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REVIEW

Bed rest after an embryo transfer: a systematic review and meta-analysis

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Abstract

Introduction Bed rest for the variable duration is commonly recommended after an embryo transfer (ET) carried out during an in vitro fertilization (IVF). This is based on beliefs that supine position and the reduction of physical activity—to the minimum—might prevent the risk of embryo expulsion once is transferred to the uterus. Therefore, we have designed a meta-analysis based exclusively on evidence from published randomized controlled trials (RCTs), in the attempt to analyze the effectiveness of bed rest after an ET to improve the chance for success in vitro fertilization.

Methods The review protocol was registered in PROSPERO (CRD42019122758), and data extraction started before protocol publication. Five RCTs were included; 499 women were assigned to the intervention group and 503 to the control group.

Results The analysis of 1002 women did not show any significant change in clinical pregnancy rate between groups [RR 0.86, 95% CI (0.74–1.00), $p=0.06$, $I^2=0\%$]. Likewise, no difference was found in live birth [RR 0.93, 95% CI (0.51–1.69) $p=0.81$, $I^2=68\%$], ongoing pregnancy rate [RR 0.84, 95% CI (0.60–1.20), $p=0.34$, $I^2=63\%$], miscarriage rate [RR 1.08, 95% CI (0.46–2.57), $p=0.86$, $I^2=64\%$], multiple pregnancy rate [RR 0.08, 95% CI (0.50–1.04), $p=0.71$, $I^2=0\%$] or implantation rate [RR 0.90, 95% CI (0.72–1.13), $p=0.38$, $I^2=0\%$]. Subgroup analyses—considering only immediate mobilization or bed rest 24 h—did not show significant differences regarding the outcome.

Conclusion Our findings showed that immediate mobilization after an ET does not have a negative influence over the success rates of IVF. Therefore, bed rest should not be recommended.

Keywords Bed rest · Embryo transfer · Clinical pregnancy rate · Ongoing pregnancy · Miscarriage

Introduction

In 2018, we commemorated the 40th birthday of the first baby who was born after an IVF treatment. Since the first successful IVF cycle, medical science has been developing several novel approaches such as ovulation induction, oocyte retrieval, and advanced laboratory techniques to achieve maximal success rates in artificial reproductive technology (ART). Nevertheless, although there are constant improvements in IVF protocols and procedures, the scientific community is still struggling with some simple common concepts. For example, one of them is the bed rest (BR) after an embryo transfer (ET). BR following an ET is usually recommended in the early days of IVF as it prevents the possible embryo expulsion [1]. In that same mindset, it has also been hypothesized that bed rest could decrease the rate of expulsion after an ET by reducing uterine contractile activity. Consequently, most IVF clinics around the world routinely recommend a variable period of BR after an ET without any scientific evidence about its benefits [2]. At the patient level, despite factual information about its effectiveness in implantation success rates, many patients still perceive BR beneficial for embryo implantation. Consequently, most of them limit their daily activities following an ET [3]. From a psychological point of view, success rate of IVF

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is influenced by a number of factors such as anxiety and depression [4]. On the other hand, extended periods of rest by fertility clinics or by patients perception, increase the psychological stress of the couple. So, procedures simplification can diminish this overall stress and improve patients' experience during ART [5]. Furthermore, it has been speculated that, with immediate return to routine daily activities, there is a decrease in maternal stress following embryo transfer [6].

Moreover, many authors in independent studies confirmed that BR does not improve IVF outcomes [7, 8]. So, the scientific community should be in a shared commitment to unhinge false myths and pursue evidence-based medicine by eliminating unnecessary procedures which have not been proven to be beneficial for the couples seeking fertility treatment.

The aim of our systematic review and meta-analysis was to evaluate the effectiveness of bed rest protocols, and then evaluate if the immediate mobilization after an embryo transfer could reduce IVF outcomes.

Methods

Study design

This is a systematic review and meta-analysis of randomized controlled trials (RCTs) evaluating the effectiveness of bed rest after an embryo transfer in IVF patients. The study protocol was registered in PROSPERO after the literature search with the number CRD42019122758. The review was written following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9].

Search strategy

Electronic databases (MEDLINE, Scopus, EMBASE, Science Direct, and The Cochrane Database of Systematic Reviews, and ClinicalTrials.gov) were searched from their inception until April 2019. The search strategy for medical subject headings (MeSH) were the following terms: "bed rest" OR "in vitro fertilization" AND "embryo transfer" OR "intracytoplasmic sperm injection" OR "embryo transplantation" AND "randomized controlled trials" AND "immediate mobilization".

Inclusion criteria

On one side, only randomized controlled trials including infertile women undergoing IVF/ICSI cycle with bed rest after an embryo transfer were selected for this systematic review and meta-analysis. On the other, the control group was composed of infertile women undergoing embryo transfer without bed rest or early bed rest.

