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REVIEW

What is the contribution of embryo-endometrial asynchrony to implantation failure?

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Abstract
Purpose The synchronized development of a viable embryo and a receptive endometrium is critical for successful implantation to take place. The aim of this paper is to review current thinking about the importance of embryo-endometrial synchrony in in vitro fertilization (IVF).
Methods Detailed review of the literature on embryo-endometrial synchrony.
Results By convention, the time when the blastocyst first attaches and starts to invade into the endometrium has been defined as the 'window of implantation'. The term window of implantation can be misleading when it is used to imply that there is a single critical window in time that determines whether implantation will be successful or not. Embryo maturation and endometrial development are two independent continuous processes. Implantation occurs when the two tissues fuse and pregnancy is established. A key concept in understanding this event is developmental 'synchrony', defined as when the early embryo and the uterus are both developing at the same rate such that they will be ready to commence and successfully continue implantation at the same time. Many different events, including controlled ovarian hyperstimulation as routinely used in IVF, can potentially disrupt embryo-endometrial synchrony. There is some evidence in humans that implantation rates are significantly reduced when embryo-endometrial development asynchrony is greater than 3 days (±1.5 days).
Conclusions Embryo-endometrial synchrony is critical for successful implantation. There is an unmet need for improved precision in the evaluation of endometrial development to permit better synchronization of the embryo and the endometrium prior to implantation.

Keywords Endometrium · Embryo · Uterine receptivity · Implantation · Synchrony

Capsule Embryo-endometrial synchrony is critical for successful implantation. There is an unmet need for improved precision in the evaluation of endometrial development to permit better synchronization of the embryo and the endometrium prior to implantation.

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Introduction

Successful implantation is a critical event for establishment of an ongoing pregnancy. Implantation happens when a free-floating mature blastocyst attaches onto the endometrium invades the stroma and establishes the placenta. For this process to be successfully accomplished, the endometrium must be in a receptive state. This is a complex series of events that happen during a well-defined period when the development of both the embryo and the endometrium are in synchrony. The three pre-requisite factors for successful implantation to take place are an embryo with implantation competency, an endometrium in receptive state and a synchronized development between the embryo and the endometrium. (Fig. 1a)

'Uterine receptivity' refers to the status of the uterus when the endometrium is available to accept the embryo for implantation. In a normal ovulatory cycle, the receptive endometrium is achieved following sequential exposure to sex steroids—oestrogen and progesterone, secreted by the ovaries during follicular development, ovulation and formation of a corpus luteum. This short, self-limited period when the endometrium

