USE OF VAGINAL SILDENAFIL IN PATIENTS UNDERGOING INTRACYTOPLASMIC SPERM INJECTION (ICSI) PROCEDURE

Thesis

Submitted for fulfillment of Master Degree in
Obstetrics and Gynecology

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Faculty of Medicine
Cairo University
2009

Abstract

Background:

Progress in reproductive technology has shown that Nitric Oxide (NO) is involved in fertilization process and is found in the follicle as well as the sperm, decidualization and implantation. Endometrial growth is thought to depend on uterine artery blood flow and the importance of endometrial development on in-vitro fertilization (IVF) outcome has been previously reported. Sildenafil citrate (Viagra) is a type 5-specific PDE inhibitor that prevents the breakdown of cGMP and potentiates the effect of NO on vascular smooth muscle.

Patient and methods:

This is a prospective randomized controlled study. Fifteen cases will be given sildenafil citrate with IVF preparatory protocol and the other Fifteen cases will be used as a control cases (they will be given IVF induction protocol without sildenafil).Inclusion and exclusion were set.

Conclusion:

The notion of increasing pregnancy rate among women undergoing ICSI is still far from reality. Among factors affecting implantation rate and pregnancy rate, endometrial thickness remain poorly understood.The use of vaginal sildenafil showed no significant increase in endometrial thickness in cases undergoing ICSI. Yet metaphase II, cleaved embryos, number of embryo transfer/cycle and finally implantation rate increased which may be due to improvement of endometrial and ovarian microvascular circulation or decrease NK activity.More controlled randomized trials with large sample size are needed to address these issues.

Key words:

Endometrium / Implantation / Intracytoplasmic sperm injection/ Sildenafil/Uterine artery blood flow.

ACKNOWLEDGMENT

*I wish to express my deepest thanks and grattitude to **Prof. Dr. Soumaya Mohamed Hassan Abou Elew**, Professor of Obstetrics and Gynecology Kasr El Aini Faculty of Medicine, Cairo University who gave me the honor of working under her supervision and who was kind enough to offer me much of her valiable time and sincere advice.*

*I wish to express my deepest gratitude to **Assistant Prof. Dr. Osama Mahmoud Azmy**, Assistant Professor of obstetrics and gynecology National Research Center for his kind supervision, continous encouragement and guidance as well as his moral support throughout work.*

*I would also like to thank very much **Dr. Ahmed Mohamed Ahmed Said**, Assisstant professor of Obstetrics and Gynecology Kasr El Aini Faculty of Medicine, Cairo University for his encouragement and supervision on this work and the valuable discussions with objective criticism which are gratefully appreciated.*

*I am especially and deeply gratefull to **Dr. Tamer Fouad Taha**, Lecturer of Obstetrics and Gynecology National Research Center, and **Dr. Mamdouh Abd El Asis**, Lecturer of Obstetrics and Gynecology National Research Center for their encouragement and guidance.*

DEDICATION

TO MY FATHER, MOTHER AND SISTER FOR

THEIR SUPPORT AND ENCOURAGMENT

CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

ART	Assissted Reproductive Technology
CAMs	Cell Adhesion Molecules
cGMP	Cyclic Guanosine Monophosphate
CPR	Clinical Pregnancy Rate
CSF-1	Colony Stimulating Factor
DF	Dominant Follicle
EEC	Endometrial Epithilial Cells
EFP	Early folliclar phase
EPF	Early Pregnancy Factor
FDA	Food and Drug Administration
FET	Frozen Embryo Transfer
GIFT	Gamete Intra Fallopian Transfer
GNRH	Gonadotropin Releasing Hormone
HB-EGF	Heparin- Binding Epidermal Growth Factor
HCG	Human Chorionic Gonadotropin
HEPES	4-(2-Hydroxyethyl)-I-Pirazine-Ethane-Sulphonic Acid
HIV	Human Immunodefeciency Virus
ICAM-1	Intercellular Adhesion Molecule-1
ICSI	Intra Cytoplasmic Sperm Injection
IGF	Immunoglobulin Factor
IL-1	Interleukin 1
IUI	Intra Uterine Insemenation
IVF	Invitro Fertilization
LH	Leutinizing Hormone
LIF	Leukima Inhibitory Factor
LPD	Leuteal Phase Defect
MDMA	Methylene dioxymethamphetamine
MESA	Microsurgical Epidedimal Sperm Aspiration
MUC1	Mucin 1
NK	Natural Killer

