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ARTICLE

Implantation in assisted reproduction: a look at endometrial receptivity

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Abstract Implantation failure in assisted reproduction is thought to be mainly due to impaired uterine receptivity. With normal uterine anatomy, changes in endocrine profile during ovarian stimulation and medical conditions of the mother (i.e. thrombophilia and abnormal immunological response) could result in a non-receptive endometrium. High oestradiol concentrations during ovarian stimulation lead to premature progesterone elevation, causing endometrial advancement and hampering implantation, which can be overcome by a freeze-all approach and embryo transfer in natural cycles or by milder stimulation protocols. Patients with recurrent implantation failure (RIF) should be tested for inherited and acquired thrombophilias. Each patient should be individually assessed and counselled regarding therapy with low-molecular-weight heparin (LMWH). Empirical treatment with LMWH, aspirin or corticosteroids is not effective for women with RIF who have negative thrombophilic tests. If thrombophilic tests are normal, patients should be tested for immunological causes. If human leukocyte antigen dissimilarity is proven, treatment with intravenous immunoglobulin might be beneficial. Preliminary observational studies using intralipid infusion in the presence of increased natural killer cytotoxic activity are interesting but the proposed rationale is controversial and randomized controlled trials are needed. Hysteroscopy and/or endometrial scratching in the cycle preceding ovarian stimulation should become standard for patients with RIF.

KEYWORDS: endometrial scratch, freeze all, implantation failure, IVF, thrombophilia

Introduction

Assisted reproduction technologies have provided considerable insight into the human reproductive processes. However, lower implantation rates per transferred embryo than those in natural cycles remain a major problem. The limiting factor in achieving pregnancy for most couples is implantation, which is still poorly understood.

Embryo implantation represents the most critical step of the reproductive process in many species. It consists of a

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unique biological phenomenon, by which the blastocyst becomes intimately connected to the maternal endometrial surface to form the placenta that will provide an interface between the growing fetus and the maternal circulation (Aplin, 2000; Denker, 1993). Successful implantation requires a receptive endometrium, a normal and functional embryo at the blastocyst developmental stage and a synchronized dialogue between maternal and embryonic tissues (Simón et al., 2000). The process of implantation may be classified into three stages: apposition, adhesion and invasion (Enders and Nelson, 1973). During blastocyst apposition, trophoblast cells adhere to the receptive endometrial epithelium. The blastocyst will subsequently anchor to the endometrial basal lamina and stromal extracellular matrix. At this point, the achieved embryo–endometrial linkage can no longer be dislocated by uterine flushing.

This is followed by the invasive blastocyst penetration through the luminal epithelium (Enders and Nelson, 1973). Even though the blastocyst can implant in different human tissues, surprisingly in the endometrium, this phenomenon can only occur during a self-limited period spanning days 20 and 24 of a regular menstrual cycle (day LH +7–11). Throughout this period, namely the window of implantation (Psychoyos, 1973), the human endometrium is primed for blastocyst attachment, given that it has acquired an accurate morphological and functional state initiated by ovarian steroid hormones (Finn and Martin, 1974; Paria et al., 2002; Yoshinaga, 1988). The relative inefficiency of the implantation process is paradoxical in view of the fact that reproduction is critical to species survival. Implantation failure remains an unsolved problem in reproductive medicine and is considered as a major cause of infertility in otherwise healthy women. Indeed, the average implantation rate in IVF is around 25% (de los Santos et al., 2003).

Inadequate uterine receptivity may be responsible for approximately two-thirds of implantation failures (Edwards, 1994; Lédée-Bataille et al., 2002; Simon et al., 1998). The other component of successful implantation, the selection of embryos with the highest potential for implantation, is reviewed in an accompanying article in this issue (Montag et al., 2013). In women with unexplained implantation failure, despite good hormonal response, good-quality embryos, satisfactory endometrial development and no identifiable pathology, suboptimal endometrial receptivity is considered a key factor in inhibiting embryo implantation.

