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Mobilization versus Bed Rest following Embryo Transfer (review)

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ABSTRACT

Background

Embryo transfer (ET) is a final step in the in vitro fertilization (IVF) treatment cycle. Since the early days of human IVF and ET, bed rest for hours immediately following the transfer has been advocated and widely practiced. However, there is no scientific validation for this practice, which is both time-consuming for patients and increases space occupancy in hospitals, and has never been shown to be related to a higher success rate.

Objectives

To evaluate the effect of bed rest and mobilization following embryo transfer on the results of in vitro fertilization.

Materials and Methods

An electronic search of Medline and the Cochrane library from 1995 to 2004 for randomized controlled trials (RCTs), concerning bed rest or free mobilization following embryo transfer was undertaken. Three randomized controlled trials, all comparing bed rest and mobilization following embryo transfer were included in the analysis.

Results

Three studies were included in the review, including 598 infertile women, 301 women underwent ET followed by 20-60 minutes period of bed rest, 297 women underwent treatment cycles and ET followed by 24 hours of bed rest.
In all RCTs the patients, who rested for 20-60 min after embryo transfer demonstrated a higher implantation rate per embryo transfer compared with the patients, who rested for 24 hours. Live birth in one study was higher in the ‘no bed rest’ group.
No statistical significant differences were found between the two groups for twin pregnancies and miscarriages.

Conclusions

There is no evidence supporting the use of bed rest in hospital or at home after embryo transfer to increase the implantation, clinical and ongoing pregnancy rates.

INTRODUCTION

The success of in-vitro fertilization (IVF) depends on maximizing the efficiency of each step of procedure. Improvements in ovulation induction, oocyte retrieval and laboratory techniques to achieve maximal rates of fertilization and embryo development have resulted in at least one embryo transfer in 90 % of all cases where oocytes have been retrieved (1).
Embryo transfer is the final step in the in -vitro fertilization treatment cycle. This step associated with success or failure. Failure of implantation is the most common cause of

failed embryo transfer (2). This procedure may be influenced by technique, embryo quality, stage of development, endometrial status and endometrium support (5).
Different interventions during embryo transfer have been evaluated, including position of the patient (26, 27), quantity of culture medium (28), number of embryos transferred (29) and the type of catheter used (3).
Mechanical expulsion of the transferred embryo is a possible cause of failure of implantation, and may be the reason why most women are asked to stay in bed for several hours following ET (1, 4, 30). However, this has never been shown to be related to a higher success rate. Furthermore, an immediate return to routine daily activities, may lead to a decrease in maternal stress following embryo transfer (5).
The aim of this review is to compare “no bed rest “and “bed rest” policy, following ET.

METHODS

Titles and abstracts identified by the search were assessed and full text articles were reviewed if found eligible.
Quality of the trials was assessed by whether groups were comparable at baseline, the extent of loss of follow-up, and if intention-to-treat analysis was undertaken.

Criteria for considering studies for this review

Inclusion criteria
Randomized controlled trials comparing bed rest and free mobilization following embryo transfer were included. Clinically relevant outcomes had to be reported.
Type of participant
Infertile women who undergo complete in vitro fertilization with Gonadotrophin-releasing hormone (GnRH) pituitary down- regulation and controlled ovarian stimulation
Type of intervention
Bed rest or immediate mobilization after embryo transfer
Type of outcome

- Clinical pregnancy per cycle rate (the percentage of cycles started that demonstrated a live fetus on ultrasound examination)
- Implantation rate per embryo
- Take home baby rate
- Miscarriage
- Twin pregnancies

Methodological quality

Generally, all studies had small sample sizes.
Due to the intervention, blinding of treatment was not applicable.
All studies reported to have been performed at university-based clinics. Four countries were represented in the included trials: England and Italy (Botta 1997), Saudi Arabia (Amarin 2004) and Czech Republic (Rezabek 2001).
None of the studies mentioned exclusion after randomization.
The method of randomization was stated in all, except one study (Botta 1997). The study of Botta (1997) does not specify how participants were “randomly” assigned to groups. Amarin (2004) reports random allocation and the concealment of the assignment by

sealed opaque envelopes. In Rezabek (2001) allocation was performed according the "number of medical chart".
All studies stated the time frame during which data was collected.
In the trial by Amarin (2004) the exclusion criteria was age more than 40 years, in Rezabek (2001) women over 35 were excluded. None of the studies reported loss of follow-up.
Ethical approval was stated to have been obtained in all studies.
Intention-to-treat (ITT) analysis was performed in one study (Rezabek 2001). Two other studies did not state that ITT analysis was performed. Identification of patients failing to have an embryo transfer was not stated in these trials.

