IVF Outcome Comparisons Between Fresh Embryo Transfers and Embryo Banking Cycles With Subsequent Thawed Transfers Vary Between Good-, Intermediate- and Poor-prognosis Patients

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Abstract

Never investigated before in poor prognosis patients, we here determined how in vitro fertilization (IVF) outcomes after fresh embryo transfers compare to frozen-thawed transfers after embryo banking. Using data from our center's anonymized electronic research data bank, we in a retrospective controlled observational study investigated IVF cycle outcomes of poor-prognosis infertility patients, utilizing autologous eggs, while utilizing donor-egg recipient cycles as controls for covariables. To accomplish statistically valid comparisons, 4 different pairings of 1st IVF cycles were utilized: (i) 127 fresh vs. 193 frozen donor recipient cycles; (ii) 741 autologous fresh unselected non-donor IVF cycles vs. 217 autologous frozen non-donor IVF cycles; (iii) 143 favorably selected autologous non-donor IVF cycles vs. the same 217 frozen autologous cycles non-donor; and (iv) 598 selected average and poor-prognosis autologous non-donor cycles vs. the same 217 frozen autologous non-donor cycles. Main outcome measures were pregnancies and live births. Even within poor-prognosis patients, patient selection to significant degrees impacted how fresh and frozen-thawed IVF cycles compared. Though embryo banking with delayed embryo transfer in best-prognosis patients marginally improved IVF outcomes, in unselected patients it had no effect on outcomes, while in poor-prognosis patients it adversely affected IVF outcomes. Unexpectedly, the study also discovered a previously unreported effect of recipient-age on miscarriage risk in donor-egg recipient cycles, which apparently is independent of age-associated increases in chromosomal abnormalities and, therefore, must have other causes. This study suggests that in poor-prognosis patient banking cycles should be considered contraindicated, in intermediate-prognosis patients they do not appear to change outcomes and, therefore, do not warrant additional costs from thaw cycles, leaving only good-prognosis patients as potential candidates for such a strategy.

Background

Traditionally, embryo cryopreservation in association with in vitro fertilization (IVF) has been a last resort treatment, reserved for clinical circumstances where fresh embryo transfers are contraindicated and/or more embryos are produced in an IVF cycle than can safely be transferred. More recently, however, a concept of all-freeze IVF cycles with routine embryo banking has been proposed [1, 2], expanding the use of cryopreservation under the hypothesis that elective cryopreservation of all embryos followed by subsequent transfer of frozen-thawed embryos in either a natural or an artificial cycle would improve pregnancy and live birth chances [1–3].

This concept, however, has remained controversial [4–6]. Disagreements about newly added treatments to IVF, so-called “add-ons,”⁷ have in recent years become more common, as many entered routine clinical IVF practice without proper prior validation studies and have been accused of being responsible for recent worldwide declines in IVF pregnancy and live birth rates in fresh non-donor cycles [8]. The concept of routine all-freeze IVF cycles, abandoning fresh embryo transfers and insisting on delayed transfers in a later thaw-cycle is one of these newly proposed treatments and has remained controversial [9]. Rather than reflecting true differences, diverging results reported for many “add-ons,” often, are caused by different characteristics of investigated patient populations.

That patient selection can explain most differences of opinion regarding automatic embryo banking, is well demonstrated by two large, almost identical, Chinese studies, executed by the same group of investigators. Those two studies, nevertheless, reported opposing outcomes: Comparing fresh transfers to transfers of cryopreserved embryos in later thaw cycles, one study demonstrated mild outcome benefits from embryo banking [10], while the other did not [11]. Both studies were performed on women with identical genetic background (Han Chinese); their only difference was that the former transferred embryos at blastocyst stage and the latter study at cleavage stage.

Transfers at blastocyst stage, however, select better prognosis patients since such transfers presuppose that at least one embryo reaches blastocyst-stage. Poorer prognosis patients, such as older women or younger women with low functional ovarian reserve often do not have embryos that survive extended culture to blastocyst-stage. As Wei's study well demonstrates [10], poor-prognosis patients, therefore, are frequently automatically excluded from IVF-related studies. Such IVF studies, therefore, reflect only outcomes in relatively good-prognosis patients but, routinely, in recent years have been extrapolated to unselected patient populations.

