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Chapter

Effect of Assisted Reproductive Technology (ART) on Babies Born: Compared by IVF Laboratories of Two Countries

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Abstract

Assisted reproductive technology (ART) has been widely used for infertility treatment, but many people have concern about their baby's health. The objective of this chapter is to provide some detailed data about the effect of ART on human birth babies by analyzing the data from in vitro fertilization (IVF) centers in two countries. All recent records related to a baby's birth including mother's age, gestational days, baby's sex, and birth weight data were collected and analyzed according to fresh or frozen embryo transfer procedure. Normal delivery data without ART were used as control. The result showed that ART patient age is significantly older than non-IVF women; the gestation of fresh and frozen embryo transfer is the same as normal spontaneous conception gestation days, but women pregnant with multiple gestations have shorter gestational period and early birth rate as well as low birth weight; and there is no significant difference in the baby's weight between ART singleton babies and normal conception babies, but male babies weight is more than female babies, and multiple gestation's birth weights are significantly lower than singletons, while frozen embryo transfer babies have significantly heavier birth weight than fresh embryo transfer. Also, the frozen embryo transfer technique may significantly decrease premature birth rate. Thus, frozen embryo transfer may be recommended as a health strategy in ART.

Keywords: in vitro fertilization, frozen embryo transfer, baby birth, outcome

1. Introduction

This year is the 41st anniversary of the first test-tube human birth. In 1978, Dr. Robert Edwards, who won the Nobel Prize a few years ago, became the first physician to create a test-tube baby in a laboratory using an in vitro fertilization (IVF) technique on humans. Since this technique's creation, assisted reproductive technology (ART) has been widely used for the treatment of infertile couples to realize their dream of having a baby. Currently, this technology mainly contains in vitro fertilization (IVF) and its related procedures—intracytoplasmic sperm injection (ICSI), frozen embryo transfer (FET), and preimplantation genetic testing (PGT) including

aneuploidies (PGT-A, previously known as PGS), monogenic/single-gene defects (PGT-M, previously known as PGD), and chromosomal structural rearrangements (PGT-SR, previously known as PGD screen or PGS) [Note: New PGT nomenclature announced by the International Committee Monitoring Assisted Reproductive Technologies (CMART) in collaboration with the American Society for Reproductive Medicine (ASRM), the European Society of Human Reproduction and Embryology (ESHRE), and other professional medical societies (2018).] [1]. So far, more than 10 million IVF/ICSI and frozen embryo transfer babies have been born throughout the world. This technique indeed brings many infertile families happiness. However, the key point of the assisted reproductive techniques is that the patient needs to be injected with some medicine to stimulate the ovaries to produce more oocytes during one reproductive period cycle and the retrieved oocytes need to be fertilized under an in vitro environment, such as a laboratory. As more infants are born through this technique, there are concerns of whether fertilizing a female egg outside the human body will lead to any negative outcomes on the infant or the mother. For example, if a baby is born through IVF technique, will he or she be at an increased risk for any defects, or will an IVF baby have the same birthweight as a baby conceived naturally? Thus, many people have worried about ART neonatal health outcomes. Recently, many scientists, physicians, general practitioners, reproductive medicine experts, and social media all had a public debut together in Chicago to discuss the birth of the first IVF baby [2]. In early 2005, Bower and Hansen [3] published an overview for assisted reproductive technologies and birth outcomes based on systematic reviews and meta-analyses of randomized controlled trials which included perinatal mortality, preterm birth, low birthweight, and birth defects. In recent years, many IVF centers have reported the IVF baby birth outcome [4]. Overall, they showed that few differences between outcomes in ART twins compared with twins conceived spontaneously, but in singleton pregnancies, ART infants had twofold increases in risk of perinatal mortality, low birthweight and preterm birth, shortened gestational age, and increased birth defects [3]. In November 2005, the *Fertility and Sterility* journal published seven papers related to IVF increased birth defect, and all these studies indicated that ART techniques really increased some risk of birth defects [5–11].

