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Original Article

# Cost-effectiveness of freeze-all policy – A retrospective study based upon the outcome of cumulative live births☆

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ABSTRACT

*Object:* We have previously reported that cumulative live birth rates (CLBRs) are higher in the freeze-all group compared with controls (64.3% vs. 45.8%, p = 0.001). Here, we aim to determine if the freeze-all policy is more cost-effective than fresh embryo transfer followed by frozen-thawed embryo transfer (FET).

*Materials and methods:* The analysis consisted of 704 ART (Assisted reproductive technology) cycles, which included in IVF (In vitro fertilisation) and ICSI (Intra Cytoplasmic Sperm Injection) cycles performed in Taichung Veterans General Hospital, Taiwan between January 2012 and June 2014. The freeze-all group involved 84 patients and the fresh Group 625 patients. Patients were followed up until all embryos obtained from a single controlled ovarian hyper-stimulation cycle were used up, or a live birth had been achieved. The total cost related to treatment of each patient was recorded. The incremental cost-effectiveness ratio (ICER) was based on the incremental cost per couple and the incremental live birth rate of the freeze-all strategy compared with the fresh ET strategy. Probabilistic sensitivity analysis (PSA) and a cost-effectiveness acceptability curve (CEAC) were performed.

*Results:* The total treatment cost per patient was significantly higher for the freeze-all group than in the fresh group (USD 3419.93 ± 638.13 vs. $2920.59 ± 711.08 p < 0.001). However, the total treatment cost per live birth in the freeze-all group was US $5319.89, vs. US $6382.42 in the fresh group. CEAC show that the freeze-all policy was a cost-effective treatment at a threshold of US $2703.57 for one additional live birth. Considering the Willingness-to-pay threshold per live birth, the probability was 60.1% at the threshold of US $2896.5, with the freeze-all group being more cost-effective than the fresh-ET group; or 90.1% at the threshold of $4183.8.

*Conclusion:* The freeze-all policy is a cost-effective treatment, as long as the additional cost of US $2703.57 per additional live birth is financially acceptable for the subjects.



## Introduction

Fresh embryo transfer (ET) is currently the standard procedure in Assisted Reproductive Therapy. In recent years the 'freeze-all' policy has become increasingly popular, in which all embryos are cryopreserved for future transfers in subsequent cycles [1]. Studies have been done to compare success rates between freeze-all and fresh ET. The freeze-all strategy is mostly used when looking at a number of considerations: in preventing the ovarian hyperstimulation syndrome (OHSS), arranging pre-implantation genetic testing for monogenic disorders or structural rearrangements (PGT-M or PGT-SR), preimplantation genetic testing for aneuploidy (PGT-A), and avoiding the transfer of embryos to an impaired endometrium such as premature progesterone elevation owing to controlled ovarian hyperstimulation (COH) [2–5]. Growing evidence has shown that the FET can improve perinatal outcome by reducing ectopic episodes, preterm births, low birth weights and young gestational age [6,7].

☆ The material contained in this manuscript has not been previously published and is not being concurrently submitted elsewhere.

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Whether the freeze-only strategy is more expensive remains unclear, particularly when considering the additional costs of embryo cryopreservation, endometrial priming, extra medication use, hormonal measurements, and ultrasound scanning for FET. In our previous study, we retrospectively analyzed our data and found that the CLBRs were significantly better in the freeze-all group than in the fresh group (64.3% vs. 45.8%, $p = 0.001$) [8]. But what about the increased costs in the freeze-all group? The main goal of this study was to evaluate the cost-effectiveness between the freeze-all technique against the fresh embryo transfers.

## Materials and methods

### *Study participants*

All of the patients ($n = 853$) analyzed had undergone the procedures of COH and IVF/ICSI at our medical center (Center for Reproductive Medicine in the Division of Reproductive Endocrinology and Infertility, Department of Obstetrics, Gynecology and Women's Health, Taichung Veterans General Hospital, Taichung, Taiwan), during the period from January 2012 to June 2014. Patients were followed up until November 2017. We excluded those cycles in which no oocyte retrievable or any embryos transferable ($n = 52$), where there was a donated oocyte ($n = 1$), if a patient was planned for PGS/PGD ($n = 7$) or where oocytes were collected prior to the study period ($n = 2$). The study group (freeze-all policy) including patients whose embryos were cryopreserved for later FET without fresh ET. The control group (fresh ET) including patients who received fresh ET cycle ± subsequent FET. After excluding patients whose embryos were not yet completely transferred, the study group had 84 cycles, and the control group had 625 cycles. Details of the two groups have been reported earlier [8]. Patients were further divided according to their age and the number of OPU (i.e., OPU <4, OPU 4 to 15 and OPU >15).

