Human Reproduction, Vol.36, No.7, pp. 1821–1831, 2021
Advance Access Publication on April 30, 2021 doi:10.1093/humrep/deab093

human reproduction

ORIGINAL ARTICLE *Infertility*

Micronized progesterone plus dydrogesterone versus micronized progesterone alone for luteal phase support in frozen-thawed cycles (MIDRONE): a prospective cohort study

Lan N. Vuong [1,2,*], Toan D. Pham[2], Khanh T.Q. Le[2], Trung T. Ly[2], Ho L. Le [2], Diem T.N. Nguyen[2], Vu N.A. Ho [2], Vinh Q. Dang[2], Tuan H. Phung[2], Robert J. Norman[3], Ben W. Mol[4,5], and Tuong M. Ho[2]

[1]University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam[2]IVFMD, My Duc Hospital and HOPE Research Center, Ho Chi Minh City, Vietnam [3]Robinson Research Institute and Adelaide Medical School, The University of Adelaide, Adelaide, South Australia, Australia [4]Monash University, Melbourne, Australia [5]Aberdeen Centre for Women's Health Research, School of Medicine, University of Aberdeen, Aberdeen, UK

*Correspondence address. Department of Obstetrics and Gynaecology, University of Medicine and Pharmacy at Ho Chi Minh City, 217 Hong Bang Street, District 5, Ho Chi Minh City, Vietnam. Tel: +84-903008889; E-mail: lanvuong@ump.edu.vn; drlan@yahoo.com.vn https://orcid.org/0000-0001-6529-6912

Submitted on December 17, 2020; resubmitted on March 16, 2021; editorial decision on March 23, 2021

STUDY QUESTION: Does the addition of oral dydrogesterone to vaginal progesterone as luteal phase support improve pregnancy outcomes during frozen embryo transfer (FET) cycles compared with vaginal progesterone alone?

SUMMARY ANSWER: Luteal phase support with oral dydrogesterone added to vaginal progesterone had a higher live birth rate and lower miscarriage rate compared with vaginal progesterone alone.

WHAT IS KNOWN ALREADY: Progesterone is an important hormone that triggers secretory transformation of the endometrium to allow implantation of the embryo. During IVF, exogenous progesterone is administered for luteal phase support. However, there is wide inter-individual variation in absorption of progesterone via the vaginal wall. Oral dydrogesterone is effective and well tolerated when used to provide luteal phase support after fresh embryo transfer. However, there are currently no data on the effectiveness of luteal phase support with the combination of dydrogesterone with vaginal micronized progesterone compared with vaginal micronized progesterone after FET.

STUDY DESIGN, SIZE, DURATION: Prospective cohort study conducted at an academic infertility center in Vietnam from 26 June 2019 to 30 March 2020.

PARTICIPANTS/MATERIALS, SETTING, METHODS: We studied 1364 women undergoing IVF with FET. Luteal support was started when endometrial thickness reached ≥8 mm. The luteal support regimen was either vaginal micronized progesterone 400 mg twice daily plus oral dydrogesterone 10 mg twice daily (second part of the study) or vaginal micronized progesterone 400 mg twice daily (first 4 months of the study). In women with a positive pregnancy test, the appropriate luteal phase support regimen was continued until 7 weeks' gestation. The primary endpoint was live birth after the first FET of the started cycle, with miscarriage <12 weeks as one of the secondary endpoints.

MAIN RESULTS AND THE ROLE OF CHANCE: The vaginal progesterone + dydrogesterone group and vaginal progesterone groups included 732 and 632 participants, respectively. Live birth rates were 46.3% versus 41.3%, respectively (rate ratio [RR] 1.12, 95%

CI 0.99–1.27, $P = 0.06$; multivariate analysis RR 1.30 (95% CI 1.01–1.68), $P = 0.042$), with a statistically significant lower rate of miscarriage at <12 weeks in the progesterone + dydrogesterone versus progesterone group (3.4% versus 6.6%; RR 0.51, 95% CI 0.32–0.83; $P = 0.009$). Birth weight of both singletons (2971.0 ± 628.4 versus 3118.8 ± 559.2 g; $P = 0.004$) and twins (2175.5 ± 494.8 versus 2494.2 ± 584.7; $P = 0.002$) was significantly lower in the progesterone plus dydrogesterone versus progesterone group.

LIMITATIONS, REASONS FOR CAUTION: The main limitations of the study were the open-label design and the non-randomized nature of the sequential administration of study treatments. However, our systematic comparison of the two strategies was able to be performed much more rapidly than a conventional randomized controlled trial. In addition, the single ethnicity population limits external generalizability.

WIDER IMPLICATIONS OF THE FINDINGS: Our findings study suggest a role for oral dydrogesterone in addition to vaginal progesterone as luteal phase support in FET cycles to reduce the miscarriage rate and improve the live birth rate. Carefully planned prospective cohort studies with limited bias could be used as an alternative to randomized controlled clinical trials to inform clinical practice.

STUDY FUNDING/COMPETING INTERESTS: This study received no external funding. LNV has received speaker and conference fees from Merck, grant, speaker and conference fees from Merck Sharpe and Dohme, and speaker, conference and scientific board fees from Ferring; TMH has received speaker fees from Merck, Merck Sharp and Dohme, and Ferring; R.J.N. has received scientific board fees from Ferring and receives grant funding from the National Health and Medical Research Council (NHMRC) of Australia; BWM has acted as a paid consultant to Merck, ObsEva and Guerbet, and is the recipient of grant money from an NHMRC Investigator Grant.

TRIAL REGISTRATION NUMBER: NCT0399876.

Key words: *in vitro* fertilization / frozen embryo transfer / luteal phase support / progesterone / dydrogesterone

Introduction

Progesterone plays an essential role in the secretory transformation of the endometrium that permits implantation of a fertilized oocyte and helps to maintain early pregnancy (Daya, 2009). In fertility treatments, the role of progesterone is particularly crucial in frozen embryo transfer (FET) cycles due to the lack of endogenous progesterone secreted by the corpus luteum. This is increasingly relevant due to the growing use of FET in IVF programs.

Vaginally-administered micronized progesterone is commonly used to provide luteal support in IVF cycles with fresh embryo transfer due to the convenience and effectiveness of this approach compared with intramuscular progesterone injection (Yanushpolsky *et al.*, 2010; van der Linden *et al.*, 2015). A global survey indicated that vaginal progesterone is used in nearly two-thirds of cycles (Vaisbuch *et al.*, 2014). However, vaginal progesterone alone may be insufficient for luteal phase support during FET cycles.

