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Does nifedipine improve outcomes of embryo transfer?

Interim analysis of a randomized, double blinded, placebo-controlled trial

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Abstract

Background: Implantation failure is the main factor affecting the success rate of in vitro fertilization (IVF) procedures. Studies have reported that uterine contractions (UC) at the time of embryo transfer (ET) were inversely related to implantation and pregnancy rate, hence reducing the success of IVF treatments. Various pharmacological agents, with the exception of calcium channel blockers, have been investigated to improve ET outcomes by reducing UC. Thus, a double-blinded randomized, placebo-controlled trial was conducted to determine whether nifedipine, a calcium channel blocker with potent smooth muscle relaxing activity and an excellent safety profile, can improve the outcome of patients undergoing ET treatments.

Methods: Ninety-three infertile women were recruited into 1 of 2 groups: placebo (n = 47) or nifedipine 20 mg (n = 46). Study participants were admitted 30 minutes prior to ET and given either tablet after their baseline vital signs were recorded. They then underwent ET and were observed for adverse events for another 30 minutes post-ET. Follow up of the participants' outcomes was conducted via electronic medical records. The primary outcomes are implantation and clinical pregnancy rates. Secondary outcomes include any maternal or fetal adverse events, miscarriage, pregnancy, live births, and neonatal outcomes. Resulting data were then analyzed using *t* test, Pearson chi-square test, and Fisher exact test to compare outcomes between the 2 groups.

Results: No statistical differences in the implantation rate (42.6% vs 39.1%, $P = .737$, rate ratio 0.868, 95% confidence interval [CI]: 0.379–1.986) and the clinical pregnancy rate (23.4% vs 26.1%, $P = .764$, rate ratio 1.155, 95% CI: 0.450–2.966) were detected between the placebo and the treatment groups. In addition, no statistical significance between the placebo and the treatment groups for any secondary outcomes were detected.

Conclusions: This double blinded, randomized, and placebo-controlled trial demonstrated that the single use of 20 mg nifedipine given 30 minutes before embryo transfer did not improve the implantation rate or the clinical pregnancy rate of the infertility treatment. Further studies are required to demonstrate the clinical benefits and risks of nifedipine usage in embryo transfer.

Abbreviations: ART = assisted reproductive technology, CCB = calcium channel blocker, CPR = clinical pregnancy rate, ET = embryo transfer, FSH = follicle stimulating hormone, hCG = human chorionic gonadotropin, ICSI = intracytoplasmic sperm injection, IR = implantation rate, IVF = in vitro fertilization, NICU = Neonatal Intensive Care Unit, RCT = randomized controlled trial, UC = uterine contraction.

Keywords: calcium channel blocker, contraction, embryo transfer, frozen-thawed, intracytoplasmic sperm injection, implantation rate, in vitro fertilization, nifedipine, pregnancy rate, uterus

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1. Introduction

Assisted reproductive technology (ART) is the technology used to achieve pregnancy in patients who suffer from fertility issues. In vitro fertilization (IVF), a procedure of ART, is the most well-known procedure conducted to circumvent fertility issues since 1978. IVF is a process where eggs are collected from the ovary and fertilized with sperm in the laboratory to become an embryo. Intracytoplasmic sperm injection is a specialized form of IVF that involves a direct injection of a single sperm into an oocyte. After the fertilization process, the embryo is placed back into the uterus via a procedure called embryo transfer (ET). Implantation and pregnancy would then hopefully occur.

Since the birth of IVF, techniques of the procedure, from ovarian stimulation to the choice of catheters used, have benefitted from major advances and improvements. However, implantation rate (IR) and clinical pregnancy rate (CPR) in women following ET have remained lower than desired. This result is thought to be due to multiple factors such as the quality of embryo and the receptivity of the endometrium.[1] Extensive research has been undertaken to understand and to improve the success of ET following IVF treatments.