Study outcomes

The primary outcome was the clinical pregnancy rate whenever it was available. Additionally, secondary outcomes also included: live birth rate, implantation rate, ongoing pregnancy rate, miscarriage rate, and multiple pregnancy rate.

Outcomes measures and definitions

Clinical pregnancy rate (per woman [CPR]): was defined as the presence of a gestational sac on transvaginal ultrasound.

Live birth rate (per woman [LBR]): was defined as the delivery of one or more living and viable infants.

Ongoing pregnancy rate (per woman [OPR]): was defined as a pregnancy beyond 12 weeks gestation.

Multiple pregnancy rate (per clinical pregnancy [MPR]): was defined as the presence of more than one gestational sac on transvaginal ultrasound.

Miscarriage rate (per woman [MR]): was defined as fetal loss prior to the 20th week of gestation.

Implantation rate: was defined as the number of gestational sacs observed on vaginal ultrasound 5–6 weeks after embryo transfer divided by the number of transferred embryos.

Study selection and data extraction

Titles and abstracts were screened independently by two authors (MC, GT). These same authors independently assessed studies for inclusion and extracted data on study features (design, country, and time of the study), populations (number and characteristics of the participants), type of intervention, and IVF outcomes. Afterwards, a manual search of references within the included studies was also performed to avoid missing any relevant data. Disagreements concerning the extracted data were resolved by *consensus.* Furthermore, a third reviewer (EE) was consulted when necessary. RCTs selected for meta-analysis were fully read by all authors.

Assessment of risk of bias

Both authors (MC, GT) independently assessed the methodological quality of included studies using the criteria outlined in Cochrane Handbook for Systematic Reviews

of Interventions [10]. In addition, seven specific domains related to the risk of bias were assessed: *random sequence generation*, *allocation concealment*, *blinding of participants and personnel*, *blinding of outcome assessment*, *incomplete outcome data*, *selective data reporting*, and *other bias*. Authors' judgments were expressed as "low", "high", or "unclear" risk of bias. On this matter, for the estimation of "selective data reporting", we evaluated study protocols when available. Moreover, when those were not available, studies were judged as unclear risk of bias. Ultimately, results were compared and disagreements were resolved by consensus.

Statistical analysis

Data analysis was performed by two authors (MC, GT) using the Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, London). All the design, interpretation of data, drafting and revisions followed Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The significance level was set as $p < 0.05$. To evaluate heterogeneity, Higgins heterogeneity test or I^2 test was used. The value of I^2 describes the percentage of variability due to heterogeneity rather than a simple sampling error. In fact, I^2 is not affected by the small number of samples. With this test, heterogeneity is considered as "low" when I^2 value is less than 30%, as "moderate" if between 30 and 50%, as "high" if higher than 50%. Therefore, when heterogeneity is described by an I^2 above 30%, it was decided to report models with both "fixed" and "random" effects to highlight the role of heterogeneity between studies. The difference between both models consists of excluding or including heterogeneity in the calculation of the overall estimate: one with fixed effects excludes any heterogeneity; while the random-effects model includes it. Therefore, the overall estimate will have wider confidence intervals. In the case of low heterogeneity, both models give very similar results. Hence, it was agreed to present the results only with random effects because it would be a more conservative way.

Results

Study selection

After evaluating the full selected texts, three studies were excluded. In total, five studies [2, 11–14] were included in the present meta-analysis (Fig. 1). All five trials included a total number of 1002 participants; the summary of the main characteristics of the included studies is available in Table 1. All studies were single-center trials. Only one out of the five was blinded [2, 11, 13, 14]. In one study, the physicians, the staff, embryologists and the statistician were blinded for the randomizing patient groups [12].

Type of patients and intervention

All the studies included exclusively infertile patients undergoing embryo transfer following an IVF cycle [1, 8–10]. Two studies compared a 24 h period of bed rest to a 20 min period of bed rest following an ET [11, 14]; one studied 24 h versus a 1 h of bed rest after an ET [2]; another one compared 30 min of bed rest versus immediate discharge from the clinic following an ET [13]; and the last study compared results of 10 min of bed rest versus immediate ambulation after an ET [12].

Assessment of the risk of study bias

Selection bias: three studies [2, 12, 13] used an adequate method of random sequence generation (computer-generated sequence). The other two did not provide clear information on random sequence generation [11, 14]. In the same studies [11, 14], the method of allocation was not reported (so then, unclear risk of bias) and remaining studies used an adequate allocation strategy [2, 12, 13].

Performance bias: all studies, except one [12], were not blinded either for personnel or participants. Nevertheless, four studies were judged to have a high risk of bias [2, 11, 13, 14].

Detection bias: the outcomes evaluated were unlikely to be influenced by open-label design in the majority of studies. Nevertheless, all studies were judged to have a low risk of bias.