In the study group, the clinical reasons for not adopting the fresh ET included the following: a high serum progesterone (P4) level (P4 >1.5 ng/mL) on the day of triggering ovulation ($n = 44$), a high risk of OHSS ($n = 10$), adenomyosis or endometriosis with a high serum CA-125 level ($n = 16$), and personal considerations such as a need to accumulate embryos or inconvenient timing ($n = 14$).

### *The procedures of IVF*

Patients underwent ovarian stimulation, oocyte retrieval and embryo transfer according to the procedures previously described [8]. Which protocol (either agonist or antagonist protocol) to use for the patient was at the discretion of the caring physician. Stimulation was monitored using transvaginal ultrasound. Ovulation triggering was induced by injecting the recombinant hCG (Ovidrel, Merck Serono), and/or GnRH agonist (in patients with a predicted high risk of OHSS). Ultrasound-guided transvaginal oocyte retrieval was carried out approximately 35–36 h post-triggering. Oocytes were either inseminated (IVF) or underwent ICSI approximately 4–5 h after collection with fertilization confirmed 16–18 h afterwards. For the fresh group, D2 or D3 cleavage stage embryos or D5 blastocysts were transferred in their fresh cycle. The surplus embryos were cryopreserved through vitrification by CryoTop (before July 2013) or CryoTech (after July 2013), according to the method of Kuwayama [9,10]. In the study group, embryos were cryopreserved by vitrification either at the 2 pronuclear stage (2 PN), cleavage embryo stage (day 2–3) or blastocyst stage (day 5–6). The endometrial preparations in the following frozen ET cycles were programmed either by hormone replacement cycles or modified natural cycles, depending on the individual conditions of each patient. Details of the endometrium priming and luteal phase support have been reported earlier [8].

### *Outcome measures*

The follow-up analysis (performed until November 2017) included only subjects who were already pregnant or had completed the replacement with all available frozen embryos. A live birth was defined as the delivery of a live infant after at least 24 weeks of gestation. The CLBRs obtained with fresh and/or vitrified embryos from the same oocyte retrieval cycle were then determined by counting the first live birth which resulted from either fresh or FET cycles. The total costs incurred during the treatment were calculated.

The outcome measures included both the costs and effectiveness of the two different strategies in the study, based on hospital charges for the patients. Charges included all treatment-related direct healthcare costs. The costs were based on the real cost of each patient, as recorded in their clinical records, and in the database of our Clinical Information Research & Development Center in TCVGH. The cost of OPU included charges for the procedures regarding oocyte retrieval, pre-op test, anesthesia, insemination and embryo culture costs. The costs of for hormonal testing included the test of FSH, estradiol, progesterone and LH during the COH and FET cycles. The costs of ultrasonography included those involved in monitoring during the COH and FET cycles. The cost of COH medication included drugs for COH and trigger of ovulation. The cost of luteal phase support (LPS) medication was accumulated up until the day of the hCG test for an unsuccessful pregnancy, a gestational age of 8 weeks (for fresh ET), of 10 weeks (for frozen ET) or a confirmed missed abortion if pregnancy failed later. The cost of miscarriage management included ultrasound monitoring, OPD follow up, medication and surgery for missed abortions. The cost of ectopic pregnancy included HCG level monitoring, and MTX or surgery. The cost of OHSS was applied to only those patients who had visited an ER or had been admitted for abdominal tapping, hydration and close observation. Other costs included fresh ET, embryo cryopreservation, and embryo thaw with FET, all of which were all calculated separately.

We excluded for calculation, any costs supported by the individuals, including transport, absence from work or examination for pregnancy assistance. For an easy comparison with other countries, all charges, originally paid in Taiwanese Dollars (NTD), were converted to their equivalent in US dollars (USD), at the exchange rate of 31.07 NTD to 1 USD, after the study was completed. There were some patients, including 3 in the freeze-all group and 4 in the fresh group who received oocyte retrieval and embryo transfers in our hospital, but later received medication in the local clinics allied with our hospital. Their medication costs, along with the costs for hormone measurements and ultrasound scans at those clinics were different from those in our hospital and were substituted with our average costs for the purpose of consistency.

