Utility of Hysteroscopy Earlier Than IVF In Increasing Live Birth in Patients with Normal Transvaginal Scan Following the First Failed IVF Trial

Ahmed Dabash Abdel lateef [1], Ahmed Abdelbaky Mubarak[2], Osama Ahmed Mohamed Ali[2]

1.Faculty of Medicine, Suez University, Egypt.

2.Faculty of Medicine, Qena, South Valley University, Egypt.

Abstract:

Background: Implantation failure following in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) is frequently extremely challenging for patients as well as healthcare providers. Hysteroscopy is a highly trustworthy approach for evaluating the uterine cavity and detecting any intrauterine pathology.

Purpose: To determine if hysteroscopy before the subsequent IVF/ICSI trial increases the likelihood of a live birth among women who had one failed IVF and normal transvaginal scan results

Methods: This retrospective study involved two groups, the study group (n=150) and the control group (n=200), HSC and TVS were carried out during the initial proliferative stage of the menstrual cycle (days 3–9). The primary outcome was live birth. The secondary outcomes included unusual hysteroscopic outcomes, clinical pregnancy, and abortion rates

Results: Live birth rates were higher in the study group (72.0% vs. 55.0% p = 0.01). Abnormal endometrial findings were identified in 32.0% of the patients of the study group.

Conclusions: The incorporation of hysteroscopy as a further inquiry for patients with a first failed IVF/ICSI could increase the number of live births.

Keywords: Gluteus maximus inhibition, mechanical low back pain, lumbo-pelvic stability, neuromuscular dysfunction, rehabilitation strategies.

1. Introduction

Enhancing embryo quality and endometrial receptivity have been identified as the most essential variables in achieving effective implantation, which stays a rate-limiting stage in assisted reproductive technology (ART) (Nahshon et al., 2020). Recurrent implantation failure (RIF) is an accidental scenario caused by repeated failed In vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) treatments (Polanski et al., 2014).

Transvaginal sonography, hysterosalpingography, and hysteroscopy (HSC) are the most efficient techniques for detecting uterine defects (Phillips et al., 2015). Nevertheless, hysterosalpingography has minimal specificity, high false-negative and false-positive rates. Transvaginal sonography is a noninvasive and reproducible approach, but it is not particularly sensitive (Mao et al., 2019). Outpatient HSC is the most prevalent procedure carried out after IVF failure due to examinations reveal an abnormal uterine cavity(Phillips et al., 2015).

Hysteroscopy (HSC) provides an accurate visual evaluation of the cervical canal and uterine cavity for intrauterine adhesions, endometrial polyps, submucous fibroids, endometritis, or uterine abnormalities that might cause problems with implantation, as well as the ability to execute treatment in the same setting, including elimination or endometrial cutting for endometrial polyps, submucosal fibroids, or uterine tumors (El-Toukhy et al., 2008). As a result, HSC has become the only direct technique for noticing physiological and pathological endometrial modifications, in addition to performing precise specimens and therapies (Gao et al., 2015).

Research findings on the beneficial effects of hysteroscopy in IVF cycles have yielded inconsistent findings. The TROPHY study, a multicenter randomised controlled trial, found that hysteroscopy had no impact on the live birth rate (LBR), particularly for women with persistent, failed implantation after IVF (El-Toukhy et al., 2016). But this opposes with the findings of an earlier systematic review demonstrated that routine hysteroscopy enhanced the LBR for women with recurrent unsuccessful IVF cycles (El-Toukhy et al., 2008). When contrasting the efficacy of hysteroscopy with no hysteroscopy before any (the initial or next) IVF/ICSI attempt in infertile asymptomatic patients, there was very little evidence that hysteroscopy increased LBR (Di Spiezio Sardo et al., 2016).

This retrospective study aimed to determine if hysteroscopy before the subsequent IVF/ICSI trial increases the likelihood of a live birth among women who had one failed IVF and normal transvaginal scan results.

2. Patients and methods:

This retrospective study was carried out in infertile women at Qena fertility center in the period from December 2020 till December 2023. The inclusion criteria were age 35-45 years, past record of failed IVF/ICSI with high quality embryos (defined as good quality on day 3 and good morphology blastocysts grade A and B) and normal TVS findings, BMI < 30 kg/m2, and absence of hematological and immunological conditions. Patients were excluded if they had a history of lower abdominal or pelvic infection, intestinal surgery,

endometriosis grade three or four, earlier caesarean section with niche development, untreated hydrosalpinx, endometrial scratching, menstrual irregularities, and neglected endocrine defects.