In spite of ART resulting in some birth defects, in the past decade, many assisted reproductive centers have been built throughout the world, and more and more babies have been conceived by assisted reproductive technologies because these techniques provide many infertile couples the opportunity to have a child in their family. Thus, when we use these assisted reproductive technologies to treat infertility, we should concern more current birth baby situation. Currently, many articles and some reviews of ART effects on babies born have reported, but it is very difficult to find systematic data about ART outcomes on sex ratio and the effect of frozen embryo transfer. The objective of this study is to provide detailed data about the effect of ART on babies born by comparing data of two assisted reproductive centers from two different countries.

2. Materials and methods

2.1 Data source

In the USA, based on the reported Society for Assisted Reproductive Technology (SART) data of the Arizona Center for Reproductive Endocrinology and Infertility from 2010 to 2014, all records related to baby births including

mother's age, gestational days, baby sex, and birthweight were collected and analyzed according to fresh or frozen embryo transfer procedures. A total of 519 babies were born from 411 mothers from fresh embryo transfer or frozen-thawed embryo transfer techniques. Normal conception data without undergoing ART was also collected from a local obstetrical hospital as control (Tucson Medical Center).

In China, according to delivery records of the Obstetrical Department in Luohu Hospital of Shenzhen City, all data related to baby births including the mother's age, gestational days, sex, and birthweight and length were collected based on fresh or frozen embryo transfer procedures and natural conception delivery situations. A total of 856 babies were born from 657 mothers from fresh embryo transfer or frozen-thawed embryo transfer techniques. Normal conception delivery data without undergoing ART were also collected on babies from 265 mothers at the same obstetrical hospital as control.

2.2 Data classification

For the purpose of this analysis, all ART procedure includes IVF or ICSI treatment and FET data. Characteristics of infants in IVF and FET and control populations may be defined as different groups based on Helmerhorst et al. report [12]: gestation days as preterm (<37 weeks or 259 days) birth, very preterm (<32 weeks or 224 days) birth, and full-term birth and birthweight as low birthweight (<2500 g), very low birthweight (<1500 g), and normal birthweight.

2.3 Data analysis

The average and standard deviation (means) of all data were calculated by Microsoft Excel Ware. The significant differences between the averages were examined by student t-test statistical analysis, the baby sex ratio difference was examined by χ^2 test, and the difference between the percentages was examined by percentage test method. The differences were considered statistically significant at $P < 0.05$.

3. Results

Based on the analysis of the Arizona center data, the summary of birth information is listed in **Table 1**.

From this table, we may see some important points on outcomes of ART babies:

- A. Women undergoing ART with fresh embryo transfer and frozen embryo transfer are significantly older than women with normal conception women ($P < 0.05$), while the ages of women with multiple conception are significantly younger than normal ART procedures but older than women with natural pregnancy ($P < 0.05$).
- B. The gestational days following fresh embryo transfer are similar to babies born naturally (269.6 vs. 272.2 days, $P > 0.05$), but women with multiple gestations have a shorter gestation period (240 days, $P < 0.01$), and frozen embryo transfer women have a slightly longer gestation period (273 days, $P < 0.05$), but it did not have significant difference with normal conception infant (272.2 vs. 273 days, $P > 0.05$).

