Routine use of hysteroscopy before in-vitro fertilization: Systematic review and meta-analysis of randomized controlled trials

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Review Article

ABSTRACT

Objective: This study aimed to synthesize evidence from published Randomized Controlled Trials (RCTs) about the effectiveness of hysteroscopy in both women scheduled for first in-vitro fertilization (IVF) and women with recurrent IVF failure.

Study Design: We searched the following electronic databases: PubMed, Scopus, Web of Science and Cochrane Central. Retrieved records were screened for eligibility. Dichotomous data were pooled as relative risk (RR) in a random-effect model. We used Review Manager 5.3 for windows.

Results: Five unique RCTs with a total of 2636 patients were included. The overall effect estimates did not favour hysteroscopy group in terms of live birth from a pregnancy, ongoing pregnancy during the trial period, clinical pregnancy during the trial period, and incidence of miscarriage. The pooled analysis were not homogenous *(P <0.1)*.

Conclusion: The current evidence is insufficient to support the routine use of hysteroscopy in both women scheduled for first IVF and women with recurrent IVF failure.

Key Words: Hysteroscopy, in-vitro fertilization, meta-analysis, recurrent IVF failure

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INTRODUCTION

Infertility is a challenging medical condition that nearly affects every fifth couple at the reproductive age. In many cases, infertility can be attributed to organic conditions which require medical intervention[10]. Moreover, infertility was strongly linked to high level of psychological stress which may need a combination of different psychosocial interventions[18]. In vitro fertilization (IVF), which is a multi-stage procedure including stimulation of ovulation, oocytes retrieval, ova fertilization, culture of embryos and subsequently, the transfer of embryos to the uterine cavity, is one of the most effective treatment modalities for non-male factor infertility in the last decades[21]. IVF was reportedly resulted in born of more than 5 million livebirths since its introduction in 1970s[26]. Despite its high cost, the success rate of IVF remains a major challenge with a large unexplained gap remains between the number of embryo transfers and the number of ongoing pregnancies[2,25].

Implantation failure may be attributed to a variety of reasons including the embryo quality and the uterine receptivity. However, unexplained implantation failure accounts for considerable proportion of the cases[13]. The prevalence of unsuspected uterine pathology in asymptomatic women that may negatively affect the uterine receptivity and reduce the chance of implantation has been reported to be as high as 50%[1]. Therefore, a detailed examination of the intra uterine integrity prior to IVF and subsequent management of any abnormal findings is proposed as an

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effective strategy for reducing the implantation failure[3,12]. Hysteroscopy has been proposed as a minimally invasive, well tolerated, procedure that allows reliable visual assessment of the cervical canal and uterine cavity to detect any abnormality prior to IVF[12,24]. However, the current body of evidence shows a conflicting results regarding the clinical utility of routine hysteroscopy prior to IVF[7,19].

AIM OF THE WORK

The aim of the present meta-analysis is to synthesis evidence from the published randomized controlled trials (RCTs) about the effectiveness of routine hysteroscopy in improving the pregnancy outcomes of IVF.

PATIENTS AND METHODS

We performed this review according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement[14].

Inclusion and Exclusion criteria:

We included RCTs with the following criteria ; trials whose population was infertile women undergoing IVF for the first time or due to recurrent failure, the study group included women who had hysteroscopy performed prior to the IVF and the control group was those who undergoing IVF without prior hysteroscopy. In the case of multiple reports for the same study population, we analyzed data of the most complete dataset. Studies were excluded for the following reasons ; studies without reliable data for extraction, thesis and conference papers and non-English studies.

Literature Search Strategy:

We performed a comprehensive search of four electronic databases; PubMed, Scopus, Web of science and Cochrane CENTRAL using the following query (Hysteroscopy AND invitro-fertilization). We conducted an additional manual search for relevant studies in the references of included studies. Three independent reviewers screened the titles and abstracts of retrieved records, followed by full-texts screening for eligibility. Any disagreements were resolved by discussion and consensus.

Data Extraction:

The extracted data included the following domains; characteristics of study design, baseline criteria of included population, risk of bias domains and study outcomes. Four reviewers extracted the data from the included articles and any discrepancies were solved by discussion. We extracted data from graphs using PlotDigitizer software (http://plotdigitizer.sourceforge.net/).