### *Statistical analyses*

Data was presented as the mean ± Standard Deviation (SD), or as a percentage. Group comparison was performed using the Chi-square test, or Student t-test, using SPSS (Version 18). Significance of differences was set at $p < 0.05$ for all the above tests. In order to conduct probabilistic sensitivity analysis (PSA), we generated 1000 pseudo-replicates based on the bootstrap method, which is a resampling technique with replacement and can be implemented using the R programming language [11]. Based on the 1000 pseudo-replicates, we could draw a cost-effectiveness plane (C-E plane) as shown in Fig. 1, which outlines the mean differences

in costs (incremental cost) per couple on the y-axis, and the incremental effectiveness in the live birth rates (incremental effectiveness) on the x-axis. To summarize the information on uncertainty in the cost-effectiveness estimates, we also generated a cost-effectiveness acceptability curve (CEAC), which was expressed as an incremental cost-effectiveness ratio (ICER) in relation to the possible values of the cost-effectiveness threshold.

## Results

The basic characteristics of the patient groups have been reported in our previous study [8]. The fertility outcomes and complications are shown in Table 1. The overall CLBRs in the study group were significantly higher 64.3% (54/84), than those in the controls, 45.8% (286/625) ($p = 0.01$). The fresh group had a higher ectopic pregnancy rate (fresh group vs. freeze-all group: 14.3% vs. 0% respectively), and a higher miscarriage rate (9.28% vs 2.3% respectively). The freeze-all group had more moderate to severe OHSS patients requiring abdominal tapping (fresh group vs. freeze-all Group 0.32% vs. 7.1% respectively).

The total treatment costs per patient were significantly higher in the freeze-all group than in the fresh group ($3419.93 ± 638.13 vs. $2920.59 ± 711.08 respectively, $p < 0.001$). However, the total treatment cost per live birth was more cost-effective in the freeze-all group ($5319.89) compared with the fresh group ($6382.42). Breakdown of the treatment costs are shown in Table 2.

The total treatment cost per patient in those subgroups with OPU <4 was $2825.42 ± $680.32 in the freeze-all group, compared with $2392.24 ± $655.17 ($p = 0.028$) in the fresh group. The total treatment cost per *live birth* was $12,243.49 in the freeze-all group, compared with $12,758.6, in the fresh group. In the subgroup of OPU between 4 and 15, the total treatment cost per patient was $3400 ± $588.36 in the freeze-all group, compared with $2868.59 ± $679.57 in the fresh group ($p < 0.001$). The total treatment cost per *live birth* was $5829.33 in the freeze-all group, compared with $7021.89 in the fresh controls. In the subgroup with OPU >15, the total treatment cost per patient was $3660.78 ± $528.29 in the freeze-all group, compared with $3470.36 ± $756.75 ($p = 0.164$) in the fresh group. The total treatment cost per *live birth* was $4270.92 for the freeze-all group, compared with $4296.63 in the fresh group.

The cost-effectiveness plane (Fig. 1) shows the results of the PSA based on 1000 bootstrap pseudo-replicates, by which the uncertainty (variation) of the ICER was evaluated. Since the normality assumption does not hold for the pseudo-replicates of ICER, we considered constructing a confidence interval (CI) using the percentile bootstrap method. The 95% CI of the ICER ranged from $1704.48 to $5748.1. Out of 1000 replicates, 9.9% resulted in positive incremental effectiveness and positive incremental costs, as shown in the first quadrant of Fig. 1, indicating that a high effectiveness with the freeze-only strategy occurs with a higher probability at a high cost compared to a low cost. Fig. 2 displays a CEAC, which shows the probabilities of the freeze-only strategy being cost-effective over the fresh-ET strategy at different WTP thresholds. The data shows that at the WTP threshold of $2252.8, $2574.66, $2896.5, $3540.16 and $4183.83 per live birth, the probability of the freeze-only strategy being more cost-effective than the fresh-ET strategy was 25.6%, 43.2%, 60.1%, 81.1% and 90.1%, respectively.

Due to the CLBRs were significantly improved in the subgroup of OPU 4–15 [8]. We also do the cost-effective analysis in this subgroup. The results also showed that a high probability of the freeze-all policy being more cost-effective than the fresh ET (Fig. 3 and Fig. 4).

