A multitude of variables play a major part in successful implantation and pregnancy, nonetheless in cycles of assisted reproduction. It is established that the endometrium is a key factor during the so-called “implantation window”, a short period of time of maximal endometrial receptivity to blastocyst signals [1,2], during which the human embryo is nearing the endometrium in secretory phase in order to attach and invade. This embryo-maternal dialogue is crucial for the establishment of a healthy pregnancy [3]. During the natural menstrual cycle the endometrium is under constant influence of hormones, estradiol (E$_2$) from the maturing follicles and later progesterone (P) from the corpus luteum [4]. These hormones lead directly and indirectly to endometrial proliferation, transformation and secretion [5], and this process becomes apparent as a change in thickness and pattern. During the proliferative phase the endometrium thickens and thus provides an ideal site for attachment and nourishment for an implanting embryo in the first few weeks until the development of the placenta is completed [6]. This post-ovulatory state of the endometrium

Endometrial Receptivity and its Predictive Value for IVF/ICSI-Outcome

Die endometriale Rezeptivität in der IVF-Therapie

Key words
• assisted reproductive technology (ART)
• pregnancy
• sonography

Schlüsselwörter
• assistierte Reproduktion
• Schwangerschaft
• Ultraschall

Abstract

Endometrial receptivity plays a crucial role in the establishment of a healthy pregnancy in cycles of assisted reproduction. The endometrium as a key factor during reproduction can be assessed in multiple ways, most commonly through transvaginal grey-scale or 3-D ultrasound. It has been shown that controlled ovarian hyperstimulation has a great impact on the uterine lining, which leads to different study results for the predictive value of endometrial factors measured on different cycle days. There is no clear consensus on whether endometrial factors are appropriate to predict treatment outcome and if so, which one is suited best. The aim of this review is to summarize recent findings of studies about the influence of endometrial thickness, volume and pattern on IVF- and ICSI-treatment outcome and provide an overview of future developments in the field.

Zusammenfassung


Introduction

A multitude of variables play a major part in successful implantation and pregnancy, nonetheless in cycles of assisted reproduction. It is established that the endometrium is a key factor during the so-called “implantation window”, a short period of time of maximal endometrial receptivity to blastocyst signals [1,2], during which the human embryo is nearing the endometrium in secretory phase in order to attach and invade. This embryo-maternal dialogue is crucial for the establishment of a healthy pregnancy [3]. During the natural

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Endometrial Assessment

Endometrial receptivity is the ability of the endometrium to successfully attach the blastocyst, to nourish it and keep it alive. This can only be achieved after the endometrium underwent a number of histological changes while also increasing in thickness [4]. While histological changes can only be examined by biopsy, transvaginal ultrasound is a non-invasive, easy and reliable method to measure parameters like thickness and pattern [2, 31]. Practitioners performing in vitro fertilization (IVF) or any other ART method (e.g. intracytoplasmic sperm injection, ICSI) are in need of an objective measurement to determine the probability of a successful pregnancy. Therefore, using a simple and accurate measuring tool like grey-scale ultrasound and evaluating endometrial thickness, pattern or volume as surrogate parameters for endometrial receptivity seems appropriate [4]. These parameters are likely to be indirect indications of the receptive quality of the endometrium and we are going to discuss some recent findings on each of these factors and examine if any one of them can be used to predict the chances of a positive outcome.

Endometrial thickness

Endometrial thickness is commonly measured in the midsagittal plane, from the outer edge of the endometrial-myometrial junction to the outer edge of the thickest part of the endometrium by two-dimensional ultrasonography [11–14, 16, 32, 33]. The measurement of endometrial thickness and its predictive value is, above all, a question of timing. Most authors have used the thickness as measured on the day of ovulation induction (triggered by hCG administration) for their analyses. But since the endometrium is under constant influence of hormones it changes incessantly and still increases its thickness after ovulation in natural cycles [34]. This may suggest that the exact day of ultrasound evaluation has a great influence on the results of studies.

A statistically significant association between total pregnancy rate (PR) and endometrial thickness, measured before induction of ovulation, has been found by Kehila et al. [35]. They argue that the chances of a successful pregnancy are about three times higher if the endometrium is more than 12 mm wide [35]. The study of Bozdag et al. [36] reaches roughly the same conclusion, as they found a significantly higher clinical PR in patients with an endometrial thickness of > 14 mm on the day of hCG administration. In some studies there was neither a correlation between pregnancy rates and endometrial thickness on the day of hCG application [37–40] nor a significant difference in mean endometrial thickness between pregnant and non-pregnant groups [12, 14, 15, 37–43].

