

**META-ANALYSIS OF OUTCOME OF IVF/ICSI EFFECTED BY BED REST
FOLLOWING EMBRYO TRANSFER*****¹Dr. Sara Jamil Khan, ²Dr. Annum Sarfraz and ³Dr. Tahira Zainib**¹Assistant Professor Gynae & Obs, Frontier Medical College, Abbotabad, Pakistan.²PMDC # 81803-P.³PMDC #: 93066-P.***Corresponding Author: Dr. Sara Jamil Khan**

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Article Received on 19/05/2018

Article Revised on 09/06/2018

Article Accepted on 30/06/2018

INTRODUCTION

In vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) represent the last option for couples suffering from subfertility. Much progress has been made since the birth of the first IVF baby in 1978 and the majority of patients undergoing IVF/ICSI treatment will reach the stage of embryo transfer (ET), but only a small proportion of transferred embryos implant (Edwards, 1995) leading to an overall success rate of 10–40% (Clinic Summary Report, 2012).

ET is a critical and delicate step in assisted reproduction and many interventions have been attempted in order to increase the implantation rate following ET. Depending on the time relation with the ET, these can be divided in three main groups (Craciunas, Tsampras, & Fitzgerald, 2014): (i) pre ET (dummy ET, cervical and endometrial preparation), (ii) at the time of ET (catheter choice, site of embryo placement, ultrasound guidance) and (iii) post ET (fibrin sealant, mechanical closure of the cervix, bed rest).

Bed rest following ET was recommended in the early days of IVF as a way of preventing embryo expulsion by gravity (Edwards, Steptoe, & Purdy, 1980). It has also been suggested that bed rest might reduce the expulsion rate by decreasing uterine activity following ET.

Several studies failed to confirm the benefit of bed rest following ET (Bar-Hava et al., 2005; Sharif et al., 1995, 1998) and medical staff no longer consider it an important factor of ET success (Salha, Lamb, & Balen, 2001). Furthermore, a prospective observational randomized controlled study evaluating the transfer content (transfer medium and air bubbles) by ultrasound at the time of transfer and 15 min following immediate ambulation demonstrated that the intrauterine content is not affected by immediate ambulation after transfer (Lambers, Lambalk, Schats, & Hompes, 2009).

Despite this evidence of non-effectiveness, many patients perceive complete bed rest to be of benefit and most of them restrict their daily activities following ET but without improvement of success rates (Hawkins et al.,

2014; Kucuk, Doymaz, & Urman, 2010; Su, Chen, Hung, & Yang, 2001).

In a recent review of bed rest following ET, Kucuk (2013) hypothesized that bed rest might be detrimental to the success rate of IVF/ICSI cycles by mechanisms involving stress, anxiety and depression.

The objective of this study was to appraise critically the randomized controlled trials (RCTs) reporting the effect of bed rest following ET in terms of implantation, clinical pregnancy and live birth rates.

METHODS

The authors performed a comprehensive literature search of Medline (via PubMed web interface), EMBASE (via OVID), Cochrane Central Register of Controlled Trials (via Cochrane web interface), ClinicalTrials.gov (via U.S. National Institutes of Health web interface) and Google Scholar (via scholar.google.com/), independently, using the PICO method (Richardson, Wilson, Nishikawa, & Hayward, 1995) for medical subject headings (MeSH) 'ET', 'bed rest', 'embryo implantation', 'pregnancy rate' in combination with free terms 'ambulation', 'physical activity', 'mobilization', 'implantation rate', 'live birth rate', 'complications', 'stress', 'anxiety', 'satisfaction' and 'cost'.

We defined the inclusion criteria as RCTs (irrespective of study design and method of randomization) indexed in the searched databases from 1978 to May 2014, reporting on the effect of bed rest following ET, with no restrictions on language, blinding, sample size or country of origin.

The primary endpoints were selected as: implantation rate (the number of foetal sacs present on ultrasound scan divided by the total number of transferred embryos), clinical pregnancy (the presence of a gestational sac on ultrasound scan) and live birth rates (the delivery of a live foetus after 24 completed weeks of gestational age), and secondary endpoints: complications, stress markers, woman/couple satisfaction and costs.

We extracted the data related to year and country of study, age of participants, cause of infertility, number of oocytes retrieved, timing of ET, number of embryos transferred, bed rest and mobilization, number of transfers, implantation, clinical pregnancy and live birth rates, complications, stress markers, costs, women/couple satisfaction, randomization, concealment and blinding. The data are presented in tables.