One potential issue for luteal phase support with vaginal progesterone preparations is the large inter-individual variation in serum progesterone levels achieved after treatment (Yovich et al., 2015; Boelig *et al.*, 2019). A simple increase of the vaginal progesterone dosage does not appear to result in a proportional increase in serum levels (Archer *et al.*, 1995; Paulson *et al.*, 2014; Yovich et al., 2015). Furthermore, the vaginal mucosa or total surface area of the vagina may limit the absorption of progesterone from the vagina (Archer *et al.*, 1995). It is possible that lower progesterone levels in endometrial tissue result in a lower implantation rate and higher miscarriage rate, and therefore a lower live birth rate.

Dydrogesterone is an oral progestin with good bioavailability and a good tolerability profile (Griesinger *et al.*, 2018). In clinical studies, the effectiveness of dydrogesterone for luteal phase support has been shown to be comparable to that of vaginal micronized progesterone after fresh (van der Linden *et al.*, 2015; Wang *et al.*, 2015; Barbosa *et al.*, 2016; Tournaye *et al.*, 2017; Griesinger *et al.*, 2018) or frozen (Rashidi *et al.*, 2016) embryo transfer. In addition, the combination of dydrogesterone and vaginal micronized progesterone was recently used to provide luteal support in a randomized study comparing fresh versus frozen blastocyst transfer in ovulatory women (Wei *et al.*, 2019). However, the choice of regimen in that study was not based on comparative effectiveness research of luteal phase support with dydrogesterone, but rather made arbitrarily.

Here, we compare the effectiveness of a combination of vaginal micronized progesterone with oral dydrogesterone versus vaginal micronized progesterone alone as luteal phase support during FET cycles in infertile women undergoing IVF.

Materials and methods

Study design

This prospective cohort study was conducted at IVFMD, My Duc Hospital in Ho Chi Minh City, Vietnam between 26 June 2019 and 30 March 2020. The study was approved by the Ethics Review Board at My Duc Hospital (approval number 07/19/ĐĐ-BVMĐ; date: 22 May 2019), prospectively registered on 26 June 2019 (NCT03998761), and conducted according to the principles of Good Clinical Practice and the Declaration of Helsinki 2002. There was oversight by an independent data and safety monitoring committee, and all participants provided written informed consent.

Study population

Women aged ≥18 years who were permanent residents of Vietnam and undergoing IVF with FET and endometrial preparation using an exogenous hormone regimen were eligible for this study. Women who had >2 previous embryo transfers and those with endometrial abnormalities (including polyps, submucosal fibroids, Cesarian scar defects, hyperplasia, fluid accumulation, adhesion), or were participating in

another IVF study at the same time, were not eligible. In addition, *in vitro* maturation, oocyte donation and preimplantation genetic diagnosis cycles were excluded.

At our center, criteria for an elective freeze-all strategy were abnormal endometrium; large cesarean scar defect; hydrosalpinx and patient request. A non-elective freeze-only strategy was applied in the following situations: premature progesterone rise; risk of ovarian hyperstimulation; gonadotropin-releasing hormone agonist trigger cycle; endometrium <7 mm on day of trigger; and fluid inside cavity on the day of embryo transfer.

Treatments

To prepare the endometrium for FET, all women received oral estradiol valerate (Valiera®; Laboratories Recalcine) 8 mg/day for 6 days starting from the second or third day of menstruation. Endometrial thickness was monitored from Day 6 onwards. After 6 days of treatment (i.e. from days 8 to 9 after the start of menstruation), the estradiol dose could be increased to a maximum of 16 mg/day depending on the thickness of the endometrium. Overall, estradiol was given from the day of starting progesterone until the day of pregnancy testing. Progesterone-based luteal support was started when endometrial thickness reached ≥8 mm. If endometrial thickness was <7 mm after 14 days' treatment with estradiol, the cycle was canceled.

In the first phase of the study (26 June 2019 to 31 October 2019), women received luteal phase support with micronized vaginal progesterone (Cyclogest®; Actavis) 400 mg twice daily (in the morning and evening; control group). Allocation of participants to this regimen was continued until the target sample size was achieved.

In the second phase of the study (1 November 2019 to 30 March 2020), women received dydrogesterone (Duphaston®; Abbott) 10 mg twice daily plus micronized vaginal progesterone (Cyclogest®; Actavis) 400 mg twice daily plus (both given in the morning and evening; intervention group). The second phase of the study included the 1-month lunar new year (Tết) holiday in Vietnam. Therefore, it was planned to recruit for 5 months to ensure that each period included a 4-month recruitment period with the aim of ensuring similar numbers of participants allocated to each regimen. Outcomes were not analyzed prior to the additional month of recruitment.

Fertility treatments

Embryo transfer was performed at 4 days (Day 3 embryo transfer) or 6 days (Day 5 embryo transfer) after starting progesterone. All embryos were warmed on the day of transfer. After warming, surviving embryos (maximum 2) were transferred into the uterus under ultrasound guidance. In both groups, estradiol and progesterone were continued until the day of pregnancy testing. If the pregnancy test was positive, the luteal phase support regimen was continued until 7 weeks of gestation. Only one FET cycle per participant was included in the study.

Outcomes

The primary outcome was live birth after one cycle of FET, defined as the birth of at least one newborn after 24 weeks' gestation exhibiting any sign of life (twins were a single count). Predefined secondary outcomes included the following (all after the first embryo transfer): luteal phase progesterone level (determined using a blood sample taken in the morning of the fourth day after starting progesterone at ~2–3 h after the morning dose of micronized progesterone ± dydrogesterone); and length of the luteal phase (staring on the day of progesterone initiation and ending on the last day prior to menstruation). The following parameters were also assessed: positive pregnancy test (serum hCG level >5 mIU/ml); clinical pregnancy (≥1 gestational sac on ultrasound at 7 weeks' gestation with detection of heart beat activity); ongoing pregnancy (pregnancy with a detectable heart beat at >12 weeks' gestation); ectopic pregnancy (gestational sac outside the uterine cavity); miscarriage (pregnancy loss at <12 weeks' gestation); and multiple pregnancy (presence of >1 sac at early pregnancy ultrasound), all after the first embryo transfer of the started cycle. In addition, the implantation rate was calculated as the number of gestational sacs per number of embryos transferred. Embryo quality was assessed using the Istanbul criteria (Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology, 2011). A good Day 3 embryo was defined as grade I, cell number of 7–9, even cell size, <10% fragmentation, and no multinucleation. A good blastocyst was defined as good inner cell mass that was prominent and easily discernible, with many cells compacted and tightly adhered together and good trophectoderm with many cells forming a cohesive epithelium and stage of development of expanded or hatched/hatching.