Quality assessment:

The quality of the retrieved RCTs was assessed according to Cochrane handbook of systematic reviews of interventions 5.1.0 (updated March 2011). Risk of bias assessment included the following domains: sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias. The authors' judgments are categorized as low risk, high risk or unclear risk of bias. We used the quality assessment table provided in (part 2, Chapter 8.5) the same book[8].

Measures of treatment effect:

The primary outcomes, in studies assessed the efficacy of hyeteroscopy, were:

1- A live birth from a pregnancy which defined as delivery of a live fetus after 24 weeks of gestation.

2- Ongoing pregnancy defined as the detection of a fetal heartbeat on ultrasound at four or more weeks of gestation

3- Clinical pregnancy defined as the presence of a gestational sac four or more weeks after embryo transfer.

Data Synthesis:

Dichotomous data were pooled as relative risk (RR) in a random-effect model using inverse-variance method. We used Review Manager 5.3 for windows.

Assessment of heterogeneity:

Heterogeneity was assessed by visual inspection of the forest plots and measured by I-square and Chi-Square tests. Chi-square test was used to test the existence of significant heterogeneity while I-square quantifies the variability in effect estimates that is due to heterogeneity, if present. I-Square test was interpreted according to recommendations of Cochrane Handbook of Systematic Reviews and meta-analysis (0% to 40% might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity and 75% to 100% considerable heterogeneity). Significant heterogeneity was considered at Chi-Square $P<0.1$.

Sensitivity analysis:

In order to resolve detected statistical heterogeneity, we performed sensitivity analysis excluding one study in each scenario.

Publication bias:

According to Egger andcolleagues[5,23], publication bias assessment is not reliable for less than 10 pooled studies.

Therefore, in the present study, we could not assess the existence of publication bias by Egger's test for funnel plot asymmetry.

RESULTS

We retrieved 664 unique citations. From which, five unique RCTs with a total of 2636 patients (Hysteroscopy group n= 1285 and Control group n=31351) were included in the present systematic review and meta-analysis. (See PRISMA flow diagram; Figure.1).

Two included trials performed hysteroscopy to infertile women with no prior IVF[7,20], while the remaining trials included infertile women with recurrent IVF failure[4,6,17]. Investigators involved in the embryo transfer were masked to group allocation in two included trials[6,20] and the sample size of included studies ranged from 200 to 750 participants. Hysteroscopy and control groups did not differ significantly regarding any of baseline variables in included trials. Interestingly, Smith *et al.* and El-Toukhy, *et al.* reported that routine use of hysteroscopy does not improve live birth rates, clinical pregnancy, or ongoing pregnancy in infertile women scheduled for IVF treatment[6,20]. In contrast, the remaining three trials concluded that hysteroscopy is recommended for infertility workup before IVF even in patients with normal ultrasound finding[4,7,17]. Summary of included studies and baseline characteristics are shown in Table 1.

The quality of the included RCTs was from moderate to high quality according to Cochrane risk of bias assessment tool. Summary of quality assessment domains of included studies is shown in Figure 2. Authors' judgments with justifications are shown in supplementary file no.1.

Effect of hysteroscopy prior to IVF in pregnancy outcomes:

The overall effect estimates did not favor hysteroscopy group in any of the following terms; a live birth from a pregnancy during the trial period (No prior IVF group' RR 1.06, 95% CI [0.93, 1.20], p =0.41; Recurrent IVF failure group' RR 1.29, 95% CI [0.77, 2.16], p =0.33; Figure 3), ongoing pregnancy during the trial period (No prior IVF group' RR 1.25, 95% CI [0.86, 1.80], p =0.24; Recurrent IVF failure group' RR 0.98, 95% CI [0.82, 1.19], p =0.86; Figure 4), clinical pregnancy during the trial period (No prior IVF group' RR 1.03, 95% CI [0.88, 1.21], p =0.68; Recurrent IVF failure group' RR 1.31, 95% CI [0.90, 1.90], p =0.15; Figure 5) and incidence of miscarriage (No prior IVF group' RR 1.23, 95% CI [0.82, 1.83], p =0.32; Recurrent IVF failure group' RR 0.91, 95% CI [0.74, 1.13], p =0.39). The pooled analysis were not homogenous (P <0.1).

