Comparison of Oral Dydrogesterone with a Micronized Vaginal Progesterone in Fresh Embryo Transfer in IVF ± ICSI

Marion Cessot
Hospices Civils de Lyon, Hôpital Mère Enfant https://orcid.org/0000-0001-8780-3495
Eloise Fraison (fraison.eloise@yahoo.fr)
Hospices Civils de Lyon, Hôpital Mère Enfant https://orcid.org/0000-0001-8083-1346
Elsa Labrune
Hospices Civils de Lyon, Hôpital Mère Enfant
Mehdi Benchaib
Hospices Civils de Lyon, Hôpital Mère Enfant
Bruno Salle
Hospices Civils de Lyon, Hôpital Mère Enfant

Research Article

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Abstract

Introduction: Luteal insufficiency corresponds to a progesterone deficiency affecting women who receive treatment for in vitro fertilization (IVF). Different routes of progesterone administration exist and have varying degrees of acceptability to patients. The aim of this study was to compare two luteal phase support (LPS) treatments: oral dydrogesterone versus micronized vaginal progesterone on the clinical pregnancy rates after fresh embryo transfert.

Material and Methods: This study was a retrospective, monocentric and observational study carried out in the reproductive medicine department at the University Hospital, Femme Mère Enfant in Lyon. 580 consecutive women between 18 and 43 years old, who completed an IVF cycle with or without ICSI, followed by fresh embryo transfer on the second or third day after oocyte retrieval (D2 or D3) or at the blastocyst stage (D5 or D6) between July 2019 and July 2020 were included.

Results: In the univariate analysis, the clinical pregnancy rate per transfer was comparable between the MVP and OD groups (29.7% and 27.6% respectively with p = 0.6460). In the multivariate analysis, OD also appeared to be associated with a similar pregnancy rate compared to MVP, with a non-significant difference (p > 0.05) (OR [95% CI]): 0.922 [0.626; 1,358] with p = 0.6817.

The use of OD compared to MVP did not significantly influence the clinical pregnancy rate in any age group (p > 0.05) (OR [95% CI]): 0.954 [0.657; 1.386] with p = 0.8057. There was no significant difference between the two groups in the clinical pregnancy rate, whether the patients belonged to the reference population of the center or not (p > 0.05) (OR [95% CI]): 2.367 [0.568; 3.568] with p < 0.0001.

Conclusion: This is the largest retrospective study comparing these two routes of progestogens in LPS during IVF and it reinforces the use of the oral form to improve patients' comfort.

Introduction

Luteal phase deficiency affects women undergoing *in vitro* fertilization (IVF) procedures. It is a progesterone insufficiency leading to an inadequate endometrium with a negative impact on embryo implantation and development. Several theories may explain this deficiency during ovarian stimulation. Negative hypothalamic-pituitary feedback on LH secretion with supra-physiological doses of gonadotropins delivered (1) and high serum concentrations of steroids secreted by the large number of maturing follicles, could be one of these hypotheses (2). The mechanical withdrawal of granulosa cells, useful for the progesterone production, during oocyte retrieval could be another one (3). In addition, most IVF cycles currently using GnRH modulators (agonists or antagonists) disrupt the physiological pulsatility of GnRH. This may result in a dysfunctional corpus luteum shortening the progesterone production (3).

Progesterone, GnRH agonists or human chorionic gonadotropin (hCG) are used in luteal phase support (LPS). However, the increased risk of ovarian hyperstimulation syndrome (OHSS) generated by hCG and the heterogeneity of results concerning GnRH agonists (1,4) led to a consensus of progesterone-only use.

Moreover, administration of progestogens during luteal phase in IVF is associated with an improvement in the live birth rate (1,2,5,6).

Progesterone can be administered orally, vaginally, subcutaneously or intramuscularly. The optimal duration of treatment remains controversial and may be continued until the first positive hCG plasma test, to the day of the first ultrasound, or as late as the 12th week of pregnancy (7). Oral administration of progesterone is associated with a low bioavailability due to the hepatic first-pass effect (8) but seems well tolerated (5). High absorption in vaginal administration is permitted by the vaginal first-pass effect (9). However, it can be lowered after sexual intercourse (10,11) and can cause irritations, vaginal discharges and bleedings (10). Daily intramuscular or subcutaneous injection of progesterone has good bioavailability, nevertheless may be responsible for local pain or even abscesses (10,12). Finding the optimal progesterone treatment combining efficacy and high tolerance with the best compliance seems crucial to obtain and remains a challenge in IVF.