The study population is formed of two groups, the study group (n=150) and the control group (n=200), HSC and TVS were carried out during the initial proliferative stage of the menstrual cycle (days 3–9). A 4.3 mm constantly rigid scope with a 30-degree field of view and normal saline were employed as tention media. The endocervical canal, uterine cavity, tubal ostiums, and endometrium were thoroughly inspected and documented in a standardised form. When endometritis was suspected, hysteroscopy and endometrial biopsy were performed concurrently. The control group included patients who failed their first IVF/ICSI try and required a repeat TVS prior to attempting again.

Ovarian stimulation protocol

All the females underwent ovarian stimulation with GnRH antagonists and recombinant or purified FSH (150-300 IU) every day. To induce ovulation with hCG, 250 mcg of choriogonadotrophin alfa was administered when at least three 17 mm follicles were detected on ultrasound. Ultrasound-guided oocyte extraction was carried out thirty six hours following last maturation. On day 3, embryos were transferred using a soft catheter. In cases of a positive pregnancy test, vaginal progesterone supplemental intake was administered to promote the luteal phase for as long as four weeks after embryo transfer. A pregnancy test was performed two weeks after oocyte extraction, followed by a TVS at weeks seven and twelve.

Embryo choice and transfer in a fresh cycle

Embryos were selected for transfer according to the morphological features and developmental rate. The quality was assessed using morphological standards, including blastomere count, size, and appearance.

Outcome measures

The primary outcome was live birth. The secondary outcomes included unusual hysteroscopic outcomes, clinical pregnancy, and abortion rates. Atypical hysteroscopy results have been recorded and managed as needed, including endometrial polyps and endometritis, either before or following the procedure.

Statistical analyses

Recorded data were analyzed using the statistical package for social sciences, version 23.0 (SPSS Inc., Chicago, Illinois, USA). The quantitative data were presented as mean± standard deviation and ranges when their distribution was parametric (normal) while non-normally distributed variables (non-parametric data) were presented as median with inter-quartile range (IQR). Also, qualitative variables were presented as number and percentages. Data were explored for normality using Kolmogorov-Smirnov and Shapiro-Wilk Test.

3. Results:

The results of the current study are displayed in the following tables and figures:

The mean age of the study group was 39.53 ± 16.84 years and 43.08 ± 17.25 in the control group; the mean BMI was 25.35 ± 2.97 kg/m2 in the study group and 25.76 ± 1.89 kg/m2 in the control group; the duration of infertility was 4.02 ± 0.43 years in the study group and 25.76 ± 1.89 in the control group; infertility causes in the study group were poly cystic ovarian syndrome (PCOS) in 45(30.0 %), endometriosis in 37(24.67 %), male factor in 28(18.67 %) and unexplained infertility in 40(26.66 %). Infertility causes in the control group were poly cystic ovarian syndrome (PCOS) in 66 (33.0 %), endometriosis in 58(29.0 %), male factor in 27(13.5%) and unexplained infertility in 49(24.50 %). There were none statistically significant differences between both groups as regards baseline characteristics (p>0.05) (Table 1)

Table (1) Baseline characteristics of the study groups

	Study group (n=150)	Control group (n=200)	p-value
Age (years)	39.53 ± 16.84	43.08 ± 17.25	0.671
BMI (kg/m^2)	25.35 ± 2.97	25.76 ± 1.89	0.161
Infertility duration(years)	4.02 ± 0.43	3.88 ± 0.37	0.33
Infertility causes			0.3
PCOS	45(30.0 %)	66(33.0 %)	
Endometritis	37(24.67 %)	58(29.0 %)	
Male factor	28(18.67 %)	27(13.50%)	
Unexplained	40(26.66 %)	49(24.50 %)	

