

Hysteroscopy Findings after Two Previous Failed *In vitro* Fertilisation Cycles: A Case for Routine Hysteroscopy before *In vitro* Fertilisation?

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Abstract

Background: The success rates of *in vitro* fertilisation (IVF) cycles have remained low. The condition of the uterus plays a significant role in the IVF treatment outcome. Unfortunately, some uterine pathologies are missed on routine ultrasound scans performed before IVF. **Objective:** To document the hysteroscopy findings following normal ultrasound scan endometrial assessments in women with two previous failed IVF cycles, seen at a private fertility unit. **Materials and Methods:** This is a retrospective descriptive study. The electronic medical records were retrieved for patients who underwent hysteroscopy after two consecutive failed IVF cycles despite normal ultrasound scan findings between April 1, 2010, and March 31, 2017. Data, including age, findings at hysteroscopy, and IVF/intracytoplasmic sperm injection treatment outcomes following hysteroscopy, were documented. The results are presented as frequency distribution tables. **Results:** A total of 77 patients had normal ultrasound scan findings after two previous failed IVF cycles, requiring a hysteroscopy during the study period. This represented 7.7% of the 1,002 hysteroscopies performed during the same period. The age range was 25–54 years, with a mean age of 37 ± 4.3 years. A majority of the women (59, 76.6%) had no pathology on hysteroscopy, while 14 (18.2%) had intrauterine adhesions. Three patients (3.9%) had endometrial polyps, and one patient (1.3%) had a subseptate uterus. Following hysteroscopy, 24 patients (31.2%) became pregnant, 29 patients (37.6%) had failed IVF cycles, while the remaining 24 patients (31.2%) were lost to follow up. **Conclusion:** This study has added to the body of evidence that suggests that routine hysteroscopy before IVF is capable of picking up missed pathologies that might otherwise negatively impart IVF success rates. More RCT are, however, needed to determine the effect of routine hysteroscopy on IVF treatment outcomes.

Keywords: *In vitro* fertilisation, intrauterine adhesions, routine hysteroscopy

INTRODUCTION

Since the birth of Louise Brown in 1978, technologies involving *in vitro* fertilisation (IVF) have grown in leaps and bounds. The number of assisted reproductive technology (ART) cycles performed worldwide has continued to rise.¹ In 2015, ART contributed to 1.7% of all infants born in the United States of America.² Despite this, the success rate of each IVF and intracytoplasmic sperm injection (ICSI) cycle remains low.¹

Embryo aneuploidy remains one of the most important contributors to poor IVF outcomes.³ However, the condition of the uterus also plays a significant role in the success of IVF.^{4,5} Conditions such as polyps, fibroids, intrauterine adhesions, and uterine anomalies are known to interfere with fertility because they negatively impact sperm migration and embryo

implantation.⁶ Despite advances in technology, ultrasound scanning has been shown to miss certain uterine/endometrial pathologies that can be detrimental to IVF success.⁶ Diagnostic hysteroscopy remains the gold standard for evaluating the uterine cavity.⁷ There is no consensus regarding whether routine hysteroscopy improves the IVF success rate. While a 2014 meta-analysis showed that increased live birth rates

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were achieved after routine hysteroscopy in women scheduled for their first IVF cycle, another randomized controlled trial (RCT) published in 2015 showed a 70% improvement in the pregnancy rate in women scheduled for their first ICSI treatment cycle who underwent hysteroscopy before the treatment cycle.^{8,9} In contrast, one RCT (the TROPHY trial) that investigated the role of hysteroscopy in women with two to four failed IVF cycles concluded that hysteroscopy did not improve live birth rates.¹⁰ A recent multicentre RCT also came to a similar conclusion.¹¹

We, therefore, set out to document the hysteroscopic findings in women with normal ultrasound scan findings and two previous failed IVF cycles seen at a fertility unit in the Niger-Delta region of Nigeria, a country with highly restrictive abortion laws.

Objectives

To document the hysteroscopy findings following normal ultrasound scan endometrial assessments in women with two previous failed IVF cycles, seen at a private fertility unit.

