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# Evidence-based reproductive medicine: a critical appraisal

M. Dhont

*Department of Obstetrics and Gynaecology, Ghent University Hospital, De Pintelaan 185, 9000 Gent, Belgium.*

Correspondence at: marc.dhont@ugent.be

## *Abstract*

**Evidence-based medicine has become the golden standard of good medical practice. I analysed meta-analyses and systematic reviews, the cornerstones of evidence-based medicine, pertaining to two important problems in in vitro fertilization: failed implantation and poor ovarian response to ovarian stimulation. Numerous interventions and procedures have been tried to facilitate implantation and to enhance the ovarian response to stimulation. Notwithstanding the fact that many clinical trials have been performed, very few procedures can as yet stand the critical test of evidence-based medicine. A plea is made for co-ordination between clinicians and reviewers and co-operation between infertility centres to combine their efforts to set up sufficiently powered clinical trials to arrive at more solid evidence for a number of interventions in in vitro fertilization programmes.**

*Key words:* **Evidence-based medicine, reproductive medicine, IVF, failed implantation, poor responder.**

## Introduction

The concept of evidence-based medicine (EBM) is ascribed to Archie Cochrane with the publication of his book *Effectiveness and Efficiency: Random Reflections on Health Services* (Cochrane, 1972). In a later essay, Cochrane (1979) awarded the 'wooden spoon' to obstetrics and gynaecology for being the least scientific and evaluative of medical specialities. This challenge was taken up for obstetrics by Chalmers et al. (1989) with the publication of a systematic review of randomized controlled trials (RCTs) of care during pregnancy and childbirth. In 1992 the Cochrane Centre was opened in Oxford and in 1993, a Subfertility Group was registered. At present, there are more than 100 systematic reviews on this topic in the Cochrane library.

Though it seems self-evident that health care should be based on objective and proven criteria, EBM has only recently come of age and is now generally accepted to be the standard for good medical practice. The evidence is derived from well-conceived randomized trials, compilation of evidence through meta-analysis and systematic reviews. One objection to EBM is that it measures the average effect of a group of patients but does not take into account the individual variation in response. Sackett et al. (1995;1996) stressed that EBM is more than the blind application of the results of a clinical trial but 'the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research'. Meta-analysis of individual patient data provided by the authors of original studies would allow to consider relevant subgroup analyses or to put patient characteristics as covariates in a regression model (Broeze et al., 2010). Whether this time-consuming approach will be feasible and will outperform the classical meta-analyses remains to be seen.

Anyway, evidence-based practice cannot be applied in all circumstances; otherwise, it would be impossible to develop new procedures. In some cases, the advantage of a new procedure is so overwhelming that clinical trials are unnecessary and even harmful. For instance, there was no need of many randomized trial to show that oocyte retrieval by transvaginal puncture was superior in all aspects to the laparoscopic route. Furthermore, before any evidence for some protocols of treatment can be gathered, a number of pioneering studies, based on physiological principles, animal experiments, a

personal observation or pure hypothetical speculation have to be performed. Finally, the absence of evidence should not impede the clinician to treat patients according to his experience and based on common sense because there is a well-known saying that 'absence of evidence does not automatically imply evidence of absence'.

The aim of this paper is to investigate in how far some treatment modalities in assisted reproduction are evidence-based. I will focus on two aspects that pertain to the outcome of IVF: failed implantation and poor responders.