The following outcomes were evaluated in women achieving pregnancy: gestational diabetes (defined as any of the following plasma glucose values after an oral glucose tolerance test: ≥92 mg/dl or 5.1 mmol/l [fasting]; ≥180 mg/dl or 10.0 mmol/l [at 1 h]; 153 mg/dl or 8.5 mmol/l [at 2 h]) (American Diabetes Association, 2018); hypertensive disorders of pregnancy (including pregnancy-induced hypertension [new-onset hypertension arising after 20 weeks' gestation without features of pre-eclampsia and resolving within 3 months post-partum], pre-eclampsia and eclampsia [hypertension arising after at least 20 weeks' gestation confirmed on 2 occasions plus one or more of the organ/system features related to the mother and/or fetus including renal, hematological, liver, neurological, pulmonary or uteroplacental]) (Queensland Health); antepartum hemorrhage (bleeding from or into the genital tract, occurring from 24 weeks' gestation up to birth, including placenta previa, placenta accreta and unexplained bleeding); preterm delivery (at <24, <28, <32 and <37 completed weeks of pregnancy); birth weight; rate of low (<2500 g), very low (<1500 g), high (>4000 g) and very high (>4500 g) birth weight; congenital abnormality; venous thromboembolism; and other side effects (including gastrointestinal disorders, nervous system disorders, vaginal discharge, vaginal discomfort and vulvovaginal pruritus).

Measurement of progesterone

Blood samples (2 ml) for determination of serum progesterone levels were collected on Day 4 after starting progesterone. On that morning, women applied micronized vaginal progesterone and/or dydrogesterone (depending on their treatment group), and blood was taken 2−3 h later (at approximately at 8 a.m.). All samples were processed immediately and stored at -20°C. Serum progesterone levels were determined using electrochemiluminescence immunoassay (ECLIA; Roche Cobas E 801, Roche Diagnostics, Germany), with a lower level

of quantification of 0.5 ng/ml, inter-assay variability of 2–6% and intra-assay variability of 2–4%.

Sample size calculation

The live birth rate in cycles that included luteal phase support with vaginal micronized progesterone in frozen-thawed cycles in a previous study at our center was 33.8% per initiated cycle (Vuong *et al.*, 2018). To detect a minimally important difference of 8% in live birth rate between the groups with 80% power and alpha of 5%, and allowing for a drop-out rate of 10%, it was calculated that a total of 1264 women (632 per group) would be required. The required number of participants (n = 632) were recruited to the vaginal progesterone group in the first 4-month study period, but the number of women treated with the combination regimen and recruited to the study during the 4 months of recruitment during the second study period (n = 732) was greater than the number recruited during the first part of the study; this difference in patient numbers between groups simply reflected the number of women undergoing FET during the two 4-month recruitment periods (of which the second lasted 5 months because it contained the 1-month lunar new year [Tết] holiday) and was unintentional.

Statistical analyses

Baseline characteristics were described using mean (with SD), median (quartiles) and count (with percentage), as appropriate. The rate of live birth and the associated 95% confidence interval (CI) were estimated for each group using the exact method for a binomial proportion. Rates of secondary outcomes were estimated for each treatment group, and the difference between groups was analyzed using the rate ratio (RR) with 95% CI. For the main analyses, statistical significance was defined as $P < 0.05$ (with corresponding 95% CI).

A prespecified subgroup analysis was planned based on serum progesterone level quartiles determined based on Day 4 progesterone levels. Outcomes in the two treatment groups were compared within each progesterone level quartile. For these analyses, statistical significance was defined as $P < 0.01$ (with corresponding 99% CI).

A univariate analysis was performed that included all potential confounding variables. Variables with a *P*-value of <0.25 in the univariate analysis were then included in a multivariate logistic regression adjusted analysis to identify significant independent predictors of live birth.

All statistical analyses were performed using the R statistical package (R version 3.3.3, R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

A total of 3614 women were screened, of whom 1721 met the eligibility criteria, and 1364 provided informed consent (reasons for non-inclusion were desire to have three embryos transferred [n = 73] and use of other luteal support regimens [n = 284]). The vaginal progesterone plus dydrogesterone and vaginal progesterone groups included 732 and 632 participants, respectively. All patients were followed for the duration of the first started cycle, including through to delivery in those who achieved pregnancy. Women in the progesterone plus dydrogesterone group had a significantly lower body mass index and anti-Müllerian hormone level at baseline and were significantly less likely to be undergoing their first embryo transfer cycle (Table I). Women were relatively equally distributed across the four quartiles of serum progesterone levels in both treatment groups (Table II).

Live birth

The live birth rate was higher in the progesterone plus dydrogesterone group compared with the progesterone group, but this difference was not statistically significant (46.3% versus 41.3%; RR 1.1, 95% CI 1.0–1.3; $P = 0.06$) (Table II). Predictors of live birth on univariate analysis were age, body mass index, anti-Müllerian hormone level, duration of infertility, type of infertility, ovulation disorder and diminished ovarian reserve as the cause of infertility, serum progesterone level, number of embryos transferred, and stage of embryo at transfer. In the multivariate analysis adjusted for these predictors, the RR value of live birth for patients treated with progesterone plus dydrogesterone versus progesterone alone was 1.30 (95% CI 1.01–1.68; $P = 0.042$).

Other fertility outcomes

Endometrial thickness on the day of embryo transfer was slightly, but significantly, lower in the progesterone plus dydrogesterone versus progesterone alone group (difference of –0.3 mm, 95% CI –0.4 to –0.1; $P < 0.001$) (Table II). The number of embryos and good embryos transferred was similar between groups. In both groups, the proportion of women who had Day 3 cleavage stage embryo transfer was 37–39%, while the remaining women had Day 5 embryo blastocysts transfer (Table II). There were no significant differences between the progesterone plus dydrogesterone versus progesterone alone group with respect to rates of implantation, positive pregnancy test, clinical pregnancy and ongoing pregnancy (Table II).

Complications

The rate of miscarriage at <12 weeks was significantly lower in women who received progesterone plus dydrogesterone compared with progesterone alone (3.4% versus 6.6%; RR 0.51, 95% CI 0.32–0.83; $P = 0.009$) (Table II). The rate of gestational diabetes mellitus was higher in the group that received luteal phase support with progesterone plus dydrogesterone versus progesterone alone (12.6% versus 8.5%; $P = 0.02$) (Table II). Birth weight of both singletons (2971.0 ± 628.4 versus 3118.8 ± 559.2 g; $P = 0.004$) and twins (2175.5 ± 494.8 versus 2494.2 ± 584.7 g; $P = 0.002$) was significantly lower in the progesterone plus dydrogesterone group compared to the group who received luteal phase support with progesterone alone (Table II). The distribution of birth weights in the two treatment groups are represented graphically in Fig. 1. Rates of all other obstetric and perinatal complications were comparable in both treatment groups (Table II).

Predictors of live birth

In addition to treatment with progesterone plus dydrogesterone versus progesterone (as reported above), other statistically significant predictors of live birth on multivariate analysis were lower age of the

Table I Demographic and clinical characteristics of study participants at baseline.

