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Review

Endometrial injury prior to assisted reproductive techniques for recurrent implantation failure: a systematic literature review

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ABSTRACT

Endometrial injury to improve implantation for women undergoing assisted reproductive techniques has attracted a lot of attention recently and has rapidly become incorporated into clinical practice. The aim of this study is, thus, to assess the effectiveness and safety of endometrial injury performed in the cycle preceding assisted reproductive techniques in women with recurrent implantation failure. Electronic database searches, including MEDLINE, EMBASE, CENTRAL and grey literature, up to 30th May 2015 were conducted with no restrictions. Randomized controlled trials comparing endometrial injury versus placebo or no treatment in the cycle preceding assisted reproductive techniques in women with recurrent implantation failure were selected. The primary outcome was live birth rate. Secondary outcomes were clinical pregnancy, implantation, miscarriage and procedure-related complication rates. Of the 1115 publications identified, 4 met the inclusion criteria. Meta-analysis was not possible due to significant clinical heterogeneity among the included studies. Patients' characteristics differed, as did the intervention used with endometrial injury being performed at different phases of the preceding menstrual cycle. Moreover, the effect of endometrial injury on live birth and clinical pregnancy rates were inconsistent among the included studies. In summary, there is currently insufficient evidence to support the use of endometrial injury in women with recurrent implantation failure undergoing assisted reproductive techniques while the procedure-associated complication rate has not been assessed. Clinical implementation should, thus, be deferred until robust evidence becomes available.

Contents

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Introduction

Endometrial injury, which is defined as the intentional trauma to the endometrium by biopsy or curettage [1], has recently attracted a lot of attention as a new promising treatment for women who undergo assisted reproductive techniques (ART) and suffer from recurrent implantation failure. This reflects attempts from reproductive clinicians and researchers to further improve ART clinical outcomes and effectively treat fertility problems, which could affect one in four couples at some point during their reproductive life [2]. Despite the recent advances in reproductive technologies and the overall increasing trend of live birth rates, the success rate of ART is still low with an overall live birth rate per cycle of only 24.5% in the UK [3] and approximately 25–35% in North America [4,5].

The most likely stage for an ART cycle to fail is following embryo transfer. Despite the fact that approximately 86% of all treatment cycles reach the stage of embryo transfer, only 29% result in clinical pregnancies [3] indicating failed implantation in two out of three embryo transfers. Moreover, if the practice of double or triple embryo transfer is to be taken into consideration, the implantation failure rate per embryo transferred would actually be even higher. Indeed, it is estimated that the implantation rate following IVF is not higher than 20% [6]. It is thus apparent that imperfect transfer techniques and/or implantation failure continue to impair ART treatment outcomes causing distress for patients and clinicians [7].

Embryo implantation remains 'one of the last frontiers of reproductive medicine' [8]. It involves a complex interaction between the embryo and the uterus [9]. An essential feature of this interaction is the synchronized development of a healthy embryo to the blastocyst stage and receptive endometrium which is coordinated by various signalling pathways, influencing cell–cell and cell–matrix interactions between the embryo and the uterus [10,11]. Factors affecting embryo implantation can therefore be divided into embryo factors, uterine factors – including endometrial factors and uterine contractility [12] – and the embryo/endometrial synchrony [13,14].

It has been postulated that local endometrial injury increases implantation rate through the induction of decidualization [15,16] and the release of cytokines, interleukins, growth factors, macrophages and dendritic cells that improve the chances of embryonic implantation [17]. It is also thought to lead to better synchronicity between endometrium and the transferred embryo, which appears to be the limiting factor in cases of recurrent implantation failure.

The definition of recurrent implantation failure (RIF) remains controversial, as does its management. RIF can be defined as the repeated lack of implantation after the transfer of embryo(s) and has become a clinically identifiable phenomenon because of ART, which has enabled compartmentalization of pregnancy events. The majority of fertility specialists agree that recurrent implantation failure is defined as a failure to achieve a pregnancy after 3 completed fresh ART-embryo transfer cycles with good morphology embryos to a normal uterus [18,19]. This definition has been challenged due to the variability of the number of embryos transferred on any given cycle, the quality of the embryos, and the day of embryo transfer [20]. Other experts utter concerns regarding possible pathophysiological conditions amenable to treatment much sooner during the ART process and raise the issue of implantation failure even after one or none previous ART-embryo transfer cycle. By definition, implantation failure can only recur if it has happened at least two times. Therefore, in an attempt to incorporate all current views on the matter, we define RIF as a failure to achieve a pregnancy after 2 completed fresh ART-embryo transfer cycles with good quality embryos to otherwise healthy women.