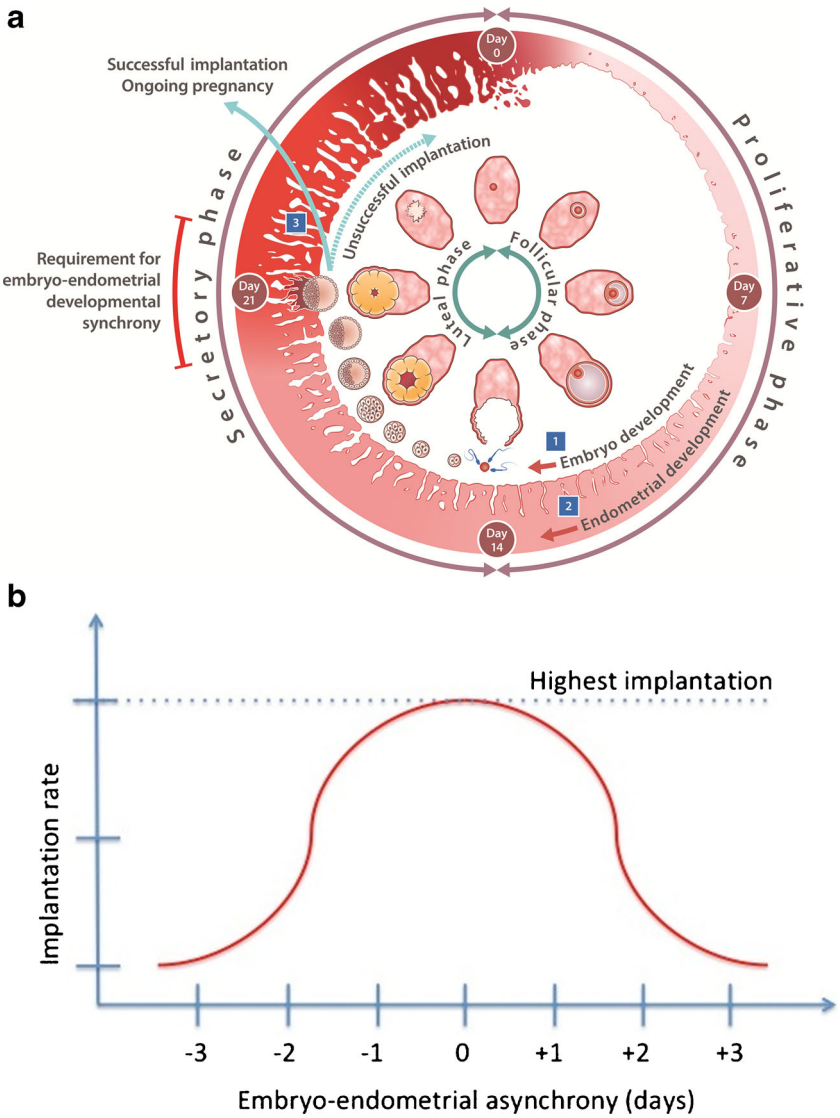

Fig. 1 **a** A functional embryo, a receptive endometrium and a synchrony between the embryo and the endometrium are the three pre-requisites for successful implantation. This figure demonstrates the developmental synchrony between the endometrium and the embryo within a 'cycle'. The main causes of implantation failure have been noted: (1) Embryo developmental defects, e.g. chromosomal anomalies. (2) Endometrial developmental defects, e.g. luteal phase deficiency, reduced endometrial receptivity. (3) Embryo-endometrial developmental asynchrony. **b** Human implantation rates reduce as asynchrony between the embryo and the endometrium increases. Evidence suggests that the human embryo implantation rate is significantly reduced when asynchrony between the embryo and the endometrium is greater than ±1.5 days

acquires a functional status that allows blastocyst adhesion has commonly been referred to as the 'window of uterine receptivity'.

Over the past 30 years, there have been many advances in embryology that have resulted in significant improvements in embryo viability and overall in vitro fertilization (IVF) success rates. Embryos with chromosomal and genetic abnormalities can now be detected with pre-implantation genetic testing. In recent years, the contribution that reduced uterine receptivity makes to human infertility has also been receiving increased attention as part of the effort to improve IVF success rates. Various markers of uterine receptivity and potential modalities to improve uterine receptivity have been proposed and investigated by different groups around the world. The aim of this review is to explore the concept of embryo-endometrial asynchronous development, leading to reduced implantation success and to bring the reader up to date with current thinking about the importance of embryo-endometrial synchrony in present day IVF.

Endometrial receptivity

Hormonal induction of endometrial receptivity

The human endometrium gains its receptive state after sequential exposure to oestrogen and progesterone. However, there is still relatively limited understanding of the amounts or sequence of these hormones that are required for optimal receptivity. The length of human menstrual cycles and the level of circulating gonadal hormones are also highly variable.

In response to gonadotropin stimulation, the granulosa cells of the developing follicle produce oestrogen in the follicular phase. Oestrogen priming of the endometrium to induce endometrial proliferation and progesterone receptor recruitment before exposure to progesterone is an essential step in the acquisition of endometrial receptivity [1, 2]. In response to progesterone, the endometrium undergoes profound cellular and biochemical changes from proliferative to secretory,

with a concomitant induction of the changes that lead to endometrial receptivity. As it is the exposure of the uterus to progesterone that triggers development of the endometrium towards the receptive phase, endometrial age is commonly calculated as either days post-ovulation or in an artificial cycle when the uterus is first exposed to progesterone. On the other hand, embryonic age either is taken from the time of fertilization or is based on an assessment of embryo stage.

The role of oestrogen during the luteal phase is not well established, but it is likely that a small amount of oestrogen is necessary for normal luteal phase endometrial development [3]. It has been suggested that luteal phase oestrogen modulates endometrial progesterone receptors, and oestrogen antagonism has been found to result in disrupted secretory development of the endometrium [4].

To date, there is no evidence to suggest that a receptive endometrium in the human can be achieved by anything other than sequential exposure to oestrogen and progesterone.

Artificial preparation of endometrium in assisted reproductive technology

The successful establishment of pregnancy in a woman with primary ovarian failure using oocyte donation in 1983 launched a new era of understanding of endometrial receptivity as an entity that could be achieved artificially [5]. This demonstrated that estrogen and progesterone are the two key hormones required for preparation of the human endometrium for implantation [6].

Endometrial receptivity can be induced by exogenous administration of oestrogen and progesterone in a variety of regimens. The optimal duration of oestrogen stimulation before the commencement of progesterone has not been established. Successful pregnancies have been reported in women with simulated follicular phases lasting between days and weeks of oestrogen replacement [7, 8]. This has provided important insights into the flexibility of the uterine requirement for oestrogen and indicates that oestrogen does not act on the uterus by initiating a time-sensitive series of molecular and cellular events, as what apparently occurs with progesterone. Assessment of adequate priming of oestrogen on the endometrium can be performed via endometrial biopsies or ultrasonic measurement of endometrial thickness [9, 10].

Progesterone is an absolute requirement for embryo implantation and pregnancy maintenance. Exposure of the uterus to increasing levels of progesterone after ovulation triggers the start of the endometrial secretory phase transformation and the development of receptivity for implantation.