Above noted two Chinese studies, indeed, perfectly demonstrated the often-overlooked effects of patient selection on study outcomes by offering improved pregnancy rates after blastocyst-stage transfer but no such effect with cleavage-stage transfer. Consequently, only good-prognosis patients may marginally benefit from all-freeze IVF cycles but such patients, already, will achieve good IVF outcomes because of who they are. Whether additional required time and additional costs from having to start another treatment cycle are warranted by such a minor effect on only relatively few patients is, at best, questionable. A review of studies favoring routine embryo freezing, indeed, confirms this observation, as uniformly alleged outcome advantages from all-freeze cycles disappear once appropriate adjustments are made [1, 3, 10–12], and recently also supported by a European multicenter study (a patient population with distinctively different genetic background than above noted two Chinese studies). Though also performed in favorably selected patients receiving single blastocyst-stage embryo transfers and having regular menses, all-freeze cycles, all-freeze cycles with delayed transfer did not elicit better IVF outcomes [12].

This study, therefore, confirmed a recent observation, that all patient populations contain a mix of good-, middle-range, and poor-prognosis individuals [13], since an obviously present good-prognosis sub-population must be counterbalanced by an equal-size poor prognosis population for the whole study to neither demonstrate better or poorer outcomes with embryo banking. These patients in a large majority can be assumed to be older and/or younger women with low functional ovarian reserve.

To explore the effects of embryo banking on patients, we, in a single-center study never before attempted, investigated effects of embryo cryopreservation in a patient population with, a priori, highly unfavorable prognosis.

Methods

Participants

Our center, likely, serves the prognostically most unfavorable patient population among all reporting IVF centers in the U.S. This statement is based on our center serving the by-far oldest patient population undergoing IVF in the U.S. (between 2016–2019, median age at our center was 43.0 years; national average was 36 years) (<https://www.cdc.gov/art/artdata/index.html>). Moreover, over 90% of newly presenting patients have previously failed IVF cycles elsewhere, often at multiple centers. Additional evidence for adverse selection comes from the observation that our center hardly ever sees phenotype-A polycystic ovary syndrome (PCOS) patients; yet does treat large numbers of phenotype-D PCOS patients, who apparently are more resistant to routine fertility treatments and, therefore, reach our center in disproportionately large numbers [14]. Finally, as this study will also demonstrate, even younger patients who present to our center, almost without exception, have previously failed IVF cycles and present with low functional ovarian reserve. Our center's patient population is, therefore, well-suited for investigations of IVF treatment effects upon poor-prognosis patients.

Utilizing the same clinical staffing as well as laboratory personnel, this study investigated in our center's patient population effects of embryo freezing in poor-prognosis patients between 2017 and 2020 in four distinct patient groupings:

(i) In a first investigation, we compared IVF cycle outcomes in 127 infertile women who had fresh embryos transferred, produced from young anonymous egg donors, to 193 infertile women who had frozen embryos transferred, produced with oocytes from young donors (Table 1). Because of the very advanced age of both recipient groups and a desire to avoid all multiple pregnancies at this age, most transfers involved only single embryos.

(ii) In a second investigation, we compared outcomes in 741 fresh and 217 frozen embryo transfers, produced with autologous oocytes of patients (Table 2). Here, the number of transferred embryos was less restricted not because of the age of the patients; but because of too small egg and embryo yields, since transferred embryos rarely exceeded two.

(iii and iv) In this investigation, we selectively looked at a favorably selected group of 143 women from among above noted 741 women and, independently, compared those (Table 3) and the remaining 598 (Table 4) to the same group of 217 frozen autologous IVF cycles, also used in the second investigation. The group of prognostically favorable patients was defined by their ability to produce extra-numerous embryo yields in their fresh IVF cycle that then were available for cryopreservation. This selection criterion was based on the observation that, after female age, the number of transferrable embryos represents the second-most important predictor of IVF success in poor prognosis patients [13].

All patients were consecutive patients entered into the center's anonymized electronic research data base during the study years after providing informed consent. Excluded were repeat cycles and cycles that were cancelled before embryo transfer.

