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Kay Neumann M.D. , Georg Griesinger M.D.

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# Is the administration of an oxytocin receptor antagonist around the time of embryo transfer associated with in-vitro fertilization treatment success? A systematic review and meta-analysis

*Kay Neumann, M.D.*[1,2], *Georg Griesinger, M.D.*[1]

[1]Department of Gynaecological Endocrinology and Reproductive Medicine, University Hospital of Schleswig-Holstein, Campus Luebeck, Luebeck, Germany

[2]**Correspondence**

Kay Neumann, MD

Kinderwunsch Praxisklinik Fleetinsel Hamburg

Admiralitätstraße 4

20459 Hamburg, Germany

tel: +49 40 38605553

e-mail: neumann@kinderwunschfleetinsel.de

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oxytocin receptor antagonist, atosiban, nolasiban, barusiban, vitro fertilization, uterine contractions

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**Abstract**

To evaluate whether the administration of an oxytocin receptor antagonist around embryo transfer is associated with live birth and pregnancy achievement in IVF treatment a systematic literature review and meta-analysis was conducted. Multiple databases were searched for randomized controlled trials comparing the outcome of IVF treatment with administration of an oxytocin receptor antagonist before, during or after embryo transfer versus administration of placebo/*nil*. The literature search identified n=11 eligible randomized trials. The active compound was intravenous atosiban (n=7), subcutaneous barusiban (n=1) and oral nolasiban (n=3). Live birth rate was higher, albeit not statistically significant, in women receiving an oxytocin receptor antagonist around embryo transfer (relative risk: 1.09, 95%CI: 0.98-1.20, p=0.11, $I^2$=25%, n=5 studies, n=2,765), while clinical pregnancy rate was significantly higher (relative risk: 1.31, 95% CI: 1.13-1.51, p=0.0002, $I^2$=61%, n=11 studies, n=3,611). A sensitivity analysis on low risk of bias studies likewise indicates a higher pregnancy chance (relative risk: 1.11, 95% CI: 1.01 - 1.22, p=0.03, $I^2$=5%, n=5 RCTs, n=2.765) while the increase in live birth rate does not reach statistical significance. Oxytocin receptor antagonist administration in IVF treatment has the potential to increase IVF efficacy, though the so-far observed treatment effects are small and have not sufficiently been corroborated.

## Introduction

Despite significant improvements and standardization of IVF treatment regimen in the last decades, the success rate has remained stable at a likelihood of live birth per IVF treatment cycle of approximately 25-30% (CDC 2016, Luke *et al.,* 2012, Toftager *et al.,* 2017). New technologies are therefore constantly proposed to improve IVF treatment outcomes (Harper *et al.,* 2017). The list of currently offered, presumably beneficial adjuncts is long and includes pharmacological add-ons (dehydro-epiandrostenedione, growth hormones, testosterone, Coenzyme Q 10, heparin, low-dose aspirin, vasodilators, myo-inositol, *etc*.), laboratory technology (sperm DNA fragmentation testing, sperm selection procedures, time-lapse embryo monitoring, preimplantation genetic testing, assisted hatching, endometrial injury or embryo adherence compounds, *etc.*) and others such as life-style interventions or acupuncture. Since failure of embryonic implantation is the most frequent cause of IVF failure, maternal mechanisms around embryo attachment and invasion have attained great interest.

Uterine contractions have been described to negatively correlate with the likelihood of embryonic implantation (Fanchin *et al.,* 1998, Zhu *et al.,* 2014). Additionally, endometrial blood flow was postulated to be a positive predictor for endometrial receptivity. In the myometrium, endometrium and in blood vessels of the uterus, oxytocin receptors have been shown to be expressed around the time of implantation (Kim *et al.,* 2014). Blocking of oxytocin receptors was found to decrease uterine contractility and increase endometrial perfusion (Pierzynski *et al.*, 2007, Pierzynski 2011, Kalmantis *et al.*, 2012). Additionally, evidence for increased endometrial receptivity and decidualization after oxytocin receptor antagonist administration was reported by previous studies (Sztachelska *et al.,* 2019). Recent investigations reported an altered gene expression profile favourable for embryo implantation following administration of an OTR-a (Pierzyński *et al.,* 2021). A previous clinical study showing an increased likelihood for embryo implantation for patients having an OTR-a administered irrespective of the frequency of uterine contractions points towards a potential clinical significance of these effects (Lan *et al.,* 2012).

Accordingly, it has been hypothesized that antagonism of oxytocin receptors around embryo transfer may have the potential to increase the likelihood of an implantation of an embryo.

The drug atosiban is a peptide functioning as mixed OTR-a and vasopressin receptor antagonist. It is approved for use in pregnancy to delay imminent preterm birth. Atosiban administration, however, is rather challenging in an IVF treatment due to its short half-life (t1/2) of 13 minutes necessitating intravenous administration. The utilization of atosiban around embryo transfer has been reported for the first time in the literature within a case report on an implantation failure patient (Pierzynski *et al.*, 2007) and has later been investigated by a number of clinical studies. A systematic review and meta-analysis including four RCTs and two observational studies suggested an association of atosiban administration with improved IVF-outcomes (Schwarze *et al.,* 2020). As an alternative to atosiban, the OTR-a barusiban has been developed for subcutaneous administration (Bosch *et al.,* 2019). Barusiban is a peptide with a longer half-life of eight hours and higher selectivity for oxytocin-receptors. While found ineffective for the indication of preterm birth delay (Reinheimer *et al.,* 2005), some preliminary data on barusiban administration in IVF treatment have been released recently. A further OTR-a is the orally active compound nolasiban (Kim *et al.,* 2017). Nolasiban is a non-peptide and shows a higher specificity for oxytocin receptors and has a longer t1/2 of up to two days compared to atosiban. Recently the use of nolasiban has been investigated in a large phase II/III trial program. The present systematic literature review and meta-analysis collates the existing evidence from randomized trials (RCTs) on the use of all drugs functioning as OTR-a in the context of improving IVF treatment outcome.

## Material and Methods

This systematic review was prospectively registered at PROSPERO (ID CRD42021227919). An electronic was performed in the databases PubMed, EMBASE, Web of Science, Google Scholar, Cochrane Library and ClinicalTrial.gov. No restrictions for language or on timeframe were applied.

The literature search aimed at identifying RCTs from which comparative data on clinical outcomes after application of an OTR-a versus placebo or *nil* in IVF patients were retrieved. The computerized literature search was performed using various combinations of involved terminology and key words and was completed on the 12$^{th}$ of February 2021 (supplemental *Appendix* a).