The software package RevMan 5.2.11, Copenhagen, Denmark (Review Manager, 2012), provided by the Cochrane Collaboration, was used for statistical analysis. The risk ratio (RR) with a 95% confidence interval (CI) was calculated for binary data variables using the Mantel–Haenszel method and for rate variables (implantation) using the generic inverse-variance method. Heterogeneity was quantified using the ν^2 and I^2

tests and the fixed effect model was used for RR calculation in the case of low heterogeneity ($I^2 < 40\%$). A forest plot was used for the graphical display of the results from the meta-analysis.

The quality of included trials was assessed using the Cochrane Risk of Bias tool and the summary of the evidence was generated using GradePro (Version 3.2 for Windows, Hamilton, Canada), a tool provided by the Cochrane Collaboration.

RESULTS

The systematic literature search identified 36 different studies related to the effect of bed rest following ET. The PRISMA flow chart to explain the RCTs selection is shown in Figure 1. Four RCTs (Amarin & Obeidat, 2004; Botta & Grudzinskas, 1997; Purcell, Schembri, Telles, Fujimoto, & Cedars, 2007; Rezabek, Koryntova, & Zivny, 2001) evaluating 757 women allocated to experimental group (bed rest) or control group (no bed rest) for reporting the effect of bed rest following ET were included in the systematic review and meta-analysis. There were 377 women in the experimental group and 380 women in the control group. The characteristics of the RCTs included are shown in Table 1, and the procedure protocols used for the women in all of the RCTs are shown in Table 2.

Table 1: Characteristics of trials included.

Trial	Year	Country	Mean age	Cause of infertility	Mean number of oocytes retrieved	Timing of transfer after oocyte retrieval	Mean number of embryos transferred
Amarin and Obeidat Experimental Control	2004	Saudi Arabia	33.8 33.4	<ul style="list-style-type: none"> - Oligomenorrhoea - Endometriosis - Tubal disease - Uterine factor - Male factor - Unexplained 	11.72 12.21	36–48 hours	3.29 3.31
Botta and Grudzinskas Experimental Control	1997	Italy	32 30	<ul style="list-style-type: none"> - Ovulation disorders - Tubal disease - Unexplained - Male factor 	5.2 5.4	46–50 hours	2.1 2.3
Purcell et al. Experimental Control	2006	USA	36.99 36.76	<ul style="list-style-type: none"> - Male factor - Unexplained - Endometriosis - Ovulatory dysfunction - Diminished ovarian reserve - Tubal factor - Uterine 	12.06 13.4	Day 2, 3 or 5	3.3 3.0
Rezabek et al. Experimental Control	2001	Czech Republic	28.9 29.2	<ul style="list-style-type: none"> - Tubal factor - Other 	Not available	Day 2 or 3	3.1 3.6

Variables used in the systematic review and meta-analysis are shown in Table 3.

Risk of bias in the studies included

Based upon the guidelines suggested by the Cochrane Collaboration, the quality of most of the included RCTs

was moderate because of attrition bias and possible reporting bias (Figures 2 and 3).

Implantation rate per embryo transferred

Two RCTs (Amarin & Obeidat, 2004; Rezabek et al., 2001) reported on implantation rate per embryo transferred. There was low heterogeneity [$I^2=0.03$, $df=1$, ($p=0.85$); $I^2=40\%$] among the trials, therefore in the fixed effect model the implantation rate was higher in the control group compared with the experimental group (RR, 0.60; 95% CI, 0.45 to 0.81; $z=3.41$; $p=0.0006$; Figure 4A).

Clinical pregnancy rate per transfer

All RCTs included in the meta-analysis reported on clinical pregnancy rate per transfer. There was low

heterogeneity [$I^2=2.89$, $df=3$, ($p=0.41$); $I^2=40\%$] among the trials, and the fixed effect model the pregnancy rate per transfer was therefore similar in the experimental group (RR, 0.91; 95% CI, 0.73 to 1.13; $z=0.88$; $p=0.38$; Figure 4B) compared with the control group. Subgroup analyses based on the duration of bed rest in the experimental group and trial quality revealed similar results.

Live birth rate One RCT (Rezabek et al., 2001) reported on live birth rate and found no difference between the groups ($p=0.08$).

