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La dydrogestérone orale est-elle équivalente à la progestérone micronisée vaginale en soutien de phase lutéale chez les femmes recevant un don d'ovocytes?

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Au Pôle Formation

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DYD	DYDROGESTERONE	DYDROGESTERONE
MVP	MICRONIZED VAGINALE PROGESTERONE	PROGESTERONE MICRONISEE VAGINALE
LPS	LUTEAL PHASE SUPPORT	SOUTIEN DE PHASE LUTEALE
IVF	IN VITRO FERTILIZATION	FECONDATION IN VITRO
ART	ASSISTED REPRODUCTIVE TECHNOLOGY	ASSISTANCE MEDICALE A LA PROCREATION
HRT	HORMONE REPLACEMENT TREATMENT	TRAITEMENT HORMONAL SUBSTITUTIF
LH	LUTEINIZING HORMONE	HORMONE LUTEINISANTE
IM	INTRAMUSCULARLY	INTRA-MUSCULAIRE
AMH	ANTI MULLERIAN HORMONE	HORMONE ANTI-MULLERIENNE
AFC	ANTRAL FOLLICLE COUNT	COMPTE DES FOLLICULES ANTRAUX
HIV	HUMAN IMMUNODEFICIENCY VIRUS	VIRUS DE L'IMMUNODEFICIENCE HUMAINE
HBV	HEPATISIS B VIRUS	VIRUS DE L'HEPATITE B
HCV	HEPATISIS C VIRUS	VIRUS DE L'HEPATITE C
CMV	CYTOMEGALOVIRUS	CYTOMEGALOVIRUS
BMI	BODY MASS INDEX	INDICE DE MASSE CORPORELLE
ICSI	INTRACYTOPLASMIQUE SPERM INJECTION	INJECTION INTRA-CYTOPLASMIQUE DE SPERMOTOZOIDE
NO	NUMBER	NOMBRE
FET	FROZEN EMBRYO TRANSFER	TRANSFERT D EMBRYONS CONGELES

INTRODUCTION THESE

La phase lutéale est définie comme la période entre l'ovulation et l'apparition des menstruations suite à la lutéolyse. Lors du pic pré-ovulatoire de gonadotrophines, la LH (hormone lutéinisante) permet la transformation des cellules de la granulosa en grandes cellules lutéales qui assurent la production de progestérone (1). Pendant la phase lutéale, cette même gonadotrophine permet le maintien d'une sécrétion optimale de progestérone. Cette hormone stéroïde permet par la suite la transformation sécrétoire de l'endomètre et l'ouverture de la courte fenêtre implantatoire. De plus, la progestérone sécrétée par le corps jaune permet le maintien de la grossesse pendant tout ou partie du 1er trimestre. Elle exerce un effet immunomodulateur et régule le flux sanguin sous endométrial luttant ainsi contre le phénomène de rejet embryonnaire (2).

En parcours de don d'ovocytes, les femmes receveuses ayant une fonction ovarienne le plus souvent profondément altérée doivent bénéficier d'une préparation endométriale pour permettre l'implantation (3). Le cycle artificiel ou traitement hormonal substitutif (THS) est alors utilisé en cas d'insuffisance ovarienne avérée. Il consiste à administrer de manière séquentielle les hormones exogènes naturellement produites par le corps jaune (œstrogènes seuls puis œstrogènes + progestérone) pour mimer le cycle endométrial et permettre l'ouverture d'une fenêtre d'implantation. En cas de grossesse, l'association d'œstrogènes et de progestérone sera maintenue pendant tout le 1er trimestre de la grossesse pour pallier l'absence de corps jaune jusqu'à ce que le placenta prenne le relais (4,5).

Différents progestatifs ont été successivement étudiés pour optimiser la phase lutéale et seules la progestérone, la dydrogestérone et l'hydroxyprogestérone caproate

ont été validées pendant la grossesse par l'absence de réactions croisées avec d'autres récepteurs (androgéniques, glucocorticoïdes et oestrogéniques) (2).

La progestérone est généralement administrée par voie vaginale, orale, sous-cutanée ou intramusculaire. La faible biodisponibilité orale et vaginale de la progestérone a été améliorée grâce aux techniques de micronisation. Actuellement, la voie vaginale avec la progestérone micronisée reste la voie préférée des praticiens bien qu'il n'existe aucun consensus en termes de voie optimale d'utilisation (6) (Figure 1).

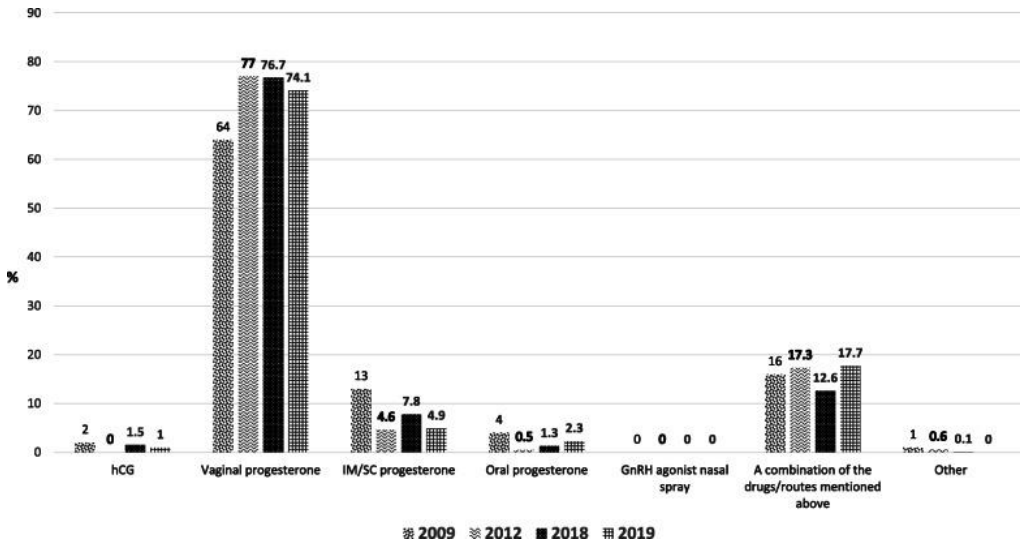

Figure 1 : Responses to the survey question: In the majority of the cases, what is your treatment agent/route of choice to support the luteal phase ? (Soham et al., 2021)