Dydrogesterone is an oral retroprogesterone used in the treatment of threatened or recurrent miscarriage (with proven progesterone deficiency) and repeated implantation failure (13,14). Recently, a positive association has been found between early luteal serum progesterone level and live birth rate in IVF using oral dydrogestérone (OD) for luteal support (15). Dydrogesterone has a good and almost exclusive affinity for progesterone receptors. Its high bioavailability and the progestogenic nature of the metabolites allows it to be used at lower oral doses than progesterone (16). Dydrogesterone safety in pregnancy, as well as tolerability during treatment, have already been described (17,18). Dydrogesterone half-life varies between 5 to 7 hours and involves 3 intakes per day to avoid serum concentration fluctuations (19).

In a study by Tournaye et al. in 2017, a non-inferiority of OD compared to micronized vaginal progesterone (MVP) was found on the clinical pregnancy rate in IVF, with good tolerance and higher patient satisfaction. Similar results have been obtained in intrauterine insemination after controlled ovarian stimulation and support the use of dydrogesterone (20,21). Thus, we changed our habits in order to provide patients with the best possible comfort.

The aim of this study was to compare the pregnancy rate between OD and MVP in LPS after IVF or intracytoplasmic sperm injection (ICSI) and fresh embryo transfer.

Material And Methods

Study design and participants

This retrospective, monocentric and observational study was carried out in the reproductive medicine department at the University Hospital, Femme Mère Enfant in Lyon. This study compared two types of LPS treatments. All consecutive women between 18 and 43 years old, who completed an IVF cycle with or without ICSI, followed by fresh embryo transfer on the second or third day after oocyte retrieval (D2 or D3) or at the blastocyst stage (D5 or D6) were included. Exclusion criteria were: oocyte retrieval complications

(hemoperitoneum), the absence of collected oocytes, oocyte dysmaturity, unsuitable endometrium for transfer (thickness < 7 mm), the absence of embryo due to a fertilization or embryo culture failure, a risk of OHSS, patient who did not take LPS treatment or who did not show the day of transfer. Subjects with adenomyosis, untreated intracavitary fibroid or polyp, untreated symptomatic hydrosalpinx, stage IV endometriosis, or with a history of more than 3 recurrent early miscarriages were also excluded. If the embryo transfer was difficult, meaning a change of catheter or a technical difficulty during the transfer, it was specified in the clinical file. Either single embryo transfer (SET) or dual embryo transfer (DET) were done. The transferred blastocysts were discriminated in 3 categories according to Gardner's classification

(22). Embryos classified as "good" included blastocysts AA, AB and BA; embryos classified as "average" included BB. Embryos classified as "bad", all the other types of blastocysts were not transferred. The quality of the best embryo was retained in case of DET (23). 845 patients were pre-selected between July 2019 and July 2020.

Ethical approval

Written consent for the use of personal medical and research data was collected for each patient prior to inclusion. The institutional review board of the Hospices Civils de Lyon gave its approval.

Study procedures

GnRH agonist or antagonist protocols were used for ovarian stimulation according to the center’s habits. LPS with progesterone began on the day of the oocyte retrieval (D0) and was continued until 12 weeks of gestation. In the MVP group, patients were treated as follows: 1 vaginal tablet of 200 mg of micronized progesterone in the morning and 2 vaginal tablets in the evening (i.e. 600 mg per day). In the OD group, the regimen was: 1 oral tablet of 10 mg of dydrogesterone, taken three times daily (TID) (i.e. 30 mg per day). On Day 15 ± 3 (2 weeks after embryo transfer), a pregnancy test (serum β-hCG) was performed to determine whether treatment should be continued in cases of ongoing pregnancy until 12 weeks of gestation. The main investigator collected patient’s data retrospectively using the services software (Médifirst® and Easily®). Data for the MVP group came from the year 2019 and data for the OD group from the year 2020, according to the chronology of the change in practice previously decided.

