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HYPOTHESIS

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Is oral dydrogesterone equivalent to vaginal micronized progesterone for luteal phase support in women receiving 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 provides equivalent clinical and ongoing pregnancy, delivery and miscarriage rates as micronized vaginal progesterone (MVP) in oocyte donation recipients.

Design This was a retrospective observational study of prospectively collected data from the assisted 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/2 ml) and either DYD (40 mg/day) or MVP (800 mg/day) for 12 weeks if the pregnancy test was positive. The primary endpoint was the clinical pregnancy rate.

Results Our study analysed 372 oocyte donation cycles with embryo transfer: 162 embryo transfers with DYD + IM progesterone and 210 embryo transfers with MVP + IM progesterone. After adjustment for confounding factors, our two groups were comparable in terms of clinical pregnancy rates, with 36.7% in the MVP group versus 30.3% in the DYD group ($p = 0.55$); ongoing pregnancy rates (29,1% versus 25.3%, $p = 0.95$); miscarriage rates (7.6% versus 4.9%, $p = 0.35$); and live birth rates (26.7% versus 25.3%, $p = 0.86$).

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

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

Introduction

The luteal phase was defined as the period between ovulation and the onset of menses following luteolysis. During the preovulatory peak of gonadotropins, luteinizing hormone (LH) allows the transformation of granulosa cells into large luteal cells, which ensures the production of progesterone. During the luteal phase, this same gonadotropin allows the maintenance of optimal secretion of progesterone. This steroid hormone subsequently enables secretory transformation of the endometrium and opening of the short window of

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implantation. In addition, progesterone secreted by the corpus luteum allows maintenance of pregnancy during all or part of the first trimester. It has an immunomodulatory effect and regulates subendometrial blood flow, thus combating the phenomenon of embryo rejection [13].

In the context of oocyte donation, endometrial preparation is imperative to facilitate implantation. The artificial cycle or hormone replacement therapy (HRT) consists of sequentially administering exogenous hormones naturally produced by the corpus luteum (oestrogen alone then oestrogen + progesterone) to mimic the endometrial cycle and create an implantation window. In the event of pregnancy, the combination of oestrogen and progesterone will be maintained throughout the first trimester of pregnancy to compensate for the absence of the corpus luteum until the placenta takes over [10, 11, 28].

Different progestogens have been successively studied for their ability to optimize the luteal phase, and only progesterone, dydrogesterone and hydroxyprogesterone caproate have been validated for use during pregnancy because of the absence of cross-reactivity with other receptors (androgenic, glucocorticoid and oestrogenic) [13, 18].

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 [5, 24, 26].

Dydrogesterone (6-dehydroretroprogesterone) (DYD), a retrosteroid with excellent oral bioavailability, offers an alternative. The strong progestational activity of its metabolites allows the use of much lower oral doses than micronized progesterone, which has much poorer intestinal absorption [13, 22]. Despite its established role in fresh embryo transfers [1, 4, 12–14, 27, 29], particularly validated by studies like LOTUS I and LOTUS II [9, 15, 16], data on dydrogesterone's application in frozen embryo transfert (FET), especially in artificial cycles and within the oocyte recipient population, remain limited. Furthermore, the oocyte recipient cohort, theoretically neutral to oocyte quality issues, presents an ideal study population for investigating implantation factors.

Our study seeks to address this gap by comparing clinical and ongoing pregnancy rates, 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 analysed 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 the donors were younger than 38 years 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.) [8] and an antral follicle count (AFC) [6] 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 [7].

Women with any hereditary disease, an abnormal karyotype, a body mass index (BMI) > 34 kg/m^2, an AMH concentration < 5 pmol/l, an AFC < 8 or abnormal serology were excluded [7].

Phenotypic characteristics (color 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 [7].

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, autoimmune or genetic), at risk of maternal genetic disease or couples in intraconjugal ART failure were eligible to receive oocyte donation. In addition, they had to be younger than 40 years at registration, as the average waiting time was estimated to be 2 years. Couples with very severe sperm impairment were mostly referred for embryo donation and were subsequently excluded from oocyte donation. Women with contraindications to oral estrogens were excluded. An interview with a psychologist, serology (HIV 1–2, HCV, HBV, syphilis, CMV and chlamydia), and early recognition of parenthood were required at registration [7].