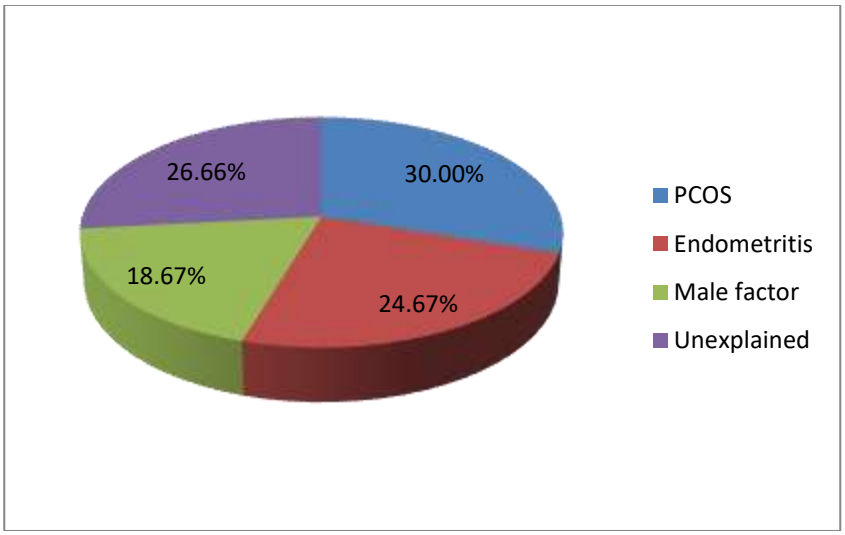

Figure (1): Infertility causes in the study group (n=150)

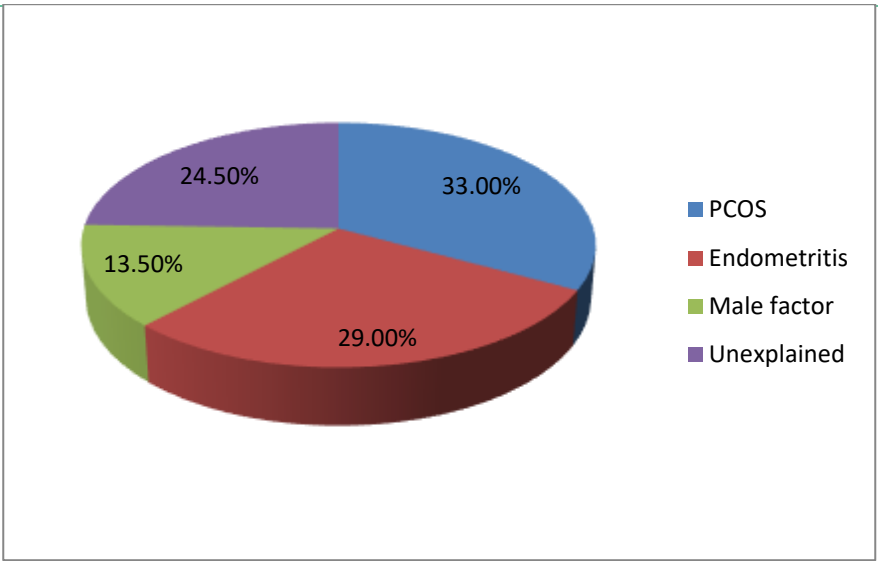

Figure (2): Infertility causes in the control group (n=200)

Forty-eight (32.0%) of the patients who underwent a hysteroscopy had abnormal hysteroscopic findings (Table 2 and Figure 3).

Table (2) Abnormal hysteroscopic findings of the study group (n=150)

Abnormality	No.	%
Endometritis	6	12.5%
Intra uterine polyps	16	33.33%
Adhesions	7	14.58%
Sub mucosal fibroids	14	29.17%
Endocervical polyps	5	10.42%

