

CASE REPORT

Same Cycle Shift from IVF with Own Oocytes to Oocyte Donation in No or Poor Response Cycles

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Abstract

Our In-Vitro Fertilisation Centre is situated in a large developing country, Madagascar, with very bad roads and low income patients. Therefore we try to find ways to reduce as much as possible the number of attempts to obtain a pregnancy. Poor or no response to ovarian stimulation in *In Vitro* Fertilization (IVF) cycles is a great challenge. Here we describe a method whereby we shift from IVF to Oocyte Donation (OD) during the same cycle for patients whose ovaries do not respond properly to ovulation stimulation. Patients were superovulated with a long protocol agonist treatment and ultrasonically monitored for IVF/ICSI. When, at half way of the stimulation, it was clear that there was a no or poor response, gonadotropin administration was stopped and immediately replaced by estrogens; when the endometrium was considered to be sufficiently receptive, some donated oocytes from our concomitant oocyte donation (OD) program were fertilized with the patient's husband sperm and progesterone was added to the patients' treatment. After 48 hours the resulting embryos were transferred. Five poor responders patients underwent the described procedure. Three conceived, one of which aborted at 9 weeks, while the other two are ongoing. These patients signed the consent form accepting the possibility to shift from IVF to OD during the same cycle and three clinical pregnancies were obtained. OD through this technique seems more acceptable by poor responders than planned OD. This is a preliminary report and to our knowledge it is the first report of such a method. (*Afr J Reprod Health* 2018; 22[2]: 91-95).

Keywords: IVF, Poor responders, Oocyte donation, Same cycle, Shift, Conversion

Résumé

Notre Centre est situé dans un grand pays en développement, Madagascar, avec de très mauvaises routes et des patientes à faibles revenus. Par conséquent, nous essayons de trouver des moyens de réduire autant que possible le nombre de tentatives d'obtenir une grossesse. Une réponse faible ou nulle à la stimulation ovarienne dans les cycles de fécondation in vitro (FIV) est un grand défi. Nous décrivons ici une méthode par laquelle nous passons de la FIV au don d'ovocytes (DO) au cours du même cycle pour les patientes dont les ovaires ne répondent pas correctement à la stimulation de l'ovulation. Les patientes ont été suroovulées avec un traitement agoniste à long protocole et surveillées par ultrasons pour la FIV / ICSI. Lorsque, à mi-chemin de la stimulation, il était clair qu'il n'y avait pas de réponse ou qu'il n'y avait qu'une faible réponse, l'administration de gonadotrophine a été arrêtée et immédiatement remplacée par des œstrogènes; lorsque l'endomètre était suffisamment réceptif, certains ovocytes de notre programme concomitant de don d'ovocytes (DO) ont été fécondés avec le sperme du mari du patiente et de la progestérone a été ajoutée au traitement des patientes. Après 48 heures, les embryons résultants ont été transférés. Cinq patientes pauvres répondeuses ont subi la procédure décrite. Trois ont été conçus, dont un avorté à 9 semaines, tandis que les deux autres sont en cours. Ces patientes ont signé le formulaire de consentement acceptant la possibilité de passer de la FIV au DO au cours du même cycle et trois grossesses cliniques ont été obtenues. Le DO par cette technique semble plus acceptable par les mauvaises répondeuses que prévu le DD. Ceci est un rapport préliminaire et à notre connaissance c'est le premier rapport d'une telle méthode. (*Afr J Reprod Health* 2018; 22[2]:91-95).

Mots-clés: FIV, répondeuses pauvres, don d'ovocytes, même cycle, shift, conversion

Introduction

No or poor response to ovarian stimulation in an *In vitro* Fertilization program is a frustrating

experience both for patient and physician and quite often the use of a different stimulation protocol in further attempts does not stimulate the ovary satisfactorily. Besides, for many patients, the lack

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or poorness of ovarian reaction to the stimulating agents is already known, due to previous attempts of ovarian stimulation combined with natural intercourse, artificial inseminations or IVF attempts¹. Also natural unstimulated IVF had been tried unsuccessfully in these patients. However, many such patients are reluctant to accept a planned Oocyte Donation (OD) but prefer to keep trying with the stimulation of their own ovaries, because they hope that the “next stimulation will be the good one”. Therefore, we offered to our patients the possibility, and obtained their informed consent, to convert that same cycle into an OD cycle if there was no response to stimulation. The donated oocytes came from the oocyte donors of our centre. In fact, until recently, we used to offer the alternative of OD only after the cancellation of the no/poor response cycle and OD was planned a few months following the cancelled cycle. However, the simple cancellation of the cycle is very distressful to the couple, time consuming and expensive. In addition, many of our patients come from as far as 700/800 kms away. Moreover, we noticed that patients are more favourably disposed to accept a shift from IVF with their oocytes to an OD during the same cycle, rather than a planned, postponed OD procedure.