En effet, la voie vaginale est connue pour induire un fort effet progestatif local grâce à un effet de 1er passage utérin (7) et un faible passage systémique évitant ainsi l'effet de premier passage hépatique (8). Cependant, elle engendre beaucoup d'effets indésirables locaux comme des pertes abondantes, une irritation vaginale avec des saignements ce qui peut engendrer un inconfort important et affecter la sexualité des patientes au cours du premier trimestre grossesse (9). En outre, les rapports sexuels pourraient altérer l'efficacité de cette voie d'administration de la progestérone micronisée (10). Par ailleurs, il existe probablement une variabilité interindividuelle de l'absorption de la progestérone vaginale liée à des déterminants encore mal connus (âge, poids, fréquences des rapports…) (11). D'une manière plus générale, une étude clinique sur le traitement de la

candidose vaginale a prouvé que la voie orale rapportait des meilleurs taux de satisfaction par les patientes en comparaison à la voie vaginale (12).

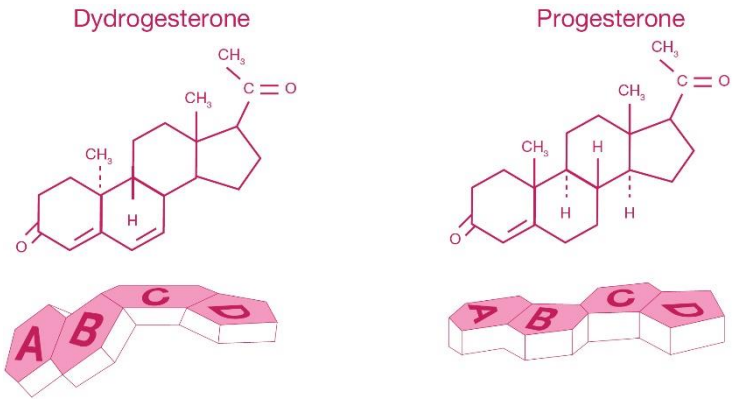

Figure 2 : La dydrogestérone se différencie chimiquement de la progestérone par l'existence d'une double liaison supplémentaire.

La dydrogestérone (6-dehydro-retroprogesterone) (DYD) est un rétro-stéroïde qui présente une excellente biodisponibilité orale (Figure 2). De plus, elle possède une sélectivité élevée pour les récepteurs de la progestérone. L'activité progestative forte de ses métabolites permet l'utilisation de doses orales beaucoup plus faibles par rapport à la progestérone micronisée qui possède une bien moins bonne absorption intestinale. Ainsi, La dydrogestérone permet d'induire une transformation endométriale à une posologie 10 à 20 fois inférieure à celle de la progestérone micronisée vaginale (MVP). Cette propriété pharmacologique permet de minimiser les effets secondaires de la dydrogestérone (2,8).

Depuis 20 ans, de nombreuses études randomisées ont validé l'utilisation de la dydrogestérone en soutien de phase lutéale (SPL) en AMP (2,13–15). Cette hormone est maintenant utilisée en pratique courante dans les transferts d'embryon frais en FIV en particulier depuis les études randomisées et contrôlées LOTUS I et LOTUS II qui ont formellement établi la non-infériorité de la dydrogestérone orale en comparaison avec la progestérone vaginale micronisée (16–18).

Actuellement, les données concernant l'utilisation de la dydrogestérone pour le soutien de phase lutéale dans le transfert d'embryons congelés (TEC) restent peu nombreuses notamment concernant le cycle artificiel et encore plus dans la population des receveuses de don d'ovocytes. Par ailleurs, la population de receveuse d'ovocyte est une population d'étude neutre, théoriquement peu influencée par les problèmes de qualité ovocytaire et donc idéale pour étudier les facteurs implantatoires.

Notre étude vise à comparer le taux de grossesse clinique et évolutive, le taux de naissance vivante et le taux de fausse couche spontanée précoce chez les femmes bénéficiant d'un don d'ovocytes en fonction du type de progestatif utilisé en cycle artificiel pour le soutien de de phase lutéale en complément d'une injection hebdomadaire de progestérone retard : progestérone micronisée vaginale versus dydrogestérone orale.

ARTICLE

TITLE : Is oral dydrogesterone equivalent to vaginal micronized progesterone for luteal phase support in women receiving oocyte donation ?

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KEYWORDS : Dydrogesterone, Micronized vaginal progesterone, Luteal phase support, Embryo transfer, Intramuscular progesterone, Oocyte donation

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ABSTRACT

Research question : To determine whether the use of oral dydrogesterone (DYD) in luteal phase support (LPS) during an artificial cycle provide equivalent clinical and ongoing pregnancy, delivery and miscarriage rates as micronized vaginal progesterone (MVP) in oocyte donation recipients.

Design : Retrospective observational study from prospectively collected data in the assistance reproductive technology (ART) Department of Lille University Hospital from July 2018 to July 2022. All recipients underwent endometrial preparation by an artificial cycle. Luteal phase support (LPS) was provided by weekly intramuscular progesterone (IM) (500 mg/2ml) and either DYD 40 mg/day or MVP 800 mg/day for 12 weeks if the pregnancy test was positive. The primary endpoint was clinical pregnancy rate.

Result : Our study analyzed 372 oocyte donation cycles with embryo transfer : 162 embryo transfers with DYD + IM progesterone and 210 embryo transfers with the MVP + IM progesterone. After adjustment for confounding factors, such as the number of embryos transferred, embryo quality, donor BMI and fresh or frozen status of the embryo., our two groups were comparable in clinical pregnancy rates with 36.67% in the MVP group versus 30.25% in the DYD group (p=0.57), ongoing pregnancy rates (29.05% versus 25.31%, p=0.97), miscarriage rates (7.62% versus 4.94%, p= 0.35) and live birth rates (26.67% versus 17.69%, p=0.27).

Conclusion : Oral Dydrogesterone seems to be a good alternative to vaginal micronized progesterone for LPS during an artificial cycle, especially in combination with a weekly injection of intramuscular progesterone in an oocyte donation course.