Uterus determines the success of implantation

It is generally believed that in the presence of a healthy blastocyst, it is the uterus, appropriately conditioned by ovarian hormones, that predominantly determines the success or otherwise of implantation [11]. This concept is supported by animal studies, which have shown that the uterus can maintain the embryo in a viable but dormant state until conditions are optimal for implantation to take place. Nidation of embryos can be delayed after mating in ovariectomized rats and mice until uterine receptivity is achieved through appropriate supplementation with oestrogen and progesterone [12]. It has been demonstrated that under these circumstances, a blastocyst that has paused development due to uterine conditions and is subsequently activated by hormonal treatment of the uterus can still revert to a dormant state if placed in the uterine cavity of a mouse that is in a delayed implantation condition [13]. These observations clearly demonstrate that in some species, at least, it is the uterus and not the embryo that plays the dominant role in controlling the implantation process.

In addition to the receptive state, there is evidence in some species that the uterus goes through neutral and refractory non-receptive states. In the rats, both the receptive phase and the refractory non-receptive state follow a precise time course after the administration of a pulse of oestrogen to a progesterone-primed uterus. Progesterone priming of the uterus establishes a pre-receptive neutral state, during which the embryo can survive in the uterus but will not implant. Exposure of this neutral uterus to oestrogen induces a state of refractoriness by 36 h. During the refractory non-receptive state, the uterine environment becomes hostile to the blastocyst and the embryo is actively destroyed [14].

Previous studies have also shown that blastocysts are capable of implanting in a variety of organs including the uterus; however, in contrast to the uterus, implantation occurs in ectopic sites regardless of hormonal conditioning [15]. Ectopic sites that have been studied in this way include the anterior chamber of the eye, the kidney, the testis and the spleen [16–20]. Reported ectopic site implantation rates were as high as 95 % in the mouse cryptorchid testis [19]. Embryo implantations at ectopic sites, such as the broad ligament, omentum and bowel, with successful pregnancy development to term have also been reported in humans [21, 22]. The high success rates for embryos implanting at ectopic sites regardless of the hormonal status of the hosts have further supported the hypothesis that the uterus is the major controlling partner in the implantation process.

In several species such as rats, embryonic diapause or delayed implantation is used to maximize reproductive efficiency. During diapause, the uterus arrests blastocyst development until environmental conditions are suitable for pregnancy to continue [23]. On the contrary, in some species, developmentally younger embryos when placed in advanced endometrium can be forced to accelerate their development in order to be ready for implantation at the proper time, as in the case of sheep and cattle [24, 25]. Recent human data derived from in vitro model studies have suggested that the endometrium is capable of rejecting incompetent embryos. In reaction to signals from the embryo, endometrial stromal cells tend to migrate towards a developing embryo; however, this is not observed in the presence of an arrested embryo [26].

This evidence from animal and in vitro models suggests that the uterus plays a leading and controlling role in the

process of implantation. Interpreting these data in the context of human endometrial receptivity is difficult because of the significant differences in reproductive physiology between humans and animal species. However, these animal studies have provided valuable insights into the concepts that almost certainly govern successful implantation in human.

Embryo-endometrial developmental synchrony

Concept of embryo-endometrial synchrony versus window of implantation

By convention, the time when the blastocyst first attaches and starts to invade into the endometrium, usually around days 19–23 of the menstrual cycle is defined as the 'window of implantation'. This term has gained in popularity since the advent of assisted reproduction technologies in clinical medicine. This is primarily due to the need to critically define the optimal time for transferring the embryo into the uterus to ensure the best chance for establishment of pregnancy.

The term window of implantation is commonly used to imply a single critical window in the menstrual cycle that determines whether implantation will occur or not. This interpretation can be misleading. Embryo and endometrial developments are two independent continuous processes. Implantation occurs when the two tissues fuse and pregnancy is established. A key concept in understanding this event is developmental 'synchrony', defined as when the early embryo and the uterus are both developing at the same rate such that they will be ready to commence and successfully continue implantation at the same time.

Embryo-endometrial synchrony in successful implantation

Implantation can occur over a range of times in a normal cycle. The initial detection of urinary human chorionic gonadotropin (hCG) in women attempting to conceive occurred over a range of 6–18 days post-ovulation [27]. However, amongst pregnancies that survived for at least 6 weeks, the range was only 6–12 days. The majority of successful pregnancies (84 %) had first detection of urinary hCG from day 8–10 post-ovulation. These data support the concept that under ideal conditions, optimal implantation rates occur with embryo-endometrial developmental asynchrony of ±1.5 days or less. Based on these data, we can infer that successful implantation can still occur with asynchrony of up to 3 days (i.e. optimal synchrony ±1.5 days). However, the implantation process may be initiated but fail to progress normally with asynchrony of up to 9 days (±4.5 days) [27].

