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The Effect of Single Endometrial Curettage on Pregnancy Rate in Unexplained Infertility in Primary Care Setting

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Author's contribution

This whole work was carried out by author FAR.

Original Research Article

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ABSTRACT

Aims: To examine the effect of single endometrial curettage (EC), performed during the menstrual period in primary clinical care setting, on pregnancy rate (PR) in women with unexplained infertility and subgroup analysis based on age and primary and secondary infertility.
Study Design: Randomized controlled clinical study.
Place and Duration of Study: Private practice setting, Baghdad, between February 2009 and January 2012.
Methodology: A total of 197 couples aged 20-40 years with unexplained infertility were randomly allocated into two groups: group A comprised 110 women who underwent EC during the menstrual period; and group B included 87 women, who represent the control group, with no EC done. Both groups received no further fertility treatment. The main outcome measured was cumulative clinical (PR) during 6 months after the endometrial curettage.
Results: PR was higher in control group compared to EC group (48.3% vs. 45.5%), and in secondary infertility in women aged 31-40 years (75% vs. 58.8%), and in primary infertility in women aged 20-30 years (35% vs. 5.4%) and 31-40 years (25% vs. 5.5%).
Conclusion: EC may improve PR in couples with primary unexplained infertility independent of the age group, and in secondary infertility age group 31-40 years. Adequately powered studies are suggested to confirm or refute the findings.

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Keywords: Endometrial curettage; pregnancy rate; primary care; unexplained infertility.

1. INTRODUCTION

The term unexplained infertility describes the condition of infertile couples, especially when the currently utilized investigations including semen analysis, ovarian condition and patency of tubules have shown no abnormality [1]. The incidence of such condition was estimated to be 30-40% among infertile couples [2]. In most cases of unexplained infertility, although no practical solutions for repeated implantation failure have emerged, an improved ability to control the endometrial environment for implantation promises to have a significant and positive impact on the chances of conception. Among the various potential causes of repeated implantation failure, uterine factors (e.g., thin endometrium, poor endometrial receptivity, and immunological incompatibility) have received the most attention in recent years [3]. Different causes had been already proposed to define the unexplained infertility, including cervical, uterine, ovulatory, peritoneal, immunological, endocrinological, genetic defects and reproductive physiology disturbances, which had been proposed as potential etiologies [4,5]. However, none of the previously suggested causes was exclusively able to explain all cases of reproductive failure. Generally, many types of interventions are widely adopted for managing unexplained infertility, including expectant management, intrauterine insemination with ovarian stimulation and *In vitro* fertilization (IVF) [6,7]. Endometrial curettage (EC) was defined as a scraping of the endometrium to obtain tissue for histologic evaluation; however, this intervention has been suggested to boost embryo implantation following recurrent implantation failure after IVF [8,9]. Many investigators suggested that endometrial curettage (EC) could have a favorable endometrial healing effect on the implantation process, which may trigger the release of many biochemical mediators involved in the enhancement of implantation [8,10]. Meanwhile, since impaired endometrial receptivity represents the most expected cause of subfertility in a group of couples diagnosed with unexplained infertility [11,12], EC may be helpful as a treatment approach for those couples. Various approaches have been proposed to improve endometrial receptivity and implantation rate, with local injury to the endometrium undergoing evaluation. Endometrial curettage has been associated with increased implantation rate in an increasing number of studies [13,9]. In the present study, the impact of single EC, performed during the menstrual period, on patients with unexplained primary and secondary infertility aged 20-40 years was evaluated in primary care private setting.

2. MATERIALS AND METHOD

2.1 Study Patients

This was a prospective study conducted in the period from February 2009 to January 2012. A total of 899 infertile couples diagnosed with primary or secondary infertility and categorized as unexplained infertility among those attending a private outpatient clinic in Baghdad city were approached and asked to participate in the study. Of these, 197 couples agreed to participate. Inclusion criteria were women aged between 20 and 40 years with at least 1 year of infertility, regular menstruation with the length of the cycle between 22 and 34 days and ovulation confirmed by appropriately timed mid-luteal progesterone (>5ng/ml), fertile semen variables (according to WHO criteria 1999), and bilateral tubal patency (demonstrated by laparoscopy or hystero-salpingography). The exclusion criteria include male factors for infertility, tubal obstruction and period of follow up less than six months. A written informed consent was obtained from the participants. The Institutional Ethics

Committee Review Board of Alkindy College of Medicine, University of Baghdad, has approved this prospective study. Institutional Review Board approval was obtained in accordance with the Helsinki Declaration of 1998 on clinical experiments.