NO	Nitric oxide
PAH	Pulmonary Artirial Hypertension
PAI-1	Plasminogen Activator Inhibitor 1
PDE5	Phosphodiesterase type 5
PFBF	Ovarian perifollicular blood flow
PGD	Preimplantation Genetic Diagnosis
PGD-AS	Preimplantation Genetic Diagnosis–Aneuploidy Screening
PN	ProNuclei
PR	Progesterone Receptor
PVP	PolyViniylPyrrolidone
PZD	Partial Zona Dessection
RM	Recurrent miscarriage
SUZI	SubZonal Insemination
TEP	Tubal Ectopic Pregnancy
TESE	Testicular Sperm Extraction
TET	Tubal Embryo Transfer
TGF-B	Transforming Growth Factot b
TIMP	Tissue Inhibitor of Metalloprotinases
VGR	Viagra
ZIFT	Zygote Intra Fallopian Transfer

INTRODUCTION

Infertility is one of the major medical and social problems and has received considerable international attention. Infertility affects approximately 10-15% of the couples and is important part of clinical practice for many clinicans **(Mosher and Partt, 1991).** Fortunately for many of these couples, the problem is over when some conceive spontaneously without undergoing any investigation or therapy, few others become pregnant after being investigated and treated for the correctable factors **(Robert et al., 1991).**

Assisted reproductive technologies (ART) encompass all techniques involving direct manipulation of oocytes outside of the body. The commonest forms of ART are Invitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI).These techniques provide hope for many couples who are unable to concive naturally.While results of ICSI have improved much and are associated with pregnancy rates that approach spontaneous fecundity, unfortunately there is considerable discrepancy between results of fertilization and implantation resulting into what is called implantation failure **(Stern and Chamley, 2006).**

Implantation itself is governed by an array of endocrine, paracrine and autocrine modulators, of embryonic and maternal origin. Implantation failure is thought to occur as a consequence of impairment of embryo developmental potential and/or impairment of uterine receptivity and the embryo-uterine dialogue. Therefore a better comprehension of implantation, and the relative importance of the factors involved, is warranted. New techniques for monitoring changes in the

endometrium and/or the embryo at the level of gene regulation and protein expression may lead to the identification of better markers for implantation. Moreover, the use of predictive sets of markers may prove to be more reliable than a single marker. Continuing refinements to ART protocols, such as optimizing ovarian stimulation regimens, the timing of human chorionic gonadotrophin injection, or the timing of embryo transfer, should help to increase implantation rates further **(Diedrich et al., 2007).**

There is a lot of debate on the administration of low-dose aspirin, estrogen, vaginal sildenafil citrate, pentoxifylline, vitamin E, and gonadotropin - releasing hormone agonist for the management of thin endometrium with an aim to increase the pregnancy and implantation rates in assisted reproductive technology cycles. Various recent modalities proposed for the treatment of thin endometrium seem to be useless and inefficient from an evidence-based medicine point of view **(Senturk, 2008).**

AIM OF WORK:

To assess the role of sildenafil in increasing pregnancy rate in cases undergoing intracytoplasmic sperm injection through improving the endometrial vascular blood supply.

CHAPTER I

Assisted Reproductive Technology

Definition:

Assisted reproductive technologies (ART) encompass all techniques involving direct manipulation of oocytes outside of the body. The first and still most common form of ART is in vitro fertilization (IVF), but there are a number of other related techniques within the realm of ART ***(Sabatini et al., 2006).***

ART also includes methods for assisted fertilization by intracytoplasmic sperm injection (1CSI) using sperm isolated from the ejaculate or obtained by microsurgical epididymal sperm aspiration (MESA) or testicular sperm extraction (TESE), assisted embryo hatching, and preimplantation genetic diagnosis ***(Anderson and Erb, 2006).***

Other forms of ART involve the tubal transfer of oocytes and spermatozoa (gamete intrafallopian transfer; GIFT), zygotes (zygote intrafallopian transfer; ZIFT), or embryos (tubal embryo transfer; TET) via laparoscopy ***(Basso and Olsen, 2005).***

In vitro fertilization (IVF):

IVF involves a sequence of highly coordinated steps beginning with controlled ovarian hyper-stimulation with exogenous gonadotropins, followed by retrieval of oocytes from the ovaries under transvaginal ultrasound guidance, fertilization in the laboratory, and transcervical transfer of embryos into the uterus. The first child resulting from IVF was born in 1978 **(Mikkelsen, 2005)**. (FIG. 1)

