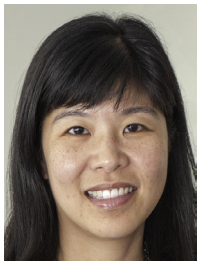
RBMO

REVIEW

Management of thin endometrium in assisted reproduction: a clinical practice guideline from the Canadian Fertility and Andrology Society (CFAS)



BIOGRAPHY

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KEY MESSAGE

Thin endometrium is commonly encountered in patients undergoing assisted reproduction. Endometrial thickness may impact pregnancy and live birth rates in fresh and frozen IVF cycles. There is insufficient evidence for the use of any adjuvants to increase pregnancy or live birth rates in patients with thin endometrium.

ABSTRACT

The impact and management of thin endometrium is a common challenge for patients undergoing assisted reproduction. The objective of this CFAS guideline is to provide evidence-based recommendations using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework on the assessment, impact and management of thin endometrium in assisted reproduction. The effect of endometrial thickness on pregnancy and live birth outcomes in ovarian stimulation and IVF (fresh and frozen cycles) is addressed. In addition, recommendations on the use of adjuvants to improve endometrial thickness and pregnancy outcomes are provided.

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This article is a Clinical Practice Guideline prepared by the Canadian Fertility and Andrology Society (CFAS) Clinical Practice Guideline Committee†, and approved by the CFAS Clinical Practice Guideline Committee and the Board of CFAS. It has not been submitted for external peer review by *RBMO*.
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KEYWORDS

Adjuvants
Assisted Reproduction
Endometrium

SUMMARY STATEMENTS AND RECOMMENDATIONS

Summary statements	Quality of evidence	Justification
Various factors can limit the accuracy of endometrial measurements such as fibroids, adenomyosis, polyps, uterine orientation, body habitus, previous surgeries, uterine contractions, ultrasound machine quality, interobserver and intra-observer variability, and patient intolerance.	⊕⊕◯◯	
Thin endometrium in assisted reproduction is often defined as endometrial thickness <7 mm or <8 mm. The incidence of thin endometrium in ovarian stimulation cycles can be as high as 38–66%; the incidence of thin endometrium in IVF is between 1% and 2.5% in most studies.	⊕⊕◯◯	Based on retrospective and prospective observational studies. These are likely to underestimate the true incidence of thin endometrium as they do not include cancelled cycles.
Potential pathological causes of thin endometrium may include Asherman syndrome, history of uterine surgery, infection or radiation, although the incidence of thin endometrium in these scenarios is unclear.	⊕◯◯◯	Retrospective case series show an association of thin endometrium with the risk factors listed.
Thin endometrium may not impact pregnancy outcomes in ovarian stimulation treatment cycles.	⊕◯◯◯ TABLE 1	Most observational studies do not show a difference in pregnancy rates with thin endometrium at different cut-offs. A systematic review did not find a difference in endometrial thickness in patients who were pregnant versus not pregnant.

Recommendations	Strength	Quality of evidence	Justification
The endometrium should be measured transvaginally in the sagittal plane at the thickest portion near the fundus.	Strong	⊕◯◯◯	Recommendation is based on commonly accepted practice and to ensure consistency in measurements to aid in clinical assessment, research and reporting.
Repeat any thin endometrium measurement.	Weak	⊕◯◯◯	Recommendation is based on commonly accepted practice and intra-observer variability.
Patients undergoing ovarian stimulation with thin endometrium may be counselled that the effect on pregnancy rates is unclear.	Weak	⊕◯◯◯ TABLE 1	Most observational studies do not show a difference in pregnancy rates with thin endometrium at different cut-offs. A systematic review did not find a difference in endometrial thickness in patients undergoing ovarian stimulation who were pregnant versus not pregnant.
In ovarian stimulation treatment cycles, there is insufficient evidence to recommend changing stimulation medications or a specific stimulation medication.	Weak	⊕◯◯◯	There are insufficient studies evaluating the effect of specific ovarian stimulation protocols for patients with thin endometrium.
In ovarian stimulation treatment cycles, there is insufficient evidence to recommend the use of adjuvants to improve endometrial thickness or pregnancy rates.	Weak	⊕◯◯◯	There are insufficient studies evaluating the effect of adjuvants in ovarian stimulation protocols for patients with thin endometrium.
In fresh IVF-embryo transfer cycles, patients should be counselled that endometrial thickness <8 mm may have a negative impact on pregnancy and live birth rates.	Strong	⊕⊕◯◯ TABLE 2	Observational studies consistently demonstrate lower pregnancy rates in fresh IVF cycles with endometrial thickness <8 mm.
In fresh IVF-embryo transfer cycles, patients with thin endometrium can be offered elective cryopreservation of embryos and transfer in a subsequent cycle.	Weak	⊕◯◯◯	One poorly designed small observational study found lower pregnancy rates with fresh embryo transfer compared with cryopreservation and transfer in a subsequent cycle.
In frozen IVF-embryo transfer cycles, patients should be counselled that endometrial thickness <7 mm may have a negative impact on pregnancy and live birth rates.	Strong	⊕⊕◯◯	Observational study demonstrates lower pregnancy rates in frozen IVF-embryo transfer cycles with endometrial thickness <7 mm. Oocyte donation studies did not show an impact on pregnancy rates.
For patients with a history of thin endometrium in ART treatment undergoing endometrial preparation for embryo transfer, there is insufficient evidence that any specific protocol (natural cycle or hormone replacement) for endometrial preparation provides better pregnancy outcomes.	Weak	⊕◯◯◯	There are no studies which compare different endometrial preparation protocols for frozen embryo transfers.
In patients with thin endometrium undergoing embryo transfer cycles, we suggest against the use of aspirin to improve pregnancy rates.	Weak	⊕◯◯◯ TABLE 3	No effect in one small RCT.
In patients with thin endometrium undergoing fresh IVF-embryo transfer cycles, we suggest against the use of luteal oestradiol to improve pregnancy rates.	Weak	⊕◯◯◯ TABLE 4	No benefit seen in one small observational study.
In patients with thin endometrium undergoing embryo transfer cycles, there is insufficient evidence to recommend the use of sildenafil to improve pregnancy rates.	Weak	⊕◯◯◯ TABLE 5	No improvement in pregnancy rates seen in poorly designed RCT; however, there was an improvement in endometrial thickness.
In patients with thin endometrium undergoing embryo transfer cycles, we suggest against the use of intrauterine infusion of G-CSF to improve pregnancy rates.	Weak	⊕⊕◯◯ TABLE 6	No benefit for clinical pregnancy or live birth rates in observational data or one RCT. Potential side effects and complications with G-CSF intrauterine infusion also need to be further studied. G-CSF intrauterine infusion may improve endometrial thickness based on observational data.
In patients with thin endometrium undergoing embryo transfer cycles, we suggest against the use of pentoxifylline, HCG, gonadotropin-releasing hormone agonists, platelet-rich plasma or stem cells to improve pregnancy rates.	Weak	⊕◯◯◯	Only case reports and case series are in the literature, with no controlled studies reported. Further research to evaluate the potential risks and benefits of these adjuvants is needed.

INTRODUCTION

Assessment of the endometrium is an essential component in assisted reproduction. Endometrial thickness has been identified as a prognostic factor for success in assisted reproduction. When the endometrium is assessed to be 'thin', physicians and patients face a decision of whether or not to proceed with the treatment cycle. This guideline seeks to provide an evidence-based approach to the assessment and management of patients with thin endometrium in assisted reproduction, including controlled ovarian stimulation and IVF.