IVF cycles

Oocyte donation cycles of anonymous egg donors were stimulated in long agonist protocols, using a human menopausal gonadotropin product at a dosage of 225IU daily.

Autologous cycles were only initiated after prior priming of ovaries if patients were over age 40 years and/or demonstrated LFOR, defined as abnormally high age-specific FSH [15] and/or abnormally low age-specific AMH [16]. Priming involved supplementation with dehydroepiandrosterone (DHEA; Fertinatal®, Fertility Nutraceuticals, LLC, New York, N.Y.), 25mg TID, for at least 6 weeks or until androgen and sex hormone binding globulin (SHBG) were in normal ranges. All patients, in addition, received the antioxidant CoQ10 at a dosage of 900-1000mg/day (OvoEnergen®, Fertility Nutraceuticals, LLC, New York, N.Y.). A large majority of autologous cycles received direct gonadotropin stimulation, starting on day-2 of menses with daily gonadotropins (300–450 IU of an FSH product and 150 IU of an hMG product, both from different manufacturers based on patient preference and/or insurance mandates). Because patients underwent HIER (highly individualized egg retrieval) [17, 18] and, therefore, had early egg retrievals, they did not require either agonists or antagonists to prevent premature ovulation. The default method in some younger patients who were not expected to have early retrievals was a previously described microdose agonist protocol first reported by Surrey et al [19]. Ovulation was triggered with 10,000 IU of human chorionic gonadotropin (hCG, from different manufacturers).

Except for very rare exceptions in donor recipient cycles, embryo transfers occurred at cleavage-stage (usually day-3; but sometimes day-2). Similarly, except for rare exceptions, embryos did not undergo preimplantation genetic testing for aneuploidy (PGT-A).

A clinical diagnosis of pregnancy required visualization of at least one gestational sac with fetal heart on ultrasound. A diagnosis of clinical miscarriage required at least prior visualization of a gestational sac. Chemical pregnancies were not considered in here reported statistics.

Statistical analyses

Patient demographics were compared by a two-sample t-test and presented as mean and standard deviation. Clinical pregnancies, live birth and miscarriage rates were compared with a Chi-square test and logistic regression model, controlling for age and AMH. All statistics were preformed using SAS version 9.4. A P-value < 0.05 was considered statistically significant.

Institutional Review Board (IRB)

This study was approved by the center's IRB on an expedited basis since here reported data were extracted from the center's anonymized electronic patient data base, which includes all data from patients who signed a written consent that allowed use of their medical record data for research purposes, as long as those data remained confidential, and their identity remained protected.

Results

Third-party egg donation cycles: Fresh vs. frozen

In this first part of the study, we compared IVF cycle outcomes in 127 fresh donor egg recipient cycles to 193 frozen-thawed cycle in which embryos had been produced with fresh donor eggs (Table 1).

Patient characteristics: As the table demonstrates, ages of recipient patients were similar (45.6 ± 5.1 and 45.7 ± 5.9 years; $P = 0.9330$), as were AMH (0.4 ± 0.5 vs. 0.6 ± 0.8 ng/mL; $P = 0.0775$) and highest FSH levels (27.5 ± 31.0 vs. 24.5 ± 26.9 ; $P = 0.4213$) as well as number of transferred embryos (1.6 ± 0.6 vs. 1.7 ± 0.6 ; $P = 0.2208$).

IVF outcomes: In fresh donor recipient cycles, 46/127 (36.2%) conceived and 34/46 (73.9%) delivered, while 12/46 (26.1%) miscarried. In contrast, 56/193 (29.0%) frozen cycles led to clinical pregnancy ($P = 0.1760$), 42/56 (75.0%) delivered and 14/56 miscarried (25.0%). Adjustments for age and AMH values, barely moved the P-value ($P = 0.2487$), reaffirming the close similarity of both study groups.

Autologous non-donor cycles: Fresh vs. frozen

Here we had 741 fresh transfer cycles and 217 frozen cycles for comparison, with embryo numbers transferred again being similar but patient characteristics significantly differing (Table 2).