A link between endometrial injury and increased pregnancy rates in subsequent ART procedures has been described in recent publications of variable quality. This comprehensive systematic literature review, thus, aims to find and summarize the best available evidence on the effectiveness and safety of endometrial injury for women with recurrent implantation failure undergoing ART procedures.

Materials and methods

We systematically searched the MEDLINE (from 1948 to May 2015), EMBASE (from 1969 to May 2015), Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (issue 4, 2015) in order to identify all reports of endometrial injury prior to ART for women with recurrent implantation failure. There were no language, publication date or publication status restrictions. In addition, we performed a cross-reference search of all included studies and relevant reviews that were identified during the search process. Moreover, in order to identify unpublished studies and studies in progress, we searched the grey literature including clinical trials registers, conference proceedings, relevant Internet sources and clinical guidelines. An electronic search strategy was developed and adapted in order to ensure high sensitivity in the expense of specificity. The search strategy for the main databases is presented in Supplementary data S1.

Studies were included if they: (1) were randomized controlled trial (RCTs) comparing endometrial injury in the cycle preceding ART with placebo or no intervention; (2) included women undergoing ART with 2 or more previous implantation failures; (3) reported at least one of the outcomes of interest: clinical pregnancy rate, defined as the number of clinical pregnancies expressed per 100 embryo transfer cycles [21]; live birth rate, defined as the number of deliveries that resulted in at least one live born baby, expressed per 100 initiated embryo transfer cycles [21]; implantation rate, defined as the number of gestational sacs observed divided by the number of embryos transferred [21]; miscarriage rate, defined as the number of spontaneous clinical pregnancy losses before 20 completed weeks of gestational age or losses of an embryo/fetus of less than 400 g per 100 clinical pregnancies; procedure-related complications [21]; defined as undesirable and unintended deviation from the ideal intra- or post-operative course, regardless of the type of intervention required to restore normality [22]. All studies failing to meet these criteria or studies that included women with one or less implantation failure or women with other causes of recurrent implantation failure such as uterine cavity pathology, structural uterine anomaly, hydrosalpinx, were excluded.

Data were extracted independently by two reviewers using a standardized data collection sheet. Disagreements were resolved by consensus. The methodological quality of the included studies was evaluated independently by two reviewers. In case of uncertainty, consensus was reached by discussion. The risk of bias within studies was assessed using the Cochrane tool [23].

Results

We identified 1115 citations through the electronic literature searches (Fig. 1) and excluded 1068 after screening titles and abstracts. A further 43 were excluded for studying different population or intervention or different timing of intervention or not offering ART or not being randomized controlled trial or being unfinished trials (Supplementary data S2). After detailed evaluation of the citations, 4 primary articles met the inclusion criteria and their population was included in the evidence synthesis (either a whole trial population or a subgroup reported separately) (Fig. 1). The majority of the included studies were found to be well