	Fresh IVF/ICSI single birth	Frozen embryo transfer single birth	Multiple births (twin/triplet)	Normal delivery birth
Patient no.	235	78	98	95
Patient age	33.84 ± 4.96 ^a 20–45	34.59 ± 4.11 ^a 24–45	32.95 ± 4.60 ^b 22–43	27.93 ± 5.68 ^c
Gestation days	269.57 ± 13.28 ^a 211–297	273.00 ± 11.12 ^b 234–293	239.60 ± 27.46 ^c	272.16 ± 8.8 ^{a,b}
Male no.*	126	36	100	47
Female no.	109	42	106	48
Male birthweight (g)	3227.71 ± 587.06 ^a 1470–4706	3401 ± 479.81 ^b 2637–4621	2242.21 ± 598.98 ^c 680–3402	3310.21 ± 461.88 ^b
Female birthweight (g)	3005.36 ± 427.15 ^d 1250–4337	3229 ± 423.34 ^a 2070–4163	2046.97 ± 654.98 ^e 482–3317	3188.5 ± 424.86 ^a
Total birthweight (g)	3122 ± 530.28 ^a 1250–4706	3308.83 ± 453.25 ^b 2070–4621	2133.17 ± 631.88 ^c 482–3402	3248.72 ± 445.41 ^b 2040–4690
<1500 g (%)	0.85	0	17	1.05
<2500 g (%)	11.50	3.85	67.96	4.21
Full-term birth (%)	86.81	92.31	27.83	94.73
Preterm (%)	11.49 ^a	7.69 ^b	51.76 ^c	5.27
Very preterm	1.7	0	20.41	0
Multiple rate	25.39	18.75		3.00

The different small letters indicate significant difference (P<0.05).

Table 1.

Summary for birth outcomes from various ART procedures of the Arizona IVF Center.

C. Based on gestational day analysis, there is no significant difference on very preterm birth (<224 days) or preterm delivery (<259 days) between fresh embryo transfer, frozen embryo transfer singletons, and normal deliveries (13.19 vs. 13.91%, $P > 0.05$), but multiple gestations have significantly higher preterm birth rate (72%), and frozen embryo transfer has lower early birth rate (7.69%, $P < 0.01$).

D. After χ^2 test, there is no significant difference in the incidence of male or female babies although fresh embryo transfer had a trend of more male babies (53.6%) and frozen embryo transfer had more female babies (53.8%).

E. Based on birthweight comparison, there is a significant difference among the singleton infant of fresh embryo transfer, frozen embryo transfer, and normal normally conceived babies ($P < 0.05$). The fresh embryo transfer infants have lower birthweight than frozen embryo transfer and normally conceived babies, but there is no difference between the frozen embryo transfer and natural conception babies. Also, male infant birthweight is heavier than female infant birthweight (3227 vs. 3005 g, $P < 0.05$), and multiple gestation birthweights are significantly less than singletons (2242 vs. 3227 g, $P < 0.05$), while frozen embryo transfer babies have significantly heavier birthweights than fresh embryo transfer (3401 vs. 3227 g, $P < 0.01$). Meanwhile we have found that 11.5% infants of fresh transfer singletons have less 2500 g birthweight, which is a significantly higher rate than frozen embryo transfer and natural conception babies. Further, 68% of multiple gestations have a very low birthweight.

F. The rate of multiple gestational births is significantly higher in ART group than the natural conception group.

Based on the China ART center data (**Table 2**), the following several points may be observed.

From this table, we may observe the following important points:

- a. Patients undergoing ART are significantly older than natural conception patients.
- b. The gestational days of singleton following fresh embryo transfer and frozen-thawed embryo transfer are similar to babies born from natural conception (268 vs. 270 days, $P > 0.05$), but multiple gestations have a shorter gestation period (253 or 251 days, $P < 0.01$). Based on gestational day analysis, there is no significant difference on preterm birth (<259 days) or full-term birth among fresh embryo transfer, frozen embryo transfer singletons, and natural conception babies ($P > 0.05$), but multiple gestations have a significantly higher preterm birth rate (41%) with fresh and frozen-thawed embryo transfer (52%, $P < 0.01$).
- c. Based on total birthweight comparison, there is no significant difference on the baby weight among the singleton infants of fresh embryo transfer, frozen embryo transfer, and normal conception babies ($P > 0.05$). However, the male babies with fresh and frozen-thawed embryos have a heavier birthweight than female babies ($P < 0.05$), but there is no difference between the male and female birthweights with natural conception babies. The multiple birthweights are significantly less than singletons ($P < 0.05$), while frozen embryo transfer