In general, the limiting factors of embryo implantation, which is essential for pregnancy, are separated into 2 categories: embryonic and endometrial. Within the embryonic limiting factor, aneuploidy is thought to the major cause of implantation failure[2]; within the endometrial factor, excessive uterine contractions (UC) is proposed to be the major cause contributing to the reduced IR in IVF/ICSI cycles.[2–4] In this study, excessive UC will be targeted as the modifiable factor to improve IVF outcomes. A recently published study demonstrated that the uterine peristaltic wave frequency before embryo transfer was inversely related to CPR in fresh and frozen–thawed cycles.[5] It has been shown that contractile or peristaltic activities of the uterus could move the implanted embryo towards the fallopian tube, or cervix and vagina,[6] or even expel it completely out of the uterus.[2,3]

If excessive UC indeed reduces IR and CPR in women undergoing IVF/ICSI cycles, then it represents a potential target for pharmacological agents to improve the success of IVF/ICSI cycles. Various pharmacological agents have been investigated to improve the outcomes of ET by reducing UC. These include, cyclo-oxygenase inhibitors, β2 adrenoreceptor agonists, anti-inflammatories, phosphodiesterase inhibitors, progesterone, and antispasmodics.[6–21] However, results from these studies have only been variable. It is to our best knowledge that there are no investigation results available on the efficacy of calcium channel blockers (CCBs) used to reduce UC or to improve IVF/ICSI cycle outcomes.

CCBs are non-specific smooth muscle relaxants, predominantly used for the treatment of hypertension in adults. It specifically inhibits the transmembrane calcium influx at the voltage-gated L-type channels.[22] By inhibiting the slow inward current of the action potential via reducing the intracellular levels of calcium,[23] it decreases the contractility of the smooth muscles and hence causes vasodilation, uterine relaxation, and other effects throughout the body.[22]

The most widely used and studied calcium channel blocker is nifedipine and there is evidence for its safety in pregnancy.[24–28] Nifedipine belongs to a subclass of CCBs, namely dihydropyridine, which is selective to vascular over cardiac tissues at about 10:1.[24] Nifedipine has vasodilatory and potent uterine relaxation properties.[22] It has been used in obstetrics as a tocolytic and antihypertensive since 1980.[29] It appears that nifedipine is a very safe drug with limited major adverse effects and has demonstrated superiority, as a first-line agent, over other drugs in the management of preterm labor or pregnancy induced hypertension consistently.[22,24–26,30–35] The most common maternal side effects reported are: transient facial flushing, headache, nausea, tachycardia and hypotension; less common side effects are: palpitations, dizziness, chest pain, nasal congestion, oedema, and heartburn.[25,35–38] These side effects are mostly benign and are resolved spontaneously or by withdrawal of the drug.[35–38]

Current evidence has demonstrated no suggestion of teratogenicity[34,39,40] and no toxicity on human embryos.[41–45] More importantly, a long-term study following 94 neonates for up to 18 months of life has found no impact on malformations, diseases incidences, motor function, or childhood education following nifedipine exposure in utero.[46] Another large case control study also found no increased risk of congenital anomalies.[47]

Given nifedipine's excellent safety profile and potent uterine relaxing property, it is a promising candidate to reduce excessive UC and hence improve outcomes for patients undergoing IVF/ICSI cycles. This study therefore aims to establish the clinical effect and the associated pregnancy outcome of a single dose immediate-release nifedipine administration 30 minutes pre-ET.

2. Methods

2.1. Participants recruitment

Between September 2016 and April 2017, 93 participants were prospectively recruited at Melbourne IVF centers across Victoria, Australia. Participants are identified via an online medical record system. Once identified as requiring embryo transfer treatment and satisfying the following inclusion and exclusion criteria, they were then provided with detailed written information and invited to participate via the phone or an email by the study's researchers. These participants are formally enrolled by the study researchers once they have signed and dated an informed consent (see Figure, Supplemental Content, a copy of an informed consent, http://links.lww.com/MD/C779), with a witness. No financial aid or any other incentives were given to participants. No changes were made to any of the following methods even after the trial has commenced.