This paper evaluates different options to improve the implantation in stimulated IVF cycles, focusing on the maternal causes.

Impact of ovarian stimulation on endometrial receptivity

The endometrium is controlled ultimately by the combined actions of oestrogen and progesterone. The mechanisms by which progesterone acts to bring about endometrial receptivity is discussed in this issue by Young et al. (2013). Abnormal concentrations of these hormones during IVF treatment secondary to ovarian stimulation might affect the endometrial morphology and thereby the endometrial receptivity (Thomas et al., 2002). High implantation and pregnancy rates in oocyte donation cycles irrespective of the recipient's age imply that ovarian stimulation impairs endometrial receptivity in stimulated cycles (Soares et al., 2005). Increased sensitivity to progesterone resulting in secretory advancement could be induced by elevated oestrogen concentrations (Simon et al., 1995). Although there is a lot of heterogeneity in the studies on endometrial morphology in stimulated cycles, a general trend involves endometrial advancement in the peri- and post-ovulatory period followed by a 'normal' aspect of endometrium in the early luteal phase and frequent glandular-stromal dyssynchrony in the mid- and late luteal phase (Bourgain and Devroey, 2003).

Schoolcraft et al. (1991) reported that in certain patients, progesterone concentrations rose above normal follicular-phase concentrations prior to human chorionic gonadotrophin (HCG) administration despite the suppression of endogenous LH by gonadotrophin-releasing hormone (GnRH) analogues (Schoolcraft et al., 1991). Since the early 1990s, there has been an ongoing debate regarding the impact of premature progesterone rise on the IVF outcome (Fanchin et al., 1997; Shulman et al., 1996).

Recent studies did confirm that progesterone elevation on the day of HCG administration was significantly associated with a lower probability of clinical pregnancy (Bosch et al., 2010; Kolibianakis et al., 2012). Moreover, Bosch et al. (2010) reported that elevated progesterone concentrations on the day of HCG administration were associated with a decreased probability of an ongoing pregnancy. In particular, serum progesterone concentrations of >1.5 ng/ml were associated with lower ongoing pregnancy rates following GnRH agonist and antagonist IVF cycles.

Kyrou et al. (2009) demonstrated that patients with high oestradiol concentrations have significantly higher progesterone concentrations and significantly more oocytes. The association of high oestradiol and progesterone elevation suggests that at least one of the mechanisms that plays a role in progesterone rise is linked to the high response of the ovary to ovarian stimulation. An excess number of follicles, and consequently an excess of proliferating granulosa cells, can lead to an increased progesterone production. Recently, Al-Azemi et al. (2012) demonstrated that by measuring the oestradiol concentrations and number of follicles, one could anticipate the risk of premature progesterone rise (Al-Azemi et al., 2012). Based on the above finding, it seems that an early progesterone rise could be prevented by modification of the protocol and timing of triggering of final oocyte maturation. These data indicate that responses to ovarian stimulation are associated with IVF outcome, necessitating the development of strategies to prevent premature progesterone rise and increase the probability of pregnancy.

The time to trigger the final oocyte maturation for both GnRH agonist and antagonist protocols should be defined. Unfortunately, limited data are available in the literature evaluating the appropriate time for triggering in different stimulation protocols. Currently, clinicians rely on the size and number of follicles to administer HCG. Moreover, for that purpose, it might be necessary to take into consideration the patient's response to a certain treatment protocol. It might be preferable, for example, to trigger earlier in high responders than in normal and poor responders to avoid premature progesterone rise and consequently poor outcome. Another question that needs to be answered is related to the maturity of the oocyte and its relation to

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the size of the follicle. Jones et al. (1982) investigated the association between follicular fluid volume (follicle size) and oocyte morphology in follicles stimulated by human chorionic gonadotrophin (Jones et al., 1982). The authors evaluated this in terms of oocyte maturity, which is responsible for establishment of pregnancy after single-embryo transfer. Their findings revealed that mature oocytes can be obtained from follicles as small as 11 mm in diameter. Edwards (1980), reported 69% recovery of mature oocytes from follicles 10–17.5 mm in size. These data suggest that an earlier trigger in high responders in order to avoid premature progesterone elevation is feasible (Kyrou et al., 2011).