Attrition bias: drop-out of a few participants occurred in one study [13]. However, it was judged as insubstantial according to Cochrane Handbook Recommendations ("a drop-out not exceeding 20% should not lead to substantial bias").

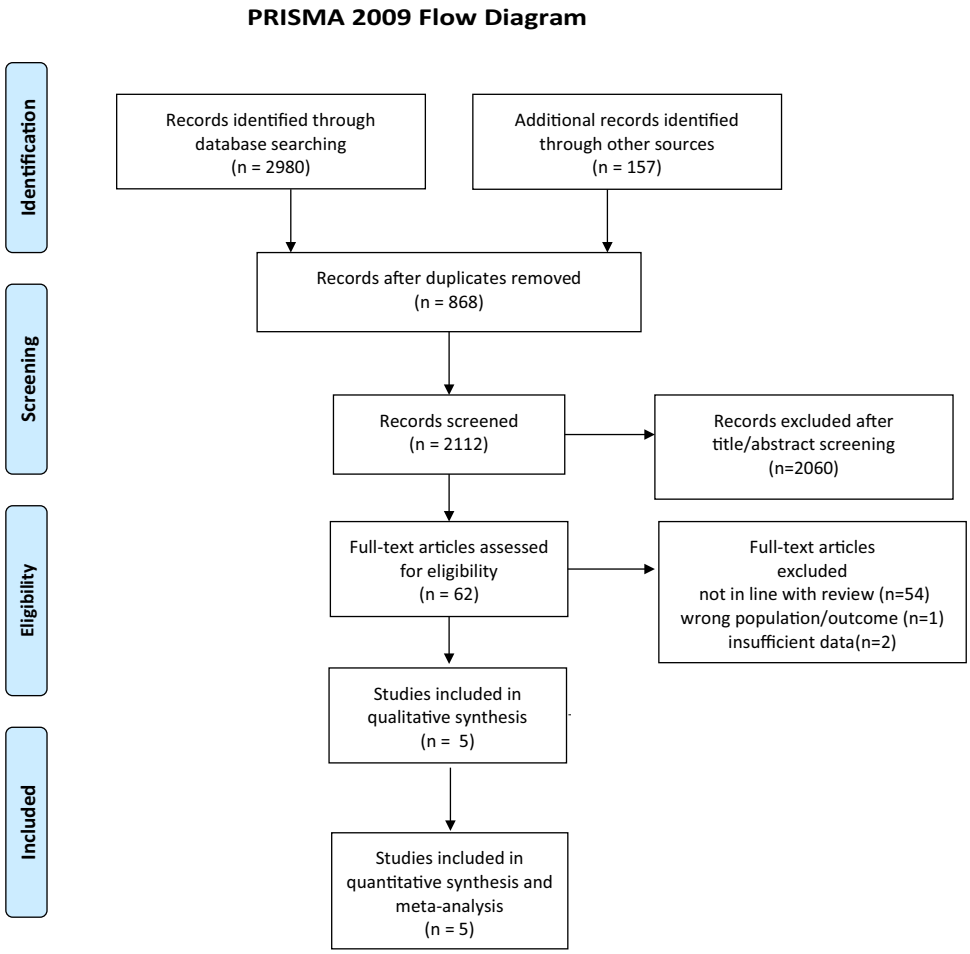
Reporting bias: all studies were considered to have a high risk of bias because their protocol registration references were not available [2, 10–13]

Other bias: all studies were considered to have a low risk of other bias (see Fig. S1).

Primary analysis

A total number of 1002 participants ($n = 499$ in intervention Group and $n = 503$ in the control Group) from five studies were evaluated.

Fig. 1 PRISMA flow diagram



Clinical pregnancy: all RCTs included in this meta-analysis reported clinical pregnancy RR as 0.86, 95% CI (0.74–1.00), $p=0.06$, $I^2=0\%$, using the random-effects model. Therefore, it can be concluded to be similar in the experimental group and the control group (Fig. 2).

Live birth: the meta-analysis conducted on two studies reported live birth rate demonstrated RR to be 0.93, 95% CI (0.51–1.69), $p=0.81$, $I^2=68\%$, using the random-effects model. This means that bed rest is not a statistically significant variable on live birth (Fig. 3).

Implantation rate: the meta-analysis conducted on three of the studies that reported implantation rate demonstrated RR to be 0.90, 95% CI (0.72–1.13), $p=0.38$, $I^2=0\%$, by using the random-effects model. This means bed rest is not a statistically significant variable on implantation rate (Fig. 4).

Ongoing pregnancy: using the random-effects model, the meta-analysis conducted on four studies that reported this data shows that bed rest is not a statistically significant variable on ongoing pregnancies, RR 0.84,95% CI (0.66–1.20), $p=0.34$, $I^2=63\%$ (Fig. 5).