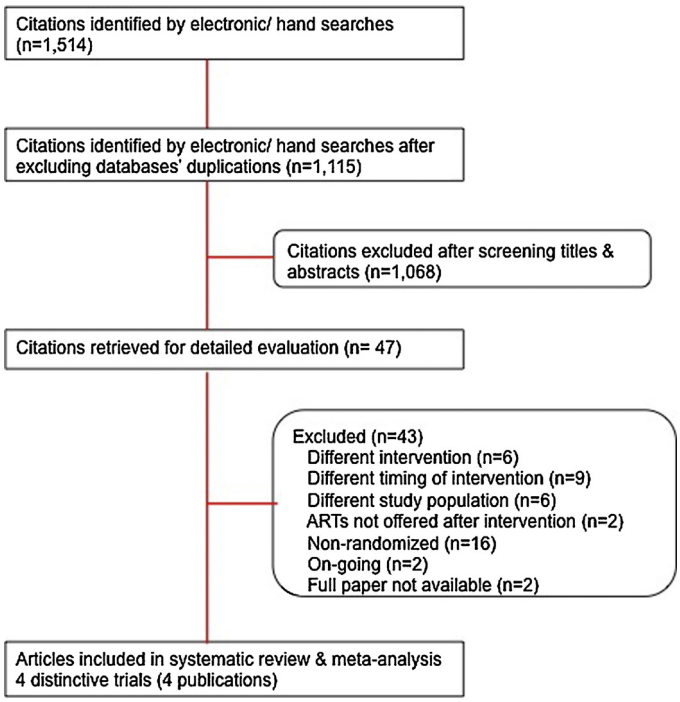

Fig. 1. Study selection process for systematic review of endometrial injury for recurrent implantation failure prior to assisted reproductive techniques.

performed with low risk of bias (Fig. 2). However, the study by Karimzadeh et al. [24] was thought to have high risk of bias due to lack of blinding, incomplete outcome data and selective reporting (Fig. 2). Moreover, intention-to-treat analysis was only followed in the study by Nastri et al. [26] and, therefore, is unclear whether prognostic balance generated by the original random allocation is maintained in the remaining three included studies [24,25,27]. The number of included studies was small and hence funnel plots were not useful in assessing the presence of publication bias or other bias related to trials size. We summarized results narratively due to significant differences in study quality, population and intervention characteristics.

The characteristics of the three included studies are summarized in Table 1. Study settings were varied: Iran [24], Israel [25], Brazil [26] and Egypt [27]. All studies were conducted in units outside Europe or North America. The study sample sizes ranged from 32 to 200 patients and together these studies involved a total of 416, with 208 being in the treatment arm and 208 in the control arm. All included trials used a two-armed, parallel group design. The subgroup of patients with recurrent implantation failure from the Nastri et al. [26] RCT met the inclusion criteria and were studied for the purposes of this systematic review. Population characteristics varied across studies (Table 1) with the Baum et al.'s study [25] having recruited older women (average age 34 years of age). The number of previous assisted reproductive technique–embryo transfer cycles (ART-ET) were similarly varied between comparison treatments groups (Table 1). Variations in co-interventions used were, also, apparent with women recruited in the Nastri et al. [26] study using the oral contraceptive pill in the cycle preceding controlled ovarian stimulation and embryo transfer. Last but not least, even though all studies used endometrial biopsy as the studied intervention, its timing differed across studies with the Shohayeb and El-Khayat's study [27] offering endometrial biopsy during the proliferative phase, the Karimzadeh et al.'s study [24] during the luteal phase and, finally, the Baum et al.'s study [25] during both phases of the preceding menstrual cycle (Table 1). The timing of endometrial injury was not specified in the Nastri et al.'s [26] study. Endometrial biopsy was compared with either no intervention [24] or sham procedures [25,26]. The last included study [27], though, used diagnostic hysteroscopy in the control group, which could work as an effect modifier and haze endometrial injury's effects.

The results for the efficacy and safety outcomes are summarized in Table 2. In assessments of efficacy, most studies used standard outcome measures such as clinical pregnancy, live birth, implantation, miscarriage and complication rates. Three of the included studies [24,26,27] comparing endometrial biopsy against no intervention or sham procedure showed that endometrial biopsy was superior to sham procedure for most of the outcome