Additional preventive measures include the use of mild stimulation protocols. This approach will prevent high oestradiol concentrations, which are associated with progesterone rise in the follicular phase (Kyrou et al., 2009). Similarly, oestradiol concentrations were found to be predictive of progesterone rise (Al-Azemi et al., 2012) and subsequently, by monitoring oestradiol concentration, clinicians can trigger once the oestradiol concentration reaches the point of having a risk of premature progesterone rise.

Once the progesterone concentration has reached a concentration incompatible with a successful outcome, the solution might be vitrification of all embryos and transfer in a natural cycle (Fatemi et al., 2010). This approach is supported by Melo et al. (2006) who concluded that progesterone rise does not appear to have a negative impact on ongoing pregnancy rate in oocyte-donation programmes (Melo et al., 2006). This confirms the negative impact of progesterone rise on the endometrium rather than the oocyte/embryo quality. Furthermore, Polotsky et al. (2009) and Shapiro et al. (2010) demonstrated that in cycles with elevated preovulatory progesterone, the probabilities of implantation and ongoing pregnancy are increased if all 2-pronuclear oocytes are cryopreserved and subsequently thawed and cultured to the blastocyst stage before transfer.

Progesterone should be measured in each cycle using appropriate assay methods and defined threshold values. Furthermore, the design of prospective randomized studies comparing embryo cryopreservation and transfer in a subsequent cycle in one arm and fresh transfer in the other arm, when progesterone concentration is over 1.5 ng/ml, seems to be necessary, in order to draw solid conclusions regarding the effect of progesterone elevation on pregnancy outcomes.

The deleterious effects of ovarian stimulation on endometrial receptivity was shown in two studies comparing success rates in both normal and high responders between fresh and frozen–thawed embryo transfers (Shapiro et al., 2011a,b). In both studies, higher clinical rates were observed in frozen–thawed embryo transfers, reiterating the need for a change in current ovarian stimulation approaches and more well-designed randomized controlled trials.

Recurrent implantation failure

Recurrent implantation failure (RIF) is a challenging and extremely disappointing problem faced by the clinicians and the couples alike, despite the clinical and scientific advances in reproductive medicine (Potdar et al., 2012.) Currently, RIF is defined as a failure to conceive after three consecutive transfers of one or more good quality embryos; however, this definition may vary (Margalioth et al., 2006). As a general consensus, failure to achieve a pregnancy following 2–6 IVF cycles with three fresh IVF attempts is used by most clinicians as the definition of RIF (Tan et al., 2005).

Thrombophilias and immunological factors

It has been suggested that thrombophilias, inherited or acquired, have been associated not only with recurrent pregnancy loss but also with RIF (Grandone et al., 2001). It is assumed that the mechanism of implantation failure is similar to that of pregnancy loss: disturbed blood flow to the endometrium and placenta which can on one hand hamper normal endometrial receptivity and on the other cause miscarriage.

Inherited thrombophilia such as mutations in the factor V Leiden, prothrombin G20210A and MTHFR C677T genes, as well as deficiencies in protein C, protein S and antithrombin III, and acquired thrombophilia such as the antiphospholipid syndrome, are all associated with recurrent miscarriages (Toth et al., 2010). To investigate the impact of haemostatic disorders in RIF patients, several authors have analysed inherited and acquired thrombophilias together with other risk factors such as thyroid abnormalities and natural killer (NK) cell levels in RIF patients (Bellver et al., 2008; Qublan et al., 2006; Simur et al., 2009). Although it has not been possible to identify one single risk factor, it seems that multiple prothrombotic disorders are more prevalent in RIF patients than in controls. Evaluation of associated risk factors gave evidence that thyroid autoimmunity is not only linked to recurrent pregnancy loss but to RIF (Vaquero et al., 2006).