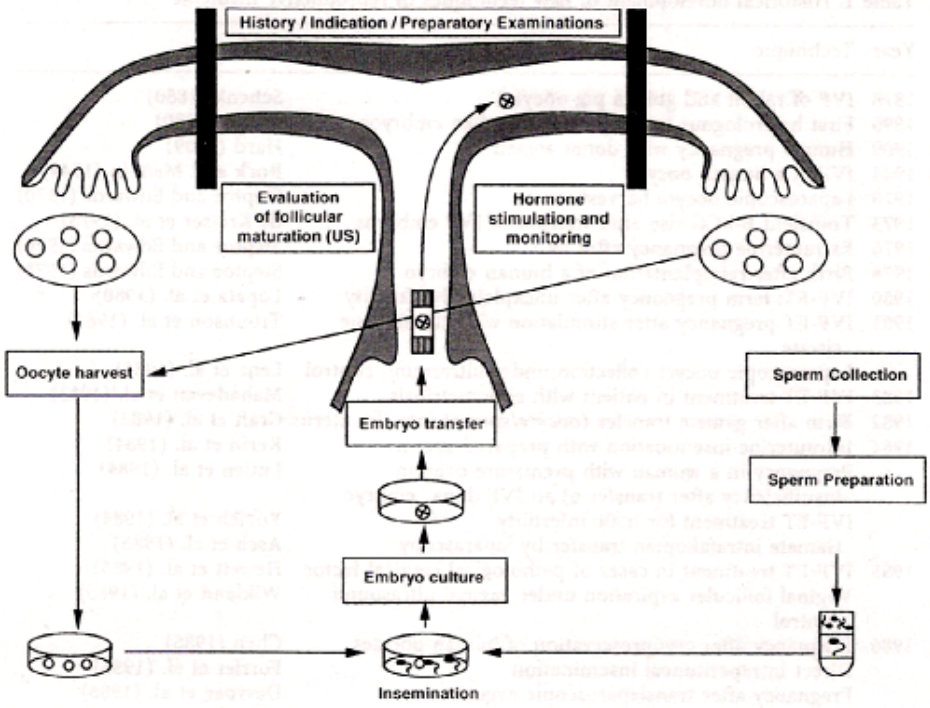

Figure (1): Invitro fertilization principle and procedure **(Rabe et al., 2000).**

Indications for IVF:

IVF was first developed as a means to overcome infertility resulting from irreparable tubal disease, but it is now applied much more broadly for the treatment of almost all causes of infertility as:

1- Tubal Factor Infertility:

- *Distal Tubal Obstruction:*

IVF is now the treatment of choice for infertile women with severe tubal disease. IVF is also the best treatment for women who remain infertile for a year or more after successful tubal surgery, for older women with any significant degree of distal tubal disease and for women with recurrent distal tubal obstruction (repeated attempts to correct distal tubal occlusive disease are rarely successful) **(American Society for**

Reproductive Medicine and Centers for disease Control and Prevention, 2003).

Accumulated evidence indicates that communicating hydrosalpinges (proximal patency and distal occlusion) decrease the probability of both pregnancy and live birth after IVF by approximately one-half **(Johnson et al., 2001).** The most possible mechanism is that hydrosalpingeal fluid is an inflammatory exudate and may have toxic effects on embryos or the endometrium or may mechanically interfere with implantation **(Strandell and Lindhard, 2002).**

- *Proximal Tubal Obstruction:*

  Although bilateral proximal tubal obstruction can often be treated successfully with fluoroscopic or hysteroscopic tubal • cannulation or more traditional microsurgical techniques, IVF is the obvious alternative when surgery is technically unsuccessful, relatively contraindicated (salpingitis isthmica nodosa), or infertility persists for more than 6-12 months postoperatively **(Thompson, 2006).**

  Tubal cannulation can be used effectively to restore patency in a proportion of cases of proximal tubal obstruction thus avoiding the need for expensive assisted reproductive techniques **(Das et al., 2007).**

- *Bipolar Tubal Obstruction:*

  IVF is the best and most logical treatment for women with bipolar (proximal and distal) tubal obstruction because success rates achieved with surgery are extremely poor **(Stephen and Chandra, 2000).**