Multiple pregnancies: the intervention was not associated with a significant improvement in twin pregnancies in the meta-analysis conducted on four studies. Using the random-effects model, the results were RR 0.73, 95% CI (0.51–1.06), $p=0.10$, $I^2=0\%$ (Fig. 6).

Miscarriages: the meta-analysis conducted on three studies that reported this data shows, using the random-effects model, that bed rest is not a statistically significant variable in miscarriages rates, RR 1.08, 95% CI (0.46–2.57), $p=0.86$, $I^2=64\%$ (Fig. 7).

Meanwhile, the subgroup analyzes on the immediate mobilization did not show such statistically difference between outcomes, clinical pregnancy rate RR 0.87, 95% CI (0.71–1.07), $p=0.26$, $I^2=21\%$, ongoing pregnancy rate RR 0.79, 95% CI (0.50–1.20), $p=0.09$, $I^2=76\%$, implantation rate RR 0.98, 95% CI (0.76–1.25), $p=0.47$, $I^2=0\%$, twin pregnancy rate RR 0.76, 95% CI (0.51–1.13), $p=0.98$, $I^2=0\%$; live birth rate and miscarriage rate could not be analyzed. The subgroup analyzes—on 24 h bed rest—did not show any significant results for all outcomes that were analyzed. Clinical pregnancy rate RR 0.72, 95% CI (0.41–1.25), $p=0.24$, $I^2=31\%$, ongoing pregnancy rate RR 1.05, 95% CI

Table 1 General features of the studies evaluated in this systematic review and meta-analysis

References	Study design	Participants	Indication	Causes of infertility	Intervention and timing	Main outcomes
Botta and Grudzinskas [11]	Randomized controlled trial	Total 182 (87/95)	Infertile patients undergoing IVF embryo transfer	Ovulatory dysfunction Tubal disease Unexplained Male factor	20 min of bed rest or 24 h of bed rest following embryo transfer	Clinical pregnancy rate Miscarriages rate Twin pregnancies rate
Rezábek et al. [14]	Randomized controlled trial	Total 38 (20/18)	Infertile patients undergoing IVF embryo transfer	Ovulatory dysfunction Tubal disease Unexplained Male factor	20 min or 24 h following embryo transfer	Clinical pregnancy Implantation rate Embryos quality
Amarin and Obeidat [2]	Randomized controlled trial	Total 378 (192/186)	Infertile patients undergoing IVF embryo transfer	Oligomenorrhoea Endometriosis Tubal disease Uterine factor Male factor Unexplained	1 or 24 h bed rest following embryo transfer	Clinical pregnancy Implantation rate Miscarriages rate Twin pregnancies rate
Purcell et al. [13]	Randomized controlled trial	Total 164 (82/82)	Infertile patients undergoing IVF embryo transfer	Male factor Unexplained Endometriosis Ovulatory dysfunction Diminished ovarian reserve Tubal factor Uterine	30 min of bed rest after embryo transfer or immediate discharge after embryo transfer	Clinical pregnancy rate Ongoing pregnancy rate
Gaikwad et al. [12]	Randomized controlled trial Double blind	Total 240 (120/120)	Infertile patients undergoing IVF embryo transfer	Male factor Unexplained Endometriosis Ovulatory dysfunction Diminished ovarian reserve Tubal factor Uterine	10 min of bed rest after embryo transfer or patients to ambulate immediately after embryo transfer	β-hCG positive test Implantation rate Live birth Multiple pregnancies Ectopic pregnancy Miscarriage

