

**EFFECT OF SILDENAFIL CITRATE ON TOTAL
ANTIOXIDANT CAPACITY SERUM LEVELS IN
PATIENTS WITH UNEXPLAINED RECURRENT
MISCARRIAGES: A RANDOMIZED CLINICAL TRIAL**

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

وَقُلْ رَبِّ
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List of Abbreviations

Abb.	Meaning
ACL	: Anticardiolipin antibodies
APAS	: Antiphospholipid antibody syndrome
APS	: Antiphospholipid syndrome
ARDS	: Adult respiratory distress syndrome
AUC	: Area under the curve
BV	: Bacterial vaginosis
CAT	: Catalase
cGMP	: Cyclic guanosine monophosphate
CMV	: Cytomegalovirus
D&C	: Dilatation and curettage
DNA	: Deoxyribonucleic acid
ED	: Erectile dysfunction
EDRF	: Endothelium-derived relaxing factor
eNOS	: Endothelial nitric oxide synthase
EU	: European union
FDA	: Federal drug administration
FIEI	: Female intervention efficacy index
FSAD	: Female sexual arousal disorder
FSAD	: Female sexual arousal disorder
FSFI	: Female sexual function index
FSH	: Follicle stimulating hormone
GP	: Glycoprotein
GR	: Glutathione reductase
GSH	: Reduced glutathione
GSH-S-T	: Glutathione S-transferase
GSSG	: Disulfideoxidized glutathione
HCG	: Human chorionic gonadotropin
HIV	: Human immunodeficiency virus
HLA	: Histocompatibility leukocyte antigen
HSDD	: Hypoactive sexual desire disorder
HSG	: Hysterosalpingogram
IFN- γ	: Interferon-gamma
Ig	: Immunoglobulin

List of Abbreviations (Cont.).

Abb.	Meaning
IL	: Interleukin
INR	: International normalized ratio
ISMO	: Isosorbide mononitrate
IUFD	: Intrauterine fetal demise
IUGR	: Intrauterine growth restriction
IVF	: In vitro fertilization
IVIg	: Intravenous immunoglobulins
Las	: Lupus anticoagulants
LH	: Luteinizing hormone
LMWH	: Low-molecular-weight heparin
LPD	: Luteal phase deficiency
MDA	: Malondialdehyde
MRHD	: Maximum recommended human dose
MRI	: Magnetic resonance imaging
MTD	: Maximum tolerated dose
MTHFR	: Methylene tetrahydrofolate reductase
NADH	: Nicotinamide adenine dinucleotide
NAION	: Non-arteritic anterior ischemic optic neuropathy
NANC	: Non-adrenergic, non-cholinergic
NK	: Natural killer
NO	: Nitric oxide
NO-cGMP	: Nitric oxide-cyclic guanosine monophosphate pathway
OD	: Optical density
PCOS	: Polycystic ovary syndrome
PDE5	: Phosphodiesterase type 5
PGD	: Preimplantation genetic diagnosis
PIH	: Pregnancy-induced hypertension
Prn	: Pro – re – nata latin word means as needed
PT	: Prothrombin time
RCOG	: Royal college of obstetricians and gynecologists
ROS	: Reactive oxygen species
RPL	: Recurrent pregnancy loss

List of Abbreviations (Cont.).

Abb.	Meaning
SD	: Standard deviation
SLE	: Systemic lupus erythematosus
SOD	: Superoxide dismutase
SSRIs	: Selective serotonin uptake inhibitors
TAC	: Total antioxidant capacity
TGF-β	: Transforming growth factor-beta
TH	: T-helper cell
TNF	: Tumor necrosis factor
TSH	: Thyrotropin secreting hormone
URSA	: Unexplained recurrent spontaneous abortion
VSS	: Visual sexual stimulation

INTRODUCTION

Recurrent miscarriages are the loss of three or more consecutive pregnancies before the 24th 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., 2002*).

It affects about 0.5-1% of pregnant women. Altogether for most women who experience miscarriage, the recurrence rate is below 30% and the chance of live birth after three consecutive losses is only 35% - 45% (*Diane, 2002*).

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*).

Antioxidants are substances that protect against free radicals. Free radicals are molecules produced due to food breakdown, or by environmental exposures like tobacco smoke and radiation. Free radicals can damage cells (*Jenkins et al., 2000*).

Impaired antioxidant defense and an increase in oxidative reactive species may be responsible for recurrent abortion due to possible damage produced by their generation (*El-Far et al., 2007*).

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

In a comparison between levels of total antioxidant capacity, lipid hydroperoxide and total free sulfhydryl in healthy pregnant women without early pregnancy loss (EPL) and women with EPL, the level of total antioxidant capacity along with total free sulfhydryl and serum prolidase were lower in women with EPL than women without EPL (*Toy et al., 2010*).

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 use of sildenafil citrate in women with unexplained recurrent abortions showed that the drug helped to increase total antioxidant capacity levels in these patients (*El-Far et al., 2009b*).

SUBJECTS AND METHODS

This prospective, randomized, double blinded, placebo controlled trial will be conducted at Ain Shams University maternity hospital Recurrent Abortion Clinic after approval of the Research and Ethics Committee of Ain Shams University Maternity Hospital, Cairo, Egypt in accordance with local research governance requirements, after which the protocol will be registered at ClinicalTrials.gov.

It will include 180 patients with three or more unexplained recurrent miscarriages who will be randomly allocated (computer based randomization using Random Allocation Software[®] version 1.0.0) to receive either (figure 1 (*Schulz et al., 2010*)):

- Sildenafil citrate 25 mg to be self-administered by the patient oral, 4 times per day for 21 days (Silden[®] 25 mg tablet, EIPICO, Inc, Cairo, Egypt) OR
- Matching placebo self-administered by the patient intravaginally, 4 times per day for 21 days.

Randomization codes will be placed in sequentially numbered, opaque, sealed envelopes to be opened at time of enrollment by an investigator who will prepare the study drug and will have no further involvement with the patient's care.

All data will be analyzed before it is determined which group is receiving sildenafil citrate and which is receiving placebo.

All women with recurrent miscarriages will have systematic investigations including hysterosalpingogram, coagulation profile, thyroid function test, pelvic ultrasound scan, anticardiolipin antibodies IgG and IgM, lupus anticoagulant antibodies, and hormonal analysis (including progesterone, prolactin, androgens, and early follicular FSH, and LH).

Our inclusion criteria will be:

- 1) Age 18-35 years.
- 2) Three or more recurrent miscarriages before the 24th week of gestation with no apparent cause for their previous losses.
- 3) Six or more months have elapsed since the last abortion.
- 4) Postmenstrual period.
- 5) No other therapy allowed during our treatment course.

Our exclusion criteria will be:

- 1) Concomitant use of organic nitrites, or nitrates.
- 2) Severe hepatic, renal, or cardiovascular impairment.
- 3) Hypotension.
- 4) History of stroke or myocardial infarction.
- 5) Patients with retinitis pigmentosa.