There has been a lot of debate regarding the thrombophilias and IVF treatment. Interpretation of results regarding this issue is hampered by a large degree of clinical heterogeneity and methodological variability between the studies. In a meta-analysis on the thrombophilias and outcome of assisted reproduction treatment, the initial search identified 692 studies and the final analysis involved only 33 studies (Di Nisio et al., 2011). The authors state that the relationship between thrombophilias remains largely inconclusive. For example, a number of studies have shown that for patients with RIF, diagnosed with thrombophilia, treatment with heparin significantly improves implantation, as well as the clinical pregnancy rate in subsequent IVF attempts (Qublan et al., 2008). However, the data in the literature are still conflicting regarding the role of adjuvant heparin therapy and it has not been adequately evaluated. It must be kept in mind that on the basis of published literature, the group of patients who could benefit from heparin therapy could not be identified with certainty (Seshadri et al., 2012).

In summary, although the association between the thrombophilias and RIF is still debatable, it seems that prothrombotic disorders are more prevalent in RIF patients than in controls (Toth et al., 2011). While patients with RIF who have prothrombotic disorder might benefit from heparin treatment, for those without this abnormality, empirical treatment with heparin is absolutely not justifiable (Urman et al., 2005). Patients diagnosed with RIF should be investigated for acquired as well as hereditary

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thrombophilia disorders and be treated accordingly (Simon and Laufer, 2012).

The immune system has also been highlighted for its major role in the process of implantation and in the subsequent maintenance of pregnancy (Singh et al., 2011). One idea is that a conception must be recognized as non-self in order to trigger immunological processes that prevent the maternal immune system from rejecting it. The human leukocyte antigen (HLA) compatibility system plays a role in this recognition and couples that share common HLA alleles may experience higher rates of RIF (Elram et al., 2005). However, it is not at all clear how an 'inadequate' response of the maternal immune system to stimulation by paternal antigens, due to HLA sharing, might be implicated in implantation failure. Advocates of abnormal immune responses point to studies suggesting that systemic cytokine concentrations are altered in patients with RIF and propose that this involves the imbalance of T helper 1:T helper 2 (TH1:TH2) responses. Though, it is not known whether altered cytokine responses are generated systemically or locally in the decidua where maternal leukocytes encounter allogeneic extravillous trophoblasts. What is clear is that extravillous trophoblasts express a unique combination of class 1 major histocompatability complex (MHC) molecules including HLA-C and the non-polymorphic polymorphic HLA-E, and HLA-G molecules. These are believed to perform immunoregulatory functions associated with local maternal tolerance to the extravillous trophoblasts within the decidua (Dahl and Hviid, 2012). However, to date there is no proven mechanism described in humans by which these MHC molecules might be involved in implantation failure through a failure to regulate T-cell responses either systemically or locally in the decidua (Trowsdale and Betz, 2006). The rationale for any therapy based on modulating maternal T-cell responses to fetal alloantigens thus remains unclear.

Nonetheless, high-dose intravenous immunoglobulin (IVIg) administration has been found to benefit patients with RIF who share HLA alleles with their partner. The number of shared alleles justifying administration of IVIg treatment has not been determined. One study demonstrated an improvement in patients with as few as one shared allele (Elram et al., 2005). Treatment consisted of 30 g of IVIg before embryo transfer and a second similar dose when a fetal heart rate was noticed (Elram et al., 2005). Other studies in which IVIg was administered to patients reported to have abnormal cytokine profiles have reported benefits, but patient numbers were limited. As the authors themselves state: 'Prospective controlled studies (preferably double-blind, stratified, and randomized) are needed for confirmation' (Winger et al., 2011). In the absence of clear evidence of efficacy or understanding of which patient groups might benefit, empirical treatment of patients with IVIg is not recommended due to lack of large randomized controlled trials.