### Selection criteria

Randomized clinical trials (i.e. trials having a control group and a random allocation to either group) in IVF patients utilizing an OTR-a around embryo transfer were considered for inclusion in this systematic review. There were no exclusion criteria regarding specific drugs, patient number, route of drug administration, patient population or stage/quality of transferred embryos. Two review authors (KN, GG) independently scanned titles and abstracts identified from the searches. Potentially relevant trials were selected and independently assessed for inclusion into this review.



### Criteria for considering studies for this review

### Types of included studies

Randomized controlled trials (RCTs) were included in the review. Non randomized studies were excluded from the review. Studies in which one subject could contribute more than once treatment cycle (for example cross-over study designs) were considered for exclusion.

### Types of participants and treatment cycles

Subfertile women undergoing IVF or ICSI for treatment of infertility who were randomly assigned to receive an OTR-a or placebo/*nil* shortly before, during or after embryo transfer.

Women who were not undergoing IVF or ICSI (i.e. those undergoing intrauterine insemination) were not included.

**Types of interventions**

OTR-a in comparison with placebo or *nil* administered around embryo transfer with or without luteal phase support, in autologous or donor cycles, in fresh or frozen embryo transfer cycles.

**Types of outcome measures**

Primary outcomes

Live birth rate and clinical pregnancy rate per intention-to-treat analysis (Duffy *et al.,* 2021).

**Secondary outcomes**

Ongoing pregnancy rate per intention-to-treat analysis; Miscarriage rate per intention-to-treat analysis; Multiple pregnancy per intention-to-treat analysis; Ectopic pregnancy per intention-to-treat analysis; Implantation rate is not an outcome of the present meta-analysis as methodological issues are associated with its use (Griesinger 2016, Harbin Consensus Conference Workshop Group, 2014).

**Subgroup and sensitivity analyses**

**Subgroup: by compound**

A subgroup analysis was planned for type of investigated compound.

**Sensitivity: by randomization (true, with allocation concealment versus pseudo-randomized or unclear and unclear allocation concealment)**

A sensitivity analysis was planned by excluding trials with a high-risk of bias in any of the domains of the grading table (Table 2).

**Data extraction and analysis**

Features of studies and results were assembled in tabular form and a formal meta-analysis was conducted. For each study the dichotomous data results were expressed as a relative risk (RR) with a 95% confidence interval (CI). For meta-analysis, these results were combined with the software Review Manager (RevMan) Version 5.4.1, The Cochrane Collaboration, 2020, using the Mantel/Haenszel method. Study-to-study variation was assessed by using the Cochrane Q test. For heterogeneity $I^2$ ≥40% a random-effect model was used and for values <40% a fixed-effect model was chosen based on considerations of the Cochrane Handbook (Cochrane Handbook for Systematic Reviews of Interventions).

## Results

### Literature search

Six registrations of RCTs were found by the electronic literature search at the databases clinicaltrials.gov and at the WHO trials registry platform. Five of these studies were described to investigate the compound atosiban, one study description did not specify the type of investigated OTR-a. Investigators of these studies were contacted for further information on the status of theses RCTs, however a response was received from none. Figure 1 depicts a flowchart of identified and included studies according to PRISMA guidelines (Moher *et al.,* 2009).

### Studies selected

Eleven studies fulfilled the inclusion criteria. One RCT (Ahn *et al.,* 2009) had to be partially translated to English. The studies of Song *et al.,* 2013 and Bosch *et al.,* 2019 were only published as an abstract and a poster at a conference, respectively, but no full text publication was available. Characteristics of all included RCTs are shown in Table 1.

Only five studies had the objective of testing for a difference in the likelihood of a live birth (Ng *et al.,* 2014, Bosch *et al.* 2019, Griesinger *et al*., 2021) and in all five trials the necessary sample size was determined *a-priori*. All included studies reported on the clinical pregnancy rate. In seven RCTs, the OTR-a atosiban, in three nolasiban and in one RCT barusiban was administered. Administration of the respective drug was performed before (nolasiban, atosiban (Hebisha *et al.,* 2018)) or before and after (barusiban) or before, during and after embryo transfer procedure (atosiban). In the control group, in eight trials a placebo and in two trials *nil* was administered. The trials were conducted between 2007 (Ahn *et al.,* 2009) and 2019 (Griesinger *et al.,* 2021).

### Grading of studies and publication bias

Only four out of the eleven included studies reported the chance of a live birth which was defined *a-priori*. Authors of the seven studies not reporting number of live births were contacted, however, further data could be retrieved for the study from Bosch *et al.,* 2019 only. All included studies investigated the likelihood of a clinical pregnancy per embryo transfer/intention-to-treat analysis. Adverse outcomes such as risk of a miscarriage, an ectopic pregnancy or the chance of a multiple pregnancy were reported by eight, five and seven RCTs, respectively. Authors of two studies were contacted for clarification of outcomes (Bosch *et al*., 2019, Moraloglu *et al.,* 2010), no response was received from Moraloglu *et al.,* 2010 which is why the data on miscarriages from that study could not be included into the meta-analysis.

Double-blinding was described by six studies (Bosch *et al.*, 2019, Griesinger *et al.*, 2021, Ng *et al.*, 2014, Yuan *et al.*, 2019) whereas two studies reported blinding of either staff (He *et al.,* 2016) or patients (Moraloglu *et al.,* 2010) and three studies did not provide information on blinding (Ahn *et al.,* 2009, Hebisha *et al.,* 2018, Song *et al.,* 2013). A bias stemming from absence of allocation concealment was avoided by two studies using sealed envelopes (He *et al.*, 2016, Ng *et al.*, 2014) and by five studies by a web response system/electronic case report form (Bosch *et al.,* 2019, Griesinger *et al.*, 2021, Yuan *et al.,* 2019,). Four studies (Ahn et *al.,* 2009, Hebisha *et al.,* 2018, Moraloglu *et al.,* 2010, Song *et al.,* 2013) did not report the presence of allocation concealment.

A valid randomization was performed by using computer generated sequences (Bosch *et al.* 2019, Griesinger *et al.*, 2021, Ng *et al.,* 2014, He *et al.*, 2016, Yuan *et al.,* 2019) or a quasi-randomization was performed according to weekday of patient entry (Moraloglu *et al.*, 2010) or no information on the generation of a random allocation of patients was provided (Ahn et *al.,* 2009, Hebisha *et al.,* 2018, Song *et al.,* 2013). Grading of studies is depicted in Table 2 and Figure 2. A visual inspection of the funnel plot for the outcome clinical pregnancy rate does not indicate selective publication (Figure 3).