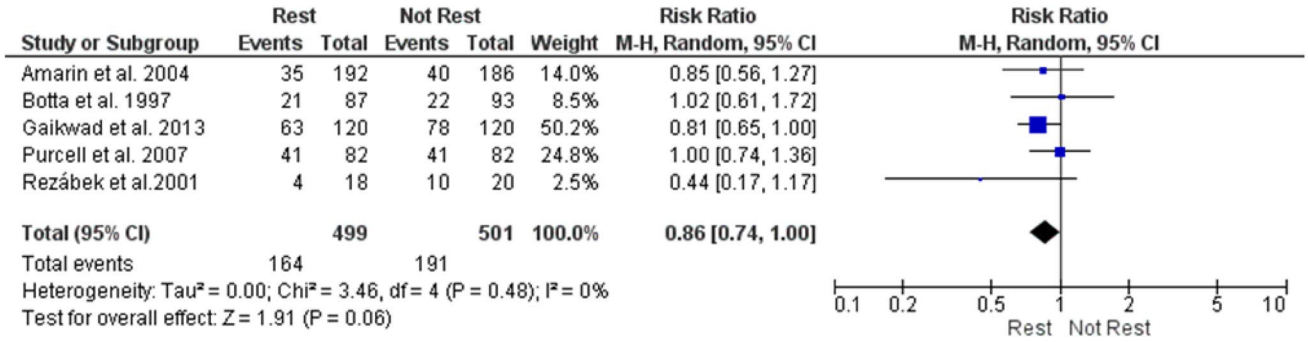
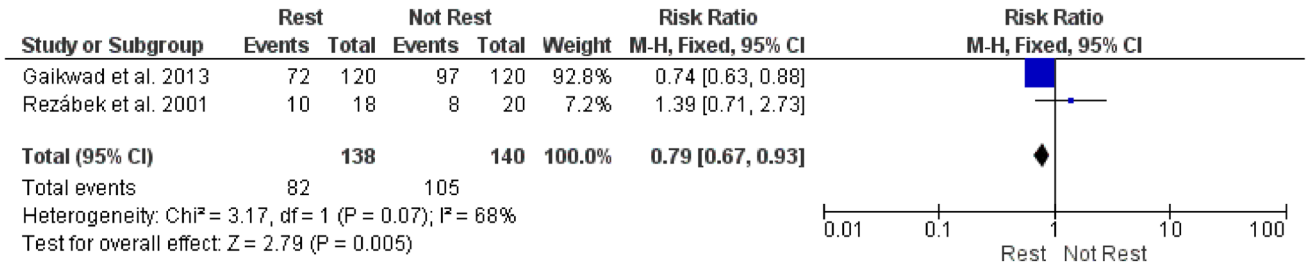


Fig. 2 Clinical pregnancy rate with intervention (bed rest) and control



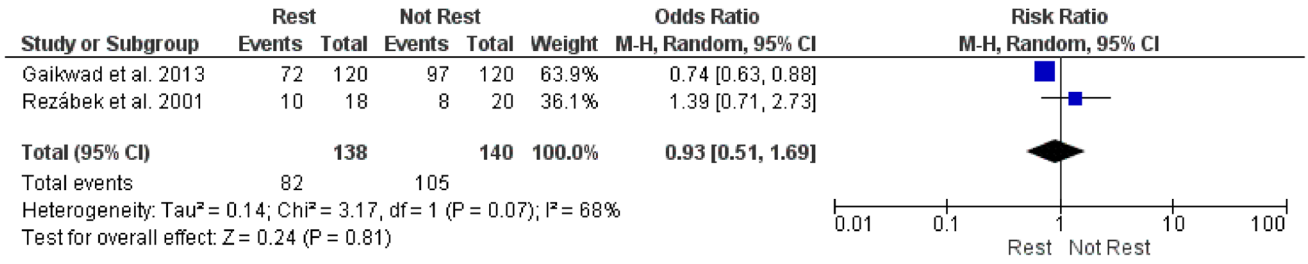


Fig. 3 Live birth rate with intervention (bed rest) and control

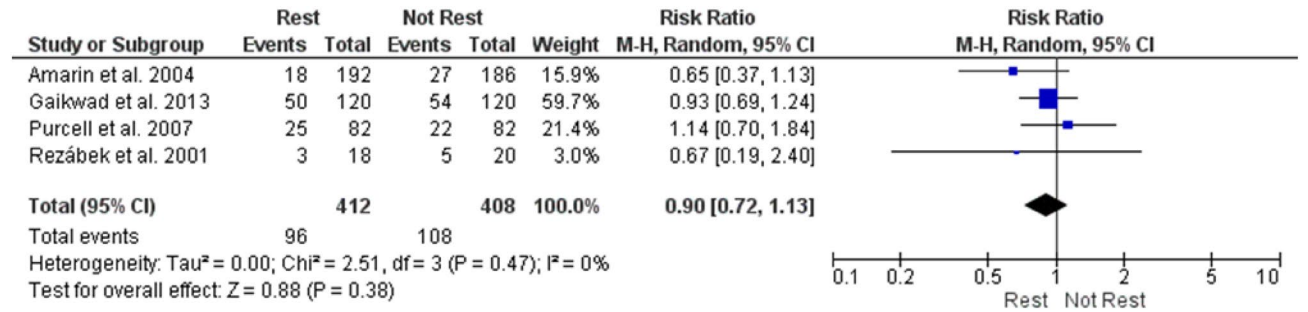


Fig. 4 Implantation rate with intervention (bed rest) and control

(0.72–1.05), $p = 0.81$, $I^2 = 0\%$, implantation rate RR 0.65, 95% CI (0.39–1.09), $p = 0.10$, $I^2 = 0\%$, twin pregnancy rate RR 0.58, 95% CI (0.20–1.67), $p = 0.31$, $I^2 = 10\%$; live birth rate could not be analyzed.