INTRODUCTION

The luteal phase is defined as the period between ovulation and the onset of menses following luteolysis. During the pre-ovulatory peak of gonadotropins, LH (luteinizing hormone) allows the transformation of granulosa cells into large luteal cells which ensure the production of progesterone. During the luteal phase, this same gonadotropin allows the maintenance of an optimal secretion of progesterone. This steroid hormone subsequently enables the secretory transformation of the endometrium and the opening of the short implant window. In addition, progesterone secreted by the corpus luteum allows the maintenance of the pregnancy during all or part of the 1er trimester. It has an immunomodulatory effect and regulates the sub-endometrial blood flow, thus combating the phenomenon of embryo rejection (1).

In oocyte donation, recipient women whose ovarian function is most often profoundly impaired must undergo endometrial preparation to allow implantation. The artificial cycle or hormone replacement therapy (HRT) is then used in the case of proven ovarian insufficiency. It consists of sequentially administering exogenous hormones naturally produced by the corpus luteum (oestrogen alone then oestrogen + progesterone) to mimic the endometrial cycle and allow the opening of a window for implantation. In the event of pregnancy, the combination of oestrogen and progesterone will be maintained throughout the 1er trimester of the pregnancy to compensate for the absence of the corpus luteum until the placenta takes over (2,3).

Different progestogens have been successively studied to optimize the luteal phase and only progesterone, dydrogesterone and hydroxyprogesterone caproate have been validated in pregnancy by the absence of cross-reactivity with other receptors (androgenic, glucocorticoid and oestrogenic) (1).

Progesterone is usually administered vaginally, orally, subcutaneously or intramuscularly. The poor oral and vaginal bioavailability of progesterone has been improved by micronization techniques. Currently, the vaginal route with micronized progesterone remains the preferred route for practitioners although there is no consensus on the optimal route of use (4,7,10).

Dydrogesterone (6-dehydroretroprogesterone) (DYD) is a retro steroid with excellent oral bioavailability. The strong progestational activity of its metabolites allows the use of much lower oral doses compared to micronized progesterone which has much poorer intestinal absorption (1,6). Over the past 20 years, numerous randomized studies have validated the use of dydrogesterone for luteal phase support (LPS) in ART (1,11-13). This hormone is now used in current practice in fresh embryo transfers in IVF, particularly since the randomized controlled studies LOTUS I and LOTUS II, which formally established the non-inferiority of oral dydrogesterone in comparison with micronized vaginal progesterone (14-16). Currently, data on the use of dydrogesterone for luteal phase support in frozen embryo transfer (FET) remain limited, especially in the artificial cycle and even more so in the oocyte recipient population. Furthermore, the oocyte recipient population is a neutral study population, theoretically not very influenced by oocyte quality issues and therefore ideal for studying implant factors.

The aim of our study is to compare the clinical and ongoing pregnancy rate, live birth rate and miscarriage rate in oocyte donation recipients according to the type of progestogen used in the artificial cycle for luteal phase support in addition to a weekly injection of delayed progesterone : vaginal micronized progesterone versus oral dydrogesterone.

MATERIALS AND METHODS

This study retrospectively analyzed all oocyte donation cycles performed between July 2018 and July 2022 in the Department of Reproductive Medicine at the University Hospital of Lille, France.

Donors

All donors were younger than 38 years old and were recruited by the same referring physician. Donors were systematically evaluated for contraindications such as hereditary conditions or contraindications to controlled ovarian stimulation. Their ovarian reserve was assessed by a serum anti-Müllerian hormone (AMH) assay (Access Anti-Müllerian Hormone [AMH] Assay; Beckman Coulter, Inc.) (19) and an antral follicle count (AFC) (20), using real-time two-dimensional ultrasound (Voluson™ E8 Expert; GE Healthcare) performed during the same consultation.

The assessment was completed by karyotype, psychological evaluation, and human immunodeficiency virus (HIV1–2), hepatitis B virus (HBV), hepatitis C virus (HCV), syphilis, chlamydia and cytomegalovirus (CMV) serology (3).

Women with any hereditary disease, an abnormal karyotype, body mass index (BMI) >34 kg/m², AMH < 5 pmol/l and/ or AFC < 8, abnormal serology or with contraindications to oral estrogens were excluded (3).

Phenotypic characteristics (colour of skin, eyes and hair, geographic origin, weight and height) and blood group were used to match donors and recipients. A donor was allocated to one or two recipients according to her ovarian reserve and the number of oocytes at the time of oocyte retrieval (3).

Recipients

Couples seeking oocyte donation were seen at a specialized consultation conducted by a single practitioner at the center. Women with premature ovarian failure (idiopathic, iatrogenic, auto-immune or genetics), at risk of maternal genetic disease or couples in intra-conjugal ART failure were eligible to receive oocyte donation. In addition, they had to be younger than 40 years old at registration, as the average waiting time was estimated at 2 years. Couples with very severe sperm impairment were mostly referred for embryo donation and then excluded from oocyte donation. An interview with a psychologist, serology (HIV 1–2, HCV, HBV, syphilis, CMV and chlamydia), and early recognition of parenthood were required at registration (3).

Treatments

One cycle of controlled ovarian stimulation was performed per donor. An antagonist protocol was used and the gonadotrophin starting dose was individually adjusted according to AFC, AMH, age and BMI values, and then adapted during stimulation according to ultrasound findings and estradiol levels (3).

A bolus of gonadotrophin-releasing hormone (GnRH) agonist (0.2 mg of triptoreline, Decapeptyl®) was administered as soon as at least two dominant follicles with a mean diameter >18 mm were obtained. Oocyte retrieval was performed by transvaginal ultrasound-guided needle aspiration, 36 h after triptoreline injection (3).

Synchronously with donor stimulation, the recipients received endometrial preparation by hormone replacement treatment, with the use of long-acting GnRH agonist (3 mg, Triptoreline, Decapeptyl®) if they still had spontaneous cycles. The endometrial preparation used oral micronized oestradiol 6 mg/day (Provames®, estradiol 2mg/tablet), with endometrial thickness checked at Day 12 of treatment. When endometrial thickness

was > 6.5 mm, treatment with vaginal micronized progesterone 400 mg twice a day (Progestan®, progesterone 200mg/caps) or oral dydrogesterone 20 mg twice a day (Duphaston®, dydrogesterone 10mg/tablet), both associated with weekly intramuscular progesterone (Progesterone Retard®, hydroxyprogesterone caproate 500 mg/2 ml, Bayer Healthcare, France), was initiated on the evening of donor oocyte retrieval.