Patient characteristics: Patients who had fresh cycles were significantly older (41.2 ± 4.8 vs. 39.5 ± 5.9 years ($P < 0.0001$)) had significantly lower AMH (1.2 ± 1.7 vs. 2.4 ± 2.6 ng/mL; $P < 0.0001$) and significantly higher FSH (14.8 ± 12.7 vs. 11.5 ± 7.8 ; $P = 0.0003$) Embryo numbers transferred were, however, similar: 2.2 ± 1.2 vs. 2.1 ± 1.0 ($P = 0.2536$).

IVF outcomes: Fresh cycle in this head-to-head comparison demonstrated significantly lower clinical pregnancy rates (82/741; 11.1%) than frozen cycles (42/217; 19.4%; $P = 0.0014$). But, once outcomes were adjusted for age and AMH, the significant outcome difference between both groups became statistically insignificant ($P = 0.2991$). Of the pregnancies in frozen cycles, 26/42 (61.9%) delivered, while 16/42 (38.1%) miscarried. While in fresh cycles 53/82 (64.6%) delivered and 29/82 miscarried (35.4%), ($P = 0.7648$).

Autologous non-donor cycles: Fresh vs. frozen cycles in favorably selected patients

Here, the frozen group remained the same as in the preceding comparison, but fresh cycles were selected for favorable patients by selecting cycles of 143 women who produced enough embryos in fresh cycles to have at least one embryo cryopreserved. That this group represented only 19.0% of all 741 fresh cycles, again reflects the poor overall prognosis of this patient cohort (Table 3). This left 598 cycles, now presumably representing women with average and poor prognosis (Table 4).

Patient characteristics: In this analysis, demographics of favorably selected fresh cycle patients significantly differed from the preceding analysis: While in the whole group of 741 women, women with

fresh had been significantly older than patients undergoing frozen-thawed cycles (Table 2), the now favorably selected women among that group of patients were significantly younger (37.1 ± 4.9 vs. 39.5 ± 5.9 years; $P = 0.0001$) than women having frozen-thawed embryo transfers. Moreover, neither AMH (2.4 ± 2.2 vs. 2.4 ± 2.6 ng/mL; $P = 0.8457$) nor FSH (10.9 ± 11.2 vs. 11.5 ± 7.8 mIU/mL; $P = 0.5717$) were any longer significantly different. In addition, a non-significant trend toward larger embryo transfer numbers developed in fresh cycles (2.3 ± 1.0 vs. 2.1 ± 1.0 ; $P = 0.0874$).

Comparing in the remaining 598 average and poor prognosis patients between fresh and frozen transfers, patients who had fresh cycles were significantly older (42.2 ± 4.2 vs. 39.5 ± 5.9 years ($P < 0.0001$), had significantly lower AMH (0.9 ± 1.4 vs. 2.4 ± 2.6 ng/mL; $P < 0.0001$) and significantly higher FSH (15.8 ± 12.9 vs. 11.5 ± 7.8 ; $P < 0.0001$). Embryo numbers transferred were, however, again similar: 2.2 ± 1.2 vs. 2.1 ± 1.0 ($P = 0.3874$, Table 4).

IVF outcomes: In this scenario, however, 45/143 clinical pregnancies occurred in fresh cycles (31.5%) vs. only 42/217 (19.4%) in frozen cycles, producing a significant difference to the benefit of fresh cycles ($P = 0.0086$), which remained significant upon adjustment for age and AMH ($P = 0.0451$). Of the pregnancies in the frozen cycle, 26/42 (61.9%) delivered, while 16/42 (38.1%) miscarried. While in fresh cycles 31/45 (68.9%) delivered and 14/45 miscarried (31.1%), ($P = 0.4934$).

In contrast, remaining average- and poorer-prognosis patients, 37/598 (6.2%) had clinical pregnancies with 22 (59.5%) live births and 15 (40.5%) miscarriages. This was an insignificant finding when compared to frozen cycles ($P = 0.8242$, Table 4).

Discussion

As before noted, our center serves overall a very adversely selected patient population, mostly patients who have failed multiple IVF cycles, often at multiple IVF clinics in the U.S. and overseas, before presenting to *The CHR*. Such patients require very different treatment approaches because their responses to standard ovarian stimulation protocols often greatly differs from better-prognosis patients. Our center, therefore, on repeated occasions discovered that treatments proposed based on investigations in better-prognosis patients were not applicable to our center's patient population. Good examples were closed incubation and imaging systems which we found in our patients to produce similar outcomes to standard embryology in third-party egg donor cycles but to adversely affect IVF outcomes in poor-prognosis patients, still pursuing treatments with autologous oocytes [20].