2.2 Randomization and Interventions

Based on each alternate week referral to the clinic, the patients were assigned to one of two groups, group A and group B. Group A was (intervention group) (*n*=110) and group B (control group) (*n*=87). Written consents were taken from both groups. Patients were blinded for their allocation. Women were followed up for 6 months after randomization, and none of the patients received any fertility treatment during the follow-up time. Endometrial curettage was performed using endometrial curette (Gynetics medical products NV, Rembert Dodoeness, Belgium) in the intervention group (group A) in an outpatient setting. The procedure was conducted at the 1st to 3rd days of the spontaneous menstrual cycle. A similar placebo procedure was conducted at the first day of spontaneous menstrual cycles for women in the control group (group B). After explaining the procedure, the patient was kept in lithotomy position and the cervix is exposed by a Casco speculum; then the disposable endometrial curette passed to the fundus and the stellate is pulled throughout with rotation during pulling. The curette then emptied in formalin and send for histopathology. If there was any difficulty in introducing the curette or the woman experienced intolerable pain the procedure is stopped. All women with EC received paracetamol tablets 1000 mg before the procedure; no antibiotics were used after the procedure. The women were asked about the convenience of the procedure. Couples in both groups were asked to phone a contact person whenever there was a missed period. Couples were advised to practice sexual intercourse according to their convenience. A pregnancy test was performed few days after a missed period. Clinical pregnancy was diagnosed using serum human chorionic gonadotropin estimation and confirmed by the presence of an intrauterine gestational sac on ultrasonography. The measured outcome was cumulative pregnancy rate during 6 months after the endometrial curettage. Pregnancy rates were compared in both groups in accordance with sub classification based on age groups or the infertility type (20 to 29 years, 30 to 39 years, primary and secondary infertility). Miscarriage rate was not followed because of the short follow up period after the occurrence of pregnancy (6 months from the EC date).

2.3 Statistical Analysis

The Statistical Package for the Social Sciences (SPSS 15.0) software was used for data analysis. The baseline characteristics of the two groups of patients were compared using the Mann–Whitney test. Differences in the pregnancy outcomes of the study and control groups were analyzed using the chi-square test. The rate of clinical pregnancy was expressed as the ratio of the number of patients in whom clinical pregnancy was diagnosed to the total number of patients within the group. A *p*-value of <0.05 was considered statistically significant.

3. RESULT

Table 1 showed that there was no significant differences between groups A and group B regarding age, infertility period, number of visits to the clinic, and the previous follow up period before inclusion. They show significant differences only in the incidence of primary infertility, where group A (intervention group) demonstrates significantly higher incidence of primary infertility compared to controls (group B). In Fig.1, after performing EC in group A,

the PR in group B appears to be significantly greater compared to group A (48.3%vs.45.5%). When the patients were sub-grouped according to the type of infertility (secondary or primary) within the two major groups, the PR within the primary infertility subgroup was significantly higher in group B compared to group A (38.5%vs.34.6%) Fig.2. Mean while, group A shows significantly higher PR compared to group B (68.8%vs.62.8%) in the secondary infertility subgroup. In Fig. 3, when the patients sub-grouped according to ages, no significant differences were reported between group A and group B within the age group 20-30 years (49.4% vs .52.6%, $p>0.05$), while group A demonstrates significantly higher PR compared to group B (45.5% vs. 36.7%, $p<0.05$) within the age range of 31-40 years. When the patients were sub-grouped according to the type of infertility (primary or secondary) within the age ranges followed in the study, Fig. 4 indicates that primary infertility within the age range 20-30 years, EC results in greater PR in group A compared to controls (35% *vs.* 5.4%, $P<0.05$). Meanwhile, when secondary infertility was considered within the same age range, group B showed significantly higher PR (76.4 vs. 47.6%) compared to group A Fig. 4. Fig. 5 demonstrates the PR in patients aged 31-40 years, where those with primary infertility in group A showed significantly higher PR after performing EC (25% vs. 5.5%) compared to their comparators in group B. Meanwhile, regarding secondary infertility patients within the age range 31-40 years, group A also showed significantly higher PR (75% vs. 58.8%) compared to group B.