Sperm microinjection using the ICSI technique with the partner's frozen spermatozoa was performed on each M2 oocyte. An evaluation of normal diploid fertilization was made at 16-18 h after the injection, by observation of the two pronuclei and the second polar body (PB) expelled in the perivitelline space (PVS). Early cleavage was observed 27 h after injection. Embryo quality was estimated at 44-46 h (or 68 h) from injection. Embryo quality classification in our IVF laboratory is based on the number and size of blastomeres, the degree of fragmentation, and the presence or absence of multi-nucleated blastomeres according to the Istanbul Consensus Conference (21). On day 2, an embryo was considered to be of good quality if it had 4 blastomeres of equal size, without multi-nucleation and with less than 10% fragmentation. If the embryo transfer was to take place on day 3 after injection, a good quality embryo had to have 8 cells of equal size, without multi-nucleation and with less than 10% fragmentation. Only supernumerary embryos of good quality were frozen for subsequent embryo transfers.

The transfer of cleaved-staged embryo(s) was performed to recipients at D2 or D3 post-oocyte retrieval. For frozen embryo transfers, intramuscular supplementation was initiated at the same time as vaginal progesterone or dydrogesterone.

A blood test for hCG assessment was performed 14 days after the embryo transfer. Pregnancy was subsequently confirmed with transvaginal ultrasonography at 5–6 weeks' gestation, by visualization of a gestational sac.

Clinical pregnancy was defined by an hCG assay >100 IU/l, 14 days after embryo transfer, with at least a gestational sac visualized by early ultrasound at 6 weeks of pregnancy. Ongoing pregnancy was defined by the ultrasound visualization of at least one gestational sac with an embryo with cardiac activity after 12 weeks of pregnancy. The miscarriage rate was defined as the rate of clinical pregnancies resulting in pregnancy loss by 12 weeks. The live birth rate was defined as the number of deliveries that resulted in a live born neonate on the number of transfers. The primary endpoint was clinical pregnancy rate. The secondary endpoints were ongoing pregnancy, live birth and miscarriage rates (3).

From July 2018 to April 2021 (Figure 1), progesterone was administered to all recipients by the micronized vaginal progesterone 800 mg per day (Progestan®, progesterone 200mg/caps : 400 mg twice a day) associated with weekly intramuscular progesterone (Progesterone Retard®, hydroxyprogesterone caproate 500 mg/2 ml, Bayer Healthcare, France).

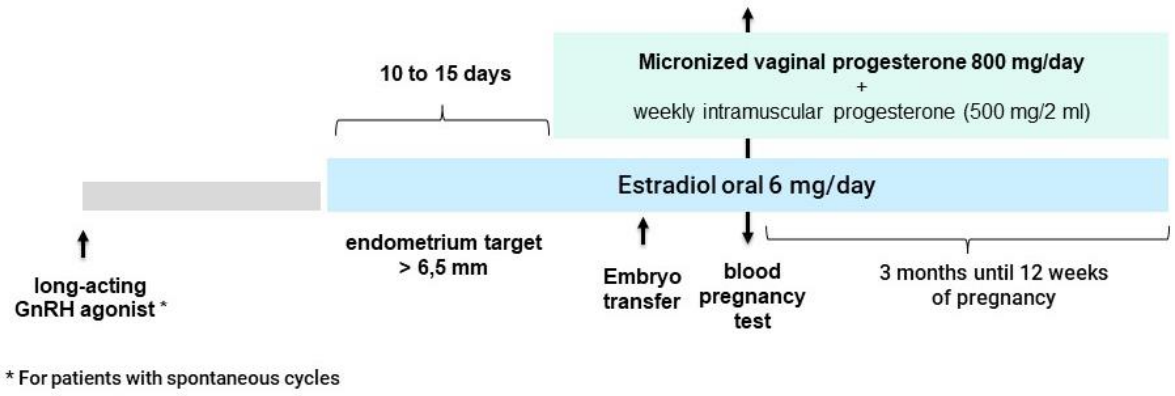

Figure 1 : treatment of recipients from July 2018 to April 2021

From April 2021 until July 2022 (Figure 2), all the recipients received oral dydrogesterone 40 mg per day (Duphaston®, dydrogesterone 10mg/tablet : 20 mg twice a day) with weekly intramuscular progesterone.

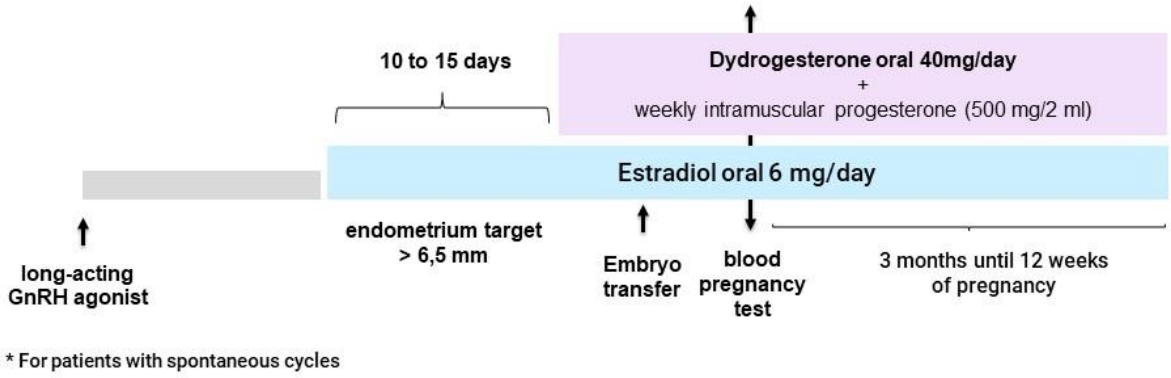

Figure 2 treatment of recipients from April 2021 to July 2022

These various treatments (estradiol, vaginal progesterone or dydrogesterone with intramuscular progesterone) continued until the twelfth week of pregnancy, unless they stopped earlier after a diagnosis of miscarriage.

