The effect of early administration of rectal progesterone in IVF/ICSI twin pregnancies on the preterm birth rate: A randomized trial

Mona Aboulghar (✉ monaaboulghar71@gmail.com)

Cairo University <https://orcid.org/0000-0003-4835-509X>

Yahia El-Faissal

The Egyptian ivf center

Ahmed Kamel

Department of Obstetrics and Gynecology Cairo University

Yomna Islam

The Egyptian IVF-ET Center <https://orcid.org/0000-0001-6258-1371>

Ragaa Mansour

The Egyptian IVF-ET Center

Gamal Aboulserour

The Egyptian IVF-ET Center

Mohamed Aboulghar

The Egyptian IVF-ET Center <https://orcid.org/0000-0002-3935-6501>

Research article

Keywords: IVF/ICSI, twins, preterm birth, rectal progesterone, first trimester scan, randomized placebo controlled double blind study

Posted Date: August 21st, 2019

DOI: <https://doi.org/10.21203/rs.2.13317/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at BMC Pregnancy and Childbirth on June 9th, 2020. See the published version at <https://doi.org/10.1186/s12884-020-03033-4>.

Abstract

Background: The rate of multiple pregnancies in IVF/ICSI ranges from 20-30% . The incidence of preterm birth in multiple pregnancies is as high as 60% and is even higher in pregnancies conceived after IVF & ICSI. The effect of progesterone on prevention of preterm birth in twins is controversial . Our group has proven a positive effect in reduction of preterm birth ,by starting progesterone from the mid-trimester ,in exclusively IVF/ICSI singleton pregnancies but not twins. The purpose of our current study was to explore the effect of earlier administration of natural progesterone, in IVF/ICSI twin pregnancies starting at 11-14 weeks for prevention of preterm birth. **Methods:** This is a double-blind, placebo controlled, single center, randomized clinical trial. Women with dichorionic twin gestations, following an IVF/ICSI trial were randomized to receive natural rectal progesterone (800 mg daily) vs placebo, starting early from 11-14 weeks. They were randomized regardless of cervical length and had no previous history of preterm birth or known Mullerian anomalies. The primary outcome was, preterm birth rate <37 weeks. The secondary Outcome was; preterm birth <34,32,28 weeks and neonatal outcome. **Results:** A total of 203 women were randomized to both groups, final analysis included 199 women as 4 were lost to follow up. The base line characteristics as well as gestational age at delivery were not significantly different between the study and the placebo group (34.7 ± 3.6 vs 34.5 ± 4.5 , $P=0.626$). Progesterone administration was not associated with a significant decrease in the preterm birth rates <37 weeks (73.5% vs 68%, $P = 0.551$), <34 (20.6% vs 21.6%, $P = 0.649$), <32 (8.8% vs 12.4%, $P = 0.46$) & <28 (4.9 % vs 3.1 %, $P = 0.555$). **Conclusions:** Rectal natural progesterone starting from the first trimester in IVF/ICSI twin pregnancies did not reduce preterm birth. The trial was registered on 31 January 2014 at www.ISRCTN.com, 69810120.

Background

Multiple pregnancy remains one of the major complications of assisted reproductive techniques. It was repeatedly reported that a large percentage of ART-conceived babies were twin pregnancies. It is well documented that multiple pregnancies are associated with a high rate of preterm birth, perinatal morbidity and mortality [1,2] and therefore, it is considered to be the most serious complication of multiple pregnancy. Our published data showed a 64.8 % preterm birth rate (<37 weeks) in twin pregnancies [3].

There is also evidence that, the incidence of preterm birth is higher for ART-conceived infants when compared to spontaneous pregnancies (31.2% vs 9.7%, and in very early preterm birth 5.2 vs 1.6, respectively)[4].