Inclusion criteria

(1) 18 to 45 years females undergoing IVF/ICSI cycles and fresh or frozen–thawed embryo transfer.
(2) Baseline BP ≥100/60 mmHg measured pre-embryo transfer.

Exclusion Criteria

(1) Body mass index (BMI) >38
(2) Early follicular phase (day 2–4) serum follicle stimulating hormone (FSH) level >20 mIU/mL.
(3) Abnormal uterine cavity as evidenced by sonohysterogram or hysterosalpingography
(4) Any contraindication to being pregnant and carrying a pregnancy to term.
(5) Contraindication for the use of nifedipine, estrogen, and progesterone suppositories.
(6) Patient being treated with other drugs that interact with cytochrome P450 activity: azole antifungals, cimetidine, cyclosporine, erythromycin, quinidine, terfenadine, warfarin, benzodiazepines, flecainide, imipramine, propafenone, and theophylline.

(7) Irregular heart beat or already being treated with another medication for high blood pressure.
(8) Any ovarian or abdominal abnormality that may interfere with adequate transvaginal sonography (TVS) evaluation.
(9) Administration of any investigational drugs within 3 months prior to study enrollment.
(10) Patient not able to communicate adequately with the investigators and to comply with the requirements of the entire study.
(11) Unwillingness to give written informed consent.
(12) Previous entry into this study.
(13) Embryos that have undergone preimplantation genetic screening.

2.2. Randomization and masking

Four hundred eight patients were assessed for eligibility with a total of 315 patients excluded, 154 of them declined to participate and 161 of them did not meet criteria. Ninety participants were recruited and randomized for the study. Fourty-seven participants were randomly allocated to the placebo-controlled group while the other 46 participants were randomly allocated to the treatment group.

Randomization was performed via a computer generated sequence in blocks of 10 recruited subjects and balanced for study sites by an independent research assistant of Melbourne IVF. The allocation ratio into each arm was 1:1. The randomization was stratified for age into 4 groups: <30 years old, 30 to 34 years old, 35 to 40 years old, and >40 years old. This randomization result was then stored in a sealed opaque envelop, which neither patients nor caregivers being aware of the allocation. All study staff and researchers were remained blinded to allocation of interventions until the statistical data base was cleaned and locked.

All participants were women and other characteristic, demographic, and treatment data, such as mean age and mean treatment number are summarized in the result section (see Table 1).

Data were recorded in hardcopy and electronic form. Hardcopies were stored in a secured filing cabinet at the administering institution. Electronic copies were stored in encrypted files on a password protected computer. These outcome data were recorded in clinically settings at various Melbourne IVF Centres across Victoria, Australia. Organic samples were stored until analysis in a securely locked temperature-controlled freezer at Melbourne IVF that can only be accessed by authorized staff. Samples and participant records did not contain any directly identifiable information and no additional biological samples were kept for use in ancillary studies.

2.3. Procedure and material

This trial followed an interventional double-blinded and randomized placebo-controlled design.

After a valid consent form was received from a participant, she was allocated randomly to either the treatment group or the controlled group. Participants continued to attend their usual appointments with standard concomitant care. Stimulation protocols for egg retrieval, cryopreservation, and ET were the standard procedures at Melbourne IVF Centres. For patients with cryopreserved embryos transfer, vitrification was used. Vitrifying and warming of embryo were also performed according to a standard protocol. Embryo quality after warming was defined using existing criteria of Melbourne IVF guideline. These embryos were assigned a score according to the number and regularity of blastomeres and the degree of fragmentation.