Characteristic	Progesterone + dydrogesterone (n = 732)	Progesterone (n = 632)	*P*-value
Age, years	31.33 ± 4.50	31.36 ± 4.42	0.921
BMI, kg/m^2	20.90 ± 3.53	21.44 ± 2.63	0.002
Anti-Müllerian hormone, ng/ml	3.55 [2.13, 5.52]	3.85 [2.33, 6.01]	0.044
Duration of infertility, years	3.00 [2.00, 5.00]	3.00 [2.00, 5.00]	0.911
Type of infertility, n (%)			0.433
Primary	487 (66.5)	434 (68.7)	
Secondary	245 (33.5)	198 (31.3)	
Number of IVF attempts, n (%)			0.165
1	703 (96.0)	593 (93.8)	
2	28 (3.8)	37 (5.9)	
3	1 (0.1)	2 (0.3)	
Number of previous ET cycles, n (%)			0.017
0	637 (87.0)	573 (90.7)	
1	86 (11.7)	59 (9.3)	
Fresh ET	7 (8.1)	5 (8.5)	0.99
Freeze-all	81 (91.9)	54 (91.5)	
2	9(1.2)	0 (0.0)	
Fresh ET	0 (0)	0 (0)	–
Freeze-all	9 (100)	0 (0)	
Indication for IVF, n (%)			0.056
Male factor	179 (24.5)	174 (27.5)	
Unexplained	123 (16.8)	107 (16.9)	
Tubal factor	128 (17.5)	120 (19.0)	
Ovulation disorder	141 (19.3)	118 (18.7)	
Diminished ovarian reserve	100 (13.7)	85 (13.4)	
Endometriosis	22 (3.0)	5 (0.8)	
Others	39 (5.3)	23 (3.6)	

Values are mean ± SD, median [quartiles], or number of participants (%).
ET, embryo transfer.

woman, primary versus secondary infertility, transfer of one versus two embryos, transfer of Day 5 versus Day 3 embryos (Table III).

Subgroup analyses

Analysis in subgroups with different serum progesterone levels showed that the live birth rate and miscarriage rate did not differ significantly between the two luteal phase support regimen groups in any serum progesterone level quartile (interaction *P*-values of 0.350 and 0.687, respectively) (Table IV).

Discussion

To the best of our knowledge, this is the largest study to date investigating the combination of dydrogesterone plus micronized vaginal progesterone compared with vaginal progesterone alone in the setting of FET. The results showed that the addition of oral dydrogesterone to vaginal progesterone was associated with a higher live birth rate and lower rate of miscarriage. Thus, alternatives to the vaginal route of progesterone administration might be one way to overcome issues relating to vaginal absorption of progesterone.

Key strengths of this study include the large sample size and the fact that it is the first to compare live birth rates after luteal phase support with oral dydrogesterone plus vaginal progesterone compared with vaginal progesterone alone. However, several important limitations need to be taken into account when interpreting the results. Firstly, this was not a randomized trial, which means that bias was not optimally controlled and there are potential differences between the groups that might have influenced the findings. However, multivariate analysis showed a larger treatment effect of oral dydrogesterone plus vaginal progesterone and, in addition to a higher live birth rate, we observed a lower miscarriage rate, which explains the treatment effect. Secondly, study treatments were not given in parallel, but instead were used sequentially in different groups of participants. The influence of time-related effects was not formally tested. However, treatment practices at the study center remained consistent over this period and

Table II Fertility outcomes and complications after the first embryo transfer (intention-to-treat analysis).

	Progesterone + dydrogesterone (n = 732)	Progesterone (n = 632)	Between-group difference (95% CI)	Rate ratio (95% CI)	*P*-value
Fertility outcomes					
Endometrial thickness, mm	10.84 ± 1.24	11.11 ± 1.08	–0.3 (–0.4, –0.1)	–	<0.001
Length of luteal phase, days	19.5 ± 2.3	19.6 ± 2.5	–0.1 (–0.5, 0.3)	–	0.70
Serum progesterone level quartile, n (%)	16.19 ± 10.99	16.14 ± 11.57	–	–	
1 (0.873 to <10.9 ng/ml)	186 (25.4)	155 (24.5)	–	–	
2 (10.9 to <13.9 ng/ml)	190 (26.0)	152 (24.1)	–	–	
3 (13.9 to <18.2 ng/ml)	181 (24.7)	159 (25.2)	–	–	
4 (18.2 to 207.0 ng/ml)	175 (23.9)	166 (26.3)	–	–	
Live birth, n (%)	339 (46.3)	261 (41.3)	5 (–0.4, 10.4)	1.12 (0.99, 1.27)	0.06
Number of embryos transferred, n (%)					0.562
1	389 (53.1)	325 (51.4)	–	–	
2	343 (46.9)	307 (48.6)	–	–	
Number of good embryos transferred, n (%)					0.32
0	81 (11.1)	82 (13.0)	–	–	
1	432 (59.0)	349 (55.2)	–	–	
2	219 (29.9)	201 (31.8)	–	–	
Stage of embryo at transfer, n (%)					0.733
Day 3 (cleavage)	281 (38.4)	236 (37.3)	–	–	
Day 5 (blastocyst)	451 (61.6)	396 (62.7)	–	–	
Positive pregnancy test, n (%)	444 (60.7)	375 (59.3)	1.3 (–4, 6.7)	1.02 (0.94, 1.12)	0.659
Clinical pregnancy, n (%)	406 (55.5)	351 (55.5)	0.1 (–5.4, 5.3)	1.00 (0.91, 1.1)	0.99
Implantation, n (%)	47.4 ± 45.8	45.2 ± 44.3	2.2 (–2.6, 7.0)	–	0.36
Ongoing pregnancy, n (%)	375 (51.2)	304 (48.1)	3.1 (–2.3, 8.6)	1.07 (0.96, 1.19)	0.272
Multiple pregnancy	54 (7.4)	42 (6.6)	0.7 (–2.1, 3.6)	1.11 (0.75, 1.64)	0.67
Complications					
Pregnancy complications, n (%)					
Ectopic pregnancy	6 (0.8)	5 (0.8)	0 (−1, 1)	1.04 (0.32, 3.38)	0.99
Miscarriage <12 weeks	25 (3.4)	42 (6.6)	–3.2 (–5.7, –0.7)	0.51 (0.32, 0.83)	0.009
Obstetric and perinatal complications, n (%)					
Singleton delivery					
Gestational diabetes mellitus	86 (11.75)	52 (8.23)	3.5 (0.2, 6.8)	1.43 (1.03, 1.98)	0.04
Hypertensive disorders of pregnancy	25 (3.42)	17 (2.69)	0.7 (–1.2, 2.7)	1.27 (0.69, 2.33)	0.53
Antepartum hemorrhage	0 (0)	0 (0)	–	–	–
Preterm delivery					
Delivery at <24 weeks' gestation	36 (4.92)	43 (6.8)	–1.9 (–4.5, 0.8)	0.72 (0.47, 1.11)	0.16
Delivery at 24 to <28 weeks' gestation	8 (1.09)	6 (0.95)	0.1 (–1.1, 1.4)	1.15 (0.4, 3.3)	0.99
Delivery at 28 to <32 weeks' gestation	10 (1.37)	3 (0.47)	0.9 (–0.3, 2)	2.88 (0.8, 10.41)	0.1
Delivery at 32 to <37 weeks' gestation	41 (5.6)	31 (4.91)	0.7 (–1.8, 3.2)	1.14 (0.73, 1.8)	0.63
Birth weight, g	2971.0 ± 628.4	3118.8 ± 559.2	–247.8 (–248.3, 47.3)	–	0.004
Low birth weight, n (%)	41 (5.6)	24 (3.8)	1.8 (−0.6, 4.2)	1.47 (0.9, 2.41)	0.13
Very low birth weight, n (%)	14 (1.91)	6 (0.95)	1 (−0.4, 2.4)	2.01 (0.78, 5.21)	0.18
High birth weight, n (%)	6 (0.82)	6 (0.95)	−0.1 (−1.3, 1)	0.86 (0.28, 2.66)	0.99
Very high birth weight, n (%)	0 (0)	0 (0)	–	–	–
Growth < 5th percentile	8 (1.09)	2 (0.32)	0.8 (−0.2, 1.8)	3.45 (0.74, 16.2)	0.12
Growth < 10th percentile	16 (2.19)	5 (0.79)	1.4 (0, 2.8)	2.76 (1.02, 7.5)	0.05
Congenital anomaly, n (%)	2 (0.27)	2 (0.32)	0 (−0.7, 0.6)	0.86 (0.12, 6.11)	0.99