**Demography and treatment**

Neither trial reported a difference in baseline characteristics such as age, body weight, BMI or overall gonadotropin consumption.

The embryo transfer took place in nine studies in the setting of a fresh IVF cycle whereas two trials investigated OTR-as in a frozen embryo transfer cycle (He *et al.*, 2016, Yuan *et al.,* 2019). The availability of a good- or top-quality embryo was an inclusion criterion in six studies and the transfer of a day five embryo in two RCTs (Griesinger *et al.,* 2021 IMPLANT 4, He *et al.,* 2016). With respect to patient population, one trial (He *et al.,* 2016) focused exclusively on endometriosis patients whereas the other RCTs excluded patients with (severe) endometriosis (Griesinger *et al.* 2021, Hebisha *et al.,* 2018, Moraloglu *et al.,* 2010). The age of included patients varied from 25-35 (Hebisha *et al.,* 2018), 18-36 (Griesinger *et al.*, 2021, IMPLANT 1, 2) 18-37 (IMPLANT 4, Griesinger *et al.*, 2021, Bosch *et al.,* 2019), 20-45 (He *et al.,* 2016) or <43 years (Ng *et al.,* 2014, Yuan *et al.,* 2019). Features of all included studies are shown in Table 1.

**Clinical and ongoing pregnancy and live birth rates**

Administration of an OTR-a around embryo transfer is associated with a tendency towards an increase in the live birth likelihood, but statistical significance defined as $p<0.05$ is not present (relative risk: 1.09, 95% CI: 0.98-1.20, p=0.11, $I^2$=25%, n=5 studies, n=2,765). The ongoing pregnancy rate is significantly increased (relative risk: 1.14, 95% CI: 1.03-1.26, p=0.01, $I^2$=18%, n=4 RCTs, n=2,510) as well as the clinical pregnancy rate (relative risk: 1.31, 95% CI: 1.13-1.51, p=0.0002, $I^2$=61%, n=11 RCTs, n=3,611) by the administration of an OTR-a. A sensitivity analysis on studies with low risk of bias only (Bosch *et al.,* 2019, Griesinger *et al.,* 2021, Ng *et al.,* 2014) confirmed a significant increase in the clinical pregnancy chance for patients having an OTR-a administered (relative risk: 1.11, 95% CI: 1.01-1.22, p=0.03, $I^2$=5%, n=5 RCTs, n=2.765). Exclusion of the studies without full publication available (Bosch *et al.,* 2019, Song *et al.,* 2013) and with translation to English (Ahn *et al.,* 2009) does not alter the findings of the present meta-analysis (clinical pregnancy rate: relative risk: 1.33, 95% CI: 1.13-1.57, p=0.0007, $I^2$=68%, n=8 RCTs, n=3.196). Figure 4 shows forest plots for the clinical and ongoing pregnancy and live birth rate comprising all studies.

**Subanalysis for compound and day of embryo transfer**

A stratification for each investigated compound shows a significant increase in the clinical pregnancy rate for the studies on nolasiban (relative risk: 1.16, 95% CI: 1.02-1.31 p=0.02, $I^2$=36%, n=3 RCTs, n=1,710) and atosiban (relative risk: 1.50, 95% CI: 1.18 - 1.89, p=0.0008, $I^2$=69%, n=7 RCTs, n=1,646) whereas the study on barusiban does not report a difference in favour of the OTR-a (relative risk: 0.98, 95% CI: 0.72 - 1.34, p=0.91, $I^2$=not applicable, n=1 RCT, n=255). Stratification of studies for day of embryo transfer shows a significant effect in favour of an OTR-a on the clinical pregnancy rate for day 2/3 transfers (relative risk: 1.52, 95% CI: 1.10 - 2.09, p=0.01, $I^2$=78%, n=5 RCTs, n=1,429) which, however, does not reach significance for D5 embryo transfers (relative risk: 1.22, 95% CI: 0.98 - 1.53, p=0.08, $I^2$=55%, n=3 RCT, n=1,109).

**Miscarriage, ectopic pregnancy and multiple pregnancy**

The risk of miscarriage has no statistically significant association to the OTR-a administration (relative risk: 0.90, 95% CI: 0.72-1.12, p=0.35, $I^2$=0%, n=7 RCTs, n=2,936). The ectopic pregnancy rate is not significantly different between groups (relative risk: 0.88 95% CI: 0.43-1.8, p=0.73, $I^2$=0%, n=4 RCTs, n=2,714) as is the risk for a multiple pregnancy (relative risk: 1.05 95% CI: 0.81-1.36, p=0.73, $I^2$=5%, n=7 RCTs, n=3,014) (Figure 5).

## Discussion

The present meta-analysis collates data from n=11 RCTs comprising n=3,611 patients which were performed to test for an increase in the likelihood of live birth and/or clinical pregnancy in patients having an oxytocin receptor antagonist administered around embryo transfer. The clinical pregnancy rate was found to be significantly increased in patients having an OTR-a administered, and a higher chance of a live birth should be a consequence, however statistical significance is missed (p=0.11) as only n=5 RCTs report live birth incidences. The present systematic review also highlights a number of important limitations and shortcomings of the existing evidence. While the funnel plot does, formally, not indicate publication bias, the smaller studies on atosiban utilization show strong positive effect sizes, which is not the case for the large study of Ng *et al.*, 2014, which is the methologically most robust of the atosiban trials. Accordingly, a potential overestimation of the underlying effect has to be considered. A sensitivity analysis, however, including low risk of bias studies only confirms a positive effect of OTR-as on the clinical pregnancy rate but shows a smaller effect size (relative risk: 1.11, 95% CI: 1.01-1.22) vs. all studies (relative risk: 1.31, 95% CI: 1.13-1.51).

Another issue of concern is that within a robust and large clinical trial program (IMPLANT 1,2 and 4 studies), the OTR-a effect is not consistent across trials (Griesinger *et al.,* 2021) and the single trial on barusiban being negative for clinical pregnancy rate increase per randomized woman and only suggesting a benefit in a strata of women and on a surrogate outcome, implantation rate (Bosch *et al.* 2019). The use of surrogate outcome for live birth is another deficit of a number of trials identified. The outcomes of six of the included studies which are the clinical pregnancy and implantation rate. Only five studies examined live births as recommended outcome for clinical studies in IVF (Harbin Consensus Conference Workshop Group).

