

Effect of Endometrial Scratch on Heparin Binding Epidermal Growth Factor Level in Women Undergoing Intrauterine Insemination

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Abstract

Despite many improvements in Assisted reproductive techniques during the last three decades, clinical pregnancy and live-birth rates still nearly 30–40% and 20–30%, respectively. To enhance endometrial receptivity many attempts done one of the endometrial scratching could provoke delay in endometrial maturation reforms asynchrony between endometrium and the concepts and indeed induce wound healing by producing a considerable raise in the local secretion of pro-inflammatory cytokines and growth factors like Heparin Binding Epidermal Growth Factor (HBEGF) and its receptors has role in mediate the receptivity, maturation, and decidualization of endometrium and facilitates the implantation and development of both placenta and embryo. All women were undergone IUI procedure. They divided into two groups. Intervention group who did endometrial scratching by using pipelle catheter in luteal phase of preceding cycle and another blood sample aspirated before scratch. Control group include women without intervention of endometrial scratch. Both groups underwent controlled ovarian stimulation, triggering of ovulation and another blood sample was aspirated at day of IUI to measure level of HBEGF. 14 days later with luteal support, BHCG test underwent in blood to check pregnancy. Higher pregnancy rate among patients with scratch group (5/20) 25% than non-interventional group (3/25)12%. These result showed that HBEGF level in scratch group (386.1 ± 124.7) is significantly higher than control group (279 ± 189.3) as P-value was (0.035). Moreover, the HBEGF level at day of IUI (455.67 ± 157.34) and in pregnant (563.9 ± 163.66) is significantly higher than before scratch in scratch group (279.0 ± 124.67), (406.26 ± 138.89), as P-values were (0.00007, 0.049) respectively. Intentional local damage to the endometrium is a cost-effective procedure can be used to enhance the uterine receptivity that may help to overcome implantation failure problem.

Keywords: Endometrial scratch, IUI, Pregnancy rate, HBEGF, Endometrial thickness.

1. Introduction

Assisted reproductive technology (ART) is used to describe collectively several non-coital techniques of conception that are used to treat infertility including intrauterine insemination (IUI) and in vitro fertilization (IVF). IUI is one of the methods used as assisted reproductive technology mainly to manage infertility utilizing sperm from the woman's partner (The ESHRE Capri Workshop Group [1]). Overall, the clinical pregnancy rate per cycle of donor IUI is approximately 10-20% (Jayakrishan, et al. [2]). Endometrial receptivity (ER) refers to the capability of the endometrium to adapt embryos, ER alters through the menstrual cycle. The normal endometrium just receptive to the maximal degree through a limited and critical period, the “implantation window”, which is in general 6~10 days after ovulation, that correspond to the 20th to 24th day of the normal menstrual cycle (Singh, et al. [3]). It is closely associated to infertility, and optimal endometrial receptivity is a precondition for optimal

implantation of the blastocyst, around two-thirds of implantation failures are the result from poor ER in which good ER enhance the success rate of embryo transfer (ET) (Cakmak and Taylor, [4], Ledee-Bataille, et al. [5]). Implantation is considered as the qualified step in the process of conception not either in in-vitro fertilization (IVF) cycles but also in intrauterine insemination (IUI) cycles. ER is regulated by various signaling molecules such as prostaglandins, cytokines, integrins, leukemia inhibitory factor, and growth factors. Dysregulation in these factors might cause repeated implantation failure (Achache and Revel [6]). In controlled ovarian stimulation (COS) achieved through Assisted reproductive technology (ART), the implantation rate is decline due to altering in endometrial maturation which becomes abnormally advanced and unbalanced endocrine and paracrine factors (Margalioth, et al. [7]). Cytokines, natural killer cells, and growth factors such as Heparin Binding Epidermal Growth

Factor (HBEGF) are also responsible for increased angiogenesis, thereby supplying adequate blood flow to the tissue and preventing embryo rejection (Siristatidis, et al. [8]). Endometrial scratching is described as an obligatory injury to the endometrium (Nastri, et al. [9]). It is an easy, simple, cost-effective, and practical procedure that could be undergone in an Out Patient Department (OPD) set, it confirmed as efficient in enhancing reproductive outcome. It results in stimulating delay in endometrial maturation reforms asynchrony between endometrium and the concepts and aids in wound healing by producing a considerable raise in the local secretion of pro-inflammatory cytokines, interleukins and growth factors (Nastri, et al. [9]). The association between local damage to the endometrium and raised reproductive rates in ART cycles was initially reported in 2003 (Barash, et al. [10]; Nastri, et al. [9]; Abdelhamid, AMS [11]). Were firstly described the benefits of endometrial injury in previous failed IUI cycles in their