The rapidly gaining popularity of embryo banking has attracted our skepticism because it was primarily built on the hypothesis that ovarian hyperstimulation creates an unfavorable environment for embryo implantation that can be overcome by delaying the embryo transfer from the stimulation cycle into a future implantation cycle. Though skeptical of the hypothesis based on in-house data [6, 21], we have been especially concerned about adverse effects cryopreservation may have on the cumulative pregnancy chances of a cycle's embryo cohort in poorer prognosis patients and about additional costs created by adding an additional thaw cycle. Those concern grew after analyzing the published literature

and as noted in the introduction section, recognizing that practically all reports in the literature that claimed improved pregnancy and live birth rates after embryo banking, had been conducted in only good prognosis patients [1–3, 10, 12]. Where no such patient selection took place, delayed frozen-thawed transfers did not result in cycle improvements.

We then from these observations further concluded that in presence of good prognosis patients who, in a general infertile population, seemingly benefit from all-freeze cycles, such an unselected patient population must also contain a counterbalancing group of patients who experience detrimental effects from such a clinical approach. That such a counterbalancing patient population, likely, had to be made up of patients on the opposing prognostic extreme to good-prognosis patients, seemed obvious and that meant that this group must mostly represent older women and/or younger women with prematurely aging ovaries, the two patient groups that make up over 90% of our center's patient population.

Though, because of potential treatment delays due to randomization to placebo, for ethical reasons our center's patient population does not support many randomized placebo-controlled studies, the unique quality of our center's patients allows for the retrospective analysis of highly homogenous patient groups *in extremis*, where pregnancy chances are very low and, therefore, smaller study sizes allow for statistically valid observations.

Such a study is presented here and confirms our current understanding of the published literature that has led us to the following conclusions regarding all-freeze IVF cycles with embryo banking and deferred embryo transfers: (i) Embryo banking, overall, does not improve IVF outcomes in unselected patient populations. (ii) In favorably selected patients, embryo banking may, with reference point embryo transfer, lead to improved pregnancy and live birth chances. (iii) While patient selection processes may benefit good-prognosis patients, they usually have compensatory detrimental effects on poorer prognosis patients. (iv) As this study demonstrates, this is also the case in utilizing embryo banking in poorer prognosis patients. We here demonstrated the latter point in a four-step study.

Third-party egg donation cycles: Fresh vs. frozen

We in a carefully case-controlled study of practically identical patients in fresh and frozen third-party donor egg cycles (Table 1), demonstrate no difference in clinical pregnancy rates ($P = 0.1760$), with adjustments for age and AMH not at all affecting this conclusion ($P = 0.2487$). Since oocyte donors are highly selected and since recipients in this study were practically identical in basic characteristics, this study can be viewed as a baseline control study, demonstrating no visible effect of embryo freezing on IVF outcomes in unselected patients. This study, thus, reaffirms prior prospectively randomized studies of unselected patient populations [11], and thereby, also reaffirms the format of our retroactive third-party donor analysis.

In Table 1, reported basically identical miscarriage rates in donor recipient cycles, whether fresh (26.1%) or frozen-thawed (25.0%), are, however, deserving of further commentary: Both rates are unexpectedly high, considering that oocytes in these cycles came from young third-party egg donors in their 20s. The

2016 CDC National ART Summary Report suggests in third-party egg donation cycles only an approximately 10.4% miscarriage rate (<https://www.cdc.gov/art/pdf/2016-report/ART-2016-National-Summary-Report-pdf>). Here observed more than double as high miscarriage rate in both study groups, therefore, must reflect the very advanced (also practically identical) ages of both recipient patient groups (45.6 ± 5.1 and 45.7 ± 5.9 years, respectively). While the literature extensively comments on implantation, pregnancy, and live birth rates in donor egg recipient cycles at different ages, surprisingly, we were unable to locate even a single study centered on miscarriage rates depending on recipient ages. Two publications commented peripherally on the subject, with one noting no differences [22] and the other noting small increases in pregnancy losses [23]. Here reported outcome data, therefore, for the first time offer evidence that recipient age does matter when it comes to miscarriages. The likely reasons are accumulating medical problems, unrelated to age of oocytes and, therefore, unrelated to chromosomal abnormalities.