(continued)

Table II Continued

	Progesterone + dydrogesterone (n = 732)	Progesterone (n = 632)	Between-group difference (95% CI)	Rate ratio (95% CI)	*P*-value
Twin delivery					
Gestational diabetes mellitus	6 (0.82)	2 (0.32)	0.5 (−0.4, 1.4)	2.59 (0.52, 12.79)	0.3
Hypertensive disorders of pregnancy	1 (0.14)	4 (0.63)	−0.5 (−1.3, 0.3)	0.22 (0.02, 1.93)	0.19
Antepartum hemorrhage					
Preterm delivery					
Delivery at <24 weeks' gestation	0 (0)	0 (0)	–	–	–
Delivery at 24 to <28 weeks' gestation	0 (0)	1 (0.16)	–	–	–
Delivery at 28 to <32 weeks' gestation	3 (0.41)	0 (0)	–	–	–
Delivery at 32 to <37 weeks' gestation	19 (2.6)	13 (2.06)	0.5 (–1.2, 2.3)	1.26 (0.63, 2.53)	0.59
Birth weight, grams	2175.5 ± 494.8	2494.2 ± 584.7	–318.7 (–522.3, 115.2)	–	0.002
Congenital anomaly, n (%)	0 (0)	0 (0)	–	–	–

Values are mean ± SD, median [quartiles], or number of participants (%).
NICU, neonatal intensive care unit.

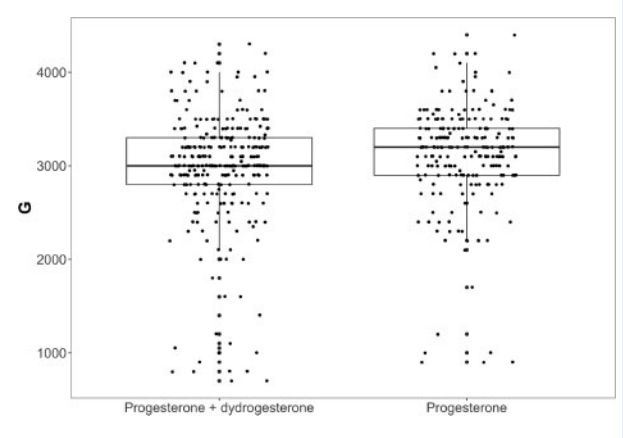

Figure 1. Box and whisker plot showing singleton birth weight in the two treatment groups. Bold central line median, box 25th to 75th centile, whiskers ± 1.5 × interquartile range; dots show individual observations.

therefore these should have been the same throughout both study periods. For example, overall ongoing pregnancy rates after fresh embryo transfer at our center over the first and second study periods were 37.3 and 37.5% per started cycle, respectively. In addition, participants undergoing FET at the same times who were not enrolled in the study had ongoing pregnancy rates per started cycle of 46.1% in the first phase and 45.0% in the second phase, comparable to those in study participants. Thirdly, some parameters differed significantly between treatment groups at baseline, however, these parameters have been adjusted for using multivariate analysis. Finally, our study included women from Vietnam only. Therefore, results need to be replicated in populations of different ethnicity.

The sequential trial design was chosen for a variety of reasons. Firstly, it meant that we were able to get data on the comparative effectiveness of the study regimens more quickly than from a randomized controlled trial (RCT). It was also easier to recruit women, who often do not want the uncertainty of treatment options inherent in a randomized trial. Workload for staff was also reduced compared with an RCT, making the study more feasible. As such, our study is an attempt to overcome the issue that RCTs, even if they are completed or even started, are often underpowered. While our study was not randomized, it still introduced a treatment directed by the research. Although this might still introduce some bias, it increases precision of the treatment effect due to the large sample size that we created.

Publication of data from a planned preliminary analysis of an RCT comparing different luteal phase support regimens for cycles including vitrified blastocyst transfer showed that regimens that only included vaginal progesterone were associated with a lower rate of ongoing pregnancy (31% versus 50 and 47% with regimens containing intramuscular progesterone; $P \leq 0.001$) and a higher rate of miscarriage (48% versus 22 and 29%; $P \leq 0.001$) (Devine *et al.*, 2018). Our findings of a significantly higher miscarriage rate in the progesterone only group of our study are consistent with this.

The serum progesterone level in our study reflects absorption of vaginally-administered progesterone only. Therefore, adding oral dydrogesterone to vaginal luteal phase support approaches could help to avoid potential problems associated with poor absorption of vaginal progesterone and improve the possibility of achieving live birth. Identification of biomarkers able to predict which women will have low absorption of vaginal progesterone would be useful to help determine those who would benefit most from the addition of oral dydrogesterone for luteal phase support.

Other studies utilizing luteal phase support regimens containing micronized vaginal progesterone have also reported that women with lower serum progesterone levels have worse pregnancy outcomes. In a study of oocyte donation cycles, the ongoing pregnancy rate differed significantly by quartile of progesterone level on the day of embryo transfer, being substantially lower in quartile 1 (33%, serum progesterone <9.2 ng/ml) compared with 49, 59 and 51% in quartiles 2, 3 and 4, respectively ($P = 0.016$) (Labarta *et al.*, 2017). In contrast, the

Table III Univariate and multivariate logistic regression analysis for factors affecting the live birth rate after one frozen embryo transfer cycle.

