

Evaluating the Role of Hysteroscopy in the Success Rate of In-Vitro Fertilization

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ABSTRACT

Background and Aims: High in-vitro fertilization (IVF) failure risk in patients with asymptomatic intrauterine pathologies can be diminished with the use of hysteroscopy. This study assesses the impact of pre-IVF hysteroscopy on IVF success in women without infertility pathology and with no history of previous IVF.

Methods and Materials: In a randomized clinical trial involving 168 women with infertility history who intended IVF, participants were allocated into intervention and control groups using Balanced Block Randomization. Hysteroscopy, performed 1-2 months prior to embryo transfer, was the intervention. IVF procedures were consistent between groups. Categorical variables were chi-square tested; quantitative ones underwent independent t-tests. Multiple logistic model was used to detect significant factors affecting pregnancy outcome. STATA V.17.0 was used for data cleaning and analysis.

Results: Mean age was 31 (± 5.02) in the intervention group and 31.14 (± 5.10) in the control group ($p=0.897$). BMI, infertility duration, ovocytes count, hMG injections, and other factors showed no significant between group differences ($p>0.05$). Finally, 45 (53.57%) women in intervention group had positive BhCG test, compared to the controls (31, 36.90%, p -value = 0.030). Also, the number of positive clinical pregnancies was significantly higher (p -value = 0.045) among the intervention group (32, 38.10%) compared to the control group (20, 23.81%). Multiple logistic regression showed hysteroscopy increased odds of positive clinical pregnancy [aOR: 3.42 (95% CI: 1.18 - 9.96), $p=0.024$].

Conclusion: Based on our randomized clinical trial hysteroscopy significantly raised the odds of positive clinical pregnancy. This highlights hysteroscopy's potential role in improving successful pregnancy outcomes. These findings offer crucial insights for clinicians and patients in fertility treatments.

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INTRODUCTION

Infertility is defined as the absence of a chemical pregnancy following 12 months of regular unprotected intercourse due to impaired reproductive capacity in either the individual or their partner. This clinical challenge impacts 13-15% of couples worldwide. A recent study detailing infertility prevalence across 195 countries from 1990 to 2017 revealed a global increase, rising from 1,366.85 cases per 100,000 in 1990 to 1,571.35 cases per 100,000 in 2017, marking a surge of 14.962% (1-4). Assisted reproductive technologies have expanded globally to aid infertile couples, yet despite their considerable costs, success rates remain modest. According to a Centres for Disease Control and Prevention report, the implantation rate and successful fetal births stand at only about 34%, varying at 43% for patients aged 35-37, 35.8% for those aged 38-40, and 24.9% for individuals aged 41-42. Implantation failure can stem from various reasons, encompassing embryo quality and endometrial receptivity, with unknown causes accounting for numerous cases (5-9).

Efforts to enhance embryo transfer and culture conditions or select blastocysts have managed to improve pregnancy rates, but these improvements have not exceeded a 40% to 50% increase. As we know, pregnancy rates can be affected by intrauterine pathologies. As a result, assessing the intrauterine environment is crucial to optimizing the implantation rate of high-quality embryos (10-14). Hysteroscopy is believed to enhance pregnancy rates in women undergoing IVF by identifying and surgically addressing abnormalities in the uterine cavity, facilitating the dilation of the cervical canal for subsequent embryo transfer, or inducing an inflammatory response in the endometrium as a result of the procedure (10-14).

KEYWORDS:

In-vitro fertilization,
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Hysteroscopy stands as the gold-standard test for evaluating intrauterine pathologies. This technique enables the diagnosis of abnormalities such as intrauterine adhesions, endometrial polyps, submucosal fibroids, endometritis, or structural uterine irregularities. Through direct observation of the cervix and the interior of the uterus, hysteroscopy facilitates both diagnosis and concurrent corrective interventions when required (15-17). Furthermore, it serves as a means for performing biopsies. Notably, the treatment of intrauterine pathologies via hysteroscopy has been shown to result in enhanced reproductive outcomes, as intrauterine lesions can have a detrimental impact on implantation rates. Numerous studies have comprehensively documented the advantages of using interventional hysteroscopy to address intrauterine pathologies (18-21).