Types of infertility

Male infertility was defined by abnormal sperm characteristics according to the World Health Organization’s criteria (24). Infertility by poor ovarian reserve was defined by the Bologna criteria (25) with antral follicle count of less than 5-7 follicles or an anti-Müllerian hormone (AMH) dosage < 0.5-1.1 ng/ml. Infertility by anovulation or dysovulation was defined as oligomenorrhoea or amenorrhoea and polycystic ovary syndrome (PCOS) was defined according to the Rotterdam criteria of 2018 (26).

Study objectives

The primary objective of this study was to compare the clinical pregnancy rate between the MVP and OD groups, assessed by the presence of fetal heartbeats on transvaginal ultrasound between 6 and 12 weeks of gestation (weeks 4 to 10 of treatment). The secondary objectives were the comparison of clinical pregnancy rate between the MVP and the OD group among two subgroups: the reference population of the center (defined as follows: age < 35 years; number of previous IVF attempts < 3; number of oocytes retrieved > 6; embryo freezing done) and by different age groups (< 30 years, 30 ≤ - < 35 years, 35 ≤ - < 40 years, ≥ 40 years).

Statistical analysis

Statistical analysis was carried out with the software R (v4.02). Quantitative data are represented as mean ± standard deviation (M±SD) and qualitative data as: number (percentage). In the bivariate analysis, quantitative variables were compared with a Student's t-test and qualitative variables with the χ^2 test. The general linear model (multivariate logistic regression) was used for the multivariate analysis, the mixed general linear model (mixed multivariate logistic regression) was used to account for the repetition of the same patient within the same sample. A test was considered significant when p was less than 0.05. We defined therefore a required number of subjects of 580 (290 in each group) to ensure a study power of 80%.

Results

Study population

845 subjects were eligible and 580 were included in the statistical analysis, with 290 in each group (Figure 1).

Clinical and biological characteristics of patients and IVF cycles are summarized in Tables 1 and 2. The mean age was 34.1 ± 4.6 years, with a majority of nulliparous patients (70.5%). In the univariate analysis, there was a significant difference between the 2 groups on body mass index (BMI), smoking habits, PCOS's patients and the number of transferred embryos (Table 1). The groups were comparable on all other criteria, including age, gravidity and parity, type of IVF protocol received, number of oocytes retrieved, sperm characteristics, number of embryos, stage and embryo quality at the time of transfer (Table 2). Only 22.1% of the population analyzed corresponded to our reference population. Table 2 shows that the majority of embryo transfers were transfers of a single good quality blastocyst. In 94.7% of the time, the transfer was easy. Regarding difficult transfers, the difference between groups was not significant.

Table 3 shows that the clinical pregnancy rate per transfer was comparable between the MVP and OD groups (29.7% and 27.6% respectively with p = 0.6460).

Multivariate analysis

Data for the multivariate analysis are summarized in Table 4. Variables significantly associated with a decrease in the clinical pregnancy rate between 6 and 12 weeks of gestation regardless of treatment were ($p < 0.05$) (OR [95% CI]): age ≥ 35 years (0. 414 [0.260; 0.749] with $p = 0.0001$), history of ≥ 3 previous IVF attempts (0.407 [0.218; 0.739] with $p = 0.0042$), the embryonic stage D2-D3 at the time of transfer (0.597 [0.341; 1.017] with p= 0.0631). All variables with a significant difference in univariate analysis turned out to be insignificant when analyzed in the multivariate model. Finally, OD appeared to be associated with a similar pregnancy rate compared to MVP, with a non-significant difference ($p > 0.05$) (OR [95% CI]): 0.922 [0.626; 1,358] with $p = 0.6817$.

Table 5a shows that the use of OD compared to MVP did not significantly influence the clinical pregnancy rate in any age group ($p > 0.05$) (OR [95% CI]): 0.954 [0.657; 1.386] with $p = 0.8057$. Table 5b illustrates that belonging to the reference population was positively associated with the clinical pregnancy rate. There was no significant difference between the two groups in the clinical pregnancy rate, whether the patients belonged to the reference population or not ($p > 0.05$) (OR [95% CI]): 2.367 [0.568; 3.568] with $p < 0.0001$.

An additional mixed analysis considering repeated IVF attempts within the inclusion period for some patients did not provide any additional information and did not change the results.

Discussion

Our study found no significant difference between DO and MVP for the LPS after fresh embryo transfer in IVF ± ICSI, for the main objective which was the presence of fetal cardiac activity between 6 and 12 weeks of gestation. The use of OD compared to MVP also did not significantly influence the clinical pregnancy rate by transfer in the center's reference population, nor by age group. Our results reinforce the interest in the use of dydrogesterone for LPS in IVF with or without ICSI in the local population of our center and support the results of similar published studies.