SENSITIVITY ANALYSIS

Statistically significant heterogeneity was detected in most of pooled outcomes. This heterogeneity was best resolved by excluding either Smit *et al.* or El-Toukhy, *et al*. Both trials reported statistically insignificant effect of hysteroscopy in pregnancy outcomes[6,20].

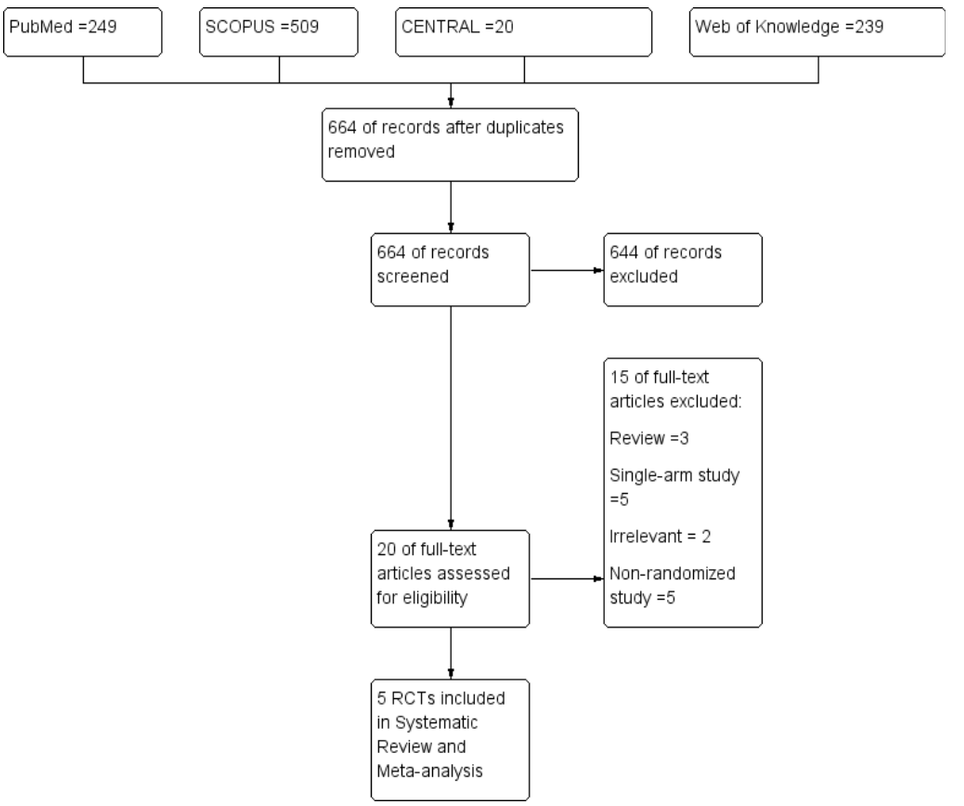

Fig. 1: Shows the PRISMA flow diagram of studies' screening and selection

Fig. 2: Shows the risk of bias summary and risk of bias graph according to Cochrane Risk of Bias assessment tool