Heterogeneity in drug and administration regimen between studies is a potential source of significant confounding. Additionally, studies of the present meta-analysis differ in ART treatment type, patient populations and quality and stage of embryos transferred which could also impact findings. Adequate information on randomization is provided by eight studies, double-blinding, the gold standard for RCTs, was

conducted by six RCTs only which underlines the need for high-quality RCTs for evaluation of interventions.

Looking at the different OTR-a compounds in more detail, conflicting results from the registration studies of nolasiban become evident. The IMPLANT 4 trial could not replicate the significant increase in the likelihood of live birth which was observed in the IMPLANT 1 and 2 study (Griesinger *et al.,* 2021). Based on pharmacokinetic investigations, it was speculated whether adjustment of nolasibans posology may provide a higher efficacy suspecting an underexposure of some patients as a possible explanation for the ambiguous results from the IMPLANT trials. For barusiban, only one study investigated its association with clinical outcomes. An increased pregnancy chance exclusively for transfer of day 5 embryos was observed by that study. Thus, it was discussed whether an administration closer to the time frame of embryo implantation may impact the efficacy of barusiban (Bosch *et al.*, 2019).

For atosiban, a previous SR and meta-analysis reported an increased likelihood of a clinical pregnancy with moderate between study heterogeneity, however with inclusion of observational studies (Schwarze *et al.,* 2020). The present meta-analysis focuses on RCTs only and adds with respect to atosiban the study of Yuan *et al.,* 2019. Of note, the majority of available studies on atosiban are generally limited by insufficient information on randomization, blinding and reporting on outcomes as outlines in Table 2 and Figure 2.

The strength of the present meta-analysis is the inclusion of all RCTs utilizing drugs functioning as OTR-a thereby summing up a sufficient sample size to test for clinical relevant differences.

Adverse events were systematically reported by the included studies for OTR-a administration by n=4 studies only (Griesinger *et al.,* 2021, Ng *et al.,* 2014). The same is true for obstetric (live birth, gestational age at delivery, type of delivery, etc.) and neonatal (APGAR scores, birth weight, sex, malformations, etc.) outcomes.

From a cost-effectiveness perspective, a significant increase in the chance of a live birth per embryo transfer via administration of an OTR-a would appear attractive as an additional drug administration around embryo transfer is a rather simple add-on

versus other more complex and more costly procedures (PGT-A, *etc.*,). To date, no cost-effect models or studies on the use of OTR-a been published. The present meta-analysis may, however, serve as a starting point for such an exercise.

In summary, administration of an OTR-a around embryo transfer is associated with a significant increase in the likelihood of a clinical pregnancy and a tendency towards a higher chance to achieve a live birth. However, high-quality studies investigating further adjustments of posology, timeframe of administration and reporting on the likelihood of a live birth are warranted.

**Author's roles**

Both authors equally contributed to the conception and design of this review as well as drafting and revising the manuscript. Both authors approved the final version of the manuscript and agree to be accountable for the work. GG has been investigator in the IMPLANT trial program.

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**Legend to Tables and Figures**

**Table 1**. Included randomized controlled studies investigation the utilization of oxytocin receptor antagonists.

**Table 2.** Table of risk of bias assessment of included studies based on PRISMA guidelines [Moher *et al.* 2009].

**Figure 1.** PRISMA flowchart of studies.

**Figure 2**. Risk of bias assessment.

**Figure 3.** Funnel plot of the clinical pregnancy rate (effect on x-axis vs. precision on the y-axis).

**Figure 4.** Forest plots of (a) clinical pregnancy rate, (b) ongoing pregnancy rate and (c) live birth rate.

**Figure 5.** Forest plots of (a) miscarriage rate, (b) multiple pregnancy rate and (c) ectopic pregnancy rate.

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Kay Neumann is a physician and was undergoing subspeciality training in reproductive medicine at the Department of Gynaecological Endocrinology and Reproductive Medicine of the University of Luebeck, Germany. In 2020 he completed his Phd thesis ("*Habilitation*") at the University of Luebeck. In 02/2021 he has started to work at the Kinderwunsch Praxisklinik Fleetinsel in Hamburg, Germany.

## Key Message

Compounds acting as oxytocin receptor antagonists have the potential to increase pregnancy rate and live birth rate when administered around the time of embryo transfer to women undergoing IVF treatment. However, more data are needed to corroborate this general notion and more research needs to be done into the optimal compound, dosage and administration regimen.

**Table 1**

| **Study** | **Year of publication** | **Randomization/Blinding** | **Primary end-point** | **Patients (n) randomized** | **Hypothesis/sample size calculation** | **Patient population** | **Drug** | **Dose & Administration** | **Control group intervention** | **Embryo quality/day of ET** |
|---|---|---|---|---|---|---|---|---|---|---|
| Ahn *et al.,*[1] | 2009 | 1:1/blinding unclear | Clinical pregnancy rate; implantation rate | 40 | No sample size calculation and primary hypothesis provided | Two or more previously failed IVF/ICSI cycles; exclusion of patients with low ovarian reserve; no previous hormonal treatment for 3 month before inclusion | Atosiban | Bolus dose i.v. of 6.25 mg one hour before ET and continuous infusion rate of 18 mg/h; *post* transfer infusion was reduced to 6 mg/h for 2h | Information not provided | No specific stipulations |
| Bosch *et al.;* BASIC study | 2019 | 1:1/double-blind | Ongoing implantation (= viable fetuses 10-11 weeks after transfer divided by the number of embryos/blastocysts transferred) | 255 | Sample size calculation unclear, superiority design | Patients with IVF/ICSI;18-37 years with 'history of repeated implantation failure'; normal karyotype; no uterine pathology or hydrosalpinx; single or double embryo transfer in a fresh cycle | Barusiban | 40 mg 45 minutes before transfer and 10 mg 15 minutes *post* transfer subcutaneously | Placebo | Single or double transfer of good-quality embryos on D3 or D5 |