Development of embryo freezing techniques and availability of embryo/oocyte donation programmes in IVF have provided an opportunity, whereby the embryo age and endometrial chronology can be dissociated, thus allowing separate assessment of oocyte development and the induction of endometrial receptivity. In previous reviews of published pregnancies established in patients receiving donated oocytes for premature ovarian failure, it was estimated that successful implantation occurred when the embryo was anything from 39 h in front to 48 h behind the uterus. These data suggest that embryo-endometrial asynchrony of ±2 days can be tolerable for at least some embryo implantation to take place but give no indication of degree of asynchrony that still results in optimal implantation rates [28, 29].

A study of 52 oocyte donation cycles in women with ovarian failure demonstrated a viable pregnancy rate of 32.4 % when the embryos were transferred with embryo-endometrial asynchrony of not more than ±1.5 days (between days 17 and 19). No implantation was reported when the embryos were transferred before or after this time frame (4 transfers on cycle day 16, 11 transfers after day 19) [30].

A statistically significant reduction in pregnancy rate by almost half is seen when endometrial development is 1 day behind or up to 2 days more advanced than the embryo age (clinical pregnancy rate 20.5 % versus 11 %, $P < 0.05$) [31]. This study involved 249 synchronous transfers when day 2 embryos were transferred on the fourth day following the start of the luteinizing hormone (LH) surge, and 117 asynchronous transfers when the uterus was 1 day behind the embryo or 1 or 2 days older than the embryo. This further supports the concept that optimal implantation happens when embryo-endometrial asynchrony is less than ±1.5 days.

Similar results were reported in IVF cycles involving different protocols. A study involving 40 women having IVF/intra-cytoplasmic sperm injection (ICSI) cycles, who had histologic dating of endometrium on the day of oocyte retrieval, reported no pregnancy if development of the endometrium was greater than 3 days more advanced than the embryos [32]. Gonadotropin-releasing hormone (GnRH) agonist and hMG were used for controlled ovarian hyperstimulation in the IVF/ICSI cycles in this study. Similar results were demonstrated in other studies involving the use of GnRH antagonists and recombinant FSH. No clinical pregnancy was observed when the endometrium showed a discrepancy of more than 3 days when compared to the expected chronological date [33, 34].

It is highly unlikely for ethical reasons that systematic investigation of the optimal timing of human uterine receptivity will ever be undertaken again. Evidence from these earlier investigations seems to suggest that in humans, the highest implantation rates will be achieved within a limited period of embryo-endometrial developmental asynchrony and that the implantation rates will reduce as asynchrony increases. While it is possible that in some cases of asynchronous transfer pregnancy may be established [35], the overall

implantation rate is likely to be significantly reduced when asynchrony is greater than ±1.5 days. (Fig. 1b)

Recent evidence supporting the importance of embryo-endometrial synchrony in ART

A more recent study compared the effect of day 5 and day 6 blastocyst transfers on patterns of implantation rates and pregnancy rates between 377 fresh autologous and 106 frozen embryo transfer cycles. The clinical pregnancy rate for day 5 blastocyst transfers was higher than for day 6 blastocyst transfers in fresh autologous cycles (51 % versus 33.3 %, $P = 0.0006$). However, there was no significant difference between transfers of blastocysts cryopreserved on day 5 and day 6 in frozen embryo transfer (FET) cycles (63.6 versus 58.9 %) [36]. It is known that ovarian stimulation with pituitary suppression can induce a more histologically advanced endometrium than in natural cycles [33, 37, 38]. This advancement may lead to better synchrony between day 5 blastocysts and the endometrium than their day 6 counterparts. In the study by Shapiro et al. [36], the superior performance of day 5 blastocysts in fresh autologous cycles may have been due to better synchrony between these faster-growing embryos and the advanced endometrium in stimulated cycles. The embryo-endometrial synchrony was similar between day 5 and day 6 blastocysts in FET (assuming similar stage of embryonic development in blastocysts, disregards whether the developmental stage was achieved on day 5 or day 6), resulting in similar clinical outcomes.

Assessment of embryo-endometrial developmental synchrony

In assisted reproductive technology (ART), embryo maturation and endometrial development can be dissociated. While it is possible to precisely monitor the growth of an embryo in an IVF laboratory, development of the endometrium can only be assessed by less accurate methods (Fig. 2).

Histology

Historically, development of the endometrium is assessed via histological examination of the tissue from endometrial biopsy. More than 60 years have passed since the traditional histologic dating of endometrium was initially described by Rock and Bartlett, which was then revised by Hertig and subsequently fine-tuned by Noyes and colleagues [39, 40]. The validity and accuracy of histologic dating of the endometrium have been questioned many times [41, 42], with the inherent subjectivity of endometrial dating resulting in inter- and intra-observer variation [43, 44]. However, the secretory activity in the second half of the menstrual cycle is characterized by a diversity of structural changes that are apparent on routine examination of endometrial biopsies, showing a different pattern on every day of the cycle [45]. Histologic assessment also requires biopsy of the endometrium, which is not feasible in the same cycle that a woman is undergoing an embryo transfer.

