

ORIGINAL ARTICLE

From conception to childhood: Anthropometric characteristics of children conceived by assisted reproductive technologies in Kazakhstan

ZHANAR NURGALIYEVA¹, SEVARA ILMURATOVA², KANATZHAN KEMELBEKOV³, VYACHESLAV LOKSHIN², KARLYGASH ZHUBANYSHEVA⁴, AIGYUL IZHANOVA⁵, LYAZZAT UMBETYAROVA⁶, ROZA SEISEBAYEVA¹, BIBIGUL TUKBEKOVA⁷, LYAZAT MANZHUOVA⁸, TAKHMINA USSENOVA⁹

¹Department of Outpatient Pediatrics, School of Pediatrics, Kazakh National Medical University named after S.D.Asfendiyarov, Almaty, Kazakhstan; ²International Clinical Centre of Reproduction "PERSONA", Almaty, Kazakhstan; ³Department "Pediatrics-1", JSC South Kazakhstan Medical Academy, Shymkent, Kazakhstan; ⁴Department of Neonatology, Kazakh National Medical University named after S.D.Asfendiyarov, Almaty, Kazakhstan; ⁵Department of Internal Medicine, Kazakh National Medical University named after S.D.Asfendiyarov, Almaty, Kazakhstan; ⁶Department of Biophysics, Biomedicine and Neuroscience, Al Farabi Kazakh National University, Almaty, Kazakhstan; ⁷Department of Pediatrics and Neonatology, Karaganda Medical University, Karaganda, Kazakhstan; ⁸Scientific Center of Pediatrics and Pediatric Surgery, Almaty, Kazakhstan; ⁹Department of Gastroenterology, Kazakh National Medical University named after S.D.Asfendiyarov, Almaty, Kazakhstan.

ABSTRACT

Background and aim: As assisted reproductive technologies (ART) expand globally and in Kazakhstan, monitoring the long-term health of resulting offspring has become a public health priority. This study aimed to compare growth patterns and anthropometric characteristics in children under five years old born after ART versus natural conception (NC) to understand the influence of different conception modes.

Methods: A retrospective analysis was conducted on 120 ART-conceived children and 132 NC children, with measurements standardized using WHO weight-for-age, height-for-age, and weight-for-height charts.

Results: Results indicated that preterm births were 4.56 times more frequent in the ART group (95% CI: 2.06–10.07), contributing to a significantly higher incidence of low birth weight ($p=0.004$). Additionally, mothers in the ART group exhibited significantly higher BMI and weight compared to NC mothers ($p<0.001$). However, after age and sex standardization, no statistically significant differences in anthropometric indicators were found between NC and ART groups, nor between frozen and fresh embryo transfer cohorts. While



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Correspondence: Sevara Ilmuratova, MD, PhD / International Clinical Centre of Reproduction "PERSONA" / Bostandyk district, 32a Utepova street 050060, Almaty, Kazakhstan / E-mail: ilmuratova.s@gmail.com
ORCID: 0000-0001-5445-8293

the ART group showed a higher percentage of overweight children (8.3% vs. 4.5%), this was not statistically significant.

Conclusions: We conclude that ART is generally safe regarding physical development, as initial perinatal disparities tend to normalize by early childhood. (www.actabiomedica.it)

Key words: assisted reproductive technology (ART), in vitro fertilization (IVF), anthropometric characteristics, frozen embryo transfer (FET), Childhood Growth, Physical Development.

Introduction

Assisted reproductive technologies (ART) have become a cornerstone of modern reproductive medicine, frequently representing the only effective option for achieving parenthood among couples affected by infertility. Over the past four decades, the global use of ART has increased substantially, driven by the expanding availability of specialized reproductive centres and continuous technological and clinical advances that have enhanced treatment efficacy and improved patient outcomes (1,2). Globally, more than 13 million children have been born after ART (3), with approximately 2.6 million ART cycles performed annually, resulting in around 500,000 live births worldwide (4). In Kazakhstan, the field has seen rapid growth since the first ART-conceived birth in 1996, with over 40,000 children born to date and approximately 7,000 state-funded In Vitro Fertilization (IVF) cycles provided annually since 2021 (5–7). In that year alone, 20,380 ART cycles were performed nationwide, resulting in more than 6,000 live births. This rapid expansion has heightened scientific interest in the long-term safety and potential intergenerational effects of these technologies (8). While the majority of studies report no significant differences in anthropometric characteristics between ART-conceived and naturally conceived (NC) children (2,9), some investigations have identified variations in growth parameters at specific developmental stages (10,11). Furthermore, ART are continuously advancing, with an increasing number of novel techniques being incorporated into clinical practice. These innovations have been shown to significantly influence offspring outcomes. The first

