Case Series

The Effect of Endometrial Polyp Resection by Office Hysteroscopy during In Vitro Fertilization/Intracytoplasmic Sperm Injection Treatment Cycle on Pregnancy Rate  A Series of 25 Cases

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Aim: This study aims to evaluate the effect of endometrial polyp resection by office hysteroscopy during in vitro fertilisation/intracytoplasmic sperm injection (IVF/ICSI) treatment cycle on pregnancy rate. Setting and Design: A retrospective observational study (case series). Materials and Methods: Twenty-five patients from a total of 346 patients that started IVF/ICSI treatment due to different causes of infertility over the period from January 2018 to December 2019 underwent an office hysteroscopy during ovarian stimulation (day 7–8) due to suspected endometrial polyp by transvaginal ultrasound and confirmed at day 7 of ovarian stimulation were retrospectively investigated. Results: Eighteen patients from the 25 patients that started IVF/ICSI treatment; endometrial polyp was confirmed by office hysteroscopy and resected, egg collection performed after 4–5 days after the hysteroscopy, embryo transfer done Double ET) at Day 3 and 5, the clinical Pregnancy rate was 56% (10 from the 18). No hysteroscopy‑related adverse events were reported. Conclusion: Office hysteroscopy during ovarian stimulation in the IVF/ICSI treatment cycle may be useful in confirming the diagnosis and resection of endometrial polyp suspected by transvaginal ultrasound and is safe on the endometrium in terms of receptivity and improvement of the pregnancy rate. As the sample size of our study is relatively small, a well‑designed large RCT is required to confirm our results before clinical advice is released.

Keywords: Endometrial polyp, infertility, in vitro fertilization and hysteroscopy

INTRODUCTION

Pregnancy to occur naturally or through assisted reproductive technology (ART) it needs three things: a healthy sperm to fertilise an ovum that released every month (in the fallopian tubes for natural pregnancy or in the laboratory in in vitro fertilization/intracytoplasmic sperm injection [IVF/ICSI]) and a healthy place for the embryo to implant there (a healthy receptive endometrial cavity), so any defect in one of the above three pregnancy requirements will affect the occurrence of the pregnancy in both types, the natural one or that resulted from ART.

The uterine cavity hosts the suitable environment where implantation, placentation and subsequent conception maintenance occur. Implantation is a complex not fully understood process that needs an excess of regulatory molecules such as protease, cytokines and chemokines.[1] Uterine secretions provide the optimum PH, temperature, viscosity and other factors that are essential for spermatozoa travel into the uterus and

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subsequent implantation to occur.\textsuperscript{[2]} Uterine anomalies and acquired pathologies such as polyps, fibroids and synechiae are known to have a role in infertility, implantation failure and recurrent miscarriages.\textsuperscript{[3,4]} The incidence of endometrial polyps in women with infertility at reproductive age about 15\%.\textsuperscript{[5]} It was found that 32\% of hysteroscopies before IVF have shown endometrial polyps in a study of 1000 patients suggesting increased prevalence among infertile women.\textsuperscript{[6]} Endometrial polyps’ diameter ranges from few millimetres to several centimetres, with polyps less than 2 cm seems not adversely affecting pregnancy rate.\textsuperscript{[7]} Endometrial polyps are classified according to their location into uterotubal junction (8.0\%), posterior uterine wall (32.0\%), anterior uterine wall (15.4\%) and lateral uterine wall (9.2\%) and they might be more than one with mixed locations. With uterine polyps showing the most effect on infertility as they impede sperm transport, with pregnancy rate after polypectomy of (57.4\%), while the least effecting were polyps in the anterior uterine wall with a pregnancy rate of (14.8\%) after polypectomy.\textsuperscript{[8]} In a study that examined 34 infertile women who were found to have an endometrial polyp(s), 50\% pregnancy rate was gained after doing hysteroscopic polypectomy, showing that functional polyps even the small ones affect fertility and its removal might enhance and increase the following conceptions’ performance.\textsuperscript{[9]} Hysteroscopy is highly recommended for screening for endometrial polyps as it shows a sensitivity rate of 95.3\% and a specificity rate of 95.4\%.\textsuperscript{[10]} In our study, we are investigating endometrial polypectomy using office hysteroscopy during IVF/ICSI treatment cycles and its effect on pregnancy rate.