The infusion of 20% intralipid solution has been suggested to improve outcomes in women with RIF (Ndukwe, 2011). It has been implied that intralipid, administered intravenously, may enhance implantation and maintenance of pregnancy in the patient with abnormal NK cell levels or function. Intralipid is a 20% intravenous fat emulsion that is usually used as a source of fat and calories for patients requiring parenteral nutrition. Intralipid consists of soybean oil as well as egg yolk phospholipids, glycerine and water. In a small and still unpublished non-randomized trial, presented at a scientific meeting in the UK (Ndukwe, 2011), a 50% pregnancy rate and 46% clinical pregnancy rate were achieved in patients with RIF who had an elevated TH1 cytokine response. Intralipid infusion was administered once between days 4 and 9 of ovarian stimulation, and again within 7 days of a positive pregnancy test. This alteration of TH1:TH2 cytokine activity ratio, which decreased in all cases, appeared to correlate with the successful outcome that resulted. The mechanism by which intralipid modulates the immune system is still unclear. It has been postulated that fatty acids within the emulsion serve as ligands to activate peroxisome proliferator-activated receptors expressed by the NK cells. Activation of such nuclear receptors has been shown to decrease NK cytotoxic activity, enhancing implantation (Roussev et al., 2008).

However, after assessing the relevant available data, Shreeve and Sadek (2012) found that large-scale confirmatory studies are necessary to prove the efficacy of intralipid before it should be recommended for routine use. Moreover, the underlying premise that high levels of NK cells in peripheral blood or decidua are of clinical significance in implantation failure continues to be debated. In contrast, in a newly emerging paradigm it is clear that interactions between HLA-C and killer-immunoglobulin-like receptors (KIR) on decidual NK cells can influence the success of early pregnancy events, after implantation has occurred (Colucci et al., 2011). Both genetic and functional studies support the view that in fact, activation of decidual NK cells by MHC ligands on trophoblast has beneficial effects on pregnancy outcome.

In conclusion, the investigations of immunological factors are costly, well-designed randomized controlled trials are lacking and current experimental treatment suggestions such as IVIg should be considered with considerable caution.

Possible luteal-phase co-treatment in RIF

Ascorbic acid

Ascorbic acid is a pre-eminent water-soluble antioxidant (Buettner, 1993) that has long been associated with fertility (Paeschke, 1969). Luteal regression is associated with ascorbate depletion and the generation of reactive oxygen species, which inhibit the action of LH and block steroidogenesis (Margolin et al., 1990). Women with unexplained infertility have a lower total antioxidant status in their peritoneal fluid (Polak et al., 2001). Griesinger et al. (2002) conducted a prospective, randomized, placebo-controlled study to evaluate the impact of ascorbic acid of different doses (1, 5 or 10 g/day) as additional support during luteal phase (n = 620). There was no clinical evidence of any beneficial effect of ascorbic acid, defined by ongoing pregnancy rate, in stimulated IVF cycles, regardless of the dose used.

Prednisolone

One line of research has investigated whether immunosuppression by exogenous corticosteroids as a co-treatment for LPS can be used to improve the rates of embryo implantation and pregnancy in IVF patients (Lee et al., 1994).

It has been proposed that glucocorticoids may improve the intrauterine environment by acting as immunomodula-

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tors to reduce the NK cell count to the normal range and normalize the cytokine expression profile in the endometrium and by suppression of endometrial inflammation. The last Cochrane review showed that there was no clear evidence that administration of peri-implantation glucocorticoids in assisted reproduction cycles significantly improved the clinical outcome (Boomsma et al., 2012).

Aspirin

Vane et al. (1990) described the mechanism of action of aspirin, showing that it inhibits the enzyme cyclo-oxygenase, thus reducing prostaglandin synthesis. In species such as cattle and sheep, luteal regression is caused by a pulsatile release of prostaglandins from the uterus in the late luteal phase; however, the mechanism responsible in humans is unclear (Okuda et al., 2002).