MATERIALS AND METHODS

This is a retrospective descriptive study. The electronic medical records were retrieved for patients who underwent hysteroscopy after two consecutive failed IVF cycles despite normal ultrasound scan findings between April 1, 2010, and March 31, 2017. All the medical records were available. Data, including age, findings at hysteroscopy, and IVF/ICSI treatment outcomes following hysteroscopy, were documented. The results are presented as frequency distribution tables.

The choice of IVF treatment protocol was determined by the perceived response of the patient. While high responders used the antagonist protocol, normal and poor responders were managed with the gonadotropin-releasing hormone agonist (GnRH agonist) protocol.

The unit's protocol for endometrial assessment before the first IVF includes performing a transvaginal ultrasound scan during the proliferative phase of the menstrual cycle, using a two-dimensional (2D) vaginal probe with the endometrial cavity visualized in the longitudinal and transverse planes. All ultrasound scans were performed by a single certified sonologist with over 13 years of experience. All suspicious endometria were subjected to either hysterosalpingography (HSG) or saline infusion sonography (SIS). Hysteroscopy was subsequently performed when any abnormality was found. Following a failed IVF cycle, the same procedure for endometrial assessment was followed before a second, repeat IVF treatment.

Hysteroscopy was performed during the proliferative phase of the menstrual cycle using a 2.9 mm, 25° hysteroscope with a single compact inflow and outflow channels (Richard Wolf). All hysteroscopies were performed in an in-office setting under conscious sedation and intracervical lignocaine. Normal saline was used as distension media. All the pathologies were treated on a "see and treat" basis using 5F hysteroscopic scissors and graspers.

The Institutional Ethics Committee gave approval for the conduct of this study.

RESULTS

A total of 77 patients had normal ultrasound scan findings after two previous failed IVF/ICSI cycles and underwent a hysteroscopy during the study period. This represented 7.7% of the 1,002 hysteroscopies performed during the same period. As shown in Table 1, the age range of the patients was 25–54 years, with a mean age of 37 ± 4.3 years.

Table 2 shows the findings at hysteroscopy. The majority of the women (59, 76.6%) had no pathology on hysteroscopy, while 14 (18.2%) had intrauterine adhesions. Three patients (3.9%) had endometrial polyps, and one patient (1.3%) had a subseptate uterus. Following hysteroscopy, as shown in Table 3, 24 patients (31.2%) became pregnant, 29 patients (37.6%) had failed cycles, and the remaining 24 patients (31.2%) were lost to follow-up. Of the 8 patients who underwent hysteroscopic adhesiolysis, 2 (25%) became pregnant.

DISCUSSION

Couples undergoing IVF/ICSI treatment cycles are burdened with anxiety and uncertainties following their first procedure.¹² Subsequent failure to achieve conception through IVF/ICSI has been shown to further worsen their quality of life.¹³ For this reason, it is imperative from the outset that all efforts are put in place to ensure a successful outcome. This should include removing all known obstacles that could jeopardize their chances.

Table 1: Demographic and clinical characteristics (n=77)

Variable	Mean \pm SD (range)
Age (years)	3.7 \pm 4.3 (25-54)
Parity	1.12 \pm 0.64 (0-3)
Duration of infertility	6.9 \pm 3.1 (2-15)

SD – Standard deviation

Table 2: Findings at hysteroscopy

Pathology	Frequency (%)
None	59 (76.6)
Intrauterine adhesions	14 (18.2)
Polyps	3 (3.9)
Subseptate uterus	1 (1.3)
Total	77 (100)

Table 3: *In vitro* fertilisation/intracytoplasmic sperm injection outcomes following hysteroscopy

Treatment outcome	Frequency (%)
Pregnant	24 (31.2)
Not pregnant	29 (37.6)
No subsequent cycle	24 (31.2)
Total	77 (100)

The age range of the patients was 25–54 years, with a mean age of 37 ± 4.3 years. It is the policy of the unit to set the upper age limit for offering treatment at 55 years of age. As shown in Table 2, 23.4% of the women with two previous failed IVF/ICSI cycles showed abnormalities following hysteroscopy. Fatemi *et al.* reported finding previously unsuspected and missed intrauterine pathologies, including polyps, adhesions, septa, and fibroids, in 11% of women who planned to undergo IVF treatment.⁶ Similarly, in a more recent study, Bahadur *et al.* evaluated 870 asymptomatic women enrolled for IVF. Among the 757 patients who had normal ultrasound scan findings, abnormal findings were observed in 108 patients (14.2%) following a hysteroscopic assessment of the endometrial cavity.¹⁴ Cenksoy *et al.* reported a much higher figure of 44.9% for abnormal hysteroscopy findings in patients with two or more previous failed IVF cycles.¹⁵