research published recently in the year 2013 a decade after the first report in the IVF cycle (Barash, et al. [10]). Recent studies and evidence suggest that scratching the lining of the endometrial cavity leads to a ‘repair reaction that could increase embryo implantation rates. This repair mechanism discharges growth factors, chemicals, and hormones. The fresh lining that develops after the procedure is supposed to have better receptive to an implanting embryo and so raise the chances of pregnancy rates (Nastri, et al. [12]). ‘Gene switching’, scientists consider that the genes that are needing for embryos implantation are occasionally not ‘switched on’ when embryos implantation are assumed. Endometrial scratching might ‘switch on’ the genes which are needing to prepare the endometrium for implantation, which raises the opportunity of pregnancy. plausibility to a useful effect from endometrial scratching (Gnainsky, et al. [13]). HB-EGF has played the main function in the reproducing system of

women throughout the menstruation cycle, implantation, and also decidualization (Lim and Dey ^[14]). HB-EGF mRNA is emerged during the menstrual cycle in human being and is mainly restricted to the stromal compartment of the endometrium (Chobotova, et al. ^[15]; Leach, et al. ^[16]). Throughout the process of implantation, HB-EGF is founded on the superficial surface of human luminal epithelial cells and the apices of pinopodes (Stavreus-Evers, et al. ^[17]) and have further a critical role in the blastocyst adherence and growth (Leach, et al. ^[16]). It performs a function in the decidualization of human endometrial stromal cells produced via the highest amounts of insulin-like growth factor binding protein-1, prolactin and triggers stromal cell development through HER1 (Chobotova, et al. ^[15]). Also, it is effective throughout placental development and is found in the decidua, the first and second-trimester chorionic villi, and also in term placenta (Paria, et al. ^[18]). HB-EGF with its receptors facilitates the receptivity, maturation,

decidualization of the endometrium, implantation, and development of both placenta and embryo.

2. Materials and Methods

A randomized prospective comparative study was performed in the High Institute of Infertility Diagnosis and Assisted Reproductive Technologies, Al Nahrain University, from Oct. 2018 to Apr. 2019 which involved a total of 45 women who were treated with Intra-uterine insemination (IUI) technique. These 45 women undergoing IUI-cycles were randomized into two groups. A) Scratching group: 20 IUI patient women had undergone endometrial scratching once between days 19–21 of Oral Contraceptive Pills menstrual cycle (in the cycle before IUI cycle) and blood samples were taken to measure HB-EGF before doing scratch. B) Control group: 25 IUI patient women were the scratching had not been done. For both groups letrozole tab (2.5 mg) for ovarian stimulation was used, follow up by ultrasound till at least 1 to 2 follicles reaching a size of 17-18 mm,

where hCG trigger was given, 34-36 hours later IUI was done. On the day of IUI, for both groups blood samples were taken to measure the level of HB-EGF in serum, ultrasound to measure the endometrial thickness was done. Fourteen days later, the B-HCG test was done in the blood to check pregnancy. Inclusion criteria 1) Age between 20-40 years 2) No endometrial pathology (fibroid or polyp). 3) Normal or mild male infertility 4) Patent uterine tubes. Exclusion criteria 1) All cases of endometrioses. 2) Cases of congenital anomalies of the reproductive system. 3) Generalized or local infection or inflammation. 4) Sever male infertility 5) Closed uterine tubes.

3. Results

Regarding the demographic parameters, the statistical analysis showed that these differences are not significant between scratch and non-scratch groups of IUI patients, concerning age, BMI of the patients and duration of infertility, Type of infertility, cause of infertility, p-value

(0.197, 0.252, 0.231, 0.249, 0.434 respectively), as in Table 1. Although of non-significant results of pregnancy rate between the two groups, P-Value (0.257). Out of 20 patients with endometrial scratching 5 patients get pregnancy (25%), while we have 3 out of 25 patients with a control group get pregnancy (12%) as shown in Figure 1. HBEGF level in the scratch group (386.1 ± 124.7) is significantly higher than the control group (279 ± 189.3) as P-Value was (0.035), as shown in Figure 2. Moreover, the HBEGF level on the day of IUI (455.67 ± 157.34) is significantly higher than before scratching in the scratch group (279.0 ± 124.67) as P-Value was (0.00007), as shown in Figure 3. Additionally, the HBEGF level in pregnant (563.9 ± 163.66) is significantly higher than non-pregnant in the scratch group (406.26 ± 138.89) as P-Value was (0.049), as shown in Figure 4.