successful pregnancy resulting from frozen embryo transfer (FET) was reported in 1983 (12). FET allows excess embryos to be stored and reduces the number of embryos transferred, which lowers the risk of multiple pregnancies. Consequently, FET is currently the most common method used as a supplement to IVF or IVF/ICSI (intracytoplasmic sperm injection). Current literature presents diverging hypotheses regarding the impact of FET on offspring. Several studies associate FET with a higher incidence of large-for-gestational-age (LGA) infants and macrosomia compared with fresh embryo transfer (Fresh-ET) and NC pregnancies (13–15). This observation is clinically significant, as LGA births may increase the risk of adverse obstetric and neonatal outcomes affecting both the mother and the fetus (16). Current literature presents diverging hypotheses regarding the impact of FET on offspring weight. While some identify a higher incidence of large-for-gestational-age infants (13–15,17,18), research by Ainsworth et al. (19) demonstrated that such associations often lose statistical significance when adjusted for maternal factors, including pre-pregnancy BMI, gestational weight gain, and breastfeeding practices. These findings underscore the importance of considering maternal factors when assessing ART outcomes. Elias et al. found that FET in IVF/ICSI is linked to lower risks of low birth weight and small for gestational age. Both Fresh-ET and FET were associated with higher preterm birth rates than spontaneous conception, but the risk was greater with Fresh-ET. FET was also uniquely associated with an increased risk of LGA infants, though the cause remains unclear. Maternal characteristics such as weight, smoking status, infertility diagnosis, race, socioeconomic status,

and ethnicity may influence neonatal risks after ART and warrant further study (20). An observational cohort study found no significant differences in childhood growth among full-term singletons conceived via FET, Fresh-ET, or IVF after adjusting for relevant parental factors (21). Vuong et al. reported that a freeze-all strategy does not adversely affect early childhood health and development (22). A Danish cohort study (23) found no link between ART and body mass index (BMI) at ages 5 to 8 when comparing ART with ovulation induction, intrauterine insemination, or between ICSI and conventional IVF. However, FET was associated with a modestly increased risk of obesity in offspring compared to Fresh-ET. A registry-based cohort study (24) demonstrated sex-specific differences in growth outcomes. Boys conceived by FET exhibited higher body weight and BMI and had a greater prevalence of overweight compared with those conceived by Fresh-ET, while no differences in height were observed. In contrast, among girls, no significant differences in height, weight, or BMI were identified; however, girls conceived via FET showed a slightly lower likelihood of being overweight compared with those conceived spontaneously. Thus, a review of existing publications provides conflicting results. The potential health risks to children associated with ART, compared to those conceived without ART, are significant for public health and require further study and guideline development. The aim of this study is to explore and compare growth patterns and anthropometric characteristics in children under five years of age born after ART and those conceived naturally in Kazakhstan.

Patients and Methods

Study design and patients

This study is a cross-sectional, observational controlled study utilizing a case-control design. Medical records of 120 women who successfully completed ART programmes resulting in live births were retrospectively reviewed at the PERSONA International Clinical Centre for Reproductive Medicine, the Institute of Reproductive Medicine, and the ECOMED

Clinic in Almaty. The inclusion criteria comprised successful ART outcomes following IVF or ICSI, including both Fresh-ET and FET, resulting in singleton or multiple live births between 2017 and 2022. Exclusion criteria included pregnancies achieved via intrauterine insemination (using partner or donor sperm), ART cycles involving donor gametes, and surrogacy arrangements.