## Discussion

Our results show that the freeze-all policy is more cost-effective in the freeze-all group than in the fresh controls, in terms of live birth outcome, and treatment cost per *live birth*. This advantage was particularly clear in the *normal responder subgroup* (OPU 4–15). To the best of our knowledge, only three studies have been published evaluating the cost-effectiveness of the freeze-all policy, and their results are inconsistent with one another. Our results are compatible with those of Roque and colleagues [12] in that this strategy is

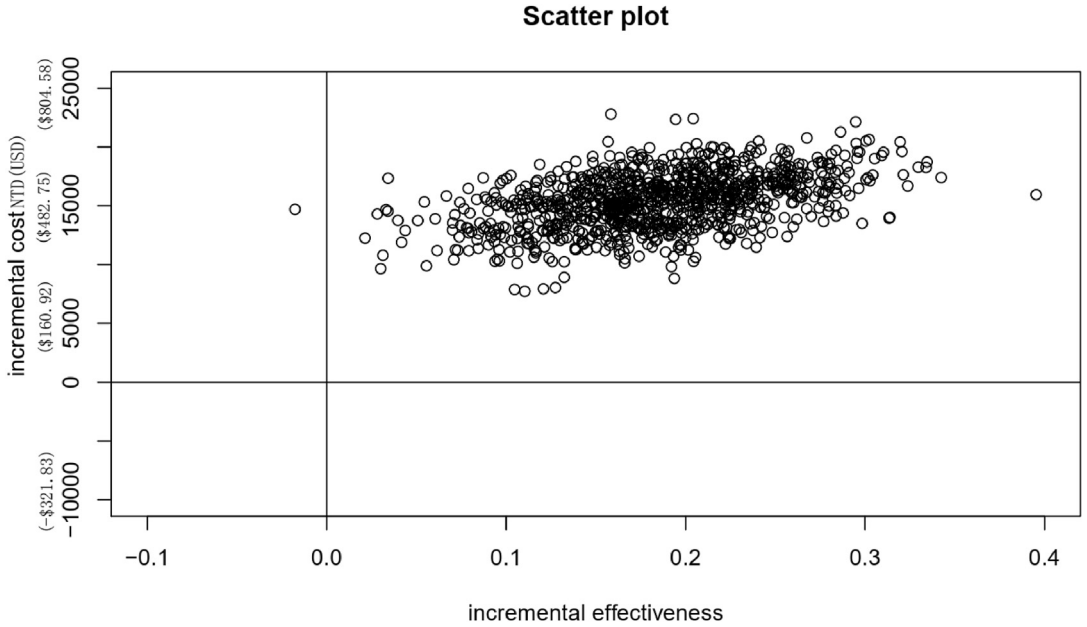


**Fig. 1.** Cost–Effectiveness Plane: Scatter plot showing the mean differences in costs per patient (incremental cost) and in the live birth rates (incremental effectiveness). Note this Cost–Effectiveness Plane represents results of the Probabilistic Sensitivity Analysis based on bootstrapping 1000 trials. IC: incremental cost, NTD; IE: incremental effectiveness, %. (I) North-East quadrant: trials in which Freeze-only strategy increased effectiveness at increased cost. ICERs in these trials have positive values. (II) South-East quadrant: Trials in which Freeze-only strategy increased effectiveness at decreased cost. ICERs in these trials are negative values.

**Table 1**
Fertility outcomes and treatment complications after one completed IVF/ICSI cycle, *P < 0.05

| | Fresh (625) | Freeze-all (84) | P value |
|---|---|---|---|
| LB per ET cycle (%) | | | |
| Fresh cycle | 196/625 (31.4%) | 0 (0%) | |
| 1st frozen | 72/145 (49.6%) | 42/84 (50%) | 0.959 |
| 2nd frozen | 13/23 (56.5%) | 10/19 (52.6%) | 0.801 |
| 3rd frozen | 3/8 (37.5%) | 1/3 (33.3%) | 0.898 |
| 4th frozen | 2/2 (100%) | 1/1 (100%) | |
| Cumulative Live birth n (%) | 286 (45.8%) | 54 (64.3%) | 0.04* |
| Treatment complication, n (%) | | | |
| Ectopic pregnancy | 5 | 0 | 0.41 |
| Miscarriage | 58 (9.28%) | 2 (2.3%) | 0.033* |
| Moderate/severe OHSS go to ER or admission | 2 (0.32) | 6 (7.1%) | <0.001* |

