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Comparison Of Endometrial Receptivity And Pregnancy Rate Between Fresh Embryo Transfer (ET) And Frozen-Thawed ET After Gonadotrophin-Releasing Hormone (Gnrh) Antagonist Protocol In Normal Ovarian Responders

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Abstract

Background: Gonadotrophin-releasing hormone (GnRH) antagonist protocol has grown in popularity in the in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) treatment .
Purpose: The goal of this study was to assess endometrial receptivity by means of uterine, endometrial, and subendometrial blood flows using transvaginal colour Doppler power ultrasound. It also compared rates of pregnancies between fresh and frozen-thawed ET following GnRH antagonist protocol in normal ovarian responders.
Methods: This retrospective cohort study involved a total of (450) patients divided into two groups; Fresh ET group (n=230) and frozen hawed ET (n=220).
Results: The uterine artery RI and endometrial thickness were significantly lower in the frozen-thawed ET group. The frozen-thawed ET group had a substantially greater clinical pregnancy rate (57.27% vs. 33.04%) (p=0.033); implantation rate (33.11% vs. 23.11%) (p=0.025), ongoing pregnancy rate (55.0% vs. 30.0%) (p=0.013) and live birth rate (45.9% vs. 23.47%) (p=0.02) than the fresh ET group after the GnRH antagonist protocol
Conclusions: Frozen-thawed transfer cycles have been identified to be associated in higher live birth rates and clinical pregnancy rates than fresh embryo transfers. The findings could offer medical professionals with useful information for practice in the clinic.

Key words: Embryo transfer, Fresh transfer; Frozen-thawed transfer, Gonadotrophin-releasing hormone.

Introduction

Previous research had demonstrated that enhancing the total amount of oocytes might enhance the cumulative live birth rate (Polyzos et al., 2018; Law et al., 2019). Through the establishment of the gonadotropin-releasing hormone (GnRH) antagonist protocol in research and practice, GnRH antagonists have grown in popularity means of controlled ovarian stimulation (COS) cycles due to their benefits, involving less periods of stimulation, affordable price, along with low prevalence of ovarian hyper stimulation syndrome (OHSS) (Al-Inany et al., 2016).Human in vitro fertilization (IVF) has grown into the most popular infertility treatment since it became available in 1978 (Talaulikar and Arulkumaran, 2013). Since that time, many assisted reproductive technologies (ARTs) had been established and enhanced, such as intracytoplasmic sperm injection (ICSI), in vitro embryos, ovulation induction, and cryopreservation. Frozen-thawed embryo transfer

(FET) was initially implemented in 1983 to avoid embryo replacement under difficult maternal conditions (Trounson and Mohr, 1983). The application of FET had grown substantially in the past few years (Fan et al., 2022).
Fresh cycles require embryos to be moved into the uterus right away following their cultivation in vitro for two or three days; otherwise, they are thrown away. Later, cryopreservation was developed for preserving embryos for use later on (Wong et al., 2014). Frozen embryos will be thawed and transferred into the uterus when the appropriate conditions are met. Frozen-thawed embryo transfer (FET) addresses the drawbacks of fresh cycles and gives healthcare professionals and patients more options when fresh transfer is uncomfortable or not possible (e.g., high risk of ovarian hyper stimulation syndrome, emergent medical issues, and other potential explanations) (Zhang et al., 2018).
A systematic review stated that frozen-thawed ET might enhance IVF results in contrast to fresh ET, possibly because of better embryo-endometrium synchrony achieved during endometrium preparation cycles. Optimal conditions allow for greater control over endometrial preparation during frozen-thaw cycles. Frozen-thawed ET offers an atmosphere that is more natural for ET to exist (Wang and Hu 2021).
This prospective study aimed to assess endometrial receptivity by means of uterine, endometrial, and subendometrial blood flows using transvaginal colour Doppler power ultrasound. It also compared rates of pregnancies between fresh and frozen-thawed ET following GnRH antagonist protocol in normal ovarian responders.

Patients and methods:

This retrospective cohort study was conducted at Qena fertility center, with Ethics Committee approval. The data were gathered from individuals who had their initial IVF/ICSI cycles between November 2020 and November 2023. The information was stripped of identification to guarantee patient confidentiality.
Inclusion criteria were; age between 20–40 years; basal FSH less than10mIU/ml; body mass index (BMI) of 18–29 kg/m2 and normal menstrual cycle. Patients were excluded if they had ovarian cysts, polycystic ovarian syndrome (PCOS), adenomyosis, uterine fibroids, sever adhesions of pelvis, hydrosalpinx, and uterine anomaly. Evidence for the freeze-all approach encompassed an increased probability of establishing OHSS, suboptimal endometrium (e.g., less than seven mm and uterine effusion), and increased concentrations of progesterone (more than 2.0 ng/ml).

