D</b>	: Systolic diastolic ratio
<b>SD</b>	: Standard deviation
<b>SLE</b>	: Systemic lupus erythematosus

<b>SOD</b>	: Superoxide dismutase
<b>SSRIs</b>	: Selective serotonin uptake inhibitors
<b>TAC</b>	: Total antioxidant capacity
<b>TGF-<math>\beta</math></b>	: Transforming growth factor-beta
<b>TNF</b>	: Tumor necrosis factor
<b>TSH</b>	: Thyrotropin secreting hormone
<b>URSA</b>	: Unexplained recurrent spontaneous abortion
<b>VSS</b>	: Visual sexual stimulation

## INTRODUCTION

Recurrent miscarriages are the loss of three or more consecutive pregnancies before the 24<sup>th</sup> week of gestation. It is either primary (women without previous live born infant) or secondary (women with at least one prior live born infant) (*Farquharson et al.*, 2007).

It affects about 1,0-1% of pregnant women. Altogether for most women who experience miscarriage, the recurrence rate is below 3% and the chance of live birth after three consecutive losses is only 30%-40% (*Diane* 2007).

The etiology of most recurrent miscarriage remains unclear. The majority of cases, after excluding anatomic, genetic, microbiologic, and hormonal causes of abortions and complete medical, surgical, and social history, remain idiopathic (*El-Far et al.*, 2007).

Endometrial growth seems to be dependent on uterine artery blood flow and the importance of endometrial development on pregnancy outcome has been reported (*Sher and Fisch*, 2007).

The quality of the endometrium is an important factor in achieving successful implantation. A typical trilaminar appearance with a minimum thickness of 9 mm

and a uterine artery pulsatility index of  $<3$ , are regarded as sound markers of endometrial receptivity (*Jerzak et al.*, 2008).

Several regimens have been proposed to improve a poor endometrial response, including treatment with estrogen and low dose aspirin, while in past few years much interest have been focused on role of nitric oxide as a modulator of uterine blood flow (*Weckstein et al.*, 2004).

It was demonstrated that oxidative stress (nitric oxide and malondialdehyde), as well as tumor necrosis factor- $\alpha$ , have a detrimental effect on pregnancy (*El-Far et al.*, 2009).

Sildenafil citrate is a type 5-specific phosphodiesterase inhibitor, augments the vasodilator effect of nitric oxide by preventing the degradation of cyclic guanosine monophosphate. It has been used with great success in the treatment of male erectile dysfunction (*Sher and Fisch*, 2002).

The effect of sildenafil has been evaluated on endometrial development in women who had thin endometrium; improved endometrial development was achieved among 90% of cases. Among these women, a 99% ongoing pregnancy rate was achieved (*Paulus et al.*, 2002).

The use of sildenafil citrate in women with unexplained recurrent abortions showed that the drug helped to improve the uterine artery blood flow and endometrial thickness (*Fisch et al., ۲۰۰۳*).