Uterine Haemodynamic Changes in Patients with Copper Intrauterine Device Induced Bleeding

Thesis

Submitted for Partial Fulfillment of Master Degree in Obstetrics & Gynecology

By

Ayman Abd Elazeem Elgamal

(M.B., B.Ch.)
Ain Shams University,2005
Resident in Shobra General Hospital

Supervised by

Prof. HazemFadelElshahawy

Professor of Obstetrics & Gynecology
Faculty of Medicine
Ain Shams University

Dr. Mohamed Elmandooh Mohamed

Assistant Professor of Obstetrics & Gynecology
Faculty of Medicine
Ain Shams University

Dr. Mohammed Saeed El Din El Safty

Lecturer of Obstetrics & Gynecology
Faculty of Medicine
Ain Shams University

Faculty of Medicine
Ain Shams University
2013

CONTENTS

LIST OF ABBREVIATIONS

Ang	angioprotein
AUB	Abnormal Uterine Bleeding
AUC	Area under The curve
&	And
BFGF	Basic Fibroblast Growth Factor
BMI	Body Mass Index
B-Mode	Brightness mode
CIUD	copper Intra Uterine Device
Cm	Centimeter
COX-2	Cyclo-Oxygenase-2
CS	Cesarean Section
CW Doppler	continous wave Doppler
DUB	Dysfunctional Uterine Bleeding
Fig	Figure
FSH	Follicular Stimulating Hormone
HCG	Human Chorionic Gonadotrophin
HZ	Hertz
IUCD	Intrauterine contraceptive device
IUD	Intrauterine device
KDR	Kinase insert domain-containing receptor
Kg	Killo-gram
LNG	levonorgestrel
M	Meter
MBL	Menstrual blood loss

Mg	Milli-gram
MHZ	Mega Hertz
Ml	Milli-liter
MVD	Micro-vessel density
NO	Nitric Oxide
NSAIDs	non-steroidal anti-inflammatory drugs
P value	Probability value
PDGF	Platelet Derived Growth Factor
PGE	Prostaglandins E
PGF	Prostaglandins F
PI	Pulsitility index
PID	Pelvic inflammatory disease
PW Doppler	Pulsed Wave Doppler
RI	Resistance index
ROC	Receiver operator Characteristic Analysis
S/D ratio	systolic diastolic ratio
SD	Standard deviation
STDs	Sexually transmitted diseases
TAM	time-averaged mean
U/S	Ultrasound
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

LIST OF TABLES

LIST OF FIGURES

Acknowledgement

My sincere thanks and deep appreciation are offered to my **Prof. Dr. Hazem Fadel Elshahawy** , ***Professor of Obstetrics and Gynecology , Faculty of medicine, Ain Shams University***, for his kind guidance; keen supervision; encouragement.

I would like to express my gratitude to **Dr. Mohamed Elmandooh Mohamed**, ***Assistant Professor of Obstetrics and Gynecology, Faculty of medicine, Ain Shams University***, for giving me the honor to work under his supervision and learning from him.

I wish I could properly express my sincere thanks to **Dr.** ***Mohammed Saeed El Din El Safty*** , ***Lecturer of Obstetrics and Gynecology, Faculty of medicine, Ain Shams University***, for the invaluable help; great support and his patience with me until this work has been completed.

Special thanks to ***Ultrasound unite and special care Unite of the fetus of Ain Shams Maternity Hospital*** for the great help and coopration throughout this work.

Ayman Abd Elazeem Elgamal

INTRODUCTION

Intrauterine contraceptive device (IUD) is one of the most frequently used methods of birth control around the world. IUD induced irregular uterine bleeding is one of the main problems for many women using this method. In the first year of insertion of the IUDs, between 5 to 15% of women will have their IUDs removed because of bleeding. The use of IUD has been unfortunately associated with functional failure on one hand, and medical complications on the other hand. Despite the increasing use of intrauterine device, their further dissemination has been limited by high expulsion rates and the withdrawal of their use for medical reasons, mainly bleeding and pain ***(Castro et al., 1993)***.

Following insertion of modern copper IUD, menstrual blood loss increases by about 55%, and this level of bleeding continues for the duration of IUD use ***(Milsom et al., 1995)***.These changes occur more rapidly, and iron supplementation is recommended ***(Hassan et al., 1999)***.

There are several possible mechanisms that explain the cause of excessive bleeding in patients using IUD. Several studies reported that IUD insertion increase the production of prostaglandins in the endometrium which cause increased vascularity, vascular permeability, and inhibit platelet activity and therefore increase menstrual bleeding ***(Sales et al., 2002)***.