	Fresh IVF/ ICSI single birth	Frozen ET single birth	Multiple birth (fresh ET)	Multiple birth (frozen ET)	Naturally delivered baby birth
Patient no.	251	207	100	99	265
Patient age	33.7 ± 3.7 ^a	34.8 ± 4.2 ^a	32.2 ± 3.8 ^a	33.1 ± 3.2 ^a	27.2 ± 3.0 ^b
Gestation days	268.2 ± 11 ^a 231–294	268.1 ± 14 ^a 189–287	253 ± 12 ^b 210–273	251 ± 14 ^b 182–273	270.6 ± 16 ^a 235–289
Male no.	120	116	108	115	139
Female no.	131	91	94	81	126
Male birthweight (g)	3314 ± 560 ^{a,A} 2000–4900	3353 ± 474.76 ^{a,A} 1150–5900	2431 ± 382 ^b 1250–3250	2537 ± 393 ^{b,A} 1150–3600	3200 ± 600 ^a 1550–4850
Female birthweight (g)	3140 ± 510 ^{a,B} 1790–4300	3215 ± 423.34 ^{a,B} 1600–4200	2423 ± 381 ^b 1500–3500	2433 ± 461 ^{b,B} 930–3400	3200 ± 500 ^a 1750–4750
Total	3223.40 ± 476 ^a 1790–4900	3292.44 ± 557 ^a 1150–5900	2474.18 ± 398 ^b 1250–3650	2493.8 ± 442 ^b 930–3600	3200 ± 550 ^a 1550–4850
Full-term birth (%)	88.05 ^a	87.98 ^a	59.0 ^b	47.48 ^b	89.2 ^a
Early birth (%)	11.95 ^a	12.02 ^a	41.0 ^b	52.52 ^b	10.8 ^a

The different small letters indicate row significant difference, and the different capital letters indicate column significant difference.

Table 2.
 Summary of birth outcomes from the Chinese Luohu IVF Center.

babies have slightly heavier birthweight than fresh embryo transfer (3292 vs. 3223 g, $P < 0.05$).

d. Based on sex ratio analysis, there is a significant difference between the numbers of male and female infants in ART babies ($P < 0.05$). In general, there are more male than female babies (53.6 vs. 46.4%) in ART, which is similar to natural conception births (52.5 vs. 47.5%). However, the fresh embryo transfer showed less male than female babies (47.8 vs. 52.2%). In the frozen embryo transfer program, male babies were significantly higher than female babies (56 vs. 44%). In natural conception babies, although there is no statistically significant difference between sex ratio, 52.5% are male babies and 47.5% are female babies.

4. Discussion

Forty years ago, the first baby was born by IVF. So far, thousands of human IVF centers or clinics have been set up, and hundreds and thousands of IVF babies have been born all over the world [13–16]. This technology has brought many infertile families happiness. However, there has been a concern as to the safety of this technology and the health of the babies. Currently, many reports have shown that there is no clear evidence that these babies are more at risk from abnormalities than those born through natural conception. Indeed, it seems that certain types of abnormalities, such as chromosomal problems, are less common with IVF, but IVF babies tend to have more problems at birth, and stillbirth may be slightly more common. This may not be due to IVF technological problem, and it is probably because women who conceive through IVF are more likely to be at high risk in pregnancy. Different countries or different IVF centers often report various outcomes. In order to get a common knowledge of IVF's influence on birth, our study compared the outcomes of two different IVF laboratories in two different countries. The comparative results showed that the ages of patients undergoing IVF are significantly older than normal conception in both countries (**Figure 1**). This is mainly due to problems with infertility. Many patients tried to conceive by natural methods for many years, but they did not get pregnancy. Thus, these patients' final hope was to undergo IVF to resolve their problems. This often results in some high-risk complications due to the advancing age.

Figure 2 showed that the gestational days of two laboratories following fresh embryo transfer are similar to babies conceived naturally, but multiple gestations have a shorter gestational period (240 days at the Arizona center and 252 days at the Luohu center). The Arizona center had less gestational days because it had more triplets than the Luohu center, which had more twin gestations.