**Table 2**
Costs in the two study groups (in USD), Costs are expressed as the mean ± SD, **P < 0.001.

| | Freeze-all (n = 84) | Fresh (n = 625) | *p* value |
|---|---|---|---|
| OPU | 1118.46 ± 288.98 | 995.83 ± 245.57 | **<0.001**** |
| COH medication | 1296.37 ± 467.76 | 1345.84 ± 482.63 | 0.376 |
| Hormonal test | 87.48 ± 23 | 69.17 ± 18.21 | **<0.001**** |
| Ultrasonography | 104.89 ± 29.65 | 67.15 ± 28.4 | **<0.001**** |
| Fresh ET | – | 165.54 ± 11.29 | |
| LPS fresh cycle | – | 43.17 ± 64.74 | |
| Embryo cryopreservation | 349.8 ± 154.76 | 129.13 ± 182.68 | **<0.001**** |
| EM priming | 90.54 ± 57.65 | 20.71 ± 49.61 | **<0.001**** |
| LPS FET cycle | 80.71 ± 92.83 | 17.33 ± 65.64 | **<0.001**** |
| Embryo thaw and FET | 293.81 ± 141.2 | 66.7 ± 137.97 | **<0.001**** |
| Total cost | 287274.2 | 1825370.7 | |
| Total treatment cost per patient | 3419.93 ± 638.13 | 2920.59 ± 711.08 | **<0.001**** |
| Treatment cost per live birth (mean) | 5319.89 | 6382.42 | |
| Miscarriage management cost | 6.31 ± 49.67 | 16.67 ± 96.75 | 0.335 |
| Ectopic pregnancy cost | – | 12.97 ± 145.24 | |

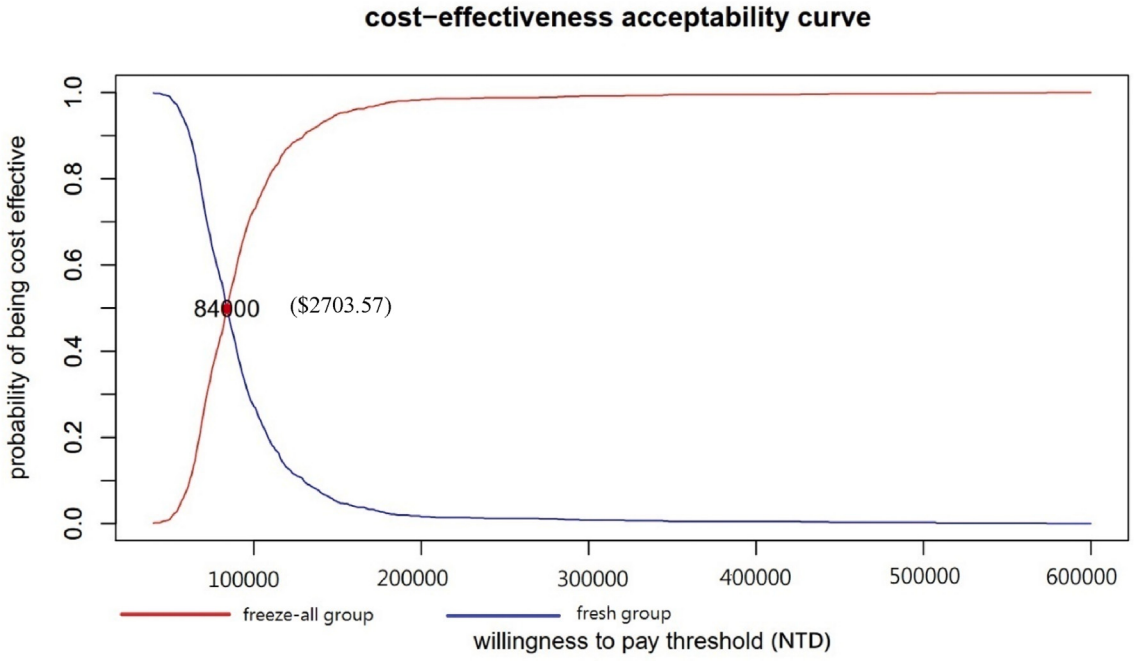


**Fig. 2.** Cost-effectiveness acceptability curves for a freeze-only versus fresh embryo transfer strategy. CEACs showing freeze-all ET and fresh ET have equal probabilities of being cost-effective at a threshold of $2703.57 (84,000 NTD). Beyond this threshold, freeze-all policy had a higher probability of being cost-effectiveness.