Recent studies have reported that IUD causes cyclo-oxygenase-2 (COX-2) up expression, the subsequent elevated prostanoid biosynthesis and signaling can promote the expression of pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), platelet derived growth factor (PDGF), angioprotein-1 (Ang-1) and angioprotein-2 (Ang-2) ***(Sales et al., 2002)*** or down-regulate

the expression of anti-angiogenic genes such as cathepsin-D ***(Perchick and Jabbour, 2003)***.

There are several mechanisms explaining the association of the pulsatility index (PI) and resistance index (RI) of uterine artery with menstrual blood loss. It has been suggested that menorrhagia, may be caused by an increased uterine secretion of prostanoids leading to impaired haemostasis***(Smith et al., 2007)***.

Temporary post-insertion rise in prostaglandin concentrations coincided with the phase of increased bleeding and pain. There is over expression of mRNA and protein of COX-2 enzyme leading to overproduction of prostaglandins in the endometrium after the insertion of copper intrauterine device (CIUD) ***(Xin et al., 2004)***.

Other vasoactive substances may also be involved, including nitric oxide (NO) which is a potent vasodilator produced the vascular endothelium. NO is present in the human endometrium and myometrium ***(Telfer et al., 1995)***.

There is evidence that NO may play a part in acute and chronic inflammation ***(Laroux et al., 2000)***. The introduction of intrauterine device into the uterine cavity induces a foreign body reaction in the surrounding endometrium ***(Ortiz and croxatto, 2007)***. NO is present in the foreign body inflammatory reaction around loosened joint replacement implants ***(Moilanen et al., 1997)***. Thus, it is possible that IUD also induces NO synthesis in the surrounding tissue. There is also a connection between NO synthesis and prostaglandin synthesis. NO directly interacts with COX, which is responsible for prostaglandin synthesis and causes an increase in enzymatic activity ***(Roberto da Costa et al., 2008)***.

There are also other possible mechanisms explaining the association of the PI of uterine artery with menstrual blood loss. Women

with menorrhagia show a significant increase in endothelial cell proliferation, reflecting disturbed angiogenesis ***(Mints et al., 2007)***.

It is possible that there are also other vascular abnormalities resulting from disturbed angiogenesis. In abnormal vessels, poor contractibility and dysfunction of the haemostatic system may cause menorrhagia and decreased impedance ***(Mints et al., 2007)***.

The expression of VEGF and its receptor, kinase insert domain-containing receptor (KDR) and microvessel density (MVD) were increased in endometrium after using CIUD ***(Xin et al., 2004)***.

Based on these findings, uterine artery Doppler indices RI, PI were widely investigated in order to identify the uterine hemodynamic changes in patients with IUD induced bleeding ***(Maulik, 1995)***.

AIM OF THE WORK

The purpose of this study is to assess the uterine hemodynamic changes of uterine artery in patients with CIUD induced bleeding by using transvaginal color Doppler indices (uterine artery resistance index and pulsatility index) to prove the relationship between these changes and bleeding in these patients.

INTRAUTERINE CONTRACEPTIVE DEVICES

Historical background on development of intrauterine device :

According to popular legend, Arab traders inserted small stones into the uteruses of their camels to prevent pregnancy during long desert treks. The story was originally a tall tale to entertain delegates at a scientific conference on family planning; although it was later repeated as truth, it has no known historical**(Speroff et al., 2005).**

Precursors to IUDs were first marketed in 1902. Developed from stem pessaries (where the stem held the pessary in place over the cervix), the 'stem' on these devices actually extended into the uterus itself. Because they occupied both the vagina and the uterus, this type of stem pessary was also known as an intrauterine device. Use of intrauterine devices was associated with high rates of infection; for this reason, they were condemned by the medical community **(Lynch et al.2006).**

In 1909, Richter in Germany reported success with a silkworm catgut ring that had a nickel and bronze wire protruding through the cervix **(Richter, 1909)**. Shortly, Pust combined Richter's ring with the old button-type pessary and replaced the wire with a catgut thread **(Pust, 1923**). In the 1920s Grafenberg removed the tail and pessary because he believed this was the cause of infection. He reported his experience in 1930, using rings made coiled silver and gold then steel **(Grafenberg, 1930).**

The Grafenberg ring was associated with a high rate of expulsion. This was solved by Ota in Japan who added a supportive structure to the center of his gold or silver-plated ring in 1934 **(Ota, 1934).**

In the 1960s and 1970s, the IUD thrived. Techniques were modified and a plethora of types were introduced. The various devices developed in the