Four prospective studies in the meta-analysis of Barbosa and colleagues (27) are comparable to our study and find similar efficacy on the clinical pregnancy rate in IVF +/- ICSI between the use of OD and MVP (28–31). The RCT, published by Tournaye and colleagues (28) showed the non-inferiority of OD compared to MVP on the pregnancy rate with 974 randomized double-blind patients with sufficient statistical power. In the four studies mentioned above, the daily dose of dydrogesterone ranged from 20 to 40 mg per day, but 10 mg twice daily was shown to reduce endometrial development compared to MVP given at a dose of 200 mg three times daily (32). We, therefore, chose the 10 mg dose TID on validated data from the Tournaye's study. Chakravarty's study has a selection bias because of a higher proportion of women aged 40 and over in the dydrogesterone group (29). As our study was retrospective, we included all eligible patients consecutively in order to minimise selection bias (33). Our study power is also guaranteed by the large sample size calculated beforehand. An attrition bias was found in the Saharkhiz et al. study, as 10.3% of participants were excluded after randomisation (31). This led to an imbalance regarding loss of sight (LOS) between groups: 17.9% LOS in the OD group and 2.6% in the

vaginal progesterone group. We had no LOS and only one missing data concerning embryo transfer characteristics in our cohort.

The results of our study support previous studies, confirming that maternal age and embryonic stage are predominant elements in the prognosis for successful IVF. Pregnancy and live birth rates in IVF are increased before the age of 35 and when embryos are preferentially transferred at the blastocyst stage (34–36). It has to be mentioned that there were only 22% of good prognosis patients in our center explaining our low pregnancy rate.

Like most published studies, we chose the clinical pregnancy rate as the primary endpoint because we did not have the necessary hindsight to use the live birth rate during the analysis. However, the latter seems to be a criterion of higher clinical interest because it is more objective in evaluating the effectiveness of a technique. Only one study comparing oral dydrogesterone and vaginal progesterone after fresh embryo transfer was interested in the live birth rate, but it contains the biases mentioned above (29). An additional study with live birth records would therefore be necessary to support our findings.

The retrospective nature of our study did not allow us to collect relevant data such as patient compliance or satisfaction toward treatments. Therefore, we were not aware of possible therapeutic discontinuities. Nevertheless, the Chakravarty (29) study seems to report a patient preference for oral dydrogesterone compared to vaginal micronized progesterone and Carp's meta-analysis (37) did not describe any significant adverse effect of dydrogesterone over the 22 studies studied. A specific study looking at patient compliance with these treatments would be of interest.

According to several studies, the supra-physiological concentrations of progesterone used vaginally and the possible manual contamination during administration would alter the local microbiota, which is currently of growing interest in the field of IVF (38,39). Indeed, the success of an embryo transfer depends on many factors, and in particular on utero-cervical microbial colonization (40). This may influence the IVF pregnancy rate by the potential upward colonization of the endometrium or embryo during the embryo transfer through the cervix.

Finally, few studies compare oral and vaginal dydrogesterone in frozen embryo transfers. Unlike fresh transfer, the absence of corpus luteum in frozen embryo transfer, makes the endometrium entirely dependent on exogenous progesterone supplementation (41). Although two randomized studies have examined the use of OD in LPS in frozen cycles (42,43), they were small and larger additional studies are needed to establish its effectiveness in this context.

To conclude, this is the largest retrospective study comparing these two routes of progestogens in LPS during IVF and it reinforces the use of the oral form to improve patients’ comfort.

Declarations

Fundings

None

Conflict of interest

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication.

Availability of data and material

Not applicable

Code availability

Not applicable

Author's contribution

M.C., E.F. and B.S. contributed to the conception of the study. M.C. collected the data.

M.C., E.F. and M.B. contributed to the exploitation of the data.

M.C. and E.F. contributed to the writing of the manuscript.

M.C., E.F., M.B., E.L. and B.S. read and approved the manuscript.