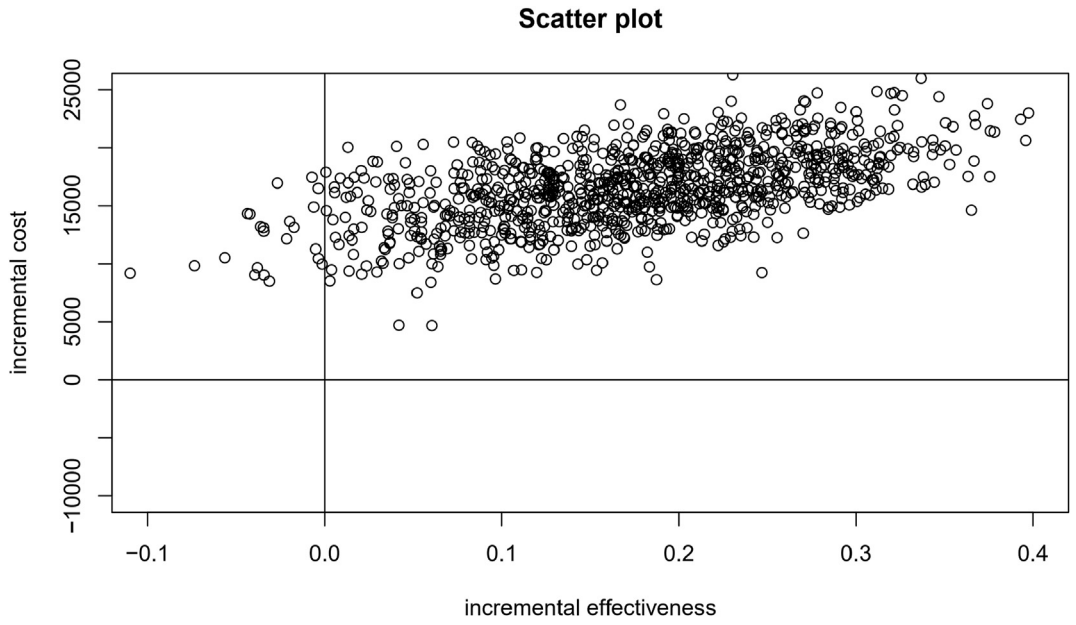


**Fig. 3.** Cost–Effectiveness Plane for subgroup of OPU 4–15: Scatter plot showing the mean differences in costs per patient (incremental cost) and in the live birth rates (incremental effectiveness). This Cost–Effectiveness Plane represents results of the Probabilistic Sensitivity Analysis based on bootstrapping 1000 trials. Among the 1000 pairs, 978 pairs have positive incremental effectiveness and positive incremental cost, resulting in positive ICERs. 22 pair have negative incremental effectiveness and positive incremental.