The gestational day analysis also showed that there is no significant difference on very preterm birth (<224 days) or preterm delivery (<259 days) between fresh embryo transfer, frozen embryo transfer singletons, and normal conceptions, but multiple gestations have significantly higher preterm birth rate, and frozen embryo transfer has lower preterm birth rate (**Figures 3 and 4**). The frozen embryo transfer showed a similar full-term birth to natural conception pregnancies (92 vs. 94%). Recently a meta-analysis confirmed that singleton babies conceived by frozen embryo transfers are at lower risk of preterm delivery, small for gestational age, and low birthweight, but it may increase risks of large for gestational age and macrosomia [17, 18]. Also, researchers from the USA found that extremely high estrogen levels at the time of embryo transfer may increase the risk that infants will be born small for their gestational age as well as an increased risk of preeclampsia. They proposed freezing embryos of women who

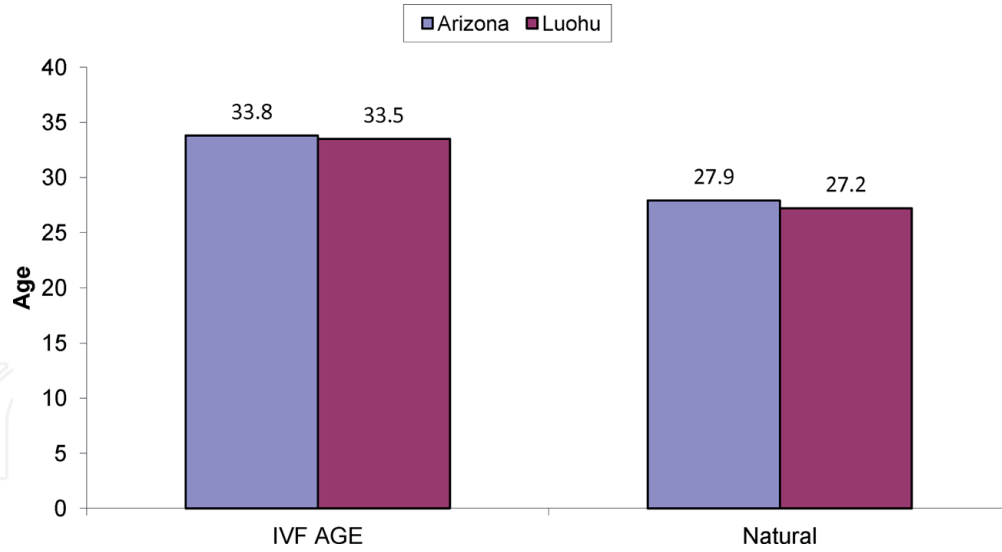


Figure 1.
 Age comparison of IVF patients and natural conception patients.

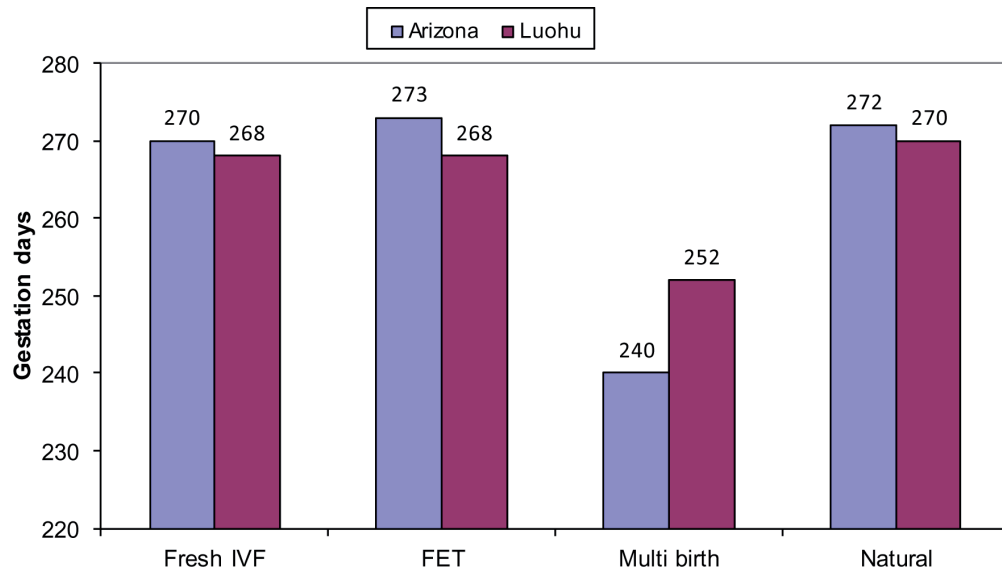


Figure 2.
 The comparison of gestational days with various ART procedures.

