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Review: The Influence of Endometrial Thickness on IVF Outcomes

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Abstract

Background: Assisted Reproductive Technology (ART) including In-Vitro Fertilisation (IVF) has led to improved outcomes for sub fertile couples and individuals. Endometrial thickness, a sensitive and reproducible marker of endometrial receptivity has been linked to success rates in IVF. Consequently, the purpose of this study was to review this association.

Methods: A literature search using the Cochrane library, EMBASE and MEDLINE was performed for eligible articles (n=11).

Results: Seven studies suggested that endometrial thickness had no impact on pregnancy rates. Four studies suggested that increased endometrial thickness had a positive effect on pregnancy rates. Two studies concluded that extreme endometrial thicknesses were negatively associated with pregnancy rates.

Conclusions: Existing prospective and retrospective studies suggest that extreme endometrial thicknesses may have a negative impact on IVF pregnancy rates. However, no definitive conclusions for clinical practice have been reached in terms of appropriate endometrial thickness thresholds.

Keywords: In vitro fertilization; Infertility; Endometrial thickness; Pregnancy

Abbreviations: ART – Assisted Reproduction Technology; ICSI – Intracytoplasmic Sperm Injection; IVF – In-Vitro Fertilisation

Introduction

Approximately 85% of couples will successfully conceive a pregnancy after 12 months of unprotected intercourse. Of the remaining 15% with a degree of subfertility, a proportion will embark on the journey to assisted reproductive technology (ART) technique whereby gametes are manipulated to improve the probability of pregnancy [1]. In-vitro fertilisation (IVF) and/ or Intracytoplasmic Sperm Injection (ICSI) has led to successful live pregnancies in this group of patients. Although ART success rates have improved dramatically over the last two decades, only 36% of women aged less than 30 years and 9% of women aged between 40-44 years will fall pregnant through a single ART cycle [2]. Such low implantation and pregnancy rates combined with the high cost of in IVF have instigated an evaluation of factors that can predict success for this group of patients.

Embryo implantation is a major rate-limiting step in the success of ART. A variety of factors can impact embryo implantation including endometrial differentiation, embryo quality and the method of embryo transfer. It is well established that endometrial differentiation and receptivity is critical in determining the possibility of success in ART treatments. Defined as a physiological condition of the endometrium whereby it is ideal for embryo implantation, endometrial receptivity is a state mainly induced by ovarian steroid hormones [3]. In the normal menstrual cycle, the endometrium undergoes cyclic morphological changes beginning with mitotic growth of the functional layer in the follicular phase in response to oestrogen. The luteal phase under the control of progesterone, readies the endometrium for implantation [4,5]. However, the molecular mechanisms underpinning receptivity and readiness for implantation and the interplay between ovarian hormones, cytokines, growth factors and adhesion molecules are not well understood [6]. As endometrial morphology may reveal such "readiness", endometrial blood flow, pattern and thickness have all been evaluated as markers of receptivity and consequently implantation and pregnancy in IVF [5,7].

Endometrial thickness as measured by ultrasonographic examination is a simple, non-invasive and reproducible means of assessing endometrial development and may act as a surrogate marker of receptivity [8]. It has been studied extensively as a predictor of successful pregnancy in IVF, albeit with conflicting evidence. It is well accepted that poor pregnancy rates occur with thin endometrial linings as shown on transvaginal ultrasound scan. A thin endometrium is associated with implantation failure and numerous studies have demonstrated that implantation rarely occurs with thicknesses of < 6-7 mm [9,10]. However, there is conflicting evidence surrounding the impact of extremely increased endometrial thickness and the optimal thickness for implantation to occur. Such conflicting evidence may be in part due to the multiple confounding factors that influence the likelihood of success in any IVF cycle. In light of this conflicting evidence, this review will evaluate the available evidence in regards to endometrial thickness on the day of human chorionic gonadatrophin administration and its influence on pregnancy outcome in IVF cycles.

Methods

The Cochrane library, MEDLINE and EMBASE databases were searched using different combinations of the terms: "assisted reproductive technologies" OR "in vitro fertlisation" OR "infertility" AND "endometrial thickness" OR "thin endometrium" OR "thick endometrium" AND "pregnancy".

Inclusion criteria were as follows:

1. Articles that were published in English and between 1992 and 2012
2. Studies where endometrial thickness was measured on the day

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of hCG injection via transvaginal ultrasound in the midsagittal plane

3. Studies where gonadotrophins were used in the stimulation protocol

Exclusion criteria were as follows:

1. Studies that evaluated endometrial thickness in natural conception or intrauterine insemination
2. Studies that did not provide quantitative data on endometrial thickness or pregnancy rates
3. Studies in which frozen embryos were used
4. Studies in which clomiphene citrate was used for ovarian stimulation
5. Case reports

A total of 427 articles were identified from the search strategy of which 11 were included for the literature review.