Autologous non-donor cycles: Fresh vs. frozen

In part two of here presented study, we switched to the investigation of the use of autologous oocytes in an overall highly unfavorable patient population and, as a first step, simply compared all fresh and all frozen-thawed cycles performed at the center during the study period (Table 2). Unsurprisingly, this comparison, in contrast to previously described third-party donor cycles, demonstrated two highly divergent patient populations; fresh cycles, not only were three -times as common but also represented significantly older women ($P < 0.0001$), with much lower AMH ($P < 0.0001$) higher FSH ($P = 0.0003$), though very similar number of transferred embryos. Describing both study groups in summary, one, therefore, can clearly state that women who underwent frozen-thawed cycles were not only significantly younger but also had much better functional ovarian reserve. That they achieved significantly better clinical pregnancy rates ($P = 0.0014$) with transfer of identical embryo numbers ($P = 0.2536$), therefore, cannot surprise and does *not* suggest that this improved outcome is consequential to delayed frozen-thawed embryo transfers.

This conclusion is confirmed by the observation that, once pregnancy outcomes were adjusted for age and AMH (as a representative of functional ovarian reserve), the significant difference in pregnancy rate disappeared ($P = 0.2991$). Adjusting for FSH instead of AMH made no differences in significance ($P = 0.1564$) and, since both FSH and AMH reflect FOR, we formally adjusted only for one (AMH). This observation, therefore, offers further evidence that seeming improvements in IVF cycle outcomes in frozen thawed over fresh cycles with use of autologous eggs are mostly due to underlying patient characteristics and not caused by embryo cryopreservation in place of fresh transfers.

Here, too, a comment on miscarriages is necessary: Though both patient groups in this study section are significantly younger than in above presented third party-donor section, fresh and frozen cycles, still, involved older women (41.2 ± 4.8 vs. 39.5 ± 5.9 years, respectively). Frozen cycles were, however, overall performed in younger women than fresh cycles ($P < 0.0001$). The fact that miscarriages were nominally lower in frozen cycles (28.1%) than fresh cycles (35.4%), therefore, has no practical meaning. What, however, is of interest, is the observation that miscarriages were uniformly higher in autologous than

donor-recipient cycles, whether fresh or frozen, even though donor egg recipients were significantly older. Third-party egg donation in older women, therefore, clearly does appear to reduce miscarriage risk in comparison to autologous oocyte cycles; this advantage, however, shrinks with advancing recipient age, likely due to non-chromosomal maternal causes.

Autologous non-donor cycles: Fresh vs. frozen cycles in good-, intermediate- and poor-prognosis patients

Addressing the third and fourth steps of this study (Tables 3 and 4), we argued that every study population can be divided into better-, average-, and poorer-prognosis patients [13]. This must also have been the case in our 741 fresh cycles. Trying to identify within that total group of patients a best-prognosis sub-group must be possible by selecting patients based on number of embryos they produced in their IVF cycles since transferrable embryo numbers, after female age, are the second-most important predictor of pregnancy chances in IVF [13]. Moreover, since this study investigated an older patient population in which current IVF practice allows for transfer of multiple embryos, further patients selection should be achievable by selecting-out patients who produced more embryos than were immediately transferrable. In other words, among those 741 women, the 143 (19%) who ended up with cryopreserved embryos after undergoing a fresh transfer, must have been among best prognosis patients. We now compared these best-prognosis patients in fresh transfers to the same 217 frozen embryo transfer cycles from the previous analysis.

This change in patient selection resulted in highly significant outcome changes: Women undergoing fresh cycles now were suddenly significantly younger ($P = 0.0001$) from previously being significantly older in the complete autologous group ($P < 0.0001$), and significant differences in AMH and FSH to the benefit of frozen cycles completely disappeared, together with all prior outcome advantages in pregnancy rates for frozen cycles ($P = 0.0086$ before and $P = 0.0451$ after adjustment for age and AMH).