## Failed implantation

It's a frustrating experience for both patients and doctors when no pregnancy occurs after the transfer of one or more embryos. This failure is commonly called failed implantation but this in fact is a misnomer. What happens to the embryo between the transfer and implantation is beyond observation. Implantation is a dynamic process in which the embryo itself plays a determining role. The relation between the microscopically estimated quality of the embryo and the success rate attests to the fact that the embryo is the key player in the implantation process. Nevertheless, in a sometimes desperate search for a solution, a great variety of interventions have been devised to enhance the process of implantation going from simple procedures to keep the embryo in place to more sophisticated methods to influence the uterine environment. An example of the first type was the knee-to-chest position for the embryo transfer when the uterus is in an anteverted position comparing the transfer of the embryo to putting a ball in a basket. Except for one limited study (Englert et al., 1986) who found no difference in success rates after transfer in dorsal versus knee-to chest position the usefulness of this procedure has never largely been tested and has long been abandoned. But the search for enhancing implantation is still going on. For example, Decleer et al. (2012), hypothesizing that uterine motility at the time of transfer could play a role in the retention of the embryo, treated patients with repeated failed implantation with an oxytocin antagonist at the time of transfer and concluded that in patients with good quality embryos this procedure could be enhance the success rate. This, however, was a non-randomized open trial that failed to take into account the principle of regression to the mean. Anyway, this study proved once more that quality of the embryo is the determining factor for success. But are there evidence-based standard practices that can improve the probability of implantation? Distinction should be made between interventions meant to keep the embryo inside the uterus after transfer, technique of transfer and interventions to facilitate implantation.

### *Bed rest*

It is not uncommon for the transfer fluid containing the embryo to be expulsed (Schulman, 1986) and it has been shown that this may contain the transferred embryo (Ghazzawi, 1999). It seems logical therefore to let patients rest in a recumbent position after transfer. A Cochrane review (Abou-Setta et al., 2009) found 4 randomized trials on the effect of bed rest on the pregnancy rate but in only one of them were ongoing pregnancy rates reported (Purcell et al., 2007). No difference in pregnancy rates was found between immediate ambulation and bed rest for 30 minutes. Notwithstanding the lack of evidence, bed rest is still prescribed in many centres albeit the duration of rest can go from half an hour to half a day.

### *Adherence compounds*

Can't you fix the embryo in the uterus is a question sometimes posed by patients. It may indeed seem logical to fix the embryo in the uterus by applying some kind of glue to the embryo. Several compounds have been proposed to this purpose although the exact mechanism of action is unknown. Do they work by helping to retain the embryo in the uterus or are they also facilitating implantation? The effect of the addition of a fibrin sealant was tested in a randomized trial by Ben-Rafael (1995). There was no evidence that the addition of fibrin sealant to the embryo transfer medium improved the pregnancy outcome.

In a systematic Cochrane review, hyaluronic acid was found to increase the chances of pregnancy but also increased the chances of multiple pregnancies, which is a less positive result. However, the live birth rate was infrequently reported and no conclusions can be made (Bontekoe et al., 2010).

### *Ultrasound-guided transfer*

Traditionally, the 'clinical touch' method has been used to guide placement of the transfer catheter to within ~10 mm from the uterine fundus prior to injection of the embryos. This method is essentially blind and relies on the clinician's tactile senses to judge when the transfer catheter is in the correct position. There are several arguments in favour of an ultrasound-guided transfer. The exact position of the uterus and the cervical canal are visualized, the location of the catheter near the uterine fundus can be ascertained and the fluid containing the embryos

with the accompanying air bubble can be seen. A subjective advantage is that the patient can follow the procedure on the screen and can be assured that the embryo is in place. Ultrasound guidance can also be useful in manoeuvring the catheter trough a distorted cervical canal or uterine cavity.

A Cochrane review identified seventeen randomized studies on the effect of ultrasound-guided transfer versus the so-call clinical touch method. Only 7 studies reported on ongoing pregnancy rates. From these studies it could be concluded that with ultrasound-guided transfer the ongoing pregnancy rate is higher than with the clinical touch method (Brown et al., 2010).

*Type of catheter*

Several types of transfer catheters have been devised and many of them are still widely used. In general catheters can be divided into soft and rigid catheters, and each of them has some pros and cons. The rigid catheter can be easily steered in de direction of the uterine cavity but can also traumatize the endometrium. The soft catheter has to find its own way into the uterine cavity but its application is not traumatic for the endometrium. A systematic review from 2005 concluded that pregnancy rates were significantly higher when using a soft catheter (Abou-Setta et al., 2005) but a few years later, the same authors concluded that with ultrasound guidance both types of catheters perform equally well (Aboulfotouh et al., 2008).