Table 1. Characteristics of patients in both groups

Parameters	Group A *n*=110	Group B *n*=87	*P* value
Age (year)	27.7±7.6	28.3±8.5	0.16
Infertility period (year)	4.47±0.91	3.5±0.72	0.18
Primary infertility (%)	(87) 71	(43) 59.5*	0.04
No. of visits	7.4±1.3	9.4±1.8	0.082
Previous follow up (Months)	14.3±2.4	14.7±3.1	0.23

Values are presented as mean±SD; n= number of subjects

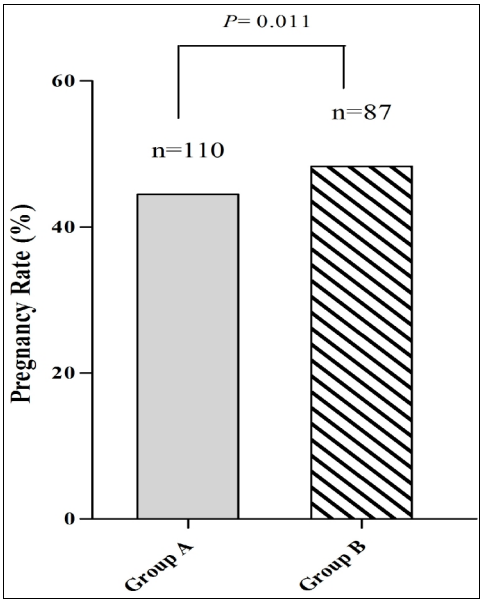

Fig. 1. Pregnancy rate (%) after endometrial curettage (EC) in patients with unexplained infertility; A:EC done; B:control

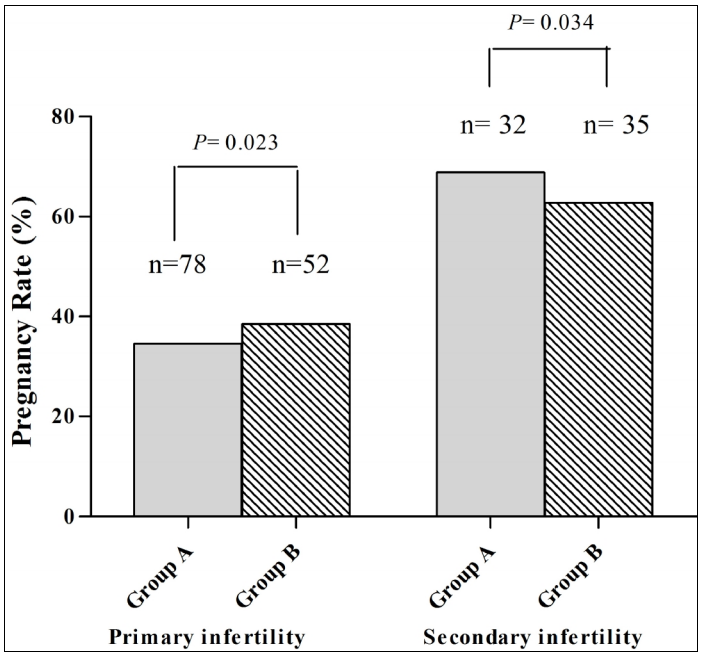

Fig. 2. Pregnancy rate after endometrial curettage (EC) in patients with unexplained infertility randomized according to the type of infertility; A:EC done; B:control

