Clinical Obstetrics, Gynecology and Reproductive Medicine

Research Article ISSN: 2059-4828

A new and alternative pharmacological protocol for endometrial preparation in oocyte donation cycles: Human menopausal gonadotrophins followed by estrogens

Rindra Rakotobe Andriamaro[1], Ramarolahy Rija[2], Graziella Badulli[1]*, Andriantsirombaka Rakotobe Andriamaro[1] and Leonardo Formigli[1]

[1]CEFERMAD (Centre de Fertilité de Madagascar) Lot VK 25 bis, Ambohimanoro, Antananarivo, Madagascar

[2]Service de Réanimation Chirurgicale-Hôpital Universitaire Ravoahangy, Antananarivo, Madagascar

Abstract

The usual, standard pharmacological preparation of the endometrium in oocyte donation (OD) cycles deals with the administration of oestrogens for the proliferative phase followed by oestrogens coupled with progesterone for the secretive phase of the endometrium preparation. Due to our previous successful experience with some low responders where we shifted from human menopausal gonadotrophins (HMG) to oestrogens at around day 10 of therapy and we converted the cycle from an own oocyte to an oocyte donation cycle, it was decided to adopt this same protocol for planned OD cycles. Forty five recipient patients agreed to be treated with this new, alternative treatment and gave their written consent. After 10 days of HMG treatment, this therapy was replaced by oral oestrogens. However, six patients showed by ultrasound the development of a certain number of follicles and it was decided to continue with the HMG and proceed to ovum pick up (OPU) and in vitro fertilization (IVF) of their own oocytes. Two obtained a clinical pregnancy (33%). In the remaining thirty nine patients, there was no follicle development and the HMG was replaced after ten days of treatment by oral oestrogens and by OD. Twenty two clinical pregnancies were obtained (56%).

Acceptance of oocyte donation is a difficult decision for the patients. This described alternative pharmacological protocol gives to the patients the opportunity to ascertain whether their own ovaries have responded to HMG or not. In the affirmative, the HMG treatment may be continued and OPU and IVF may be performed with their own oocytes. Otherwise, HMG is stopped after 10 days of treatment and replaced by oestrogens in order to complete the proliferative phase of the endometrium and proceed with the OD. The results obtained with this new pharmacologic protocol in OD, 56%, was slightly higher than the results obtained in the same time period with the standard oestrogens/progesterone protocol for OD: eleven clinical pregnancies out of twenty four cases (46%). In addition, the new here described protocol is more acceptable by the majority of patients, since they may decide at the last minute whether to use own oocyte or donated oocytes. Conversely, in planned OD, with oestrogens administered from the very start of the treatment, the use of donated oocytes is planned from the beginning and there is no place for a possible conversion to own oocytes. With the exception of genetic indications and absolute absence of ovarian reserve, there is always a possibility, though small, that patients candidate for OD may develop own oocytes and the depicted protocol gives a chance to these patients who reluctantly accept OD as a last and ultimate resort. Whether this new approach to OD is better than the usual complete hormonal replacement protocol needs a prospective statistically well designed study.

Introduction

The major indications for OD are various: repeated failures of IVF with own oocytes, low responders, primary ovarian failure, premature menopause, genetic diseases and so on. The usual, standard hormonal replacement protocol deals with the administration of estrogens from the first day of the cycle and when the endometrium reaches a thickness of at least 8 mm, Progesterone is added to the treatment and concomitantly some donated mature oocytes from the egg donor are fertilised in vitro with the husband's sperm and embryo transfer (ET) is performed after 2 to 5 days of embryo culture [1]. Many different kinds of estrogens are being used for the hormonal replacement therapy, from the old conjugated estrogens [2], oral micronized estradiol, to the newer oral estradiol valerate, dermal patches, vaginal administration and the like.

Oocyte donation has become an important, growing procedure in artificial reproduction. However the majority of recipient patients are reluctant to accept donated oocytes and resort to OD only as a last resort procedure. Only genetic indications and total absence of ovarian reserve are absolute indications for OD, whereas the majority of the other indications are not always absolute and there is always a chance, albeit small, that some patients may surprisingly develop some own oocytes which may be fertilized and produce viable pregnancies.