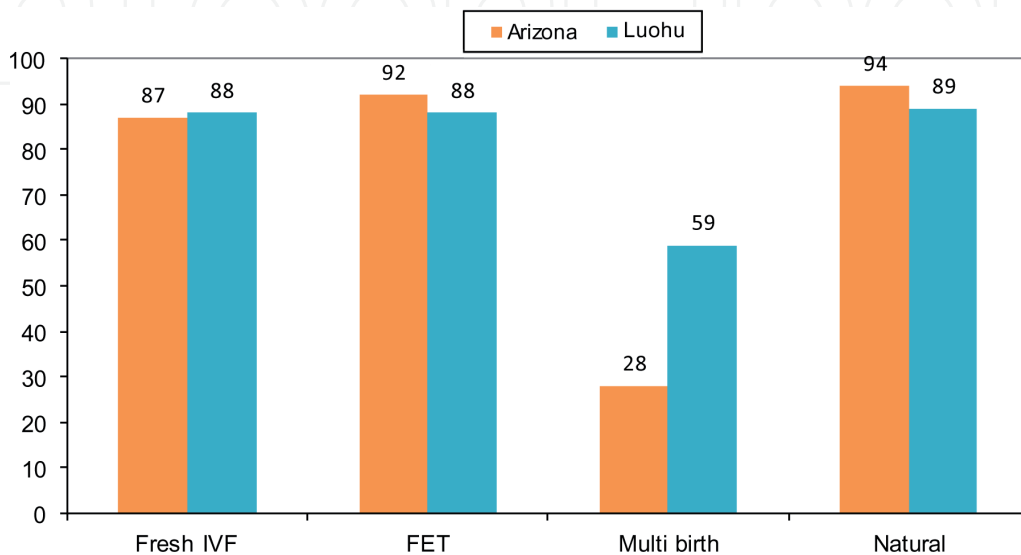


Figure 3.
 The comparison of full-term birth percentage in various procedures.

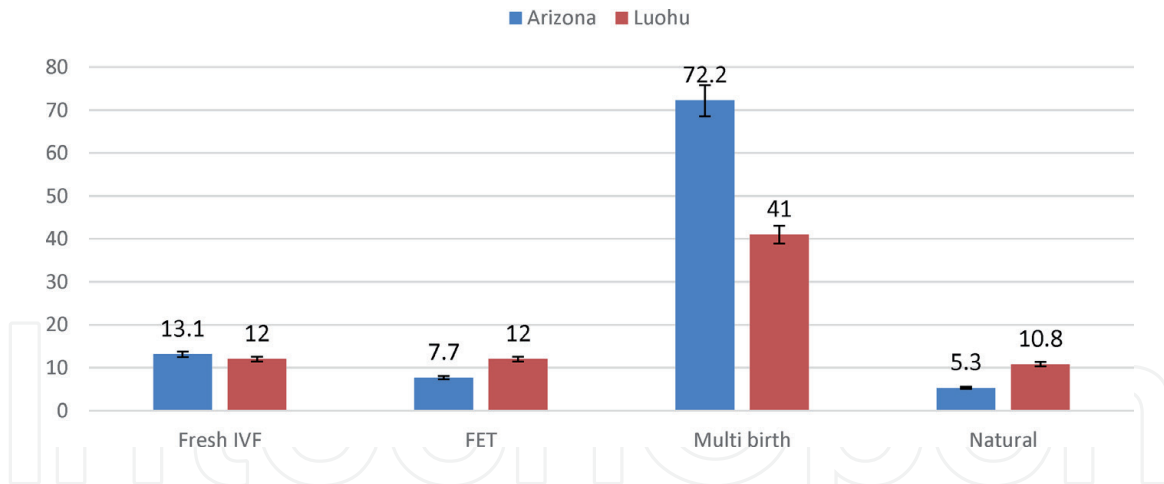


Figure 4.
The percentage of preterm birth with various procedures.