*Techniques for preparation prior to embryo transfer*

Several interventions at the time of embryo transfer have been tried: full bladder, removal of cervical mucus, flushing the endocervical canal or the endometrial cavity, dummy transfer, changing patient position, the use of a tenaculum, or embryo after loading. A Cochrane review in 2010 concluded that there is no sufficient evidence for specific recommendations for transfer practice and recommend that more, larger studies are done on ET preparation techniques. The studies need to be of a higher quality with better-explained methods, more specified inclusion and exclusion criteria, and more participants (Derks et al., 2009). A similar conclusion is reached concerning the effect of prophylactic administration of antibiotics (Kroon B et al., 2012).

*Aspirin and heparin*

Apart from its well established effect on pain and fever, low-dose aspirin was found to have many additional indications mainly through its inhibiting effect on cyclo-oxygenase. It is thought to increase the uterine and ovarian blood flow and therefore could enhance endometrial receptivity and ovarian responsiveness. This hypothesis was taken up by Rubinstein and co-workers (Rubinstein et al., 1999) who in a randomized trial showed a highly significant beneficial effect of aspirin treatment both in terms of oocyte recruitment as in clinical pregnancy rate. Spurred by these findings our own group started a randomized trial of aspirin versus placebo but failed to show any benefit (Dirckx et al., 2009). This was confirmed both by a systematic Cochrane review (Siristatidis et al., 2011) and in an individual patient data meta-analysis (Groeneveld et al., 2011).

Ovarian stimulation activates the coagulation cascade due to the exponential increase of oestradiol. On the other hand, thrombophilia is known to be associated with adverse perinatal outcome. It was therefore hypothesized by Nelson and Greer (2008) that haemostaticmechanisms have an important role in implantation and that treatment with heparin could be useful particularly in patients with repeated implantation failure. A meta-analysis of all randomized studies, however, showed no difference in the clinical pregnancy rate, live birth rate and miscarriage rate in women receiving heparin compared with placebo during IVF treatment (Seshadri et al., 2012). As in so many systematic reviews, the authors add that the role of heparin as an adjuvant therapy during IVF treatment requires further evaluation in adequately powered high-quality randomized studies.

*Glucocorticoids*

Natural killer (NK) cells have been shown to play an important role in early implantation (Croy et al., 2002). Glucocorticoidsmay improve the intrauterine environment by acting as immunomodulators to reduce the NK cell count to the normal range and normalise the cytokine expression profile in the endometrium and by suppression of endometrial inflammation. It seemed appropriate then to treat patients with repeated implantation failure with glucocorticoids. Several studies have indeed been performed but unfortunately with different types of glucocorticoids, different doses, timing and duration of administration. Overall, there was no clear evidence that administration of peri-implantation glucocorticoids in ART cycles significantly improved the clinical outcome (Boomsma et al., 2012).

*Assisted hatching*

Cultured embryos hatch and implant at lower rates than occurs naturally (Mercader et al., 2001). It is

unclear whether this is due to 'hardening' of the zona pellucida as a result of cross-linking of its constituent glycoproteins (ZP1, ZP2, ZP3) in an in vitro environment (Cohen, 1991) or some intrinsic embryonic effect. Zona thickness appears to be influenced by a woman's age, hormone profile (high early proliferative phase follicle-stimulating hormone (FSH)), smoking and the cause of infertility, and correlates negatively with embryo implantation rates (Loret de Mola et al., 1997). If zona hardening impedes implantation, it is tempting to manipulate the zona by mechanically breaching it or thinning it by some chemical substances. Our group was one of the first to perform a randomized trial of partial zona dissection prior to embryo transfer in unselected patients but we found no beneficial effect (Hellebaut et al., 1996). A recent Cochrane systematic review analysed 31 randomized controlled trials of assisted hatching (all types combined) and found no significant effect on live birth rate (Carney et al., 2012). Subgroup analysis of women who had had a previous failed attempt at IVF, however, revealed improved clinical pregnancy rates in the women undergoing AH compared with the women in the control group. The authors of this review conclude that the potential of assisted hatching in assisted conception makes it imperative that studies of high methodological quality (preferably multicentre trials with appropriate design, adequate power and appropriate duration of follow up) are undertaken to provide these urgently needed answers.