Methods

This is a short and preliminary communication since we performed so far only five cases. All patients were superovulated with a long agonist protocol and Human Menopausal Gonadotropin (HMG) treatment – these are the only drugs available in Madagascar to superovulate patients⁵. After 9/11 days of treatment, when it became obvious that there was no response, HMG was stopped and, if the patient agreed to shift to OD, HMG was replaced by oral estradiol valerate (Progynova-Bayer) 6mg daily.

Our center organizes for each wave a recruitment of some oocyte donors. Six metaphase II (MII) oocytes from a donor are intended for a well-determined recipient. The criteria for recruiting a donor are based on age (18-30 years), on parity (a donor must have had a birth or an abortion), on good health (normal serology of

Syphilis, Hepatitis B and C, HIV, Chlamydia, Toxoplasmosis and Rubella), and on a similar physiognomy to that of her recipient. Donors are stimulated early in the IVF wave; they will have Oocyte Pick-Up (OPU) like all women applying for IVF using their own oocytes.

When we have surplus oocytes, we propose them to a woman candidate for IVF who wanted to use her own oocytes but who turned out to be a poor responder. It is our care not to deprive of donated oocytes the legitimate recipients.

Estrogens were administered to the poor responder patients until the endometrium thickness grew at least to 8 mm. When the time came to proceed to the donor's OPU, 3 to 4 Metaphase II (MII) oocytes were fertilized with the patient husband's sperm and incubated for 48 hours. On the day of donor's OPU, the patient started also progesterone, 500 mg im, which was repeated every 7 days, and 400 mg daily of vaginal micronized progesterone (Utrogestan-Besins). Embryo transfer was performed on day two after OPU.

Case 1

Patient 35 years old; treated with Human Menopausal Gonadotropin (HMG) 225 IU daily. On day 10 of treatment there was no follicle development and the endometrium was 5 mm thick. It was decided to shift from own oocytes to donated oocytes. On day 16, the endometrium had reached a thickness of 8 mm and 4 MII oocytes were donated to the patient. On day 18 Embryo Transfer (ET) of 3 embryos (two at the 8 cell stage, grade I and one at the 6 cell stage, grade I) was performed. The patient achieved a clinical pregnancy. She continued with the estrogen/progesterone treatment for 3 months after ET.

Case 2

Patient 41 years old; treated with HMG 300 IU daily. On day 10 it was decided to shift to egg donation since no follicles were detected; the endometrium was 4 mm thick. On day 16 the endometrium had reached a thickness of 8 mm and 4 MII oocytes from a matched donor were fertilized by ICSI; two embryos (both 4 cell stage,

grade I) were replaced after 48 hours. The attempt was unsuccessful.

Case 3

Patient 34 years old; treated with HMG 225 IU daily. On day 11 there was a single small follicle, diameter 6 mm and the endometrium was 6 mm thick. The cycle was shifted to OD. On day 17 the endometrium had reached a thickness of 8 mm and 3 MII oocytes from a matched donor were fertilized; two embryos (both 4 cell stage, grade I) were transferred on day 19. No pregnancy occurred.

Case 4

Patient 42 years old; treated with HMG 300 IU daily. On day 9 no follicle was evident by ultrasound and the endometrial thickness was 4 mm. The cycle was shifted to OD. On day 17 the endometrium was 9 mm thick and 4 MII oocytes were available from a matched egg donor. Three embryos (all 4 cell stage, grade I) were transferred. The patient conceived and continued the replacement treatment, but aborted a twin pregnancy at nine weeks.

Case 5

Patient 40 years old; treated with HMG 225 IU daily. On day 9 no follicle was present, the endometrium was unclear by ultrasound and there was a brownish discharge from the uterus. It was decided, with the agreement of the patient, to shift from HMG to estrogen treatment and check again the patient after 4 days. Surprisingly, the patient on day 13, had a normal trilinear endometrium, 8 mm thick and the discharge had stopped. Therefore next day an ICSI was performed on 4 MII donated oocytes. On day 3 after OPU three embryos were transferred (one morula and two embryos at the 6 cell stage, grade I). The patient is pregnant and carrying on a twin pregnancy uneventfully.