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 the AFC, AMH concentration, age and BMI and subsequently adjusted during stimulation according to ultrasound findings and estradiol levels [7].

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 was obtained. Oocyte retrieval was performed by transvaginal ultrasound-guided needle aspiration 36 h after triptoreline injection [7].

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®, oestradiol 2 mg/tablet), and endometrial thickness was checked on day 12 of treatment. When the endometrial thickness was > 6.5 mm, treatment with vaginal micronized progesterone 400 mg twice a day (Progestan®, progesterone 200 mg/caps) or oral dydrogesterone 20 mg twice a day (Duphaston®, dydrogesterone 10 mg/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 via the ICSI technique with the partner's frozen spermatozoa was performed on each M2 oocyte. Normal diploid fertilization was evaluated 16–18 h after the injection by observing 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) after 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 multinucleated blastomeres according to the Istanbul Consensus Conference [1]. On day 2, an embryo was considered to be of good quality if it had 4 blastomeres of equal size, no multinucleation and less than 10% fragmentation. If embryo transfer occurred on day 3 after injection, a good-quality embryo was required to have 8 cells of equal size without multinucleation and with less than 10% fragmentation. Only supernumerary embryos of good quality were frozen for subsequent embryo transfers.

The transfer of cleaved-stage embryo(s) to recipients was performed at D2 or D3 postoocyte 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 embryo transfer. Pregnancy was subsequently confirmed via transvaginal ultrasonography at 5–6 weeks of gestation via visualization of the gestational sac.

Clinical pregnancy was defined by an hCG concentration > 100 IU/l 14 days after embryo transfer, with at least one 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 pregnancy 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 relative to the total number of transfers. The primary endpoint was the clinical pregnancy rate. The secondary endpoints were ongoing pregnancy, live birth and miscarriage rates [7].

From July 2018 to April 2021 (Fig. 1), progesterone was administered to all the recipients by the micronized vaginal progesterone 800 mg per day (Progestan®, progesterone 200 mg/caps: 400 mg twice a day) combined with weekly intramuscular progesterone (Progesterone

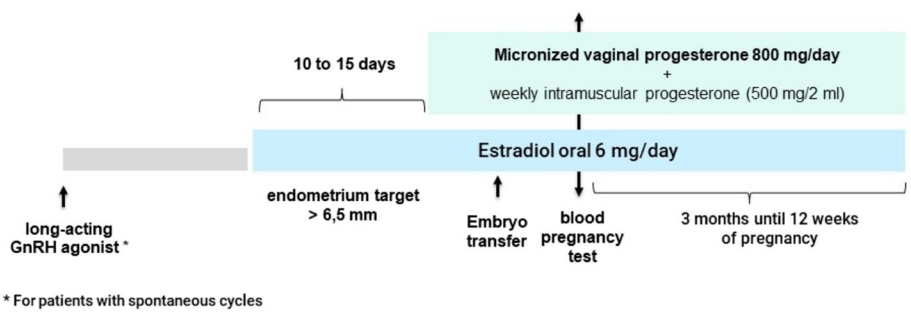

Fig. 1 Treatment of recipients from July 2018 to April 2021

Retard®, hydroxyprogesterone caproate 500 mg/2 ml; Bayer Healthcare, France).

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

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 in any of the laboratory techniques from July 2018 through the end of the study.

Statistical analysis

Qualitative variables are described in terms of frequencies and percentages. Quantitative variables are described as mean and standard deviation or median (interquartile range) in the case of a non-Gaussian distribution. The normality of the distributions was checked graphically and using the Shapiro–Wilk test. The initial characteristics of the donors, recipients, their partners, and laboratory parameters were compared between the 2 treatment groups using the chi-square test for qualitative variables and Student's t test (or the Mann–Whitney U test in the 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 were imputed by logistic regression models (binomial, ordinal or multinomial). Outcomes were compared between the 2 treatment groups using a logistic regression model adjusted for 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%. All the statistical analyses were performed using SAS software (SAS Institute version 9.4).