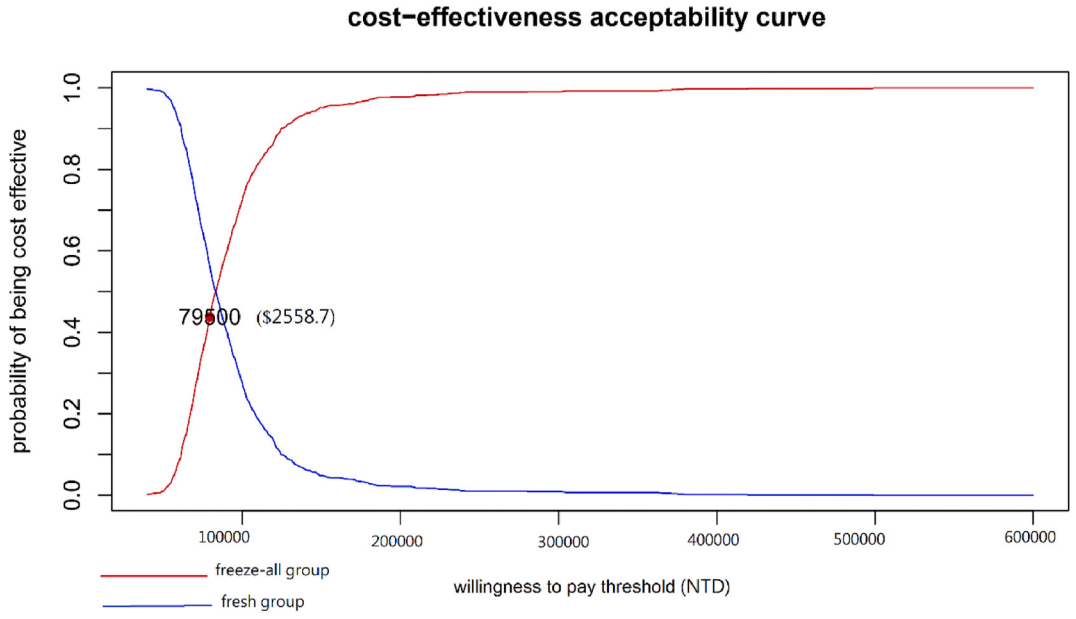


**Fig. 4.** Cost -effectiveness acceptability curves (CEAC) for a freeze-only versus fresh embryo transfer strategy of the subgroup of OPU 4–15. CEACs showing freeze-all ET and fresh ET have equal probabilities of being cost-effective at a threshold of $2703.57 (84,000 NTD). Beyond this threshold, freeze-all policy had a higher probability of being cost-effectiveness.

also more cost-effective when compared with fresh embryo transfers. The total cost (in USD) per *ongoing pregnancy* is statistically lower in the freeze-all cycles ($19,156.73 ± 1732.99), when compared with the fresh cycles ($23,059.72 ± 2347.02). Their study group included patients with normal responders (yet excluded patients with an antral follicle count (AFC) of ≤5, and those with estradiol >3000 pg/mL and/or >15 follicles on trigger day). In our subgroup analysis, the total treatment cost per *live birth* in normal responders (OPU 4–15) was also lower in the freeze-all group ($5829.33 vs. $7021.89).

A study performed by Enrico Papaleo showed that the total cost per patient and mean cost per *live birth* were similar (€6952 versus €6863), while the freeze-all strategy (€13,101, 95% CI 10,686 to 17,041, $14,401.9 95%CI 11,747.12 to 18,733.17) had a cost lower than the fresh transfer IVF (€15,279, 95% CI 13,212 to 18,030 $16796.20, 95% CI 14.523.95 to 19820.38) in the normal- and high-responders subgroups. These authors concluded that the freeze-all policy does not increase costs over the fresh transfer [13].

A recent randomized controlled trial (RCT) cost study on patients with non-PCOS revealed that the average cost per couple

(including direct medical costs relating to treatment, direct non-medical costs (such as travel and accommodation), and indirect costs (such as income lost)) were similar between the freeze-all group and fresh ET (€3906 vs. €3,512, p = 0.1). Additionally, the cost per live birth in the freeze-only group (€8037) is similar to the fresh ET group (€7425). In their probabilistic sensitivity analysis and CEAC, they found that at the patient's willingness to pay a threshold of €300,000, there was a 58% probability that the freeze-only strategy was more cost-effective than the fresh ET strategy. These authors concluded that from the perspective of patients, the freeze-only strategy was not more cost-effective than fresh ET [14]. Their results are incompatible with ours. As shown in Fig. 2, our CEACs data shows that the freeze-all group and fresh ET group have equal probabilities of being cost-effective at a threshold of $2703.57 per live birth. Beyond this threshold, the freeze-all policy has a higher probability of being more cost effective. At a threshold of $4183.8 (€3648.01), a probability of 90.1% was found, with the freeze-only strategy being more cost-effective than the controls. However, our data did not include direct non-medical costs and indirect costs.

For our patients, the main part of the total cost (in both groups it was consistently the cost of COH medication) (37.9% in the freeze-all group and 46.1% in the fresh group), followed by the oocyte retrieval procedure (32.7% in the freeze-all and 34.09% in the fresh group). Embryo transfer is a procedure constituting 8–9% of the total cost in both groups. This is an observation different from the previous study, in which embryo transfer procedures accounted for >40% of all costs in both strategies [13]. As our analysis was based on our real-life IVF data and our own contemporary medical costs, other centers may have health care and ART cost infra-structures different from ours. For example, our total treatment cost and treatment per live birth cost were much lower than those in the US and Europe [12,13]. Additionally, in our study, the additional cost of cryopreservation (10%) and medicine for endometrial preparation (0.7%) formed only a small part of the total cost for freeze-all patients. Therefore, this could contribute to more cost-effectiveness for freeze-all patients in our ART program.