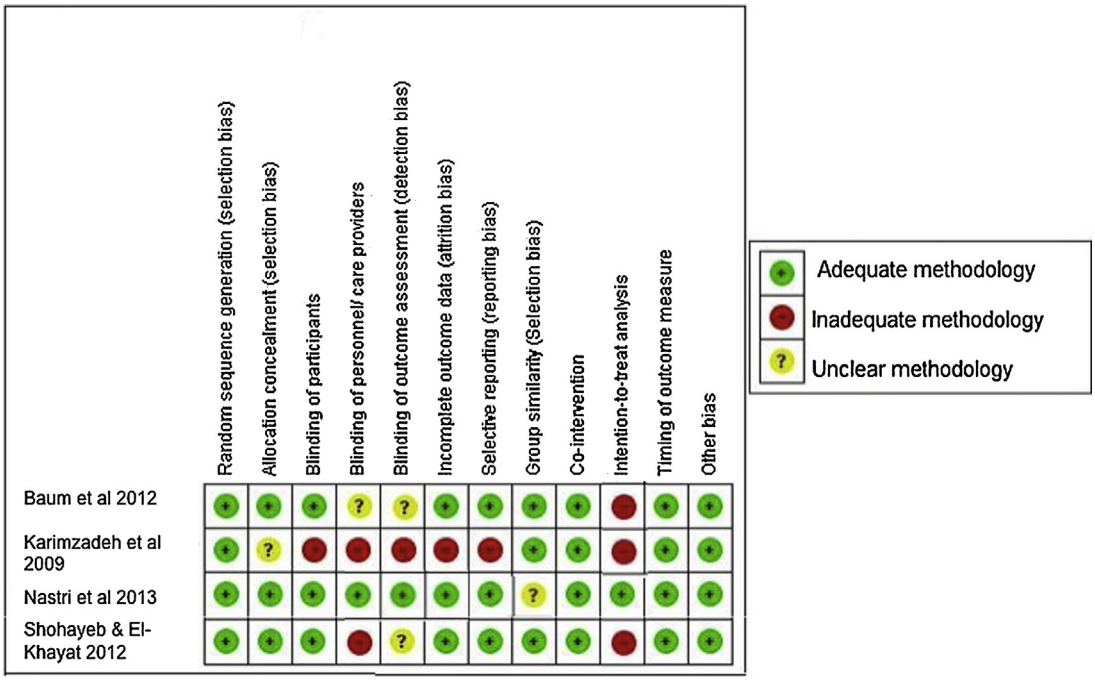

Fig. 2. Methodological characteristics of the three included trials.

Table 1
Characteristics of included studies.

Study	Design	Study size	Setting	Population	Mean age	Failed ART-ET (No; mean)	Gonadotrophins (iu; mean)	Oocyte on OR (No; mean)	Embryos transferred (No; mean)	Intervention(s)	Control	Co-interventions
Baum et al. [25]	RCT	36 randomized 32 analyzed	Israel	*Inclusions:* Age 18–41; ≥3 previous failed ART-ET cycles with good ovarian response *Exclusions:* Uterine malformation; endometrioma, hydrosalpinx	*Ix* 34.8 *Control* 34.4	*Ix* 8.5 *Control* 8.8	*Ix* 2735 *Control* 2667	*Ix* 8.4 *Control* 10.4	*Ix* 2.9 *Control* 2.9	EB which was performed during the preceding cycle (days 9–12 and 21–24). EB was performed with Pipelle de Cornier	Cervical biopsy	No additional tx was used
Karimzadeh et al. [24]	RCT	115 randomized 93 analyzed	Iran	*Inclusions:* Age 20–40; no hx of blood diseases; 2–6 failed ART-ET cycles *Exclusions:* Age >40; hx of poor previous response; Uterine malformation, endometrioma, hydrosalpinx	*Ix* 29.9 *Control* 29.7	*Ix* 2.52 *Control* 2.18	*Ix* 1491 *Control* 1479	*Ix* 5.42 *Control* 5.89	*Ix* 2.48 *Control* 2.65	EB which was performed during the preceding cycle (luteal phase: days 21–26). EB was performed with Pipelle de Cornier	No intervention	No additional tx was used
Nastri et al. [26]	RCT	91 randomized & analyzed	Brazil	*Inclusions:* Age <38; submitted to COS, oocyte retrieval & embryo transfer *Exclusions:* Not specified	*Ix* 32.78 *Control* 32.35	*Ix* n/r *Control* n/r	*Ix* n/r *Control* n/r	*Ix* n/r *Control* n/r	*Ix* n/r *Control* n/r	EB which was performed during the preceding cycle (days not specified). EB was performed with Pipelle de Cornier	Sham procedure: drying of cervix with gauze for 30 s	OCP (ethinyl estradiol 30 mcg+ levonorgestrel 150 mcg) for at least 10 days
Shohayeb and El-Khayat [27]	RCT	210 randomized 200 analyzed	Egypt	*Inclusions:* Age < 39; ET < 5 mm on day 4, ≥2 previous failed ART-ET *Exclusions:* Abnormal endometrial cavity	*Ix* 30.7 *Control* 30.6	*Ix* 2.9 *Control* 2.92	*Ix* n/r *Control* n/r	*Ix* 11.6 *Control* 11.6	*Ix* 3.2 *Control* 3.3	Diagnostic HS & EB which were performed during the preceding cycle (days 4–7) EB was performed with Novak curette	Diagnostic HS	No additional tx was used