Description of the studies

So far, the search strategies identified four randomized controlled trials. One study was excluded as it was an observational study (31). The total amount of participants was 598: 38 in the Rezabek study (2001), 182 in Botta (1997), 378 in Amarin (2004).
All trials provided baseline information about the included patient population.
Characteristic of the participants were described in all studies (age, duration of infertility and its cause, number of women who had previously undergone an IVF/ET procedure, stimulation protocol, number of transferred embryos, percentage of intracytoplasmic sperm injection (ICSI) and age of the embryos on the day of ET, as well as technical procedures were comparable in all studies
Follow-up was until the pregnancies were determined by vaginal ultrasound scan in the third or fourth week after embryo transfer in Botta (1997), live fetus at six or seven week of gestation in Amarin (2004), until "take home baby" in Rezabek (2001). Amarin (2004) and Botta (1997) did not report live birth rates.
Rezabek (2001) and Amarin (2004) reported the mean age of women in the study at 32-33 years, in Botta (1997) the mean age was younger (28-29).
All trials reported on the causes of infertility in each group to demonstrate that they were similar. Rezabek (2001) and Amarin (2004) included male factor patients treated with ICSI.
The trials provided details on the ovarian stimulation regiment. All patients underwent similar ovarian stimulation using luteal phase GnRH down regulation, followed by stimulation with intramuscular human menopausal gonadotropin (hMG). Follicular growth was monitored by serial ultrasonography in all studies. Ovulation was initiated using a dose of 10,000 IU of human chorionic gonadotropin (hCG) when two or more follicles reached a minimum mean diameter of 17-18 mm. Embryo transfers were performed 60 hours after oocyte retrieval in the trial by Rezabek (2001), 46-50 hours in Botta (1997), 36-48 hours in Amarin (2004). In all trials the transfer was performed by one person and without ultrasound guidance. Amarin (2004) and Botta (1997) provided details about the number of oocytes retrieved (12 and 5 per patient). The mean number of transferred embryos was 2-3 in all studies. In Rezabek (2001) and Amarin (2004) embryos were graded morphologically, based on blastomere number, symmetry and degree of fragmentation. The same technique of transfer was used in all trials.Vaginal progesterone was prescribed for luteal phase support in all studies. The only difference was therefore the duration of bed rest: in Rezabek (2001) and Botta (1997) 20min and 24h, in Amarin (2004) 60min and 24 h, following embryo transfer.

RESULTS

Three studies were included in the review, including 598 women. Three hundred and one women underwent ET followed by 20-60 min period of bed rest, 297 women underwent treatment cycles and ET followed by a 24 hour period of bed rest.
The data are shown in tables 1-4.
Two of the studies were of high quality (Rezabek (2001) and Amarin (2004), one of them medium (Botta 1997).
Not all studies provided data for each of the outcome measures reported.
Prolonged bed rest (24 hours) after embryo transfer was not associated with better implantation rate and clinical pregnancy rate.
“Take home baby” rate in one randomized trial was higher in the ‘no bed rest group’ (Rezabek 2001).
In all RCTs the patients who rested for 20-60 min after embryo transfer demonstrated a higher implantation rate per embryo transfer compared with the patients, who rested for 24 hours.
Two RCTs reported on twin pregnancies and miscarriages (Botta 1997; Amarin 2004).
No statistical significant difference was found between the two groups for twin pregnancies and miscarriages.

DISCUSSION

In-vitro fertilization and embryo transfer was first successfully used in humans over 25 years ago. Since the report of the first IVF child (Edwards and Steptoe1978) more than one million children have been born after IVF. In several countries, IVF children represent up to 4 % of children born yearly (6).
IVF is a complex process that involves multiple steps resulting in the fertilization of oocytes in laboratory. The embryos created in this process are then placed into the uterus for potential implantation. The embryo transfer procedure is the last one of the in-vitro fertilization process and therefore is a very important procedure. No matter how good the IVF laboratory culture environment is, a careless performed embryo transfer may lead to an unsuccessful procedure.
Many factors have been proposed to increase the success of this step. Various refinement of the technique of ET has been suggested in order to improve the pregnancy and implantation rates.
In previous years, different investigators have examined various aspects of embryo transfer techniques, including position, characteristic of catheters, optimal timing of ET after oocyte collection, and the amount of medium needed for the transfer, the use of a fibrin sealant and rest after embryo transfer (3).
For example, no significant differences regarding difficulties encountered during ET or in pregnancy rates were found in women with and without filled bladder (32).
Cervical infection can diminish the pregnancy and implantation rate. The presence of microbial flora of the cervix on ET catheters is associated with poor IVF-ET outcome (24). However, a recent publication did not show an improvement of implantation rates with antibiotics administration at the time of embryo transfer (25).
Low-dose glucocorticoids after in vitro fertilization did not show a significant effect on pregnancy rates (33).

