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Title:

Comparing Pregnancy Outcomes Between Natural Cycles and Artificial Cycles Following Frozen-Thaw Embryo Transfers

Running Title:

A retrospective cohort analysis

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Abstract:

Background:

Frozen embryo transfer (FET) is increasing in prevalence. In contrast to the amount of research performed on the actual cryopreservation procedure, there are limited data with respect to optimal endometrial preparation in FET cycles. Increasingly artificial cycle (AC) preparation is being adopted over the natural cycle (NC) to facilitate greater access to FET. However, there remains a paucity of data comparing pregnancy outcomes between these two commonly used cycle types.

Aims:

To examine the efficacy of AC vs NC following FET, by comparing pregnancy outcomes including biochemical, clinical and live birth rates, along with miscarriage rates.

Materials and Method:

This is a large single-centre retrospective analysis, examining a standardised data set from January 2015 to July 2018. It included 3030 cycles (NC=2033, AC=997). Main outcomes were biochemical pregnancy (beta-hCG >5IU), ultrasound-diagnosed clinical pregnancy, and live births. Using the chi-squared test, the above pregnancy outcomes were compared between AC and NC. A multivariate logistic regression, controlling for factors such as age, embryo quality, and day of blastocyst freeze was further utilised to assess for confounding variables.

Results:

No difference was observed between biochemical pregnancy rates (NC=39.45% vs AC=37.71%, P=0.357), statistically significant differences were observed between clinical pregnancy (30.84% vs 26.08%, P=0.007), and live birth rates (24.40% vs 18.86% P=0.001). Multivariate analysis confirmed that NC produces superior pregnancy outcomes when controlling for confounding variables.

Conclusion:
This analysis demonstrates the non-inferiority of NC thaw compared to AC, on continuing pregnancy rates. Taken together with patient acceptability and possibly increased obstetric risks with AC, these findings support the use of NC when medically possible.

INTRODUCTION

The use of Frozen Embryo Transfer (FET) in assisted reproductive technique (ART) centres is increasing in frequency, partially driven by the increase in pre-implantation genetic testing (PGT)[1] and also by the desire to move away from the transfer of embryos to the uterus in the same stimulation cycle[2]. Modern vitrification methods have allowed safe and efficient cryopreservation, storage and warming of embryos, with increased utilization of freeze-all cycles. Current evidence suggests that freeze all cycles produce similar ongoing pregnancy rates to fresh cycles[3,4]. A practical advantage of FET is its convenience, enabling clinics with scheduling limitations to have greater control over cycle timing, and there are potential benefits to patients, who have lower rates of complications such as OHSS as a result of FET. In spite of this, a consensus has still not been reached regarding the optimal method of endometrial preparation prior to FET[5].

There are several methods used for endometrial preparation prior to FET, the most common of which remains the natural cycle (NC). In a natural cycle, FET success is dependent on a patient's endogenous cycle and the corpus luteum to maintain the normal hormonal milieu of early pregnancy. As such, FET must coincide with a woman's natural cycle and ovulation.

Alternatively, in artificial cycles (AC), this physiological process is overridden through the administration of exogenous oestrogen (E2) and progesterone (P4). E2 is used to prime the endometrium, while P4 is supplemented to complete endometrial maturation, and support the presumptive new pregnancy through to the end of the first trimester[6].

In certain clinical situations, such as anovulatory women, NC may not be possible. Hence, alternative methods such as AC are sometimes necessary. Additionally, AC is increasingly adopted over NC for practical purposes, even in normo-ovulatory women, in order to facilitate greater control over FET timing and improve access to treatment. However, questions remain regarding whether AC can produce equivalent pregnancy outcomes to NC[5,7-11], and whether this increased patients' and clinicians' convenience comes at the cost of more favourable pregnancy outcomes. Furthermore, several recent publications have questioned whether obstetric complications, such as hypertensive disorders of pregnancy, may be increased in the absence of a corpus luteum[4,12,13].

Consequently, we sought to examine the efficacy of AC vs NC, comparing pregnancy outcomes including biochemical, clinical and live birth rates, along with miscarriage rates, following each cycle type.

MATERIALS AND METHODS

This was a large single-centre retrospective analysis of prospectively collected data, examining a standardised data set from January 2015 to July 2018. It included 3030 first thaw cycles (NC=2033, AC=997) performed at a single site utilising the same laboratory. We specifically excluded ovulation induction (OI) cycles, as well as cycles which involved trophectoderm biopsy, and donor egg cycles. The main outcomes of interest were biochemical pregnancy (beta-hCG >5IU), ultrasound-diagnosed clinical pregnancy (gestational sac seen on ultrasound), miscarriage rate, and live birth. Patient characteristics were prospectively recorded in the clinic database and were extracted for analysis.