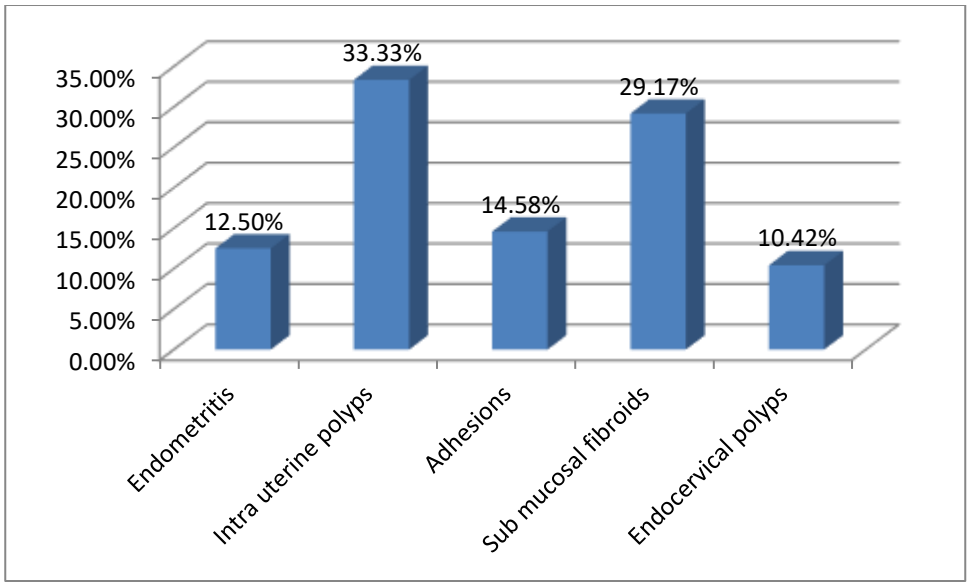

Figure (3): Abnormal hysteroscopic findings of the study group

There were statistically significant differences between the study group and the control group as regards clinical pregnancy rate (p=0.03) and live birth rate (p=0.01) while there were none statistically significant differences between both groups as regards oocyte retrieved (p=0.544), number of transferred embryo (p=0.15), early abortion rate (p=0.36) and late abortion rate (p=0.190) Table 3

Table (3) Post operative pregnancy outcomes in the study group and the control group

	Study group (n=150)	Control group (n=200)	p-value
Oocyte retrieved (n)	6(2-11)	4(2-7)	0.544
Number of transferred embryo	2.45 ± 0.94	2.02 ± 0.43	0.15
Clinical pregnancy rate %	126/150(84.0%)	134/200(67.0%)	0.03
Live birth rate %	108/150(72.0%)	110/200(55.0%)	0.01
Early abortion rate %	8/126 (6.35%)	5/134 (3.73%)	0.36
Late abortion rate %	10/126 (7.93%)	19/134 (14.18%)	0.190

4. Discussion:

Hysteroscopy has quickly spread in (IVF) because it appears to increase the likelihood of clinical pregnancy or live birth (Kamath et al., 2019). Several reproductive healthcare professionals propose hysteroscopy as a more precise tool for detecting intrauterine abnormalities than hysterosalpingography (HSG), which has high false-positive and false-negative rates (Campo et al., 2014).

Different uterine lesions detected by HS could adversely affect endometrial receptivity (ER) in several mechanisms, such as mechanical obstruction or the induction of immune and inflammatory pathways (Gao et al., 2015). Abnormal endometrial findings were identified in 32.0% of the study group. Our findings are in agreement with Gao et al., (2015) who reported that the prevalence of intrauterine abnormalities in the HS group was 37.13%. The most prevalent abnormalities were endometrial polyps, polypoid endometrium, hyperplasia, and intrauterine adhesions.

The current study results revealed that clinical pregnancy rate and live birth rates were higher in the study group than the control group (84.0% vs. 67.0% p = 0.03); (72.0% vs. 55.0% p = 0.01), respectively.

Our findings were consistent with a meta-analysis published by Pundir et al., (2014), which found that LBR elevated after hysteroscopy in women planned for their first IVF cycle (risk ratio: 1.30, 95% confidence interval: 1.00-1.67; p=0.05). Another randomized controlled trial of LBR found up to 70% higher pregnancy rates after hysteroscopy (Elsetohy et al., 2015). Additionally, Chung et al., (2006) stated that HSC enhanced the live birth rate in women with repeated implantation failure, irrespective of uterine abnormalities. Shawki et al., (2012) randomly assigned 240 patients with normal hysterosalpingograms and/or transvaginal sonography to get HSC prior to ICSI. The pregnancy rate was significantly greater in the HSC group than in the non-HSC group. Mao et al., (2019) study revealed that HSC increased implantation and clinical pregnancy rates

in women with repeated implantation failure undergoing IVF, but failed to boost live births or reduce miscarriages.

Rama Raju et al., (2006) proposed that small intrauterine lesions can be effectively treated employing office HSC, which plays an important role in changing the uterine environment and, eventually, enhancing pregnancy outcomes. Shohayeb & El-Khayat, (2012) found that a single endometrial biopsy (endometrial scratching) during HSC resulted in a substantially greater implantation rate, clinical pregnancy rate, and live birth rate after ICSI than if no biopsy was carried out. In a similar manner, Seval et al., (2016) stated that "endometrial scratching" during HSC enhanced the implantation and pregnancy rates in women with RIF when contrasted with HSC alone.

