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REVIEW

# Strategies to manage refractory endometrium: state of the art in 2016

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**Abstract** The endometrium is one of a number of factors involved in achieving optimal outcomes after assisted reproductive treatment. Owing to its "passive" growth following adequate ovarian stimulation, it has received virtually no attention. Only when either endometrial thickness or ultrasonographic pattern seem inadequate have different strategies been assessed to try to improve it, especially in those cases where it seems difficult or impossible to make it grow. The objective of this review is to summarize the different strategies that have been investigated in patients with inadequate endometrium, to attempt to provide solid evidence of therapies that may be beneficial and to move away from empirism. A review of the existing literature was performed by searching MEDLINE, EMBASE, Cochrane library and Web of Science for publications in English related to refractory endometrium. Most current treatments are based on anecdotal cases and not on solid data, although worldwide many doctors and patients use them. In conclusion, this review found that it is not easy to provide a pragmatic, evidence-based approach to help physicians and patients confused by the available data on how to improve a poor endometrium. Honest balanced information provided to our patients is the best that we can do.



**KEYWORDS:** assisted reproductive treatment, endometrial lining, IVF, refractory endometrium

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## Introduction and definition of refractory endometrium

Trying to define an optimal endometrium in which to transfer a good embryo has been a goal for researchers. Since ultrasonography became available, both endometrial thickness and pattern have been intensely evaluated. Later, further investigation on uterine irrigation was conducted. Early research quickly identified that the hypoechogenic endometrium was more receptive than the iso- or hyperechogenic endometrium (Check et al., 1993). However, no agreement has been reached on endometrial thickness. Although most clinicians empirically prefer endometria >7 mm, available evidence does not support any specific thickness, as pregnancies with similar success have been described from 5 mm to more than 15 mm (Cai et al., 2011; Remohí et al., 1997). When Doppler technology became available, attempts were made to find the utility of this new technology in predicting embryo implantation, but unfortunately with very little success (Mercé et al., 2008). Nowadays it is understood that imaging technologies can provide information about endometrial receptivity up to a certain stage, as pregnancies have been described even in thin endometria <5 mm, as well as in hyperechogenic endometria. So molecular technologies will help us to further understand endometrial receptivity (Cruz and Bellver, 2014).

These new molecular technologies still need to be validated in prospective trials and new generations of the early tests in use today will be developed, and may be used across centres. Yet today clinicians judge the endometrium from the image they obtain from transvaginal ultrasonography. According to the most recent evidence, endometrial thickness under 7 mm would define a refractory endometrium with compromised success rates (Dix and Check, 2010; Kasius et al., 2014). Although prevalence is low (2.4% according to Kasius et al., 2014), it still represents a challenge today.

When endometrial growth is inadequate, diverse therapeutic approaches are proposed and tested. This review will go over the different known causes for inadequate endometrium growth, as well as the conventional and unconventional treatment options that are being assessed.

## Search methodology

Refractory endometrium management is still generally being debated. This comprenhensive mini-review paper aims to present and discuss current evidence to help provide clinicians with relevant information in their decision-making process with patients.

PubMed was searched for articles published in English between January 1990 and January 2016 using the following MeSH search terms: "endometrium" OR "endometrial lining" combined with "inadequate" OR "refractory" OR "thin", and with "fertility" OR "infertility" OR "surgical" OR "pregnancy" OR "Assisted Reproductive Technology" OR "ART" OR "*in vitro* fertilization" OR "IVF" OR "intracytoplasmatic sperm injection" OR "ICSI" with restriction to humans. Data were extracted independently by two authors, who also performed an initial screening of the title and abstract of all the articles to exclude any citations deemed irrelevant. A manual search of the review articles and cross references completed the search. The data that are presented exclusively as abstracts in national and international meetings were also excluded.

**Table 1** Causes of refractory endometrium.

| *Cause* |
|---|
| Surgical: |
| dilation and curettage |
| partial ablation |
| aggressive myomectomy |
| post-Strassman |
| Radiotherapy |
| Infections |
| Congenital Müllerian anomalies |
| Idiopathic |

## Causes of refractory endometrium

### Surgical aetiology

The most frequent cause of refractory endometrium lies in its surgical origin through the development of intrauterine adhesions (IUA) (**Table 1**). In over 90% of cases, these IUA are the result of cervical dilation and post-abortion obstetrical curettage (Schipper et al., 2010), shown as alterations of menstruation (hypo-amenorrhoea), sterility-infertility with implantation failure in assisted reproductive treatment. It also determines obstetric pathologies, such as recurrent abortion, preterm delivery, placenta accreta and uterine rupture (Al-Serehi et al., 2008; Shiau et al., 2005). The most severe grades are Asherman syndrome whose suspected diagnosis is made by clinical and transvaginal ultrasound, and is confirmed by hysteroscopy or hysterosonography (Taskin et al., 2000).

#### Pathophysiology

Any trauma or accidental resection on the endometrial lining, particularly during pregnancy, can develop fibrosis bridges or adhesions between opposite myometrial surfaces, which distorts the uterine cavity (Galliano et al., 2015; Schipper et al., 2010). In the field of reproduction, adhesions interfere negatively with embryo implantation, and also with correct sperm migration (Revel, 2012). Similarly, placenta accreta would occur because the defect in the basal decidua allows the direct attachment of the chorionic villus to the myometrium (Taskin et al., 2000).

There are three main causes of post-surgical IUA formation: cervical dilation and curettage; intrauterine surgery; and Strassman operation.

#### Cervical dilation and curettage

It is estimated that 15% of all pregnancies end in spontaneous abortion and about 40% of patients with IUA present obstetric curettage in their medical history, making dilation and curettage (D and C) a risk factor for adhesion formation (Hooker et al., 2014). The most common locations of IUA are