Our Centre is located in Madagascar, a poor country with very bad roads. Patients frequently come from remote areas of the country and may take one or two full days to reach our Centre. In addition, because of the general low income of the population, we must do our best to generate pregnancies in the least number of attempts and limiting preliminary tests and laboratory tests to the minimum. Also monitoring of ovulation and endometrial growth is only performed by vaginal ultrasound with no hormonal monitoring [3].

Correspondence to: Graziella Badulli, CEFERMAD (Centre de Fertilité de Madagascar) Lot VK 25 bis, Ambohimanoro, Antananarivo 101, Madagascar, E-mail: graziellaparda@yahoo.it

Key words: *new, alternative, hormonal replacement protocol, oocyte donation, egg donation, endometrial preparation, human menopausal gonadotrophins, estrogens*

Received: September 05, 2019; **Accepted:** September 23, 2019; **Published:** September 26, 2019

Since 2017, in cases of low response to ovarian stimulation[3], rather than cancelling the cycle and starting '*ex novo*' a planned OD cycle, we ask the patients whether they would accept to convert that same cycle from own oocytes to an OD cycle. In the affirmative, the patients sign a consent form, HMG is stopped on day 10 of stimulation and replaced by oestrogens. After a few days, when the endometrium has reached a thickness of 8 mm, 4 to 6 mature (MII) oocytes coming from our concomitant egg donation program are fertilised with the patients' husband sperm, progesterone is added to the treatment and the embryo transfer is performed at the four to six cell stage. Due to the good success rate obtained with this last minute conversion in poor responders, it was decided to extend this pharmacologic protocol also in planned OD [4].

Methods

This new, alternative pharmacologic protocol for endometrial preparation deals with the administration of a long acting gonadotrophin releasing hormone (GnRh), Triptorelin (Decapeptyl IPSEN) 1.87 mg in a single i.m. dose in the mid-luteal phase of the previous cycle, followed by HMG 150 IU daily s.c. or i.m. from the first day of the following cycle. Ovarian stimulation is monitored by vaginal ultrasound , starting from day 7 of HMG. In case of no or poor response, on day 11, HMG is stopped and replaced by oral estradiol valerate (EV) (Progynova, BAYER) 6 mg daily. After a few days of EV, when the endometrium reaches a thickness of at least 8 mm, 4 to 6 MII donated oocytes from our concomitant OD program are fertilized in vitro with the sperm of the patient's husband, intravaginal Progesterone (P) (Utrogestan, Besins) 800 mg daily is started and after two days of culture, the resulting embryos are transferred into the patient's uterus at the four to six cell stage.

On the other hand, if the ovaries respond with the development of some growing follicles, the patients are asked whether to perform a homologous IVF with their own oocytes. If the patients accept, HMG is continued until the dominant follicles reach an average diameter of 20 mm, human chorionic gonadotrophins (HCG) 10,000 IU are administered and OPU is performed 36 hours later. IVF and Embryo Transfer (ET) are performed as usual after 2 culture days, at the four to six cell stage.

Table 1 depicts the novel, alternative pharmacologic protocol for endometrial preparation. By comparison, Table 2 shows the usual, standard protocol.

Results

Number of patients

Sixty nine recipients were given the opportunity to choose between the usual, standard protocol and the new alternative protocol after having been explained the caracteristics of both treatments. Fourty five patients (65%) chose the new protocol. The remaining twenty four (35%) chose the usual standard protocol.

Thickness of endometrium

In half of the cases, the thickness of the endometrium with the depicted new protocol (Table 1) reached an average of 8 mm with a trilinear morphology after the first 10 days of HMG, before starting EV. Interestingly enough, relatively thick endometria were observed in some cases, after ten days of HMG even in the complete absence of visible ovarian follicles. In the remaining half, the endometria were thinner, but after 2 to 4 days of EV, they reached a thickness of 8 mm, which is considered the minimum for starting the administration of P. In two cases, there was a slight uterine bleeding, which stopped after a few days of EV. In one of these two cases, a pregnancy took place. On the other hand, even with the standard replacement method (Table 2) some cases have still a thin endometrium after many days of EV replacement.