Endometrial scratching or biopsy throughout HSC could change the endometrium's inflammatory or developmental status, making it more suitable for embryo implantation (Seval et al., 2016). Since implantation and subsequent pregnancy require a complex interaction of maternal and fetal variables, in addition to an exacting equilibrium of pro-inflammatory and anti-inflammatory cytokines, every one of this may impact endometrial receptivity and implantation (Fatemi & Popovic-Todorovic, 2013, Dekel et al., 2014).

Our findings are contrasting with Eserol et al., (2021) results who showed that diagnostic hysteroscopy prior to fresh and frozen-thawed embryo transfers (FET) does not increase pregnancy rates in this cohort. Smit et al., (2016) proposed that routine hysteroscopy before IVF or ICSI treatments has no influence on fertility results in infertile women with normal uterine cavity on transvaginal ultrasound.

In conclusion, the incorporation of hysteroscopy as a further inquiry for patients with a first failed IVF/ICSI could increase the number of live births.

References:

1. Campo, R., Meier, R., Dhont, N., Mestdagh, G., & Ombelet, W. (2014). Implementation of hysteroscopy in an infertility clinic: The one-stop uterine diagnosis and treatment. Facts, views & vision in ObGyn, 6(4), 235–239.
2. Chung, Y., Suh, C., Choi, Y. (2006). Effects of endometrial evaluation with office hysteroscopy in IVF–ET patients with repeated failures. Fertil Steril ;86Suppl. 2: S152
3. Dekel, N., Gnainsky, Y., Granot, I., Racicot, K., & Mor, G. (2014). The role of inflammation for a successful implantation. American journal of reproductive immunology (New York, N.Y.: 1989), 72(2), 141–147. https://doi.org/10.1111/aji.12266
4. Di Spiezio Sardo, A., Di Carlo, C., Minozzi, S., Spinelli, M., Pistotti, V., Alviggi, C., De Placido, G., Nappi, C., & Bifulco, G. (2016). Efficacy of hysteroscopy in improving reproductive outcomes of infertile couples: a systematic review and meta-analysis. Human reproduction update, 22(4), 479–496. https://doi.org/10.1093/humupd/dmw008
5. Elsetohy, K. A., Askalany, A. H., Hassan, M., & Dawood, Z. (2015). Routine office hysteroscopy prior to ICSI vs. ICSI alone in patients with normal transvaginal ultrasound: a randomized controlled trial. Archives of gynecology and obstetrics, 291(1), 193–199. https://doi.org/10.1007/s00404-014-3397-z