There were no changes in either the selection of donors or recipients, or any laboratory techniques, from July 2018 through to the end of the study.

Statistical analysis

Qualitative variables were described in terms of frequencies and percentages. Quantitative variables were described by the mean and standard deviation or by the median and interquartile range in case of a non-Gaussian distribution. The normality of the distributions was checked graphically and using the Shapiro-Wilk test. The initial characteristics of donors, recipients, their partners, and laboratory parameters were compared between the 2 treatment groups using the Chi-square test for qualitative variables and the Student t test (or Mann-Whitney U test in case of non-Gaussian

distribution) for quantitative variables. For further analysis, parameters with missing values were treated by simple imputation. Missing data were imputed under the "missing at random" assumption using the chained equation method with m=1 imputation. Quantitative variables were imputed by “ the predictive mean matching method ” and qualitative variables by logistic regression models (binomial, ordinal or multinomial). Outcomes were compared between the 2 treatment groups using a logistic regression model adjusted on the confounding factors found (at the 5% threshold). The clinical pregnancy rate was compared between embryo quality grades and between fresh and frozen embryos using the Chi-square test. The level of significance was set at 5%. Statistical analyses were performed using SAS software (SAS Institute version 9.4).

Ethical approval

As this study was retrospective and without intervention, the opinion of the Ethics Committee on the study was not required. All patients had given prior consent for the use of their clinical, hormonal and ultrasound record. The study was approved by the French Data Protection Authority (CNIL) on 19 July 2016 (reference: DEC16-25).

RESULTS

In total, this study included 372 fresh or frozen embryo transfers from an oocyte donation between July 2018 and July 2022. (Figure 3)

The patients were divided into two groups : the first group received 800mg/day of micronized vaginal progesterone combined with IM progesterone and the second received 40 mg/day of dydrogesterone combined with IM progesterone in the same modalities.

The analysis included 210 embryo transfer cycles with vaginal luteal phase support (MVP) + IM prog and 162 cycles with oral luteal phase support (DYD) + IM prog. (Figure 3)

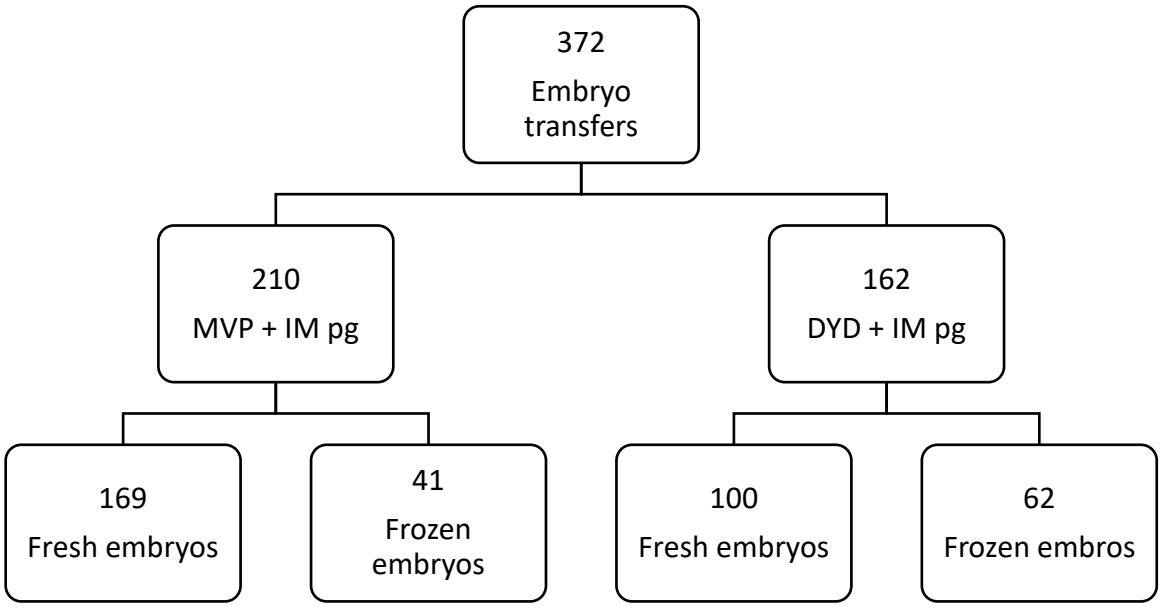

Figure 3 Flow chart

The baseline characteristics of the recipients and their partners were comparable between the two groups (Table 1).

The baseline characteristics of donors were comparable between the two groups except for BMI, with higher BMI in the MVP group (Table 1).

Concerning the laboratory parameters, there was a significant difference for the number of embryos transferred (1 or 2) with more transfer of two embryos in the MVP group. There was also a significant difference in the fresh or frozen status of the embryo with more frozen embryo transfers in the DYD group.

Regarding embryo quality, in most cycles at least one good quality embryo was transferred. There was a statistically significant difference in distribution with more grade 2 in the DYD group. (Table 1)

All these parameters were included in the adjustment of the final analysis. Regarding the reproductive parameters, there was no difference between the two groups before and after adjustment of the analysis for the clinical pregnancy rate, the ongoing pregnancy rate and the live birth rate. Likewise, the miscarriage rate was not statistically different between the two groups. (Table 2)

TABLE 1 Demographic and clinical characteristics of study participants at baseline