Data collection

The ART cohort consisted of 120 children conceived by ART, while the control group included 132 NC children born during the same study period (2017–2022), with an overall age range of up to 60 months (5 years). Comprehensive maternal medical histories and anthropometric data of the offspring, including birth weight and other neonatal parameters, were collected for all participants in both cohorts.

Anthropometric assessment

Anthropometric measurements, including weight, height, head circumference, and chest circumference, were conducted in accordance with the WHO Child Growth Standards. To minimize physiological fluctuations, all measurements were performed in the morning, ideally on an empty stomach. For children up to the age of two years, measurements were taken in the supine position (Supine Length) using electronic scales with an accuracy of 10 grams and a horizontal infantometer. During length measurement, the child was placed in a recumbent position with the legs fully extended at the knees. For children older than two years, measurements were taken as Standing Height using electronic floor scales with an accuracy of 50 grams and a vertical stadiometer. The measurement procedure followed a standardized protocol: the child's heels, buttocks, shoulder blades, and the back of the head were required to remain in contact with the vertical stand. The head was positioned so that the Frankfurt plane (the line connecting the lower margin of the orbit and the upper margin of the external auditory canal) was strictly horizontal. Retrospective neonatal data (birth weight and length) were retrieved from the original medical birth records.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was applied to assess the normality of data distribution. As the anthropometric data followed a non-parametric distribution, continuous variables are expressed as Median and Interquartile Range (Me [IQR]). Comparisons between two independent groups (ART vs. NC and FET vs. Fresh-ET) were performed using the Mann-Whitney U test. Categorical data, including birth weight classes and WHO growth standard categories, are presented as absolute frequencies and percentages. These were compared using Pearson's chi-squared (χ^2) or Fisher's exact test where appropriate. To evaluate the risk of perinatal outcomes (e.g., preterm birth), Odds Ratios (OR) with 95% Confidence Intervals (CI) were calculated. A p-value < 0.05 was considered statistically significant.

Results

Study cohort and perinatal outcomes

The analysis of baseline characteristics revealed significant differences in maternal and perinatal factors

between the groups. Mothers in the ART group were significantly older than those in the NC group (median age 34 [IQR 30–38] vs. 28 [25–32] years; $p < 0.001$). Furthermore, the incidence of multiple pregnancies was substantially higher in the ART cohort compared to the control group (18.3% vs. 2.3%; $p < 0.001$). Regarding birth outcomes, NC children had a higher gestational age at delivery than ART-conceived children (median 39 [38–40] vs. 38 [36.3–39] weeks; $p = 0.001$). However, the sex distribution remained comparable between the cohorts, with boys representing 56.7% of the ART group and 56.8% of the NC group ($p = 0.981$). The median age of children at the time of examination was 14.5 months [IQR 8.0–22.0] for the ART group and 23.0 months [IQR 14.5–35.0] for the NC group ($p < 0.001$). While the study included children up to 60 months, the majority of the ART cohort (as shown in Figure 1) was followed up to 30 months (2.5 years).

Birth weight categories were analyzed for children born after ART in comparison to those conceived spontaneously, using the World Health Organization (WHO) classification (25):

- Normal weight 2500–3999g
- High birth weight >4000g
- Low birth weight <2500 g = 1500–2499g