The protocol for natural cycles was USS on Day eight to measure endometrial thickness, then monitoring for ovulation with urinary home test or LH/P4 bloods until ovulation confirmed. FET was subsequently undertaken five days later, as previously described [14]. Additionally, most patients commenced P4 supplementation on two days following ovulation. Beta-HCG samples were obtained ten days following FET.

The hormonal replacement protocol for AC FETs included oestradiol 2mg BD from day five of the cycle, as previously described [15]. This was adjusted as required to achieve a transvaginal ultrasound measurement of endometrial thickness of ≥8mm. Progesterone supplementation was then commenced PV 200mg eight-hourly. After five full days of P4 replacement, embryo transfer occurred. Both E2 and P4 were continued until pregnancy testing, with beta-HCG samples taken ten days following FET. If positive, both were continued until twelve weeks gestation, if negative or in the event of miscarriage, all medications were ceased. Serum P4 was measured on the day of FET and if levels were less than 25mmol/L, then P4 replacement was increased at the discretion of the treating clinician.

Embryos were derived from in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycles. The vitrification and warming protocols on either day 5 (D5) or day 6 (D6) were performed using the Rapid-I[16] (Vitrolife AB, Sweden), and the RapidVit Blast and RapidWarm Blast kits (Vitrolife). The quality of each blastocyst was recorded on day of cryopreservation as per the Gardner classification[17,18]. A 'Good quality' embryo transfer was considered to occur where a blastocyst had an expansion grade of three or higher (full blastocyst to hatched blastocyst), an inner cell mass grade of A or B, and a Trophectoderm grade of A or B, i.e. 3BB or superior. All embryo transfers were performed as recommended by the American Society for Reproductive Medicine[19] using Guardia AccessET Embryo Transfer Catheter Set (Cook Medical, USA) by experienced clinicians who have performed at least 100 embryo transfer procedures prior to the index transfer.

The main outcomes measured were biochemical pregnancy (beta human chorionic gonadotropin ≥5), ultrasound-diagnosed clinical pregnancy, and miscarriage and live birth rates.

Univariate analyses for patient characteristics and pregnancy outcomes were compared between these cohorts using the Chi squared test, or the student t-test for continuous variables. A multivariate logistic regression, controlling for factors including patient age, D5 or D6 blastocyst, and blastocyst quality at freeze was utilised to assess for confounding variables.

This study was approved by Melbourne IVF Human Research Ethics Committee, ID 71/19-MIVF.

RESULTS

A total of 3030 FET cycles were included in the data set. The characteristics of patients were compared between the two cohorts of those that underwent NC vs those undergoing AC. Some heterogeneity was observed between the two cohorts, particularly with respect to age and embryo quality (Table 1).

Whilst no difference was observed between biochemical pregnancy rates for the two cycle types (NC vs. AC, 39.45% vs. 37.71%, P = 0.357), statistically significant differences were observed with respect to clinical pregnancy (30.84% vs. 26.08%, P = 0.007), and live birth rates (24.40% and 18.86% P = 0.001) (Figure 1).

A multivariate logistic regression was performed, again demonstrating that NC produces superior pregnancy outcomes when controlling for the afore-mentioned factors (Table 2). Logistic regression was adjusted for fertilisation method, age of blastocyst (D5 vs. D6), and maternal age at embryo creation. These factors had statistical significance in predicting biochemical pregnancy (P <0.1) and therefore were included. When controlling for these variables, a trend towards NC was observed, that became increasingly more significant as pregnancy progressed. Interestingly, when examining biochemical pregnancy rates in the multivariate analysis, a statistically significant difference between AC and NC was observed for the first time (OR 0.79, P=0.005).

Miscarriage rates were further examined in greater detail. Given the lack of significant observed difference between biochemical pregnancy rates following the two cycle types, we examined the pregnancy rates further to determine at what point AC pregnancy outcomes began to deteriorate. As demonstrated in Figure 2, the miscarriage rate rose significantly in the AC cohort as the pregnancy progressed further. As such, even though the biochemical pregnancy rates between NC and AC cohorts were similar, 30.85% of these failed before an ultrasound diagnosis of pregnancy could be made in the AC cohort, compared to 21.82% in the NC cohort. By the time live births could be reached, 50% of pregnancies resulting from AC FETs had failed, compared to 38% in the NC cohort (P <0.001).

DISCUSSION

This analysis has revealed that while there was no difference in biochemical pregnancy rates, the increased pregnancy loss associated with AC lead to a statistically significant decline in clinical pregnancy and live birth rates compared to NC in the univariate analysis. The multivariate analysis additionally demonstrated that AC is associated with lower continuing pregnancy rates when compared with NC. Interestingly, this also demonstrated a trend towards improved biochemical rates suggesting that NC may facilitate a superior implantation rate.

