Hussein *et al.*
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Fresh versus frozen embryo transfer in women with polycystic ovaries syndrome undergoing in vitro fertilisation

Mohamed Hussein[1], Abdullah Sayed[1], Ashraf Eldaly[1], Ahmed H. AlSawaf[1], Marwa M. Eid[1], Mazen Abdel-Rasheed[2*] and Ahmed S. Rashwan[1]

Abstract

Background Polycystic ovarian syndrome (PCOS) cases undergoing in vitro fertilisation (IVF) are widely at risk of ovarian hyperstimulation; therefore, elective freezing of all embryos to be transferred in a later cycle is preferred. We aimed to compare the pregnancy outcome between the fresh and the frozen embryo transfer (ET) in PCOS cases undergoing IVF with antagonist ovarian induction using human chorionic gonadotropin (HCG) as a trigger.

Methods In this prospective randomised study, 110 infertile PCOS women underwent fresh ET (group A) or frozen ET (group B) with GnRH-antagonist protocol. The primary outcome was the chemical and clinical pregnancy rates. The secondary outcomes were the ongoing pregnancy rate, ovarian hyperstimulation syndrome (OHSS) rate, pregnancy loss rate, ectopic pregnancy rate, and congenital anomalies rate.

Results There was no significant difference between both groups regarding chemical pregnancy rate (44.23% vs 47.27%, $P=0.752$), clinical pregnancy rate (42.31% vs 43.64%, $P=0.89$), ongoing pregnancy rate (38.46% vs 41.82%, $P=0.723$), pregnancy loss rate (17.39% vs 15.4%, $P=1$), ectopic pregnancy rate (1.92% vs 0%, $P=0.486$) and anomaly malformation rate (4.35% vs 3.85%, $P=1$). On the other hand, the incidence of OHSS was significantly less in group B than in group A (3.64% vs 19.23%, $P=0.011$), and the OHSS grade was less severe in group B than in group A ($P=0.033$). However, there was no statistically significant difference between both regarding the need for hospitalisation ($P=0.111$), ICU admission ($P=0.486$), and ascites tapping ($P=0.486$).

Conclusions Under GnRH-antagonist protocol, frozen ET has the upper hand in PCOS undergoing IVF treatment for infertility, as it protects against OHSS and decreases its severity.

Trial registration It was first registered at ClinicalTrials.gov on 22/12/2021 with registration number NCT05167838.

Keywords Polycystic ovarian syndrome, Ovarian hyperstimulation syndrome, Fresh embryo transfer, Frozen embryo transfer

Introduction

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder in women of reproductive age (4- 15%), according to the criteria used in diagnosis [1]. PCOS is associated with either irregular ovulation or anovulation, which is considered a primary cause of infertility. In vitro fertilisation (IVF) is a technique commonly used to assist such cases with either failed induction or those with other factors of infertility [2].

*Correspondence:
Mazen Abdel-Rasheed
doctor_mazen@hotmail.com
[1] Obstetrics and Gynaecology Department, Faculty of Medicine, Cairo University, Cairo, Egypt
[2] Reproductive Health Research Department, National Research Centre, 33 El-Buhouth St, Dokki 12622, Cairo, Egypt

The safety of these techniques on either women or their infants cannot be guaranteed [3, 4].

Ovarian hyperstimulation syndrome (OHSS) consists of enlargement of the ovaries, intravascular haemoconcentration, increased vascular permeability, and ascites; therefore, considered a serious problem resulting from the induction of ovulation [5]. In addition, these pregnancies are at higher risk for maternal and neonatal complications, including preeclampsia, low birth weight, preterm labour, and congenital anomalies, than spontaneous pregnancies [6, 7]. The incidence of OHSS was found to be higher in PCOS cases performing IVF [5, 8].

The frozen embryo transfer (ET) results are supposed to be better than the fresh transfer, possibly due to altered endometrial receptivity caused by the high level of steroid hormones in the stimulated cycles [9]. In PCOS, the endometrial receptivity is altered due to reduced expression of glycodelin and αvβ3 integrin [10]. Observational studies have demonstrated higher singleton pregnancy rates after frozen ET than those with fresh ET [11].

Increased live birth rate (LBR) and better perinatal outcomes were found more in favour of the frozen ET cycles [12, 13]. Some studies reinforced the freeze-all technique, where all embryos are frozen to improve the success rates [14]. Other studies established insignificant differences in the pregnancy and neonatal outcome between the fresh or frozen embryos in women without PCOS [15, 16]. This study aims to determine if there is a difference between the fresh and the frozen ET regarding the pregnancy rate and complications in PCOS cases performing IVF.

