The Oral Contraceptive Pill Effectively Permits Cycle Batching for an Intermittent In Vitro Fertilization Programme in Trinidad and Tobago

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ABSTRACT

Assisted reproductive technology (ART) in small island states like Trinidad and Tobago is usually provided in batches so as to minimize the cost of providing the service. As a result, patients' cycles have to be synchronized in order to coincide with the arrival of a visiting embryologist. This is a retrospective study which evaluates the experience of pre-treatment with an oral contraceptive pill (OCP) as a means of batching cycles for an intermittent ART programme. Seventy-four in vitro *fertilization (IVF) and intracytoplasmic sperm injection (ICSI) cycles in which OCP usage was employed (Group A), were compared with 121 cycles which did not require pharmaceutical manipulation (Group B). In both groups more than 50% of women were older than 36-years. Two cycles were cancelled in Group A and seven in Group B, because of poor ovarian response. Although the pregnancy rate per treatment cycle was higher in Group A than in Group B (26.3%* vs *17.3%), this difference was not significant. More spontaneous miscarriages occurred in the non-OCP women and ovarian cyst formation was more common in these women. The authors experience indicates that the OCP is a simple, cheap and efficient means of batching patients for an intermittent ART programme and can be utilized in other small ART centres.*

Las Píldoras Anticonceptivas Orales Permiten la Agrupación Eficaz de los Ciclos para un Programa Intermitente de FIV en Trinidad y Tobago

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RESUMEN

La tecnología de reproducción asistida (TRA) en los pequeños estados insulares como Trinidad y Tobago, usualmente se ofrece por tandas a fin de minimizar los costos del servicio brindado. En consecuencia, los ciclos de las pacientes tienen que ser sincronizados de modo que coincidan con la visita del embriólogo. Éste es un estudio retrospectivo que evalúa la experiencia del pretratamiento con píldoras anticonceptivas orales (PAO) como medio de agrupar los ciclos con el propósito de organizar un programa intermitente de TRA. Setenta y cuatro ciclos de fertilización in vitro (FIV) e inyección intracitoplasmática de esperma (ICSI) en los que se recurrió al uso de PAO (Grupo A), fueron comparados con 121 ciclos que no requirieron manipulación farmacéutica (Grupo B). En ambos grupos, > 50% de las mujeres tenían más de 36 años de edad. Dos ciclos fueron cancelados en el grupo A y siete en el grupo B, debido a una respuesta ovárica pobre. Aunque la tasa de embarazo por ciclo de tratamiento fue más alta en el grupo A que en el grupo B (26.3% vs. 17.3%), esta diferencia no fue significativa. El número de abortos espontáneos fue mayor y la formación de quistes ováricos más común, en las mujeres que tomaron PAO. La experiencia de los autores indica que la PAO es un medio simple, económico y eficaz de agrupar a los pacientes en un programa intermitente de TRA, y puede utilizarse en otros centros pequeños de TRA.

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INTRODUCTION

The provision of assisted reproductive technology (ART) in a small developing state such as Trinidad and Tobago poses certain peculiar challenges. These include a high mean patient age, lack of a resident embryologist and no systems for state or insurance funding. Infertile couples requiring ART, therefore present a major challenge. In 1996, Trinidad

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and Tobago became the first island state in the Caribbean to develop a successful Assisted Reproduction Unit and has managed to operate within the context of these limitations (1).

Since this option was not previously available in the island, the couples presenting for treatment and, in particular, the women tended to be of a more advanced age. The cost of foreign treatment (in the United Kingdom or United States of America), which would also include air travel, hotel accommodation and treatment fees, coupled with loss of earnings, was financially prohibitive for most couples.

In order to distribute costs, arrangements are made to have a visiting embryologist for periods of two to four weeks, during which time oocyte recovery, laboratory procedures and embryo transfer have to be accomplished. As a result, patients have to be 'batched'. With this *modus operandi*, we noted that the cycling patterns of some patients did not permit utilization of the orthodox long or short protocols. As a result, these couples could not be accommodated, and in this setting, it was decided to use the combined oral contraceptive pill (OCP) as a means of obtaining cycle synchronization. The mechanism of action of the OCP in abolishing the LH surge is well understood (2) and it has been used previously in order to facilitate scheduling of cycles and thus to permit treatment start-up as required (3–6).

MATERIALS AND METHODS

This was a retrospective study of 195 treatment cycles, which were allocated into two groups depending on the availability of a visiting embryologist. Patients were assessed approximately three months prior to intended treatment by the senior clinician (SR) who analyzed the menstrual cycle patterns and the results of all investigations. Particular attention was paid to day three serum follicle stimulating hormone (FSH) and oestradiol (E_2). An elevated FSH (> 10mIU/L) was followed by a clomiphene citrate challenge test, in which serum FSH and E_2 were measured on day three and then on day ten after using clomiphene citrate 100 mg daily from days two to six. Elevated FSH (>10 mIU/L) and E_2 (>200 pmol/L) were considered to be suggestive of diminished ovarian function and the couple were informed of the chance of sub-optimal follicle development. Women up to the age of 42-years were accepted for treatment, and the clinician was also responsible for deciding upon the appropriate ART procedure, limited to either *in vitro* fertilization (IVF) or intra-cytoplasmic sperm injection (ICSI). Group A patients were those whose cycling patterns had to be adjusted with the OCP while Group B women allowed seamless utilization of the day 21 'long protocol' or the day two 'short protocol' (1). The latter method was used for older women (> 37 years) and in those with elevated FSH as described above.