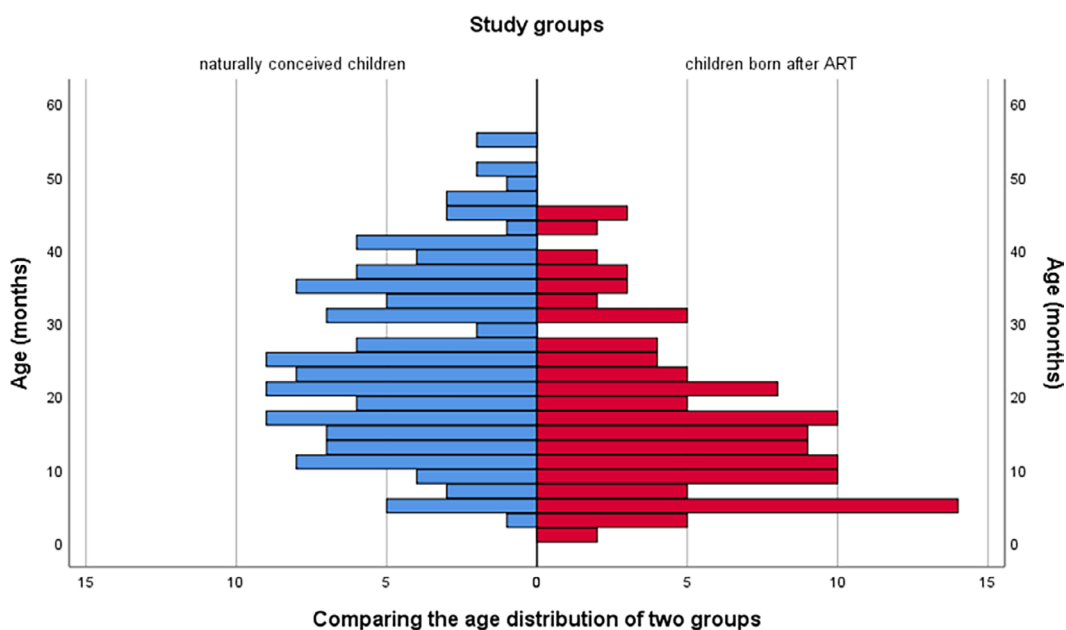


Figure 1. Distribution of study groups by age.

Table 1. Distribution of groups according to birth weight

Study groups	Birth weight categories					p
	2500-3999 g	>4000 g	1500-2499 g	1000-1499 g	<1000 g	
ART (n = 120)	69.2% (83)	10.0% (12)	18.3% (22)	1.7% (2)	0.8% (1)	<0.001* p ₁₋₃ =0.004
NC (n = 132)	86.4% (114)	7.6% (10)	5.3% (7)	0.8% (1)	0% (0)	

Note: Data are presented as percentage (absolute frequency). *Differences are statistically significant (p < 0.05).

Table 2. Distribution of groups according to birth weight among children conceived after FET or Fresh-ET

Study groups	Birth weight categories					p
	2500-3999 g	>4000 g	1500-2499 g	1000-1499 g	<1000 g	
Fresh-ET (n=29)	82.8% (24)	0% (0)	17.2% (5)	0% (0)	0.0% (0)	0.171
FET (n=91)	64.8% (59)	13.2% (12)	18.7% (17)	2.2% (2)	1.1% (1)	

Note: Data are presented as percentage (absolute frequency). *Differences are statistically significant (p < 0.05).

- Very low birth weight <1500 = 1000-1499g
- Extremely low birth weight <1000g

The distribution of birth weight categories within each study group is presented in Table 1.

Analysis of birth weight categories revealed statistically significant differences between the two groups (p<0.001), largely driven by a higher frequency of low birth weight in the ART group (18.3% vs. 5.3% in the NC group; p=0.004). This disparity is primarily attributed to the incidence of prematurity; preterm births (PTB) were 4.56 times more common in the ART group (95% CI: 2.06-10.07).

Birth weight category frequencies among children born after FET or Fresh-ET are presented in Table 2.

No statistically significant differences were found when comparing FET and Fresh-ET children (p = 0.171).

Comparison of anthropometric parameters

Anthropometric parameters for both study groups are summarized in Table 3.

At birth and at the time of examination, NC children exhibited significantly higher values of weight, supine length / standing height, head circumference

(HC), and chest circumference (CC) compared with ART children (birth: p < 0.001, p = 0.002, p = 0.008, p = 0.022; at examination: p < 0.001, p < 0.001, p = 0.015, p < 0.001, respectively). Median birth weight and length were lower in ART children than in NC children but remained within the normal range (birth weight: 3160 g vs. 3453 g; birth length: 51 cm vs. 53 cm).

Fresh-ET vs. FET

Anthropometric outcomes were further evaluated according to ART method. Data comparing FET and Fresh-ET children are presented in Table 4.

When comparing ART methods, no statistically significant differences were found in birth weight categories between FET and Fresh-ET children (p=0.171). Although measurements at the time of examination (weight, supine length / standing height, HC, CC) were significantly higher in the FET group, this was associated with the fact that FET children were older at the time of examination (median 17 months vs. 10 months; p=0.001). Birth anthropometric parameters, including gestational age, weight, and length, did not differ significantly between these two sub-groups.