Once the time of ET was determined, participants then arrived 30 minutes pre-ET to have their blood pressure taken (Vital Signs Monitor, Edan Instruments Inc., Melbourne Victoria; Model M3A; Used since 2012; 100–240 V; 50 Hz/60 Hz) by the clinical staff. If the participant's baseline blood pressure satisfied the study eligibility criteria, then an envelope with the participant's study number was opened. The envelop contained a tablet, either a placebo tablet (HealthSmart Pharmacy VCCC, Melbourne) or a 20 mg nifedipine immediate release tablet (HealthSmart Pharmacy VCCC, Melbourne), that was administered orally with a glass of water by the participant. The 2 kinds of tablets appeared identical with no markings to ensure double blinding of the participants and the care providers.

Once the tablet was administered, a standard ET was performed by a clinician after 30 minutes of tablet administration. Embryo transfer was performed using a catheter (GuardiaAccess Embryo Transfer Catheter; Cook Medical; Version: K-JETS-7019; Manufactured in 2016; Disposable usage; 6.6 Fr & 2.8Fr catheters); vaginal specula (KleenSpec Disposable Vaginal Specula, Welch Allyn) under ultrasound guidance (Portable Digital Color Doppler Ultrasound System; Model S6; SonoScape Co., Ltd.; Used since: 2011–06; 200 V; 50 Hz).

In order to monitor for any adverse effects, another set of blood pressure values was recorded 30 minutes post-ET. Adverse events or side effects reported by the participants, the time of drug administration, time of blood pressures recordings, and the time of ET were all recorded on the patient record form. Serious adverse events were recorded separately and followed up until resolution.

If the time of ET was conducted later than 60 minutes after drug administration, the result of that participation was deemed invalid and excluded from analysis.

Table 1

Baseline characteristics of participants (n = 93).

Characteristic	Placebo group (n = 47)	Treatment group (n = 46)	*P*-value[#]
Age, y[†]	36.4 ± 4.3 (21–42)	36.8 ± 4.7 (29–45)	.602
Treatment type[*]	IVF: 14.9% (7/47); ICSI 72.3% (34/47); cryopreservation: 12.8% (6/47)	IVF: 17.4% (8/46); ICSI 76.1% (35/46); cryopreservation: 6.5% (3/46)	.586[##]
Number of treatment inclusive of current treatment[†]	4.7 ± 3.9 (1–20)	4.4 ± 3.7 (1–17)	.740
Number of embryo transferred[†]	1.2 ± 0.4 (1–2)	1.2 ± 0.4 (1–2)	.760

[†] Mean ± SD (range).
[*] Percentage (absolute values).
[#] Student *t* test.
[##] Pearson chi-square test.

Following ET, participants attended appointments as per clinicians' instruction.

The primary and secondary outcomes of this study were followed up via Virtus Patient System (Virtus Patient System; VPS - 1.7.3.173; Virtus Health), the online medical history system across all Melbourne IVF Centres. The primary and secondary outcomes are listed as below:

2.4. Primary outcomes

(1) Implantation rate, defined the clinical embryo implantation rate as the number of gestational sacs observed at transvaginal ultrasound screening at 3 to 5 weeks of pregnancy (this is measured with Portable Digital Color Doppler Ultrasound System; Model S6; SonoScape Co., Ltd.; Used since: 2011–06; 200 V; 50 Hz).
(2) Clinical pregnancy rate, defined as the number of patients with a presence of a live pregnancy in the uterine cavity at a transvaginal ultrasound (this is measured with Portable Digital Color Doppler Ultrasound System; Model S6; SonoScape Co., Ltd.; Used since: 2011–06; 200 V; 50 Hz) at 6 weeks' gestation onwards.