	Live birth [n (%)]		Univariate analysis	Multivariate analysis[a]
	Yes (n = 600)	No (n = 764)	Odds ratio (95% CI), *P*-value	Rate ratio (95% CI), *P*-value
Treatment, n (%)				
Progesterone + dydrogesterone	339 (56.5)	393 (51.4)	1.23 (0.99, 1.52), 0.063	1.30 (1.01, 1.68), 0.042
Progesterone	261 (43.5)	371 (48.6)	Ref	Ref
Age, years	30.41 ± 3.98	32.07 ± 4.68	0.92 (0.89, 0.94), <0.001	0.94 (0.91, 0.97), <0.001
BMI, kg/m^2	21.27 ± 3.28	21.07 ± 3.05	1.02 (0.99, 1.06), 0.255	1.02 (0.98, 1.07), 0.29
Anti-Müllerian hormone, ng/ml	4.89 ± 3.43	4.07 ± 2.89	1.09 (1.05, 1.13), <0.001	1.01 (0.96, 1.06), 0.668
Duration of infertility, years	3.74 ± 2.56	4.00 ± 2.68	0.96 (0.92, 1.00), 0.067	0.99 (0.94, 1.04), 0.681
Type of infertility, n (%)				
Primary	435 (72.5)	486 (63.6)	Ref	Ref
Secondary	165 (27.5)	278 (36.4)	0.66 (0.53, 0.84), 0.001	0.73 (0.55, 0.97), 0.029
Number of IVF attempts, n (%)				
1	572 (95.3)	724 (94.8)	Ref	–
2	26 (4.3)	39 (5.1)	0.84 (0.50, 1.40), 0.513	–
3	2 (0.3)	1 (0.1)	2.53 (0.24, 54.55), 0.449	–
Number of previous ET cycles, n (%)				–
0	536 (89.3)	674 (88.2)	Ref	–
1	58 (9.7)	87 (11.4)	0.84 (0.59, 1.19), 0.325	–
2	6 (1.0)	3 (0.4)	2.51 (0.66, 11.96), 0.294	–
Indication for IVF, n (%)				–
Male factors	163 (27.2)	190 (24.9)	Ref	–
Unexplained	96 (16.0)	134 (17.5)	0.84 (0.60, 1.17), 0.292	–
Tubal factors	99 (16.5)	149 (19.5)	0.77 (0.56, 1.08), 0.128	0.95 (0.67, 1.35), 0.767
Ovulation disorder	148 (24.7)	111 (14.5)	1.55 (1.13, 2.15), 0.007	1.29 (0.89, 1.87), 0.182
Diminished ovarian reserve	57 (9.5)	128 (16.8)	0.52 (0.35, 0.75), 0.001	1.08 (0.69, 1.68), 0.741
Endometriosis	12 (2.0)	15 (2.0)	0.93 (0.42, 2.05), 0.862	–
Others	25 (4.2)	37 (4.8)	0.79 (0.45, 1.36), 0.394	–
Endometrial thickness, mm	11.00 ± 1.13	10.92 ± 1.22	1.06 (0.96, 1.17), 0.243	1.03 (0.92, 1.15), 0.602
Serum progesterone level, ng/ml	15.55 ± 9.44	16.65 ± 12.48	0.99 (0.98, 1.00), 0.079	0.99 (0.98, 1.00), 0.296
Serum progesterone level quartile, n (%)				
1 (0.873 to <10.9 ng/ml)	155 (25.8)	186 (24.3)	Ref	–
2 (10.9 to <13.9 ng/ml)	153 (25.5)	189 (24.7)	0.97 (0.72, 1.31), 0.851	–
3 (13.9 to <18.2 ng/ml)	160 (26.7)	180 (23.6)	1.07 (0.79, 1.44), 0.675	–
4 (18.2 to 207.0 ng/ml)	132 (22.0)	209 (27.4)	0.76 (0.56, 1.03), 0.075	–
Number of embryos transferred, n (%)				
1	335 (55.8)	379 (49.6)	Ref	Ref
2	265 (44.2)	385 (50.4)	0.78 (0.63, 0.96), 0.022	1.50 (1.08, 2.08), 0.015
Number of good embryos transferred, n (%)				
0	73 (12.2)	90 (11.8)	Ref	–
1	354 (59.0)	427 (55.9)	1.02 (0.73, 1.44), 0.9	–
2	173 (28.8)	247 (32.3)	0.86 (0.60, 1.25), 0.43	–
Stage of embryo at transfer, n (%)				
Day 3 (cleavage)	170 (28.3)	347 (45.4)	Ref	Ref
Day 5 (blastocyst)	430 (71.7)	417 (54.6)	2.10 (1.68, 2.65), <0.001	2.53 (1.79, 3.61), <0.001

[a]The multivariate analysis adjusted for all factors with a *P*-value of <0.25 in the univariate analysis (i.e. age, body mass index, anti-Müllerian hormone level, duration of infertility, type of infertility, ovulation disorder and diminished ovarian reserve as the cause of infertility, serum progesterone level, number of embryos transferred and stage of embryo at transfer).
ET, embryo transfer; Ref, reference.

Table IV Subgroup analysis showing rates of ongoing pregnancy, live birth and miscarriage by serum progesterone level quartile (interaction *P*-values were 0.350 and 0.687, respectively).

	Progesterone + dydrogesterone (n = 732)	Progesterone (n = 632)	Rate ratio (99% CI)	*P*-value
Ongoing pregnancy				
Serum progesterone level quartile, n (%)				
1 (0.873 to <10.9 ng/ml)	102/186 (54.8)	70/155 (45.2)	1.21 (0.91, 1.62)	0.08
2 (10.9 to <13.9 ng/ml)	102/190 (53.7)	76/152 (50)	1.07 (0.82, 1.41)	0.52
3 (13.9 to <18.2 ng/ml)	92/181 (50.8)	85/159 (53.5)	0.95 (0.73, 1.24)	0.66
4 (18.2 to 207.0 ng/ml)	79/175 (45.1)	73/166 (44)	1.03 (0.75, 1.40)	0.91
Live birth				
Serum progesterone level quartile, n (%)				
1 (0.873 to <10.9 ng/ml)	92/186 (49.5)	63/155 (40.6)	1.22 (0.89, 1.67)	0.13
2 (10.9 to <13.9 ng/ml)	88/190 (46.3)	65/152 (42.8)	1.08 (0.79, 1.48)	0.79
3 (13.9 to <18.2 ng/ml)	90/181 (49.7)	70/159 (44)	1.13 (0.84, 1.52)	0.33
4 (18.2 to 207.0 ng/ml)	69/175 (39.4)	63/166 (38)	1.04 (0.73, 1.48)	0.82
Miscarriage at <12 weeks				
Serum progesterone level quartile, n (%)				
1 (0.873 to <10.9 ng/ml)	6/186 (3.2)	14/155 (9)	0.36 (0.10, 1.22)	0.04
2 (10.9 to <13.9 ng/ml)	6/190 (3.2)	9/152 (5.9)	0.53 (0.14, 2.01)	0.29
3 (13.9 to <18.2 ng/ml)	8/181 (4.4)	13/159 (8.2)	0.54 (0.18, 1.66)	0.18
4 (18.2 to 207.0 ng/ml)	5/175 (2.9)	6/166 (3.6)	0.79 (0.17, 3.67)	0.77

between-group comparison in live birth rate in our study did not differ by serum progesterone level quartile.