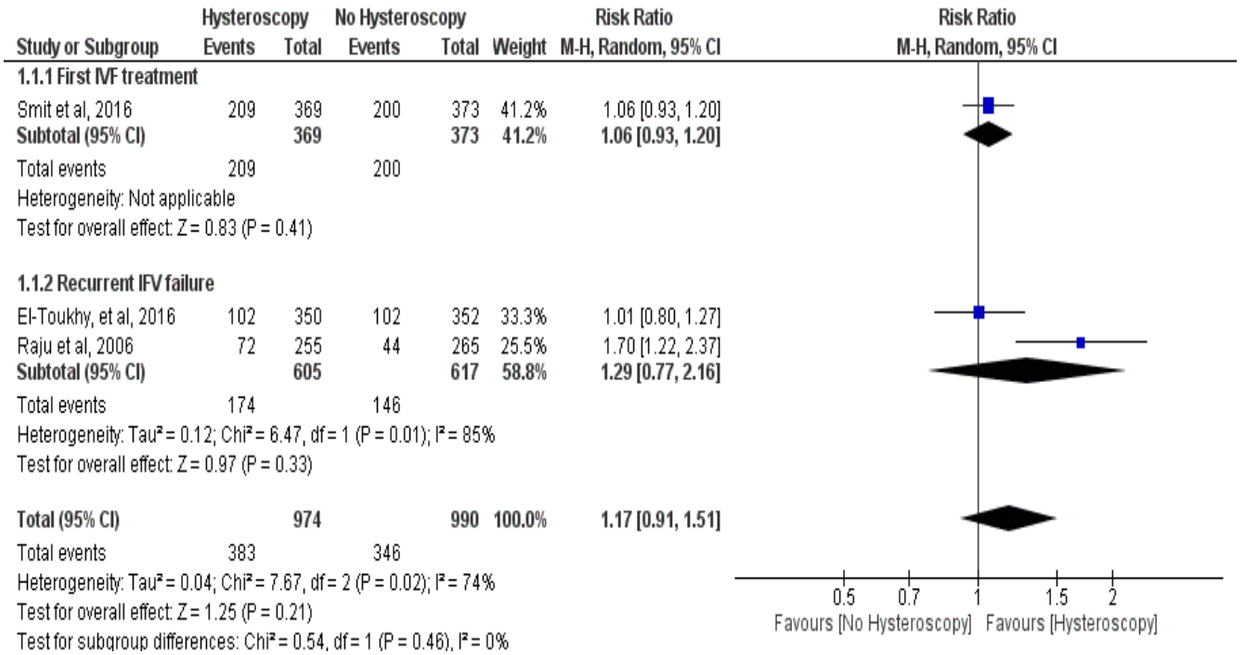

Fig. 3 : Shows forest plots of relative risk in a live birth from a pregnancy during the trial period. RR=Relative risk, M-H=Mantel-Haenzel, CI=confidence interval

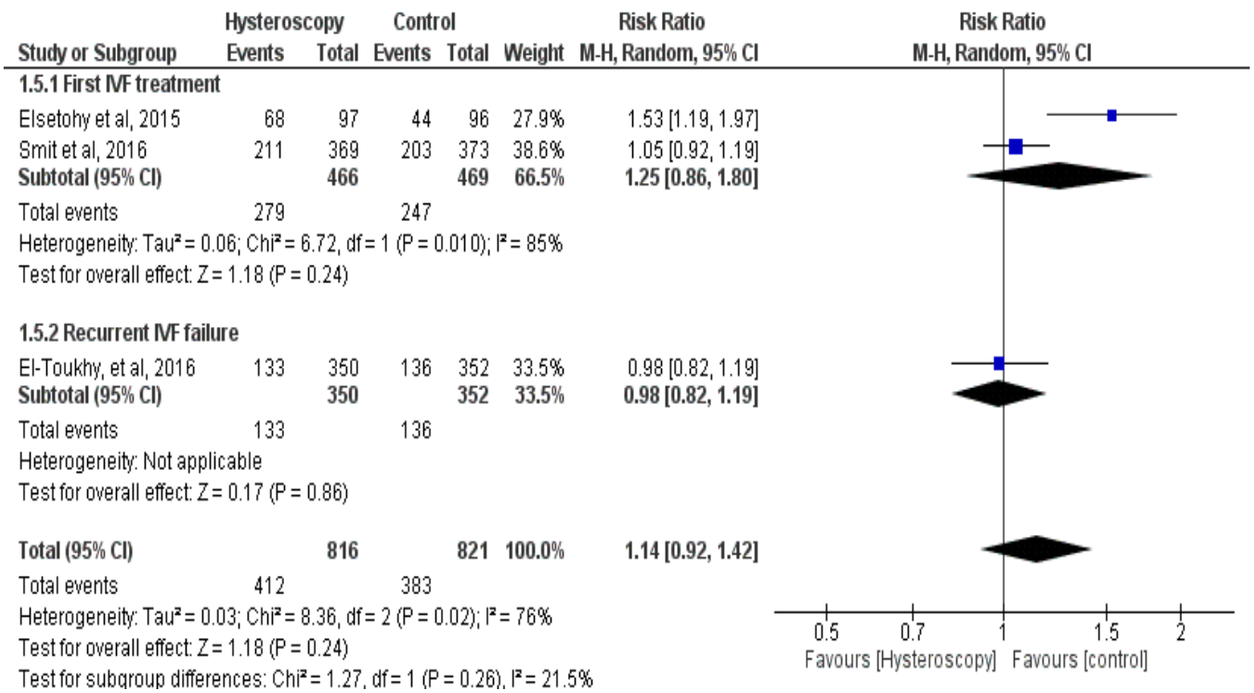

Fig. 4: Shows forest plots of relative risk in ongoing pregnancy during the trial period. RR=Relative risk, M-H=Mantel-Haenzel, CI=confidence interval