Radiology

Unlike histological assessment, radiological modalities, such as ultrasound imaging, allow non-invasive assessments of the uterus. Morphological changes of endometrium are evident throughout the menstrual cycles with ultrasonography. The endometrial appearance has been correlated with IVF outcome, with a trilaminar pattern shown to be associated with higher implantation rates than a homogenous hyperechogenic pattern at the time of hCG administration [46–48]. It is likely that the appearance of homogenous hyperechogenic endometrium at late follicular phase is indicative of premature secretory maturation of the endometrium. If correct, this may subsequently lead to embryo-endometrial developmental asynchrony and reduce implantation rates. Several studies have shown that greater endometrial thickness measured on the day of hCG administration in an IVF cycle is associated with better outcome [49–52]; however, others have shown negative results [53, 54]. A recent meta-analysis involving 14 studies and 4922 IVF cycles has shown a statistically significant difference in the mean endometrial thickness between pregnant and non-pregnant groups. However, the mean difference between the two groups was <1 mm, which may not be diagnostically meaningful [55]. Although endometrial thickness is the most studied ultrasonographic parameter, ultrasonographic measurement of endometrial thickness cannot accurately predict histological dating [56].

Molecular markers

A variety of molecular mediators, particularly those expressed by endometrium around the time of embryo implantation, has been identified as potential markers for uterine receptivity. Potential biomarkers include uterine natural killer cells, cell adhesion molecules, cytokines, growth factors and others, such as calcitonin and homeobox genes [57]. Uterine natural killer (uNK) cells are granular lymphocytes derived from haematopoietic progenitor cells in the bone marrow that plays a role in the innate immune system [58]. uNK cells proliferate during the menstrual cycle and constitute 70 % of endometrial leucocytes at the time of embryo implantation [59]. These cells express a variety of angiogenic and chemoattractant factors that facilitate vascular remodelling and trophoblast invasion during placental development [60, 61]. It has been suggested that they play a role in human reproductive failure [62], although results in the literature remain controversial. There is