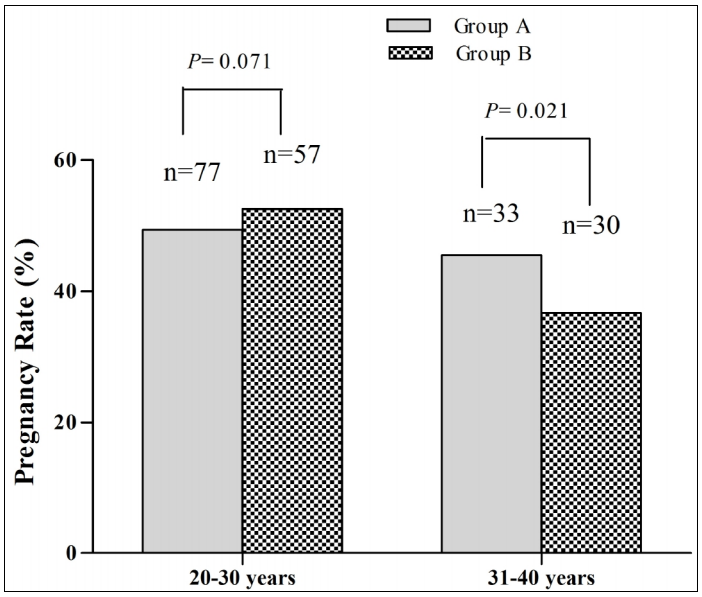

Fig. 3. Pregnancy rate after endometrial curettage (EC) in patients with unexplained infertility randomized according to age groups; A:EC done; B:control

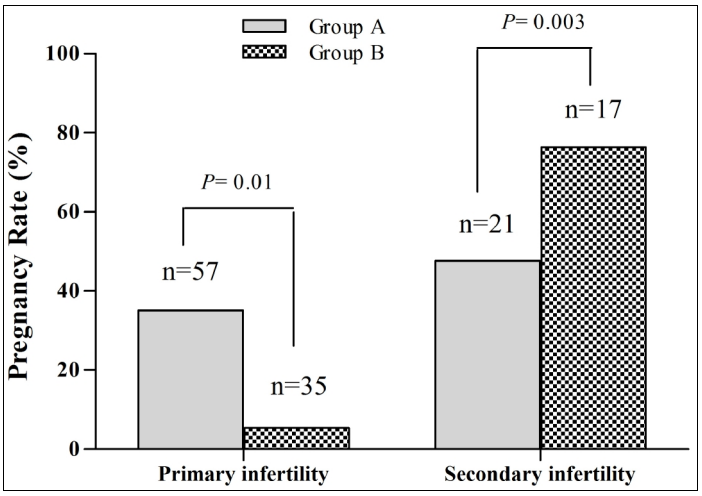

Fig. 4. Pregnancy rate after endometrial curettage (EC) in patients with unexplained infertility randomized according the type of infertility within the age group 20-30 years; A:EC done; B:control

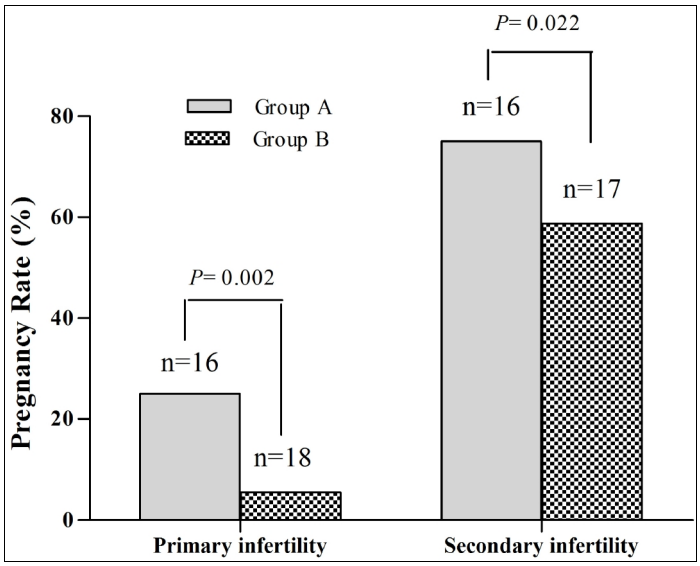

Fig. 5. Pregnancy rate after endometrial curettage (EC) in patients with unexplained infertility randomized according the type of infertility within the age group 31-40 years; A:EC done; B:control