Oocytes and embryos

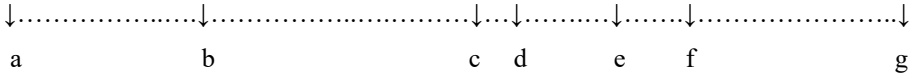
Oocytes were obtained from our concomitant OD program. Four to six MII oocytes were donated to the recipients and fertilized *in vitro* with the patient husbands' sperm. The resulting embryos were transferred on Day 2, at the four to six cell stage. The average number of embryos transferred was 3.1 for each recipient having chosen the new method and 3.2 for each recipient with the standard protocol.

Pregnancies

Sixty nine patients took part in the present investigation (Table 3). Out of forty five recipients who chose the new protocol, thirty nine patients completed the new method and were actually donated the oocytes. Twenty two clinical pregnancies were obtained (56%). Six responded positively to ovarian stimulation and decided to continue the procedure with their own oocytes. Two clinical pregnancies were obtained (33%).

Out of the twenty four patients treated with the standard protocol, eleven achieved a clinical pregnancy (46%) (Table 3).

Table 1. Novel, alternative pharmacologic protocol for endometrial preparation in oocyte donation cycles.



a: Administration of a single dose of Triptorelin 1.85 mg i.m. around day 20 of previous cycle.

b: Day 1 of cycle. Start HMG 150 IU daily for 10 days.

c: Day 10 of cycle. Last day of HMG.

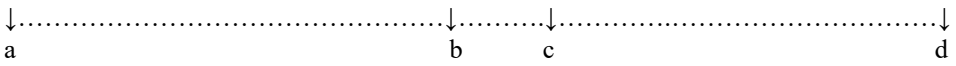
d: Day 11 of cycle. Start oral EV 6 mg daily.

e: Day 13 to 15, depending on thickness of endometrium (endometrium should reach at least 8 mm thickness), fertilise donated oocytes and start vaginal P 800 mg daily.

f: ET at Day 2, of four to six cell stage embryos.

g: 14 days after P start, perform a pregnancy test.

Table 2. Standard pharmacologic protocol for endometrial preparation in oocyte donation cycles



a: Day 1 of cycle. Start estrogens.

b: Day 13 to 15, depending on thickness of endometrium (endometrium should reach at least 8 mm thickness), fertilise donated oocytes and start vaginal P 800 mg daily.

c: ET at Day 2 of four to six cell stage embryos (some authors transfer at Day three or five).

d: 14 days after P start, perform a pregnancy test.

Table 3. Results of the novel, alternative pharmacologic protocol for endometrial preparation in oocyte donation cycles. Comparison with the standard protocol

	Number	Average n. embryos	Pregnancies
Recipients completing the new protocol	39	3.1	22 (56%)
Recipients having an unexpected ovarian response with the new protocol and choosing to shift to own oocytes	6	1.9	2 (33%)
Recipients treated with the standard protocol	24	3.2	11 (46%)

Discussion

Professionals dealing with OD know well that most recipient patients usually accept very reluctantly the use of egg donors. They wish trying whenever possible with their own eggs and the decision to finally go for egg donation is quite dramatic and upsetting. The present study deals with a new, alternative protocol for OD in recipients. It gives the chance to these patients to try the stimulation of their own ovaries and if after 10 days of stimulation, there is a no or scanty follicular development, they may decide during that same cycle to convert to OD, rather than cancelling the cycle and deferring the OD to a subsequent cycle. This last minute conversion towards OD is psychologically easier to make and the overall cost in terms of money and time is considerably lower.