ART = assisted reproductive techniques; COS = controlled ovarian stimulation; EB = endometrial biopsy; ET = embryo transfer; HS = hysteroscopy; hx = history; Ix = intervention; No = number; n/r = not reported; OCP = oral contraceptive pill; OR = oocyte retrieval day; PGD = preimplantation genetic diagnosis; tx = treatment.

Table 2
Results of individual studies.

Study	Intervention and no. of subjects		Outcome measure	Outcomes		Treatment effect
	Treatment group	Control group		Treatment group	Control group	
Baum et al. [25][a]	EB	Cervical biopsy	Clinical pregnancy rate	1/16 (6.25%)	5/16 (31.25%)	$P<0.05$*
			Live birth rate	0/16 (0%)	4/16 (25%)	$P=0.1$
	$N=16$	$N=16$	Implantation rate	2.08%	11.11%	$P=0.1$
			Miscarriage rate	1/1 (100%)	1/5 (20%)	P value not reported
			Complication rate	0	0	n/a
Karimzadeh et al. [24][a]	EB	No intervention	Clinical pregnancy rate	13/48 (27.1%)	4/47 (8.9%)	$P=0.02$*
			Implantation rate	10.9%	3.38%	$P=0.039$*
	$N=48$	$N=45$	Complication rate	0	0	n/a
Nastri et al. [26][b]	EB	Sham procedure	Clinical pregnancy rate	23/44 (52.3%)	11/47 (23.4%)	$P<0.01$*
			Live birth rate	20/44 (45.5%)	8/47 (17.0%)	$P<0.01$*
	$N=44$	$N=47$	Miscarriage rate	3/23 (13%)	3/11 (27.3%)	$P=0.31$
			Complication rate: VAS Pain	Mean: 6.22 SD 2.07	Mean: 2.04 SD 1.61	$P<0.01$*
	Sub-group with $\geq$2 failed ART-ET cycles					
Shohayeb and El-Khayat [27][a]	Diagnostic HS & EB	Diagnostic HS	Clinical pregnancy rate	32/100 (32%)	18/100 (18%)	$P=0.034$*
			Live birth rate	28%	14%	$P=0.024$*
	$N=100$	$N=100$	Implantation rate	12%	7%	$P=0.015$*
			Miscarriage rate	4/32 (12.5%)	4/18 (22%)	$P=0.618$

EB = endometrial biopsy; HS = hysteroscopy; n/a = not applicable.
[a] Analysis performed without an intention-to-treat approach.
[b] Analysis performed with an intention-to-treat approach.
* P value <0.05 means statistical significance.

measures with the exemption of miscarriage rate (Table 2). Karimzadeh et al. [24] found that women in the endometrial biopsy group had greater clinical pregnancy (27.1% vs. 8.9%, p-value= 0.02) and implantation rates (10.9% vs. 3.38%, p-value = 0.039) than those in the control group. Nastri et al. [26] and Shohayed and El-Khayat [27] showed that the endometrial biopsy group had significantly greater clinical pregnancy and live birth rates when compared to the sham procedure group. However, the study by Baum et al. [25] showed that endometrial biopsy had a detrimental effect on clinical pregnancy rate (6.25% for the endometrial biopsy group vs. 31.25% for the sham procedure group, p-value < 0.05). Baum et al. [25], also, found that there was a trend towards worse live birth and implantation rates and higher miscarriage rates in the endometrial biopsy group. Adverse events were only reported in three studies [24–26]. Karimzadeh et al. [24] and Baum et al. [25] stated that no adverse event was observed during endometrial biopsy procedure. However, Nastri et al. [26] showed that women undergoing endometrial injury experienced statistically significant more pain than the sham procedure group.

