The Effect of Endometrial Scratching by Pipelle on the Pregnancy Rate in Couples With Unexplained Infertility

Thesis

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تأثيرخدش بطانة الرحم بإستخدام البيبل على معدل الحمل لدى الأزواج الذين يعانون من العقم غير معروف السبب

بحث علمى
كجزء مكمل للحصول على درجة الماجستير
فى التوليد و أمراض النساء

مقدمة من

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✍ *Anhar Mohamed Ali Shehata*

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بسم الله الرحمن الرحيم
﴿ وَأَنزَلَ اللَّهُ عَلَيْكَ الْكِتَابَ وَالْحِكْمَةَ وَعَلَّمَكَ مَا لَمْ تَكُن تَعْلَمُ وَكَانَ فَضْلُ اللَّهِ عَلَيْكَ عَظِيمًا ﴾
صدق الله العظيم
سورة النساء آية (□□)

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List of Abbreviations

Abb.	Meaning
ACL	Anticardiolipin
APL	Antiphospholipid
CG	Chorionic Gonadotropin
cGAMP	Cyclic Guanosine Monophosphate
COH	Controlled Ovarian Hyperstimulation
CT	Cytotrophoblast
DCs	Dendritic cell
E2	Estradiol
ECM	Extracellular Matrix
EE	Endometrial Epithelium
ESC	Endometrial Stromal Cell
EVCT	Extra Villous Cytotrophoblast
FSH	Follicular Stimulating Hormone
GnRH	Gonadotropin Releasing Hormone
Groa	Chemokine Growth Related Oncogene (a)
HBEGF	Heparin Binding Epidermal Growth Factor
HCG	Human Chorionic Gonadotropin
ICSI	Intracytoplasmic Sperm Injection
IGFBP-1	Insulin Like Growth Factor Binding Protein
IL	Interleukin
ITGa6	Integrin a 6
IUI	Intrauterine Insemination
IVF	In-Vitro Fertilization
LAC	Lupus Anticoagulant
LH	Leutinizing Hormon
LIF	Leukemia Inhibitory Factor

Abb.	Meaning
NK	Natural Killer
OPN	Osteopontin
PI	Pulstile Index
PL	Placental Lactogen
RI	Resistant Index
RIF	Recurrent Implantation Failure
SEM	Scanning Electric Microscope
Sol-HBEGF	Soluble Heparin Binding Epidermal Growth Factor
ST	Syncytiotrophoblast
LEI	Local Endometrial Injury
TE	Trophoectoderm
TNF	Tumor Necrosis Factor
TPA	Tissue Plasminogen Activator
UPA	Urokinase Plasminogen Activator
UI	Unexplained Infertility
UNK	Uterine Natural Killer Cells
WOI	Window of Implantation
ZP	Zona Pellucida

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Introduction

Unexplained infertility (UI) is a term used to describe infertile couples in whom standard investigations, including semen analysis, tests of ovulation and tubal patency, have failed to detect any gross abnormality ***(Crosignani et al., 1993).*** It is a diagnosis of exclusion, almost 30-40% of infertile couples would suffer from this type of subfertility ***(Simth et al., 2003).*** A diversity of causes had been hypothesized to explain the condition. Cervical, uterine, ovulatory, peritoneal, immunological, endocrinological, genetic defects and reproductive physiology disturbances had been continuously suggested as potential causative factors ***(Rov et al., 2005; Shveiky et al., 2006; Bellver et al., 2008; Golubovsky, 2008; Woodson, 2008).*** Empirically, interventions for managing unexplained infertility had been widely practiced. These interventions include expectant management, intrauterine insemination (IUI) with ovarian stimulation and in vitro fertilization ***(El-Toukhy & Khalaf, 2008; Bhattachary et al., 2010).***

In humans, the uterus becomes receptive during the midsecretory phase of the menstrual cycle (days 19-23), commonly known as the window of implantation (WOI). It is assumed that inadequate uterine receptivity is responsible for approximately two–thirds of implantation failures

(Simon et al., 1998). Since an impairment of endometrial receptivity may be a cause of subfertility in a group of couples diagnosed with unexplained infertility ***(Jasper et al., 2006; Boroujerdnia & Nikbakht, 2008; Konac et al., 2009).*** Endometrial scratching may help a group of couples with unexplained infertility.