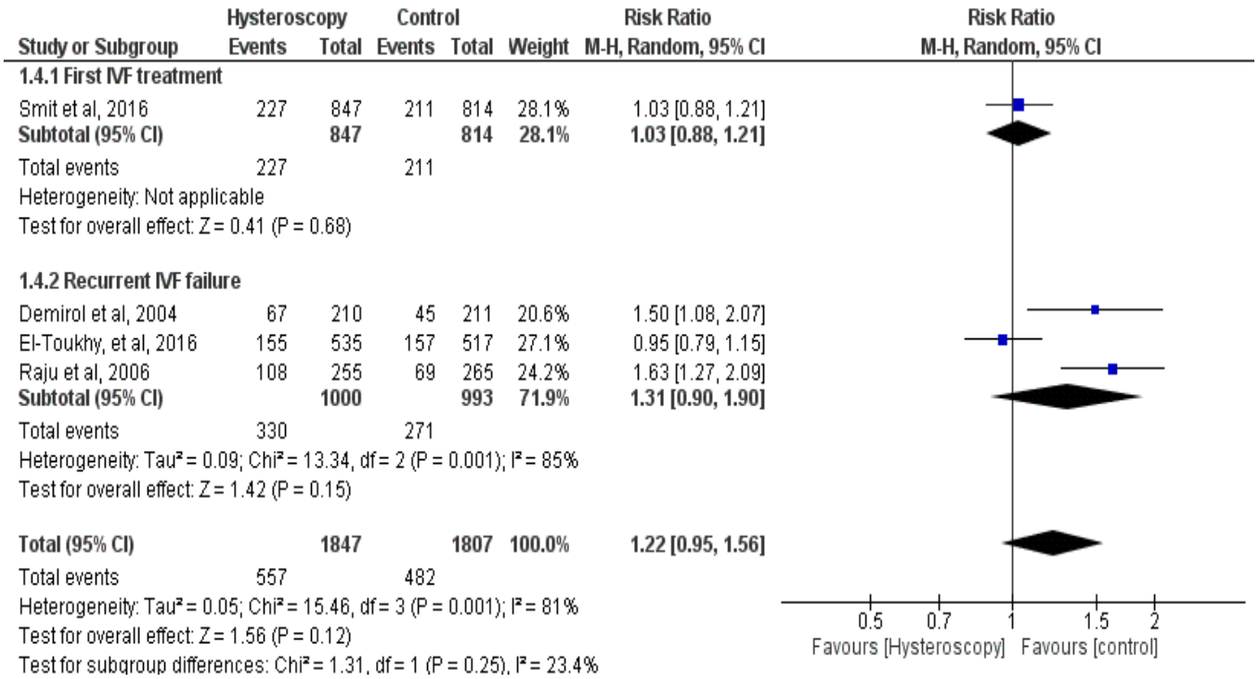

Fig. 5: Shows forest plots of relative risk in clinical pregnancy during the trial period. RR=Relative risk, M-H=Mantel-Haenzel, CI=confidence interval

Table 1: Summary of the included studies

Author, year	Study Design	Population	Sample Size	Control	Main findings
Smit *et al*, 2016	Single-blinded RCTS	Infertile women with no prior IVF	750	Immediate IVF	Routine hysteroscopy does not improve livebirth rates in infertile women scheduled for a first IVF treatment
El-Toukhy, *et al*, 2016	Single-blinded RCTs	Infertile women with recurrent IVF failure	752	Immediate IVF	Outpatient hysteroscopy before IVF in women with history of unsuccessful IVF treatment cycles does not improve the livebirth rate
Elsetohy *et al*, 2015	Open-label RCTs	Infertile women with no prior IVF	193	Immediate IVF	Routine office hysteroscopy is an essential step for infertility workup before ICSI even in patients with normal TV/US.
Raju *et al*, 2006	Open-label RCTs	Infertile women with recurrent IVF failure	520	Immediate IVF	Patients with recurrent IVF failures should evaluated using hysteroscopy prior to further commencing IVF-embryo transfer cycles in order to enhance the clinical pregnancy rates.
Demirol *et al*, 2004	Open-label RCTs	Infertile women with recurrent IVF failure	421	Immediate IVF	Women with recurrent IVF failures should evaluated using hysteroscopy prior to IVF-embryo transfer cycles.