Luteal phase support with dydrogesterone was compared with micronized vaginal progesterone in the LOTUS I (Tournaye *et al.*, 2017) and LOTUS II (Griesinger *et al.*, 2018) trials. The results showed that oral dydrogesterone was non-inferior to vaginal progesterone with respect to the presence of a fetal heartbeat at 12 weeks' gestation (difference [95% CI] with dydrogesterone versus progesterone of +4.7% [−1.2%, +10.6%] and +3.7% [−2.3, +9.7] in the two studies) (Tournaye *et al.*, 2017; Griesinger *et al.*, 2018). Accordingly, live birth rates did not differ significantly between the dydrogesterone and micronized vaginal progesterone groups (corresponding difference [95% CI] +4.9% [−0.8%, +10.7%] and +1.9% [−4.0%, +7.8%] in the two studies). However, women in these studies were undergoing fresh embryo transfer, and there was no information on live birth rate, pregnancy complications and neonatal outcomes.

In contrast to that approach, the corpus luteum is absent in FET cycles and we were concerned that oral dydrogesterone alone might not provide adequate luteal phase support. There is no reference for the dosage of dydrogesterone in FET cycles. Therefore, we followed the same protocol as Wei et al. (2019) with a dydrogesterone dosage of 10 mg, twice a day to obtain evidence for the comparative effectiveness of the dydrogesterone plus vaginal progesterone regimen versus vaginal progesterone alone in the setting of FET. These data are important to provide evidence on which to base clinical decision making. A comparison still to be made is the one between dydrogesterone plus vaginal progesterone versus dydrogesterone alone. This would allow determination the comparative benefits of luteal phase support with dydrogesterone alone versus compared with micronized vaginal progesterone after FET, as documented for fresh embryo transfer (Tournaye *et al.*, 2017; Griesinger *et al.*, 2018, 2020).

It is possible that the outcomes observed in our study were primarily due to the activity of dydrogesterone, which has high specificity for progesterone receptors (Griesinger *et al.*, 2018). Another potential benefit of dydrogesterone relates to its immunomodulatory effect. Treatment with dydrogesterone was shown to reduce pregnancy loss in patients with threatened abortion in a prospective study, and this was thought to be due to modulation of the cytokine profile and a shift from T-helper (Th) 1 to Th2 predominance (including a reduction Th1 markers such as interferon-γ (Ibrahim *et al.*, 2020)). These will be important parameters to assess in future studies with dydrogesterone.

Use of oral dydrogesterone in our study was generally well tolerated. The only statistically significant between-group difference was a higher rate of gestational diabetes in the group treated with dydrogesterone plus vaginal progesterone, while birthweight was lower in that group. Of note, there was no significant difference between treatment groups in the rate of congenital anomalies (two in each). This is in contrast to previous data from a retrospective case−control study reporting a lower rate of congenital heart disease in babies born to mothers who were not versus were exposed to oral dydrogesterone in the first trimester of pregnancy (Zaqout et al., 2015). However, another retrospective analysis found that use of dydrogesterone for luteal phase support did not increase the incidence of congenital malformations compared with a gonadotropin-releasing hormone short

protocol (Huang et al., 2019). Therefore, additional prospective data on the teratogenic potential of dydrogesterone are needed so that evidence-based recommendations can be made about its use in luteal phase support regimens.

Birth weight of both singletons and twins was significantly lower in the combination group compared with vaginal progesterone alone, and the proportion of low, very low, high and very high birth weight infants were numerically slightly lower in the combination group, although differences were not statistically significant between treatment groups. This may be due a higher rate of preterm birth in the combination therapy group, although rates of preterm birth also were not significantly different between the treatment groups. Another possibility is that the findings are influenced by the small sample size in each birth weight category group. Nevertheless, the significant between-group difference in birth weight recording in this study warrants attention in future clinical trials of dydrogesterone + progesterone.

Conclusions

The findings of this study suggest a role for oral dydrogesterone in addition to vaginal progesterone as luteal phase support in FET cycles to reduce the miscarriage rate and improve pregnancy outcomes, including live birth. Adding oral dydrogesterone was feasible and is well tolerated.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Acknowledgments

The authors would like to thank Dr NH Giang and staffs at IVFMD, My Duc Hospital for their assistance in the execution of the study and Minh NH Nguyen, Anh TL Vu and Quan T Pham, all from the HOPE Research Office, Ho Chi Minh City, Vietnam for serving on the data and safety monitoring committee.

Authors' roles

L.N.V., T.D.P., K.T.Q.L., T.T.L., H.L.L., D.T.N.N., V.N.A.H., V.Q.D., T.H.P., R.J.N., B.W.M., T.M.H. designed the study and monitored data collection. The statistical analysis plan was written by T.D.P. Data analysis was conducted by T.D.P., and L.N.V. acts as guarantor of the data and the analysis. Planning for the first draft of the manuscript was undertaken by L.N.V. and T.M.H. The first draft of the paper was written by L.N.V. and T.M.H. All authors were involved in the decision to publish the paper and in critical revisions of the manuscript. L.N.V. acts as overall guarantor and accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Funding

This study did not receive any external funding. The corresponding author had full access to all the data in the study and had final responsibility to submit for publication.

Conflict of interest

L.N.V. has received speaker and conference fees from Merck, grant, speaker and conference fees from Merck Sharpe and Dohme, and speaker, conference and scientific board fees from Ferring; T.M.H. has received speaker fees from Merck, Merck Sharp and Dohme, and Ferring; R.J.N. has received scientific board fees from Ferring and receives grant funding from the National Health and Medical Research Council (NHMRC) of Australia; B.W.M. has acted as a paid consultant to Merck, ObsEva and Guerbet, and is the recipient of grant money from an NHMRC Investigator Grant; T.D.P., K.T.Q.L., T.T.L., H.L.L., D.T.N.N., V.N.A.H., V.Q.D. and T.H.P. have no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years, and no other relationships or activities that could appear to have influenced the submitted work.