To mitigate embryo loss and IVF failures attributable to intrauterine pathologies, curbing the advancement of such disorders represents a widespread approach in global public health policies. This is especially salient due to the elevated likelihood of IVF failure in patients with asymptomatic intrauterine pathologies. The principal aim of this study is to examine the impact of conducting hysteroscopy prior to the initial IVF cycle on the efficacy of IVF treatment in women without any established infertility pathology.

METHODS AND MATERIALS

Study design and setting

In our randomised clinical trial, we included 168 women with history of infertility who intended to undergo IVF. The inclusion criteria were primary infertility, age under 40 years, body mass index ranging from 19 to 35 kg/m², and couples who underwent one year of infertility-cause investigation without identifying any specific reason for infertility (unexplained infertility). The criteria for infertility without identifiable pathology encompassed the following: a spermogram exhibiting normality as per WHO reference values (22), confirmation of open fallopian tubes through HSG (hysterosalpingography), clinical and ultrasound validation of ovulation, and a minimum count of 5 antral follicles.

The exclusion criteria were abnormal spermogram, reduction of ovarian reserve, which is defined as the total number of antral follicles less than 5 in transvaginal ultrasound, pathology in the uterus and fallopian tubes diagnosed by HSG, history of endometrial surgery, previous IVF history.

Study groups and Randomization

Participants were allocated into two intervention and control groups using the Balanced Block Randomization method. This approach ensured a random distribution of individuals into the study groups while preventing any imbalances between them. With regards to pertinent variables influencing the study process, there were 33 blocks, each containing 4 individuals. The sequence of participant enrolment dictated their placement within their respective groups. Given that this study was surgical in nature, blinding of both the researcher and patients was not feasible. The intervention involved hysteroscopy, performed by a surgeon during the initial stages of the follicular phase of the menstrual cycle, approximately 1 to 2 months prior to embryo transfer.

The IVF procedure was similar in both groups. IVF was carried out by intracytoplasmic sperm injection (ICSI) method and all

the embryos were freshly frozen immediately afterwards. Starting from the third day of menstruation, two tablets of letrozole (2.5 mg) were administered daily until the day of human chorionic gonadotropin (hCG) injection. Additionally, from the third day of letrozole initiation, daily doses of Cinnal-F (folitropin alfa, Cinnagen Company, Tehran, Iran) (150-300 mg) were given until the hCG injection day. Subsequently, starting from the second day of Cinnal-F injection, one or two menotropin injections were administered daily until the hCG injection day. When the leading follicle reached a size of 14 mm, a daily dose of one Cetorelix (250 mg) was initiated. Upon the diagnosis of at least 2 to 3 follicles of 18 mm through ultrasound, egg release was stimulated using 10,000 units of hCG and two ampoules of 0.1 mg decapeptyl. Ovocytes retrieval was carried out 36 hours after the initial trigger assisted by vaginal ultrasound. Within one to two cycles following hysteroscopy, the patient began taking 6 mg of estradiol daily from the second day of the menstrual cycle. When the endometrial thickness reached a minimum of 7 to 8 mm, the patient received intramuscular progesterone at a dose of 50-100 mg daily for 4 days. On the fourth day of progesterone injection, the patient underwent the frozen transfer of two 3-day-old embryos (cleavage). Among the intervention group, the embryos were transferred two months after the hysteroscopy.

Statistical Analysis

Variables were assessed using the Kolmogorov-Smirnov test to ascertain their normal distribution. Descriptive data analysis was conducted, presenting mean and standard deviation for variables demonstrating normal distribution. Categorical and qualitative variables were compared using the chi-square test, while quantitative variables were subjected to either the independent t-test (in cases of normality) or the Mann-Whitney test (in cases of non-normality). Univariate analysis identified potential factors. Several variables, including female age, antral follicle count, duration of infertility, BMI, total number of retrieved oocytes, total number of transferred embryos, and number of embryo transfer were entered into logistic regression analysis to estimate adjusted odds ratios with 95% confidence intervals. P-values less than 0.05 were considered as statically significant. STATA V.17.0 was used for data cleaning and data analysis.

