Efficacy of Sildenafil Citrate in improvement of Endometrial Receptivity in Unexplained Infertility

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بسم الله الرحمن الرحيم

قَالُوا سُبْحَانَكَ لا عِلْمَ لَنَا إِلا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ العَلِيمُ الحَكِيمُ

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LIST OF ABBREVIATIONS

AA	Arachidonic acid
ASRM	American society of reproductive medicine
CAM	Cell adhesion molecules
CC	Clomifene citrate
CNTF	Ciliary neurotropic factor
COH	Controlled ovarian hyperstimulation
COX	Cyclooxygenase
DES	Diethylstilbesterol
DIPI	Direct intraperitoneal insemination
ECM	Extracellular matrix
ED	Erectile dysfunction
EEC	Endometrial epithelial cells
EGF	Epidermal growth factor
ELISA	Enzyme-linked immunosorbant assay
EPDA	Endometrial power Doppler area
ER	Estrogen receptor
ESC	Endometrial stromal cells
ET	Embryo transfer
ET	Endometrial thickness
FSH	Follicle-stimulating hormone
FSP	Fallopian sperm perfusion
GIFT	Gamete intrafallopian tube
GnRH	Gonadotropin releasing hormone
HB-EGF	Heparin-binding-epidermal growth factor
hCG	Human chorionic gonadotropin
hMG	Human menopausal gonadotropin
HSG	Hysterosalpingogram
ICAM	Intercelular adhesion molecule
ICSI	Intracytoplasmic sperm injection
IGF	Insulin-like growth factor

IL-1	Interleukin-1
IUI	Intrauterine insemination
IVF	In vitro fertilization
KDR	Kinase-insert domain-containing region
LH	Luteinizing hormone
LIF	Leukemia-inhibiting factor
MW	Molecular weight
NO	Nitric oxide
NTG	Nitroglycerine
OHSS	Ovarian hyperstimulation syndrome
OSM	Oncostatin molecule
PCO	Polycystic ovaries
PCT	Postcoital test
PDE	Phosphodiesterase
PGs	Prostaglandins
PI	Pulsatility index
PLA	Phospholipase A
PR	Progesterone receptor
RI	Resistance index
r-LIF	Recombinant leukemia inhibiting factor
RPL	Recurrent pregnancy loss
TGF	Transforming growth factor
TI	Timed intercourse
TxA_2	Thromboxane A_2
VEGF	Vascular endothelial growth factor
VOCAL	Virtual organ computer-aided analysis

INTRODUCTION

Unexplained infertility refers to the absence of a definable cause for a couple's failure to achieve pregnancy after 12 months of attempting conception despite a thorough evaluation ***(Mark Hornstein, 2007)***.

In the absence of a correctable abnormality, the therapy for unexplained infertility is, by default, empiric. Proposed treatment regimens include intrauterine insemination (IUI), ovulation induction with oral or injectable medications, combination of IUI with ovulation induction, and assisted reproductive technologies (ART). There is a need for randomized controlled trials to evaluate empiric therapies because conception may occur even without treatment ***(American Society for Reproductive Medicine, 2006)***.

The average incidence of unexplained infertility has been reported to be approximately 15%. The incidence varies from 0% to 37%. This variation may be attributed to selection bias in referral-based infertility practice ***(Balasch, 2000)***.

Use of clomiphene citrate for ovulation induction is generally associated with excellent outcomes. In fact, in some populations, 80% to 85% of treated women will ovulate and 40% will conceive. Discrepancies between ovulatory rates and conception rates are most likely associated with the number of cycles attempted or are secondary to the presence of additional, nonovulatory infertility factors among treated women. Most

pregnancies resulting from induction of ovulation with clomiphene citrate occur during the first 6 months of therapy. Side effects of clomiphene citrate therapy include infrequent OHSS, vasomotor flushes, nausea, pelvic discomfort, and breast pain ***(Hammond et al., 1993)***.

Embryo implantation represent the most critical step of the reproductive process in many species, It consists of a unique biological phenomenon. By which the blactocyst becomes intimately connected to the maternal endometrial surface ***(Aplin, 2000)***.

Successful implantation requires a receptive endometrium, a normal and functional embryo at the blactocyst developmental stage and a synchronized dialogue between maternal and embryonic tissue ***(Simon et al., 2000)***.

Endometrial receptivity is defined as a temporary unique sequence of factors that make the endometrium receptive to the embryonic implantation ***(Bergh et al., 1992)***. It is the window of time when the uterine environment is conductive to blastocyst acceptance and subsequent implantation ***(Swierz et al., 1997)***.

The endometrium is normally a non-receptive environment for an embryo except during implantation window. Implantation window is a period during which the endometium is optimally receptive to implanting blastocyst. Implantation of the human embryo may occur only during a regulated "implantation window"

on days 6-10 post ovulation, and surrounded by refractory endometrial status ***(Bergh et al., 1992)***.