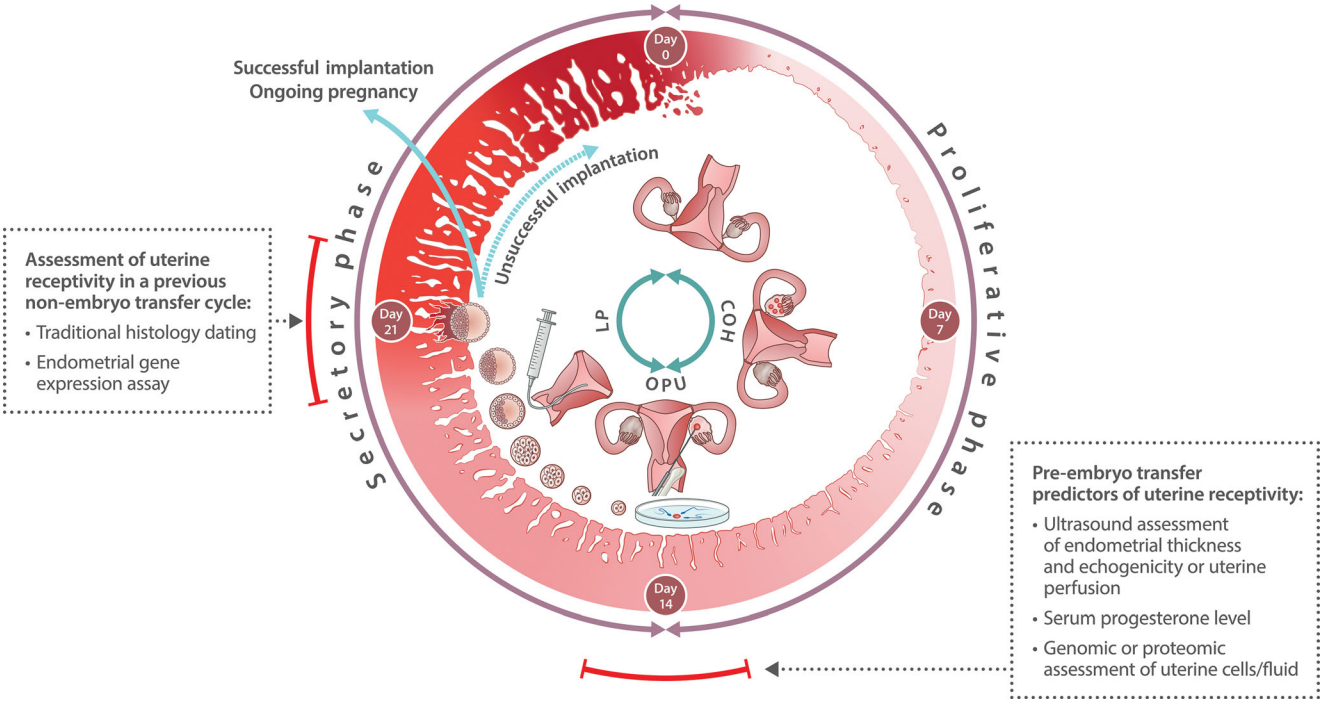

Fig. 2 Controlled ovarian hyperstimulation (COH) has a detrimental effect on uterine receptivity. Various modalities have been demonstrated in this figure for assessing uterine receptivity in an IVF cycle with COH. Potential modalities that can be used to predict uterine receptivity prior to embryo transfer include ultrasound assessment of endometrium, serum progesterone levels and genomic or proteomic assessment of uterine cells/fluid. Other assessments of uterine receptivity that can be offered in a cycle prior to an embryo transfer cycle include traditional histology dating and endometrial gene expression assays

also no consensus in the literature with regard to the method, timing and reference range for the uNK cell numbers for diagnostic testing [63].

αvβ3 integrin is a cell adhesion molecule [64]. Measurement of endometrial αvβ3 integrin is currently being offered as a clinical test to evaluate endometrial receptivity (http://www.etegritytest.com). However, the evidence is controversial, as subsequent studies failed to demonstrate a different expression pattern between fertile and infertile women [65–68]. Endometrial αvβ3 integrin expression also has poor reproducibility and high variability cycle-to-cycle [69]. Leukaemia inhibitory factor (LIF) is an interleukin-6 (IL-6) cytokine that is involved in both adhesive and invasive phases of implantation [70]. Evidence suggests that dysfunction of LIF expression may contribute to implantation failure [71–75]. Recombinant human LIF (r-hLIF) has been proposed as a treatment to improve endometrial receptivity in patients with recurrent implantation failure (RIF). However, a large multicentre, randomized study has failed to demonstrate an improvement in implantation and pregnancy rate after r-hLIF treatment when compared with placebo in women with recurrent RIF [76]. Many other molecules have been found to play a role in successful embryo implantation. These markers include prostaglandins and cyclooxygenases, MUC-1 glycoprotein, serum- and glucocorticoid-inducible kinase, placental growth factor and many others [77]. It seems unlikely that a single molecular biomarker will be able to define uterine receptivity. Given that the implantation process is a continuum of events, uterine receptivity may be better defined by a combination of key markers that occur over a period of time.

Genomic approaches

Previous studies have shown that it is possible to characterize different phases of the menstrual cycle using genomic approaches on human endometrium [78, 79]. Genes identified as being involved in implantation have been widely studied [80–86]. Global transcriptomic profiling of human endometrium has provided important insights into the biological processes and molecular mechanisms that occur in the endometrium in response to the hormonal influences across the normal menstrual cycle. With the transcriptomic profile of the human endometrium provided by these studies, it is now possible to more accurately catalogue endometrium at different cycle stages based solely on transcriptomic profile.

An endometrial receptivity array (ERA) based on the transcriptomic profile of the endometrium is now available for identification of uterine receptivity and customized timing of embryo transfer [87]. High specificity and sensitivity have been reported for the ERA test, with results showing superior concordance with LH peak when compared to histology dating. The reproducibility of the

ERA test was reported to be 100 % [88]; however, the clinical value of the ERA test is yet to be fully evaluated.

Effect of controlled ovarian stimulation on embryo-endometrial developmental synchrony

Controlled ovarian stimulation

Controlled ovarian hyperstimulation is routinely used in IVF cycles to achieve multiple oocyte development. The associated supra-physiological serum concentrations of sex hormones can impair optimal uterine receptivity and embryo implantation by disrupting embryo-endometrial synchrony and/or promoting pathological endometrial development [32–34, 89–92] (Fig. 3).

There is evidence from histological observations that ovarian hyperstimulation for IVF profoundly alters endometrial development. In stimulated cycles, advanced endometrial development with premature secretory changes is commonly observed on the day of oocyte retrieval [32–34, 90, 92]. Abnormal endometrial development with significant discordant stromal maturation was observed 2 days after oocyte retrieval in up to 91 % of women undergoing ovarian hyperstimulation for IVF [89]. Dyssynchronous glandular and stromal differentiation was also commonly seen in mid-luteal phase endometrium after ovarian hyperstimulation [91, 93]. A recent study compared endometrial histology in fertile women, fertile women undergoing hormonal stimulation for oocyte donation and infertile women undergoing fresh embryo transfers in an ART cycle with further comparisons between women who did and did not become pregnant. The study showed that endometrial histology was dramatically altered upon stimulation for ART. However, those women who became pregnant presented with significantly fewer endometrial histological alterations [94].