Characteristics		**MVP + IM Pg N= 210**	**DYD + IM pg N=162**	**P-Value[a]**
Recipients				
Age (years)		35.5 (32.0 ; 39.0)	36.0 (33.0 ; 39.0)	0.39
BMI (kg/m2)		23.0 (21.0 ; 27.0)	23.0 (21.0 ; 28.0)	0.59
Smoker		24 (11.5)	23 (14.4)	0.41
Previous children not in donation		17 (8.1)	16 (9.9)	0.55
Previous children in donation		16 (7.6)	12 (7.4)	0.94
Previous miscarriage		38 (18.1)	33 (20.4)	0.58
Etiology of	iatrogenic POI	44 (20.9)	28 (17.2)	0.71

donation recourse	Auto-immune and/or idiopathic POI	47 (22.5)	40 (24.7)	0.71
	Genetic causes: genetic POI and/or risk of transmission of a serious genetic disease	29 (13.8)	30 (18.5)	
	Intra-conjugal ART failure	90 (42.8)	64 (39.5)	
Associated endometriosis		30 (14.3)	22 (13.6)	0.85
Donors				
Age (years)		32.0 (28.0 ; 34.0)	30.0 (27.0 ; 33.0)	0.069
BMI (kg/m2)		23.0 (21.0 ; 26.0)	22.0 (20.0 ; 25.0)	0.004
AMH (pmol/l)		25.0 (17.2 ; 42.6)	27.7 (18.1 ; 43.8)	0.29
Smoker		41 (21.5)	37 (26.6)	0.28
Male partners of the recipients				
Age (years)		37.0 (33.0 ; 41.0)	37.0 (34.0 ; 41.0)	0.22
Smoker		57 (27.7)	48 (30.0)	0.62
Sperm quality	Normal	154 (75.1)	125 (77.6)	0.57
	Spermatic alterations	51 (24.9)	36 (22.4)	
Clinical and laboratory outcomes of oocyte donation cycles				
No. of injected meta2 oocytes		5.0 (4.0 ; 6.0)	5.0 (4.0 ; 6.0)	0.47
No. of embryos obtained		3.0 (2.0 ; 4.0)	3.0 (2.0 ; 4.0)	0.69
No. of embryos transferred	1	92 (43.8)	134 (82.7)	<0.001
	2	118 (56.2)	28 (17.3)	
No. of embryos frozen		0.0 (0.0 ; 1.0)	1.0 (0.0 ; 2.0)	0.12
	Fresh	169 (80.5)	100 (61.7)	<0.001

Fresh or frozen embryo	Frozen	41 (19.5)	62 (38.3)	
Embryo quality	Grade 1	142 (68.9)	100 (64.5)	<0.001
	Grade 2	51 (24.8)	52 (33.5)	
	Grade 3	13 (6.3)	3 (1.9)	

Results are expressed as median (5^{th}-95^{th} percentile) or number (percentage)
[a] P-value for global comparison between the two groups. Results were considered significant when P <0.05.

TABLE 2 Results of reproductive outcomes

Characteristics	**MVP + IM Pg N= 210**	**DYD + IM pg N=162**	**P-Value[a]**
Reproductive outcomes			
Clinical pregnancy rate	77 (36.67)	49 (30.25)	0.5748 [c]
Ongoing pregnancy rate	61 (29.05)	41 (25.31)	0.9779 [c]
Miscarriage rate	16 (7.62)	8 (4.94)	0.3553 [c]
Live birth rate	56 (26.67)	26 (17.69)	0.2715 [c]

Results are expressed as median (5^{th}-95^{th} percentile) or number (percentage)
[a] P-value for global comparison between the two groups. Results were considered significant when P <0.05.
[c] After logistic regression model adjusted on the confounding factors found : the number of embryos transferred, embryo quality, donor BMI and fresh or frozen status of the embryo (at the 5% threshold)

DISCUSSION

This study shows that there is no significant difference between DYD and MVP in luteal phase support during an artificial cycle in terms of clinical pregnancy rate, but also in terms of ongoing pregnancy, live birth and miscarriage rates. Thus, they offer physicians an alternative to the vaginal route of administration, its inconvenience and even possible absorption defects in some patients (10,11).

These results are consistent with current data in the literature. These include a few small randomized studies comparing DYD and MVP in artificial cycle. The largest is a single-blind randomized controlled trial (22) of 180 patients divided into three groups (IM 100mg/day, DYD 40 mg/day and MVP 800mg/day). Pregnancy and live birth rates were comparable in the three groups suggesting that DYD was a good alternative to IM and vaginal administration. In 2021, Macedo et al. (23) confirmed Rashidi's results in a randomized clinical trial of 73 patients by finding similar pregnancy rates between the two progestogens at the same dosages as in our study. Both studies (22,23) were randomized but with relatively small numbers of patients in each arm, probably insufficient to demonstrate significant differences in clinical pregnancy, miscarriage and live birth rates. Two other studies (24,25) were performed with lower doses of DYD in the order of 20 mg/day to 30mg/day : one found lower pregnancy rates in the 20 mg/day DYD group compared to the 800 mg MVP group (24). In contrast, Atzmon et al. found similar pregnancy rates at the 30 mg/day dosage in their retrospective cohort (25). However, none of these studies looked at the combination of two distinct and complementary routes of progesterone administration (22–25).

Other randomized studies were published recently comparing DYD and vaginal progesterone gel (Crinone® 8%) with similar reproductive results between the two methods of administration (26,27).

In our study, both luteal phase support strategies used dosages consistent with the literature to ensure quality luteal phase support (28,29). The addition of intramuscular progesterone avoided the risk of insufficient supplementation (3). Indeed, using two distinct and complementary routes of administration of progesterone probably avoids absorption defects of each route (oral or vaginal) subject to inter-individual variability (29,30). Moreover, no upper threshold of progesterone was identified as deleterious on pregnancy rate and live birth rate (28,29,31). A very recent study compared (32) the MVP + DYD association to the MVP + IM progesterone association in LPS during a FET in artificial cycle establishing the non-inferiority of these two strategies in terms of clinical pregnancy rate. This new combination may avoid IM administration, which can be painful and poorly tolerated by patients (8). It opens up the possibility of new combinations for LPS in order to better adapt to each patient while ensuring sufficient luteal phase support. It also highlights the hypothesis that administration of progesterone by two different routes appears to optimize the chances of pregnancy although further studies are needed to confirm these notions.

In 2017, Labarta et al.(29) found that low serum progesterone levels on the day of transfer (pg < 9.2 ng/ml) during an artificial cycle were associated with a decreased clinical pregnancy rate. This latest study highlights the notion of a minimum serum progesterone threshold on the day of transfer in an artificial cycle to optimize pregnancy rate. Although currently no threshold has yet been agreed upon due to a lack of good evidence-based studies on the subject and the non-reproducibility of the test kits (29,33). Furthermore, it suggests that vaginal progesterone alone is probably insufficient for a proportion of

patients. It is also thanks to this finding that another study by our team Delcour et al. in 2019 (3) showed that the addition of intramuscular progesterone during an artificial cycle was associated with a decrease in the miscarriage rate.