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|---|---|---|---|---|---|---|---|---|---|---|
| Griesinger *et al.;* IMPLANT 1 | 2021 | 1:1/double-blind | Clinical pregnancy rate | 125 (900mg) | 125 subjects calculated to provide 80% power (α = 0.05) to detect a trend in clinical pregnancy chances assuming 20% in the placebo group and up to 40% in the Nolasiban 900mg group | Patients with IVF/ICSI and fresh embryo transfer 18-36 years, no more than one previous failed stimulation cycle, evidence of at least 1.5 uterine contractions/min on transvaginal ultrasound on baseline or on day of embryo transfer, exclusion of patients with endometriosis ASRM ≥III, *etc.* | Nolasiban | Single 100, 300 or 900mg dose orally 4 h before embryo transfer | Placebo | Single or double transfer of D3 embryo of at least good quality |
| Griesinger *et al.;* IMPLANT 2 | 2021 | 1:1/double blind | Ongoing pregnancy rate | 779 | 760 subjects calculated to detect with ~90% (α = 0.05) an odds ratio ≥1.63 for increase in ongoing pregnancy rate | Patients with IVF/ICSI and fresh embryo transfer 18-36 years, no more than one previous failed stimulation cycle, exclusion criteria were serum progesterone levels >1.5 nanogram/milliliter or >20 cumulus-oophorus-complexes, endometriosis ASRM ≥III, *etc.* | Nolasiban | Single 900mg dose orally 4 h before embryo transfer | Placebo | Single D3 or D5 embryo with at least good quality |
| Griesinger *et al.;* IMPLANT 4 | 2021 | 1:1/double blind | Ongoing pregnancy rate | 1264 | 820 subjects was calculated based on the IMPLANT 2 D5 results, to provide | Patients with IVF/ICSI and fresh embryo transfer 18-37 years, no more than one | Nolasiban | Single 900mg dose orally 4 h before embryo transfer | Placebo | Single D5 embryo with at least good quality |

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| | | | | | ~90% power (α = 0.05) to detect an odds ratio ≥1.59 | previous failed stimulation cycle, exclusion criteria were serum progesterone levels >1.5 ng/mL or >20 cumulus-oophorus-complexes, endometriosis ASRM ≥III, *etc.* | | | | |
| Hebisha *et al.*; | 2018 | 1:1/details of blinding unclear | Clinical pregnancy rate, implantation rate | 182 | Unclear | Patients 25 - 35 years, BMI <35 kg/m$^2$, tubal or male factor infertility ICSI with fresh semen. Exclusion criteria: polycystic ovary, endometriosis, anti-mullerian hormone <1.5 nanogram/millileter, pre-ovulatory endometrium (≤6 milllimeter) on previous cycle | Atosiban | Slow i.v. infusion of 7.5 mg atosiban 20 minutes before embryo transfer | Placebo | D5 embryo transfer |
| He *et al.;* | 2016 | 1:1/blinding of laboratory staff and embryo transfer operator | Clinical pregnancy rate, implantation rate | 120 | 58 patients per group based on a minimum absolute difference of 25% between groups; alpha 0.05 and beta 0.20 | Patients 20–45 years having a frozen embryo transfers and baseline follicle stimulating hormone <10 IU/liter, endometriosis, confirmed by laparoscopy, <3 previously failed treatment cycles, exclusion of patients | Atosiban | Bolus dose i.v. of 6.75 mg approximately 30 minutes before embryo transfer | *Nil* | at least one day 5 good-quality embryo |

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| | | | | | | with uterine anomaly; fibroids or hydrosalpinges, *etc.* | | | | |
| Moraloglu *et al.;* | 2010 | 1:1/blinding of patients | Clinical pregnancy rate, implantation rate | 180 | 180 patients (90 per group) to detect a 20% difference in the clinical pregnancy rate between groups; alpha 0.05 and beta 0.20 | Basal FSH hormone <10 IU/l, age 20–39 years, first fresh IVF/ICSI cycle, long protocol with gonadotrophin-releasing hormone agonist, exclusion of patients with severe male factor, endometriosis, endocrine disorders, or uterine anomaly or uterine fibroids and hydrosalpinges, patients with difficult transfer, *etc*. | Atosiban | 30 min before embryo transfer bolus of 6.75 mg and continuation with a rate of 18 mg/h, *post* embryo transfer procedure, the dose was reduced to 6 mg/h and the infusion was continued for 2 h (total administered dose: 37.5 mg) | Placebo | two top-quality embryos on D2 |
| Ng *et al.;* | 2014 | 1:1/double blind | Live birth rate | 800 | Superiority trial designed to detect an increase of 10% live birth rate from 35% control group live birth rate; alpha 0.05 and beta 0.20 | Age <43 years, normal uterine cavity shown on ultrasound, exclusion of patients with three or more previous IVF cycles, use of donor oocytes, natural IVF cycles; endometrial thickness 8 millimeter, hydrosalpinx | Atosiban | 30 min before embryo transfer bolus of 6.75 mg and continuation with a rate of 18 mg/h, *post* embryo transfer the dose was reduced to 6 mg/h (total administered dose: 37.5 mg) | Placebo | No blastocysts transfers included |

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| Song *et al.*,[2] | 2013 | 1:1/blinding unclear | Clinical pregnancy rate, implantation rate | 120 | No sample size calculation and primary hypothesis available | No sample size calculation and primary hypothesis available | Atosiban | 30 minutes before embryo transfer with a total administered dose of 37.5 mg | *Nil* | transfer of embryos in 7-8 cell stage |
| Yuan *et al.*; | 2019 | 1:1/double-blind | Clinical pregnancy rate, implantation rate | 204 | No sample size calculation and primary hypothesis provided | age <43 years, frozen thawed embryo transfer, normal uterine cavity clear information about previous IVF embryo transfer cycles, history of previous difficult transfer, exclusion of patients with uterine anomaly, hydrosalpinx endometrial thickness <7.5 mm, *etc.* | Atosiban | 30 min before embryo transfer bolus of 6.75 mg and continuation with a rate of 18 mg/h, *post* embryo transfer the dose was reduced to 6 mg/h (total administered dose: 37.5 mg) | Placebo | One or more good-quality embryos on the day of transfer, no blastocysts |

**Table 2**

| Study: | Adequate sequence generation? | Authors' judgement | Allocation concealment? | Authors' judgement | Blinding? All outcomes | Authors' judgement | Incomplete outcome data addressed? All outcomes | Authors' judgement | Free of selective reporting? | Authors' judgement |
|---|---|---|---|---|---|---|---|---|---|---|
| Ahn *et al.,* 2009 | Unclear | High Risk | Unclear | High Risk | Blinding unclear | High Risk | No live birth rate, data on clinical pregnancies and implantations | High Risk | No evidence for selective reporting | Low risk |
| Bosch *et al.,* 2019 | Central randomization through electronic case report form | Low Risk | Concealment via central randomization through electronic case report form | Low Risk | Double-blind | Low risk | Live birth data and data on clinical pregnancies received on personal request to authors | Low Risk | No evidence for selective reporting | Low risk |
| Griesinger *et al.,* 2021 IMPLANT 1 | Randomization list generated by a statistician *a priori* | Low risk | Interactive web response system for concealment | Low risk | Double-blind | Low risk | Incomplete data for testing of low doses provided but adequate reporting on outcome data for 900 mg | Low risk | No evidence for selective reporting | Low risk |
| Griesinger *et al.,* 2021 IMPLANT 2 | Randomization list generated by a statistician *a priori* | Low risk | Interactive web response system for concealment | Low risk | Double-blind | Low risk | Adequate report on outcome data | Low risk | No evidence for selective reporting | Low risk |