Because aspirin has also been shown to increase uterine blood flow (Wada et al., 1994), clinicians have postulated that aspirin could improve the receptivity of the endometrium, thereby increasing implantation and birth rates. In obstetrics, aspirin is known for its potential to prevent pre-eclampsia. Furthermore, it improves the chance of a live birth in women with antiphospholipid syndrome with a history of recurrent miscarriage (Empson et al., 2005), although recent studies show that it is not effective in women with unexplained recurrent miscarriage (Kaandorp et al., 2010). In the last decade, the use of aspirin during IVF has been investigated in multiple studies (Kaandorp et al., 2010). Whereas some studies could not demonstrate any benefit in IVF outcome, others reported a statistically significant increase in pregnancy rate (Kaandorp et al., 2010). No less than five meta-analyses have been published on the subject thus far (Gelbaya et al., 2007; Groeneveld et al., 2011; Khairy et al., 2007; Poustie et al., 2007; Ruopp et al., 2008). The latest meta-analysis confirmed that aspirin does not improve pregnancy rates after IVF and concluded that this practice should be abandoned (Groeneveld et al., 2011).

It has been suggested that a small subpopulation of patients may benefit from aspirin and prednisone treatment. Combined treatment of prednisone for immunosuppression and aspirin as an antithrombotic agent, administered before ovulation induction, may improve the pregnancy rate in autoantibody sero-positive patients (those with anticardiolipin antibodies, antinuclear antibodies, anti-double-stranded DNA, rheumatoid factor and/or lupus anticoagulant) who have had repeated IVF embryo transfer failures (Geva et al., 2000). Lambers et al. (2009a,b) showed that in IVF and ICSI patients with non-tubal infertility and previous conception failure, the incidence of hypertensive pregnancy complications was significantly reduced by low-dose aspirin therapy when it was started prior to conception. On the other hand, the latest meta-analysis regarding this issue found no confirmation for the hypothesis that preconceptionally started low-dose aspirin reduces the incidence of hypertensive pregnancy complications or preterm delivery in IVF women (Groeneveld et al., 2013).

Endometrial injury

Mechanical endometrial injury (biopsy/scratch or hysteroscopy) in the cycle preceding or during the ovarian stimulation for IVF has been proposed to improve implantation in women with unexplained RIF. It has been shown that mechanical manipulation of the endometrium can enhance receptivity by modulating gene expression of factors required for implantation like glycodelin A (Mirkin et al., 2005), laminin alpha 4, integrin alpha 6 and matrix metalloproteinase 1 (Almog et al., 2010). The mechanical manipulation or local injury to the endometrium can be induced by endometrial biopsy (scratch) or hysteroscopy.

In order to improve outcomes in women with unexplained RIF, various studies have examined pregnancy rates after inducing local endometrial injury in the cycle preceding ovarian stimulation. All of the studies included (in the analysis) only patients with normal uterine cavity at hysterosalpingography as well as normal hysteroscopy findings. All showed higher clinical pregnancy rates in the hysteroscopy groups (Barash et al., 2003; Demirol and Gurgan, 2004; Karimzadeh et al., 2009; Makrakis et al., 2009; Narvekar et al., 2010; Raziel et al., 2007). The number of times the biopsy was taken differed between the studies: once (Karimzadeh et al., 2009); twice, once between days 7–10 and then days 24–25 of the preceding cycle (Narvekar et al., 2010); and four times (days 8, 12, 21, 26 in the preceding cycle of ovarian stimulation) (Barash et al., 2003). Karimzade et al. (2010) showed a negative impact of endometrial biopsy taken on the day of oocyte retrieval.

A systematic review and meta-analysis showed a beneficial effect of inducing local endometrial injury in the preceding ovarian stimulation cycle prior to IVF treatment (Potdar et al., 2012). It is postulated that with local injury there are changes initiated within the endometrium, the immune system and gene expression, all leading to improved receptivity and a favourable milieu for implantation.