Table (1): Comparison of demographic data between scratch and control groups

Variable		Group				P-Value
		Scratch (N = 20)		Non-scratch (N = 25)		
		No.	%	No.	%	
Type of Infertility	Primary	12	60	19	76	0.249 ns
	Secondary	8	40	6	24	
Cause of Infertility	Female	11	55	12	48	0.434ns
	Male	5	25	3	12	
	Unexplained	4	20	10	40	
Mean ± SD						
Age (year)		30.9±6		28.4±6.2		0.197 ns
BMI (Kg/m ²)		26.4 ± 2.7		25.5 ± 2.6		0.252 ns
Duration of Infertility (year)		4.5±1.35		5.1±1.92		0.231ns
*SD: standard deviation, ns: difference is not significant, BMI:- Body Mass Index						

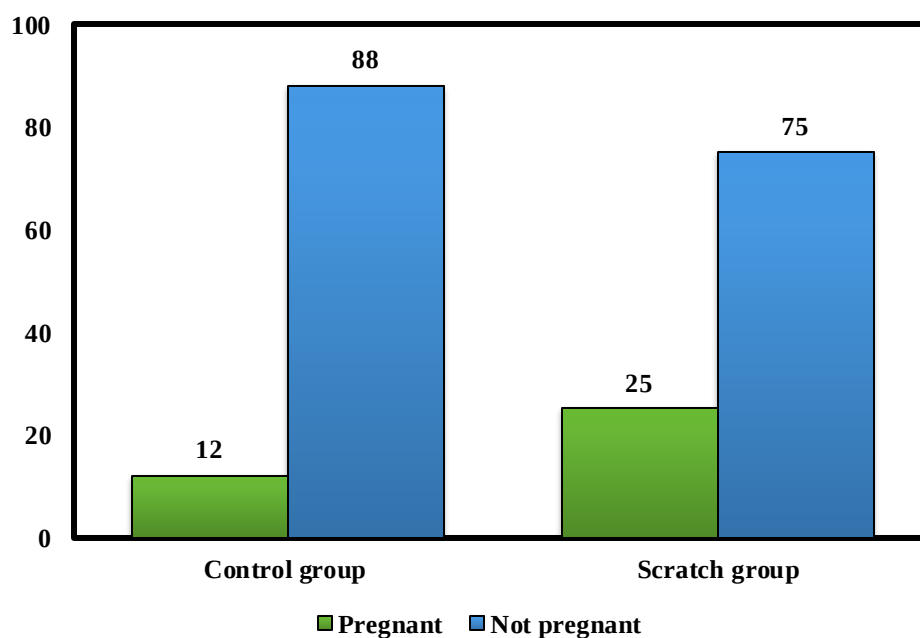


Figure (1): Comparison of pregnancy rate between control and scratch groups.

Heparin binding epidermal growth factor (HBEGF)