Nonetheless, the total treatment cost per patient was still significantly higher in the freeze-all group. Owing to the higher CLBR in the freeze-all group, the policy appears to be more cost-effective. The same trend was seen in the normal responder group, in which the CLBR was also significantly higher in the freeze-all group. In the high responder group, the total treatment cost per patient was similar in the two groups, and the treatment cost per live birth was also not different, owing to the similar CLBR (85.7% vs 80.8%). Therefore, at our institute, if a patient is a high responder, the two strategies are equally suitable. In the low responder group, the total cost per patient was significant higher in the freeze-all group, and the CLBRs were similar (23.1% vs 18.8%) in the two groups. Therefore, our results suggest that if a patient is a poor responder, her better cost-effective option is the fresh transfer.

With regards to moderate/severe OHSS, our results show that the incidence is higher in the freeze-all group. Previous studies also showed conflicting results, Shapiro et al. Vuong et al. and Aflatoonian et al. showed that the OHSS risk was not different in elective FET (eFET) or fresh ET [15–17]. Additionally, a study by Shi et al. favored the eFET group [18]. One possible explanation for our result is related to the retrospective nature of our study, as we chose patients with a risk of OHSS to receive the freeze-all policy. In our study, moderate/severe OHSS patients in the freeze-all group all received long protocols, and their numbers of oocytes obtained were all >26. During the study period, long protocol was our protocol of choice for good responders. The standard approach to prevent OHSS during that time was embryo cryopreservation, together with dopamine receptor agonist, cabergoline [19].

We did observe in the freeze-all policy a small reduction in the risk of ectopic pregnancy, although the drop was not statistically significant. These ectopic pregnancies in the fresh group all took place during the fresh ET cycle, rather than the following FET cycle. This result of ours is consistent with previous studies [20,21].

Our study had some limitations. First, due to the nature of this retrospective study, there must be some selection bias. A multivariate analysis with a correction of the results for confounders may be done in a subsequent study after we collect more patients and data. However, since our primary result is CLBR, some bias may be overlooked, such as the different stages of embryo transfer [22,23]. Second, the sample size of the freeze-all policy was also relatively small. Third, we analyzed only direct medical costs. Any travel and accommodation expenses, along with income lost were not included due to technical complexities and variabilities, although the freeze-all policy may in reality generate a higher cost for travel and accommodation [14]. Additionally, we only analyzed medical costs until the gestational age of 10 weeks, rather than the costs incurred during the entire prenatal course and/or the following pregnancy-related complications. It has previously been reported that FET, compared with fresh ET, lowers the risk of placenta previa, placental abruption, low birth weights, small gestational age, and perinatal mortality [6,7]. However, the risks become higher for pregnancy-induced hypertension, postpartum hemorrhage, and a large gestational age. Finally, the cost calculations were based on domestic prices in our government hospitals in Taiwan. Country-specific prices and assumptions need to be considered before generalizing our present results with other centers or countries.

Currently, there is no clinical data supporting use of the freeze-all strategy for all patients submitted to IVF/ICSI. A recent systemic review and meta-analysis (including 11 RCTs), concluded that a significant increase in LBR with elective FET was found solely within hyper-responders, and in patients undergoing PGT-A, whereas the cumulative LBR is comparable to the general population (RR = 1.04; 95% CI: 0.97–1.11) [20]. There are centers which use eFET for all IVF/ICSI patients, and a reported 50.74% of patients could achieve a live birth after the first complete cycle via a freeze-all strategy [24]. Moreover, there has been one recent study which revealed that nearly 60% of the participants were in favor of eFET compared with fresh embryo transfer, assuming that the clinical pregnancy rate was equivalent. Most of the participants were assuming a freeze-all strategy could potentially reduce the risks for mother and/or child regardless of the delayed embryo transfer [25]. As the freeze-all policy becomes more popular, more evidence will be needed in order to consolidate its efficiency and cost-effectiveness, particularly when using randomized control studies. All of these are needed when counselling women who are willing to follow this strategy.

In conclusion, we have provided evidence in support of better IVF outcomes through use of the freeze-all policy, majorly for normal responders. We have also shown that the freeze-all policy is cost-effective for normal responders, and it can be implemented in routine practice.

## Details of ethics approval

Institutional Review Board, TCVGH, No. CE19011B.

## Declaration of competing interest

The authors declare no conflict of interest.

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