Prevention of preterm birth in ART pregnancies became a priority. It was previously reported in several large randomized studies and meta-analysis that, administration of progesterone resulted in a significant reduction in the rate of preterm births in singleton pregnancies, when administered starting at mid trimester to all women, including those with a previous history of preterm birth as well as women with a short cervix [5-9]. Similarly, this positive effect of natural vaginal progesterone administration starting

from mid-trimester was shown by our group in IVF singleton pregnancies regardless of cervical length [3]. However, this same study did not reveal a significant reduction in preterm birth rate in IVF twins.

Controversy surrounds the use of progesterone in the prevention of preterm birth in twin gestation. Two large randomized controlled studies [10,11] found no value in its use in twin pregnancy. A recent meta-analysis showed that in asymptomatic women with a mid-trimester sonographic short cervix, progesterone significantly reduced the risk of preterm birth < 33 weeks' gestation by 31% [12].

The present study aimed to explore the effect of earlier administration of natural rectal progesterone in IVF/ICSI twin pregnancies, starting at 11-14 weeks up to 37 weeks' gestation, on preterm birth rate.

Methods

Natural rectal progesterone was administered vs placebo to twin pregnancies following IVF/ICSI.

This is a double-blind, placebo controlled, single center, randomized clinical trial performed during the period from January 2014 to July 2017.

Participants

All pregnant women, with dichorionic twins, following an IVF/ICSI trial performed at the Egyptian IVF Center Maadi Cairo Egypt, were counseled to participate in this study after performing the first trimester scan.

Inclusion Criteria:

1) Non-Smokers, 2) Normal Fetal anatomy, 3) No Uterine anomalies, 4) Only Dichorionic twins, 5) No previous history of preterm birth, 6) Healthy pregnant women not suffering from medical disorders eg diabetes and hypertension, 7) No known allergy to progesterone.

To ensure eligibility of participants, all women enrolled in the study had a first trimester scan for risk assessment of Down's Syndrome in addition to an anomaly scan at 11-14 weeks of pregnancy. Dating was performed by calculation from date of embryo transfer.

After the supervising Obstetrician explained the protocol and its aim and design, women who agreed to join the study signed a consent form and were randomized and began the suppositories immediately.

Participants received 100mg daily IM Progesterone injections (IBSA Egypt) for luteal phase support starting on the day of oocyte retrieval until the first viability ultrasound was performed at 7 weeks. Once fetal heart beats, were confirmed they were advised to stop intake of progesterone.

Participants in both study and control groups received our routine antimicrobial agents given for twin pregnancy. They received Clindamycin vaginal cream (2%) for 7 days each month and oral Amoxicillin as a single dose of 3gm once every month [13,14].

All women were followed up according to the routine antenatal care protocol of our institution. Every visit we confirmed adequate intake of the suppositories and took note of any reported side effects or adverse outcomes. Collection of data was done following delivery by direct contact with the patient's obstetrician and neonatologist in addition to phone calls to the patient to confirm compliance to the use of the suppositories. This included gestational age at delivery, neonatal condition, and reporting of neonatal intensive care unit (NICU) admission, birth weight and congenital anomalies undetected during pregnancy.

Randomization

Randomization was done into either the Progesterone group or the placebo group. Women were randomized after performing the first trimester scan at 11-14 weeks by opening a numbered, sealed, opaque envelope, with either progesterone or the placebo at a ratio of 1: 1 ratio (hand generated using the Microsoft excel Software), which was executed by a third party not involved in the trial (a nurse). Progesterone and placebo suppositories were provided by the manufacturer (IBSA Egypt) in indistinguishable packings, labeled with the patient's code, the study name. The manufacturer was not involved in the writing of the protocol or study design or writing of the paper or its submission. Suppositories were provided to the patient by the supervising nurse in sealed packages given once a month to cover the period till her next antenatal visit.