The abnormality most frequently missed by the initial ultrasound scan was intrauterine adhesions. These were subsequently detected in 18.2% of the patients following hysteroscopy, further establishing the place of hysteroscopy as the gold standard for diagnosing intrauterine adhesions. In Nigeria, as in many countries with restrictive abortion laws, unsafe abortion is a significant problem.⁷ Intrauterine adhesions are expected to be common in such a population. It is well established that intrauterine adhesions can be responsible for recurrent IVF/ICSI failure.¹⁶ Even when implantation does occur, in a study carried out at a multi-disciplinary pregnancy loss prevention centre, intrauterine adhesions were reported to be the most common diagnosis in patients with recurrent pregnancy losses.¹⁷ Intrauterine adhesions can also be responsible for some cases of cervical stenosis, which leads to difficult embryo transfer and a subsequent reduction in IVF success rates.^{18,19}

The effects of polyps on fertility, including the IVF/ICSI success rate, are conflicting as very few studies have been published, and they have reached different conclusions on this subject.²⁰ Only 3 (3.9%) patients had endometrial polyps that were missed on an initial ultrasound scan but later diagnosed following hysteroscopy. In a retrospective, descriptive study, polypectomy was the most common procedure performed in women with two or more previous failed IVF cycles, and this procedure produced a statistically significant increase in the pregnancy rate.¹⁵ Although the effect of these polyps on IVF/ICSI success rates is not clear, if diagnosed before the commencement of a cycle, it is advisable that they be removed.²⁰

Only one patient (1.3%) had a subseptate uterus (incomplete uterine septum). Similar to endometrial polyps, the effect of the uterine septum on infertility remains controversial as published results are both scarce and conflicting.²¹⁻²⁵ However, a recent cohort study suggested that the reproductive outcomes of IVF-ET after hysteroscopic correction for incomplete uterine septum in women with primary infertility were not different

from those observed in women with a normal uterine cavity.²⁶ If left untreated, the septate uterus can result in preterm delivery and subsequent pregnancy wastage.²⁷

Following hysteroscopy, there was a 31.2% clinical pregnancy rate, as shown in Table 3. Because it was hospital policy to carry out hysteroscopy following two failed IVF cycles, no patient who underwent another IVF treatment cycle without hysteroscopy were available for comparison. Cenksoy *et al.* reported a 48.1% pregnancy rate in women with abnormal but missed hysteroscopy findings after correction.¹⁵ Of the eight women in our series who underwent hysteroscopic intrauterine adhesiolysis, two (25%) achieved a clinical pregnancy. Unfortunately, 24 (31.2%) of the patients were lost to follow-up, most likely because they could not continue for financial reasons or decided to patronize a different ART centre.

IVF and related procedures are expensive ventures to undertake. This is more so in developing countries where there is a fee for these services. In Nigeria, for example, over 70% of the population lives below the poverty line, which is <2 USD per day. The result is that the majority cannot afford an IVF treatment cycle. A few are able to afford just one cycle in their lifetime. While some are sponsored by communities, others have their bills paid for by religious organisations. This situation, coupled with the love for twins, probably explains why the majority of patients who undergo IVF/ICSI desire multiple pregnancies despite the attendant complications.²⁸ The argument for performing routine hysteroscopy before IVF/ICSI in such a population might sound justifiable because missed abnormalities might jeopardize their chances of success. Unfortunately, this procedure comes with added costs to the patient, and this might further worsen their financial situation.

CONCLUSION

This study has added to the body of evidence that suggests that routine hysteroscopy before IVF is capable of picking up missed pathologies that might otherwise negatively impart IVF success rates. More RCT are however needed to determine the effect of routine hysteroscopy on IVF treatment outcomes, especially in a resource-poor environment with restrictive abortion laws. In the interim, the development of methods to provide low-cost hysteroscopy services would be welcome.

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Conflicts of interest

There are no conflicts of interest.

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