**Materials and Methods**

Of 346 patients that started IVF/ICSI treatment due to different infertility causes over the period from January 2018 to December 2019, the controlled ovarian stimulation outcome for the IVF/ICSI cycles is shown in Table 1. 25 patients (none of them had a hysteroscopy as a part of infertility investigation before) were suspected to have endometrial polyps during the first assessment in our clinic (size of polyp(s) 0.6–1.2 cm) as an incidental finding during baseline transvaginal ultrasound scan that usually performed at days 2–3 of the menstrual cycle to assess the endometrial thickness and the ovaries just before starting IVF treatment in the same cycle. The endometrial polyp, if present, may grow and increase in size during ovarian stimulation due to the supra-physiological increase in E2 level\textsuperscript{[7]} secreted by the growing follicles. The presence of endometrial polyp was confirmed at day 7 of ovarian stimulation (the first scan after starting ovarian stimulation).

| Variable                                  | Average |
|-------------------------------------------|---------|
| Total FSH dose given                      | 225     |
| Average COS days                          | 10      |
| Number of follicles                       | 13      |
| E2 Level (average)                        | 2200 pg/dl |
| Number of retrieved oocyte                | 11      |
| Number of M2 oocyte                       | 9       |
| Number of fertilised embryos              | 7       |
| Number of E.T                             | 2       |

FSH=Follicle stimulating hormone, COS=Controlled ovarian stimulation, ET=Embryo Transfer

Some patients have limited time and the cycle needs to be completed due to different reasons mainly if the couple is from outside the country and has limited time. In case of limited time this study shows an alternative option to cancelling the cycle. These patients were counselled regarding the effect of the endometrial polyp on pregnancy rate and the benefit from polyp resection by office hysteroscopy and they agreed to have a diagnostic office hysteroscopy and endometrial polyp resection if present. We used a rigid 0° view 2.9 mm diameter hysteroscope with working channel (Karl Storz.), normal saline used as a distension media (500–750 ml) at day 7–8 of ovarian stimulation, as the endometrium still not thick and allows better visualisation of the cavity to detect any existing pathology and we theoretically proposed that if done later may affect the endometrial receptivity. 18 cases were confirmed to have an endometrial polyp(s) that were resected by cold knife (scissor). 4–5 days later to hysteroscopic endometrial polyp resection, no hysteroscopy-related adverse events were reported. Eggs were collected 36 h after the trigger injection, and two embryos transferred at day 3 or 5 as the last step in the treatment.

**Results**

Twenty-five patients with suspected endometrial polyp by transvaginal ultrasound underwent hysteroscopy during the IVF treatment cycle.

Eighteen patients were diagnosed with endometrial polys larger than 0.5 cm in diameter. Seven patients had no polyps.

Hysteroscopic polypectomy was performed for all 18 patients before egg collection with informed consent. After 7–10 days, 2 embryos were transferred to all the patients. The patients’ characteristics are shown in Table 2.