Ethics approval

The study was approved by the institutional review board

Consent to participate

Written consent for the use of personal medical and research data for further publication was collected for each patient prior to inclusion

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Tables

Table 1: Demographics and baseline characteristics (full analysis sample)

	MVP (n = 290)	OD (n = 290)	p	Total (n = 580)
Age, years (M±SD)	33.8 ± 4.6	34.4 ± 4.5	0.1796	34.1 ± 4.6
≤ 35 years, n (%)	179 (61.7)	166 (57.2)	0.3101	345 (59.5)
> 35 years, n (%)	111 (38.3)	124 (42.8)		235 (40.5)
BMI, kg/m^2 (M±SD)	25.4 ± 5.5	24.3 ± 4.8	0.0136	24.9 ± 5.1
Current smokers, n (%)	64 (22 .1)	39 (13.4)	0.0091	103 (17.8)
Gravidity (M±SD)	0.9 ± 1.2	0.9 ± 1.0	0.8508	0.9 ± 1.1
Parity (M±SD)	0.4 ± 0.7	0.4 ± 0.6	0.7052	0.4 ± 0.7
Nulliparous patients, n (%)	208 (71.7)	200 (69.2)	0.5663	408 (70.5)
Prior miscarriages, n (%)				
0	214 (73.8)	211 (73.0)	0.6696	425 (73.4)
1	56 (19.3)	57 (19.7)		113 (19.5)
2	12 (4.1)	15 (5.2)		27 (4.7)
3	6 (2.1)	6 (2.1)		12 (2.1)
4	2 (0.7)	0 (0.0)		2 (0.3)

Types of infertility, n (%)				
Male infertility	177 (61.0)	168 (57.9)	0.4986	345 (59.5)
Tubal blockage	53 (18.3)	52 (17.9)	1.0000	105 (18.1)
Poor ovarian reserve	77 (26.6)	79 (27.2)	0.9254	156 (26.9)
Endometriosis	51 (17.6)	50 (17.2)	1.0000	101 (17.4)
PCOS	53 (18 .3)	30 (10.3)	0.0086	83 (14.3)
Anovulation/dysovulation	17 (5.9)	10 (3 .5)	0.2370	27 (4.7)
Unexplained infertility	16 (5.5)	27 (9.3)	0.1130	43 (7.4)
Other types	6 (2.1)	2 (0.7)	0.2855	8 (1.4)
Prior IVF attempts, n (%)				
0	134 (46.2)	138 (47.6)	0.8980	272 (46.9)
1	68 (23.4)	65 (22.4)		133 (22.9)
2	33 (11.4)	37 (12.8)		70 (12.1)
≥ 3	55 (19.0)	50 (17.2)		105 (18.1)
Reference population, n (%)	65 (22 .4)	63 (21.7)	0.9202	128 (22.1)

Note: Percentages are based on the number of subjects in the full analysis sample with data available.

M: mean; SD: standard deviation; MVP: micronized vaginal progesterone; OD: dydrogesterone; BMI: body mass index; PCOS: polycystic ovary syndrome; IVF: in vitro fertilization.

Reference population: population aged < 35 years; number of prior IVF attempts < 3; oocytes > 6; freezing embryos = yes.

Table 2: IVF and embryo transfer characteristics (full analysis sample)

	MVP (n = 290)	OD (n = 290)	p	Total (n = 580)
Protocol, n (%)				
GnRH antagonist	7105 (36.2)	124 (42.8)	0.1263	229 (39.5)
GnRH agonist	185 (63.8)	166 (57.2)		351 (60.5)
Number of Oocytes (M±SD)				
Retrieved	8.5 ± 5.3	8.7 ± 5.3	0.6081	5.6 ± 5.3
Matures	7.1 ± 4.8	7.2 ± 4.7	0.8396	7.1 ± 4.7
Sperm characteristics, n (%)				
Ejaculated sperm (F)	217 (74.8)	233 (80.3)	0.1353	450 (77.6)
Ejaculated sperm (F*)	18 (6.2)	21 (7.2)	0.7402	39 (6.7)
Testicular sperm (F*)	21 (7.2)	18 (6.2)	0.7402	39 (6.7)
Testicular sperm (F)	10 (3.5)	4 (1.4)	0.1761	14 (2.4)
Donor sperm (F*)	24 (8.3)	14 (4.8)	0.1310	38 (6.6)