Others on the contrary did find that an increasing endometrial thickness on hCG day led to a higher probability of establishing a healthy pregnancy [11, 13, 16, 17, 33, 44]. In the report of Rinaldi et al. [45] there was a significantly higher PR with a thickness of > 10 mm, but only for IVF and not for ICSI cycles.

As for the day before oocyte aspiration, but Bergh et al. [46] found a significantly thicker endometrium in patients who were able to conceive when compared to those who were not. Gonen & Casper’s study [19] reached the same conclusion.
The endometrial thickness measured on the day of oocyte retrieval proved to be no reliable predictor of conception in some cases [20,43,47–49]. Kumbak et al. [50] examined the outcome in patients with a thin endometrium (7 mm or less) on the day of ovum pick-up and concluded that it was not necessarily a negative predictor, especially when the patient age was < 35 years and the number of transferred embryos was three or more. As for the other side of the spectrum, Quintero et al. [51] reported two successful twin pregnancies with an endometrial lining of 16 and 20 mm, respectively, also measured on the day of oocyte retrieval.

The latest possible date to examine the thickness of the uterine lining is during embryo transfer (ET). Kovacs et al. [52] showed that the mean endometrial thickness was significantly higher in pregnant patients. Others found no statistically significant difference when comparing endometrial thickness between conception and non-conception groups [14,47]. Kovachev et al. [53] compared the predictive value of endometrial thickness on the day of ET to that of endometrial volume on the same day. Their results imply that volume is a better predictor for ART outcome [53].

### Endometrial volume

Some authors tried to distinguish a better predictor for endometrial receptivity than thickness alone. Kovachev et al. [53] examined the predictive value of endometrial volume as assessed by 3-D ultrasound on the day of ET and found that a volume of < 2 ml resulted in significantly lower implantation rates, whereas an endometrial volume of > 2 ml was a positive predictor for successful ART outcome. One investigator showed that endometrial volume decreased significantly after the administration of hCG.