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| Griesinger *et al.,* 2021 IMPLANT 4 | Randomization list generated by a statistician *a priori* | Low risk | Interactive web response system for concealment | Low risk | Double-blind | Low risk | Adequate report on outcome data | Low risk | No evidence for selective reporting | Low risk |
| Hebisha *et al.*, 2018 | Unclear | High Risk | Unclear | High risk | Unclear | High Risk | No adequate report on outcome data | High Risk | No evidence for selective reporting | Low risk |
| He *et al.,* 2016 | Computer-generated system | Low Risk | Sealed envelopes for concealment | Low Risk | Blinding of laboratory staff and embryo transfer operator only | High Risk | No live birth rate, data on clinical pregnancies and implantation only | High Risk | No evidence for selective reporting | Low risk |
| Moraloglu *et al.,* 2010 | Randomization based on weekdays of patient entry | High Risk | Concealment to staff unclear | High Risk | Blinding of patients only | High Risk | No live birth rate, data on clinical pregnancies, implantations and miscarriages | High Risk | No evidence for selective reporting | Low risk |
| Ng *et al.,* 2014 | Computer-generated randomization list with blocks of 10 | Low Risk | Sealed envelopes handled by a research nurse not involved in the study | Low Risk | Double-blind | Low Risk | Adequate report on outcome data | Low Risk | No evidence for selective reporting | Low risk |
| Song *et al.,* 2013***** | Unclear | High Risk | Unclear | High Risk | No blinding | High Risk | No live birth rate, data on clinical pregnancies and | High Risk | No evidence for selective reporting | Low risk |

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|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | implantations | | | |
| Yuan *et al.*, 2019 | Computer-generated randomiza- tion list by a research staff not involved in the study | Low Risk | computer-generated randomiza- tion list by a research staff not involved in the study | Low Risk | Double-blind | Low Risk | No live birth rate, data on clinical pregnancies and implantations, miscarriages, *etc*. provided | High Risk | No evidence for selective reporting | Low risk |