In contrast to the natural cycle, expression of oestrogen and progesterone receptors was dysregulated in the peri-ovulatory phase in IVF cycles with ovarian hyperstimulation [37, 92, 95, 96]. An altered pattern of gene expression has also been observed after ovarian hyperstimulation in both peri-ovulatory and peri-implantation endometrium [34, 37, 97]. The high levels of serum estradiol and progesterone from ovarian hyperstimulation affect endometrial gene expression profiles and modulate steroid receptor expression. This can lead to an advanced response of the endometrium to steroids in the luteal phase, with subsequent rapid or early secretory transformation and/or abnormal endometrial development.

Suboptimal endometrial function as a result of controlled ovarian stimulation

Poorer obstetric and perinatal outcomes have been associated with ART pregnancies [98]. A retrospective cohort study of 6730 singleton births after ART in Victoria, Australia has demonstrated that all obstetric haemorrhages were more frequent following IVF/ICSI than in the general population. Exploratory analysis of factors in the IVF/ICSI group suggests that events from the time of implantation onwards are responsible for the increase in subsequent obstetric haemorrhages. Increased antepartum haemorrhage is linked with fresh embryo transfer and with a greater number of oocytes collected, suggesting a direct association with controlled ovarian

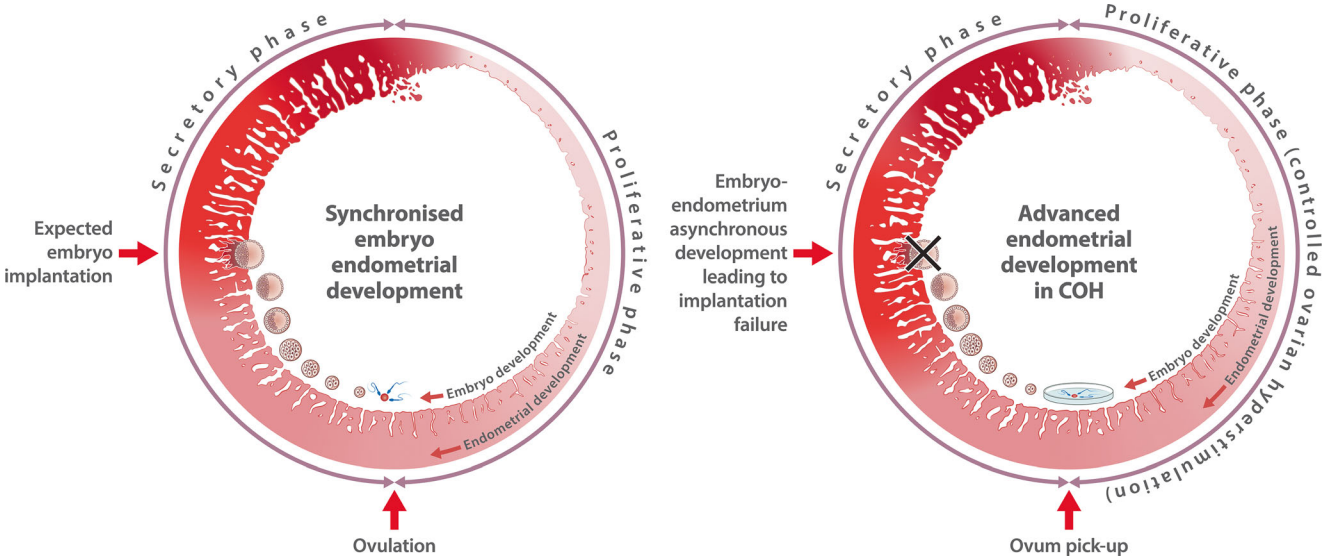

Fig. 3 Controlled ovarian hyperstimulation in IVF cycles leads to suboptimal endometrial function. Supra-physiological serum concentrations of sex hormones during ovarian hyperstimulation can negatively influence uterine receptivity by disrupting embryo-endometrial synchrony. This figure demonstrated the concept of advanced endometrial development, leading to increased embryo-endometrial asynchrony in ovarian hyperstimulation and resulting in implantation failure

hyperstimulation. This supports the concept that suboptimal endometrial function around the time of implantation may be critical [99].

A recent study has reported that birth weights were lower and low birth weight rates higher after gamete intra-fallopian transfer (GIFT) and fresh embryo transfer than after frozen thaw embryo transfer. Results for FET were similar to those for non-ART conceptions, demonstrating that IVF/ICSI laboratory procedures affecting the embryos were not causal. The logical conclusion from this work is that ovarian stimulation used in fresh cycles is causing the problem by either impairing embryo-endometrial synchrony or promoting pathological endometrial development, leading to suboptimal implantation and ultimately resulting in low birth weight with ART [100].

A more recent systematic review and meta-analysis from 11 observational studies have reported that singleton pregnancies from FETs were associated with a lower risk of perinatal mortality, small for gestational age baby, preterm birth, low birth weight baby and antepartum haemorrhage when compared with those from fresh ETs. The authors suggested that these results might be related to the more natural uterine environment in a FET cycle, which is favourable for early placentation and embryogenesis [101]. This conclusion is supported by the findings from previous studies [99, 100].