MEASUREMENT OF THE ENDOMETRIUM IN ASSISTED REPRODUCTION

The use of ultrasound is well established in assisted reproduction. While the benefit of ultrasound to characterize follicular development is well documented, its value in endometrial evaluation is less clear (*Hershko-Klement and Tepper, 2016*). Ultrasound is the ideal non-invasive tool to evaluate the endometrium (*Delisle et al., 1998*). Endometrial thickness is directly correlated to increasing circulating oestrogens (*Hershko-Klement and Tepper, 2016*), and endometrial thickness is related to endometrial receptivity and can be a predictor of success in assisted reproduction (*Momeni et al., 2011*). There is considerable controversy regarding the significance of thin endometrium (*Chen et al., 2010; De Geyter et al., 2000; Detti et al., 2008; Zhao et al., 2012, 2014*).

It is important to establish consistent parameters regarding endometrial measurement and correlation to clinical considerations. The endometrium should be measured with an empty bladder using a transvaginal probe (*Persadie, 2002*). The transducer is physically closer to the endometrium with the transvaginal probe and uses a higher frequency (≥5–8 MHz) compared with transabdominal assessment. This results in better resolution and visualization, with the trade-off being a decrease in penetration (*Persadie, 2002*). The endometrium should be measured in the sagittal plane or long axis. The measurement is of the thickest echogenic area from one stratum basalis endometrial interface across the endometrial canal to the other stratum basalis interface (FIGURE 1). The surrounding inner myometrial lucency is not included in this measurement (*Persadie, 2002*). This measurement is usually found within 1 cm of the fundal tip. In up to 10% of studies, the ideal image for measurement is difficult to obtain due to the presence of fibroids, adenomyosis, polyps, uterine orientation, body habitus, previous surgeries and patient intolerance (*Goldstein, 2004*).

Sources of error include interobserver variability and different ultrasound

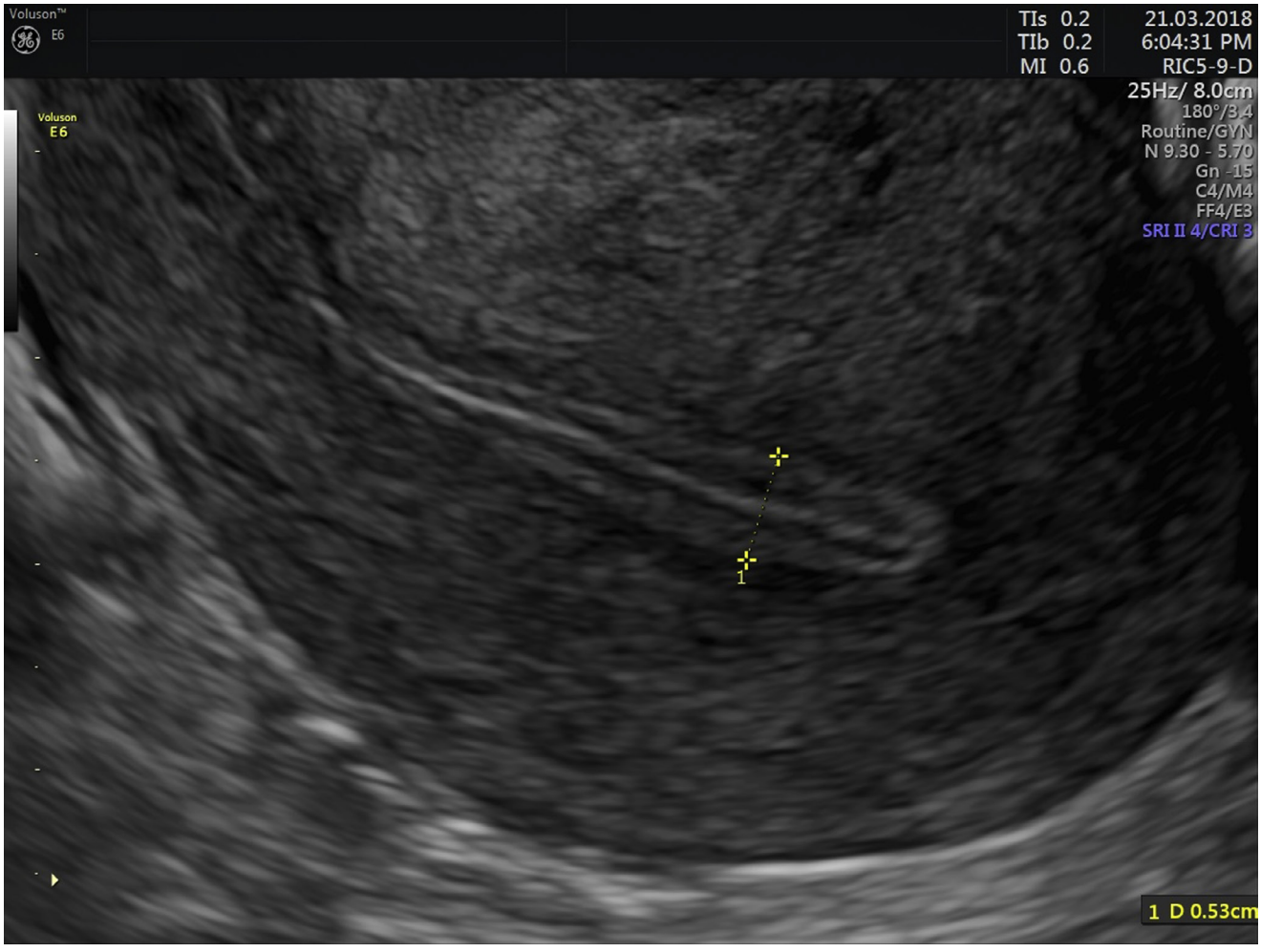

FIGURE 1 Measurement of endometrial thickness. Image provided by A. Hartman, True North Imaging.

machines. Using different angles of insonation when measuring (as opposed to measuring endometrial thickness when the endometrial echo is perpendicular to the ultrasound beam) is another potential cause of inaccuracy (*Spandorfer et al., 1998*). Studies have shown that interobserver variability for endometrial measurements was approximately 1 mm, with intra-observer variability of approximately 0.6–0.7 mm (*Delisle et al., 1998; Spandorfer et al., 1998*). The intra-observer kappa values for agreement on endometrium ≤5 mm and >5 mm were 0.70 a nd 0.81, respectively, and the interobserver kappa value was 0.74.

Uterine physiology also provides a significant potential source of bias. Uterine contractions can cause changes in endometrial thickness of up to 3–4 mm due to changes in the myometrium and subendometrium. Most patients have multiple contractions per minute. Periodicity tends to differ with stage of cycle, circulating oestradiol and progesterone concentrations, and endometrial thickness/pattern (*Dastidar and Dastidar, 2003; Pierson, 2018*). In order to ensure the most accurate and relevant endometrial thickness results, strict adherence to proper technique should be maintained. A reasonable technique would be to wait for the wave to pass and measure again (*Pierson, 2018*). This guideline focuses on endometrial thickness alone; additional methods of endometrial assessment including endometrial pattern, volume or Doppler studies are not addressed within the scope of this guideline.

DEFINITION AND INCIDENCE OF THIN ENDOMETRIUM IN ASSISTED REPRODUCTION

The definition and cut-off for thin endometrium differs between studies, although most studies use endometrial thickness <7 mm or <8 mm on the day of human chorionic gonadotropin (HCG) administration. Although several case reports have described pregnancy after embryo transfer with endometrial thickness of approximately 4 mm (*Amui et al., 2011; Check and Cohen, 2011; Sundstrom, 1998*), the chance of pregnancy is low in these cases. One study described two ongoing pregnancies from 12 embryo transfers for patients with endometrial thickness between 4 and 6 mm (*Noyes et al., 1995*). Another study reported no live births from 11 embryo transfers in patients with endometrial thickness between 4 and 4.9 mm, and four live births from 29 embryo transfers in patients with endometrial thickness between 5 and 5.9 mm (*Kumbak et al., 2009*). Pregnancies have also been described in ovarian stimulation cycles with endometrial thickness as low as 3.8 mm on the day of HCG administration (*Kolibianakis et al., 2004*).