### Table 1  Studies regarding endometrial thickness.

<table>
<thead>
<tr>
<th>Day of endometrial assessment</th>
<th>Number of cycles analysed</th>
<th>Study design</th>
<th>Main study results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before induction of ovulation</td>
<td>414</td>
<td>retro</td>
<td>statistically significant relationship between EMT and total PR</td>
</tr>
<tr>
<td>Bozdag et al. (2009)</td>
<td>758</td>
<td>retro</td>
<td>IR &amp; PR significantly higher if EMT &gt; 14 mm</td>
</tr>
<tr>
<td>Induction of ovulation</td>
<td>251</td>
<td>pro, cohort study</td>
<td>significantly more pregnancies occurred in patients with an EMT of 7–14 mm</td>
</tr>
<tr>
<td>Okohue et al. (2009)</td>
<td>155</td>
<td>pro, cohort study</td>
<td>no significant difference in mean EMT between pregnant and non-pregnant groups</td>
</tr>
<tr>
<td>Kumbak et al. (2009)</td>
<td>40</td>
<td>pro, cohort study</td>
<td>significantly more pregnancies occurred in patients with an EMT of 7–14 mm</td>
</tr>
<tr>
<td>Mercé et al. (2008)</td>
<td>80</td>
<td>pro, clinical study</td>
<td>v.s.</td>
</tr>
<tr>
<td>Corbacioglu et al. (2009)</td>
<td>241</td>
<td>retro</td>
<td>v.s.</td>
</tr>
<tr>
<td>Laasch et al. (2004)</td>
<td>1218</td>
<td>pro, clinical study</td>
<td>v.s.</td>
</tr>
<tr>
<td>Yoeli et al. (2004)</td>
<td>150</td>
<td>pro, clinical study</td>
<td>v.s.</td>
</tr>
<tr>
<td>Raishidi et al. (2004)</td>
<td>40</td>
<td>pro</td>
<td>v.s.</td>
</tr>
<tr>
<td>Coulam et al. (1994)</td>
<td>86</td>
<td>pro</td>
<td>v.s.</td>
</tr>
<tr>
<td>Sharara et al. (1999)</td>
<td>60</td>
<td>pro</td>
<td>v.s.</td>
</tr>
<tr>
<td>Lesny et al. (1999)</td>
<td>2464</td>
<td>retro, cohort study</td>
<td>significant difference in mean EMT between pregnant and non-pregnant groups</td>
</tr>
<tr>
<td>Al-Ghamdi et al. (2008)</td>
<td>2896</td>
<td>retro</td>
<td>PR was significantly higher with increasing EMT</td>
</tr>
<tr>
<td>Richter et al. (2007)</td>
<td>1294</td>
<td>retro</td>
<td>significant difference in mean EMT between pregnant and non-pregnant groups</td>
</tr>
<tr>
<td>Traub et al. (2009)</td>
<td>114</td>
<td>retro, cohort study</td>
<td>patients achieving clinical pregnancy had a thicker endometrial stripe</td>
</tr>
<tr>
<td>Amir et al. (2007)</td>
<td>2339</td>
<td>retro</td>
<td>a thicker endometrium is correlated with a higher PR only for patients &gt; 35 years of age</td>
</tr>
<tr>
<td>Zhang et al. (2005)</td>
<td>897</td>
<td>retro</td>
<td>PR was positively associated with increased EMT</td>
</tr>
<tr>
<td>Rinaldi et al. (1996)</td>
<td>158</td>
<td>pro</td>
<td>PR was positively associated with increased EMT ≥ 10 mm for IVF cycles only</td>
</tr>
<tr>
<td>Before oocyte aspiration</td>
<td>100</td>
<td>pro</td>
<td>significantly thicker endometrium in pregnant patients</td>
</tr>
<tr>
<td>Bergh et al. (1992)</td>
<td>123</td>
<td>pro, cohort study</td>
<td>v.s.</td>
</tr>
<tr>
<td>Oocyte retrieval</td>
<td>190</td>
<td>pro</td>
<td>no relationship between EMT and IR</td>
</tr>
<tr>
<td>Welker et al. (1989)</td>
<td>60</td>
<td>retro</td>
<td>no significant difference in mean EMT between pregnant and non-pregnant groups</td>
</tr>
<tr>
<td>Lesny et al. (1999)</td>
<td>153</td>
<td>pro, case-control</td>
<td>v.s.</td>
</tr>
<tr>
<td>Basill et al. (2001)</td>
<td>35</td>
<td>pro</td>
<td>v.s.</td>
</tr>
<tr>
<td>Schild et al. (2001)</td>
<td>175</td>
<td>pro, clinical study</td>
<td>no relationship between EMT and IR</td>
</tr>
<tr>
<td>Kumbak et al. (2009)</td>
<td>2</td>
<td>case report</td>
<td>two successful twin pregnancies with an EMT of 16 and 20 mm</td>
</tr>
<tr>
<td>Quintero et al. (2004)</td>
<td>1228</td>
<td>retro</td>
<td>mean EMT significantly higher in pregnant patients</td>
</tr>
<tr>
<td>Embryo transfer</td>
<td>40</td>
<td>pro, cohort study</td>
<td>no significant difference in mean EMT between pregnant and non-pregnant groups</td>
</tr>
<tr>
<td>Kovacs et al. (2003)</td>
<td>153</td>
<td>pro, case-control</td>
<td>v.s.</td>
</tr>
<tr>
<td>Bassil et al. (2001)</td>
<td>58</td>
<td>pro, clinical study</td>
<td>endometrial volume is a better predictor for ART outcome</td>
</tr>
<tr>
<td>Kovachev et al. (2005)</td>
<td>58</td>
<td>pro, clinical study</td>
<td>endometrial volume is a better predictor for ART outcome</td>
</tr>
</tbody>
</table>

Abbreviations: retro: retrospective; pro: prospective; EMT: endometrial thickness; PR: pregnancy rates; IR: implantation rates; ART: assisted reproduction techniques; v.s.: vide supra
...appearance or reflectivity... of a qualitative change in grey-scale appearance or reflectivity. In most studies two distinct patterns have been defined, one of “homogeneous” echogenicity and one of a “multi-layered” or “triple-line” echogenicity [13,19,20,46,48,56,57]. Welker et al. [20] found that endometrial pattern on the day of oocyte retrieval positively influenced implantation, whereas no such correlation was found for endometrial thickness of the same day. Another study also showed that pregnant women had a significantly higher rate of multi-layered patterns [19].