Moreover, once we compared the remaining 598 fresh cycles from women with moderate and poor prognosis with the 217 frozen cycles, patient demographics again reverted into similar ranges as had been seen previously in Table 2 for the complete autologous patient populations, with frozen transfer cycles seemingly outperforming pregnancy rates in fresh cycles. ($P < 0.0001$, $P = 0.0028$, Table 4).

Limitations And Conclusions

Using stable treatment protocols, this study used a single fertility center's highly adversely selected, yet very homogenous patient population to assess outcome differences between fresh and frozen-thawed IVF cycles. In so doing, we confirmed even in poor-prognosis IVF patients our preceding interpretation of published literature that reported outcome advantages from all-freeze cycles with subsequent delayed frozen-thawed cycles uniformly reflect unnoticed patient selection biases and not factual outcome advantages from a routine embryo banking strategy. If such a strategy has value, only good-prognosis patients may marginally benefit from such a policy, while poor-prognosis patients will be outright harmed by such practice.

Very similar conclusions were in 2018 also reached in a study of 82,935 U.S. IVF cycles from the SART registry that reached the conclusion that universal embryo freezing only serves good responders [5]. Good responders often overlap with good-prognosis patients; they, however, do not necessarily always reflect the same patient populations. For example, good responders with excessive AMH levels can demonstrate “too good” ovarian responses to stimulation and produce excessive oocyte yields, in which case pregnancy and live birth rates again start to decline [13]. At the other extreme of responses, poor response is not always necessarily the result of poor ovarian function; it can, for example, also be caused by selection of stimulation protocols, patient obesity or non-compliance. Both studies, however, strongly suggest that routine all-freeze IVF cycles, as proposed by some authors [1–3], in most patients are counterproductive and will either have no effect on IVF outcomes or even reduce pregnancy and live birth chances.

The principal limitation of this study is its retrospective nature which can lead to biased patient selection. Our center’s patient population, in characteristics and treatment modalities applied, was, however, very homogenous, thereby significantly reducing the likelihood of significant selection biases. Potential selection biases were, however, also why we here restrict our comments and conclusions to poor-prognosis patients, which in IVF always are at greatest risk to be harmed by treatment changes. Had proponent of all-freeze cycles, indeed, restricted conclusions of their studies, as this study does, to the patient population they investigated, here presented study would not have become necessary.

This study was the first to compare fresh embryo transfers to delayed frozen-thawed transfers in a clearly defined poor-prognosis IVF patient population. In poor-prognosis patients every single oocyte and embryo is of much greater importance than in women with average and good prognosis who produce larger egg and embryo numbers. They, therefore, often are the “canary in the mine” in sounding alarm about otherwise ineffective treatments. Considering that ineffective treatments increase costs and, in this case, also result in delays in treatments, this study offers solid new evidence that the concept of universal all-freeze cycles with subsequently delayed frozen-thawed cycle must be reconsidered. Under best of all circumstances, it should, even in a poor-prognosis population, only be restricted to best prognosis patients in that population. Similar population dynamics are likely also relevant in association with other recent add-ons to IVF [8].

Yet another retrospective study in a general infertile population was recently published since completion of here presented manuscript, though this time based on patient age. Once again, the study demonstrated outcome benefits for an all-freeze strategy in only good-prognosis patients, this time defined as women under age 35 [24]. That age group in a large majority, however, represent exactly the approximately 15% of good-prognosis patients in an average IVF patient population, with another 15% being poor- and 70% average-prognosis patients [13].

Declarations

Ethics approval and consent to participate: This study was approved by the IRB of The CHR. All patients in this study signed an informed consent that allowed use of their medical record for research purposes if their identity was protected, and the material remained confidential. Since this study involved only use of deidentified electronic medical records, these conditions were met.

Consent for publication: Above noted approval also includes a consent for publication.