Many different clinical situations give rise to the need of OD. A total absence of ovarian reserve may not be indicated for this novel protocol, since an ovarian reserve, albeit small, should be needed; however this has to be proven in clinical practice. Genetic indications are situations where the here described novel protocol may be used only if it may be proven to be statistically superior in term of pregnancy rate to the standard protocol; oocytes should be donated anyhow and there is no place for shifting to own oocytes. However, other situations may take advantage of the described protocol. One of these indications is the vast area of 'poor responders' [5] and another one is made up by the 'aged patients'. In both cases it is possible that the ovaries may unexpectedly respond satisfactorily to the HMG and produce several oocytes. In the present series, six such cases occurred and the patients were able to complete their cycle with their own eggs. Two remained clinically pregnant. Therefore, the use of a flexible pharmacologic approach such as the *conversion* protocol depicted in this study may help to decide at the last minute whether to go for IVF with the patient's eggs, or to shift towards OD. This is not possible with a "planned" OD.

Many different kinds of estrogens have been and are being used as replacement steroids for the development of receptive endometria. Oral conjugated estrogens have been mostly used at the beginning of the OD era [2], oral micronized estradiol was and is still used [6]. Estrogen dermal patches are also being used on the grounds that oestrogens do not undergo a liver first pass metabolic step. However the most used replacement estrogen nowadays is oral EV [6]. Also, in OD some authors prefer a recipient's natural cycle endometrium. However, depending on natural ovulation implies the need to work also on weekends, which many centers try to avoid and in addition, with natural cycles, achieving a good synchronization between the recipient's and the donor's cycle is not that easy. The present paper deals with a cycle pretty similar to the natural one at least for the first ten days of treatment.

Differently from the standard OD treatment (Table 2), where estrogens are exogenously administered from the very first day, with the present new protocol, (Table 1) natural estrogens (estriol, estradiol, estrone) are being naturally produced by the ovaries stimulated by HMG during the first 10 days. The growth of the endometrium is under the control of all these ovarian estrogens and their metabolites. The novel protocol therefore should be more '*natural*' since it takes advantage of the ovarian reserve, albeit small, which promotes the endometrial growth, compared to the standard protocol which uses only one type of exogenously administered estrogens. Interestingly, there was the formation of a trilinear thick endometrium even in some cases with a complete absence of detectable ovarian follicle development. In these cases, it may be postulated that the blood estrogen level was very low, but inspite of this, the small amount of estrogens may have reached directly, undiluted, the endometrium from the ovaries by means of an ovaro-uterine portal system [7]. Therefore the local, endometrial concentration of estrogens would have been sufficiently high, in the presence of a low estrogen level in the general circulation.

Recently, this new protocol was also administered to some patients who had a bleeding tendency when administered the replacement steroids of the standard protocol. All patients did not bleed anymore.

The power of this paper is rather low due to the small sample size; the clinical pregnancy rate with the described new protocol was 56%, whereas the pregnancy rate with the standard protocol was 46%. In view of the pretty good results obtained, a prospective randomized study has started with the aim to compare this depicted new protocol (Table 1) with the standard replacement protocol (Table 2) in homogeneous groups of patients.

References

1. Devroey P, Pados G (1998) Preparation of endometrium for egg donation. *Hum Reprod Update* 4: 856-861. [Crossref]

2. Formigli L, Formigli G (1986) In-vivo fertilised ovum donated successfully to a woman without ovaries. *The Lancet* 1: 747. [Crossref]

3. Oehninger S (2011) Poor responders in in vitro fertilization (IVF) therapy: the challenge continues. *Facts Views Vis Obgyn* 3: 101-108. [Crossref]

4. Rakotobe AA, Badulli G, Rija R, Aimée M, Formigli L (2018) Same cycle shift from IVF with own oocytes to oocyte donation in no or poor response cycles. *Afr J Reprod Health* 22: 91-95. [Crossref]

5. Ferraretti AP, La Marca A, Fauser BCJM, Tarlatzis B, Nargrund G, et al. (2011) ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization: the Bologna criteria. *Hum Reprod* 26: 1616-1624. [Crossref]

6. Cerrillo M, Herrero L, Guillén A, Mayoral M, García-Velasco JA (2017) Impact of endometrial preparation protocols for frozen embryo transfer on live birth rates. *Rambam Maimonides Med J* 8: 1-8. [Crossref]

7. Henderson JR, Daniel PM (1978) Portal circulations and their relation to countercurrent systems. *Quarterly J Exp Physiol* 63: 355-369. [Crossref]