To minimize the potential for movement and expulsion of embryos following embryo transfer, a fibrin sealant, or biological glue, has been used to attach embryos to the endometrium at the side of embryo deposition. The use of fibrin sealant can diminish the ectopic pregnancy rate after ET (36), but has no apparent effect on the ectopic pregnancy rates in patients less than 39 years and on the clinical or ongoing pregnancy rates (35).
It was found that at the time of transfer the presence of hyaluronan in the medium resulted in a significant increase in implantation rates (34).
The depth of embryo replacement into the uterine cavity may influence implantation rates, with better results being obtained when the catheter tip was positioned close to the middle area of the endometrial cavity (13, 21).
Ultrasound-guided embryo transfer increases pregnancy and implantation rates in IVF cycles, which may be due to the decrease in cervical and uterine trauma (11, 12, 18).
Different types of embryo transfer catheters and their impact on pregnancy and implantation rates were compared. It seems that the type of embryo transfer set used for ET does not affect the ongoing pregnancy rate (19, 20).
There is no significant difference between the intercourse and abstain groups regarding pregnancy rates (23% vs 21.2%), but the proportion of transferred embryos that were viable at 6-8 weeks was higher in women exposed to semen compared to those who abstained (11% vs 7.7%). Exposure to semen around the time of ET increased the likelihood of successful early embryo implantation and development (22).
Even in our days different centers advise bed rest following ET, sometimes for up to24 hours. Bed rest is still advised despite the absence of scientific evidence for this practice No evidence has been presented to show that mobilization may negatively influence the implantation rate following ET.
Two cohort studies, using historical control groups, comparing bed rest with no bed rest in hospital following embryo transfer, reported pregnancy rates of 50.6% and 37.8% pregnancy rates per embryo transfer, 40% and 30% clinical pregnancy rate per ET, respectively (2, 4). Both this rates compare very favorably with other programs.
The randomized trials included in this review showed that immediate mobilization following embryo transfer does not reduce the chances of success. Free mobilization after ET has economic implications as well - it gives the possibility to free up spaces in clinics, avoids extra costs for staying in hospital and offers immediate return to work. As any assisted reproduction process or technique is psychologically stressful, with an immediate return to routine activities there is a possibility to reduce maternal stress following embryo transfer (7, 8).
Cost comparisons of free mobilization and bed rest after ET have not been investigated in this review.

CONCLUSIONS

There is no evidence supporting the use of bed rest in hospital or at home after embryo transfer to increase the implantation, clinical and ongoing pregnancy rates. Although bed rest in hospital or at home is widely used, there is no evidence that this practice could be beneficial. Free mobilization may be of benefit to the patient and may be cost effective compared to bed rest.

Table 1: Clinical pregnancy rate per cycle

Study; number of participants	24 hours rest after ET, % (n/N)	20-60min rest after ET, % (n/N)	RR,(95%c-CI)	p
Botta 1997; 182	21.6% (21/97)	21.3% (22/103)		p>0.05
Rezabek 2001; 38	22.2% (4/18)	50% (10/20)		0.08
Amarin 2004; 378	18%	22%	1.11(0.87-1.41)	p<0.05

Table 2: Twin pregnancies

Study; number of participants	24 hours rest after ET, %	20-60min rest after ET, %	RR (95%CI)	p
Botta 1997;182	14.2%	13.6%		p>0.05
Amarin 2004;378	9%	20%	1.50(1.03-2.19)	p<0.05

Table 3: Implantation rate

Study; number of participants	24 hours rest after ET, % (n/N)	20-60min rest after ET, % (n/N)	RR (95%CI)	p
Botta 1997; 182	24.1% (21/87)	23.6% (22/93)		p>0,05
Rezabek 2001; 38	14.5% (8/55)	22.5% (16/71)		0.26
Amarin 2004; 378	9%	14.4%	1.27(1.10-1.47)	p<0.05

Table 4: "Take home baby"

Study; number of participants	24 hours rest after ET, %	20-60min rest after ET	p
Rezabek 2001; 38	11%	40%	P=0.07

Table 5: Miscarriages

Study, number of participants	24 hours rest after ET, %	20-60min rest after ET	RR (95%CI)	p
Botta 1997;182	19%	18.1%		p>0.05
Amarin 2004; 378	5%	9%	1.31(0.96-1.78)	p<0.05

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