4. DISCUSSION

Endometrial injury may have a beneficial role in implantation and improves the pregnancy rate. However, there were still many unanswered questions regarding patient selection, timing, technique and number of endometrial curettages needed. The currently available observation has led to the hypothesis that endometrial injury might improve pregnancy in patients with unexplained infertility. This may be attributed to poor receptivity of the

endometrium that follows inflammatory responses and changes in cytokine production in the endometrium [14,10]. Unfortunately, the present study do not reveal evidence consistent with the previously mentioned idea, where the control group demonstrates a slightly greater PR (but significantly different, p=0.04) compared to the intervention group before considering sub-classification according to age and type of infertility. This could be attributed to the inconsistency in patients sample between the groups (more primary infertility in the study group 71% vs. 59.5%) and the influence of other factors, including the age and type of infertility in this respect. According to the available data, most of the studies in this regard were performed on patients with impaired endometrial receptivity and during ongoing IVF process [15-17]. The present study represents a pioneer work that focus on exploring the expected benefits of single EC, done during the menstrual period, in unexplained infertility within a primary care setting. Additionally, by incorporating the intervention process into the primary clinic care, the present study enabled us to compare differences not only between treatment groups but also between different age groups and the type of infertility. Accordingly, the results indicated that within the subclass of secondary infertility, single EC results in higher PR (independent on age group); while in primary infertility subclass, slight significant increase in PR was reported in control group Fig. 2. This outcome could be attributed to the inconsistency of fertility subclass between the two groups, and the author recommends further work in this regard. Meanwhile, when the age factor was considered, single EC results in greater and highly significant PR in the intervention group compared to control within the age group 31-40 years; while in patients within the younger group (20-30 years) the results appeared comparable (p>0.05). These results can only be explained when enough data are available about the physiological influence of age on the response of the endometrium to the inflammatory challenge. Unfortunately, no information retrieved from any database in this regard and this point deserves further investigations. When both infertility subclass and age were considered, the results showed that the intervention group demonstrates significantly higher PR within the primary infertility in both age groups; while in secondary infertility subclass, similar outcome was clear only in the age group 31-40 years. Such outcome might be attributed to the high and significant incidence of primary infertility reported in the intervention group compared to the control group. Barash et al. studied the effect of endometrial injury on 134 women with repeated implantation failure; they found significantly higher clinical pregnancy and implantation rates in the endometrial curettage group compared to the control group [6]. Meanwhile, Raziel et al. also studied the effect of endometrial injury and they found a statistically significant difference in the clinical pregnancy rate in the endometrial biopsy group compared to the control group [13]. The difference between Barash et al. and Raziel et al. is that the former took four endometrial biopsies while the latter took only two endometrial biopsies [13,6]. Both investigators found statistically significant differences in the PR in spite of the difference in the number of curettages taken. A third group [18], worked on repeated implantation failure and the effect of endometrial injury on intra-cytoplasmic sperm injection (ICSI) outcome; they just took a single endometrial injury in cases with irregular endometrial echo by ultrasound, and found marked improvement in the ICSI outcome parameter. From the above-mentioned studies, it was noticed that the number of endometrial injuries did not affect the beneficial effect on outcome parameter in repeated implantation failure cases. Accordingly, taking single endometrial curettage was followed in the present study to avoid the cost of multiple curettages and the risk of infection; also, it was done during the menstrual period to avoid doing the procedure on a pregnant uterus if it was done in the luteal phase. The outcome of the present study, within the primary infertility subclass, was in tune with another one performed at the same time, where Gibreel et al. utilized single endometrial scratching to improves PR in couples with unexplained infertility [19]. The outcome of the present study can be considered of significant importance because such intervention protocol may be of

value as a standard procedure for treating unexplained infertility, since we study the effect of EC in women with unexplained infertility according to their age and type of infertility and it is one of the pioneer studies in this field. Nevertheless, this proof-of-concept study was performed with a relatively small group of patients, and there were differences in incidence of primary infertility between the two study groups. Future studies with larger sample of patients and proper matching for many variables between groups are needed to validate the current findings.

5. CONCLUSION

Single EC performed during menstrual period improves pregnancy rate in patients with primary unexplained infertility aged 20-30 and 31 to 40 years, and secondary unexplained infertility aged 31-40 years; it may preferably be done early in the management of these infertile couples.

CONSENT

The author declares that 'written informed consent was obtained from each patient for publication of this case report**.**

ETHICAL APPROVAL

The author hereby declares that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1998 Declaration of Helsinki.

COMPETING INTERESTS

The author has declared that no competing interests exist.

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