Subsequently, Labarta et al. (34) continued their work by introducing the concept of "individualized luteal phase support". Indeed, they conducted a retrospective study to demonstrate that by adding subcutaneous progesterone supplementation to patients with low progesterone levels on the day of transfer, it was possible to recover live birth rates similar to those with adequate serum progesterone levels. All these studies (29,34) were performed with MVP (800 mg/day), which is easily measured in the laboratory by electrochemiluminescence immunoassay. As DYD is used more and more frequently, some authors (28) were interested in the plasma concentration of DYD and its active metabolite DHD (20α-dihydrodrogesterone) on the evening of the embryo transfer. It should be remembered that the plasma thresholds of DYD and DHD required for implantation are currently unknown. In addition, the assay technique using tandem mass spectrometry/liquid chromatography, is too complicated to be used in routine practice. However, Neumann et al. demonstrated that the rate of ongoing pregnancy was significantly reduced in patients with plasma levels ≤ 25th percentile. They also highlighted the inter and intraindividual variability of DYD metabolism were not correlated with the patients' BMI. The dose of DYD used in this study of about 20 mg/day was probably suboptimal. These individual variabilities are probably due to different enzyme polymorphisms but further studies are needed to determine reliable correlating factors (dietary, ethnic, genetic) (28).

The main strengths of our study are : on the one hand, it is the first study on the subject to include only oocyte recipients in its study population. Indeed, this population is in fact not influenced by issues of oocyte quality. Definitely, it is an ideal model to study

implant factors. On the other hand, this is the only study comparing DYD and MVP in the context of dual routes of administration (combination with weekly intramuscular progesterone injections). Furthermore, our results are consistent with the current literature and support the fact that DYD is a good option for the practitioner. In contrast, the main limitations of our study are its retrospective design and the lack of randomization of patients between the two groups. However, our groups are broadly comparable and the analysis adjusted for potential confounders.

In conclusion, dydrogesterone seems to be a good alternative to vaginal micronized progesterone for LPS in an artificial cycle, especially in combination with weekly high dose of intramuscular progesterone in an oocyte donation course.

DISCUSSION THESE

Cette étude montre qu'il n'y a pas de différence significative entre la DYD et la MVP en soutien de phase lutéale lors d'un cycle artificiel en termes de taux de grossesse clinique mais également de taux de grossesse évolutive, de taux de naissance vivante et de taux de fausse couche spontanée précoce. Ainsi, ils offrent aux praticiens une alternative à la voie d'administration vaginale, à ses désagréments voire à ses défauts d'absorption éventuels chez certaines patientes (10,11).

Ces résultats sont concordants avec les données actuelles de la littérature. Celles-ci comportent quelques études randomisées de faibles effectifs comparant la DYD et la MVP en cycle artificiel. La plus importante est une étude randomisée contrôlée en simple aveugle (22) de 180 patientes divisées en trois groupes (IM 100mg/jour, DYD 40 mg/jour et MVP 800mg/jour). Les taux de grossesse et naissance vivante étaient comparables dans les trois groupes laissant penser que la DYD était une bonne alternative à l'administration IM et vaginale. En 2021, Macedo et al. (23) a conforté les résultats de Rashidi et al. lors d'un essai clinique randomisé de 73 patientes en retrouvant des taux de grossesse similaires entre les deux progestatifs aux mêmes posologies que dans notre étude. Ces deux dernières études (22,23) étaient randomisées mais avec des effectifs assez faibles dans chaque bras probablement insuffisants pour démontrer des différences significatives en termes de taux de grossesse, de fausse couche spontanée précoce et de naissance vivante. Deux autres études (24,25) ont été réalisées avec des posologies de DYD plus faibles de l'ordre de 20 mg/jour à 30 mg/jour : l'une retrouvait des taux de grossesse plus faibles dans le groupe 20 mg/jour de DYD par rapport au groupe 800 mg de MVP (24). En revanche, l'équipe de Atzmon et al. trouvait des taux de grossesse similaires à la posologie de 30 mg/jour au sein de sa cohorte rétrospective (25).

Néanmoins, aucune de ces études citées ne s'est intéressée à l'association de deux voies d'administrations distinctes et complémentaires de progestérone.
D'autres études randomisées sont parues récemment comparant la DYD et le gel de progestérone vaginale micronisée (Crinone® 8%) retrouvant des résultats reproductifs similaires entre les deux voies d'administrations (26,27).

Dans notre étude, les deux stratégies de soutien de phase lutéale ont utilisé des posologies cohérentes avec les données de la littérature pour assurer un soutien de phase lutéale de qualité (28,29). L'ajout de progestérone intra-musculaire a permis d'éviter le risque d'une supplémentation insuffisante (3). En effet, associer deux voies d'administration distinctes et complémentaires de progestérone permet probablement de s'affranchir des défauts d'absorption de chaque voie (orale ou vaginale) soumise à une certaine variabilité interindividuelle (28,29). A fortiori, aucun seuil supérieur de progestéronémie n'a été identifié à l'heure actuelle comme délétère sur le taux de grossesse et taux de naissance vivante (28,29,31). Une étude très récente (32) a comparé l'association MVP + DYD à l'association MVP + progestérone IM en soutien de phase lutéale lors d'un TEC en cycle artificiel établissant la non-infériorité de ces deux stratégies en termes de taux de grossesse clinique. Cette nouvelle combinaison peut permettre d'éviter l'administration IM qui peut être douloureuse et mal tolérée par les patientes (8). Elle ouvre ainsi des perspectives de nouvelles combinaisons pour le SPL afin de s'adapter au mieux à chaque patiente tout en assurant un soutien de phase lutéale suffisant. Elle met également en lumière l'hypothèse que l'administration de progestérone par deux voies différentes semble optimiser les chances de grossesse même si des études ultérieures sont nécessaires pour confirmer ces notions.