Intervention

The study group received natural progesterone suppositories of 400mg, while the Placebo was composed of 126mg hard fat, 36mg Gelucire pellets, 0.2 mg Sorbic acid, 300 mg cocoa butter, 195mg purified water (Supplied by IBSA Egypt), they both appeared exactly similar. All suppositories were administered rectally twice daily starting from the randomization process at 11-14 weeks until 37 weeks or delivery. Rectal administration was chosen as social and cultural background of our women showed that they have great fear from repeated vaginal administration, in addition we chose this route to minimize possible risks of vaginal infections from repeated prolonged periods of twice daily administration of vaginal suppositories

Participants, supervising doctors and nurses were unaware of the randomization and allocation of the women. Only an independent secretary had the key code, but had no access to the data nor to the women. The blinding code was not broken until all data was collected from all participants which took place a few weeks following delivery of the last patient. Long term follow up of the infants was not performed in this study.

Study outcomes

Primary outcome measures: Delivery before 37 weeks' gestation.

Secondary outcome measures: Preterm births <34, <32 and <28 weeks

Neonatal outcome; including: NICU admission, neonatal death.

Relevant Definitions

- Early fetal loss: fetal death between 10 and 22 weeks of gestational age [15]
- Late fetal loss: fetal death between 22 and 28 weeks of gestational age [15]
- Stillbirth: Fetal death after 28 weeks gestational age [15]
- NICU admission; neonatal admission to Intensive care for any reason other than neonatal jaundice
- Neonatal death; death up to 30 days after delivery

Sample size estimation

Sample size calculation was based on a 20% reduction of the previously reported 65% preterm birth rate in twin pregnancies before 37 weeks of gestation [5]. Calculation was done based on comparing 2 proportions from independent samples using Chi-square test wherein the α -error level was fixed at 0.05 and the power was set at 80%. Accordingly, the sample size was calculated to be 96 cases in each arm. Sample size calculation was done using PS Power and Sample Size Calculations software, version 3.0.11 for MS Windows (William D. Dupont and Walton D. Vanderbilt, USA).

Ethical Approval

All women read and signed an informed consent after full explanation of the study design and procedure. The study protocol was designed according to the CONSORT statement. Ethical approval was obtained on 15/11/2013 by our local Ethical Committee "Ethics and research Committee of the Egyptian IVF center" headed by Professor Ibrahim Fahmy, (imfahmy@gmail.com) and received an IRB number of 3/2013. The trial was registered on 31 January 2014 at www.ISRCTN.com, number 69810120.

Statistical methods:

Data was statistically described in terms of mean $\pm$ standard deviation ($\pm$ SD), or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables was done using Student *t* test for independent samples. Chi-square test was used to compare categorical data between groups. A two-tailed *P* value <0.05 was considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 20 for Microsoft Windows (2006).

Results

We counseled 250 women to join the study, 215 were enrolled, finally 203 signed the consent and were randomized (figure 1). The Analysis was performed according to the intent-to-treat principle. Four women were lost to follow up, one in the study group & three in the placebo group. The study was completed and analysis was done for 199 women. There was excellent compliance, all of the women adhering to twice daily suppository intake throughout the study period, except two women one who stopped on her own at

24 weeks & a second who suffered bleeding esophageal varices and was for her safety recommended to stop any other medications.

There was no significant difference between both groups with regards to age, BMI and gestational age at randomization as shown in Table 1. All women were Middle Eastern, Egyptians. There was no significant difference in gestational age at delivery, term births, preterm births, early fetal loss. Furthermore, there was no significant difference between the preterm birth rates at < 34, <32 and <28 weeks (Table 2).

Only two women were delivered electively preterm due to preeclampsia, the remaining women went into spontaneous preterm contractions or preterm rupture of membranes, otherwise were delivered electively by Cesarean section after 37 weeks.

Table 3, demonstrates the NICU admission, neonatal death and intrauterine fetal death, birth weight and take-home baby rate in both groups. There was no significant difference between the study and control group in these parameters.

Discussion

The wide use of assisted reproductive techniques such as IVF& ICSI as well as ovulation induction drugs for non-IVF cases increased the rate of twin pregnancy worldwide [16,17].