In IVF studies for fresh embryo transfer, the incidence of endometrial thickness <7 mm on the day of HCG administration varies between 1% and 2.5% when large IVF retrospective and prospective cohorts (between 500 and 10,000 patients) were studied (*Al-Ghamdi et al., 2008; Aydin et al., 2013; Bu and Sun, 2015; Shufaro et al., 2008; Wu et al., 2014*). As expected, the incidence is higher using a cut-off endometrial thickness <8 mm, and two studies have compared the incidence using <7 mm and <8 mm (*Al-Ghamdi et al., 2008; Wu et al., 2014*). One study of 2000 patients found that the incidence increased from 1.5% to 9.1% when the cut-off moved from <7 mm to <8 mm; however, the other study with almost 2500 patients found that the overall incidence rates were lower at 0.7% for <7 mm and 2.5% for <8 mm. Some of the differences between studies may be accounted for by measurement techniques and ultrasound equipment. It should be noted that these studies only included cycles which proceeded to embryo transfer, and are likely to underestimate the incidence of thin endometrium.

A study using the Canadian ART database (BORN-CARTR+) which included 21,900 fresh IVF-embryo transfer cycles from 2012 to 2015 showed that 12.3% of fresh IVF-embryo transfer cycles occur with endometrial thickness <8 mm and 3.9% with endometrial thickness <7 mm (*Liu et al., 2018*). In 18,900 frozen-thaw embryo transfers, 14.1% occurred with endometrial thickness <8 mm and 3.1% with endometrial thickness <7 mm (*Liu et al., 2018*). As with the previous studies, this is likely to be an underestimate of the true incidence in IVF cycles as this only represents cycles which proceeded to embryo transfer.

In controlled ovarian stimulation cycles with either oral agents or gonadotropins, the incidence of thin endometrium appears to be much higher and more variable. Retrospective cohort studies found an incidence between 5.6% and 37.9% for endometrial thickness <7 mm (*Asante et al., 2013; Chen et al., 2012; Wolff et al., 2013*), and between 12% and 66.2% for endometrial thickness <8 mm (*Asante et al., 2013; Jeon et al., 2013; Wolff et al., 2013*). The increased incidence of thin endometrium in ovarian stimulation cycles compared with IVF-embryo transfer cycles is likely to be due to ovarian stimulation cycles proceeding despite the thin endometrium whilst IVF cycles are more likely to be cancelled.

It is important to note that the above studies describe the incidence of thin endometrium during one assisted

Summary statement	Quality of evidence	Justification
Various factors can limit the accuracy of endometrial measurements such as fibroids, adenomyosis, polyps, uterine orientation, body habitus, previous surgeries, uterine contractions, ultrasound machine quality, interobserver and intra-observer variability, and patient intolerance.	⊕⊕◯◯	

Recommendations	Strength	Quality of evidence	Justification
The endometrium should be measured transvaginally in the sagittal plane at the thickest portion near the fundus.	Strong	⊕◯◯◯	Recommendation is based on commonly accepted practice and to ensure consistency in measurements to aid in clinical assessment, research and reporting.
Repeat any thin endometrium measurement.	Weak	⊕◯◯◯	Recommendation is based on commonly accepted practice and intra-observer variability.
Uterine cavity assessment by hysteroscopy or sonohysterogram may be performed in the assessment of a patient with thin endometrium to assess for pathological causes.	Weak	⊕◯◯◯	Consensus opinion from the Committee for Practice Guidelines: although the incidence of intrauterine adhesions in patients with thin endometrium is unknown, uterine assessment may identify patients who may benefit from surgical management.

reproduction treatment cycle. There is no consensus on what defines a persistent thin endometrium in assisted reproduction with regards to the number of affected treatment cycles, nor studies which describe the incidence of this phenomenon.

INVESTIGATIONS FOR THIN ENDOMETRIUM IN ASSISTED REPRODUCTION

Many of the above potential risk factors for thin endometrium will be identified from the patient's history.

Summary statement	Quality of evidence	Justification
Thin endometrium in assisted reproduction is often defined as endometrial thickness <7 mm or <8 mm. The incidence of thin endometrium in ovarian stimulation cycles can be as high as 38–66%; the incidence of thin endometrium in IVF is between 1% and 2.5% in most studies.	⊕⊕◯◯	Based on retrospective and prospective observational studies. These are likely to underestimate the true incidence of thin endometrium as they do not include cancelled cycles.

CAUSES OF THIN ENDOMETRIUM IN ASSISTED REPRODUCTION

There are limited data describing the incidence of pathological causes of thin endometrium. Commonly described causes include Asherman syndrome, previous intrauterine surgery including curettage, pelvic radiation and clomiphene citrate (*Critchley et al., 1992; Garcia-Velasco et al., 2016*). Studies on patients with thin endometrium have reported a history of dilatation and curettage (*Santamaria et al., 2016; Shufaro et al., 2008*), postpartum endometritis (*Sher and Fisch, 2002*), septic abortion (*Sher and Fisch, 2002*), fibroids (*Sher and Fisch, 2002*), radiation (*Ledee-Bataille et al., 2002; Letur-Konirsch et al., 2002*), in-utero diethylstilbestrol (*Sher and Fisch, 2002*), hypothalamic hypogonadism (*Acharya et al., 2009*), Müllerian anomalies (*Check et al., 2014*) and premature ovarian insufficiency (*Acharya et al., 2009*). A number of studies on thin endometrium have been performed in donor oocyte recipients, although it is unclear if this reflects a convenience sample, a reflection of endometrial preparation regimens, or a true higher incidence of thin endometrium during endometrial preparation in patients requiring donor oocytes. Studies of patients with thin endometrium often exclude patients with uterine pathology; therefore, the true incidence of uterine pathology is not well reported.

Summary statement	Quality of evidence	Justification
Potential pathological causes of thin endometrium may include Asherman syndrome, history of uterine surgery, infection or radiation, although the incidence of thin endometrium in these scenarios is unclear.	⊕◯◯◯	Retrospective case series show an association of thin endometrium with the risk factors listed.

Recommendation	Strength	Quality of evidence	Justification
Uterine cavity assessment by hysteroscopy or sonohysterogram may be performed in the assessment of a patient with thin endometrium to assess for pathological causes.	Weak	⊕◯◯◯	Consensus opinion from the Committee for Practice Guidelines: although the incidence of intrauterine adhesions in patients with thin endometrium is unknown, uterine assessment may identify patients who may benefit from surgical management.

Most patients undergoing assisted reproduction will have an assessment of their uterine cavity as part of their initial investigations, particularly patients with risk factors for uterine pathology or intrauterine adhesions. Most studies have only included patients with a normal endometrial cavity assessment, although some studies have targeted patients with Asherman syndrome which has been refractory to hysteroscopic adhesiolysis (*Nagori et al., 2011; Santamaria et al., 2016; Singh et al., 2014*). Although it is difficult to estimate the incidence of intrauterine pathology in patients with thin endometrium, uterine cavity assessment by hysteroscopy or sonohysterogram is low risk and can identify conditions which may require surgical management.

Although chronic endometritis has been discussed as a potential cause of thin endometrium, most studies have not identified endometritis as a contributing factor (*Garcia-Velasco et al., 2016*), and no studies on the treatment of endometritis in patients with thin endometrium could be identified.

No studies regarding the use of endometrial volume measurements or endometrial receptivity in patients with thin endometrium were identified. A commercial transcriptomic assay has been described as a tool to evaluate the window of implantation. One small uncontrolled study on 13 patients with thin endometrium has been published (*Mahajan, 2015*). Although this is a novel concept, more research is needed to evaluate its utility.