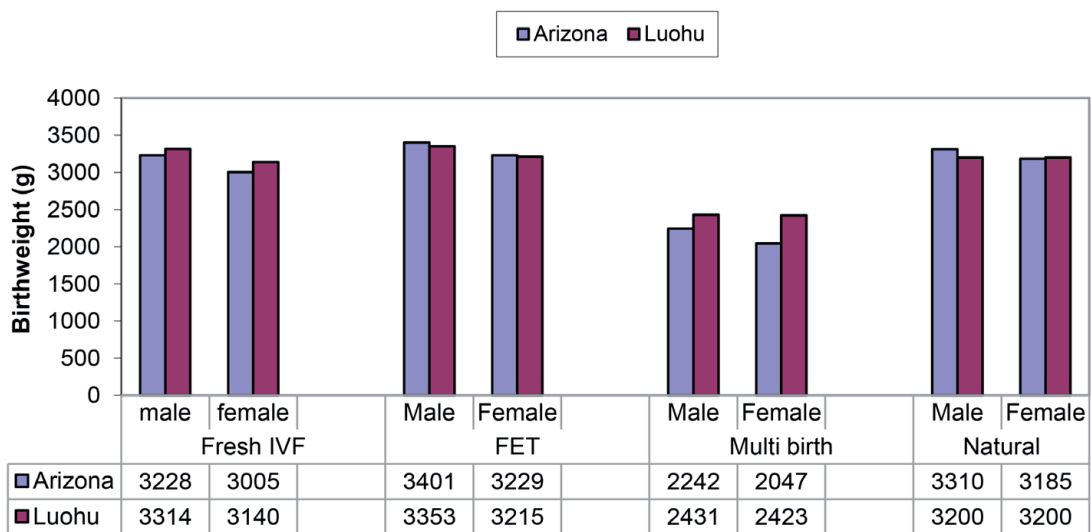


Figure 5.
The birthweight comparison of various procedures in male vs. female.

have excessively elevated estrogen at the time of egg collection, followed by embryo transfer in a later cycle when hormonal levels were closer to those of a natural cycle [17, 19].

Based on the total birthweight comparison (**Figure 5**), there is no significant difference on the baby weight among the singleton infants of fresh embryo transfer, frozen embryo transfer, and normal conception babies in the Luohu center. The fresh embryo transfer infants have a lower birthweight than frozen embryo transfer and natural conception babies in Luohu, but there is no difference between the frozen embryo transfer and natural conception babies at the Arizona center. Recently, a meta-analysis confirmed that singleton babies conceived by frozen embryo transfer were at lower risk than fresh embryo transfer [19, 20]. These results indicated that IVF technique shows no big effect on singleton IVF birth. However, multiple gestation birthweights are significantly less than singletons in the two laboratories. Further analysis indicated that male babies are heavier than female babies in all IVF groups.

According to sex ratio analysis, two laboratories displayed different results (**Figure 6**). At the Arizona center, the fresh embryo transfer often produced more male babies. This is due to the selection of fast-growing and good quality embryos on day 3 for transfer. Evidence shows that most of the fast-growing embryos are male [21]. After selection, some slow-growing embryos would be frozen, and after thawing and transfer, they often produce more female embryos. However, at the