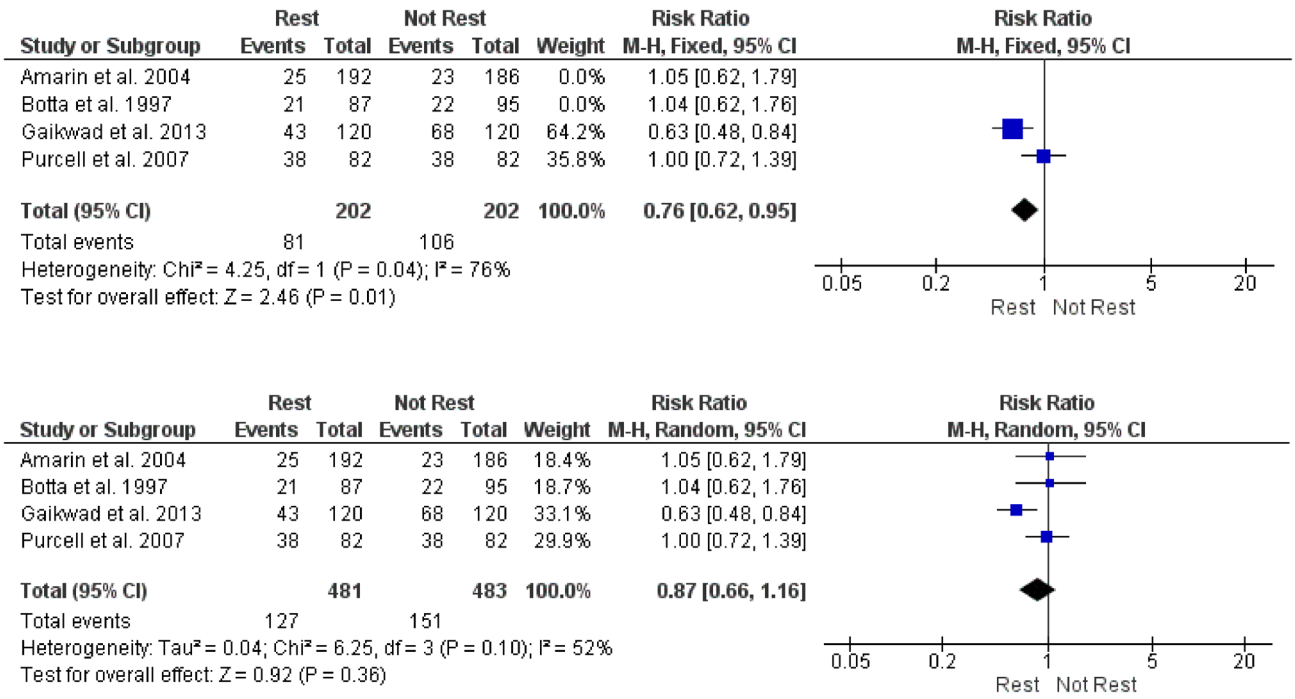


Fig. 5 Ongoing pregnancy rate with intervention (bed rest) and control

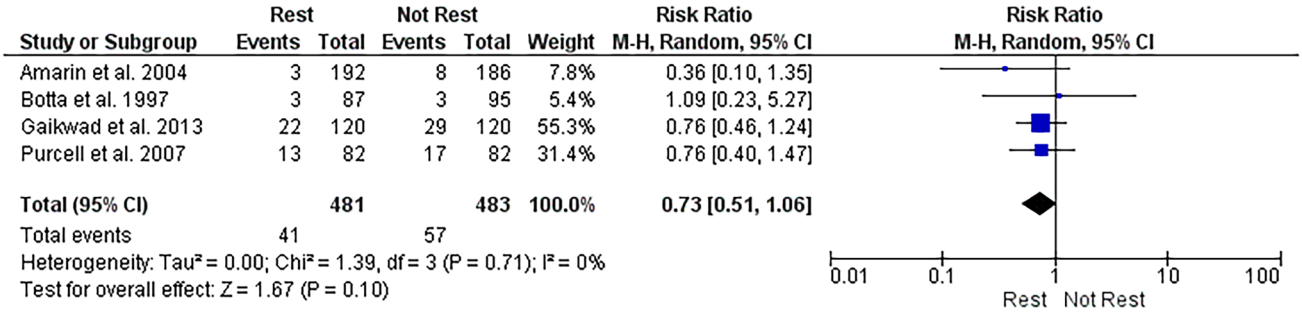


Fig. 6 Multiple pregnancy rate with intervention (bed rest) and control

Discussion

In previous years, enormous efforts have been made in conducting thorough, detailed, and novel studies to improve ET techniques: the analysis of catheter's characteristics, the use of ultrasound imaging during a embryo transfer, the accurate positioning of the catheter, the implication of washing uterine neck, the use of a fibrin sealant, the amount of medium needed for embryo transfer, and the bed rest after an ET [15–18]. However, at present, there is still no evidence to support a certain guideline for routine bed rest for women following an ET.