ICSI, n (%)	277 (95.5)	267 (92.1)	0.1214	544 (93.8)
Number of embryo (M±SD)				
Obtained	4.7 ± 3.5	4.7± 3.4	0.9520	4.7 ± 3.4
Frozen	2.7 ± 2.0	2.4 ± 1.6	0.1783	2.6 ± 1.8
Day of transfer, n (% in the range)				
D2/D3	69 (23.8)	66 (22.8)	0.8442	135 (23.3)
D5/D6	221 (76.2)	224 (77.2)		445 (76.7)
Number of transferred embryos				
Number (M±SD)	1.4 ± 0.5	1.5 ± 0.5	0.0306	1.4 ± 0.5
1, n (%)	184 (63.5)	156 (53.8)	0.0484	340 (58.6)
2, n (%)	102 (35.2)	131 (45.2)		233 (40.2)
3, n (%)	4 (1.4)	3 (1.0)		7 (1.2)
Embryo quality of the blastocysts, n (%)				
Good	191 (86.4)	195 (87.0)	0.9557	386 (86.7)
Average	18 (8.1)	16 (7.1)	0.8264	34 (7.6)
Bad	9 (4.1)	12 (5.4)	0.6778	21 (4.7)
Transfer conditions				
Easy	278 (95.9)	270 (93.4)	0.2637	548 (94.7)
Difficult	12 (4.1)	19 (6.6)		31 (5.3)

MVP: micronized vaginal progesterone; OD: dydrogesterone; M: mean; SD: standard deviation; F: fresh; F*: frozen; ICSI: intracytoplasmic sperm injection; D2/D3: day 2/day3; D5/D6: day5/day 6.

Table 3: Pregnancy rate per embryo transfer according to treatment

	MVP (n = 290)	**OD (n = 290)**	**p**	**Total (n = 580)**
hCG initial positivity, n (%)	97 (33.6)	110 (37.9)	0.3127	207 (35.8)
Clinical pregnancy, n (%)	86 (29.7)	80 (27.6)	0.6460	166 (28.6)

MVP: micronized vaginal progesterone; OD: dydrogesterone.

Table 4: Factors influencing clinical pregnancy rates in multivariate analysis in a population of women who underwent fresh embryo transfer

		OR	[IC 95%]	p
Treatments	**MVP**	1.000		
	OD	0.922	[0.626; 1.358]	0.6817
Age, years	**< 35**	1.000		
	≥ 35	0.414	[0.260; 0.640]	0.0001
BMI, kg/m^2	**< 30**	1.000		
	≥ 30	1.018	[0.579; 1.749]	0.9489
Current smoker	**No**	1.000		
	Yes	0.9324	[0.559; 1.526]	0.7840
Prior IVF attempts, n	**0**	1.000		
	1	0.635	[0.388; 1.029]	0.0669
	2	0.686	[0.359; 1.269]	0.2340
	≥ 3	0.407	[0.218; 0.739]	0.0042
PCOS	**No**	1.000		
	Yes	1.139	[0.665; 1.924]	0.6311
Number of transferred embryos, n	**1**	1.000		
	2	1.029	[0.664; 1.599]	0.8972
Embryonic stage, day	**D5/D6**	1.000		
	D2/D3	0.597	[0.341; 1.017]	0.0631

OR: odds ratio; [IC 95%]: interval of confidence 95%; MVP: micronized vaginal progesterone; OD: dydrogesterone; BMI: body mass index; IVF: in vitro fertilization; PCOS: polycystic ovary syndrome; D2/D3: day 2/day3; D5/D6: day5/day 6.

Tables 5: Influence of MVP on clinical pregnancy rates in multivariate analysis by subgroups: 5a. by age groups, 5b. by populations

Table 5a.

	OR	[IC 95%]	p
MVP	1.000		
OD	0.954	[0.657; 1.386]	0.8057
< 30 years	1.000		
30 ≤ - < 35 years	0.717	[0.456; 1.132]	0.1525
35 ≤ - < 40 years	0.300	[0.176; 0.503]	<0.0001
≥ 40 years	0.130	[0.037; 1.347]	0.0002

Table 5b.

	OR	[IC 95%]	p
MVP	1.000		
OD	0.902	[0.625; 1.302]	0.5832
Non-reference population	1.000		
Reference population	2.367	[1.568; 3.568]	<0.0001

OR: odds ratio; [IC 95%]: interval of confidence 95%; MVP: micronized vaginal progesterone; OD: dydrogesterone.