2.5. Secondary outcomes

(1) Live birth defined as the number of live born neonates.
(2) Miscarriage defined as loss of a diagnosed clinical pregnancy before 20 weeks gestation.
(3) Multiple pregnancy defined as the number of clinical pregnancy which involves >1 fetus develops in the uterus simultaneously.
(4) Pregnancy and neonatal outcomes including ectopic pregnancy, congenital or chromosomal abnormalities, stillbirth, pre-eclampsia, delivery before 34 weeks, delivery between 34 and 37 weeks, necrotising enterocolitis, abnormal neurology, placenta praevia, gestational diabetes, low birth weight, admission to NICU, duration of admission, need and duration of respiratory support or any other neonatal morbidity reported.

No changes were made to the above outcomes after the trial has commenced.

2.6. Statistical analysis

Analysis was performed based on the intention-to-treat principle. As there were no previous studies that address the potential beneficial role of nifedipine, it is assumed that nifedipine would improve primary outcomes by 20% to 30% from baseline. A sample size calculation, before the study, showed that each arm should contain at least 313 subjects to have an 80% statistical power at 95% confidence interval (CI) between treatment and control group with a 1:1 ratio.

An interim analysis was performed after the results of 93 patients were available. The interim statistical comparisons were carried out using chi-square test, Fisher exact test, and Student *t* test where appropriate with the Statistical Program for Social Science (SPSS, Inc., Version 23.0, Chicago, IL). A two-sided $P < .05$ was taken as statistically significant.

The interim analysis showed that no significant results would be achievable at the proposed sample size and the trial recruitment was stopped at 93 patients.

Baseline characteristics of participants were also analyzed using Student *t* test and Pearson chi-square test to ensure equal allocations of participants into the 2 study groups.

2.7. Ethics approval and informed consent statement

The ethical aspects of this research project have been approved by the Melbourne IVF Human Research and Ethics Committee.

This project was carried out according to the National Statement on Ethical Conduct in Human Research (2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

A copy of the informed consent statement can be found in the appendix (see Supplemental Digital Content, http://links.lww.com/MD/C779).

3. Results

From September 2016 to April 2017, a total number of 93 participants were recruited and randomized. No participants withdrew, excluded after randomization or lost to follow up. Fourty seven and 46 participants were randomly allocated to the placebo group and the treatment group, respectively. No significant differences ($P > .05$) of characteristics, such as age, treatment type, number of treatment, or number of embryo transferred were detected between the placebo and the treatment group (see Table 1). All of the participants were analyzed for primary and secondary outcomes as their original assigned groups. The last follow up of an outcome concluded the study in January 2018.

3.1. Primary outcomes

There were no statistical differences in the implantation rate (42.6% vs 39.1%, $P = .737$, rate ratio 0.868, 95% CI: 0.379–1.986; placebo vs treatment, respectively) and the clinical pregnancy rate (23.4% vs 26.1%, $P = 0.764$, rate ratio 1.155, 95% CI: 0.450–2.966; placebo vs treatment, respectively) between the placebo group and the treatment group (see Table 2 and Fig. 1). This result suggests that the single administration of 20 mg nifedipine 30 minutes pre-ET does not improve implantation rate or improve clinical pregnancy rate in ET treatment.

3.2. Secondary outcome

Part of the secondary outcome measures, such as stillbirth or premature delivery, are still ongoing, so any possible secondary outcome data to date are analyzed and presented in this paper.

No statistical significance ($P > .05$) was detected between placebo group and treatment group for the rates of miscarriage, multiple pregnancy, or ectopic pregnancy (see Table 2). This result suggests that the single administration of 20 mg nifedipine 30 minutes pre-ET does not demonstrate an increase risk in miscarriage, ectopic pregnancy, or multiple pregnancy.

4. Discussion

To the best of our knowledge, this is the first randomized, double blind, placebo-controlled trial on the use of nifedipine in ET infertility treatment. Our results did not show any improvement in pregnancy outcomes, including IR, CPR or any other secondary outcomes, such as miscarriage, multiple pregnancies,

Table 2

Comparison of pregnancy outcomes.

