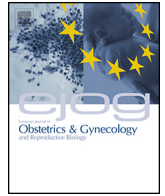




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Review

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.

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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

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