The report of Sher et al. [56] further supports those results, as they found a much higher clinical PR in patients with a multi-layered pattern and an endometrial thickness of ≥ 9 mm in comparison to those with homogeneous echogenicity and/or a thickness of < 9 mm. Other investigators produced similar results, finding a significantly higher PR in women with a triple-line pattern compared to those with a homogeneous one, both after FSH stimulation and on the day of ovum pick-up [48]. However, there are also various studies showing no statistically significant relationships between the different echogenic patterns and pregnancy rates [13,40,46,47,57], and Kuc et al. [58] found out that endometrial echogenicity significantly influenced treatment outcome only in the long GnRH agonist protocol. Sharara et al. [42] could confirm a significantly lower implantation rate in patients who had a homogeneous, hyperechogenic pattern compared to those with a triple-line pattern on the day of oocyte retrieval. Furthermore, they evaluated the endometrium on the day of hCG application as well as on the day of oocyte retrieval and noted a change from a more receptive triple-line pattern to one of homogenous echogenicity between those two dates in 12.6% of cycles [42]. A similar change in pattern was noted by Bassil et al. [47], as they recorded an alteration from a multilayered to a homogeneous, hyperechogenic pattern between the day of oocyte retrieval and the day of embryo transfer in 22.2% of cycles. This suggests that the evaluation of endometrial receptivity is probably more accurate the closer it is performed to the actual implantation of the embryo.

**Endometrial pattern**

The ultrasonic appearance of endometrial pattern has been described by Smith et al. [55] as a “qualitative change in grey-scale appearance or reflectivity”. In most studies two distinct patterns have been defined, one of “homogeneous” echogenicity and one of a “multi-layered” or “triple-line” echogenicity [13,19,20,46,48,56,57]. Welker et al. [20] found that endometrial pattern on the day of oocyte retrieval positively influenced implantation, whereas no such correlation was found for endometrial thickness of the same day. Another study also showed that pregnant women had a significantly higher rate of multi-layered patterns [19].

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**Discussion**

While it is widely accepted that the endometrium is a key factor for successful implantation and for establishing a healthy pregnancy [11,13,14], opinions are divided as to which parameter is...
suited best for predicting a positive outcome during cycles of assisted reproduction.

Many authors have tried to identify a simple method to evaluate the quality of the uterine lining. The overall consensus is that transvaginal ultrasound scan fits the criteria the best, the crucial questions are: What parameters can be obtained through grey-scale ultrasound of the endometrium? And are the ascertainment parameters suitable for predicting treatment outcome [59]?

The first question is easily answered. Four distinct factors can be measured: endometrial thickness, endometrial pattern, endometrial volume (measured by 3-D ultrasound) and subendometrial blood flow (measured by power Doppler sonography). All of these have been examined in many different studies, but the results vary from author to author.

Even though a lot of studies have shown no significant correlation between either endometrial thickness [14, 37–40, 43, 47–49] or pattern [13, 40, 46, 47, 57] and pregnancy rates, there are many who did prove that a statistical connection between these parameters and PR existed [11, 13, 16–20, 35, 36, 42, 44–46, 48, 52, 56]. The same goes for endometrial volume, where both positive [15, 53] and negative [48, 49, 54] study results have been published.

The endometrial vascularity determined by three-dimensional power Doppler ultrasound was proposed to have a predictive value on the implantation rate in IVF cycles irrespective of the morphological appearance of the endometrium [57]. However, the number of studies dealing with this topic is rather low.

Conclusions

The different and partly conflicting results of the studies may be due to varying study designs and population sizes (Tables 1 to 3), as well as the specific hormonal stimulation protocols used for COH. In spite of the abundance of studies on that subject with varying results and of the individual restrictions of these studies we suggest that prediction of successful implantation with the help of ultrasound examinations of the endometrium does not seem to be an exact science yet. However, in practice it is a possibility of getting at least some information about endometrial receptivity during ART. There is still a need for a more reliable measurement technique to predict the probability of pregnancy prior to embryo transfer to influence the decision if embryos should be transferred or rather cryopreserved for later ART cycles.

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Conflict of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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