Methods

A prospective randomised study was carried out on 110 infertile PCOS women undergoing IVF at Obstetrics and Gynaecology department, Cairo University hospitals, from January 2022 to June 2022. The study was approved by the hospital ethical committee (reference number O19010) and was registered at Clinical trial.gov (registration number NCT05167838). Informed consent was obtained from all patients after explaining the aim of the study and discussing the potential hazards. Fifty-five cases were assigned to (group A) and scheduled for a fresh transfer, and 55 cases were assigned to group B and scheduled for a frozen ET.

Included cases were infertile women aged between 20 and 40 years with a body mass index (BMI) less than 35 and PCOS criteria. Modified Rotterdam criteria were used to diagnose PCOS cases [17]. The presence of irregular menstrual cycles with either PCO or hyperandrogenism. Diagnosis of hyperandrogenism was made by the presence of either hyperandrogenaemia or hirsutism. Hirsutism was diagnosed by a score of > 6 using a modified Ferriman–Gallwey scale (on a scale of 0 to 36 assessing nine areas of the body with high scores denoting increased hair growth) [18]. Hyperandrogenaemia was diagnosed during the clinical evaluation of the patients. Polycystic ovaries were diagnosed by either an increased ovarian volume (> 10 cm^3) or by the presence of at least 12 or more follicles measuring 2 to 9 mm in the whole ovary. Other etiological factors of hyperandrogenism or ovarian dysfunction as congenital adrenal hyperplasia, tumours, hyperprolactinemia, or thyroid dysfunction, were excluded. Patients with unilateral oophorectomy, congenital or acquired uterine malformations, severe male factor for infertility, History of failed IVF trials, and non-compliant patients were also excluded from the study.

A standardized ovarian stimulation protocol was given to all patients. Highly purified follicle-stimulating hormone (Fostimon IBSA) at a daily dose of 150 IU was started on day 3 of the menstrual cycle then the dose was modified according to the patient's ovarian response in terms of the level of serum sex steroids together with the size and number of the follicles as monitored by the ultrasound. GnRH antagonist (Cetrorelix) was administered at a daily dose of 0.25 mg subcutaneous injection when at least one follicle reaches ≥ 14 mm in mean diameter (flexible antagonist protocol) until the trigger day (also given on the trigger day). HCG 5,000 IU intramuscular injection along with Decapeptyl 0.1 mg by subcutaneous injection was given when at least two follicles were ≥ 18 mm for the fresh ET group. However, two ampoules of Decapeptyl 0.1 mg by subcutaneous injection were given as a trigger for the frozen ET group. Oocyte retrieval was done after 34 h from HCG injection.

The 110 patients were randomly assigned to one of two groups on the day of the trigger after ovarian stimulation. Randomization was done via computer-generated random numbers. For the fresh ET group, at least two top-quality embryos were transferred on day 3, and vaginal progesterone pessary 400 mg was given twice daily for luteal phase support. The progesterone pessaries were started on the day of oocyte retrieval to be continued after conception for 10 weeks.

For the frozen ET group, cryopreservation for all embryos was done, and at least one straw (four cryopreserved embryos) was thawed on a later target cycle to ensure that two viable embryos would be transferred. No luteal-phase support was given in the cycle of oocyte retrieval. In the cycle of ET, endometrial preparation was done using oral oestradiol valerate (Progynova) and was started on day 2 or 3 of the menstrual cycle. When the endometrial thickness reached 8 mm or more, vaginal progesterone suppositories were added at a dose of 400 mg twice daily. Two day-3 frozen embryos were thawed and transferred on day 4 of the progesterone

regimen, and the luteal-phase support using oestradiol valerate and progesterone suppositories was continued till 10 weeks after conception.

For all patients, follow-up for symptoms and signs of OHSS, serum β-hCG was measured 14 days after the ET to detect pregnancy, and transvaginal ultrasound was done 35 days after ET. When the patient got pregnant, follow-up was done until they reached 28 weeks to check for the anomaly scan, pregnancy loss, or any medical disorder.

The primary outcome was the chemical and clinical pregnancy rates. The secondary outcomes were the ongoing pregnancy rate, OHSS rate, pregnancy loss rate, ectopic pregnancy rate, and congenital anomalies rate.