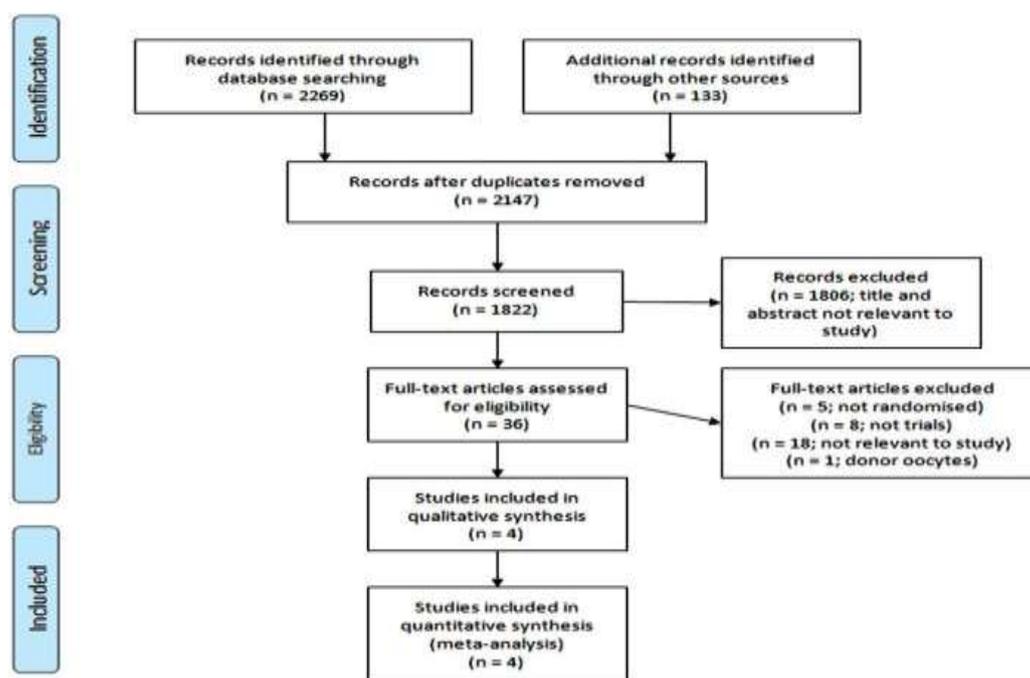


Figure 1: PRISMA flow chart showing trial selection methodology.

Table 2: Treatment protocol adopted in trials included.

Trial	Experimental group	Control group
Amarin and Obeidat (2004)	Strictly confined to the hospital bed for 24 h except for bathroom/toilet purposes	Bed rest for 1 h following ET before being allowed home to conduct the usual daily routine
Botta and Grudzinskas (1997)	Women were admitted to the clinic and transported by a trolley to a bed for 24 h	Women rested for 20 min on the gynaecological bed, after which time they returned home, with no restrictions advised concerning to the routine domestic activities
Purcell et al. (2006)	Patients were offered catheterization of the bladder at the end of the ET and then transferred gently, in the horizontal position, from the ET table to a gurney to minimize any movement after the ET. They were subsequently asked to remain supine in a comfortable position for 30 min	Patients randomized to the control group were allowed to ambulate immediately after the ET procedure, immediately empty their bladder, and were discharged from the clinic
Rezabek et al. (2001)	After 20 min lie on the gynecological table, the patients were admitted for reduced mobilization and were discharged the following day	Patients left home after 20 min lie on the gynecological table

Table 3: Variables used for meta-analysis.

Trial	Women N¼	Implantation rate/ embryos transferred	Clinical pregnancy N¼	Live birth N¼
Amarin and Obeidat (2004)	192	57/633	35	Not available
Experimental Control	186	89/590	40	available
Botta and Grudzinskas (1997)	87	Not available	21 22	Not available
Experimental Control	93			
Purcell et al. (2006) Experimental Control	80 81	Not available	41 41	Not available
Rezabek et al. (2001)	18	8/55	4	2
Experimental Control	20	16/71	10	8