THIN ENDOMETRIUM IN OVARIAN STIMULATION (NON-IVF)

Thin endometrium is commonly encountered during controlled ovarian stimulation cycles (non-IVF). When patients undergoing ovarian stimulation have a thin endometrium, clinicians may consider whether to proceed with the treatment cycle [and intrauterine insemination (IUI) if planned] or cancel the cycle. The effect of endometrial thickness on treatment outcomes has been described in many studies; however, most of these studies have been retrospective and small. Most studies have not shown an effect of thin endometrium on outcomes (*Chen et al., 2012; Kolibianakis et al., 2004; Weiss et al., 2017*), although one study (*Jeon et al., 2013*) showed a very low pregnancy rate with endometrial thickness ≤7 mm. In a prospective study of 168 patients, *Kolibianakis et al. (2004)* found comparable pregnancy rates in clomiphene citrate cycles for endometrial thickness <6 mm, 6–7.9 mm and ≥8 mm. A recent systematic review and meta-analysis evaluated the effect of endometrial thickness with ovarian stimulation-IUI (*Weiss et al., 2017*). This review included 1525 women in seven studies [two randomized controlled trials (RCT) and five cohort studies] and did not find a difference in endometrial thickness between women who conceived and women who did not

conceive. Studies using clomiphene citrate, letrozole and gonadotropins were included in the analysis. The authors acknowledged that this may not account for cycles which were cancelled due to thin endometrium. In reviewing the literature on thin endometrium and ovarian stimulation-IUI, it should be noted that absolute pregnancy and live birth rates are much lower with ovarian stimulation-IUI compared with IVF, which may account for the lack of effect.

In patients with thin endometrium, the prognosis for achieving a thicker endometrium in subsequent ovarian stimulation cycles is unclear. Clinicians will often switch stimulation medications after encountering a thin endometrium. In a systematic review and meta-analysis, clomiphene and letrozole were both associated with a thinner endometrium compared with gonadotropins in ovarian stimulation cycles (*Weiss et al., 2017*). Only one study was found which compared stimulation medications for patients with a history of thin endometrium in ovarian stimulation (*Wang et al., 2008*). In this prospective cohort study, 160 patients with a history of endometrium <8 mm with ovarian stimulation were treated with either tamoxifen or clomiphene followed by human menopausal gonadotropins. Pregnancy rates were higher, and spontaneous abortion rates and endometrial thickness <8 mm were lower in the tamoxifen group.

The use of adjuvants to improve pregnancy rates in patients with a history of thin endometrium has not been well studied. One non-blinded RCT of 136 patients evaluated the use of aspirin in patients with a history of endometrial thickness <8 mm in a preceding cycle (*Hsieh et al., 2000*). Although there was a trend towards a thicker endometrium and higher pregnancy rates with aspirin, neither trend was statistically significant. The use of sildenafil citrate as an adjuvant in ovarian stimulation has been described in a case report (*Zinger et al., 2006*) but not evaluated in a research study.

Summary statement	Quality of evidence	Justification
Thin endometrium may not impact pregnancy outcomes in ovarian stimulation treatment cycles.	⊕OOO **TABLE 1**	Most observational studies do not show a difference in pregnancy rates with thin endometrium at different cut-offs. A systematic review did not find a difference in endometrial thickness in patients who were pregnant versus not pregnant.

Recommendations	Strength	Quality of evidence	Justification
Patients undergoing ovarian stimulation with thin endometrium may be counselled that the effect on pregnancy rates is unclear.	Weak	⊕OOO **TABLE 1**	Most observational studies do not show a difference in pregnancy rates with thin endometrium at different cut-offs. A systematic review did not find a difference in endometrial thickness in patients undergoing ovarian stimulation who were pregnant versus not pregnant.
In ovarian stimulation treatment cycles, there is insufficient evidence to recommend changing stimulation medications or a specific stimulation medication.	Weak	⊕OOO	There are insufficient studies evaluating the effect of specific ovarian stimulation stimulation protocols for patients with thin endometrium.
In ovarian stimulation treatment cycles, there is insufficient evidence to recommend the use of adjuvants to improve endometrial thickness or pregnancy rates.	Weak	⊕OOO	There are insufficient studies evaluating the effect of adjuvants in ovarian stimulation protocols for patients with thin endometrium.

THIN ENDOMETRIUM IN IVF (FRESH OR FROZEN EMBRYO TRANSFER)

The impact of a thin endometrial lining on IVF-embryo transfer outcomes has been studied extensively. The quality of the available data is often low, and the studies are fairly heterogeneous. Most studies on this topic are retrospective and examine fresh IVF-embryo transfer cycles, with only a small subset looking at frozen embryo transfer cycles.

Observational studies of fresh IVF cycles have indicated a decreased chance of clinical pregnancy or live birth with thin endometrium; however, they all used different cut-offs to define thin endometrium (*Kovacs et al., 2003; Kumbak et al., 2009; Vaegter et al., 2017; Yuan et al., 2016; Zhao et al., 2014*). *Vaegter et al. (2017)* found significantly reduced live birth rates with endometrial thickness <7 mm and 7–10 mm compared with cases with a thicker endometrium. *Kumbak et al. (2009)* showed significantly reduced clinical pregnancy and live birth rates when endometrial thickness was <7 mm; however, they did not routinely evaluate the uterine cavity prior to embryo transfer. They also had substantial variability in the number of embryos transferred. *Kovacs et al. (2003)* found that endometrial thickness <10 mm was associated with a lower pregnancy rate, but only six cases with endometrial thickness <8 mm were included in this study out of a total of 1228 cycles. A very large study by *Yuan et al. (2016)* examined over 10,000 fresh IVF cycles, including over 500 embryo transfers with endometrial thickness <8 mm. They found that the clinical pregnancy rate was significantly lower in patients with endometrial thickness <8 mm (23% versus 37.2% for endometrial thickness of 8–11 mm). *Zhao et al. (2014)* found that the clinical pregnancy rate was significantly lower with endometrial thickness cut-offs of both 7 mm and ≤8 mm.

One small, older study found that endometrial thickness <7 mm was not significantly associated with a lower pregnancy rate (*Noyes et al., 1995*). Another small study of euploid embryos found that the clinical pregnancy rate was not significantly different with endometrial thickness ≤7 mm compared with endometrial thickness >7 mm (*Gingold et al., 2015*); however, this study may have been under powered.

A recent systematic review by *Kasius et al. (2014)* did not find a difference in live birth and ongoing pregnancy rates for thin endometrium, defined as ≤7 mm, although this was likely to be due to a very small sample size. However, the clinical pregnancy rate was significantly reduced with endometrial thickness ≤7 mm, with an odds ratio of 0.42 and a narrow confidence interval. The review had low heterogeneity, but the studies were a mix of prospective and retrospective studies, and most of the studies had selection bias. Many of the studies also used different cut-offs for the definition of thin endometrium.