*Endometrial injury*

My predecessor, professor Vandekerckhove, who was well acquainted with the reproduction in rodents told me several decades ago that traumatization of the endometrium fosters the process of decidualization and proposed to perform an endometrial biopsy with a Novak curette before transfer. In effect, the induction of decidual tissue formation is well recognized, at least in rodents, to be dependent on both the proper ovarian steroid hormone priming of the uterine endometrium and the type of natural (i.e. blastocyst) or experimental (e.g. chemical or mechanical) stimulus applied to the uterine stroma (DeFeo, 1963; Mitchell and Garris, 1978). Because at this time there was consensus that traumatization of the endometrium should be avoided, we dismissed the proposal of my predecessor but more recently, several studies on endometrial injury prior to transfer have been performed. A recent Cochrane review (Nastri et al., 2012) concluded that endometrial injury prior to the embryo transfer cycle in women with previous ART failure and a normal uterus improves live birthand clinical pregnancy rates. These interesting findings need confirmation and further studies on the best timing and procedure of uterine traumatization and should also answer the question whether this procedure is equally beneficial in women without previous IVF failure.

**Poor responders**

To a certain extent, the success of IVF is related to the number of oocytes that can be retrieved. That is the reason why the introduction of ovarian stimulation was a major step in boosting the success rate of IVF. Even with the most intensive stimulation protocols, however, some patients fail to respond adequately. They are called poor responders. There are several reasons for this intrinsic failure to respond to ovarian stimulation, the most important one evidently being age, which also is the best predictor of success (Broer et al., 2013). The ovarian reserve of follicles is dwindling exponentially between 37 and 40 years of age (Faddy and Gosden, 1996). Other known reasons such as endometriosis, post-infectious adhesions and smoking are related to a compromised ovarian circulation. There are indications that poor response to stimulation in younger women presages imminent menopause but the question is whether poor response also affects oocyte quality as is the case in older women. We addressed this question by a review of 2163 IVF cycles and put the cut off for poor responders at < 5 oocytes (De Sutter and Dhont, 2003). We found that rates of pregnancy and miscarriage in young poor and normal responders do not differ; provided that embryos of similar quality are transferred. In contrast, older women had a lower pregnancy rate and a higher miscarriage rate, even when two good-quality embryos were available. These results show indirectly that in young poor responders, the prognosis for the outcome of treatment is mainly determined by the number of oocytes and, hence, the probability of obtaining one or two good-quality embryos rather than by oocyte quality.

A major problem in evaluating randomized trials on the treatment of poor responders is the lack of a uniform definition. According to Polyzos and Devroey (2011) 41 different definitions of poor response were found in 43 randomized trials, which led the authors to conclude that 'meta-analyses of the currently available trials should be strongly discouraged because they may lead to the adoption of interventions of ambiguous value'. Anyway, numerous protocols for poor responders have been developed. They can be divided in two types: alternative stimulation schemes and adjuvant treatment with growth hormone and androgens or androgen modulators.