Previous reports have considered whether AC is comparable to NC in terms of efficacy but have failed to reach a consensus. The 2017 Cochrane review was unable to determine the comparability of NC and AC with respective to pregnancy outcomes including pregnancy rate and live birth rate. Furthermore, when examining other methods of endometrial preparation such as ovulation induction, modified natural cycle (where ovulation is triggered pharmacologically) and artificial cycles with GnRH analogue, no single cycle type proved most efficacious[5]. Several smaller, retrospective studies have also been inconclusive; while some found no difference between pregnancy outcomes in NC vs AC[9,10], another larger study did demonstrate an improved clinical pregnancy rate following NC compared to AC[8]. A small prospective study demonstrated a similar trend toward increased miscarriage following AC as opposed to NC (although didn't find a statistically significant difference in clinical pregnancy or ongoing pregnancy rates)[11]. A second small prospective study was published earlier this year but did not demonstrate a significant difference between the two cycles when considering pregnancy outcomes such as biochemical or clinical pregnancy rates, or livebirth[7].

The question of the safety of AC has also recently been examined. A population-wide analysis of pregnancy outcomes following ART was published from Sweden this year, in which higher rates of hypertensive disease of pregnancy, post-partum haemorrhage, postdates pregnancy deliver and macrosomia were demonstrated following AC compared to NC[4]. What this and other studies indicate, is that the presence of a corpus luteum (CL) may play a significant endocrine role during the preimplantation/implantation period, and that a failure to support optimal events at implantation (such as the absence of a CL) has consequences later in the pregnancy, including development of preeclampsia[8,11].

In considering a physiological process to explain our findings, we propose two potential factors contributing towards the inferiority of AC as a method of endometrial preparation and luteal phase support. Firstly, the AC regime is limited to the replacement of those two

hormones considered to be essential for implantation and pregnancy maintenance, E2 and P4. However, the regime is an over-simplified replica of the complex hormonal and biochemical processes present throughout ovulation, implantation and early pregnancy. Other steroidal hormones such as testosterone vary in concentration in the presence of the corpus luteum[20]; hence, in NC, conception and pregnancy may be aided by biochemical mechanisms that we do not yet fully understand. Secondly, in AC cycles, P4 replacement regimes may deliver suboptimal luteal phase support. It is very difficult to determine what comprises adequate luteal phase support in AC. There are data to suggest that serum P4 may have utility in guiding P4 administration[21-23], but there is also evidence that peripheral P4 levels do not correlate well with uterine P4 levels, particularly in the case of PV administration[24,25] as a result of the uterine first pass effect[26]. Additionally, there is a great deal of inter-individual variation in P4 serum concentrations following PV P4 administration[27,28], so there may not be a uniform 'adequate' P4 level that can be used to guide administration. Thus, we may be failing to replicate the natural hormonal environment needed to support pregnancy in AC.

We acknowledge the shortcomings of our study design, and the possibility that they may have contributed to our findings. This study was limited by its retrospective nature with the inherent possibility that the two groups are different in unindentifiable ways. The choice of thaw cycle was at clinicians' discretion, and while some use AC for most patients others use NC, with AC reserved for those where natural ovulation is sporadic or absent Also, clinician preference is dynamic and practices have changed over time. Furthermore, there was identified heterogeneity in the patient characteristics between the two groups, with patients in the AC group being significantly younger and with more good quality blastocysts on day 5, both with a known association with improved pregnancy outcomes. In spite of this, the NC outcomes were significantly better post transfer. Additionally, without specifically examining individual infertility causes, we were unable to determine the proportion of anovulatory cycles in the AC cohort; there is low level evidence that certain anovulatory conditions such as PCOS are associated with miscarriage[29]; this may have had some unrecognised contribution towards our findings. Importantly, we are not aware of any particular cause of infertility, whose disproportionate presence in the AC group, would explain the higher rate of miscarriage.

This cohort included patients first thaw cycle at our centre, as previously mentioned, but there is a possibility that, unknown to us, some may have had prior treatment elsewhere. Nevertheless, we would expect that this small number of patients would be randomly, not

unequally, distributed between the two groups and therefore not bias the results in favour of NC.

Despite the aforementioned limitations it is reasonable to conclude that NC is at least not inferior, in terms of live birth compared to AC. Taken together with recent evidence of higher obstetric complications in AC compared to NC cycles, as well as better patient tolerability, these findings suggest that
NC should be the cycle of choice, when medically possible. We highlight the need for randomised control trials to further evaluate this question and to examine whether intermediary options such as ovulation induction cycles may provide to be a viable alternative to artificial cycles in smaller centres, allowing improved FET scheduling and accessibility, without compromising cycle efficacy and safety.