References

Alpha Scientists in Reproductive Medicine, ESHRE Special Interest Group of Embryology. The Istanbul consensus workshop on embryo assessment: proceedings of an expert meeting. *Hum Reprod* 2011;**26**:1270–1283.

American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2018. *Diabetes Care* 2018;**41**:S13–S27.

Archer DF, Fahy GE, Viniegra-Sibal A, Anderson FD, Snipes W, Foldesy RG. Initial and steady-state pharmacokinetics of a vaginally administered formulation of progesterone. *Am J Obstet Gynecol* 1995;**173**:471–477; discussion 477–478.

Barbosa MW, Silva LR, Navarro PA, Ferriani RA, Nastri CO, Martins WP. Dydrogesterone vs progesterone for luteal-phase support: systematic review and meta-analysis of randomized controlled trials. *Ultrasound Obstet Gynecol* 2016;**48**:161–170.

Boelig RC, Zuppa AF, Kraft WK, Caritis S. Pharmacokinetics of vaginal progesterone in pregnancy. *Am J Obstet Gynecol* 2019;**221**:263.e261–263.e267.

Daya S. Luteal support: progestogens for pregnancy protection. *Maturitas* 2009;**65**(Suppl 1):S29–34.

Devine K, Richter KS, Widra EA, McKeeby JL. Vitrified blastocyst transfer cycles with the use of only vaginal progesterone replacement with Endometrin have inferior ongoing pregnancy rates: results from the planned interim analysis of a three-arm randomized controlled noninferiority trial. *Fertil Steril* 2018;**109**:266–275.

Griesinger G, Blockeel C, Kahler E, Pexman-Fieth C, Olofsson JI, Driessen S, Tournaye H. Dydrogesterone as an oral alternative to vaginal progesterone for IVF luteal phase support: a systematic review and individual participant data meta-analysis. *PLoS One* 2020;**15**:e0241044.

Griesinger G, Blockeel C, Sukhikh GT, Patki A, Dhorepatil B, Yang DZ, Chen ZJ, Kahler E, Pexman-Fieth C, Tournaye H. Oral

dydrogesterone versus intravaginal micronized progesterone gel for luteal phase support in IVF: a randomized clinical trial. *Hum Reprod* 2018;**33**:2212–2221.

Griesinger G, Blockeel C, Tournaye H. Oral dydrogesterone for luteal phase support in fresh in vitro fertilization cycles: a new standard? *Fertil Steril* 2018;**109**:756–762.

Huang J, Xie Q, Lin J, Lu X, Wang N, Gao H, Cai R, Kuang Y. Neonatal outcomes and congenital malformations in children born after dydrogesterone application in progestin-primed ovarian stimulation protocol for IVF: a retrospective cohort study. *Drug Des Devel Ther* 2019;**13**:2553–2563.

Ibrahim ZM, Said ME, El NK, Younes SE, Ali TYM, Taha OT. Assessment of the immunomodulatory role of dydrogesterone in preventing pregnancy loss in threatened abortion. *W J Gynecol Women's Health* 2020;**3**:doi:10.33552/WJGWH.32020.33503.000567.

Labarta E, Mariani G, Holtmann N, Celada P, Remohí J, Bosch E. Low serum progesterone on the day of embryo transfer is associated with a diminished ongoing pregnancy rate in oocyte donation cycles after artificial endometrial preparation: a prospective study. *Hum Reprod* 2017;**32**:2437–2442.

Paulson RJ, Collins MG, Yankov VI. Progesterone pharmacokinetics and pharmacodynamics with 3 dosages and 2 regimens of an effervescent micronized progesterone vaginal insert. *J Clin Endocrinol Metab* 2014;**99**:4241–4249.

Queensland Health. Queensland Clinical Guidelines. *Hypertension and Pregnancy*. Guideline No. MN21.13-V8-R26, February 2021. http://www.health.qld.gov.au/qcg. Date accessed 9 February 2021.

Rashidi BH, Ghazizadeh M, Tehrani Nejad ES, Bagheri M, Gorginzadeh M. Oral dydrogesterone for luteal support in frozen-thawed embryo transfer artificial cycles: a pilot randomized controlled trial. *Asian Pac J Reprod* 2016;**5**:490–494.

Tournaye H, Sukhikh GT, Kahler E, Griesinger G. A Phase III randomized controlled trial comparing the efficacy, safety and tolerability of oral dydrogesterone versus micronized vaginal progesterone for luteal support in in vitro fertilization. *Hum Reprod* 2017;**32**:1019–1027.

Vaisbuch E, de Ziegler D, Leong M, Weissman A, Shoham Z. Luteal-phase support in assisted reproduction treatment: real-life practices reported worldwide by an updated website-based survey. *Reprod Biomed Online* 2014;**28**:330–335.

van der Linden M, Buckingham K, Farquhar C, Kremer JA, Metwally M. Luteal phase support for assisted reproduction cycles. *Cochrane Database Syst Rev* 2015;**2015**:Cd009154.

Vuong LN, Dang VQ, Ho TM, Huynh BG, Ha DT, Pham TD, Nguyen LK, Norman RJ, Mol BW. IVF transfer of fresh or frozen embryos in women without polycystic ovaries. *N Engl J Med* 2018;**378**:137–147.

Wang Y, He Y, Zhao X, Ji X, Hong Y, Wang Y, Zhu Q, Xu B, Sun Y. Crinone gel for luteal phase support in frozen-thawed embryo transfer cycles: a prospective randomized clinical trial in the Chinese population. *PLoS One* 2015;**10**:e0133027.

Wei D, Liu JY, Sun Y, Shi Y, Zhang B, Liu JQ, Tan J, Liang X, Cao Y, Wang Z *et al.* Frozen versus fresh single blastocyst transfer in ovulatory women: a multicentre, randomised controlled trial. *Lancet* 2019;**393**:1310–1318.

Yanushpolsky E, Hurwitz S, Greenberg L, Racowsky C, Hornstein M. Crinone vaginal gel is equally effective and better tolerated than intramuscular progesterone for luteal phase support in in vitro fertilization-embryo transfer cycles: a prospective randomized study. *Fertil Steril* 2010;**94**:2596–2599.

Yovich JL, Conceicao JL, Stanger JD, Hinchliffe PM, Keane KN. Mid-luteal serum progesterone concentrations govern implantation rates for cryopreserved embryo transfers conducted under hormone replacement. *Reprod Biomed Online* 2015;**31**:180–191.

Zaqout M, Aslem E, Abuqamar M, Abughazza O, Panzer J, De Wolf D. The impact of oral intake of dydrogesterone on fetal heart development during early pregnancy. *Pediatr Cardiol* 2015;**36**:1483–1488.