BR for the variable duration is commonly recommended after an ET following an IVF. This is based on the belief that supine position, with consequent reduction of physical activity, could prevent the risk of embryo expulsion once transferred to the uterus [17]. However, the scientific basis for this practice remains undetermined. Our results show that bed rest at any period is not associated with better outcomes following an IVF. Thus, BR did not improve the clinical pregnancy rate or live birth rate. In addition, it has no effect on the implantation rate, ongoing pregnancy rate, multiple pregnancy rate, and miscarriages rate.

For a long time, more IVF clinics had adopted the practice of bed rest after an ET following the idea that it would increase pregnancy outcome rates [7]. The conclusions by Waterstone et al. showed that uterine cavity is more horizontal when a woman is in the upright position than when she is lying down; therefore, with a uterus

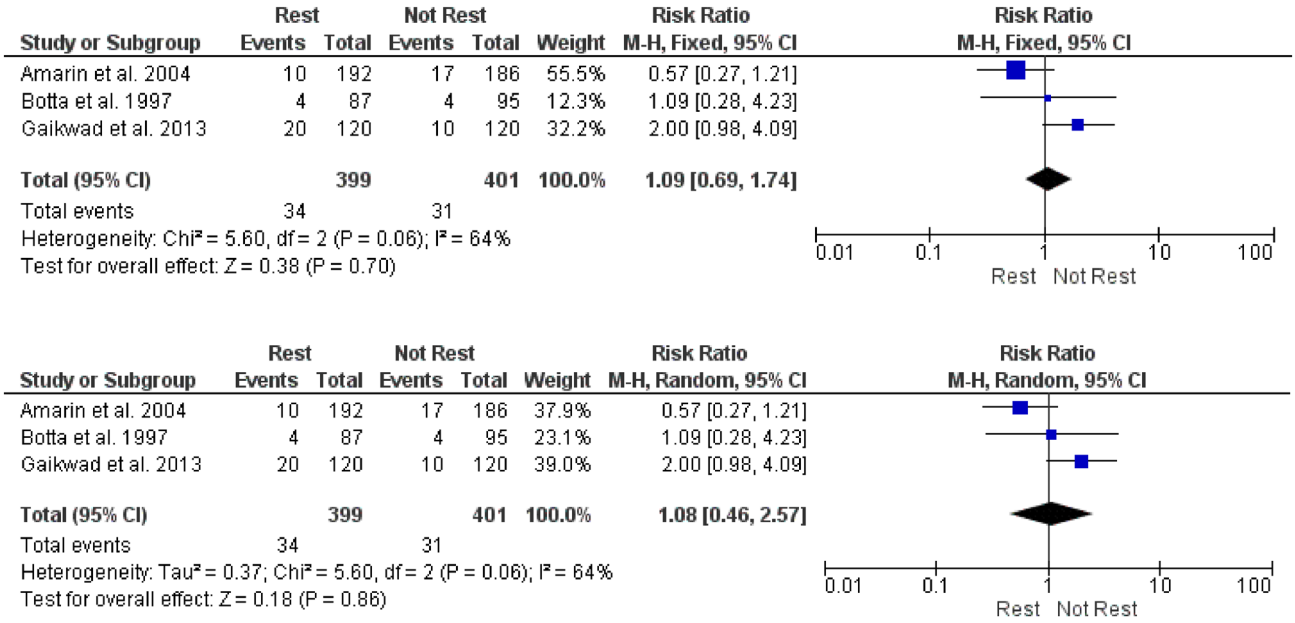


Fig. 7 Miscarriages rate with intervention (bed rest) and control

in physiological position and in absence of an expanded bladder, BR after an ET would be ineffective. In addition, assuming that gravity does not cause loss of transferred embryos, the authors concluded that a supine post-ET position is not necessary [19]. To date, no evidence has been presented to demonstrate that mobilization after an ET can adversely affect pregnancy rates. On the contrary, in 1998, the first cohort-control study was conducted in the United Kingdom to evaluate the effect of lack of bed rest after an ET on IVF results. In this study, 1019 IVF cycles without BR were compared to 19,697 IVF cycles in which BR was enforced after an ET. In conclusion, a better pregnancy rate than the national data (23.5% vs. 18.6%) was obtained, suggesting that bed rest is not necessary [8]. Moreover, Lambers et al. investigated changes in air bubble location under serial ultrasound images and compared patients with bed rest to patients with immediate ambulation after embryo transfer. They concluded that the location of air bubbles is not influenced by immediate ambulation directly after the transfer hence confirmed that BR after an ET is unnecessary [20].

In a study by Rezabek et al. [14], patients in immediate ambulation group were permitted to go home immediately following an ET, and patients in the intervention group were discharged after one night of bed rest at the hospital post ET. No significant differences were present in the age, stimulation protocol, number of previous ART cycles or number of embryos transferred between the participants of two groups. None of the outcomes assessed—by the study—changed significantly; consequently, the authors concluded that immediate ambulation is safe after an embryo transfer.