*Stimulation protocols*

Diverse stimulation protocols have been tried in poor responders including low dose gonadotropin-releasinghormone (GnRH) agonist, short GnRH-agonist using the flare-up effect, GnRh-antagonist and the combined use of clomiphene and gonadotrophins. A Cochrane review identified 15 comparative trials of which only one reported live birth rates (Pandian et al., 2010). The number of oocytes retrieved were significantly less in the conventional GnRHa long protocol compared to the short GnRH short protocol and the GnRH antagonist protocol whereas the total dose of gonadotrophins used was significantly higher in the GnRHa long protocol group compared to the short protocol and GnRH antagonist groups. On the other hand, cancellation rates were significantly higher in the GnRHa flare-up group compared to the GnRHa long protocol group. The reviewers concluded that there is insufficient evidence to support any particular stimulation scheme and that more robust data from good quality RCTs with relevant outcomes are needed. It is evident, however, that given the vast cost of gonadotrophin treatment, less seems to be as good as more.

*Dehydroepiandrosterone (DHEA)*

DHEA is a steroid hormone secreted mainly by the adrenal glands and theca cells of the ovarian follicle. In the ovarian follicle, DHEA is converted to androstenedione andestrone. Androgenexcess has been shown to stimulate early stages of follicular growth and increase the number of preantral and antral follicles. In addition, increased intra-ovarian concentration of androgens seems to augment follicle stimulating hormone (FSH) receptor expression in granulosa cells and potentially leads to enhanced responsiveness of ovaries to FSH. Exogenous androgens could induce a temporary PCO-like state with increased follicle count, improved follicular survival, and reduced apoptosis. Based on these physiological considerations, DHEA supplementation has been tried in poor responders. One of the main proponents and believers of this treatment is the group of Gleicher (Gleicher et al., 2011). They performed a systematic review of DHEA in poor responders and concluded that 'current best available evidence suggests that DHEA improves ovarian function, increases pregnancy chances and, by reducing aneuploidy, lowers miscarriage rates. DHEA over time also appears to objectively improve ovarian reserve'. This conclusion, however, has been contradicted by two recent systematic reviews who failed to show any beneficial effect of DHEA as an adjuvant to ovarian stimulation (Bosdou et al., 2012; Narkwicheanet al., 2013). In an opinion paper entitled: 'Hype or hope? Ethical and practical considerations with clinical research in women with diminished ovarian reserve' Gleicher and Barad (2012) however comment that: 'common sense as well as ethical considerations support the introduction of new treatments into the clinical mainstream even in absence of prospectively randomized studies if lower levels of evidence are supportive of positive treatment effects'.

*Testosteron and androgen modulators*

Based upon similar physiological considerations as for DHEA, testosterone and aromatase inhibitors have been tried as an adjunct of stimulation in poor responders. Inhibition of aromatase activity could increase the intra-ovarian concentration of androgens by blocking their aromatization to oestrogens thus creating a temporary PCO-like condition. According to a systematic review (Bosdou et al., 2012) clinical pregnancy rate and live birth rate were significantly increased in patients that were pre-treated with transdermal testosterone. Also the total dose of gonadotrophins required for ovarian stimulation and the duration of ovarian stimulation were significantly decreased. No beneficial effect of aromatase inhibitors was found.

*Growth hormone*

Growth hormone regulates the effect of FSH on granulose cells, by increasing the synthesis of insulin-like growthfactor-I, augments the effect of gonadotrophin on granulose and theca cells, and plays an essential role in ovarian function, including follicular development, oestrogen synthesisand oocyte maturation (Bachelot et al., 2002). In a Cochrane review of ten studies a statistically significant difference in both live birth rates and pregnancy rates favouring the use of adjuvant growth hormone in in-vitro fertilisation protocols in women who are considered poor responders without increasing adverse events was observed (Duffy et al., 2010). The authors concluded, however, that the result needs to be interpreted with caution because the included trials were few in number and had small sample sizes. Therefore, before recommending growth hormone adjuvant in IVF further research is necessary to fully define its role. A recent randomized study including 82 poor responders comparing IVF outcome after stimulation with or without the addition of growth hormone failed to observe a significant difference in clinical pregnancy rates although the number of retrieved oocytes and embryos was

**Tabel I.** — Evidence of benefit for interventions for failed implantation.

| Intervention | Benefit | Possible benefit | Doubtful benefit | No benefit |
|---|---|---|---|---|
| Bed rest | | | | x |
| Adherents | | | x | |
| Ultrasound guided ET | X | | | |
| Soft transfer catheter | | x | | |
| Aspirin | | | | x |
| Heparin | | | x | |
| Glucocorticoids | | | x | |
| Assisted hatching | | x | | |
| Endometrial injury | | x | | |

significantly higher in the group treated with growth hormone (Eftekhar et al., 2013).