Availability of data and materials: Data and materials are upon reasonable request available from The CHR's data depository by contacting Ms. Jolanta Tapper, COO at jtapper@thechr.com/

Competing interests: N.G. and D.H.B. are listed as co-owners of several already awarded and still pending U.S. patents, some claiming benefits from androgen supplementation in women with low functional ovarian reserve, a topic addressed in this manuscript. Others relate to diagnostic and potential therapeutic benefits of AMH, also marginally addressed in this manuscript. N.G. is a shareholder in Fertility Nutraceuticals, LLC, which produces a DHEA product, and is owner of The CHR., where much of the research reported in this manuscript was performed. N.G. and D.H.B. also receive patent royalties from Fertility Nutraceuticals, LLC. N.G., D.F.A and D.H.B in the past has received research support, travel funding and lecture fees from various Pharma and medical device companies, none, however, over the last 3 years and none in any way related to this manuscript

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Tables

Table 1
Comparison of fresh and frozen donor egg recipient cycles

	Fresh Cycles	Frozen Cycles	P-value/adjusted
Number of cycles	127	193	
Age (years)	45.6 ± 5.1	45.7 ± 5.9	0.933
AMH (ng/mL)	0.4 ± 0.5	0.6 ± 0.8	0.0775
Highest FSH (mIU/mL)	27.5 ± 31.0	24.5 ± 26.9	0.4213
Number embryos transferred	1.6 ± 0.6	1.7 ± 0.6	0.2208
Pregnancies (n/%)	46 (36.2%)	56 (29.0%)	0.1760/0.2487
Live births (n/%)	34 (73.9%)	42 (75.0%)	0.9003/0.1735
Miscarriages (n/%)	12 (26.1%)	14 (25.0%)	0.9003/0.1735

Table 2
Comparison of autologous fresh non-donor to frozen autologous non-donor cycles

	Fresh Cycles	Frozen Cycles	P-value/adjusted
Number of cycles	741	217	
Age (years)	41.2 ± 4.8	39.5 ± 5.9	< 0.0001
AMH (ng/mL)	1.2 ± 1.7	2.4 ± 2.6	< 0.0001
Highest FSH (mIU/mL)	14.8 ± 12.7	11.5 ± 7.8	0.0003
Number embryos transferred	2.2 ± 1.2	2.1 ± 1.0	0.2536
Pregnancies (n/%)	82 (11.1%)	42 (19.4%)	0.0014/0.2991
Live births (n/%)	53 (64.3%)	26 (61.9%)	0.7648/0.5189
Miscarriages (n/%)	29 (35.4%)	16 (28.1%)	0.7648/0.5189

Table 3
Comparison of best prognosis autologous fresh non-donor to frozen autologous non-donor cycles

	Fresh Cycles	Frozen Cycles	P-value/adjusted
Number of cycles	143	217	
Age (years)	37.1 ± 4.9	39.5 ± 5.9	0.0001
AMH (ng/mL)	2.4 ± 2.2	2.4 ± 2.6	0.8457
Highest FSH (mIU/mL)	10.9 ± 11.2	11.5 ± 7.8	0.5717
Number embryos transferred	2.3 ± 1.0	2.1 ± 1.0	0.0874
Pregnancies (n/%)	45 (31.5%)	42 (19.4%)	0.0086/0.0451
Live births (n/%)	31 (68.9%)	26 (61.9%)	0.4934/0.4693
Miscarriages (n/%)	14 (31.1%)	16 (28.1%)	0.4934/0.4693

Table 4
Comparison of intermediate and poor prognosis autologous fresh non-donor cycles to frozen autologous non-donor cycles

	Fresh Cycles	Frozen Cycles	P-value/adjusted
Number of cycles	598	217	
Age (years)	42.2 ± 4.2	39.5 ± 5.9	< 0.0001
AMH (ng/mL)	0.9 ± 1.4	2.4 ± 2.6	< 0.0001
Highest FSH (mIU/mL)	15.8 ± 12.9	11.5 ± 7.8	< 0.0001
Number embryos transferred	2.2 ± 1.2	2.1 ± 1.0	0.3874
Pregnancies (n/%)	37 (6.2%)	42 (19.4%)	<0.0001/0.0028
Live births (n/%)	22 (59.5%)	26 (61.9%)	0.8242/0.4921
Miscarriages (n/%)	15 (40.5%)	16 (28.1%)	0.8242/0.4921