Discussion

Oocyte donation has been performed in human for over 30 years²⁻³ for a wide variety of indications, namely absent ovaries, untreatable primary amenorrhoea, premature ovarian failure, genetic

diseases, but it may be used also in cases of no or poor ovarian response, oocyte abnormalities, aged patients and multiple IVF failures. In the majority of these cases, OD is planned beforehand and an oocyte donor is matched and synchronized with the recipient²⁻⁵.

In the present paper, the treatment was started with the aim to try IVF with the patients' oocytes and the decision to shift during that same cycle to OD was taken only when it was clear that the use of the patients' oocytes was not possible, due to very poor/no response. The patients were aware of the possibility to shift to OD and gave their informed consent. Due to our concomitant anonymous OD program, we were able to offer to our poor responder patients the shift from IVF to OD during the same cycle. Six MII donated oocytes were guaranteed to the designated planned OD recipient patients while three/four surplus MII oocytes were intended for the poor/no responders.

We usually monitor IVF and OD cycles only by ultrasound and these cycles were no exception. We operate in a developing country where costs are kept at a minimum and many laboratory facilities are lacking.

Stopping ovarian stimulation and shifting to estrogens to continue the growth of the endometrium is feasible, since three clinical pregnancies were obtained out of five cases. In fact, the poor or no follicular response may induce a thin endometrium, due to the low levels of endogenous estrogens. However, we observed that after a few days of estrogen therapy, the endometrium was rescued, increased in thickness and was able to allow implantation of the transferred embryos. In all five cases, the endometrium had reached a thickness of 8 mm or more. In Case 5, there was a slight uterine bleeding, which stopped after four days of estrogens, three embryos were transferred and the patient conceived. One may speculate that it is difficult to achieve a perfect synchronization between oocyte maturity and endometrium receptivity with the described technique. On the other hand, even in "planned" OD programs it is sometimes difficult to perfectly synchronize donor and recipient, since oocytes of the donor may

become mature for OPU before the recipient's endometrium is considered fit to house the embryos and *vice versa*. Several implantation windows have been reported in the literature: some are pretty strict, others are more flexible⁴⁻⁵. In addition, it is common and shared knowledge that a good morphology and thickness of the endometrium are positively correlated to the success rate in IVF⁶, even though IVF pregnancies have been obtained with pretty thin endometria⁷. In certain cases of IVF with normal ovarian response to stimulation, a low endometrium may develop and the supplementation of estrogens usually does not increase the thickness of these endometria, since there are already high levels of endogenous estrogens; one may hypothesise in these cases an abnormal interaction between estrogens and endometrial receptors or some genetic abnormalities⁸. On the contrary, in our described cases, there is a no or very poor ovarian response and hence the level of endogenous estrogens is low. This is probably the reason why there was a rapid growth of the endometria after just a few days of estrogen therapy.

Even though many patients are aware of their poor response to ovarian stimulation protocols because they already experienced these treatments, they are often reluctant to accept a planned OD procedure, since they still have their ovarian and menstrual function, as opposed for example to premature ovarian failure patients, and they hope that the next ovarian stimulation will be the good one. This is probably the reason why we observed that it was psychologically easier for these patients to shift to OD during their own IVF cycle, rather than enrolling in a planned OD program. The results obtained in this very small series of patients are quite satisfying, even though definite conclusions will be drawn only with a higher number of studied cases. To our knowledge this is the first report of a shift from IVF to OD during the same cycle.

Conflict of Interest

The authors report no conflict of interest.

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Contribution of Authors

Conception of the study: Rakotobe A.A., Badulli G. Collection and analysis of data : Ramarolahy R., Marcienne A., Formigli L. Preparation of the manuscript: Rakotobe A.A.

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Summary for the General Public

We prepared five patients for *in vitro* fertilization (IVF), so we stimulated their ovaries to produce oocytes. Unfortunately the stimulation had no response. Then we proposed to these patients to receive oocytes from donors whose ovaries were already stimulated. The oocytes were fertilized with the patient husband's sperm. Three patients conceived, one of which aborted at 9 weeks while the other two are ongoing; two patients did not conceive at all.

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