Results

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

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

Baseline characteristics

Baseline characteristics of recipients and their partners were comparable between the two groups (Table 1). Baseline characteristics of donors were also comparable between the two groups except for BMI which was significantly higher BMI in the MVP group ($p = 0.004$). Concerning the laboratory parameters, there was more transfers of two embryos in the MVP group ($p < 0.001$) and more frozen embryo transfers in the DYD group ($p < 0.001$). Regarding embryo quality, in most cycles, at least one good-quality embryo was transferred. However, there was a significant difference in distribution with more grade 2 in the DYD group ($p < 0.001$).

Outcomes

After adjustment for confounding factors (donors BMI, number of embryos transferred, frozen/fresh embryo status and embryo quality), our two groups were comparable in terms of clinical pregnancy rates, with 36.7% in the MVP group versus 30.3% in the DYD group ($p = 0.55$); ongoing pregnancy rates (29,1% versus 25.3%, $p = 0.95$); miscarriage rates (7.6% versus 4.9%, $p = 0.35$); and live birth rates (26.7% versus 25.3%, $p = 0.86$) (Table 2).

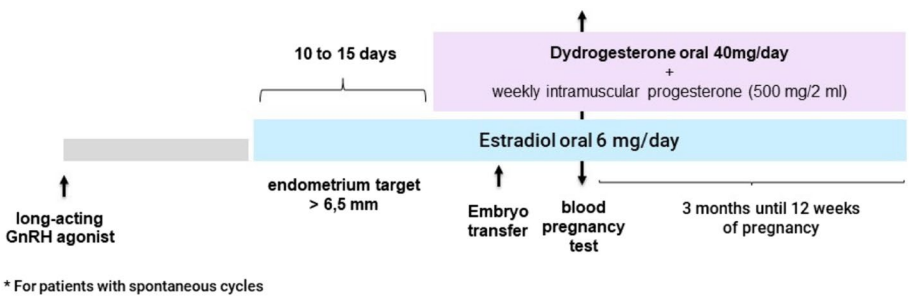

Fig. 2 Treatment of recipients from April 2021 to July 2022

Table 1 Demographic and clinical baseline characteristics between the two study groups

Characteristics	MVP + IM Pg *N* = 210	DYD + IM pg *N* = 162	*P*-Value
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 donation recourse			0.71
iatrogenic POI	44 (20.9)	28 (17.2)	
Auto-immune and/or idiopathic POI	47 (22.5)	40 (24.7)	
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
Spermatic alterations	51 (24.9)	36 (22.4)	0.57
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			< 0.001
1	92 (43.8)	134 (82.7)	
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
Frozen embryo transferred	41 (19.5)	62 (38.3)	< 0.001
Embryo quality			< 0.001
Grade 1	142 (68.9)	100 (64.5)	
Grade 2	51 (24.8)	52 (33.5)	
Grade 3	13 (6.3)	3 (1.9)	

Values are expressed as median (25th-75th percentile) or number (percentage)

Table 2 Outcomes comparison between the two study groups

	MVP + IM Pg *N* = 210	DYD + IM pg *N* = 162	OR (95%CI)[a]	*P*-Value[a]
Clinical pregnancy rate	77 (36.7)	49 (30.3)	0.86 (0.52 to 1.41)	0.55
Ongoing pregnancy rate	61 (29.1)	41 (25.3)	0.99 (0.58 to 1.66)	0.95
Miscarriage rate	16 (7.6)	8 (4.9)	0.64 (0.24 to 1.64)	0.35
Live birth rate	56 (26.7)	41 (25.3)	1.05 (0.62 to 1.78)	0.86

Values are expressed as number (percentage)

[a] adjusted on the confounding factors at the level of 5%: number of embryos transferred, embryo quality, donor BMI and fresh or frozen status of the embryo

Discussion

This study revealed that there was no significant difference between DYD and MVP in terms of the clinical pregnancy rate or in terms of ongoing pregnancy, live birth or miscarriage rate during an artificial pregnancy cycle. Thus, they offer physicians an alternative to the vaginal route of administration because of the inconvenience and even possible absorption defects in some patients [12, 17].