The overall reported incidence of twins following Assisted Reproductive Techniques (ART) in the latest ICMART (The international Committee Monitoring Assisted Reproductive Technologies) report was 20.9% [16]. The most recent data reported that approximately 33.9% of ART-conceived infants in the USA were twins, among those 62.4% were born preterm [4]. While the Preterm birth rate of twins following ART in Europe was 48.8%. [18]

The outcome of preterm neonates depends on the gestational age at birth and available resources of the Neonatology unit caring for those infants. [19]

It is of course noteworthy that care of premature neonates adds a huge financial burden on the health care provider and on the couple especially when medical care is privately funded.[20] The objective of the current study was a trial to reduce the preterm birth rate in IVF/ICSI twin pregnancies.

This randomized placebo controlled double blind study did not show any benefit of giving natural rectal progesterone starting early on in pregnancy for prevention of preterm birth < 37 weeks in IVF/ ICSI twins. It is worth noting that the mean gestational age at delivery in both groups was +/- 34 weeks. This is earlier than that reported in most literature, which could be attributed to the different ethnicity of our studied group. [21,22] In addition, women included were all exclusively IVF pregnancies which are known to be associated with higher incidence of preterm birth [4]. Furthermore, a recent study by Saccone and colleagues [23] concluded that gestational age at delivery, for IVF-conceived twins, was earlier by about 1 week on average, compared with spontaneously-conceived twins, regardless the cervical length measured in the second trimester.

The results of this study are in agreement with several previous publications [5,10,11]. However, it should be noted that all previous studies started progesterone administration at mid-trimester, while our study is unique in that it was exclusively performed for IVF/ICSI twins starting from the first trimester.

We used the rectal route instead of the vaginal route while all previously published studies used the vaginal route [5-8,10,11]. However, the rectal route has previously been studied and found to be as effective as the vaginal route [24-28]. We chose this route because our previous experience also has shown more patient acceptability, comfort, and compliance with the rectal route [24]. It may also minimize any possibility of infection through the twice daily application of vaginal suppositories.

We have previously proven that progesterone is effective in reducing preterm birth [3] rates in singleton IVF/ICSI pregnancies starting from the mid-trimester, but did not find the same significance in twins, thus we postulated that starting earlier on in pregnancy might produce a significant reduction. We also chose the twins resulting from IVF/ICSI pregnancies because they are known to have a higher incidence of preterm birth [29] and are more closely monitored and followed up. Moreover, we only included dichorionic twins as it is known that monochorionic twins are associated with higher miscarriage rates and other complications [30]. Other studies in the literature included both dichorionic and monochorionic twins [10].

Numerous trials have been published [10,11,31-43] on the use of progesterone for prevention of preterm birth in twin pregnancies, and none of them were done exclusively on IVF/ ICSI twins. Moreover, the results of these trials are controversial, as two big randomized placebo controlled trials found no significant reduction in preterm birth in twins < 34 weeks after administration of progesterone regardless of cervical length [10,11]. A more recent randomized controlled trial on twin pregnancies with short cervix 20-24 mm showed that the administration of progesterone resulted in a significant reduction of preterm birth [35].

A recent meta-analysis showed that administration of vaginal progesterone to asymptomatic women with twin gestations and a sonographic short cervix in the mid trimester reduces the risk of preterm birth occurring at <30 to < 35 gestational weeks [12]. The evidence in this study is a moderate quality evidence with a moderate risk bias because a single study included produced most of the pooled effect [35].

According to the 1995 world collaborative Report on IVF [44] 24% of pregnancies were twins, 4.1% triplets & 0.2% quadruplets giving a total of 44-45% multiple birth babies. This was due to the practice of transferring two or more embryos. It was suggested at the time to start with single embryo transfer SET.

In the latest report by the ICMART [16] including data from the years 2008- 2010, single embryo transfer (SET) increased from 25.7% to 30% with a resulting drop in Multiple twin births to 19.6% & the triplets to 1.0%. Individual European countries with strict single embryo transfer policies such as Sweden have 76.9% of their transfers SET and a resulting 5.4 % only twin births [44]. Likewise, 84.9% of transfers in 2013 in Australia were SETs, resulting in a 5.5% twin delivery rate with a persistent high 67.3% preterm

birth rate. [45] This clearly shows that SET policy is the most successful preventive measure to reduce the problem of preterm birth in twins.