In the Canadian study of almost 22,000 fresh IVF-embryo transfer cycles using the BORN/CARTR+ database, clinical pregnancy and live birth rates are

TABLE 1 SUMMARY OF FINDINGS: THIN ENDOMETRIUM COMPARED WITH NORMAL ENDOMETRIUM IN OVARIAN STIMULATION (NON-IVF) TO PREDICT PREGNANCY

Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with normal endometrium	Risk with thin endometrium				
Clinical pregnancy rate: studies that classified EMT ≤7 mm as thin	214 per 1000	43 per 1000 (14–131)	RR 0.200 (0.066–0.610)	845 (two observational studies)	⨁◯◯◯ Very low[b,c,d]	
Clinical pregnancy rate: studies that classified EMT <8 mm as thin	215 per 1000	184 per 1000 (100–342)	RR 0.856 (0.462–1.587)	168 (one observational study)	⨁◯◯◯ Very low[b,d]	
Clinical pregnancy rate: studies that classified EMT <6 mm as thin	203 per 1000	171 per 1000 (77–382)	RR 0.844 (0.379–1.884)	168 (one observational study)	⨁◯◯◯ Very low[b,d]	
Mean EMT in pregnant versus non-pregnant patients			Mean EMT in pregnant versus non-pregnant patients in the intervention group was 0.51 mm higher (0.05 mm lower to 1.07 mm higher)	1525 (systematic review and meta-analysis of two RCTs and five observational studies)	⨁⨁◯◯ Low[e,f]	Studies were mostly low to moderate quality

Patient or population: ovarian stimulation (non-IVF) to predict pregnancy.

Intervention: thin endometrium.

Comparison: normal endometrium.

EMT, endometrial thickness; RCT, randomized controlled trial; GRADE, Grading of Recommendations, Assessment, Development and Evaluations framework; CI, confidence interval; RR, risk ratio; MD, mean difference.

[a] The risk in the intervention group (and 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and 95% CI).

[b] Only followed pregnancies until 7 weeks when fetal heart beat was recorded.

[c] *Chen et al. (2012)* limited to cycles with donor sperm. *Jeon et al. (2013)* included male factor infertility but did not specify severity. Both studies used multiple stimulation regimens.

[d] Few events.

[e] Considerable heterogeneity, i^2 = 74%.

[f] Multiple stimulation protocols included.

Studies included:

Chen, X.J., Wu, L.P., Lan, H.L., Zhang, L., Zhu, Y.M., 2012. Clinical variables affecting the pregnancy rate of intracervical insemination using cryopreserved donor spermatozoa: a retrospective study in China. Int. J. Fertil. Steril. 6, 179–184.

Jeon, Y.E., Jung, J.A., Kim, H.Y., Seo, S.K., Cho, S., Choi, Y.S., Lee, B.S., 2013. Predictive factors for pregnancy during the first four intrauterine insemination cycles using gonadotropin. Gynecol. Endocrinol. 29, 834–838.

Kolibianakis, E.M., Zikopoulos, K.A., Fatemi, H.M., Osmanagaoglu, K., Evenpoel, J., Van Steirteghem, A., Devroey, P., 2004. Endometrial thickness cannot predict ongoing pregnancy achievement in cycles stimulated with clomiphene citrate for intrauterine insemination. Reprod. Biomed. Online 8, 115–118.

Weiss, N.S., van Vliet, M.N., Limpens, J., Hompes, P.G.A., Lambalk, C.B., Mochtar, M.H., van der Veen, F., Mol, B.W.J., van Wely, M., 2017. Endometrial thickness in women undergoing IUI with ovarian stimulation. How thick is too thin? A systematic review and meta-analysis. Hum. Reprod. 32, 1009–1018.

progressively lower with decreasing endometrial thickness. In fresh IVF-embryo transfer cycles, the live birth rate decreased progressively per millimetre below 8 mm: 33.7%, 25.5%, 24.6% and 18.1% in patients with endometrial thickness ≥8 mm, 7–7.9 mm, 6–6.9 mm and 5–5.9 mm, respectively (*Liu et al., 2018*).

When patients present with thin endometrium during a fresh IVF-embryo transfer cycle, a decision must be made regarding whether to proceed with treatment or freeze all the embryos to allow for different endometrial preparation protocols. There are no studies available to assess the impact of different IVF stimulation protocols for patients with thin endometrium. These studies are unlikely to be conducted as current cryopreservation techniques allow embryos to be frozen for transfer in a future cycle with minimal impact on pregnancy outcomes. One study attempted to compare a fresh embryo transfer in patients with endometrial thickness <8 mm with freezing embryos and undergoing a subsequent embryo transfer using a hormone replacement cycle (*Chen et al., 2006*). In this prospective cohort study, 23 patients proceeded with a fresh embryo transfer and one patient conceived but no live births resulted. Thirteen patients underwent a frozen embryo transfer with hormone replacement. Oestradiol was continued until endometrial thickness reached 8 mm (range 14–82 days, mean 30 days). Five patients conceived and delivered (risk ratio 18.9, 95% confidence interval 1.13–316.1).

One study to assess the effect of thin endometrium in frozen embryo transfer cycles looked at patients in their first frozen embryo transfer cycle (*El-Toukhy et al., 2008*). They found that the clinical pregnancy and live birth rates were significantly lower in patients with endometrial thickness of 7–8 mm compared with those with endometrial thickness of 9–14 mm (clinical pregnancy rate 18% versus 30%, live birth rate 14% versus 24%). Cycles with endometrial thickness <7 mm were often cancelled and the pregnancy rate was only 7% in this group. In two studies of oocyte donation recipients with hormone

replacement cycles, endometrial thickness did not impact on pregnancy rates. In one study of 4000 donor oocyte recipients, patients proceeded with endometrial transfer with endometrial thickness ≥5 mm (*Arce et al., 2015*). The second study found that endometrial thickness was not significantly associated with pregnancy or live birth rates using cut-offs of both 6 mm and 8.2 mm (*Dain et al., 2013*).

The above Canadian BORN/CARTR+ study included almost 19,000 frozen-thaw embryo transfer cycles. Live birth rates were similar for endometrial thickness of 7 and 8 mm, and decreased below 7 mm: 28.4%, 27.4%, 23.7% and 15% for ≥8 mm, 7–7.9 mm, 6–6.9 mm and 5–5.9 mm, respectively (*Liu et al., 2018*).

In clinical practice, clinicians may often switch between hormone replacement and natural cycles if they encounter difficulty with thin endometrium for frozen embryo transfers; however, no studies comparing the effectiveness of these approaches for patients with thin endometrium could be identified. There are also limited data comparing different formulations of oestrogen and progesterone for hormone replacement cycles. One small RCT of 60 patients with thin endometrium found that vaginal ethinyl oestradiol tablets improved endometrial thickness compared with vaginal conjugated equine oestrogen, although pregnancy outcomes were not reported (*Zolghadri et al., 2014*).

Recommendations	Strength	Quality of evidence	Justification
In fresh IVF-embryo transfer cycles, patients should be counselled that endometrial thickness <8 mm may have a negative impact on pregnancy and live birth rates.	Strong	⊕⊕◯◯ **TABLE 2**	Observational studies consistently demonstrate lower pregnancy rates in fresh IVF cycles with endometrial thickness <8 mm.
In fresh IVF-embryo transfer cycles, patients with thin endometrium can be offered elective cryopreservation of embryos and transfer in a subsequent cycle.	Weak	⊕◯◯◯	One poorly designed small observational study found lower pregnancy rates with fresh embryo transfer compared with cryopreservation and transfer in a subsequent cycle.
In frozen IVF-embryo transfer cycles, patients should be counselled that endometrial thickness <7 mm may have a negative impact on pregnancy and live birth rates.	Strong	⊕⊕◯◯	Observational study demonstrates lower pregnancy rates in frozen IVF-embryo transfer cycles with endometrial thickness <7 mm. Oocyte donation studies did not show an impact on pregnancy rates.
For patients with a history of thin endometrium in ART treatment undergoing endometrial preparation for embryo transfer, there is insufficient evidence that any specific protocol (natural cycle or hormone replacement) for endometrial preparation provides better pregnancy outcomes.	Weak	⊕◯◯◯	There are no studies which compare different endometrial preparation protocols for frozen embryo transfers.

Recommendation	Strength	Quality of evidence	Justification
In patients with thin endometrium undergoing embryo transfer cycles, we suggest against the use of aspirin to improve pregnancy rates.	Weak	⊕◯◯◯ **TABLE 3**	No effect in one small RCT.