Results

Eligible studies (n=11) were published in the last 20 years (1992-2012). A comparison of baseline data between the studies is shown in table 1. A comparison of findings in regards to endometrial thickness is shown in table 2. Seven studies did not find a significant difference in endometrial thickness between the pregnant and non-pregnant cohorts. Of those studies that found a significant difference in endometrial thickness between pregnant and non-pregnant groups (n=4), a thickened endometrium was associated with improved embryo implantation rates.

Author name and year	Study type	Sample size (pregnant)	Sample size (not pregnant)	Age (years, pregnant)	Age (years, not pregnant)	P value	Number of embryos (pregnant group)	Number of embryos (not pregnant group	P value
Kinay, 2010	Prospective cohort	11	29	33.3 ± 4.8	34 ± 5	NS	NA	NA	NA
Okuhue, 2009	Prospective cohort	106	145	30.2 ± 4.0	30.8 ± 2.8	NS	NA	NA	NA
Traub, 2009	Retrospective cohort	57	57	32.4 ± 3.5	34.1 ± 4.1	0.019	6.6 ± 3.3	5.9 ± 2.8	NS
Al-Ghamdi, 2008	Retrospective cohort	882	1582	30.3 ± 5.5	31.1 ± 5.4	0.0001	5.3 ± 2.82	4.44 ± 2.81	<0.0001
Merce, 2008	Prospective cohort	38	39	33.9 ± 3.4	34.3 ± 3.5	NS	5.71 ± 2.78	4.10 ± 3.19	0.021
McWilliams, 2007	Retrospective cohort	70	62	32.9 ± 3.9	34.9 ± 4.3	<0.01	11.5 ± 7.6	8.4 ± 7.0	<0.01
Richter, 2007	Retrospective cohort	864	430	33.5 ± 3.5	34 ± 3.7	0.031	NA	NA	NA
Rashidi, 2004	Prospective cohort	30	120	30.9 ± 4	30.7 ± 5	0.089	NA	NA	NA
Bassil, 2001	Prospective cohort	52	101	31.2 ± 3.7	31.4 ± 3.9	NS	7.3 ± 4.4	5.1 ± 3.5	0.0009
Yuval, 1999	Prospective cohort	31	125	32.2 ± 4.99	33.1 ± 5.49	NS	4.8 ± 1.22	3.94 ± 1.59	<0.05
Zaidi, 1995	Prospective cohort	31	65	32.3 ± 3.5	34.4 ± 4.5	0.004	7.2 ± 3.7	5.6 ± 3.2	NS

Table 1: Baseline data comparison between studies. Pregnancy is defined as a positive urinary pregnancy test 14 days after embryo transfer. Not pregnant is defined as a negative urinary pregnancy test 14 days after embryo transfer. Data presented as mean ± standard deviation. NS – not significant. NA – not applicable/ not reported in the study.

Author name and year	Mean thickness in pregnant group (mm)	Mean thickness in not pregnant group (mm)	P value	Summary of main findings
Kinay, 2010	10.2 ± 2.7	10.2 ± 2	NS	Endometrial thickness is not a significant determinant of pregnancy in gonadotrophin antagonist ICSI cycles.
Okuhue, 2009	11.82 ± 1.90	11.88 ± 3.17	NS	No pregnancy occurred with endometrial thickness < 7mm and one pregnancy with a thickness > 14mm. The detrimental effect of endometrial thickness extremes was statistically significant.
Traub, 2009	11.2 ± 3.1	10.1 ± 2.6	0.022	A thicker endometrium, younger age and Caucasian ethnicity were positively associated with clinical pregnancy.
Al-Ghamdi, 2008	11.64 ± 2.13	11.26 ± 2.17	<0.0001	Endometrial thickness on the day of hCG administration was greater where pregnancy was achieved. Multiple logistic regression analysis showed that this was an independent effect. No threshold effect was reported, but a steady and gradual increase in pregnant rates as endometrial thickness increased was observed. However, the difference in mean values between the pregnant and non-pregnant groups fell within the range of measurement error.
Merce, 2008	12.29 ± 2.71	12.15 ± 2.31	NS	Endometrial volume as measured by 3D-ultrasound was significantly increased in the pregnant cohort, however no differences in endometrial thickness were found.
McWilliams, 2007	10.0 ± 1.9	9.1 ± 2.3	<0.05	Pregnant patients had significantly greater endometrial thickness on the day of hCG injection. As baseline thickness did not differ between groups, it may be endometrial responsiveness during gonadotrophin stimulation in an IVF cycle that predicts pregnancy.
Richter, 2007	11.9 ± 2.4	11.3 ± 2.4	<0.0001	Clinical and continuing pregnancy increase significantly with increased endometrial thickness. This is independent of age and embryo quality.
Rashidi, 2004	10.1 ± 1	10.2 ± 2	NS	Endometrial thickness was not significantly different between the two groups. No pregnancies occurred at thicknesses <9mm and >12mm.
Bassil, 2001	11.5 ± 3.2	11.6 ± 3.1	NS	No significant relationship was found between endometrial thickness and pregnancy during the IVF cycle up to the time of embryo transfer.
Yuval, 1999	10.7 ± 2.4	10.9 ± 2.8	NS	Endometrial thickness did not affect pregnancy rate.
Zaidi, 1995	10.9 ± 1.8	11.3 ± 2.2	NS	There was no difference between the endometrial thickness of pregnant and non-pregnant patients.