Sample Size

Sample size was calculated to be 55 subjects for each group according to the following equation$n = \frac{[P1(1-P1)+P2(1-P2)](Z\alpha+Z\beta)^2}{(P1-P2)^2}$, where n = sample size, P1: The Clinical pregnancy rate in Fresh embryo transfer group = 63% [19], P2: The Clinical pregnancy rate in Frozen-Thawed embryo transfer group = 35.6% [19], Zα value = ± 1.96 (The critical value that divides the central 95% of the Z distribution from the 5% in the tail), Zβ value = 0.84 (The critical value that separates the lower 20% of the Z distribution from the upper 80%).

Statistical analysis

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 25 (IBM Corp., Armonk, NY, USA). Data were summarised using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann–Whitney test [20]. For comparing categorical data, the Chi-square (χ2) test was performed. Exact test was used instead when the expected frequency was less than 5 [21]. P-values less than 0.05 were considered statistically significant.

Results

Among 150 women assessed for their eligibility for this study, a total of 118 patients fulfilled the study eligibility criteria. Eight patients dropped out before randomisation (three refused to participate, and five had a poor response). Patients were randomised into two equal groups on the day of the trigger. However, three further patients dropped out in the fresh ET group; two patients had severe OHSS (cancelled cycle), and the other one was unsuitable for transfer due to poor endometrium (Fig. 1).

The demographic characteristics are demonstrated in Table 1, showing no significant differences in both study groups regarding age, BMI, number of previous suction evacuations, and duration of infertility. The number of previous caesarean sections was significantly more in group A (fresh ET) than in group B (frozen ET). However, there was no significant difference between both groups regarding the infertility types ($P = 0.083$).

The characteristics of IVF cycles are shown in Table 2. There was no significant difference between the two groups regarding the duration of ovarian stimulation ($P = 0.969$). The antral follicular count was significantly higher in group A than in group B (24.46 ± 5.44 vs 20.93 ± 6.12, respectively, $P < 001$), while the number of retrieved oocytes was significantly higher in group B than in group A (16.11 ± 3.87 vs 13.06 ± 3.86, respectively, $P < 001$). However, these findings did not affect our outcome results as there was no significant difference between the two groups regarding the number of fertilised oocytes ($P = 0.124$) nor the number of good-quality embryos available for transfer ($P = 690$).

The clinical outcomes in both groups are demonstrated in Table 3. There was no significant difference between the fresh ET and frozen ET groups regarding chemical pregnancy rate (44.23% vs 47.27%, $P = 0.752$), clinical pregnancy rate (42.31% vs 43.64%, $P = 0.89$), ongoing pregnancy rate (38.46% vs 41.82%, $P = 0.723$), pregnancy loss rate (17.39% vs 15.4%, $P = 1$), ectopic pregnancy rate (1.92% vs 0%, $P = 0.486$) and anomaly malformation rate (4.35% vs 3.85%, $P = 1$). On the other hand, the incidence of OHSS was significantly less in group B than in group A (3.64% vs 19.23%, $P = 0.011$), and the OHSS grade was less severe in group B than in group A ($P = 0.033$). However, there was no statistically significant difference between the fresh ET and frozen ET groups regarding the need for hospitalisation ($P = 0.111$), ICU admission ($P = 0.486$), and ascites tapping ($P = 0.486$).

Discussion

There is a continuous struggle to improve pregnancy outcomes in the IVF cycle, and with the advances in embryo cryopreservation (especially vitrification), the freeze-all strategy is more acceptable nowadays. This strategy is still controversial without any data supporting the wide and indiscriminate use of the freeze-all strategy [22]. This study analysed the two methods of ET in cases of PCOS, aiming to compare different IVF outcomes, including the chemical pregnancy rate, clinical pregnancy rate, ongoing pregnancy rate, OHSS rate, miscarriage rate, ectopic pregnancy rate, and presence of congenital anomalies.

In our study, the number of retrieved oocytes was intentionally lower in the fresh ET group than in the frozen ET group (13.06 ± 3.86 vs 16.11 ± 3.87). The more