## Discussion and conclusion

We have analysed a number of interventions and procedures to address the problem of failed implantation and poor responders, two aspects of IVF treatment that have been and still are the subject of numerous studies and diverse interventions. The level of evidence for the studied interventions in both situations is summarized in Table I and II.

Besides the intrinsic quality of the embryo, which appears to be the most important factor in the success of IVF, failed implantation can also be due to different external factors such as the retention of the embryo in the uterus, technical aspects of the transfer itself and the dynamic interaction between the embryo and the endometrium. Because the success of IVF depends on the number of eggs that can be retrieved and hence the number of good quality embryos that can be obtained, an adequate response to gonadotrophin stimulation is important. Depending on the study population and the definition a poor response is observed in 10 to 25% of patients. Age is the most important cause of poor response and is, apart from the number of eggs that can be retrieved, an independent predictor of the success of IVF. Nevertheless, several interventions to increase the yield of eggs have been devised. They include different stimulation schemes and the effect of adjuvant endocrine treatments.

Interventions are introduced on the base of physiological considerations, animal experiments or pure speculation. Clinical evidence of the benefit of an intervention has to be arrived at by performing well conceived randomized trials. Even when performed correctly, one randomized trial is mostly not sufficient to accept or reject a proposed intervention. Evidence-based medicine mainly relies on meta-analyses and systematic reviews of all clinical trials. Unfortunately, sometimes up to 90% of all clinical trials are rejected in meta-analyses because of one or more shortcomings. No wonder that many systematic reviews end with the following comments: ‘adequately powered trials are needed..., it is recommended, in general, that more, larger studies are done..., the studies need to be of a higher quality with better explained methods..., morespecified inclusion and exclusion criteria, and more participants..., further well designed randomised studies are required to elucidate the possible role of this therapy in well-defined patient groups... more robust data from good quality RCTs with relevant outcomes are needed’. One of the shortcomings that are repeatedly stressed is that most trials fail to report on live birth rates. Many interventions and procedures with regard to failed implantation and

**Table II.** — Evidence of benefit for interventions in poor responders.

| Intervention | Benefit | Possible benefit | Doubtful benefit | No benefit |
|---|---|---|---|---|
| Stimulation scheme | | | x | |
| DHEA | | | x | |
| Testosteron | | x | | |
| Androgen modulators | | | | x |
| Growth hormone | | | x | |

poor responders still need further research before they can be accepted as evidence-based or definitively rejected.

After browsing through many clinical trials and systematic reviews, it appears to me that there are two kinds of investigators: clinicians and reviewers. The first ones are eager to increase the success rate of IVF and are inventing procedures to enhance it. They are under the pressure of patients and also want to be the first to announce some breakthrough in the treatment. They are eager to publish even prematurely and cannot wait for the golden standard of clinical research in IVF, e.g. the live birth rate. It is a pity and frustrating to observe that so many efforts required to do randomized trials are lost because they are not up to the standard of EBM. That at least is the conclusion of many systematic reviews. It would be laudable if reviewers, who know how a good clinical trial should be organized and practitioners, join their efforts to obtain more solid results. Large scale clinical trials with sufficient power can rarely be performed by one infertility centre alone. It would be to the advantage of our patients and society in general if clinicians transcend their individual aspirations and co-operate to perform good clinical trials that can provide an evidence-based answer to the many problems that remain to be solved in IVF.

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