Table 2: Summary of endometrial thickness findings. Pregnancy is defined as a positive urinary pregnancy test 14 days after embryo transfer. Not pregnant is defined as a negative urinary pregnancy test 14 days after embryo transfer. Data presented as mean ± standard deviation. NS – not significant.

Discussion

Multiple studies in the literature have demonstrated that endometrial thickness is significantly increased in pregnant patients compared to non-pregnant patients [7,8,11-14]. However, there are also multiple studies that do not support this conclusion [15-22].

A limited number of studies have reported a detrimental impact of greatly increased endometrial thickness on pregnancy outcomes. Weissman et al demonstrated that an endometrium > 14 mm resulted in significantly reduced implantation and pregnancy rates [23]. This was supported by the findings of Rashidi et al. [20] who found no pregnancy at an endometrial thickness > 12 mm. The mechanisms proposed for this include a heightened risk of endometrial trauma during embryo transfer and an abnormal endometrial histologic pattern that does not support a pregnancy [23]. Similarly, multiple studies report poor pregnancy rates with a thin endometrial lining [19,20]. However, anecdotal case reports of successful pregnancy outcomes have been reported at both extremes of endometrial thickness [24,25]. Until a consensus is reached on the optimal threshold for endometrial thickness, the current evidence suggests that extremely thin or thick endometrial thicknesses are not an absolute contraindication to embryo transfer in an IVF cycle.

The majority of studies focus on biochemical pregnancy as the main outcome measure as opposed to continuing pregnancy. Although this may reflect an optimal state for implantation, a continuing pregnancy is of more clinical significance. As a thickened endometrium may result in a higher early pregnancy loss rate [23,26], it would be useful if future studies investigated the relationship between continuing pregnancy and endometrial thickness. Furthermore, implantation is a complex and poorly understood process. Although ultrasound measurements of thickness may be reflective of receptivity, it is not the sole determinant. Ultrasound assessments of thickness may be too simple to determine pregnancy potential. Some studies have examined the use of three-dimensional ultrasound to determine endometrial volume, which may be a better surrogate marker [27,28]. However, the limited number of studies using this technology makes it difficult to reach definitive conclusions at this time. In addition, in those studies that demonstrate a significant increase in pregnancy rates with increased endometrial thicknesses, it is possible that this reflects improved ovarian stimulation with gonadotrophins and the subsequent downstream endometrial effects, as opposed to an independently responsive endometrial lining [7].

The different measurement outcomes and stimulation protocols used in the various studies make direct comparisons difficult. In an attempt to make a homogenous comparison, the studies examined in this review looked at endometrial thickness on the day of hCG administration. This was chosen, as it was a common time point in many studies. However, differences in stimulation protocols, namely gonadotrophin agonist versus antagonist protocols adds ambiguity, as does discrepancies in the statistical methods used. Strength of some studies was the use of Receiver Operating Curves (ROC) to generate a critical threshold for endometrial thickness, as were adequately powered studies with large sample sizes. Several studies commented on the need to increase sample sizes in order to prove significance based on power calculations. Although difficult to avoid, the retrospective nature of the studies is a weakness as is the fact that only one study blinded thickness measurements to subjects and treating physicians. Furthermore, as 6/11 studies in this review documented significant age differences between the pregnant and non-pregnant cohorts, it is difficult to draw conclusions on an independent effect of endometrial thickness. Increasing age is known to negatively impact on IVF success rates. This suggests that the poor prognosis associated with advancing age cannot be overcome by favorable factors including ideal endometrial receptivity [3].

Conclusions and Implications for Practice

There is insufficient evidence to support the use of a critical endometrial thickness threshold that clearly improves implantation and pregnancy rates in fresh IVF cycles. There is evidence of lower pregnancy rates at extremes of endometrial thickness, which should be taken into account when counseling couples about the chances of conception in a particular cycle. If the endometrium is deemed unsuitable, it may be worthwhile freezing embryos until the next cycle. The small number of trials examined in this review and the different measurement outcomes between studies make it difficult to draw definitive conclusions at this time. Three-dimensional ultrasound, which allows determination of endometrial volume, may prove to be an improved surrogate marker of endometrial receptivity in the future.

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