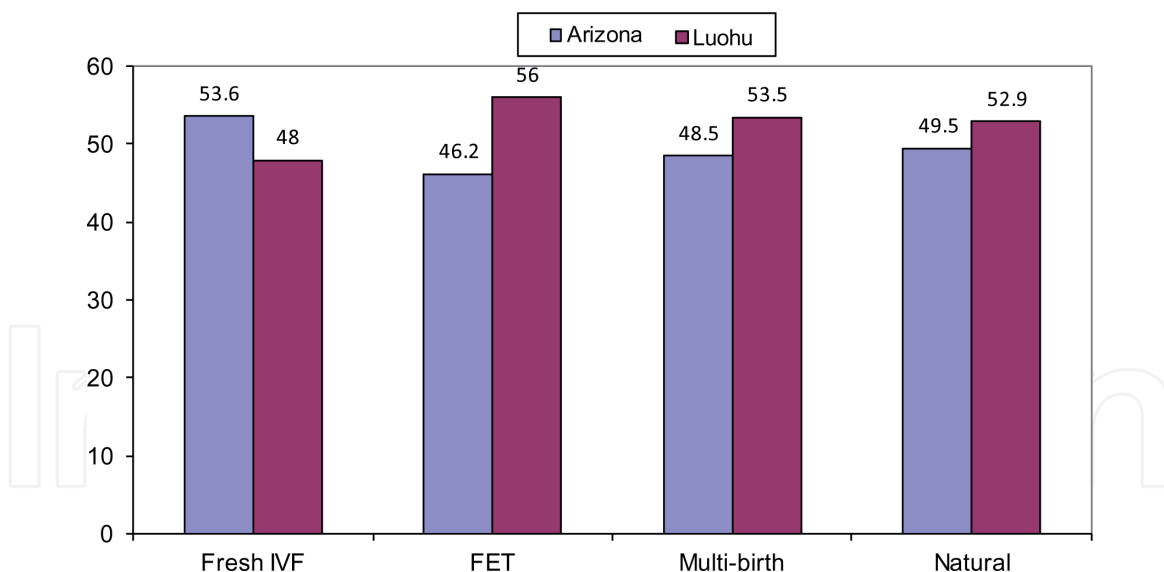


Figure 6.
Male baby percentage of various ART procedures.

Luohu center, their procedure was different from the Arizona center. Fresh embryo transfer produced more female babies, while frozen embryo transfer resulted in more male babies. Thatcher and colleagues [22] reported a higher proportion of male birth after IVF (64%), and Ghazzawi and colleagues [23] reported a higher proportion of female birth after ICSI (61.7%). More recently, Dean et al. [24] retrospectively analyzed the sex of the babies at birth following a single embryo transfer in Australia and New Zealand. There were 13,165 babies born from 13,165 women who had a single embryo transfer (SET) between 2002 and 2006. They reported that ICSI was associated with more females than males and IVF was associated with more males than females. Furthermore, they found that blastocyst transfer was associated with more males than females. They quoted the following sex birth: IVF with a single blastocyst, 56.1% males; IVF with a single cleaved embryo, 51.6 males; ICSI with single blastocyst, 52.5% males; and ICSI with single cleaved embryo, 48.7% males. Recently, Bu et al. [25] analyzed the data of 18 IVF centers in China. There were 62,700 male babies and 58,477 female babies, making the sex ratio 51.8% (male/female = 107:100). In univariate logistic regression analysis, sex ratio was imbalanced toward females at 50.3% when ICSI was performed compared to 47.7% when IVF was used ($P < 0.01$). The sex ratio in IVF/ICSI babies was significantly higher toward males in transfers of blastocyst (54.9%) and thawed embryo (52.4%) than transfers of cleavage stage embryo (51.4%) and fresh embryo (51.5%), respectively. Thus, the IVF technique itself could not change baby sex ratio, while different procedures or methods may change offspring sex ratio [26].

5. Conclusion

Generally speaking, the singleton birth from ART treatment does not have any significant differences from natural conception babies in gestational days, early birth rate, and birthweight, but multiple gestations often resulted in high early birth rate, lower birthweight, and shorter gestational days. The frozen embryo transfer technique may significantly decrease the early birth rate of babies and increase birthweight. Thus, frozen embryo transfer may be recommended as a health strategy in ART. IVF technique itself cannot change sex ratio, but different embryo selection and transfer methods may change sex ratio.

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