The clinical question raised is whether there is a role of local endometrial injury in the preceding cycle in all women undergoing IVF or whether it should be limited to women with RIF. However, several issues need to be clarified regarding the timing of intervention, phase of cycle when injury should be induced, use of hysteroscopy versus endometrial biopsy, mechanism of action for injury induced with hysteroscopy and benefit of single versus multiple biopsies. There is an urgent need for large, multicentre randomized studies investigating local endometrial injury and pregnancy outcomes in unexplained RIF and in patients with unexplained subfertility undergoing their first IVF cycle.

Future perspectives

It has been demonstrated that the endometrium of an unstimulated cycle is the most receptive endometrium (Fatemi et al., 2010). Therefore, future randomized controlled trials should evaluate, whether embryo implantation would improve in patients with RIF, if all embryos were to be frozen and transferred in a consecutive natural cycle.

New data also suggests that abnormalities of decidualization of the endometrial stromal cells that accompanies implantation is seen in some patients with RIF. It is likely that this reflects long-standing epigenetic changes in these cells that affects their subsequent differentiation. This novel hypothesis is discussed in an accompanying article in this issue (Brosens et al., 2013).

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Conclusions

Successful implantation is a complex process requiring a receptive endometrium, a functional embryo at the blastocyst stage and a synchronized dialogue between maternal and embryonic tissues. In the presence of normal uterine anatomy, non-receptive endometrium due to changes of endocrine profile and the medical condition of the mother (such as thrombophilia and abnormal immunological response) can adversely affect the dialogue between the embryo and the endometrium, which is crucial for successful implantation.

Ovarian stimulation disrupts the endocrine milieu and leads to supraphysiological steroid concentrations. High oestradiol concentrations in the follicular phase give rise to premature progesterone elevation that in turn causes endometrial advancement and lowers implantation rate. A freeze-all approach and embryo transfer in a natural cycle should be applied to all patients with high/early progesterone responses. A mild ovarian stimulation protocol is another approach to lower oestradiol concentrations and allowing for synchronized development of an implantation-competent blastocyst and a receptive endometrium.

In RIF, patients are advised to undergo blood tests for inherited and acquired thrombophilia. Once detected, a consultation with a haematologist and connective tissue disease specialist is advocated and treatment with low-molecular-weight heparin (LMWH) is individually assessed. Empirical treatment with LMWH, aspirin or corticosteroids has not been found to be effective and is not advocated for women with RIF who were negative for thrombophilic tests.

One active research question is the possibility that abnormal maternal immune responses to paternal antigens may contribute to implantation failure. There is currently considerable confusion about the possible role of altered T-cell responses in patients with RIF. Some studies report changes in so-called TH1:TH2 cytokines in peripheral blood and, on the basis of this, suggest benefits from IVIg infusions in such patients. However, the definition of which patients might benefit and the actual efficacy of such treatments have not been subjected to large-scale rigorous double-blind trials and thus remain largely unproven. This must be weighed against the significant costs and risks for the patients undertaking such treatments. Similarly, preliminary results using intralipid infusion to support implantation are encouraging. However, the real benefit of such treatment in patients with increased NK cytotoxic activity experiencing RIF has not yet been proven in large scale randomized controlled studies.

Hysteroscopy and/or endometrial scratching in the cycle preceding ovarian stimulation should become a standard for patients with RIF. The optimal timing and number of scratches remains to be determined in randomized controlled trials.

In summary, in order to improve implantation the current evidence would suggest that patients should have all embryos frozen and transferred in a natural cycle, with the hysteroscopy/endometrial scratch in the cycle preceding embryo transfer. Empirical treatment with LMWH, aspirin or corticosteroids has not been found to be effective and is not advocated for women with RIF who were negative for thrombophilic tests.

Impaired endometrial receptivity remains the bottleneck in infertility treatment, prompting the need for more randomized controlled trials dealing with all the aspects of this delicate issue.

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