Conclusions

To conclude, rectal progesterone starting from the first trimester is ineffective in reducing preterm birth in IVF/ICSI twin pregnancies. As the risk of preterm birth is known to be high in twin pregnancies, the best approach in the management would be preventive. This can be achieved to a great extent by routine single embryo transfer after IVF/ICSI.

Abbreviations

IM : intramuscular

USA: United states of America

IVF/ICSI: in vitro fertilization/ intracytoplasmic sperm injection

SET: Single embryo transfer

Declarations

Authors' contribution

All the authors contributed equally in working on the study and the have read and approved the manuscript.

Ethical approval

The study protocol was designed according to the CONSORT statement.

Ethical approval was obtained on 15/11/2013 by our local Ethical Committee "Ethics and research Committee of the Egyptian IVF center" headed by Professor Ibrahim Fahmy, (imfahmy@gmail.com) and received an IRB number of 3/2013.

The trial was registered on 31 January 2014 at www.ISRCTN.com, number 69810120.

Consent for publication

Not applicable

Availability data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Competing interests

The authors declare that they have no competing interests

Funding

The study was self funded by the Egyptian IVF center, however the suppositories and the placebo were provided for free to the patients by IBSA EGYPT

Authors contributions

MMA & YF; research idea , writing of protocol, recruitment and counseling of the women and their follow up, writing of the manuscript

AK, YI ; recruitment and follow up of the patients, writing of the manuscript

MA; writing and revision of the Manuscript

GA & RM; revision of the manuscript

Acknowledgments

We thank our supervising nurse Mrs. Bayoumy and our study secretary Mrs. Radwan for their help in follow up of participants, data collection and data entry.

Authors information

MMA has been working in the field of infertility and ART since 1998 at one of the largest units in Cairo with 5000 IVF cycles a year. She has been working with ultrasound since 2001 and has special interest in cervical measurement and preterm birth and has published 2 papers in Rbmonline about similar subjects and data of study published in 2012 has been involved in several IPD meta-analysis.

MA, GS, RM are the authors of numerous publications in the field of ART since 1987 being the founders and clinical directors of the first IVF center in Egypt which has reached 5000 cycles per year

References

1. Vogel JP, Torloni MR, Seuc A, et al. (2013) Maternal and perinatal outcomes of twin pregnancy in 23 low- and middle-income countries. *PLoS One*, 8: e70549.
2. [Giuffrè M, Piro E, Corsello G.](#) (2012) Prematurity and twinning. *J Matern Fetal Neonatal Med.* Oct;25 Suppl 3:6-10.