Ethical Considerations

All participants were ensured that their involvement in the study was purely for research purposes, and their identities would remain confidential. Informed consent was obtained from all participants, who willingly and satisfactorily answered the research questions. This study received ethical approval under the code IR.TBZMED.REC.1402.509 from the Ethics Committee of Tabriz University of Medical Sciences, Tabriz, Iran.

RESULTS

Overall, 168 participants were included in our randomized clinical trial study. The mean age among the intervention group was 31 (± 5.02) while the mean age among the control group was 31.14 (± 5.10) with no significant difference (p -value = 0.897). Further information is summarized in Table 1.

Table 1. Difference of pre-insemination variable between the study groups at baseline

	Hysteroscopy Group (n = 84)	Control Group (n = 84)	p-value
Age	31±5.02	31.14±5.10	0.897
BMI	26.21±2.57	26±2.61	0.705
Infertility Duration (years)	4.38±2.33	4.21±2.12	0.733
Number of HMG injections	6.09±1.20	5.95±1.03	0.561
Ovulation Induction (days)	12.33±0.72	12.5±0.70	0.288
Number of Ovs*	12.50±4.60	11.78±4.11	0.455
Number of GV ^s **	4.21±2.19	3.92±2.29	0.557
Number of M2 ^s ***	8.09±4.06	7.78±3.47	0.708
*Ovocytes; **germinal stage ovocytes; ***metaphase-2 stage ovocytes			

Overall, 45 (53.57%) of the intervention groups had positive BhCG test, while 31 (36.90%) of the control group had positive BhCG test (Table 2). There number of positive BhCG test was significantly higher (p -value = 0.030) among the intervention

group. Also, the number of positive clinical pregnancies was significantly higher (p -value = 0.045) among the intervention group (32, 38.10%) compared to the control group (20, 23.81%).

Table 2. Pregnancy outcomes among the intervention and control groups

		Hysteroscopy Group (n, %)		Control Group (n, %)		p-value
OHSS*	No	72	85.71%	75	89.29%	0.484
	Yes	12	14.29%	9	10.71%	
Chemical Pregnancy	Negative	39	46.43%	53	63.10%	0.030
	Positive	45	53.57%	31	36.90%	
Clinical Pregnancy	Negative	52	61.90%	64	76.19%	0.045
	Positive	32	38.10%	20	23.81%	
*Ovarian hyperstimulation syndrome						

Based on the multivariate logistic regression model (Table 3), hysteroscopy increased the odds of positive clinical pregnancy [OR: 3.42 (95% CI: 1.18 - 9.96), p -value = 0.024]. Also, higher age increased the odds of positive clinical pregnancy [OR: 1.17

(95% CI: 1.02 - 1.36), p -value = 0.024] while higher BMI lowered the odds of positive clinical pregnancy [OR: 0.74 (95% CI: 0.59 - 0.94), p -value = 0.014].

Table 3. Adjusted OR of the factors affecting clinical pregnancy outcome

	Odds ratios (CI [†])		p-value
Hysteroscopy	No**	1 (-)	0.024
	Yes***	3.42 (1.18 - 9.96)	
Age	1.17 (1.02 - 1.36)		0.024
Number of Ovs [†]	0.93 (0.52 - 1.66)		0.819
Number of GVs ^{††}	1.13 (0.64 - 1.98)		0.667
Number of M2s ^{††}	1.39 (0.78 - 2.49)		0.260
Comorbidity	No	1 (-)	0.434
	Yes	1.81 (0.40 - 8.10)	
Ovulation Induction (days)	2.17 (0.89 - 5.30)		0.087
BMI	0.74 (0.59 - 0.94)		0.014
OHSS [‡]	No	1 (-)	0.505
	Yes	0.49 (0.06 - 3.93)	
*Confidence Interval; **Control group; *** Hysteroscopy group; [†] ovocytes; ^{††} germinal stage ovocytes; ^{†††} metaphase-2 stage ovocytes; [‡] ovarian hyperstimulation syndrome			

DISCUSSION

Based on the results of our randomized clinical trial study, regarding the effect of hysteroscopy prior to in-vitro fertilisation, we found that hysteroscopy, significantly improves the odds of IVF success rate. The IVF success rate is also significantly associated with higher age and lower BMI. Our study is among the few randomised trials to investigate such an association.