Comments

This review was conducted to facilitate clinical decisions on the management of women with recurrent implantation failure undergoing ART. The four included studies presented in this systematic review provide by far the most direct assessment of endometrial injury in women with recurrent implantation failure after transfer of good quality embryos and with otherwise normal investigations. Results from these studies, which compared endometrial biopsy in the menstrual cycle preceding ART with no intervention or sham procedures, failed to fully support the role of this intervention as an effective treatment for women with recurrent implantation failures.

The studies by Karimzadeh et al. [24], Nastri et al. [26] and Shohayeb and El-Khayat [27] showed a positive impact of endometrial injury to the main reproductive outcomes even though the first study did not report on live birth rates in addition to the fact that it had increased risk of bias and therefore its conclusions should be interpreted with caution. On the other hand, the study by Baum et al. [25] found a negative impact of endometrial injury on clinical pregnancy rate for women with recurrent implantation failure even though live birth rates did not differ significantly between the two groups. The group of patients in the study by Baum et al. [25] was different from the patients in the other three included studies [24,26,27] and this could have had an impact on the procedure's effectiveness. Also, the group of patients in the study by Baum et al. [25] had more previous implantation failures in comparison to those reported for patients enrolled in the remaining three included studies. These findings might suggest that endometrial injury prior to ART may only be beneficial for younger women or those with less previous implantation failures. A negative impact of endometrial injury prior to ART on the subgroup of women who had at least one failed transfer was also observed in a recent RCT which showed reduced ongoing pregnancy and live birth rates for this population [28]. Therefore, clinicians should remain cautious over introducing this intervention at present outside the scope of research.

Initial data from more than 300 references (mainly case reports, case series, case-controlled studies and expert opinions), 5 RCTs [29–33] and 3 meta-analyses [34–36], which observed that endometrial injury improves the main reproductive outcomes in unselected women undergoing ART, have been encouraging leading to early adoption of this procedure by many reproductive units. However, evidence was either largely observational and unreliable or derived from population groups with different characteristics to women with recurrent implantation failure. Added to this, some of the studies were themselves inconsistent,

with design aspects that potentially biased the result such as the use of sham procedures in the control group, which could have led to unintentional endometrial injury. This was highlighted in the recently updated Cochrane systematic review [36] that includes data from the subgroup of patients with recurrent implantation failure undergoing ART from the recently published RCT by Gibreel et al. [33]. Even though the updated Cochrane systematic review showed a potential positive effect of endometrial injury on live birth rates for women with recurrent implantation failure undergoing ART, it highlighted that several uncertainties remain and called for further research to confirm this observation. Moreover, the methodological limitations of some of the available meta-analyses, which led to computing incorrect or incomplete conclusions, were recently highlighted by Simon and Bellver in an opinion paper [37]. This is in support of our findings and demonstrates that the current inclination of reproductive specialists towards introducing endometrial injury to clinical practice might have been premature, as it is not supported by strong scientific evidence.

Strength of this review include the fact that it was conducted according to the standards of The Cochrane Collaboration and reported according to the PRISMA standards for reporting systematic reviews and meta-analysis [38]. An extensive literature search was carried out without any language or publication status restrictions minimizing the risk of missing relevant studies. Moreover, grey literature was also searched minimizing the risk of introducing publication bias. Limitations of this review include the relatively low number of included studies and total number of patients. Moreover, included RCTs were limited by their suboptimal reporting quality and the lack of relevant data which prevented sub-group meta-analysis that could have further supported our conclusions and assisted in defining the target population for our studied intervention.

Basic research studies have shown that endometrial injury causes significant changes in the gene pattern expression [39,40] even though its effects on the preceding cycle are questionable considering that menstruation will result in endometrium shedding. Therefore, further studies are needed to clarify the mechanisms underlying the effects of endometrial injury on reproductive outcome and define the target patient population who will benefit from this intervention.

In summary, there is currently insufficient evidence to support the safety and effectiveness of endometrial injury in the cycle preceding ART as a treatment option for women with recurrent implantation failures. Thus, evidence-based recommendation about treatment for recurrent implantation failure in women undergoing ART cannot be made until further research outputs become available.

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Conflict of interest

The authors have no conflict of interest in connection with this article.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejogrb.2015.06.026.

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