3. [Aboulghar MM, Aboulghar MA, Amin YM, Al-Inany HG, Mansour RT, Serour GI. \(2012\). The use of vaginal natural progesterone for prevention of preterm birth in IVF/ICSI pregnancies. *Reprod Biomed Online*. Aug;25\(2\):133-8.](#)
4. Sunderam S, Kissin DM, Crawford SB, et al. (2018) [Assisted Reproductive Technology Surveillance - United States, 2015](#).MMWR Surveill Summ. Feb 16;67(3):1-28
5. Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH. (2007) Fetal Medicine Foundation Second Trimester Screening Group. Progesterone and the risk of preterm birth among women with a short cervix. *N Engl J Med*; 357: 462–469. ☒
6. De Franco EA, O' Brien JM, Adair CD, et al. (2007) Vaginal natural progesterone is associated with a decrease in risk for early preterm birth and improved neonatal outcome in women with a short cervix: a secondary analysis from a randomized double-blind placebo-controlled trial. *Ultrasound Obstet Gynecol*. oct;30(5):697-705
7. Hassan SS, Romero R, Vidyadhari D, et al. (2011) PREGNANT Trial. [Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial](#). *Ultrasound Obstet Gynecol*. Jul;38(1):18-31.
8. [Romero R, Conde-Agudelo A, Da Fonseca E, et al. \(2018\). Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix: a meta-analysis of individual patient data. *Am J Obstet Gynecol*. Feb;218\(2\):161-180.](#)
9. Dodd JM, Jones L, Flenady V, et al. (2013) Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. *Cochrane Database Syst Rev*. Jul 31; (7):CD004947.
10. Rode L, Klein K, [Nicolaides KH](#), et al. (2011) Group. Prevention of preterm delivery in twin gestations (PREDICT): a multicenter, randomized, placebo-controlled trial on the effect of vaginal micronized progesterone. [Ultrasound Obstet Gynecol](#). Sep;38(3):272-80.
11. Norman JE, Marlow N, Messow CM, et al. (2016) Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study) : a multicenter, randomized, double-blind trial. *Lancet* May 21;387:2106-2116.
12. Romero R, Conde-Agudelo A, El-Refaie W, et al. (2017) Vaginal progesterone decreases preterm birth and neonatal morbidity and mortality in women with a twin gestation and a short cervix: an updated meta-analysis of individual patient data. *Ultrasound Obstet Gynecol*; 49: 303–314.
13. Lamont RF, Nhan-Chang CL, Sobel JD, et al. (2011) Treatment of abnormal vaginal flora in early pregnancy with clindamycin for the prevention of spontaneous prevention of spontaneous preterm birth: a systematic review and metaanalysis. *Am J Obstet Gynecol*. Sep;205(3):177-90
14. Smaill F, Vasquez JC. (2007) Antibiotics for asymptomatic bacteriuria in pregnancy. *Cochrane Database of Systematic Reviews*. ;(Issue 2)
15. Zegers-Hochschild F, Adamson GD, Dyer S, Racowsky C, et al. (2017) The International Glossary on Infertility and Fertility Care, 2017 *Fertil Steril*, 108 (3), pp. 393-406.

16. [Dyer S, Chambers GM, de Mouzon J et al. \(2016\) International Committee for Monitoring Assisted Reproductive Technologies world report: Assisted Reproductive Technology 2008, 2009 and 2010. *Hum Reprod.* Jul;31\(7\):1588-609.](#)
17. Berkovitz A, Biron-Shental T, Pasternak Y, et al. (2017) [Predictors of twin pregnancy after ovarian stimulation and intrauterine insemination in women with unexplained infertility.](#) *Hum Fertil (Camb).* Sep;20(3):200-203.
18. Calhaz-Jorge C, De Geyter C, Kupka M, et al. (2017) Assisted reproductive technology in Europe, 2013: results generated from European registers by ESHRE. *Hum Reprod*, 32, 1957–1973
19. Loftin RW, Habli M, Snyder C, et al. (2010) Late Preterm Birth. *Reviews in Obstetrics and Gynecology*.;3(1):10-19.
20. Jacob J, Lehne M, Mischker A, et al. (2017) Cost effects of preterm birth: a comparison of health care costs associated with early preterm, late preterm, full-term birth in the first 3 years after birth. *Eur J Health Econ.* Nov;18(8):1041-1046.
21. Patel RR, Steer P, Doyle P, Little MP, Elliott P. (2004) Does gestation vary by ethnic group? A London-based study of over 122,000 pregnancies with spontaneous onset of labor *Int J Epidemiol.* Feb;33(1):107-13.
22. Steer P. (2005) The epidemiology of preterm labor. *BJOG.* Mar;112 Suppl 1:1-3.
23. [Saccone G, Zullo F, Roman A, et al. \(2019\) Risk of spontaneous preterm birth in IVF-conceived twin pregnancies. *J Matern Fetal Neonatal Med.* Feb;32\(3\):369-376.](#)
24. [Khrouf M, Slimani S, Khrouf MR, et al. \(2017\) Progesterone for Luteal Phase Support in In Vitro Fertilization: Comparison of Vaginal and Rectal Pessaries to Vaginal Capsules: A Randomized Controlled Study.](#) *Clin Med Insights Womens Health.* Jan 5;9:43-47.
25. Van der Linden M, Buckingham K, Farquhar C, Kremer JA, Metwally M. (2015) Luteal phase support for assisted reproduction cycles. *Cochrane Database Syst Rev.* 7;(7):CD009154.
26. [Aghsa MM, Rahmanpour H, Bagheri M, Davari-Tanha F, Nasr R. \(2012\) A randomized comparison of the efficacy, side effects and patient convenience between vaginal and rectal administration of Cyclogest\(®\) when used for luteal phase support in ICSI treatment. *Arch Gynecol Obstet.* Oct;286\(4\):1049-54](#)
27. Ioannidis G, Sacks G, Reddy N et al . (2005) Day 14 maternal serum progesterone levels predict pregnancy outcome in IVF/ ICSI treatment cycles: a prospective study. *Hum Reprod*;20:741–746.
28. Chakmakjian ZH, Zachariah NY. (1987) Bioavailability of progesterone with different modes of administration. *J Reprod Med*;32:443–448.
29. Henningsen AK, Pinborg A. (2014) [Birth and perinatal outcomes and complications for babies conceived following ART.](#) *Semin Fetal Neonatal Med.* Aug;19(4):234-8.
30. [Simões T, Queirós A, Marujo AT, Valdoeiros S, Silva P, Blickstein I. \(2015\) Outcome of monozygotic twins conceived by assisted reproduction. *Fertil Steril.* Sep;104\(3\):629-32.](#)

31. Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH. (2007) Group Fetal Medicine Foundation Second Trimester Screening. Progesterone and the risk of preterm birth among women with a short cervix. *N Engl J Med*; 357: 462–469.
32. Cetingoz E, Cam C, Sakalli M, Karateke A, Celik C, Sancak A. (2011) Progesterone effects on preterm birth in high-risk pregnancies: a randomized placebo-controlled trial. *Arch Gynecol Obstet*; 283: 423–429.
33. Serra V, Perales A, Meseguer J, et al. (2013) Increased doses of vaginal progesterone for the prevention of preterm birth in twin pregnancies: a randomised controlled double-blind multicentre trial. *BJOG*; 120: 50–57.
34. Brizot M, Hernandez W, Liao A, et al. (2015) Vaginal progesterone for the prevention of preterm birth in twin gestations: a randomized placebo-controlled double-blind study. *Am J Obstet Gynecol* ; 213: 82.e1–9.
35. El-Refaie W, Abdelhafez MS, Badawy A. (2016) Vaginal progesterone for prevention of preterm labor in asymptomatic twin pregnancies with sonographic short cervix: a randomized clinical trial of efficacy and safety. *Arch Gynecol Obstet*; 293: 61–67.
36. Brubaker SG, Pessel C, Zork N, Gyamfi-Bannerman C, Ananth CV. (2015) [Vaginal progesterone in women with twin gestations complicated by short cervix: a retrospective cohort study](#). *BJOG*. Apr;122(5):712-8.
37. Biggio JR. (2015) [Short cervix and twins: progesterone, yes or no?](#) *BJOG*. Apr;122(5):719.
38. Schuit E, Stock S, Rode L, et al. (2015) Global Obstetrics Network (GONet) collaboration. [Effectiveness of progestogens to improve perinatal outcome in twin pregnancies: an individual participant data meta-analysis](#). *BJOG*. Jan;122(1):27-37.
39. Norman JE, Mackenzie F, Owen P, et al. (2009) [Progesterone for the prevention of preterm birth in twin pregnancy \(STOPPIT\): a randomised, double-blind, placebo-controlled study and meta-analysis](#). *Lancet*. Jun 13;373(9680):2034-40.
40. Durnwald CP, Momirova V, Rouse DJ, et al. (2010) Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. [Second trimester cervical length and risk of preterm birth in women with twin gestations treated with 17- \$\alpha\$ hydroxyprogesterone caproate](#). *J Matern Fetal Neonatal Med*. Dec;23(12):1360-4
41. Lim AC, Schuit E, Papatsonis D, et al. (2012) [Effect of 17-alpha hydroxyprogesterone caproate on cervical length in twin pregnancies](#). *Ultrasound Obstet Gynecol*. Oct;40(4):426-30.
42. Senat MV, Porcher R, Winer N, et al. (2013) Groupe de Recherche en Obstétrique et Gynécologie. Prevention of preterm delivery by 17 α hydroxyprogesterone caproate in asymptomatic twin pregnancies with a short cervix: a randomized controlled trial. *Am J Obstet Gynecol*. Mar;208(3):194.e1-8
43. Agra IKR, Carvalho MHB, Hernandez WR, Francisco RPV, Zugaib M, Brizot ML. (2017). [The effect of prenatal vaginal progesterone on cervical length in nonselected twin pregnancies](#). *J Matern Fetal Neonatal Med*. Nov 22:1-5.