GnRH antagonist protocol

The study population (450) females were given a standardized GnRH antagonist protocol with recombinant follicle stimulating hormone (FSH) (Gonal-f; Merck Serono, Switzerland) beginning on day two or three of menstrual cycle (150 - 300 IU/day), depending on age and stimulation response on day six. A GnRH antagonist (Cetrorelix; Cetrotide, Merck Serono, Switzerland) was used to suppress the pituitary gland when a leading follicle reached 14 mm. To induce final oocyte maturation, 250 µg of recombinant human chorionic gonadotropin (hCG) (Ovidrel; Merck Serono, Switzerland) was administered once three follicles reached 18 mm in diameter by ultrasound.

Fresh ET

Fresh ET was carried out on the third day following oocyte retrieval. According to ultrasound supervision, only two of the best cleavage-stage embryos were moved, whereas the remaining embryos were employed to establish blastocysts.

Frozen thawed ET

For the frozen ET group, all embryos were cryopreserved, and a minimum of one straw (four cryopreserved embryos) was thawed on a later target cycle to ensure the transfer of two viable embryos. Endometrial preparation was performed using oral oestradiol valerate (Progynova) and began on day two or three of the menstrual cycle. When the endometrial thickness reached seven mm or more, 400 mg vaginal progesterone suppositories were administered twice a day. Two day-3 frozen embryos were thawed and transferred on day 4 of the progesterone schedule, and the luteal-phase support using oestradiol valerate and progesterone suppositories was continued until 10 weeks after conception.

Ultrasound examination

The study looked at endometrial thickness, pulsatility index (PI), resistance index (RI), systolic/diastolic (S/D) ratio of the uterine artery, and endometrial-subendometrial blood flow distribution patterns. We analyzed the average readings for ultrasonography variables from three readings per subject.

Clinical outcomes

A qualitative hCG urinalysis was conducted 14 days after ET. Four to five weeks following ET, the gestational sac was scanned with transvaginal ultrasound for verifying clinical pregnancy. The implantation rate was calculated using the total number of gestational sacs observed for each embryo transferred. An ectopic pregnancy was defined as a laparoscopic or ultrasound-confirmed additional uterine pregnancy. At week twelve, an ongoing pregnancy was defined as one that was viable.

Statistical analyses

Recorded data were analyzed using the statistical package for social sciences, version 23.0 (SPSS Inc., Chicago, Illinois, USA). The quantitative data were presented as mean± standard deviation and ranges when their distribution was parametric (normal) while non-normally distributed variables (non-parametric data) were presented as median with inter-quartile range (IQR). Also, qualitative variables were presented as number and percentages. Data were explored for normality using Kolmogorov-Smirnov and Shapiro-Wilk Test.

Results:

The results of the current study are displayed in the following tables and figures:

A total of (450) patients were included and divided into two groups; Fresh ET group (n=230) and frozen hawed ET (n=220). Table (1) shows none statistically significant difference between both groups as regards the demographic and infertility features (p>0.05) while there was statistically significant difference between both groups regarding endometrial thickness (p=0.014) as the endometrial thickness in the frozen thawed ET group was significantly lower than in the fresh ET also there was highly statistically significant difference between both groups regarding uterine artery RI (p<0.001) where the uterine artery RI was higher in the fresh ET group than the frozen-thawed ET group.