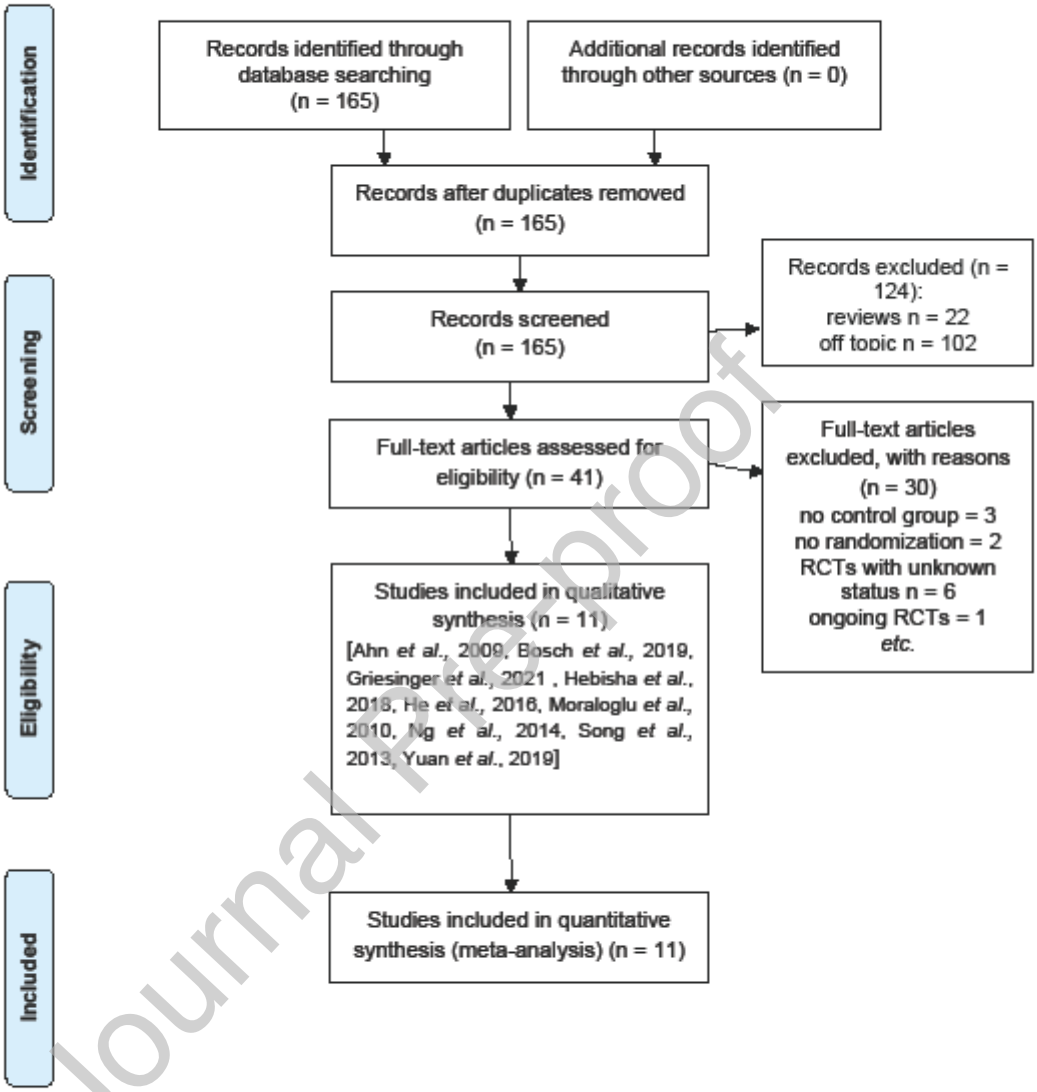




**Fig. 1**

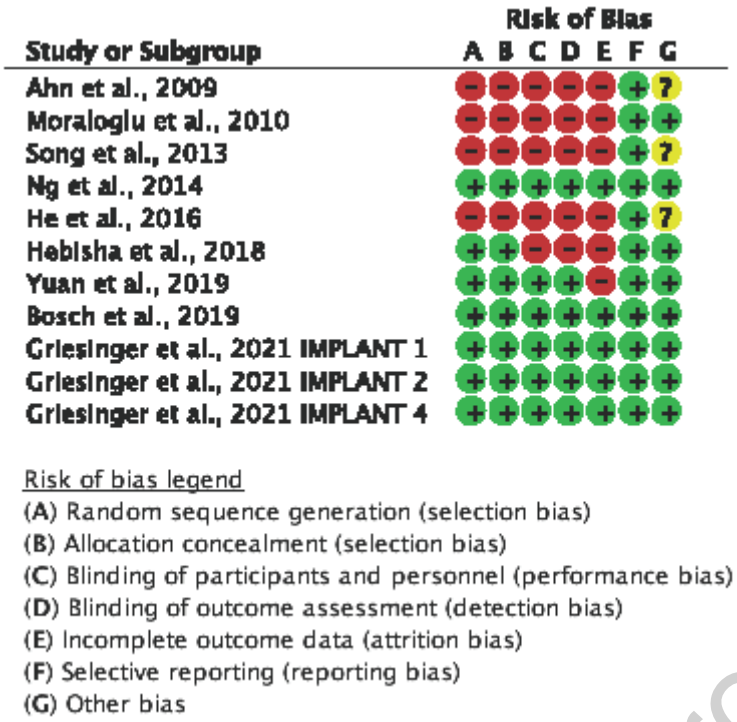


**Fig. 2**

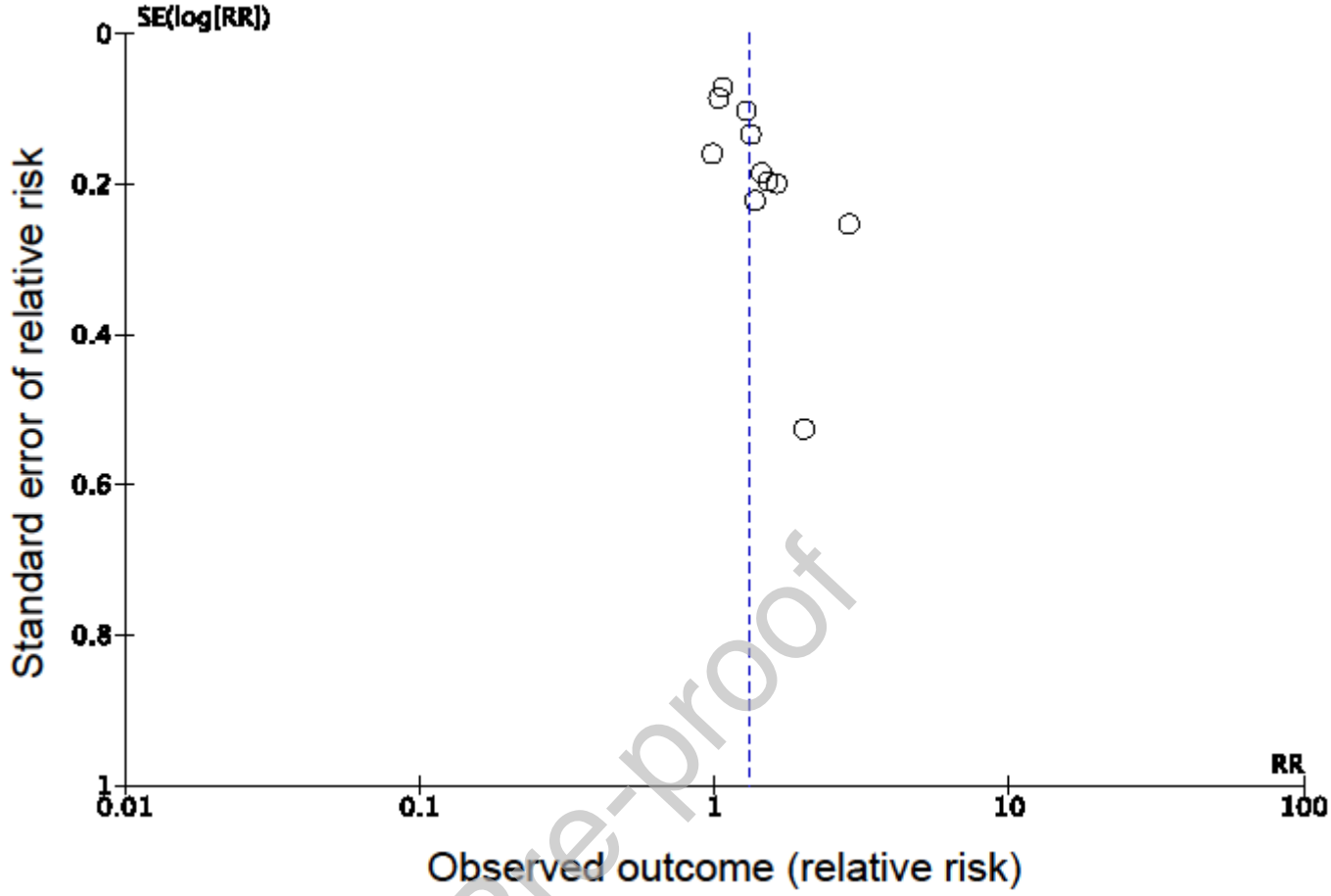