	Placebo group (n = 47)	Treatment group (n = 46)	*P*-value	Rate ratio (95% confidence interval)
Implantation rate	42.6% (20/47)	39.1% (18/46)	.737[†]	0.868 (0.379–1.986)
Clinical pregnancy rate	23.4% (11/47)	26.1% (12/46)	.764[†]	1.155 (0.450–2.966)
Live birth rate	25.5% (12/47)	26.1% (12/46)	.951[†]	1.029 (0.407–2.606)
Multiple pregnancy rate	2.1% (1/47)	0.0% (0/46)	1.000[*]	0.979 (0.938–1.021)
Ectopic pregnancy rate	2.1% (1/47)	2.2% (1/46)	1.000[*]	1.022 (0.062–16.846)
Miscarriage rate	4.3% (2/47)	4.3% (2/46)	1.000[*]	1.023 (0.138–7.584)

[†] Pearson chi-square test.
[*] Fisher exact test.

and ectopic pregnancy, with a single administration of 20 mg nifedipine 30 minutes pre-ET. Despite the treatment group showing a small magnitude of decrease in IR and increase in CPR, rate ratio of 0.868 and 1.155, respectively, this result did not reach statistical significance. No comparison of this data with the current literature is available due this study being the first to propose the potential benefits of nifidepine in ET.

Although multiple studies have suggested that excessive UC is the major cause contributing to the less than satisfactory IR and CPR in ET treatments,[2–5] our attempt to improve ET treatment outcomes with nifedipine has not been successful. Nifedipine has been used in obstetrics as a potent tocolytic since 1980 due to its well-known vasodilatory and potent uterine relaxation properties,[22] however, one of the major limitations of this study is that the uterine environment of our participants were not characterized. Without a detailed ultrasound study of the uterus before and after drug administration, the vasodilatory and tocolytic effects of a single 20 mg nifedipine dose remained un-investigated. Perhaps a different dosing regimen of nifedipine is required to demonstrate the proposed clinical benefit in ET treatments. Although controversial, there are also studies to suggest that nifedipine has little to no effect on uterine perfusion, despite it causing a clinically insignificant fall in maternal mean arterial pressure.[25,39] Future studies involving detailed investigations of the effect of nifedipine on the uterus contractility and vascular perfusion should be conducted.

Another limitation of this study is the lack of sample size. Recruitment has been difficult due to the lack of participation willingness, thus impacting the power of the study and limiting secondary outcome data. Based on this study's results, a substantially larger trial would be required to demonstrate a clinical benefit of the proposed treatment. Even though the results suggest that single dose of nifedipine treatment does not increase the risk of miscarriage, multiple pregnancy, or ectopic pregnancy rate, our sample size is small and hence the validity of this result is restricted. Interpretation of this data must be done cautiously. More data are required to analyze the safety aspects, such as adverse maternal, pregnancy, or neonatal events, associated with nifedipine usage in ET treatment. Further studies are required to determine these unknowns.

The rationale of this study was to determine if nifedipine, a calcium channel blocker (CCB), would exert any positive clinical outcome in ET treatments, as no other published studies have trialled CCB yet. Multiple studies have investigated various other pharmacological agents in an attempt to improve ET outcome by reducing UC, but only demonstrated variable results.[6–21] β2 adrenoreceptor agonists, terbutaline, and ritodrine, are both well known for their uterine relaxing property via smooth muscle relaxation. Despite this property, a large scale randomized study demonstrated no significant differences for IR or CPR between treatment and control groups.[9] On the contrary, antispasmodic agent, such as hyoscine butylbromide, has been shown with