Bed rest compared to early mobilisation after embryo transfer

Patient or population: Women undergoing embryo transfer

Settings: Assisted reproduction units

Intervention: Bed rest

Comparison: Early mobilisation

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Early mobilisation	Corresponding risk Bed rest				
Clinical pregnancy rate Follow-up: mean 6 weeks	Study population		RR 0.91 (0.73 to 1.13)	757 (4 studies)	⊕⊕⊕⊕ moderate ¹	
	297 per 1000	271 per 1000 (217 to 336)				
	Moderate					
	368 per 1000	335 per 1000 (269 to 416)				
Implantation rate Follow-up: mean 6 weeks	Study population		RR 0.6 (0.45 to 0.81)	0 (2 studies)	⊕⊕⊕⊕ moderate ^{1,2}	
	See comment	See comment				
	Moderate					
	0 per 1000	0 per 1000 (0 to 0)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Attrition bias and possible reporting bias

² Implantation is a rate variable and the combined outcome was calculated using generic inverse-variance method.

Figure 2: Summary and strength of the evidence from trials analysed on GradePro^{VR}.

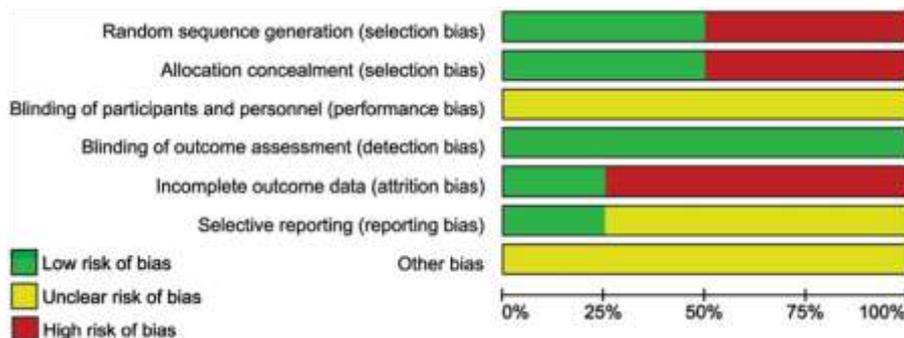


Figure 3: Risk of bias generated using Cochrane Risk of Bias Assessment Tool.