These results are consistent with the 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 [23] of 180 patients divided into three groups (IM 100 mg/day, DYD 40 mg/day and MVP 800 mg/day). Pregnancy and live birth rates were comparable among the three groups, suggesting that DYD is a good alternative to IM and vaginal administration. In 2021, Macedo et al. [9] 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 [9, 23] were randomized but included relatively small numbers of patients in each arm, which is likely insufficient to demonstrate significant differences in clinical pregnancy, miscarriage and live birth rates. Two other studies [2, 31] were performed with lower doses of DYD on the order of 20 mg/day to 30 mg/day; one study reported lower pregnancy rates in the 20 mg/day DYD group than in the 800 mg MVP group [31]. In contrast, Atzmon et al. reported similar pregnancy rates at a 30 mg/day dosage in their retrospective cohort [2]. However, none of these studies examined the combination of two distinct and complementary routes of progesterone administration [2, 9, 23, 31].

Other randomized studies were published recently comparing DYD and vaginal progesterone gel (Crinone® 8%), and similar reproductive results were obtained between the two methods of administration [20, 21].

In our study, both luteal phase support strategies used dosages consistent with those in the literature to ensure quality luteal phase support [15, 19]. The addition of intramuscular progesterone prevents the risk of insufficient supplementation [7]. Indeed, using two distinct and complementary routes of progesterone administration probably prevents absorption defects in each route (oral or vaginal) because of interindividual variability [15, 19]. Moreover, no upper threshold of progesterone was identified as deleterious for both the pregnancy rate and live birth rate [15, 19, 25]. A very recent study compared [3] the MVP + DYD association to the MVP + IM progesterone association in LPS during a FET in an artificial cycle, establishing the noninferiority of these two strategies in terms of the clinical pregnancy rate. This new combination may prevent IM administration, which can be painful and poorly tolerated by patients [22]. This finding opens up the possibility of new combinations of LPS to better adapt to each patient while ensuring sufficient luteal phase support. The findings also highlight the hypothesis that the administration of progesterone via two routes appears to optimize the likelihood of pregnancy, although further studies are needed to confirm these findings.

In 2017, Labarta et al.[15] 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 the pregnancy rate. Currently, no threshold has been agreed upon due to a lack of good evidence-based studies on the subject and the nonreproducibility of the test kits [15, 30]. Furthermore, these findings suggest that the use of vaginal progesterone alone is likely insufficient for a proportion of patients. Similarly, another 2019 study by our team, Delcour et al., [7] showed that the addition of intramuscular progesterone during an artificial cycle was associated with a decrease in the miscarriage rate.

Subsequently, Labarta et al. [16] 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 [15, 16] were performed with MVP (800 mg/day), which is easily measured in the laboratory by electrochemiluminescence immunoassay. As DYD is increasingly used, several authors [19] have investigated the plasma concentration of DYD and its active metabolite DHD (20α-dihydrodrogesterone) on the evening of embryo transfer. 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 lower in patients with plasma levels ≤ the 25th percentile. The authors also highlighted that the inter- and intraindividual variability in DYD metabolism was not correlated with patient BMI. The dose of DYD used in this study, approximately 20 mg/day, was likely suboptimal. These individual variabilities are probably due to differences in enzyme polymorphisms, but further studies are needed to determine reliable correlating factors (dietary, ethnic, genetic) [19].

The main strengths of our study are as follows: On the one hand, this was 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. It is definitely an ideal model for studying implant factors. On the other hand, this is the only study comparing DYD and MVP in the context of dual routes of administration (combined with weekly intramuscular progesterone injections). Furthermore, our results are consistent with the current literature and support the notion that DYD is a good option for practitioners. 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 was adjusted for potential confounders.

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

Authors' contributions

ML, SCJ and GR wrote the main text of the manuscript. EC carried out the statistical analyses. CD contributed to the data collection. All authors revised the manuscript.

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This study has no conflict of interest to declare.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

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

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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