Recommendation	Strength	Quality of evidence	Justification
In patients with thin endometrium undergoing fresh IVF-embryo transfer cycles, we suggest against the use of luteal oestradiol to improve pregnancy rates.	Weak	⊕◯◯◯ **TABLE 4**	No benefit seen in one small observational study.

Recommendation	Strength	Quality of evidence	Justification
In patients with thin endometrium undergoing embryo transfer cycles, there is insufficient evidence to recommend the use of sildenafil to improve pregnancy rates.	Weak	⊕◯◯◯ **TABLE 5**	No improvement in pregnancy rates seen in poorly designed RCT; however, there was an improvement in endometrial thickness.

ADJUVANTS FOR THIN ENDOMETRIUM IN ASSISTED REPRODUCTION

Aspirin

Although aspirin has been commonly used as an adjuvant in assisted reproduction and empirically for thin endometrium, only one small, non-blinded RCT has evaluated its use in patients with thin endometrium (*Weckstein et al., 1997*). This study randomized 28 donor oocyte recipients with a history of endometrial thickness <8 mm in a previous hormone replacement cycle to aspirin or no treatment. There was no significant difference in endometrial thickness, or pregnancy or live birth rates between the groups.

Luteal oestradiol

The addition of exogenous oestrogen to fresh IVF cycles has been assessed in one retrospective cohort study (*Demir et al., 2013*). Patients with endometrial thickness <8 mm on the day of HCG administration were included. Fifty-seven patients received 4 mg oestradiol from the day of HCG administration until 12 weeks of gestation, compared with 60 patients who did not receive adjuvant therapy. There were no significant differences in endometrial thickness at egg retrieval, or pregnancy or live birth rates.

Sildenafil citrate

Sildenafil has been postulated to improve endometrial thickness through increased blood flow. Many case series (*Sher and Fisch, 2000, 2002; Zinger et al., 2006*) have reported the use of sildenafil for patients with thin endometrium for fresh and frozen IVF embryo transfers. One small observational study reported a benefit in pregnancy rates (*Takasaki et al., 2010*); however, the sildenafil group all received IVF whilst the control group underwent natural cycles, human menopausal gonadotropins/IUI or IVF. One RCT of 80 patients failed to detect a difference in pregnancy rates in patients undergoing frozen embryo transfers (*Dehghani Firouzabadi et al., 2013*). Patients with a history of 'poor endometrial response' (not defined) were randomized to sildenafil 50 mg/day or no treatment. However, the study did show an improvement in endometrial thickness (9.8 mm versus 8 mm; P <0 .0001).

TABLE 2 SUMMARY OF FINDINGS: THIN ENDOMETRIUM COMPARED WITH NORMAL ENDOMETRIUM IN IVF TO PREDICT PREGNANCY

Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with normal endometrium	Risk with thin endometrium				
Clinical pregnancy rate: studies that classified thin EMT as ≤8 mm	433 per 1000	320 per 1000 (303–337)	RR 0.74 (0.70–0.78)	34607 (three observational studies)	⨁⨁◯◯ Low[b]	
Live birth rate: studies that classified thin EMT as ≤8 mm	337 per 1000	249 per 1000 (233–266)	RR 0.74 (0.69–0.79)	21,859 (one observational study)	⨁⨁◯◯ Low	
Clinical pregnancy rate: studies that classified thin EMT as ≤7 mm	454 per 1000	295 per 1000 (273–323)	RR 0.65 (0.60–0.71)	39,004 (six observational studies)	⨁⨁◯◯ Low[b,c]	
Live birth rate: studies that classified thin EMT as ≤7	355 per 1000	224 per 1000 (199–249)	RR 0.63 (0.56–0.70)	29,596 (three observational studies)	⨁⨁◯◯ Low[c]	
Clinical pregnancy rate: studies that classified thin EMT as ≤6 mm	421 per 1000	278 per 1000 (227–341)	RR 0.66 (0.54–0.81)	22,625 (two observational studies)	⨁⨁◯◯ Low[d,e]	
Live birth rate: studies that classified thin EMT as ≤6 mm	325 per 1000	179 per 1000 (133–237)	RR 0.55 (0.41–0.73)	22,596 (two observational studies)	⨁⨁◯◯ Low[d,e]	
Clinical pregnancy rate: studies that classified thin EMT as ≤10 mm	344 per 1000	301 per 1000 (262–344)	RR 0.8230 (0.6790–0.9996)	1228 (one observational study)	⨁◯◯◯ Very low[f,g]	
Clinical pregnancy rate: studies that classified thin EMT as ≤8 mm	433 per 1000	320 per 1000 (303–337)	RR 0.74 (0.70–0.78)	34,607 (three observational studies)	⨁⨁◯◯ Low[b]	

Patient or population: IVF to predict pregnancy.

Intervention: thin endometrium.

Comparison: normal endometrium.

EMT, endometrial thickness; GRADE, Grading of Recommendations, Assessment, Development and Evaluations framework; CI, confidence interval; RR, risk ratio; OR, odds ratio.

[a] The risk in the intervention group (and 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and 95% CI).

[b] *Kumbak et al. (2009)* had a large amount of variability in the number of embryos transferred.

[c] Zhao et al. did not include intracytoplasmic sperm injection cycles.

[d] Yuan and Zhao only looked at fresh embryo transfers. Zhao et al. excluded intracytoplasmic sperm injection cycles.

[e] Only oocyte donor cycles.

[f] Low event rate.

[g] Does not control for confounding variables.

Studies included:

Kasius, A., Smit, J.G., Torrance, H.L., Eijkemans, M.J., Mol, B.W., Opmeer, B.C., Broekmans, F.J., 2014. Endometrial thickness and pregnancy rates after IVF: a systematic review and meta-analysis. Hum. Reprod. Update 20, 530–541.

Kumbak, B., Erden, H.F., Tosun, S., Akbas, H., Ulug, U., Bahceci, M., 2009. Outcome of assisted reproduction treatment in patients with endometrial thickness less than 7 mm. Reprod. Biomed. Online 18, 79–84.

Liu, K.E., Hartman, M., Hartman, A., Luo, Z.C., Mahutte, N., 2018. The impact of a thin endometrial lining on fresh and frozen-thaw IVF outcomes: an analysis of over 40 000 embryo transfers. Hum. Reprod. 33, 1883–1888.

Noyes, N., Liu, H.C., Sultan, K., Schattman, G., Rosenwaks, Z., 1995. Endometrial thickness appears to be a significant factor in embryo implantation in in-vitro fertilization. Hum. Reprod. 10, 919–922.

Yuan, X., Saravelos, S.H., Wang, Q., Xu, Y., Li, T.C., Zhou, C., 2016. Endometrial thickness as a predictor of pregnancy outcomes in 10787 fresh IVF-ICSI cycles. Reprod. Biomed. Online 33, 197–205.

Zhao, J., Zhang, Q., Wang, Y., Li, Y. 2014. Endometrial pattern, thickness and growth in predicting pregnancy outcome following 3319 IVF cycle. Reprod Biomed Online 29:291–298.

Granulocyte colony-stimulating factor

Granulocyte colony-stimulating factor (G-CSF) is synthesized in humans to promote the development of neutrophils. A recombinant form of this human growth factor has been created, with the most common indication being to treat bone marrow failure and myelosuppression. Common indications include transient bone marrow failure following cytotoxic chemotherapy, aplastic anaemia and human-immunodeficiency-virus-associated neutropenia.

G-CSF was first reported for use in patients with persistent thin endometrium by *Gleicher et al. (2011)*. In this case series, four donor oocyte recipients with endometrial thickness ≤6.5 mm underwent a slow intrauterine infusion of G-CSF. After treatment, all four patients had endometrial thickness ≥7.3 mm and conceived. In a subsequent study (*Gleicher et al., 2013*), G-CSF intrauterine infusion improved endometrial thickness significantly in 21 women. Four of 21 women (with an average age of 40.5 years) conceived.