Figure 1

Pregnancy Outcomes by Cycle Type

Figure 2

A Schematic Representation of Miscarriage Rates by Cycle Type

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Table 1 – Patient Characteristics

	NC, N = 2033, 67.10%	AC, N = 997, 32.9%	P Value
No. Embryos transferred			*0.21*
1	90.61%	89.17%	
2	9.39%	10.83%	
Age at embryo creation (mean +/- SD)	35.56 ± 0.89	33.79 ± 0.14	***<0.01***
IVF vs. ICSI			*0.2*
IVF	29.71%	30.49%	
ICSI	70.29%	69.51%	
Day 5 vs. Day 6 blast			***0.01***
D5	56.42%	61.28%	
D6	43.58%	38.72%	
Good quality†	42.35%	47.64%	***0.01***
embryo transfer – D5 Blastocysts			
Good quality†	29.56%	25.48%	***0.02***
embryo transfer – D6 Blastocysts			

†Good quality, denoted by Gardner classification system. Expansion grade 3 or higher. ICM A or B, TE A or B

Table 2 – Multivariate logistic regression analysis of factors related to pregnancy outcomes

	Adjusted OR (95% CI)	P Value
Biochemical Pregnancy		
AC vs. NC	*0.79 (0.67; 0.93)*	***<0.01***
ICSI vs. IVF	0.83 (0.71; 0.98)	***0.02***
D5 vs. D6	1.46 (1.25; 1.70)	***<0.01***
Age at embryo creation	0.93 (0.91; 0.95)	***<0.01***
Clinical Pregnancy		
AC vs. NC	*0.67 (0.56; 0.80)*	***<0.01***
ICSI vs. IVF	0.91 (0.76; 1.08)	*0.26*
D5 vs. D6	1.55 (1.31; 1.82)	***<0.01***
Age at embryo creation	0.93 (0.91; 0.95)	***<0.01***
Live birth		
AC vs. NC	*0.57 (0.47; 0.70)*	***<0.01***
ICSI vs. IVF	0.81 (0.67; 0.97)	***0.02***
D5 vs. D6	1.50 (1.25; 1.80)	***<0.01***

Figure 1. Pregnancy Outcomes by Cycle Type

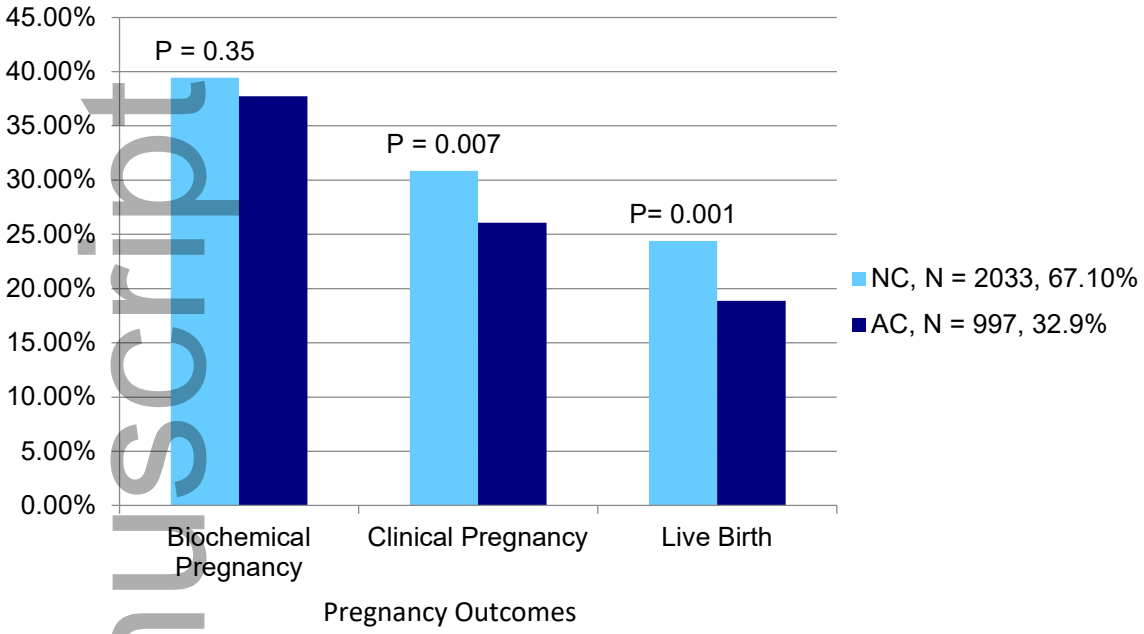

Figure 2 – A Schematic Representation of Miscarriage Rates by Cycle Type