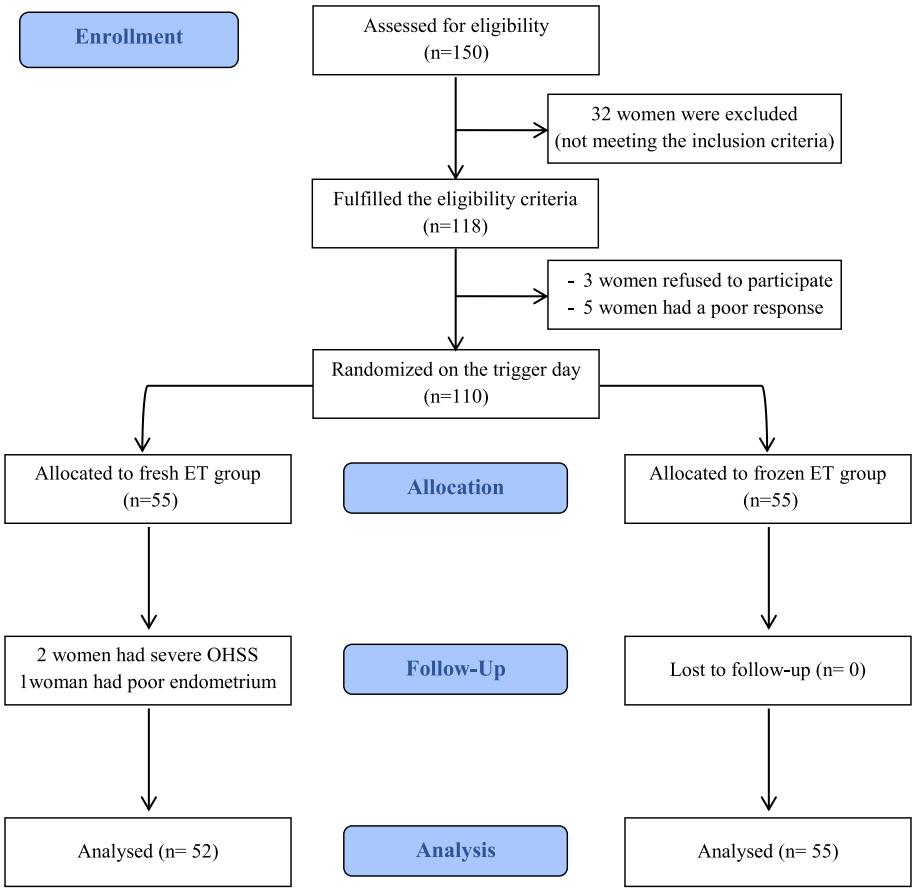

Fig. 1 Study enrolment and outcome

Table 1 The demographic characteristics of the two groups

	Fresh ET (*n* = 52)	Frozen ET (*n* = 55)	*P*-value
Age (years)	26.94 ± 4.33 26 (20—38)	28.07 ± 3.77 29 (21—38)	0.094
BMI	27.58 ± 4.44 28.5 (19—35)	27.75 ± 3.61 28 (19—35)	0.754
Number of previous CS	0.06 ± 0.24 0 (0—1)	0.35 ± 0.48 0 (0—1)	< 0.001
Number of previous surgical evacuation	0.13 ± 0.44 0 (0—2)	0.28 ± 0.89 0 (0—4)	0.704
Type of infertility			
- Primary	41 (78.85%)	35 (63.64%)	0.083
- Secondary	11 (21.15%)	20 (36.36%)	
Duration of infertility (years)	3.38 ± 0.89 3 (2—6)	3.15 ± 0.87 3 (2—5)	0.133

retrieved oocytes in PCOS women with average oestradiol levels, the less endometrial receptivity, as it is known that increased E2 levels can affect endometrial receptivity [23].

Both Gonadotropin-releasing hormone (GnRH) agonist and antagonist protocols were suggested to reduce the risk of OHSS. In our study, we used the GnRH antagonist protocol as following GnRH agonist triggering,

Table 2 Characteristics of IVF cycles

	Fresh ET (*n* = 52)	Frozen ET (*n* = 55)	*P*-value
Duration of stimulation (days)	10.23 ± 1.52 10.5 (8—12)	10.24 ± 1.53 10 (8—12)	0.969
Antral follicular count	24.46 ± 5.44 24 (15—35)	20.93 ± 6.12 20 (12—33)	0.001
Number of retrieved oocytes	13.06 ± 3.86 12 (5—20)	16.11 ± 3.87 15 (8—23)	0.001
Number of fertilised oocytes	8.44 ± 3.30 9 (3—16)	9.95 ± 4.72 9 (3—18)	0.124
Number of Good quality embryo	6.00 ± 2.89 6 (1—10)	6.25 ± 2.63 7 (1—10)	0.690