The association of mechanical manipulation with decidual formation has been reported previously in rodents ***(Ledford et al., 1976; Lejeune et al., 1982).***

Endometrial scratching has been suggested to boost embryo implantation following recurrent implantation failure after IVF ***(Karimzadeh et al., 2009; Narvekar et al., 2010).*** Endometrial scratching could have a favorable endometrial healing effect on the implantation process by releasing of biochemical mediators ***(Finn & Martin, 1972; Karimzadeh et al., 2009)*** such as endometrial proinflammatory cytokines (interleukin-6, leukemia inhibitory factor and tumor necrosis factor) that characterize early implantation ***(van Mourik et al., 2009)***. These cytokines can be secreted by the endometrial cells and cells of the immune system. Decidual leukocytes infiltrate the implantation site, of these cells 65% to 70% are uterine - specific natural killer cells ***(van Mourik et al., 2009)*** *which* have been show to be essential for the establishment of an adequate deciduas ***(Croy et al., 2003;***

Hanna and Ariel, 2006). An additional 10% to 20% of the decidual leukocytes consist of macrophage and dendritic cells ***(Gardner & Moffett, 2003; Mor & Koga, 2008)***, which remain in the decidua throughout pregnancy and secrete growth factors, chemokines, and cytokines regulating blastocyst implantation, angiogenesis, placental development, and decidual homeostasis ***(Engert et al., 2007; Renaud & Graham, 2008).***

Aim of the Work

The aim of this study is to compare the endometrial scratching by pipelle to the non scratching as regards biochemical pregnancy rate in women with unexplained infertility.

Research question:

- **Population:** Women with unexplained infertility**.**
- **Intervention**: Endometrial scratching by pipelle for women with unexplained infertility.
- **Comparison**: To compare with non endometrial scratching for women with unexplained infertility.
- **Outcome:** The biochemical pregnancy rate.

Research hypothesis:

- **Null hypothesis:** There is no difference in the rate of pregnancy between scratching and non endometrial scratching in women with unexplained infertility.
- **Alternative hypothesis:** There is difference in the rate of pregnancy between scratching and non endometrial scratching in women with unexplained infertility.

Unexplained Infertility

Definition:

Infertility is described as unexplained when standard investigations, including semen analysis, assesment of ovulation and tubal patency, fail to detect any gross abnormality in a women who has not conceive for one year of unprotected sexual intercourse ***(NICE Fertility Guidance, 2013).*** It is a diagnosis of exclusion, almost 25% of infertile couples would suffer from this type of subfertility ***(Woodson, 2008).***

A diversity of causes had been hypothesized to explain the condition. Cervical, uterine, ovulatory, peritoneal, immunological, endocrinological, genetic defects and reproductive physiology disturbances had been continuously suggested as potential causative factors ***(Rov et al., 2005; Shveiky et al., 2006; Bellver et al., 2008; Golubovsky, 2008; Woodson, 2008).***

Theories on possible causes for unexplained infertility:

Follicular and luteal phase dysfunction:

There are subtle alterations in various hormones measured across the menstrual cycle in women with

unexplained infertility compared with those in normal controls, suggesting a diminished ovarian reserve ***(Van Rooij et al., 2009)***. Basal FSH and LH levels in the early, middle and late follicular phases were increased significantly in this group (early follicular FSH levels were 7.0 ± 0.57 mIU/mL in the unexplained-infertility group and 4.7 ± 0.37 mIU/mL in the normal controls, respectively ***(Balasch et al., 2010)***. Midluteal Progesterone levels were lower in the unexplained infertility group than in the normal controls (13.7 ± 1.6 versus 24.0 ± 3.2 ng/mL. Mean E2 concentrations were elevated in the group with unexplained infertility versus normal controls in the early and late follicular phase but reached significance only in the midfollicular phase. Mean prolactin levels were elevated consistently across the menstrual cycle in the unexplained infertility group compared with those in normal controls but reached significance only in the early and late follicular and midluteal phases of the cycle. Cortisol concentrations were similar between the two groups ***(Leach et al., 2007)***.

Gamete dysfunction:

The oocytes of the woman of unexplained infertility (UI) collapsed during the preparation of the oocytes for sperm injection. These oocytes suffered from irregular ZP and abnormal appearance. This woman did not conceive in