Table 3. Comparison of anthropometric parameters between study groups

Anthropometric parameters	Study groups				p
	ART (n = 120)		Natural conception (n = 132)		
	Me [IQR]	min-max	Me [IQR]	min-max	
Birth weight (g)	3160 [2695-3600]	990-4380	3453 [3140-3690]	1340-4700	<0.001*
Weight at examination (g)	10600 [8500-12500]	3000-21000	11450 [10000-14000]	4400-20000	<0.001*
Birth length (cm)	51 [46.5-54]	35-58	53 [51-54]	38-60	0.002*
Supine length/ Standing height at examination (cm)	79 [73-87]	51-107	87 [78-95]	60-108	<0.001*
Head circumference at birth (cm)	35 [26-39]	33-36	36 [35-37]	26-39	0.008*
Head circumference at examination (cm)	47 [44-49]	32-58.5	48 [46-49.5]	31-57	0.015*
Chest circumference at birth (cm)	33 [30-36]	22-39	35 [33-36]	25-51	0.022*
Chest circumference at examination (cm)	47 [44-50]	32-60	49 [47-51]	39-70	0.001*

Note: Data are expressed as Me [IQR]. *Differences are statistically significant ($p < 0.05$).

Table 4. Comparison of anthropometric parameters in children conceived after FET or Fresh-ET

Anthropometric parameters	Study groups				p
	Fresh-ET		FET		
	Me [IQR]	min-max	Me [IQR]	min-max	
Age (months)	10 [5-15]	2-30	17 [10-25.5]	1-45	0.001*
Birth weight (g)	2940 [2730-3385]	2035-3950	3310 [2695-3665]	990-4380	0.226
Gestational age (weeks)	38 [36-39]	28-41	38 [36.65-39]	27-42	0.611
Weight at examination (g)	9800 [7100-11000]	4000-14000	10800 [8850-12850]	3000-21000	0.029*
Birth length (cm)	51 [46-53]	45-56	52 [48.5-54]	35-58	0.241
Supine length/ Standing height at examination (cm)	74 [63-79]	54-91	81 [75-89]	51-107	<0.001*
Head circumference at birth (cm)	35 [34-36]	32-37	34 [32-36]	26-39	0.135
Head circumference at examination (cm)	44 [42-47]	32-50	47 [44-49]	36-58.5	0.002*
Chest circumference at birth (cm)	34 [33-36]	31-38	33 [29.5-35.5]	22-39	0.106
Chest circumference at examination (cm)	45 [42-48.5]	34-53	48 [45-50]	32-60	0.043*

Note: Data are expressed as Me [IQR]. * Differences are statistically significant ($p < 0.05$).

Standardized growth assessment (WHO Standards)

To account for the age discrepancies between cohorts, anthropometric measures were standardized using the World Health Organization (WHO) Child Growth Standards, which provide a framework based on Z-scores (SDS) to compare children of different ages and sexes. A comparative assessment of weight-for-age, height-for-age, and weight-for-height distributions was performed between children conceived by ART and NC children (Table 5). For clinical interpretation, the 3rd and 97th percentiles were utilized as the boundaries for the -2 and +2 SDS (Z-scores) normal range.

After standardization, no statistically significant differences were observed in weight-for-age ($p=0.467$), height-for-age ($p=0.327$), or weight-for-height ($p=0.493$) between NC and ART children.

Notably, the ART group showed twice as many overweight children (8.3% vs. 4.5%), though this did not reach statistical significance. A separate comparative analysis was conducted between FET and Fresh-ET groups (Table 6).

Similarly, no significant differences were found between FET and Fresh-ET groups after applying WHO standardizations.

Maternal anthropometric characteristics

Mothers in the ART group had a significantly higher median weight and BMI compared with mothers of NC children. The median BMI for ART mothers was 22.6 kg/m² compared to 20.8 kg/m² for NC mothers ($p<0.001$). Despite this statistical difference, both groups remained within the normal physiological range.