Currently, there lacks substantial high-quality evidence endorsing the routine use of hysteroscopy as a preliminary screening tool before IVF/ICSI. While other imaging methods like hysterosalpingogram or transvaginal scans are more accessible, hysteroscopy provides a more precise visual appraisal of the endometrial cavity and offers the opportunity for suitable therapeutic interventions (23-25). Concerns against hysteroscopy include its invasive nature and uncertainty about the clinical relevance of identified intrauterine issues to fertility (26, 27). The European Society of Human Reproduction and Embryology (ESHRE) guidelines suggest that hysteroscopy is unnecessary unless it's essential for confirming and addressing questionable intrauterine pathology (28). Nonetheless, it's worth noting that hysteroscopy is a minimally invasive procedure with minimal technical failure rates, commonly conducted on an outpatient basis without hospitalization or anaesthesia requirements (29, 30). This study indicates that women undergoing their second IVF/ICSI attempt after hysteroscopy tend to achieve improved pregnancy rates.

Previous research has demonstrated a positive impact of hysteroscopy on in vitro fertilization outcomes, advocating for the inclusion of hysteroscopy before costly procedures like assisted reproduction (31, 32). The study revealed that 21.1% of patients had identified abnormalities requiring treatment prior to IVF/ICSI. In 2014, a meta-analysis indicated enhanced live birth rates following hysteroscopy for women undergoing their first IVF cycle (33). Nevertheless, contrasting findings have emerged, with some researchers suggesting the benefits of routine hysteroscopy primarily for women aged 40 and above (24, 34).

The potential benefits of hysteroscopy seem to correlate with the proportion of women within the studied population who exhibit identifiable pathology during hysteroscopy (HSC). Notably, women aged over 40 years have demonstrated a higher likelihood of endometrial issues, such as submucous myoma, endometrial hyperplasia, and polyps (35). This demographic might constitute a suitable target group for such intervention. Similarly, a comparable trend has been observed in women above 35 years of age (36). Conversely, findings from the TROPHY trial suggest that women with 2 to 4 unsuccessful IVF cycles do not experience enhanced live birth rates following hysteroscopy. Another randomized trial involving 750 patients undergoing their initial IVF cycle concluded that hysteroscopy did not yield improved live birth rates among women with normal transvaginal ultrasound results (27, 37, 38).

The conflicting outcomes observed in studies assessing the efficacy of hysteroscopy prior to IVF or ICSI cycles can be attributed to methodological limitations and a deficiency in study quality. This viewpoint finds support in a recent meta-analysis available in the Cochrane database. In this analysis, the viability of routine hysteroscopy in sub-fertile women undergoing infertility assessment and those scheduled for intrauterine insemination or IVF was explored. Through the examination of 11 publications, the researchers concluded that no study provided substantial evidence to advocate for

hysteroscopy as a screening technique among sub-fertile women with a normal basic fertility assessment, for the enhancement of live birth and clinical pregnancy rates (23, 39).

CONCLUSIONS

In conclusion, our randomized clinical trial involving 168 participants revealed that hysteroscopy was associated with a significant increase in the odds of positive clinical pregnancy. This finding underscores the potential utility of hysteroscopy as a contributing factor in enhancing the likelihood of achieving a successful clinical pregnancy outcome. Additionally, the analysis indicated that advanced age was linked to increased odds of positive clinical pregnancy, while higher BMI was associated with reduced odds of positive clinical pregnancy. These insights provide valuable considerations for clinicians and patients in the context of fertility treatments and underscore the need for further investigation into the impact of hysteroscopy on pregnancy outcomes.

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CONSORT 2010 Flow Diagram