Ten patients had a clinical pregnancy with a 56\% clinical pregnancy rate [Table 3]. There were seven singleton pregnancies, two twin pregnancies, one patient had a blighted ovum and seven patients had unsuccessful cycles [Table 2].
Table 2: Patient characteristics

| Case | Age | Cause of infertility | Day of hysteroscopy | Days between hysteroscopy and ET | Previous IVF cycles |
|------|-----|----------------------|---------------------|---------------------------------|--------------------|
| 1    | 23  | Male factor          | Day 7               | 8 days                           | Two (unsuccessful) |
| 2    | 33  | PCOS                 | Day 6               | 10 days                          | One (successful)   |
| 3    | 29  | Tubal, PCOS          | Day 8               | 9 days                           | One (successful)   |
| 4    | 39  | Secondary infertility| Day 7               | 10 days                          | None               |
| 5    | 34  | PCOS                 | Day 7               | 9 days                           | One successful and one unsuccessful |
| 6    | 27  | Unexplained          | Day 8               | 9 days                           | Two (unsuccessful) |
| 7    | 40  | Secondary infertility| Day 6               | 10 days                          | one ended by miscarriage |
| 8    | 28  | Male factor          | Day 7               | 10 days                          | Two ended by miscarriage |
| 9    | 29  | Male factor, PCOS    | Day 6               | 10 days                          | None               |
| 10   | 30  | Unexplained, secondary| Day 7              | 9 days                           | None               |
| 11   | 34  | PCOS                 | Day 6               | 10 days                          | One (successful)   |
| 12   | 22  | Male factor          | Day 7               | 9 days                           | Two (unsuccessful) |
| 13   | 32  | Unexplained          | Day 7               | 10 days                          | One (successful)   |
| 14   | 38  | PGD, gender selection| Day 8               | 9 days                           | Two (no ET)        |
| 15   | 41  | PGD, gender selection| Day 8               | 7 days                           | One (unsuccessful) |
| 16   | 33  | PGD, gender selection| Day 6               | 10 days                          | None               |
| 17   | 27  | PCOS, male factor    | Day 7               | 9 days                           | None               |
| 18   | 36  | PGD, gender selection| Day 6               | 9 days                           | One (unsuccessful) |

IVF=In vitro fertilisation, PCOS=Polycystic ovarian syndrome, PGD=Pre-implantation genetic diagnosis, ET=Embryo transfer

Table 3: Polyp characteristics and cycle outcome

| Case number | Polyp site          | Polyp size (mm) | Number of polyps | Pregnancy | Day of hysteroscopy | Days between hysteroscopy and ET | Previous IVF cycles |
|-------------|---------------------|----------------|------------------|-----------|---------------------|----------------------------------|--------------------|
| 1           | Lateral wall        | 12             | Single           | Positive  | Day 7               | 8 days                           | Two (unsuccessful) |
| 2           | Posterior wall      | 10             | Single           | Negative  | Day 6               | 10 days                          | One (successful)   |
| 3           | Ostial (utero-tubal)| 11             | Two              | Positive  | Day 8               | 9 days                           | One (successful)   |
| 4           | Fundal              | 9              | Single           | Positive  | Day 7               | 10 days                          | None               |
| 5           | Lower segment       | 10             | Single           | Negative  | Day 7               | 9 days                           | One (successful)   |
| 6           | Ostial (utero-tubal)| 11             | Bilateral        | Positive  | Day 8               | 10 days                          | Two (unsuccessful) |
| 7           | Lateral wall        | 8, 6           | Two              | Negative  | Day 7               | 9 days                           | One (successful)   |
| 8           | Fundal              | 12             | Single           | Positive  | Day 7               | 10 days                          | Two (unsuccessful) |
| 9           | Lateral wall        | 9              | Single           | Negative  | Day 7               | 10 days                          | None               |
| 10          | Lateral and posterior wall | 11 | Two | Positive | Day 7 | 9 days | One (successful) |
| 11          | Fundal              | 8              | Single           | Negative  | Day 7               | 10 days                          | Two (unsuccessful) |
| 12          | Ostial (utero-tubal)| 12             | Two              | Positive  | Day 7               | 9 days                           | None               |
| 13          | Lower segment       | 10             | Single           | Positive  | Day 7               | 9 days                           | None               |
| 14          | Endocervical        | 11             | Single           | Negative  | Day 7               | 8 days                           | One (successful)   |
| 15          | Fudo-lateral        | 12             | Single           | Positive  | Day 7               | 9 days                           | None               |
| 16          | Anterior wall       | 10, 9          | Two              | Positive  | Day 8               | 10 days                          | None               |
| 17          | Anterior wall       | 9              | Single           | Negative  | Day 7               | 9 days                           | None               |
| 18          | Ostial (utero-tubal)| 8              | Single           | Negative  | Day 6               | 9 days                           | One (successful)   |