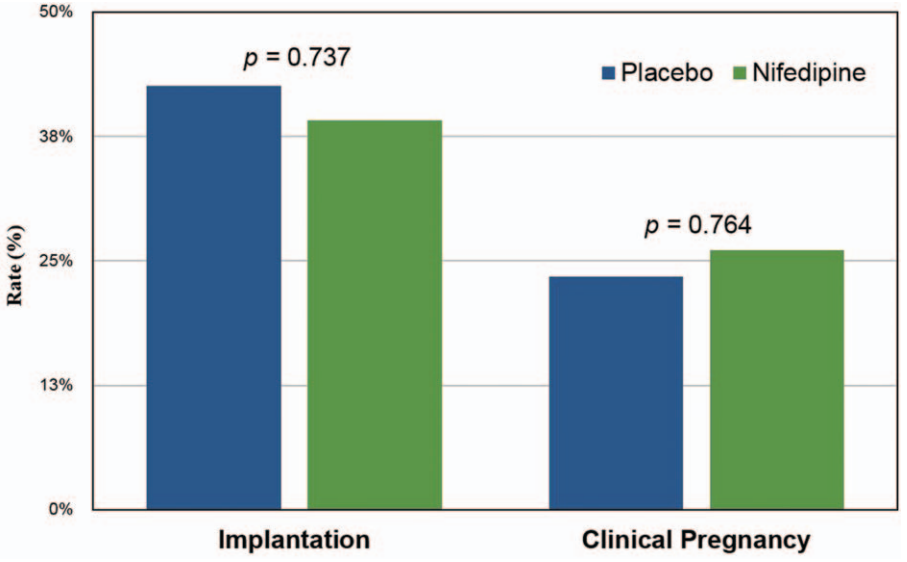

Figure 1. Comparison of primary outcomes between placebo and nifedipine group. No statistical significant differences between the groups were demonstrated ($P > .05$).

limited evidence that it improved outcomes in ET treatments.[15] The case study concluded that the use of hyoscine butylbromide decreased UC activities, evidenced by cine magnetic resonance imaging, thus facilitating embryo retention and improved CPR for women who have repeated unsuccessful ET transfers.[17] Perhaps these pharmacological agents would only be efficacious for certain subgroups of infertile patients. Although there is quality evidence to suggest that excessive UC activities contribute to implantation failure in ET treatments,[2–5] more investigations are required to translate these tocolytic agents' theoretical benefit into clinical benefit.

The class of pharmacological that has showed the most evidence in improving IVF outcome by altering UC activity is an oxytocin and vasopressin receptor antagonist, namely atosiban. Atosiban reduces UC, by decreasing the intrauterine production prostaglandin, and improves uterine blood supply. Both factors are potentially beneficial for embryo implantation.[12] In late 2016, a meta-analysis on the efficacy of atosiban in infertility treatment was published.[14] The meta-analysis concluded that the administration of atosiban on the day of ET improved IR with an odds ratio of 1.92, but not CPR[14]; despite one of the included trials claiming that the use of atosiban improved CPR from 0% to 43.7%.[11] Once again, future studies are needed to fully assess atosiban's clinical application in infertility treatment. The studies of atosiban highlighted the possibility that there is more than just UC governing the success of embryo implantation. The knowledge of the microenvironment and the complicated multifactorial interplay of the uterus necessary for an improved ET outcome is still insufficient. These issues mentioned above must be addressed before we can fully improve the outcomes of infertility treatment by targeting these multifactorial uterine factors pharmacologically.

Nonetheless, this study has essentially provided guidance for future studies on the use of nifedipine in ET treatments. A larger sample size, potentially a different drug protocol, and characterization of the uterine activities are recommended.

5. Conclusion

This double blinded, randomized, and placebo-controlled trial demonstrated that the single use of 20 mg nifedipine given 30 minutes before embryo transfer did not improve the implantation rate or the clinical pregnancy rate. This study has essentially been the first to provide guidance for future investigations on nifedipine usage in infertility treatments. Although our data suggest that the use of nifedipine does not increases the risk of adverse maternal or pregnancy events at this sample size, further studies are required to establish the clinical benefits and safety aspects of nifedipine usage in assisted reproductive treatments.

Author contributions

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