Women in Group A started the OCP on day one of a pre-treatment cycle and used it continuously, beginning a second packet if necessary until Luteinizing Hormone Releasing Hormone analogue ($LHRH_a$) down-regulation could be started. In order to mimic a 'day 21' start, treatment with subcutaneous buserelin acetate (Suprefact, Hoechst Marion Roussel, Middlesex, UK) 0.5 mg daily was initiated and the OCP discontinued three to four days after LHRH. A 'pill withdrawal' bleed would occur in the usual fashion and cycle management continued in the orthodox manner (1). After two weeks, transvaginal ultrasound scanning (TVS), serum LH and E_2 were performed to confirm sufficient ovarian suppression indicated by the absence of ovarian cysts, endometrial thickness < 4mm and serum LH and E_2 concentrations < 2 IU/L and < 200 pmol/L respectively. Ovulation induction therapy utilized human menopausal gonadotrophin (hMG, Pergonal – Serono Laboratories, Panama) used in daily dosages of 150–900 IU by IM injections.

All embryo transfers (two or three embryos) were carried out under trans-abdominal ultrasound guidance and luteal phase support was started simultaneously. This consisted of progesterone 50mg IM daily for five days followed by progesterone vaginal suppositories (Cyclogest, Shire Pharmaceuticals, Hants, UK) 400 mg inserted each night. Pregnancy was diagnosed by elevated serum βhCG (>30 IU) measured 14 days after oocyte recovery and sonographic evidence of a gestation sac two-weeks later. Ovarian cyst formation during down-regulation was managed by transvaginal ultrasound directed cyst drainage using local anaesthesia.

Apart from clinical consultations, all couples were required to undergo counselling sessions with a trained counsellor, prior to a final decision to embark on treatment, and before signing the consent form.

The chi-square test was used for statistical analysis. Analysis of women allocated to OCP and non-OCP groups in this manner was approved by the institution's Ethics Committee.

RESULTS

Group A comprised 74 cycles (69 women) with OCP usage and Group B, 121 cycles (99 women) without OCP pre-treatment. Distributions of IVF and ICSI cycles were similar in both groups, as shown in Table 1. Patients' profiles reflected the older ages of a large number of our clientele: in Group A, 38 women (51.4%) and in Group B, 69 (57.1%) were over 36-years of age (age range 23–42 years). Tubal disease and sperm dysfunction were the most common diagnoses in both groups. Cancelled cycles accounted for two women in Group A and seven in Group B. All of these women were over 36-years of age and treatment was discontinued due to poor ovarian response. No instances of ovarian cyst formation occurred in the OCP group (0/74) compared with non-OCP cycles (8/121).

Pregnancies per cycle were recorded in 20 women in Group A and 21 in Group B (26.3% *vs* 17.3%; $p > 0.01$, not significant), as shown in Table 2. Four spontaneous

Table 1: Characteristics of 74 OCP treated (Group A) and 121 non-OCP treated (Group B) batched ART cycles in Trinidad

Characteristic	Group A No (%)	Group B No (%)
Age group (years)		
< 30	11 (14.8)	14 (11.6)
30–36	25 (33.8)	38 (31.4)
> 36	38 (51.4)	69 (57.0)
Diagnosis		
Tubal	26	40
Male factor	38	63
Endometriosis	3	7
Unexplained/Other	13	21
IVF cycles	26 (35.1)	43 (35.5)
ICSI cycles	48 (64.9)	78 (64.5)
Cancelled cycles	2	7

Table 2: Outcome measures of OCP treated and non-OCP treated batched ART cycles in Trinidad

Outcome	Group A No (%)	Group B No (%)
Pregnancies	20 (26.3)	21 (17.3)
Early miscarriages	4	8
Live births	16	13

miscarriages occurred in Group A and eight in Group B so that there were 16 live-birth events in Group A and 13 in Group B. There were no ectopic pregnancies. No congenital fetal abnormalities were recorded and no perinatal or neonatal complications occurred.

DISCUSSION

In Trinidad and Tobago, the authors' experience indicates that couples eventually seek ART after many years of unsuccessful and sometimes inappropriate therapy. The centre has been able to limit costs by batching couples into groups of 15–20 over a period of two to three weeks, in order to optimize the services of a foreign-based embryologist. The challenge of programming all these couples within this time frame therefore requires certain cycle manipulations and we chose the OCP as the best means for achieving this. Previous studies with the OCP have shown it to be an effective and useful means of achieving pre-treatment LH suppression (5–8).

In one study describing 71 'minimal stimulation' IVF cycles using clomiphene citrate (4), the clinical pregnancy rate was 32.8% per treatment cycle and this result was not different from a matched cohort using stimulated IVF. A similar experience was noted with OCP pre-treatment for orthodox IVF (8), when the use of the OCP was also not shown to have a detrimental effect in 'low' responders, a group which included older women (> 39 years). Ovarian cyst formation was less frequently seen in the OCP group than in OCP users, and this is likely to be a beneficial effect of ovarian suppression and may therefore be valuable in patients at risk of cyst formation and those with PCOS. In this study utilizing an OCP pre-treatment protocol, the overall pregnancy rate was actually better than for the regime without this method of cycle alignment. Although these numbers are relatively small, it is reassuring to know that OCP usage was not a negative factor in the reproductive performance of these women.

There were only three cases of OHSS encountered, one in the OCP group (severe), and two in the non-OCP patients, both of which were mild. All three patients settled on conservative management.

The authors believe that this experience with the OCP for cycle regulation should inform the use of ART in other developing countries and small IVF units as an economical and viable option.

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