44. J. De Mouzon and P. Lancaster. (1997)World Collaborative Report on In Vitro Fertilization: Preliminary data for 1995. Journal of Assisted Reproduction and Genetics. 14/5: (Supplement) 2535,2635-2645; Edwards, "Human Conception In Vitro 1995, a Summing up," 202.
45. [European IVF-monitoring Consortium \(EIM\)](#); [European Society of Human Reproduction and Embryology \(ESHRE\)](#), Calhaz-Jorge C, De Geyter C, Kupka MS et al. (2017) Assistedreproductivetechnology in Europe, 2013: results generated from European registers by ESHRE. [Hum Reprod.](#) Oct 1;32(10):1957-1973
46. Kushnir VA,Barad DH,Albertini DF, Darmon SK, Gleicher N. (2017) Systematic review of worldwide trends in assisted reproductive technology 2004-2013. [Reprod Biol Endocrinol.](#) Jan 10;15(1):6.

Tables

Table 1: Baseline characteristics & gestational age at randomization:

	Progesterone group	Control group	P value
(n)	102	97	-
Maternal age (years)	29.5±4.8	30 ±4.6	0.498
BMI (kg/m2)	30.5±5.8	30.1±4.8	0.623
Gestational age at randomization (weeks)	12.7±0.9	12.5±1	0.341

Data is expressed either as a mean±SD or n (%)

Table 2: Comparison of gestational age at delivery between both groups

		Progesterone group	Placebo group	
Gestational age at delivery (weeks)		34.7±3.6	34.5±4.5	0.626
Term Births (n)	>37 weeks	25 (24.5%)	27 (27.8%)	0.594
Preterm Births (n)	<37 weeks	75 (73.5%)	66 (68%)	0.551
	<34 weeks	21 (20.6%)	21 (21.6%)	0.649
	<32 weeks	9 (8.8%)	12 (12.4%)	0.46
	<30 weeks	5 (4.9%)	7 (7.2%)	0.516
	<28 weeks	5 (4.9%)	3 (3.1%)	0.555
Early fetal loss(n)		2 (2%)	4 (4.1%)	0.372

Data is expressed either as a mean±SD or n (%)

Table 3: Neonatal outcome in both groups

Stillbirth admission (n)	-Single	9 (8.8%)	6 (6.2%)	0.726
	-both	13 (12.7%)	11 (11.3%)	
	-total	22 (21.6%)	17 (17.5%)	0.717
Neonatal death (n)	-single	7 (6.9%)	3 (3.1%)	0.404
	-both	6 (5.9%)	8 (8.2%)	
	-total	13 (12.7%)	11 (11.3%)	0.761
Respiratory birth (n)	-single	2 (2%)	1 (1%)	0.513
	-both	-	1 (1%)	
Birth weight (gm)	First twin	2379.4±519.3	2272.1±566.7	0.190
	Second twin	2351.8±525.5	2299.2±559.6	0.513
Home baby (n)	One	10 (9.8%)	4 (4.1%)	0.196
	Both	83 (81.4%)	80 (82.5%)	
	None	8 (7.8%)	13 (13.4%)	

Data is expressed either as a mean±SD or n (%)

Figures

Figure 1

Flow Chart of Trial

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [supplement1.pdf](#)