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

Die endometriale Rezeptivität in der IVF-Therapie

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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

Die endometriale Rezeptivität spielt eine entscheidende Rolle für den Beginn und den Erhalt einer Schwangerschaft. Die physiologische Ausbildung eines implantationsfördernden und -erhaltenden Endometriums wird daher als Schlüsselfaktor bei allen fertilitätsunterstützenden therapeutischen Behandlungen angesehen. Dabei wird in der Praxis der Zustand des Endometriums mithilfe des Einsatzes des transvaginalen Ultraschalls bestimmt. Die kontrollierte ovarielle Überstimulation, wie sie im Rahmen einer IVF-Therapie angewandt wird, kann einen erheblichen Einfluss auf den Zustand des Endometriums zum Zeitpunkt der Untersuchung haben. Bislang gibt es allerdings keinen klaren Konsens darüber, ob endometriale Faktoren geeignet sind, um das Behandlungsergebnis einer IVF-Therapie verlässlich vorhersagen zu können. Das Ziel dieser Übersichtsarbeit ist es daher, die aktuellen wissenschaftlichen Ergebnisse über den Einfluss der mithilfe von Ultraschallmessungen gewonnenen endometrialen Parametern im Rahmen der IVF-Behandlung zusammenzufassen und einen Überblick über zukünftige Entwicklungen auf diesem Gebiet zu geben.

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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 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

is therefore of great importance to the success of IVF and ICSI treatments [7].

In this review we will elaborate on the hormonal levels during assisted reproduction techniques (ART) as well as their deviation from levels during natural menstrual cycles and how that may potentially lead to changes to the endometrium. Furthermore, sonographically measureable endometrial parameters like thickness, volume and pattern will be examined in regard to their predictive value for positive treatment outcome.

Hormonal Influence During ART

In order to establish an endometrium that is able to offer the blastocyst a site for attachment and nourishment, it has to undergo certain proliferative changes [6]. Changes to the endometrium occur as an answer to hormonal signals [5]. During natural cycles these signals are estradiol and progesterone but in assisted cycles these hormones are substituted by controlled ovarian hyperstimulation (COH), using gonadotropins in various different protocols in order to induce multiple follicular growth [8]. This may lead to differing hormone levels to those in natural cycles and may potentially alter endometrial development and receptivity. Moreover, it was shown by other authors that different stimulation protocols used for COH severely affected the ART outcome with regards to pregnancy rates [9, 10].

Recently these stimulation protocols consist mostly of either hMG [11–13] or recombinant FSH [13–15] injections alone or, if the serum E_2 levels are initially too low and further stimulation of follicular growth is needed, a combination of both [13, 15–17].

Some authors have also added GnRH antagonists after at least one follicle was > 14 mm in diameter [14] or gave their patients GnRH agonists for pituitary downregulation prior to COH [11–13, 15, 18].

The protocols used until the late 1990s containing clomiphene citrate (CC) [19, 20] have long since become obsolete, because CC is claimed to have a negative influence on uterine receptivity [21–23]. This is very likely due to its partly antiestrogenic effect [24].

The effects of these pharmacological treatments on the endometrial quality may be one of the reasons for decreased implantation rates [25]. Following COH supraphysiological levels of estradiol are achieved during follicular phase and consecutively supraphysiological levels of estradiol and progesterone are being produced by multiple corpora lutea [6, 25–27].

Abnormally high E_2 levels in the early luteal phase may result in irregular endometrial structure [28]. Furthermore, changes in estrogen to progesterone ratio, growth factor concentrations and cell adhesion molecule profiles, possibly induced by ovarian stimulation, may potentially affect endometrial receptivity [26]. It was also established that under COH the endometrial pinopod expression occurred at an earlier state of endometrial maturation, which could lead to a time shift of the implantation window [29].

Valbuena et al. [25] showed in their study that there was a decline in both implantation and pregnancy rates as serum E_2 concentrations increased on days 4–6 after oocyte retrieval, implying that this abnormal endocrine level could lead to impaired implantation. Sharara et al. [30] on the other hand found no detrimental effect of high E_2 levels on pregnancy rates.

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. intracytoplasmatic 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. **Table 1** shows an overview over the main study results for the respective dates of endometrial assessment.

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, 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.

Table 1 Studies regarding endometrial thickness.