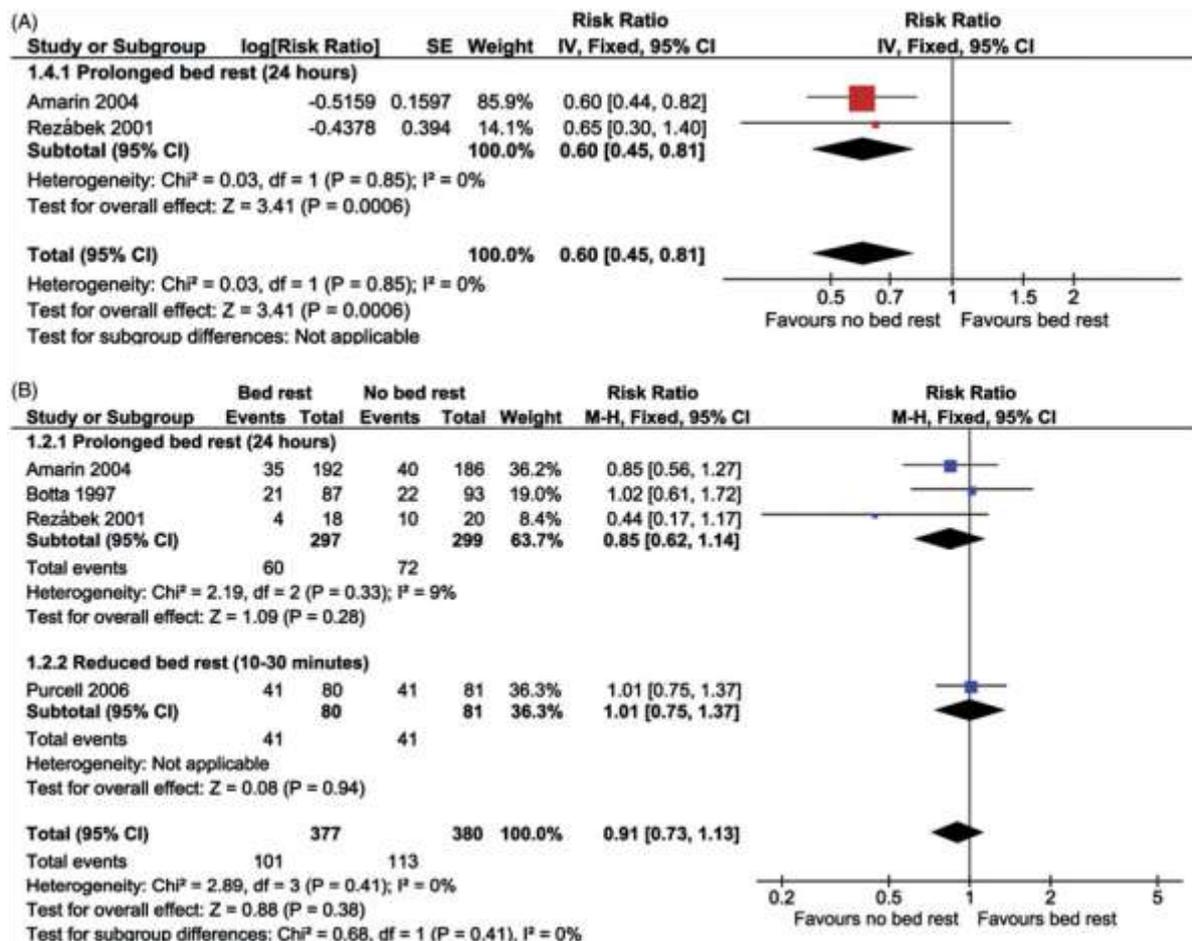


Figure 4: (A) The forest plot showing the implantation rate. Risk ratio is shown with 95% CI. (B) The forest plot showing the clinical pregnancy rate. Risk ratio is shown with 95% CI.

Complications, stress markers, women/couple satisfaction and costs
None of the RCTs reported on these outcomes.

DISCUSSION

Main findings

The findings of this systematic review and meta analysis suggest that bed rest following ET is not beneficial in terms of clinical pregnancy and live birth rates. Furthermore, prolonged bed rest may reduce the implantation rate.

Strengths and limitations

Several aspects suggest the results of this review are valid. Initially, we designed a search protocol and performed a comprehensive literature search with no restrictions on language, blinding, sample size or country of origin, which facilitated the inclusion of a non-English RCT (Rezabek et al., 2001).

Second, clear primary endpoints and relevant secondary endpoints were defined to explain the possible differences between the groups.

Third, subgroup analysis based on duration of bed rest was performed in order to address methodological

differences between the studies. Potential publication bias was reduced by including data from studies, not publications. Where the study was published in different publications the most extensive one was used.

We are fully aware of several limitations in this study. The RCTs with relatively small number of women included in this meta-analysis may not have been sufficient to recognize small differences between groups. There were significant differences regarding the inclusion and exclusion criteria among the RCTs. The quality of the trials included was moderate because of attrition bias and possible reporting bias.

All the studies included data from transfers of more than one embryo, hence extrapolation to single ETs requires caution.

Comparison with other studies and interpretation

A previously published, recently updated Cochrane review of post-ET interventions found insufficient evidence to support bed rest following ET (Abou-Setta et al., 2014). Li, Zhou, and Li (2011) performed a systematic review of bed rest after ET and included three of the present RCTs, concluding that there was insufficient evidence to support the routine use of bed

rest to improve pregnancy outcome in women undergoing ET in IVF cycles.

The main argument to support bed rest following ET is that it might prevent embryo expulsion by gravity. This hypothesis was refuted by Waterstone, Parsons, and Bolton (1988) who noted that the supine position is not anatomically rational since the anteverted uterus becomes vertical, which makes its contents more prone to the action of gravity such that bed rest might be detrimental to ET success.

There are consistent data to connect anxiety and stress levels with implantation failure and abortion (Porcu-Buisson *et al.*, 2007; Turner *et al.*, 2013). Different authors (Amarin & Obeidat, 2004; Gaikwad *et al.*, 2013; Li *et al.*, 2011) mention the negative association between bed rest following ET and reduced success rates speculating on the increasing levels of anxiety and depression as the IVF treatment cycle progresses (Yong, Martin, & Thong, 2000).

None of the RCTs included in the present study reported on the stress markers prior, during or post ET. Further research should focus on the mechanisms through which bed rest could negatively influence impact on success rates following ET. In addition, an analysis of the costs involved with prolonged bed rest for inpatients or outpatients, especially in the absence of a direct benefit, should be conducted.

Disclosure statement

Authors do not have conflicts of interest.

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