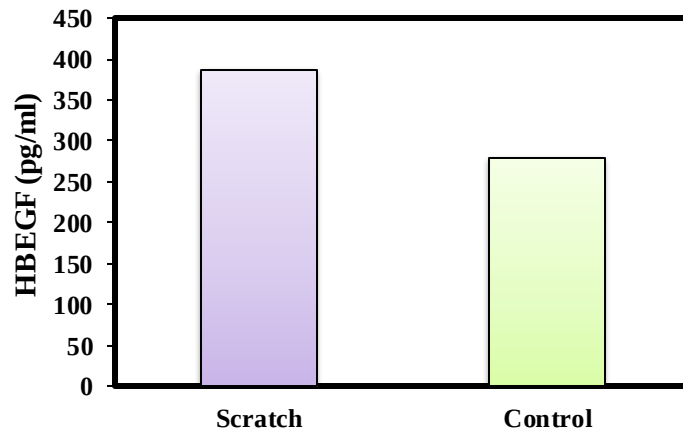


Figure (2): Comparison between HBEGF in scratch and control in study group

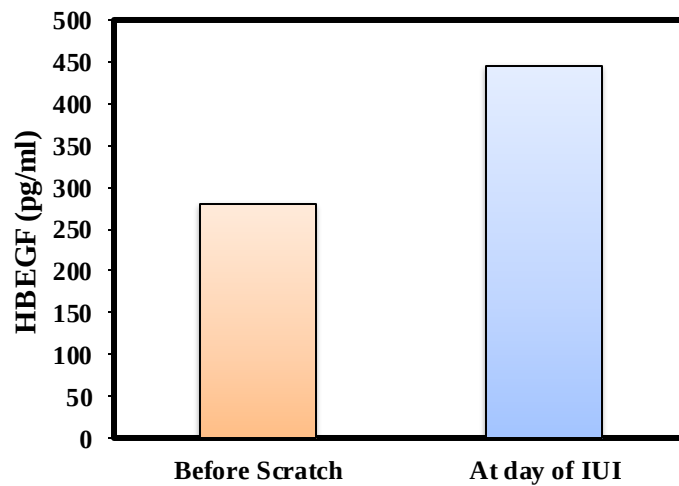


Figure (3): Comparison between HBEGF before scratch and at day of IUI in scratch group

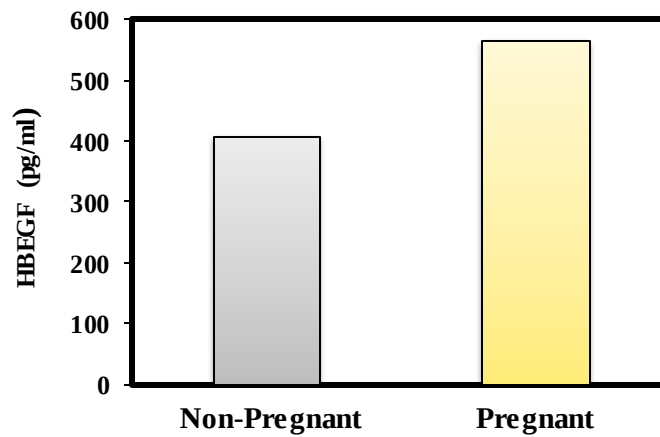


Figure (4): Comparison between HBEGF in pregnant and non-pregnant in scratch group

4. Discussion

Recently endometrial scratch is advised to perform for most women who underwent ART to increase implantation and pregnancy rate as its advantages in stimulation inflammatory reaction that lead to increase secretion of these growth factors and cytokines most likely being the responsible factor for the improved outcome after the endometrial scratching technique. This technique is suggested mostly to women who suffered from recurrent implantation failure to enhance pregnancy opportunity (Potdar, et al. [19]). Many articles had been published on the role of scratching in ART/IUI cycles. The initial study on the effect of endometrial scratching in IUI cycles was carried by (Abdelhamid, AMS [11]). He suggested through his study that patients who performed endometrial injury had significant increases in reproductive outcome whatever it is carry in the proliferative phase of the IUI cycle, or the cycle before IUI, then pregnancy rates just IUI did only. (36 vs. 38 vs. 18%,

respectively). (Wadhwa, et al. [20]) researched the influence of endometrial biopsy (EB) on IUI outcomes in controlled ovarian stimulation (COS) cycles. Their studies appear that there is a considerable maximum clinical pregnancy rate (CPR) among the group of women who did endometrial scratching either in a cycle preceding stimulation or in the same stimulation cycle. There was maximum variation in CPR after the first cycle of ovulation induction and IUI. The advantage of undergoing an intentional endometrial injury is to produce the local discharge of cytokines (such as interleukin 6 and 11), growth-factors (including HBEGF), and adhesion molecules (such as laminin α 4, integrin α 6, matrix metalloproteinase 1, and glycodelin A) and enzymes. (Goel, et al. [21]; Ashrafi, et al. [22]). This acute inflammatory process establishes an angiogenic environment, which could facilitate embryo-uterine crosstalk that leads to optimal implantation (Bahaa Eldin, et al. [23]; Maged, et al. [24]). So as assumed that a 'window of

implantation' has the maximum amount of cytokines, monocytes cells and growth factors in the endometrium (Gnainsky, et al. [13]), in which there might be the maximum effect of the endometrial injury. HBEGF is considered as an important factor to mediate the crosstalk between blastocyst and uterine during the window of implantation, and plays a crucial role in blastocyst implantation (Gnainsky, et al. [13]). Several studies showed that the HBEGF level in the proliferative phase of the menstrual cycle was very low, then gradually increased, and reached a high expression in the window of implantation (Raziel, et al. [25]; Karimzadeh, et al. [26]). These results suggest that HB-EGF in the endometrium may be used as one predictor for implantation receptivity and pregnancy outcome.

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Author Contribution

Blawa ED, performed the study, Al-Obaidi MT, and Abdulhameed WA, supervised the work.

Conflict of Interest

The authors declare no conflict of interest.

Ethical Clearance

The study was approved by the Ethical Approval Committee.

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Biography



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