In another recent study, Gaikwad et al. [12] showed that there were no statistically significant differences in IVF outcomes between patients who had 10 min of bed rest after an ET and patients who ambulated immediately following the procedure. This result was in line with Purcell et al. claims [13]. These two results are essential in assessing the role of bed rest as they used no bed rest as a control group while other studies were comparing results of bed rest for varying periods ranging between 20 min and up to 1 h.

Furthermore, another issue that has to be addressed is the difference between BR after IVF and BR after intrauterine insemination (IUI). Assuming that it may provoke a loss of the content after IUI procedure, Custers et al. [21] proposed that 15 min of bed rest improves ongoing pregnancy rates significantly compared to immediate mobilization. Although, in a recent meta-analysis the authors concluded that bed rest after intrauterine insemination did not increase pregnancy rate [22]. However, there is a substantial difference between a large amount of volume transferred during IUI and a very small volume of fluid placed into the uterus during ET. In addition, an embryo has a greater mass compared to individual spermatozoon, which leads to a decrease in the risk of expulsion of embryos from the uterus when compared to spermatozoon [23].

Another aspect that should not be neglected is the psychological effect of restriction of ambulation after embryo transfer. Compared to the fertile population, negative psycho-emotional experiences are more prevalent in the infertile population, and it is so before, during, and after the treatment [24]. Restriction of ambulation can lead to additional stress and anxiety in this group. Long periods of

stress and anxiety have been associated with changes in biological homeostasis such as the increase T cell activation in peripheral blood [25]. It has been shown that the increase of baseline stress levels has an effect on reproductive outcomes such as the number of oocytes retrieved and fertilized, the pregnancy success, the rate of delivery of a newborn and the birth weight [26, 27]. In addition, stress could play a strong role in implantation failure and miscarriage [26, 28]. In a prospective observational study, α-amylase's levels in saliva, a biological marker of stress were measured before and after the ET. The authors demonstrated that the ET was experienced as a highly stressful moment as levels of α-amylase were significantly higher following an ET [25]. However, it is important to note that the perceived stress of an ET did not reduce pregnancy rate or increase miscarriage in these patients [27]. Our goal should be to reduce the stress level experienced by patients during or following an ET as much as possible.

In addition, to assess the ineffectiveness of any procedure, its cost/effectiveness should always be evaluated. Goldenberg et al. [29] have speculated that rest is perceived as inexpensive and non-invasive, and it seems reasonable. However, variable periods of BR entail a certain cost and strain on space in busy IVF clinics. Therefore, many infertility centers find themselves with a reduction in their resources such as bed availability in a daily basis; so, interventions should be assessed in terms of their effectiveness along with their risk/benefit and cost/benefit ratios.

Physicians should be up-to-date with effective interventions and refrain from recommending bed rest [30]. Moreover, as already mentioned, patients perceive that bed rest can improve their chances of implantation. Therefore, healthcare workers play a key role in educating their patients and debulking false beliefs.

The main difference, with the previous meta-analysis, was that it was possible to analyze the live birth rate for the first time [31]. Although our meta-analysis was in agreement with Craciunas et al.—in the sense that bed rest following an ET did not improve clinical pregnancy—it also suggests that the bed rest did not affect the implantation rate [31]. Subgroup analysis based on the duration of bed rest was performed to address methodological differences between the studies. The subgroup analysis of this meta-analysis allows us to underline how the immediate mobilization does not affect the outcomes of the IVF.

However, there are some limitations to the study that we need to be aware of. First of all, some RCTs have relatively few women. Second, only two studies considered the live birth rate; for this reason, as secondary outcome. Finally, there were significant differences in the criteria for inclusion and exclusion among included RCTs.

In conclusion, this systematic review and the meta-analysis suggest that bed rest following an ET is not beneficial in terms of clinical pregnancy rate, live birth rate, ongoing pregnancy rate, implantation rate, or miscarriages rate. Our conclusions support the idea that immediate mobilization after an ET would not negatively influence success rates following an ET. This is the first meta-analysis that allows analysing the live birth rate, showing that bed rest does not improve IVF outcomes. Healthcare professionals have a key role here in providing patients with correct information about the ineffectiveness of bed rest after an ET. As a future implication, further studies could be conducted to analyze the financial burden and cost-effectiveness of prolonged bed rest.

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Author contributions MC designed the study, performed the literature search, defined inclusion criteria and selected studies for inclusion, participated in data extraction, performed the risk of bias assessment, performed the statistical analysis, and wrote the first and final drafts of the manuscript; GT performed the literature search, selected studies for inclusion, participated in the statistical analysis, EE critically revised the manuscript, participated in assessing the risk of bias within studies and the grading of evidence.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest. The completedisclosure form is available to view online as supportinginformation.

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