Some IVF programmes now promote a freeze-all embryo strategy to try and improve birth outcomes from IVF pregnancies [102]. The widely accepted Barker hypothesis suggests that people with low birth weight are at greater risk of developing chronic diseases later in life [103]. In view of the significance of the potential long-term consequences from low birth weight, more evidence is required about the effects of ovarian hyperstimulation on implantation and pregnancy outcome. The current practice of fresh embryo transfer may need to be restricted or abolished if further evidence arises regarding the negative impact of ovarian hyperstimulation on embryo-endometrial synchrony and subsequent pregnancy outcome. This would result in embryo transfer only being performed if the endometrium has not been exposed to ovarian stimulation and is in developmental synchrony with the embryo. As a compromise approach to this problem, low-dose stimulation regimens have been developed in an attempt to minimize the adverse effects of more aggressive conventional controlled ovarian hyperstimulation [104].

Premature luteinization during IVF cycles

In the proliferative phase of a natural cycle, the level of progesterone is usually <0.5 ng/mL. Serum progesterone levels start to rise in the late follicular phase before the LH surge, with levels of >5 ng/mL detected after ovulation [6]. Previous studies have reported that in IVF cycles with ovarian hyperstimulation, a modest increase in serum progesterone levels before hCG administration for induction of final oocyte maturation is associated with lower pregnancy rates and higher pregnancy loss [105–107].

The threshold level of progesterone on the day of hCG administration that has been used to classify patients with or without premature progesterone rise varies considerably in the literature, ranging from 0.9 to 1.5 ng/mL. A study involving more than 4000 cycles has shown that women with serum progesterone levels of >1.5 ng/mL on the day of hCG administration have significantly lower ongoing pregnancy rates than those with progesterone levels <1.5 ng/mL (31.0 versus 19.1 %, $P = 0.00006$) irrespective of the GnRH analogue used for pituitary down-regulation [108]. However, progesterone levels as low as 0.8–1.1 ng/mL have been shown to be associated with a decreased probability of pregnancy when compared with those without elevated progesterone in a recent meta-analysis of more than 60,000 cycles [107]. In this meta-analysis, no association was found between the elevated progesterone on the day of hCG administration in the fresh IVF cycle and the pregnancy rate in a subsequent thaw cycle using the embryos originating from that cycle. Similarly, women who receive oocytes from donors with elevated progesterone on the day of hCG administration do not have decreased pregnancy rates when compared with those who receive oocytes from donors with normal progesterone levels [107]. This confirms that the detrimental effect of elevated progesterone levels on pregnancy rates is exerted through its action on the endometrium and not the oocytes. Genomic studies have also revealed significant alterations in the gene expression profile of the endometrium in IVF cycles when the progesterone levels were elevated on the day of hCG administration [109, 110]. The association between elevated progesterone and lower pregnancy rate can be explained by the concept of embryo-endometrial synchrony. In a natural cycle, exposure of the uterus to increasing levels of progesterone after ovulation triggers the start of the endometrial secretory phase transformation and the development of receptivity for implantation. A premature rise of progesterone levels in fresh IVF cycles as a consequence of ovarian hyperstimulation triggers early transformation of the endometrium, leading to advanced endometrial development and subsequently increased embryo-endometrial asynchrony and lower pregnancy rates.

Conclusions

Successful implantation is a complex process requiring a receptive endometrium, a viable embryo and synchronized dialogue between maternal and embryonic tissues. There is increasing awareness that the synchronized development of the embryo and the endometrium play a crucial role in successful implantation, and that the routine ovarian stimulation protocols used in IVF can disrupt endometrial development and

hence endometrial-embryo synchrony. IVF and embryo culture techniques, particularly embryoscope, allow precise assessment of embryo maturation. Conversely, estimates of the development of the endometrium are based on the length of progesterone exposure, which can be imprecise. Improved embryo-endometrial developmental synchrony is reliant on better assessment of endometrial development, preferably using a non-invasive approach in the cycle of embryo transfer.

It is clear that uterine factors play a key role in determining the outcome of IVF treatment. However, there remain significant gaps in our knowledge of either markers or mechanisms that would help in understanding this problem. The ultimate goal for research in the field of uterine receptivity is to identify biomarkers or other diagnostics that are reliable and specific enough to be of clinical use in decision making during the IVF treatment process.

While a number of potential biomarkers of endometrial receptivity are now available, international collaboration will be required to sufficiently validate these before offering them for use in IVF clinics. It appears unlikely that single biomarkers will accurately identify receptive endometrium. An integrated approach with a combination of different evaluation modalities, including histologic, radiologic, transcriptomic, secretomic, and hormonal markers, may be required to accurately and reliably identify uterine receptivity.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

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