Table 5. Comparative anthropometric assessment of children conceived by assisted reproductive technologies and those conceived naturally according to the World Health Organization Child Growth Standards.

Assessments	-2 to +2 SDS		> +2 SDS		< -2 SDS		p
	ART (n = 120)	NC (n = 132)	ART (n = 120)	NC (n = 132)	ART (n = 120)	NC (n = 132)	
Weight-for-age categories	87.5% (105)	90.9% (120)	8.3% (10)	4.5% (6)	4.2% (5)	4.5% (6)	0.467
Height-for-age categories	87.9% (116)	85% (102)	6.8% (9)	11.7% (14)	5.3% (7)	3.3% (4)	0.327
Weight-for-height categories	88.6% (117)	85% (102)	6.1% (8)	5.8% (7)	5.3% (7)	9.2% (11)	0.493

Note: Data are presented as percentage (absolute frequency). *Differences are statistically significant ($p < 0.05$).

Table 6. Comparative anthropometric assessment of children conceived by frozen versus fresh embryo transfer according to the World Health Organization Child Growth Standards.

Assessments	-2 to +2 SDS		> +2 SDS		< -2 SDS		p
	Fresh-ET (n=29)	FET (n=91)	Fresh-ET (n=29)	FET (n=91)	Fresh-ET (n=29)	FET (n=91)	
Weight-for-age categories	86.2% (25)	87.9% (0)	13.8% (4)	6.6% (6)	0% (0)	5.5% (5)	0.265
Height-for-age categories	79.3% (23)	86.8% (79)	13.8% (4)	11% (10)	6.9% (2)	2.2% (2)	0.330
Weight-for-height categories	82.8% (24)	85.7% (78)	13.8% (4)	3.3% (3)	3.4% (1)	11% (10)	0.075

Note: Data are presented as percentage (absolute frequency). *Differences are statistically significant ($p < 0.05$).

Maternal health status

The analysis of maternal medical histories showed that ART mothers had a higher frequency of ectopic pregnancies (19.2% vs. 3%) and chronic salpingitis (20.8% vs. 3.8%), reflecting the primary causes of infertility. Interestingly, the ART group exhibited better clinical preparation during pregnancy, with a significantly lower incidence of anemia (32.5% vs. 53.8%; $p = 0.001$) and pathological nausea (4.2% vs. 15.2%; $p = 0.004$) compared to the NC group.

Discussion

The observed 4.56-fold increase in PTB within our ART cohort aligns with the prevailing consensus in reproductive medicine. While multiple gestations are the primary driver of prematurity in ART, recent meta-analyses confirm that singletons also face significantly higher risks of PTB compared to NC infants (9,15). This phenomenon is likely multifactorial, potentially stemming from the invasive nature of the ART procedures themselves or the underlying pathophysiology of parental infertility. Sources suggest that subfertility per se, characterized by a longer time-to-pregnancy, is an independent risk factor for adverse perinatal outcomes, effectively posing the “chicken or the egg” dilemma in determining whether the technology or the biological predisposition is to blame (9). In our results, children born after FET showed a trend toward higher birth weights (median 3310 g) compared to those from Fresh-ET (median 2940 g). Although this difference was not statistically significant in our study, it mirrors a well-documented global trend often referred to as “Large Baby Syndrome” or “Large Offspring Syndrome” (18,26). Meta-analyses consistently report that FET singletons are at a 1.5-fold increased risk of being LGA and are, on average, 200 g heavier than Fresh-ET counterparts (9,15,18). The lack of statistical significance in our cohort may be attributed to a smaller sample size or the specific endometrial preparation protocols used, as some studies suggest that FET in natural cycles provides a more physiological environment compared to the supraphysiological hormone levels associated with ovarian stimulation in fresh cycles (9,18). Our findings revealed that mothers in ART group had a