Subsequent case series (*Check et al., 2014; Kunicki et al., 2014; Lee et al., 2016; Lucena and Moreno-Ortiz, 2013; Tehraninejad et al., 2015*) have shown conflicting results for G-CSF intrauterine infusion in women with persistently thin endometrium.

Cohort studies have shown that G-CSF intrauterine infusion has some benefit for endometrial thickness, but no effect on pregnancy or live birth rates. In a small, prospective, uncontrolled cohort study of patients

TABLE 3 SUMMARY OF FINDINGS: ASPIRIN COMPARED WITH NO TREATMENT FOR PATIENTS WITH THIN ENDOMETRIUM UNDERGOING IVF-EMBRYO TRANSFER (FRESH OR FROZEN)

Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with no treatment	Risk with aspirin				
Clinical pregnancy rate: cohort studies	733 per 1000	872 per 1000 (755–1000)	RR 1.19 (1.03–1.38)	390 (one observational study)	⨁◯◯◯ Very low[b]	
Clinical pregnancy rate, EMT <8 mm: RCT	308 per 1000	600 per 1000 (240–1000)	RR 1.95 (0.78–4.86)	28 (one RCT)	⨁◯◯◯ Very low[c,d,e]	
Live birth rate, EMT <8 mm: RCT	308 per 1000	462 per 1000 (175–1000)	RR 1.50 (0.57–4.00)	28 (one RCT)	⨁◯◯◯ Very low[c,d,e]	

Patient or population: patients with thin endometrium undergoing IVF-embryo transfer (fresh or frozen).

Intervention: aspirin.

Comparison: no treatment.

EMT, endometrial thickness; RCT, randomized controlled trial; GRADE, Grading of Recommendations, Assessment, Development and Evaluations framework; CI, confidence interval; RR, risk ratio.

[a] The risk in the intervention group (and 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and 95% CI).

[b] *Frattarelli et al., (2006)* combined data for all adjuvant treatments, not just aspirin, so many confounders.

[c] Not blinded, no placebo.

[d] Only oocyte recipient patients.

[e] Small event size.

Studies included:

Fratarelli, J.L., Miller, B.T., Scott, R.T. 2006. Adjuvant therapy enhances endometrial receptivity in patients undergoing assisted reproduction. Reprod. Biomed. Online 12, 722–729.

Weckstein, L.N., Jacobson, A., Galen, D., Hampton, K., Hammel, J., 1997. Low-dose aspirin for oocyte donation recipients with a thin endometrium: prospective, randomized study. Fertil. Steril. 68, 927–930.

TABLE 4 SUMMARY OF FINDINGS: LUTEAL OESTRADIOL COMPARED WITH NO TREATMENT FOR PATIENTS WITH THIN ENDOMETRIUM UNDERGOING IVF-EMBRYO TRANSFER (FRESH OR FROZEN)

Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with no treatment	Risk with luteal oestradiol				
Clinical pregnancy rate	233 per 1000	280 per 1000 (152–520)	RR 1.20 (0.65–2.23)	117 (one observational study)	⨁◯◯◯ Very low[b,c]	
Live birth rate	133 per 1000	173 per 1000 (75–413)	RR 1.30 (0.56–3.10)	117 (one observational study)	⨁◯◯◯ Very low[b,c]	
Clinical pregnancy rate with frozen embryo transfer compared with fresh embryo transfer	43 per 1000	383 per 1000 (50–1000)	RR 8.80 (1.15–67.80)	36 (one observational study)	⨁◯◯◯ Very low[c,d]	
Live birth rate with frozen embryo transfer compared with fresh embryo transfer	0 per 1000	0 per 1000 (0–0)	RR 18.90 (1.13–316.10)	36 (one observational study)	⨁◯◯◯ Very low[c,d]	

Patient or population: patients with thin endometrium undergoing IVF-embryo transfer (fresh or frozen).

Intervention: luteal oestradiol.

Comparison: no treatment.

GRADE, Grading of Recommendations, Assessment, Development and Evaluations framework; CI, confidence interval; RR, risk ratio.

[a] The risk in the intervention group (and 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and 95% CI).

[b] *Demir et al. (2013)*: uncler how it was determined who received which treatment.

[c] Few events.

[d] *Chen et al. (2006)*: unclear how patients were selected to receive fresh or frozen embryo transfer.

Studies included:

Chen, M.J., Yang, J.H., Peng, F.H., Chen, S.U., Ho, H.N., Yang, Y.S., 2006. Extended estrogen administration for women with thin endometrium in frozen-thawed in-vitro fertilization programs. J. Assist. Reprod. Genet. 23, 337–342.

Demir, B., Dilbaz, S., Cinar, O., Ozdegirmenci, O., Dede, S., Dundar, B., Goktolga, U., 2013. Estradiol supplementation in intracytoplasmic sperm injection cycles with thin endometrium. Gynecol. Endocrinol. 29, 42–45.

TABLE 5 SUMMARY OF FINDINGS: SILDENAFIL CITRATE COMPARED WITH NO TREATMENT FOR PATIENTS WITH THIN ENDOMETRIUM UNDERGOING IVF-EMBRYO TRANSFER (FRESH OR FROZEN)

Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with no treatment	Risk with sildenafil citrate				
Clinical pregnancy rate: observational studies	0 per 1000	0 per 1000 (0–0)	RR 11.00 (0.69–174.00)	22 (one observational study)	⨁◯◯◯ Very low[b]	
Endometrial thickness >8 mm: observational studies	100 per 1000	1000 per 1000 (129–1000)	RR 19.40 (1.29–294.00)	22 (one observational study)	⨁⨁◯◯ Low[b]	
Pregnancy rate: RCT	200 per 1000	325 per 1000 (151–698)	RR 1.625 (0.757–3.489)	80 (one RCT)	⨁◯◯◯ Very low[c,d,e]	

Patient or population: patients with thin endometrium undergoing IVF-embryo transfer (fresh or frozen).

Intervention: sildenadil citrate.

Comparison: no treatment.

GRADE, Grading of Recommendations, Assessment, Development and Evaluations framework; RCT, randomized controlled trial; CI, confidence interval; RR, risk ratio.

[a] The risk in the intervention group (and 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and 95% CI).

[b] *Takasaki et al. (2010)* compared IVF patients with sildenafil with natural cycle or human menopausal gonadotropins + intrauterine insemination patients as control group.

[c] Not blinded, no allocation concealment.

[d] History of previously poor endometrium was not well defined.

[e] Small sample size in control and intervention groups.

Studies included:

Dehghani Firouzabadi, R., Davar, R., Hojjat, F., Mahdavi, M., 2013. Effect of sildenafil citrate on endometrial preparation and outcome of frozen-thawed embryo transfer cycles: a randomized clinical trial. Iran. J. Reprod. Med. 11, 151–158.

Takasaki, A., Tamura, H., Miwa, I., Taketani, T., Shimamura, K., Sugino, N., 2010. Endometrial growth and uterine blood flow: a pilot study for improving endometrial thickness in the patients with a thin endometrium. Fertil. Steril. 93, 1851–1858.

undergoing frozen embryo transfer with thin endometrium, patients who received G-CSF intrauterine infusion had a thicker endometrium, but no difference was seen in the pregnancy and live birth rates (*Kunicki et al., 2017*). Another cohort study did not find a significant difference in endometrial thickness or pregnancy rates (*Eftekhar et al., 2014*). An additional cohort study compared patients who received G-CSF intrauterine infusion with historical controls, and the pregnancy and live birth rates were not significantly higher with G-CSF (*Xu et al., 2015*). Endometrial thickness was thicker in the group who received G-CSF; however, patients were also randomized to receive endometrial scratching or not. A retrospective cohort study by *Li et al. (2014)* showed an increase in pregnancy rate, but this was not statistically significant. Using the patient's previous cycle as a control group, no significant difference in endometrial thickness was found.