Table 3 Clinical outcomes in fresh ET and frozen ET groups

	Fresh ET (*n* = 52)	Frozen ET (*n* = 55)	*P*-value
Chemical pregnancy	**23 (44.23%)**	**26 (47.27%)**	**0.752**
Clinical pregnancy	**22 (42.31%)**	**24 (43.64%)**	**0.890**
Ongoing pregnancy	**20 (38.46%)**	**23 (41.82%)**	**0.723**
Pregnancy loss	**4/23 (17.39%)**	**4/26 (15.38%)**	**1**
Ectopic pregnancy	**1 (1.92%)**	**0 (0.00%)**	**0.486**
Anomaly malformations	**1 (4.35%)**	**1 (3.85%)**	**1**
OHSS	**10 (19.23%)**	**2 (3.64%)**	**0.011**
OHSS degree			
- No	**42 (80.77%)**	**53 (96.36%)**	**0.033**
- Moderate	**8 (15.38%)**	**2 (3.64%)**	
- Severe	**2 (3.85%)**	**0 (0.00%)**	
Late OHSS	**2 (3.85%)**	**0 (0.00%)**	**0.234**
Need for hospitalisation	**3 (5.77%)**	**0 (0.00%)**	**0.111**
Need for ICU admission	**1 (1.92%)**	**0 (0.00%)**	**0.486**
Need for ascites tapping	**1 (1.92%)**	**0 (0.00%)**	**0.486**

luteal lysis may occur, which may reduce the chance of pregnancy in a fresh ET cycle [24]. Ding et al. (2021) used the GnRH-agonist protocol in their study and suggested no significant difference in pregnancy outcomes in terms of clinical pregnancy, ectopic pregnancy, and pregnancy loss rates between fresh and frozen groups. On the other hand, the implantation rate and the live birth rate were significantly higher in the fresh ET group than that in the frozen ET group [25].

This study showed that the frequency of chemical, clinical and ongoing pregnancy was slightly higher but statistically insignificant in group B (frozen group) than in group A (fresh ET group). Regarding OHSS rate and grade, It was significantly higher in the fresh ET group ($P=0.011$). On the other hand, the pregnancy loss and ectopic pregnancy rates were found to be higher but statistically insignificant in the fresh ET group.

Frozen ET is used increasingly in many countries [12], and it is suggested to provide a better and more natural environment suitable for implantation than fresh ET [26]. Moreover, the freezing technique is suggested to decrease the risk of OHSS [27]. Reduced uterine artery pulsatility index and a greater crown-rump length (CRL) growth have been demonstrated in frozen ET pregnancies compared to fresh ET in many recent studies [28, 29]. However, another factor to be considered with frozen ET is the poisonous effects of the cryoprotectants used in the vitrification, which may have a negative effect on the embryos [30].

In our study, frozen ET had the upper hand in PCOS undergoing IVF treatment for infertility. This agrees with Nayar et al. (2017), who suggested that routine elective freeze-all strategy and later transfer in a subsequent cycle results in better reproductive outcomes even in PCOS cycles triggered by HCG [31]. It also agrees with Wei et al. (2017), who suggested that the elective freeze-all strategy and later ET has a better LBR than fresh ET cycles in women with PCOS [32]. On the other hand, Ding et al. (2021) used the GnRH-a protocol and claimed that fresh ET could lead to a better reproductive outcome with an improved implantation rate and live birth rate and that the freeze-all strategy should be individualised [25].

The strength of the study is that we used a standardized ovarian stimulation protocol for all patients to avoid confounders and that we covered the pregnancy outcomes as well as possible complications of OHSS. The main limitation of the study was that we were forced to give the trigger in the fresh ET group in the form of HCG 5,000 IU along with Decapeptyl 0.1 mg, as giving Decapeptyl alone lowers the success rate of ICSI. On the contrary, in the frozen ET group, we gave two ampoules of Decapeptyl 0.1 mg to avoid OHSS as we were already going to freeze the embryos. Another limiting point is that we followed the patients until they reached only 28 weeks.

Conclusion

Frozen ET has the upper hand in PCOS undergoing IVF treatment for infertility, as it protects against OHSS formation along with a decrease in its severity. However, further studies are needed to detect IVF outcomes regarding live birth rate as it is considered the most important success determinant.

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None.

Authors' contributions
MH, AE, and AHA designed and supervised the study. AS, MME, ASR conducted the study and analysed the data. MAR analysed the data. All authors wrote and approved the manuscript.

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Availability of data and materials
The data that support the findings of this study are available from Kasr El-Ainy Hospital, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of Kasr El-Ainy Hospital.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the hospital ethical committee (reference number O19010). All methods were carried out in accordance with relevant guidelines and regulations. Informed consent was obtained from all participants. All participants gave their consent after being informed of the study's objective and design, and they were given the option to leave the study at any time.

Consent for publication
Not applicable.

Competing interests
None of the authors has financial or other conflicts of interest.

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