significantly higher BMI and median weight compared to NC mothers ($p < 0.001$). This reflects the clinical reality where patients requiring ART are often older and may present with metabolic conditions such as PCOS, which are associated with higher BMI (15,23). Maternal obesity and excessive weight gain during pregnancy are established independent risk factors for childhood obesity and LGA (15,19,23). Sources indicate that normalization of maternal weight before entering ART protocols is critical, as the intrauterine environment—including hormonal imbalances—can induce epigenetic changes that program the offspring’s metabolism long-term (9,23,27). Our data showed that at the time of the last examination (up to 60 months, with a median age of 14.5 months for the ART group and 23.0 months for the NC group), there were no statistically significant anthropometric differences between NC and ART children, nor between FET and Fresh-ET cohorts. This supports the findings of Ainsworth et al., who reported that embryo transfer type has no effect on childhood weight gain trajectory up to 5 years of age (19). Similarly, longitudinal studies from Finland and Japan suggest that the initial disparities in birth weight between these groups often normalize by age 5 to 8 (21,23,28). However, the 8.3% incidence of overweight children in our ART group twice that of the NC group remains a point of interest. Recent register studies have identified a sex-specific risk, noting that adolescent boys born after FET may have higher odds of being overweight compared to those from fresh cycles, a trend that warrants continued monitoring into late adolescence and adulthood (24).

Limitations and strengths

This study has several strengths, as it represents the first comprehensive assessment of the Kazakhstan ART cohort using standardized WHO Child Growth Standards and incorporating detailed clinical data. The use of standard protocols ensures that our findings are comparable with international datasets. However, some limitations must be acknowledged. First, the study design is partially retrospective, which relies on the accuracy of existing medical records. Second, although the age range of the study population extended up to 60 months (5 years), there was a significant age

discrepancy between groups: the median age at the time of examination was 14.5 months [IQR 8.0–22.0] for the ART group and 23.0 months [IQR 14.5–35.0] for the NC group ($p < 0.001$). As illustrated in Figure 1, the majority of children in the ART cohort were followed up only until early childhood (up to 30 months / 2.5 years). This relatively short follow-up period and the lower median age of ART children compared to the control group limit the ability to detect certain growth or developmental trends that only manifest as children reach full school age. Further longitudinal research with extended follow-up is required to fully understand the long-term health trajectory of ART-conceived children in this region.

Conclusions

Our study confirms the general safety of ART regarding the physical development of children during early childhood (median age 14.5–23.0 months), supporting international evidence that anthropometric indicators remain largely comparable to naturally conceived peers throughout development (21,22,29). Although we observed a tendency toward higher birth weights in FET infants, the lack of statistical significance suggests that these “cryo-children” do not necessarily exhibit the LGA complications reported in larger population registers (15,19). The elevated frequency of tall and overweight children in the ART group, while not significant, underscores the necessity of addressing maternal metabolic health and lifestyle factors as part of pre-conception care (19,23). Further research into the epigenetic mechanisms behind FET growth patterns is required to ensure the long-term cardiometabolic safety of this rapidly expanding technology (9,27).

Ethic Approval: This study complied with the Declaration of Helsinki and was approved by the local Ethics Committee of the “Scientific Center of Pediatrics and Pediatric Surgery” on April 13, 2022 (reference number: 2). Informed consent was obtained from all the legally authorized representatives of the research participants before enrollment in the trial.

Trial Registration: The study protocol was registered on ClinicalTrials.gov (identifier: NCT06094998) on October 17, 2023.

Data Availability: The datasets generated and analyzed during the current study are not publicly available due to ethical and privacy restrictions but are available from the corresponding author upon reasonable request.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

Declaration on the Use of AI: Generative artificial intelligence was not used in the study design, data collection, data analysis, or interpretation of results.

Authors Contribution: VL: Conceptualization, Methodology, Supervision; SI, ZN, VL: Data curation; SI, ZN: Formal analysis; SI, ZN, KK, KZ, AI, LU, RS, BT: Investigation; VL, LM: Resources; LM: Project administration, Funding acquisition; SI, KK, KZ, AI, LU, RS, BT: Writing – original draft; SI, ZN, VL, LM, TU: Writing – review and editing. The methodology was independently audited by a senior biostatistics’ consultant. SI performed the data analysis and takes responsibility for the statistical integrity of the work; ZN and SI take responsibility for the integrity of the work and the accuracy of the data analysis. All authors read and approved the final version of the manuscript.

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