Table (1): Basic characteristics of the study groups

	Fresh ET (n=230)	Frozen-thawed ET(n=220)	P-value
Age (years)	41.2 ± 12.25	41.8± 14.12	0.898
BMI(kg/m2)	25.50 ± 2.08	25.14±1.92	0.635
Primary infertility (n, %)	145(63.04%)	154(70.0%)	0.702
Causes of infertility			
Tubal	160(69.57%)	132(60.0%)	
Male	40(17.39%)	37(16.82%)	
Anovulatory	6 (2.61%)	12 (5.54%)	
Endometriosis	18 (7.83%)	15(6.82%)	
Mixed	3 (1.33%)	14(6.36%)	
Others	3 (1.33%)	10(4.55%)	
Basal FSH (IU/L)	4.25 ± 2.50	4.07 ± 1.77	0.15
Stimulation days	7.13 ± 1.89	7.30 ± 1.67	0.802
Number of M II oocytes	9.12 ± 8.85	10.80 ± 8.90	0.624
ICSI cycles (%)	37 (16.08%)	40 (18.18%)	0.24
Fertilization rate (%)	150 (65.21%)	180 (81.82%)	0.30
Good quality embryos on Day 3	4.25 ± 2.49	5.86 ± 2.67	0.15
Thickness of endometrium (mm)	8.06 ± 0.40	7.82 ± 0.53	0.014
Uterine artery PI	3.82 ± 0.38	4.08 ± 0.33	0.161
Uterine artery RI	0.66 ± 0.19	0.42 ± 0.09	<0.001
Uterine artery SD ratio	5.73 ± 0.16	5.78 ± 0.00	0.76
The pattern of endometrial–subendometrial flow distribution			
Zone 1	70	53	
Zone 2	134	122	
Zone 3	26	45	

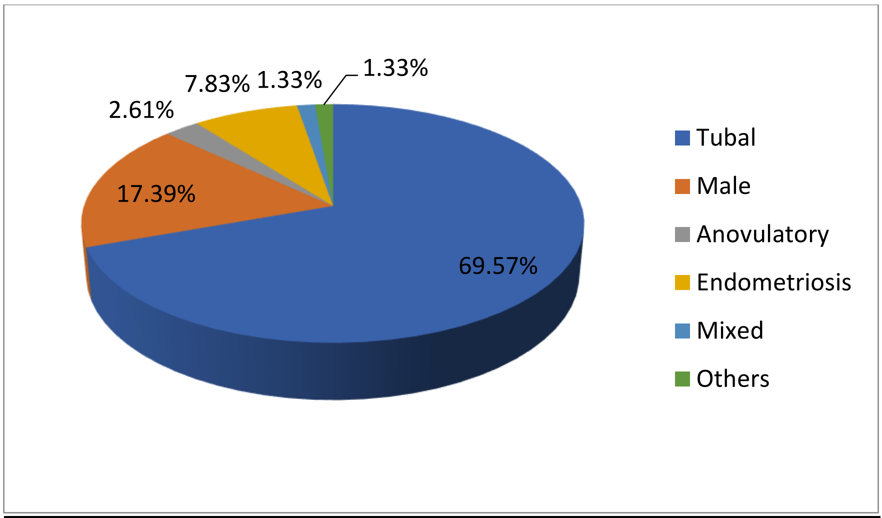

Figure (1) Causes of infertility in fresh ET group (n=230)

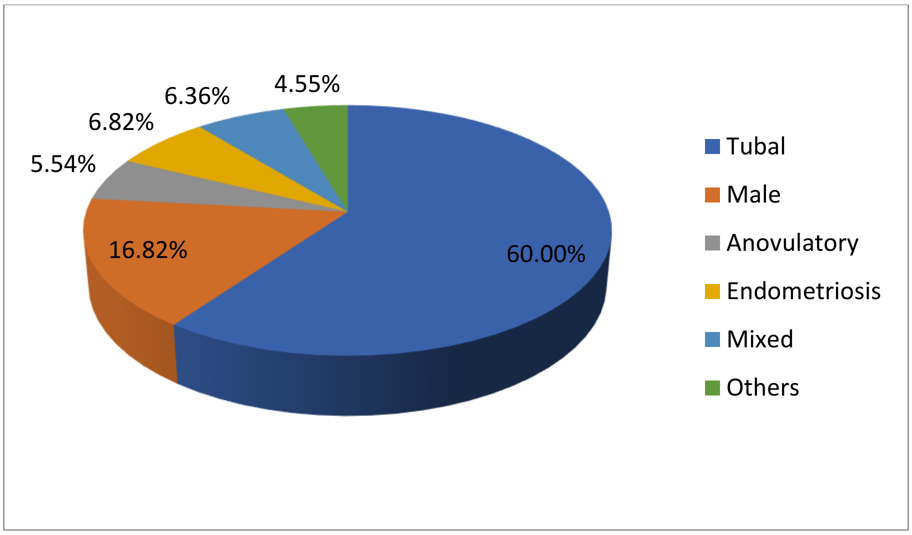

Figure (2) Causes of infertility in frozen thawed ET group (n=220)

Table (2) compared the reproductive results in the study groups. The frozen thawed ET group had a significantly higher clinical pregnancy rate (57.27% vs. 33.04%) (p=0.033); implantation rate (33.11% vs. 23.11%) (p=0.025), ongoing pregnancy rate (55.0% vs. 30.0%) (p=0.013) and live birth rate (45.9% vs. 23.47%) (p=0.02) than fresh ET group after GnRH antagonist protocol. There were none statistically significant difference between both groups as regards miscarriage rate (p=0.667) and ectopic pregnancy rate (p=0.25)