**Fig. 3**

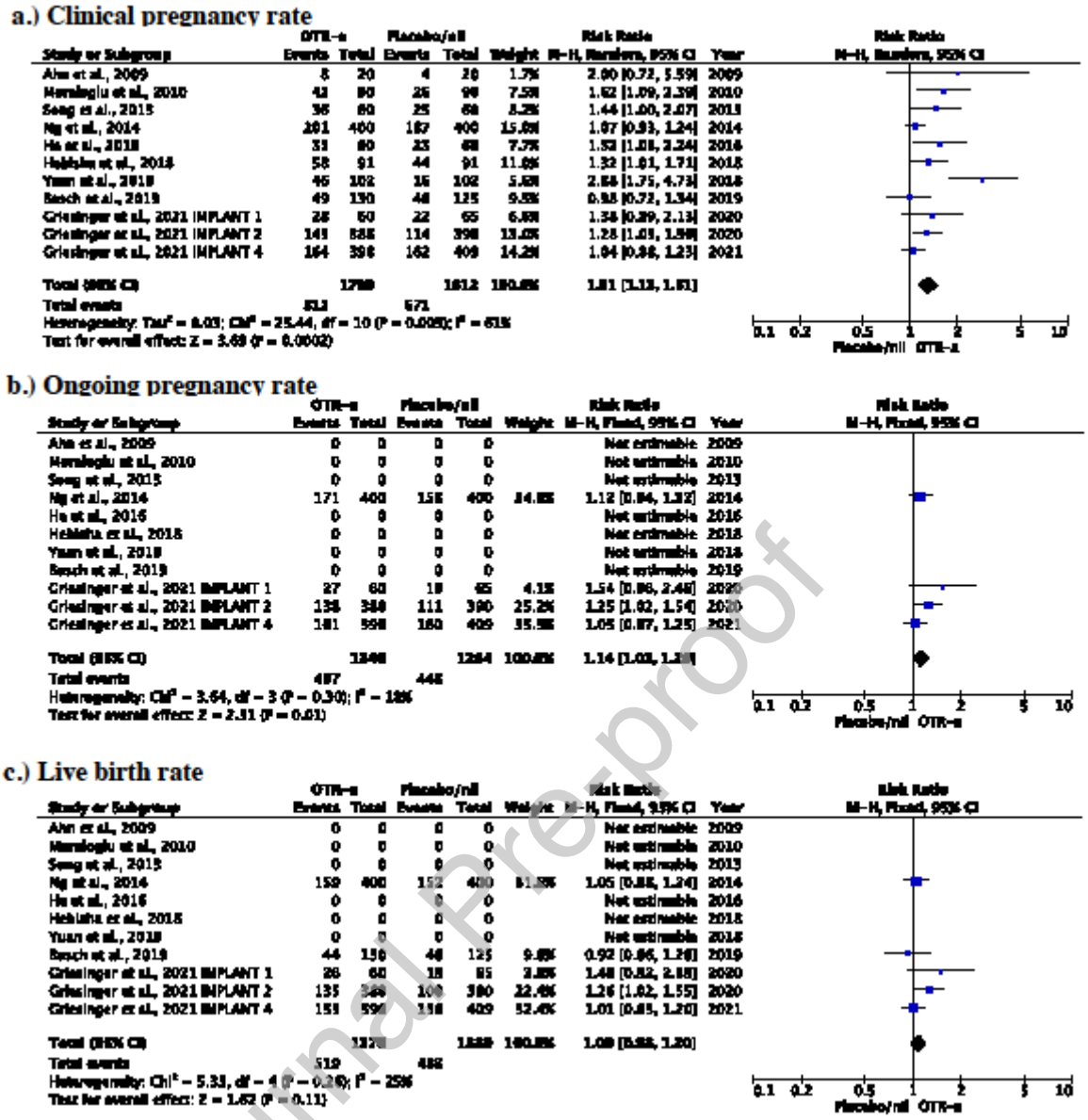


Fig. 4

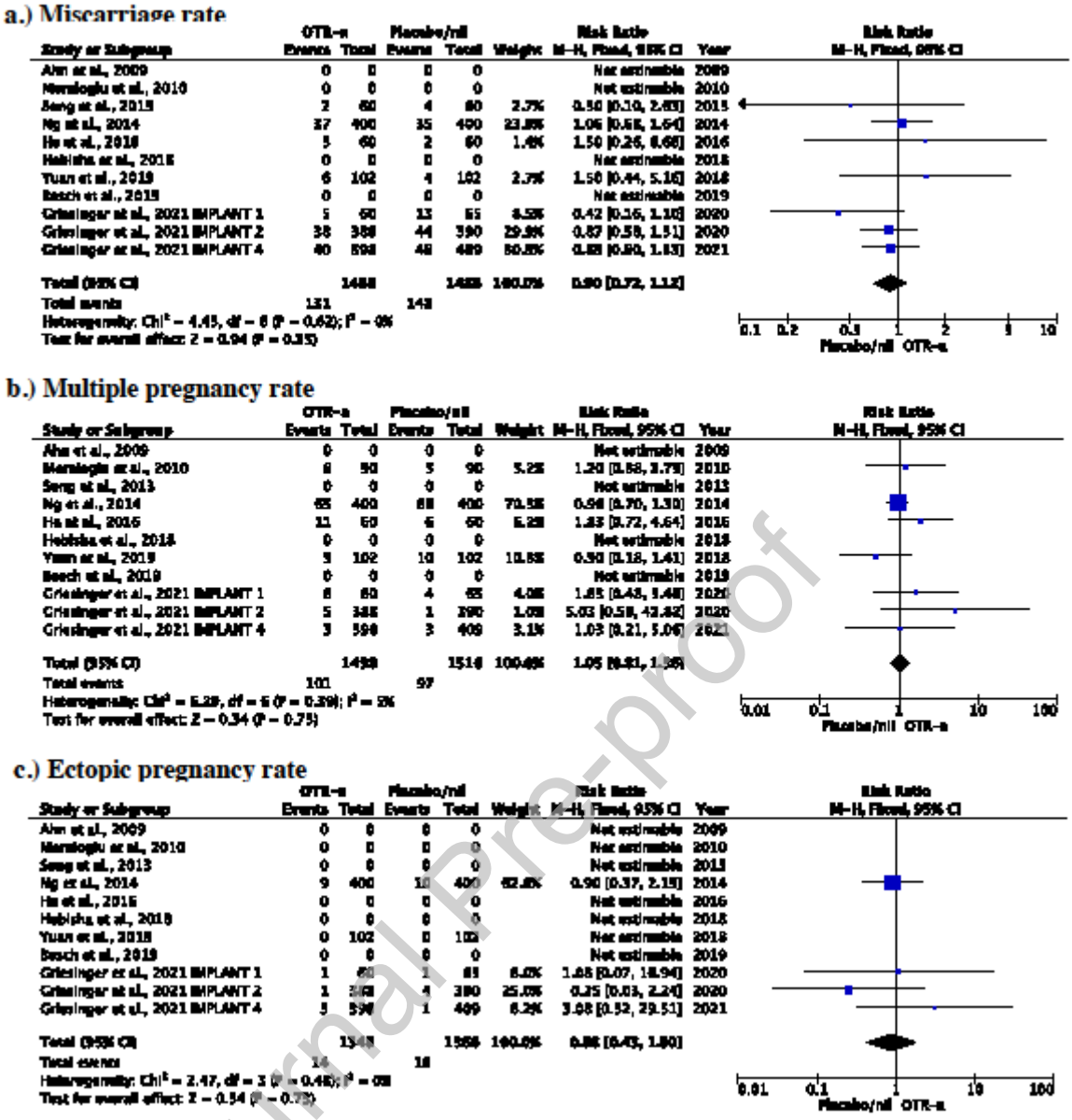


Fig. 5