Human embryo implantation is a three-stage process (apposition, adhesion and invasion) involving synchronized crosstalk between a receptive endometrium and a functional blastocyst. This ovarian steroid-dependant phenomenon can only take place during the window of implantation, a self-limited period of endometrial receptivity spanning between days 20 and 24 of the menstrual cycle. Implantation involves a complex sequence of signaling events, consisting in the acquisition of adhesion ligands together with the loss of inhibitory components, which are crucial to the establishment of pregnancy ***(Achache and Revel, 2006)***.

In order for successful implantation to occur, an adequately prepared endometrium has to be built up during the menstrual cycle. Endometrial development is regulated by steroid hormones and various growth factors and cytokines. Sufficient uterine blood supply is required for these factors to reach the endometrium ***(Kovacs et al., 2003)***.

Adequate pelvic blood supply is essential for normal reproductive and physiological performance. It has been postulated, that a disturbance of this blood supply may be responsible for some cases of unexplained infertility ***(Hoad, 2003)***.

Several regimens have been proposed to improve a poor endometrial response, including treatment with estrogens and low dose aspirin ***(Weckstein et al., 1997)***.

In the past few years, much interest has been focused on the role of nitric oxide as a modulator of uterine blood flow ***(Amit et al., 1998)***.

Nitric oxide relaxes vascular smooth muscle through cGMP mediated pathway and nitric oxide isoforms have been identified in the uterus, Sildenafil citrate is a newly developed, type 5-specific phosphodiesterase inhibitor that prevents the breakdown of cGMP and potentiate the effect of nitric oxide on vascular smooth muscle improving uterine blood flow and endometrial receptivity ***(Sher, 2002)***.

The effect of sildenafil has been evaluated on endometrial development in women who had thin endometrium (<8mm), improved endometrial development was achieved among 70%. Among these women, a 29% ongoing pregnancy rate was achieved ***(Sher, 2002)***.

The use of sildenafil citrate in women with unexplained infertility showed that the drug helped to improve the uterine artery blood flow and endometrial thickness ***(Fisch et al., 2000)***.

AIM OF THE WORK

To find out if sildenafil citrate has got any role in improvement of endometrial receptivity and pregnancy rate in case of unexplained infertility.

Chapter 1: Unexplained Infertility

Introduction

Infertility is said to be idiopathic or unexplained when a couple does not conceive and no definite cause of infertility can be diagnosed after a complete evaluation. Despite improved diagnostic techniques, the average incidence of unexplained infertility has been reported to be approximately 15% **(Templeton and Penney, 1982)**; the incidence varies from 0% to 37% **(Collins and Corsignani, 1992)**, This variation may be attributed to selection as in referral-based infertility practices or may reflect other differences among study populations **(Kim and Hornstein, 1997)**. The incidence is also affected by the duration of infertility, assigning the diagnosis after only one year results in the inclusion of many normally fertile couples. This will result in a higher incidence of unexplained infertility.

So far, there is no agreement neither regarding standard infertility evaluation **(Balasch, 2000)** nor regarding standard protocol of management of unexplained infertility **(Aboulghar et al., 1999)**. Variation in the way different investigators interpret their data, together with the difficulty in performing prospective randomised trials have resulted in today's differences in opinion and practice among specialists. This article is presented to track the best available evidence regarding different diagnostic and treatment modalities of unexplained infertility.

Diagnosis of unexplained infertility

Traditionally, complete infertility evaluation should be performed before the diagnosis of unexplained infertility is reached. There is a very long list of investigations for the diagnosis of infertility, however there is no consensus on which tests are essential before reaching the diagnosis of unexplained infertility.

The long classical of investigations included conventional semen analysis, a variety of sperm function tests such as in vitro mucous penetration test, hamster egg penetration test and post coital test. Assessment of ovulation includes basal body temperature, mid luteal serum progesterone, endometrial biopsy and ultrasound monitoring of ovulation. Tubal factor is assessed by hysterosalpingography, laparoscopy, falloscopy, hysterosonography and transvaginal hydrolaparoscopy **(Gordts et al., 1998)**. The peritoneal factors are assessed by laparoscopy and the uterine factor by hysterosalpingography and hysteroscopy. Immunological factors are evaluated by a variety of special tests. The validity of some of these tests has not been established.

It was stated that care must be taken to avoid exploitation of the infertile couple with expensive unnecessary tests, procedures, and treatments **(Jaffe and Jewelewicz, 1991; ESHRE Capri Workshop, 1996)**. It can be argued that performing comprehensive investigations may explain or define causes of otherwise unexplained infertility, but when many tests are carried out that are independent or partially independent, then the chances