Table (2): Reproductive outcome / embryo transferred

	Fresh ET (n=230)	Frozen-thawed ET(n=220)	P-value
Number of embryo transferred	2(2-2)	2(2-2)	0.65
Clinical pregnancy rate (%)	76/230 (33.04%)	126/220 (57.27%)	0.033
Ongoing pregnancy rate (%)	69/230 (30.0%)	121/220 (55.0%)	0.013
Implantation rate (%)	104/450 (23.11%)	149/450 (33.11%)	0.025
Miscarriage rate (%)	18/76 (23.68%)	22/126 (17.46%)	0.667
Live birth rate (%)	54/230 (23.47%)	101/220 (45.9%)	0.02
Ectopic pregnancy rate (%)	4/76 (5.26%)	3/126 (2.38%)	0.25

Discussion:

In our study, primary infertility was more common the frozen-thawed ET group (70.0%) than in the fresh embryo transfer group (63.04%). This result agreed with Fan et al., (2022) who found that the incidence of primary infertility was higher in frozen-thawed ET group (42.3% versus 34.2%).
The present study findings revealed that the uterine artery RI and endometrial thickness were significantly lower in the frozen-thawed ET group. According to Prasad et al., (2017), uterine artery PSV, S/D, and RI are not reliable indicators of pregnancy outcomes.
The current study results revealed that the frozen-thawed ET group had a substantially greater clinical pregnancy rate, ongoing pregnancy rate, implantation rate, and live birth rate than the fresh ET group after the GnRH antagonist protocol. Furthermore, the percentage of detectable endometrial-subendometrial blood flow was considerably greater in the frozen-thawed ET group. These findings are in the same line with previous studies. Fan et al., (2022) found that the frozen-thawed procedures increased the implantation possibility for embryos retrieved from women who were on the GnRH antagonist protocol. Frozen-thawed ET group resulted in a higher live birth rates and clinical pregnancy rates than fresh embryo transfers. In another study conducted by Liu et al., (2019) they found that the clinical pregnancy rate was substantially greater with frozen-thawed embryo transfer compared to fresh embryo transfer (63.70% versus 54.50%, $p < 0.001$). The miscarriage and ectopic pregnancy rates were comparable between the two groups. Roque et al., (2013) determined that cryopreservation of all embryos and subsequent FET produced improved outcomes than fresh embryo transfer, presumably because of improved physiologic synchronisation of the embryo and endometrium. FET appears to be the best strategy, but it necessitates skilled workers and a research facility for carrying out FET cycles.
The suggested processes for enhancing pregnancy rates using frozen-thawed embryos rather than fresh embryos in GnRH antagonist cycles had revealed that inadequate endometrial receptivity (ER) is greater likely to take place in fresh embryo transfer cycles following controlled ovarian stimulation than in FETs, in which the embryos could be cryopreserved and passed on to an additional receptive endometrium (Weinerman and Mainigi, 2014). A further potential reason for the benefits of FET over fresh embryo transfer is embryo quality, as embryos have to be carefully selected prior to freezing (Ginström Ernstad et al., 2019).
Xia and Zheng, (2021) compared the clinical outcomes of fresh and frozen-thawed transfer cycles using the depot GnRH agonist and GnRH antagonist protocols in normal ovarian responders. They found none statistically significant differences in the number of transferred embryos, clinical pregnancy rate or abortion rate between the two groups (all $P > 0.05$).
Aflatoonian et al., (2018) determined the reproductive outcomes and risk of OHSS in fresh versus frozen embryo transfer in high responder patients going through in vitro fertilization created by a GnRH agonist bolus. They found none significant differences between FET and fresh groups in terms of clinical (35.8% versus 38.3%, p=0.699), and ongoing (30.3% versus 32.7%, p=0.700) pregnancy rates, also live birth (30.3% versus 29.9%, p=0.953).

The current study has some limitations, including a retrospective planning, conducting at single center and a small sample size.

In conclusion, frozen-thawed transfer cycles have been identified to be associated in higher live birth rates and clinical pregnancy rates than fresh embryo transfers. The findings could offer medical professionals with useful information for practice in the clinic. Furthermore, all clinical trials and methods in laboratories, as well as follow-up with patients were carried out at the same IVF centre.

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