En 2017, Labarta et al.(29) ont fait le constat qu'un faible taux de progestérone sérique le jour du transfert (pg < 9,2 ng/ml) lors d'un cycle artificiel était associé à une diminution du taux de grossesse clinique. D'une part, cette dernière étude met en lumière la notion de seuil minimal de progestérone sérique le jour du transfert lors d'un cycle artificiel pour optimiser le taux de grossesse. Rappelons qu'aucun seuil n'est à ce jour encore consensuel du fait d'un manque d'étude de bon niveau de preuve sur le sujet et de la non reproductibilité des kits de dosage (29,33). D'autre part, elle suggère que la progestérone vaginale seule est probablement insuffisante pour une partie des patientes. C'est d'ailleurs grâce à ce constat qu'une autre étude de notre centre Delcour et al.(3) en 2019 a montré que l'ajout de progestérone intra-musculaire pendant un cycle artificiel était associé à une diminution du taux de fausse couche spontanée précoce. Par la suite, Labarta et al.(34) ont continué leurs travaux en amenant la notion de « soutien de phase lutéale individualisée ». En effet, leur étude rétrospective montre qu'en ajoutant un complément de progestérone sous-cutanée aux patientes qui présentaient un taux de progestérone sérique faible le jour du transfert, il était possible de retrouver des taux de naissance vivante similaires à celles qui présentaient un taux initial adéquat. Toutes ces dernières études (29,34) ont été réalisées avec de la MVP 800mg/jour facilement dosable en laboratoire par dosage immunologique en électro-chimiluminescence. La DYD étant de plus en plus utilisée couramment, quelques auteurs (28) se sont intéressés aux concentrations plasmatiques de DYD et de son métabolite actif DHD (20α-dihydrodydrogestérone) le soir du transfert d'embryon en cycle artificiel. Rappelons qu'actuellement les seuils plasmatiques de DYD et DHD nécessaire à l'implantation restent inconnus. De plus, la technique de dosage utilisant la spectrométrie de masse en tandem/chromatographie en phase liquide est trop complexe pour être utilisée en pratique courante. Cependant, Neumann et al. ont démontré que le taux de grossesse en cours était significativement réduit chez les patientes qui présentaient des taux plasmatiques ≤

25ème percentile. Ils ont également mis en exergue la variabilité inter et intra-individuelle du métabolisme de la DYD non corrélée à l'IMC des patientes. La dose de DYD utilisée dans cette étude de l'ordre de 20 mg/jour était surement sous optimale. Ces variabilités individuelles sont probablement dues à des polymorphismes enzymatiques différents mais d'autres études sont nécessaires pour déterminer des facteurs de corrélation fiables (alimentaire, ethnique, génétique) (28).

Les principales forces de notre étude sont : d'une part, qu'il s'agit de la première étude sur le sujet n'incluant dans sa population d'étude que des receveuses d'ovocytes. En effet, cette population n'est en principe pas influencée par des problèmes de qualité ovocytaire. En définitive, il s'agit d'un modèle idéal pour étudier les facteurs implantatoires. D'autre part, il s'agit de la seule étude comparant la DYD et la MVP dans un contexte de double voie d'administration (association avec les injections intramusculaires hebdomadaires de progestérone). Par ailleurs, nos résultats sont également cohérents avec les données de la littérature actuelle et appuie le fait que la DYD est une bonne option pour le praticien. A contrario, les principales limites de notre étude sont, son design rétrospectif et la non randomisation des patientes entre les deux groupes. Cependant, nos groupes sont globalement comparables et l'analyse ajustée sur les facteurs de confusion potentiels.

En conclusion, la dydrogestérone semble être une bonne alternative à la progestérone micronisée vaginale pour le SPL lors d'un cycle artificiel notamment en association avec une injection intra-musculaire hebdomadaire de progestérone retard dans un parcours de don d'ovocytes.

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Date de soutenance : 1er juin 2023

Titre de la thèse : La dydrogestérone orale est-elle équivalente à la progestérone micronisée vaginale en soutien de phase lutéale chez les femmes recevant un don d'ovocytes ?

Thèse - Médecine - Lille 2023

Cadre de classement : Médecine de la reproduction

DES + FST/option : Gynécologie médicale, FST de Médecine et biologie de la reproduction - Andrologie

Mots-clés : Dydrogestérone, cycle artificiel, don d'ovocytes, soutien de phase lutéale

Résumé :

La dydrogestérone (DYD) présente une excellente biodisponibilité orale ainsi qu'une sélectivité élevée pour les récepteurs de la progestérone permettant l'utilisation de doses orales beaucoup plus faibles par rapport à la progestérone micronisée. Cette hormone est maintenant utilisée en pratique courante dans les transferts d'embryons frais en fécondation-in-vitro (FIV). Cependant, peu de données sont encore disponibles concernant son utilisation en soutien de phase lutéale (SPL) dans les transfert d'embryons congelés-décongelés (TEC) notamment en cycle artificiel et plus particulièrement dans la population de receveuses d'ovocytes. Dans cette situation, l'absence de corps jaune entraîne une dépendance totale aux progestatifs exogènes pour l'implantation et le maintien de la grossesse.
Il s'agit d'une étude observationnelle rétrospective réalisée dans le service d'assistance médicale à la procréation du CHU de Lille de juillet 2018 à juillet 2022.
Notre étude a analysé 372 transferts d'embryons frais ou congelés issus d'un don d'ovocytes. Les receveuses ont bénéficié d'une préparation endométriale en cycle artificiel (THS). Les patientes étaient divisées en deux groupes : le premier groupe (N=210) recevait 800 mg/jour de la progestérone vaginale micronisée (MVP) combinée à de la progestérone IM et le second (N=162) recevait 40 mg/jour de DYD combinée à de la progestérone IM selon les mêmes modalités.
Le critère de jugement principal était le taux de grossesse clinique.
L'analyse a été ajustée sur les facteurs de confusion et après ajustement aucune différence significative n'a été montrée entre les deux groupes en termes de taux de grossesse clinique, de taux de grossesse en cours, de taux de fausse couche spontanée précoce et de taux de naissance vivante.

<u>Composition du Jury</u> :

Président : Madame la Professeure Sophie CATTEAU-JONARD

Assesseurs : Madame le Docteur Christine DECANTER Madame le Docteur Laura KELLER

Directeur de thèse : Monsieur le Docteur Geoffroy ROBIN