Day of endometrial assessment		Number of cycles analysed	Study design	Main study results
Before induction of ovulation		414	retro	statistically significant relationship between EMT and total PR
	Bozdag et al. (2009)	758	retro	IR & PR significantly higher if EMT > 14 mm
Induction of ovulation	Okohue et al. (2009)	251	pro, cohort study	significantly more pregnancies occured in patients with an EMT of 7–14 mm
	Kinay et al. (2010)	40	pro, cohort study	no significant difference in mean EMT between pregnant and non-pregnant groups
	Mercé et al. (2008)	80	pro, clinical study	v.s.
	Corbacioglu et al. (2009)	241	retro	v.s.
	Laasch et al. (2004)	155	retro	v.s.
	Yoeli et al. (2004)	1218	pro, clinical study	v.s.
	Rashidi et al. (2004)	150	pro	v.s.
	Coulam et al. (1994)	405	pro, case-control	v.s.
	Sharara et al. (1999)	86	pro	v.s.
	Lesny et al. (1999)	60	retro	v.s.
	Al-Ghamdi et al. (2008)	2464	retro, cohort study	significant difference in mean EMT between pregnant and non-pregnant groups
	Chen et al. (2010)	2896	retro	PR was significantly higher with increasing EMT
	Richter et al. (2007)	1294	retro	significant difference in mean EMT between pregnant and non-pregnant groups
	Traub et al. (2009)	114	retro, cohort study	patients achieving clinical pregnancy had a thicker endometrial stripe
	Amir et al. (2007)	2339	retro	a thicker endometrium is correlated with a higher PR only for patients > 35 years of age
	Zhang et al. (2005)	897	retro	PR was positively associated with increased EMT
	Rinaldi et al. (1996)	158	pro	PR was positively associated with increased EMT ≥ 10 mm for IVF cycles only
Before oocyte aspiration	Bergh et al. (1992)	100	pro	significantly thicker endometrium in pregnant patients
	Gonen & Casper (1990)	123	pro, cohort study	v.s.
Oocyte retrieval	Welker et al. (1989)	190	pro	no relationship between EMT and IR
	Lesny et al. (1999)	60	retro	no significant difference in mean EMT between pregnant and non-pregnant groups
	Bassil et al. (2001)	153	pro, case-control	v.s.
	Järvelä et al. (2005)	35	pro	v.s.
	Schild et al. (2001)	135	pro, clinical study	no relationship between EMT and IR
	Kumbak et al. (2009)	175	retro	≤ 7 mm not necessarily a negative predictor
	Quintero et al. (2004)	2	case report	two successful twin pregnancies with an EMT of 16 and 20 mm
Embryo transfer	Kovacs et al. (2003)	1228	retro	mean EMT significantly higher in pregnant patients
	Kinay et al. (2010)	40	pro, cohort study	no significant difference in mean EMT between pregnant and non-pregnant groups
	Bassil et al. (2001)	153	pro, case-control	v.s.
	Kovachev et al. (2005)	58	pro, clinical study	endometrial volume is a better predictor for ART outcome

Abbreviations: retro: retrospective; pro: prospective; EMT: endometrial thickness; PR: pregnancy rates; IR: implantation rates; ART: assisted reproduction techniques; v.s.: vide supra

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 2 Studies regarding endometrial volume.

Day of endometrial assessment		Number of cycles analysed	Study design	Main study results
Induction of ovulation	Mercé et al. (2008)	80	pro, clinical study	significantly higher EV in pregnant patients
	Järvalä et al. (2005)	35	pro	EV decreased significantly after hCG administration in patients who conceived
Oocyte retrieval	Järvelä et al. (2005)	35	pro	no difference in EV between pregnant and non-pregnant patients
	Schild et al. (2001)	135	pro, clinical study	v.s.
	Schild et al. (1999)	47	pro	v.s.
Embryo transfer	Kovachev et al. (2005)	58	pro, clinical study	EV of < 2 ml resulted in significantly lower IR

Abbreviations: retro: retrospective; pro: prospective; EV: endometrial volume; hCG: human chorionic gonadotropin; IR: implantation rates; v.s.: vide supra

Table 3 Studies regarding endometrial pattern.

Day of endometrial assessment		Number of cycles analysed	Study design	Main study results
Induction of ovulation	Sharara et al. (1999)	86	pro	significantly lower IR in patients with a homogeneous, hyperechogenic pattern
	Rashidi et al. (2005)	150	pro	no significant relationship between different EP and PR
	Chen et al. (2010)	2896	retro	v.s.
	Singh et al. (2011)	101	pro, clinical study	v.s.
Before oocyte aspiration	Bergh et al. (1992)	100	pro	v.s.
	Gonen & Casper (1990)	123	pro, cohort-study	significantly higher rate of multi-layered patterns in pregnant patients
Oocyte retrieval	Welker et al. (1989)	190	pro	EP influences implantion
	Järvelä et al. (2005)	35	pro	significantly higher PR in women with a triple-line pattern
	Bassil et al. (2001)	153	pro, case-control	no significant relationship between different EP and PR
Embryo transfer	Bassil et al. (2001)	153	pro, case-control	v.s.

Abbreviations: retro: retrospective; pro: prospective; IR: implantation rates; EP: endometrial pattern; PR: pregnancy rates; v.s.: vide supra

in women who succeeded to conceive, but not in those who failed to do so [48]. Also, endometrial volume on the day of oocyte aspiration did not differ between conception and non-conception cycles [48], confirming findings from previous studies [49,54]. Mercé et al. [15], however, have found a significantly higher endometrial volume in patients that became pregnant (**Table 2**).

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].

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. (**Table 3**) 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.

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 ascertained 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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