DISCUSSION

Uterine cavity abnormalities, as polyps, have been linked to a reduced chance of successful pregnancy among IVF treated women[15,22] which lead to the hypothesis that hysteroscopy may improve pregnancy rates through removal of such abnormalities. The present meta-analysis shows that the current evidence is insufficient to support the routine use of hysteroscopy in both women scheduled for first IVF and women with recurrent IVF failure. Our pooled analysis showed that hysteroscopy did not improve live birth rates, ongoing pregnancy rates, clinical pregnancy rates, or reduced the incidence of miscarriage.

This result comes in concordance with the recent large two RCTs. This insight trial was an open-label multicenter study that included 750 infertile women who underwent their first IVF treatment cycle, the study reported insignificant improvement in pregnancy outcomes among women who underwent hysteroscopy before IVF[20]. Similarly, TROPHY trial observed no difference in live birth rates among women with recurrent IVF failure who underwent hysteroscopy in comparison to women who scheduled for IVF directly[6]. In contrary, previous RCTs reported that hysteroscopy leads to more successful pregnancy outcome among women scheduled for first IVF treatment. However, these trials have many methodological limitations as small sample size, the quality of embryo transfer, and the single-center deign[4,7,17]. The observed heterogeneity in the published literature may be attributed to different inclusion criteria, two RCTs excluded women who had previous intrauterine surgery[6,20], three trials included only women with normal trans-vaginal ultrasound (TVUS)[6,7,20], and all studies included women with different duration of infertility. Demirol *et al.* and Raju *et al.* did not report whether the pathologies they noted at hysteroscopy were suspected or not at TVUS, which did not allow to compare their results with trials who included women with normal TVUS findings. In addition, the fact that hysteroscopy was done by different gynecologists in different studies might be regarded as a limitation because studies on the diagnostic accuracy of hysteroscopy have shown that it is associated with a considerable degree of inter-observer variability.[11,20]

Moreover, a meta-analysis by Pundir *et al.* reported a different results from our polled analysis by showing that hysteroscopy increases live birth rate among women scheduled for their first IVF treatment[16]. The mentioned meta-analysis included only one RCT and four non-randomized trials (N =3179 participants) which may increase the susceptibility to selection bias, and subsequently limit the quality of their results[9]. In contrary, our pooled analysis included only RCTs (N = 2636 patients), that is least likely to be biased, with a transparent assessment of the quality of evidence.

THE STRENGTHS AND THE LIMITATIONS OF THE STUDY:

We performed this review according to PRISMA statement[14]. The strengths of the current meta-analysis comprise a comprehensive search of published clinical trials studies from multiple electronic databases. Furthermore, there was a transparent assessment of the quality of evidence.

The main limitation of this meta-analysis is the small number of included studies. Consequently, we cannot analysis the effect of uterine cavity abnormalities detected by TVUS using a subgroup analysis with a lot of data in details. Only one trial was blinded, which increase the risk of performance bias[6].

CONCLUSION

In conclusion, the present meta-analysis shows that the current evidence is insufficient to support the routine use of hysteroscopy in both women scheduled for first IVF and women with recurrent IVF failure. Our pooled analysis showed that hysteroscopy did not improve live birth rates, ongoing pregnancy rates, clinical pregnancy rates, or reduced the incidence of miscarriage.

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Study concept and design:
Internet searching:.
Selection of studies:
Data extraction:
Quality assessment:
Data analysis:
Drafting the manuscript:
Revision and appraisal of the manuscript:
Proofreading the manuscript:
Study monitoring & supervision: Ahmed Elgebaly

CONFLICT OF INTEREST

There are no conflicts of interest.

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