1960s were made of plastic (polyethylene) impregnated with barium sulfate so that they would be visible on an x-ray. The Margulies Coil, developed by Lazer Margulies in 1960 at Mt. Sinai Hospital in New York City, was the first plastic devices with a memory, which allowed the use of an inserter and reconfiguration of the shape when it was expelled into the uterus. The Coil was a large device (sure to cause cramping and bleeding), and its hard plastic tail proved risky for the male partner **(Speroff et al., 2005).**

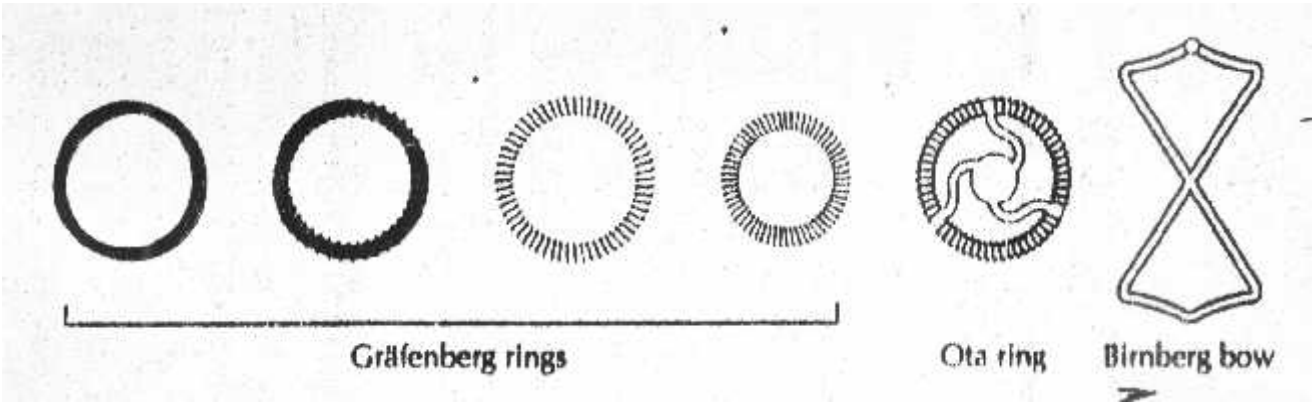

Figure 1 : Grafenberg, Ota ring and Birnberg bow

The first plastic IUD, the Margulies Coil or Margulies Spiral, was introduced in 1958. This device was some what large, causing discomfort to a large proportion of women users, and had a hard plastic tail, causing discomfort to their male partners. The modern colloquialism "coil" is based on the coil-shaped design of early IUDs. The Lippes Loop, a slightly smaller device with a monofilament tail, was introduced in 1962 and gained in popularity over the Margulies device**(Lynch et al.2006).**

The Dalkon shield was introduced in 1970. Within 3 years a high incidence of pelvic infection was recognized. There is no doubt that the problems with Dalkon shield were due to defective construction (multifilament tail providing a pathway for bacteria to ascend) pointed out as early as 1975 by Tatum **(Tatum et al., 1975).**

The addition of copper to the IUD was suggested by Jaime Zipper of Chile, whose experiments with metals indicated that copper acted locally on the endometrium **(Zipper et al., 1969).** Howard Tatum combined Zipper's suggestion with the development of the T-shape to diminish the uterine reaction to the structural frame and produced the copper - T. The first copper IUD had copper wire wound around the straight shaft of the T, the TCu-200 (200 mm of exposed copper wire), also known as the Tatum-T **(Tatum, 1983).**

Types of IUDs

➢ Unmedicated IUDs

The lippes loop made of plastic impregnated with barium sulfate is still used throughout the world (except in United States).Flexible stainless steel rings are widely used in China but not elsewhere **(Sujuan et al., 1994).**

➢ Copper IUDs

The first copper IUDs were wound with 200 to 250 mm of wire, and two of these are still available: the TCu-200 and the Multiload-250.The more modern copper IUDs contain more copper, and a part of the copper is in the form of solid tubular sleeves, rather than wire, increasing efficacy and extending lifespan. This group of IUDs is represented in the united states by the TCu-380 (the ParaGard) and in the rest of the world by the Tcu220, the Nova T, and the Mutiload-375.The modern generation of IUDs in China includes a stainless steel ring with copper wire that also releases indomethacin (very effective with a low expulsion rate and less blood loss) (**Sujuan et al., 1994).**

The TCu-380 is a T-shaped device with a polyethylene frame holding 380 $mm^2$of exposed surface of copper. The IUD frame contains barium sulfate