Non-reference population: subjects that are not belonging to the reference population.

Reference population: population aged < 35 years; number of prior IVF attempts < 3; oocytes > 6; freezing = yes.

Figures

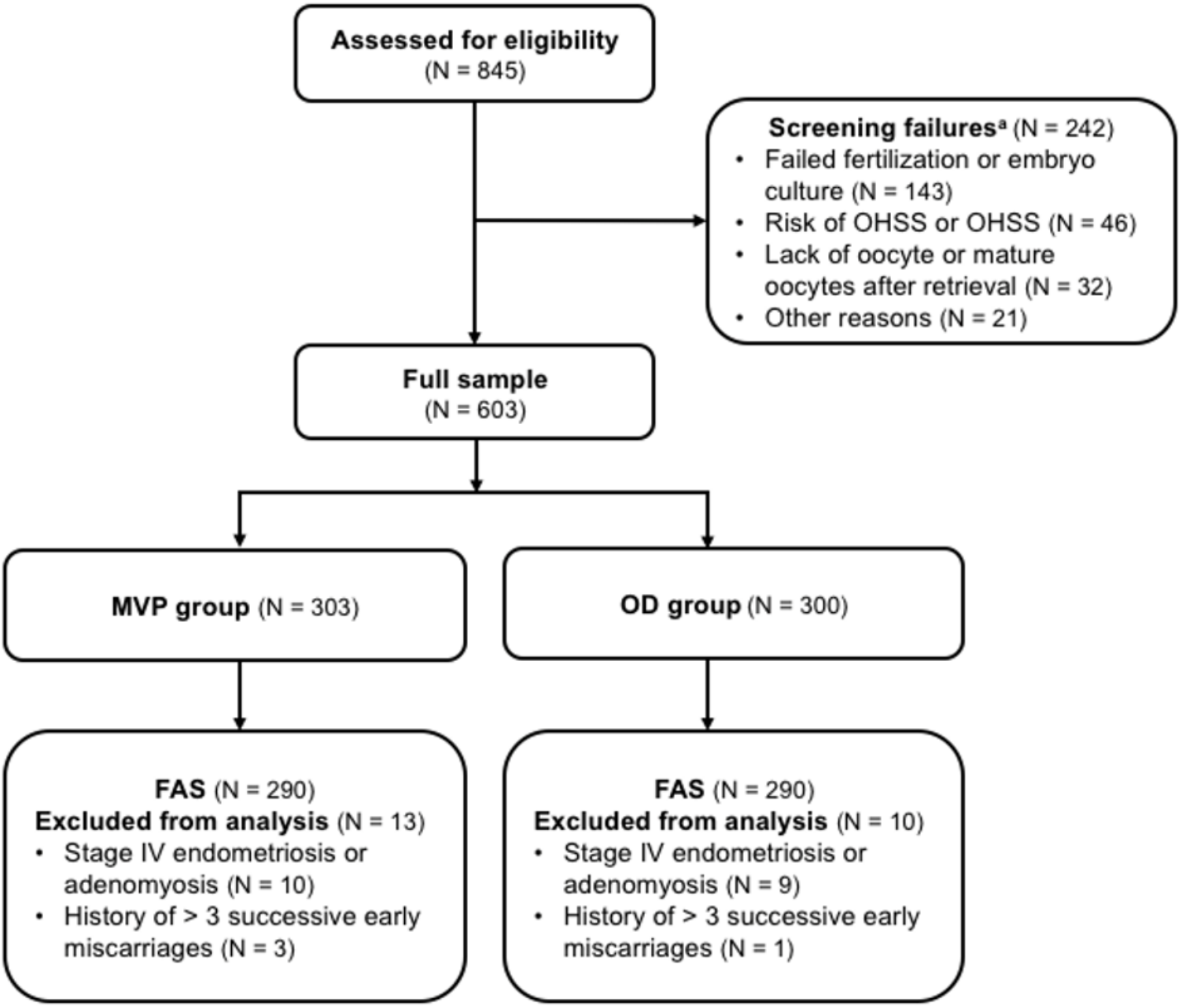

Figure 1

Patient disposition (Flow chart). a Determined by inclusion/exclusion criteria. FAS, full analysis sample; OD, oral dydrogesterone; MVP, micronized vaginal progesterone.