One double-blinded RCT investigating G-CSF in IVF cycles has been published. *Barad et al. (2014)* randomized patients to receive G-CSF intrauterine infusion or placebo. In this study, clinical pregnancy rate and mean endometrial thickness were not significantly different in the G-CSF group compared with the control group. However, this study looked at all patients undergoing IVF, not just patients with thin endometrium.

No side effects have been reported with G-CSF intrauterine infusion; however, concerns have been raised about the use of systemic G-CSF. Complications may include increased risk of therapy-related myeloid neoplasm, although this risk is deemed to be small (*Lyman et al., 2010*). There have also been case reports of sickle cell crisis and multi-organ failure in patients who have used G-CSF with sickle cell syndromes (*Abboud et al., 1998; Adler et al., 2001*). Use of G-CSF has been associated with bone pain (*Kuderer et al., 2007*). Although data suggest that G-CSF intrauterine infusion may improve endometrial thickness, there is a lack of controlled studies demonstrating an improvement in pregnancy or live birth rates, and potential harm or risk need to be considered with this treatment.

Additional adjuvants

Pentoxifylline has been described in several case series (*Acharya et al., 2009; Ledee-Bataille et al., 2002; Letur-Konirsch et al., 2002; Letur-Konirsch and Delanian, 2003*). Three of these studies focused on donor oocyte recipient patients with a history of thin endometrium, including patients with a history of premature ovarian insufficiency and pelvic radiation. There have been no controlled studies for pentoxifylline.

Two case series reported endometrial thickness, and pregnancy and live birth rates with the use of HCG in frozen embryo transfers in patients with a history of thin endometrium (*Davar et al., 2016; Papanikolaou et al., 2013*). There have been no controlled studies. The authors identified one RCT on the use of adjuvant gonadotropin-releasing hormone agonists at the time of oocyte retrieval and embryo transfer for patients with endometrial thickness <8 mm on the day of HCG administration

Recommendation	Strength	Quality of evidence	Justification
In patients with thin endometrium undergoing embryo transfer cycles, we suggest against the use of intrauterine infusion of G-CSF to improve pregnancy rates.	Weak	⨁⨁◯◯ TABLE 6	No benefit for clinical pregnancy or live birth rates in observational data or one RCT. Potential side effects and complications with G-CSF intrauterine infusion also need to be further studied. G-CSF intrauterine infusion may improve endometrial thickness based on observational data.

TABLE 6 SUMMARY OF FINDINGS: GRANULOCYTE COLONY-STIMULATING FACTOR (G-CSF) COMPARED WITH NO TREATMENT FOR PATIENTS WITH THIN ENDOMETRIUM UNDERGOING IVF-EMBRYO TRANSFER (FRESH OR FROZEN)

Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with no treatment	Risk with G-CSF				
Live birth rate: observational studies	129 per 1000	186 per 1000 (86–400)	RR 1.441 (0.669–3.102)	144 (two observational studies)	⨁◯◯◯ Very low[b,c,d]	
Clinical pregnancy rate: observational studies	166 per 1000	278 per 1000 (184–422)	RR 1.678 (1.108–2.540)	332 (four observational studies)	⨁◯◯◯ Very low[b,d]	
Clinical pregnancy rate: RCT	235 per 1000	233 per 1000 (128–423)	OR 0.990 (0.545–1.800)	141 (one RCT)	⨁⨁◯◯ Low[d,e]	

Patient or population: patients with thin endometrium undergoing IVF-embryo transfer (fresh or frozen).

Intervention: G-CSF.

Comparison: no treatment.

GRADE, Grading of Recommendations, Assessment, Development and Evaluations framework; RCT, randomized controlled trial; CI, confidence interval; RR, risk ratio; OR, odds ratio.

[a] The risk in the intervention group (and 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and 95% CI).

[b] In some studies, patients were co-treated with aspirin or sildenafil. Some studies used patient choice to decide if they received G-CSF or not.

[c] Low event rates.

[d] Most studies published in major journals showed beneficial effect of G-CSF, even in small sample sizes.

[e] Looked at all IVF patients, not just patients with thin endometrium.

Studies included:

Barad, D.H., Yu, Y., Kushnir, V.A., Shohat-Tal, A., Lazzaroni, E., Lee, H.J., Gleicher, N., 2014. A randomized clinical trial of endometrial perfusion with granulocyte colony-stimulating factor in in vitro fertilization cycles: impact on endometrial thickness and clinical pregnancy rates. Fertil. Steril. 101, 710–715.

Eftekhar, M., Sayadi, M., Arabjahvani, F., 2014. Transvaginal perfusion of G-CSF for infertile women with thin endometrium in frozen ET program: a non-randomized clinical trial. Iran. J. Reprod. Med. 12, 661–666.

Kunicki, M., Lukaszuk, K., Liss, J., Skowronska, P., Szczyptanska, J., 2017. Granulocyte colony stimulating factor treatment of resistant thin endometrium in women with frozen-thawed blastocyst transfer. Syst. Biol. Reprod. Med. 63, 49–57.

Li, Y., Pan, P., Chen, X., Li, L., Li, Y., Yang, D., 2014. Granulocyte colony-stimulating factor administration for infertile women with thin endometrium in frozen embryo transfer program. Reprod. Sci. 21, 381–385.

Xu, B., Zhang, Q., Hao, J., Xu, D., Li, Y., 2015. Two protocols to treat thin endometrium with granulocyte colony-stimulating factor during frozen embryo transfer cycles. Reprod. Biomed. Online 30, 349–358.

(*Qublan et al., 2008*). This study found a beneficial effect; however, the biological plausibility is uncertain and the results have not been replicated.

The use of platelet-rich plasma or stem cells has only been described in patients with thin endometrium resulting from Asherman syndrome (*Chang et al., 2015; Gargett and Healy, 2011; Nagori et al., 2011; Santamaria et al., 2016; Singh et al., 2014; Zadehmodarres et al., 2017*). Although these preliminary studies are promising for a population which has a poor prognosis and few options for treatment, further research and controlled studies are required given the invasiveness and expense of stem cell treatment.

Several papers have also evaluated supplements such as vitamins C and E, and L-arginine (*Kitaya et al., 2014; Takasaki et al., 2010*). These studies have been small and poorly controlled.

Recommendation	Strength	Quality of evidence	Justification
In patients with thin endometrium undergoing embryo transfer cycles, we suggest against the use of pentoxifylline, HCG, gonadotropin-releasing hormone agonists, platelet-rich plasma or stem cells to improve pregnancy rates.	Weak	⨁◯◯◯	Only case reports and case series are in the literature, with no controlled studies reported. Further research to evaluate the potential risks and benefits of these adjuvants is needed.

CONCLUSIONS

Thin endometrium is an infrequent but challenging occurrence in assisted reproduction. Physicians must balance the prognosis for patients if they proceed with treatment with a thin endometrium or consider alternative treatments. Currently, there is minimal evidence to support any specific protocols or adjuvants to significantly improve pregnancy outcomes in patients with thin endometrium.

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Arce, H., Velilla, E., Lopez-Teijon, M. **Association between endometrial thickness in oocyte donation cycles and pregnancy success rates.** Reprod. Fertil. Dev. 2015

Asante, A., Coddington, C.C., Schenck, L., Stewart, E.A. **Thin endometrial stripe does not affect likelihood of achieving pregnancy in clomiphene citrate/intrauterine insemination cycles.** Fertil. Steril. 2013; 100:1610-4.e1

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