6. El-Toukhy, T., Campo, R., Khalaf, Y., Tabanelli, C., Gianaroli, L., Gordts, S. S., Gordts, S., Mestdagh, G., Mardesic, T., Voboril, J., Marchino, G. L., Benedetto, C., Al-Shawaf, T., Sabatini, L., Seed, P. T., Gergolet, M., Grimbizis, G., Harb, H., & Coomarasamy, A. (2016). Hysteroscopy in recurrent in-vitro fertilisation failure (TROPHY): a multicentre, randomised controlled trial. Lancet (London, England), 387(10038), 2614–2621. https://doi.org/10.1016/S0140-6736(16)00258-0
7. El-Toukhy, T., Sunkara, S. K., Coomarasamy, A., Grace, J., & Khalaf, Y. (2008). Outpatient hysteroscopy and subsequent IVF cycle outcome: a systematic review and meta-analysis. Reproductive biomedicine online, 16(5), 712–719. https://doi.org/10.1016/s1472-6483(10)60486-5
8. Eserol, F., Göksever Çelik, H., Aytan, A. N., Çelik, A., Çelik, E., Buyru, F., & Bastu, E. (2021). The effect of diagnostic hysteroscopy performed before fresh and frozen-thawed embryo transfer in IVF cycles on reproductive outcomes. Journal of the Turkish German Gynecological Association, 22(3), 206–211. https://doi.org/10.4274/jtgga.galenos.2021.2020.0136
9. Fatemi, H. M., & Popovic-Todorovic, B. (2013). Implantation in assisted reproduction: a look at endometrial receptivity. Reproductive biomedicine online, 27(5), 530–538. https://doi.org/10.1016/j.rbmo.2013.05.018
10. Gao, M., Sun, Y., Xie, H., Fang, S., & Zhao, X. (2015). Hysteroscopy prior to repeat embryo transfer may improve pregnancy outcomes for asymptomatic women with repeated implantation failure. The journal of obstetrics and gynaecology research, 41(10), 1569–1576. https://doi.org/10.1111/jog.12773
11. Kamath, M. S., Bosteels, J., D'Hooghe, T. M., Seshadri, S., Weyers, S., Mol, B. W. J., Broekmans, F. J., & Sunkara, S. K. (2019). Screening hysteroscopy in subfertile women and women undergoing assisted reproduction. The Cochrane database of systematic reviews, 4(4), CD012856. https://doi.org/10.1002/14651858.CD012856.pub2
12. Mao, X., Wu, L., Chen, Q., Kuang, Y., & Zhang, S. (2019). Effect of hysteroscopy before starting in-vitro fertilization for women with recurrent implantation failure: A meta-analysis and systematic review. Medicine, 98(7), e14075. https://doi.org/10.1097/MD.0000000000014075
13. Nahshon, C., Sagi-Dain, L., & Dirnfeld, M. (2020). The impact of endometrial injury on reproductive outcomes: results of an updated meta-analysis. Reproductive medicine and biology, 19(4), 334–349. https://doi.org/10.1002/rmb2.12348
14. Phillips, C. H., Benson, C. B., Ginsburg, E. S., & Frates, M. C. (2015). Comparison of uterine and tubal pathology identified by transvaginal sonography, hysterosalpingography, and hysteroscopy in female patients with infertility. Fertility research and practice, 1, 20. https://doi.org/10.1186/s40738-015-0012-3
15. Polanski, L. T., Baumgarten, M. N., Quenby, S., Brosens, J., Campbell, B. K., & Raine-Fenning, N. J. (2014). What exactly do we mean by 'recurrent implantation failure'? A systematic review and opinion. Reproductive biomedicine online, 28(4), 409–423. https://doi.org/10.1016/j.rbmo.2013.12.006
16. Pundir, J., Pundir, V., Omanwa, K., Khalaf, Y., & El-Toukhy, T. (2014). Hysteroscopy prior to the first IVF cycle: a systematic review and meta-analysis. Reproductive biomedicine online, 28(2), 151–161. https://doi.org/10.1016/j.rbmo.2013.09.025
17. Rama Raju, G. A., Shashi Kumari, G., Krishna, K. M., Prakash, G. J., & Madan, K. (2006). Assessment of uterine cavity by hysteroscopy in assisted reproduction

programme and its influence on pregnancy outcome. Archives of gynecology and obstetrics, 274(3), 160–164. https://doi.org/10.1007/s00404-006-0174-7

18. Seval, M. M., Şükür, Y. E., Özmen, B., Kan, Ö., Sönmezer, M., Berker, B., & Atabekoğlu, C. (2016). Does adding endometrial scratching to diagnostic hysteroscopy improve pregnancy rates in women with recurrent in-vitro fertilization failure? Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology, 32(12), 957–960. https://doi.org/10.1080/09513590.2016.1190818
19. Shawki, H.E., Elmorsy, M., Eissa, M.K. (2012). Routine office hysteroscopy prior to ICSI and its impact on assisted reproduction program outcome: a randomized controlled trial. Middle East Fertil Soc J; 17:14–21.
20. Shohayeb, A., & El-Khayat, W. (2012). Does a single endometrial biopsy regimen (S-EBR) improve ICSI outcome in patients with repeated implantation failure? A randomised controlled trial. European journal of obstetrics, gynecology, and reproductive biology, 164(2), 176–179. https://doi.org/10.1016/j.ejogrb.2012.06.029
21. Smit, J. G., Kasius, J. C., Eijkemans, M. J. C., Koks, C. A. M., van Golde, R., Nap, A. W., Scheffer, G. J., Manger, P. A. P., Hoek, A., Schoot, B. C., van Heusden, A. M., Kuchenbecker, W. K. H., Perquin, D. A. M., Fleischer, K., Kaaijk, E. M., Sluijmer, A., Friederich, J., Dykgraaf, R. H. M., van Hooff, M., Louwe, L. A., … Torrance, H. L. (2016). Hysteroscopy before in-vitro fertilisation (inSIGHT): a multicentre randomised controlled trial. Lancet (London, England), 387(10038), 2622–2629. https://doi.org/10.1016/S0140-6736(16)00231-2