Discusssion

Hysteroscopy is frequently performed in infertile women and thought to improve pregnancy rates as intrauterine pathology has been reported in up to 25% of infertile women having IVF treatment. Endometrial polyps are believed to have a negative impact on the pregnancy rate by influencing endometrial receptivity and increases miscarriage rate as well, and that hysteroscopic polypectomy increases pregnancy rate if done prior to IVF treatment cycle. There is a debate about the safety of doing hysteroscopic polypectomy during the IVF treatment cycle and its effect on pregnancy rate. Some researchers showed a positive impact and increase in fertility rate. One study has shown that the pregnancy rate was 44.4% (4/9) and there was only one miscarriage (12) another research has shown a pregnancy rate of 50% (3/6) after hysteroscopic polypectomy was done during the IVF treatment cycle. A possible mechanism by which endometrial injury (polypectomy) might increase pregnancy rate is that by improving endometrial receptivity. A study showed that biopsy made before starting the IVF treatment cycle increased the chance of implantation, clinical pregnancy and live births by two folds. Another study has shown that a high amount of cytokines, growth factors and other inflammatory mediators used in the wound healing process after polypectomy are involved in the implantation process. Thus, the effect of endometrial polyp resection by hysteroscopy during the IVF treatment cycle appeared to have a positive impact on the pregnancy rate.

Hysteroscopic polypectomy within less than 5 days before embryo transfer was found to be associated with a negative impact regarding pregnancy rates. Location of polyp could also influence pregnancy rate as it was demonstrated by Yanaihara et al. who showed that excision of polyps found in the uterotubal junction improved pregnancy rate more significantly compared to other locations, as these polyps could impede sperms or embryos migration, which could be explained as a mechanical barrier to sperm transport and embryo implantation, another hypothesis is through intrauterine inflammation or due to the increased production of...
inhibitory factors as glycodelin.[8] As glycodelin, a glycoprotein, has an inhibitory effect on sperm-oocyte conjugation and natural killer cells activity, normally at its lowest values 6 days before and 5 days after ovulation, low levels of glycodelin aid fertilization but the normal increased levels 6 days after ovulation inhibit NK cells activity leaving the endometrium capable for implantation, thus any increase in glycodelin levels by polyps at that time will affect the receptivity of the endometrium and subsequent failure of implantation.[16]

Due to the lack of a large studies on the safety of hysteroscopic polypectomy during IVF treatment cycles, RCTs in future might be needed to confirm its safety and benefit.

Limitations of the study
1- Our study is a retrospective case series not RCT study
2- The sample size in our study is relatively small to draw strong evidence of our results.

Conclusion
Office hysteroscopy during ovarian stimulation in IVF/ICSI treatment cycle may be useful in confirmation of the diagnosis and resection of endometrial polyp suspected at day 2–3 of menstrual cycle and confirmed at day 7 of ovarian stimulation by transvaginal ultrasound. Hence, we may conclude that it is a safe intervention on the endometrium in terms of receptivity and improvement of the pregnancy rate if performed at least one week before the embryo transfer to provide a time for the endometrium to recover from the mechanical injury. We hope large RCTs in the future will confirm our findings to provide appropriate a clinical advice.

Compliance with ethical standards
Ethical approval: ‘All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.’

• Ethical committee approval: Approved (IRB 2/8/2021)
• Informed consent: informed consent was obtained from all patients.

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Conflicts of interest
There are no conflicts of interest.

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