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Cohort Profile

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Cohort Profile: The Jiangsu Birth Cohort

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Key Features

- The Jiangsu Birth Cohort (JBC) is a family-based prospective cohort in Jiangsu Province, China, consisting of families receiving assisted reproductive technology (ART) treatment or families with spontaneous pregnancies. The study aimed to investigate the differences between the two groups of participants regarding both short- and long-term health outcomes in women and their offspring.
- The cohort recruited couples who planned to receive ART treatment at ART clinics, and collected data on the ART procedures and outcomes. Spontaneously conceiving couples were recruited during early pregnancy (8–14 weeks of gestation) at obstetrics clinics. Thereafter, ART pregnancies and spontaneous pregnancies were followed throughout the whole gestation with the same protocol. After childbirth, all children were followed until up to 3 years of age.
- Data on health were collected through standardized and structured questionnaires and medical records, together with biospecimens from both parents and their children. The cohort thus provided a valuable resource for the research on parental and child health associated with ART pregnancies.
- Between April 2014 and June 2022, the JBC has recruited 7618 ART treated families and 14 996 families of spontaneous completed or ongoing pregnancies. For the families enrolled up to 30 June 2020 (5061 ART families and 12 793 spontaneous conception families), we have completed data from their entry throughout their fertility care (for ART families), pregnancy, birth and 1 year after childbirth when child health was evaluated by the health examination.
- Data are hosted in the China National Birth Cohort (CNBC) study group and data access may be granted via an enquiry to [cnbc@njmu.edu.cn].

Why was the cohort set up?

Following the success of the first test-tube baby in the UK in 1978, the use of assisted reproductive technology for infertility treatment has increased steadily and resulted in more than 9 million children born after assisted reproductive technology (ART) worldwide.[1,2] In China, approximately 15–25% of couples suffer infertility.[3] Consequently, ART has become a standard and common practice in reproductive medicine clinics, and more than 1.6% of children in China are conceived through ART.[4] Meanwhile, concerns are mounting over the safety of ART and its short- and long-term health impacts on maternal and fetal wellbeing. Emerging data from some, though not all, studies suggest that compared with spontaneous pregnancies, offspring conceived through ART are prone to adverse perinatal outcomes such as preterm birth, low birthweight, small size for gestational age and perinatal death.[5–7] Further, offspring conceived through ART were reported to have an elevated risk of multiple diseases such as congenital heart defect, impaired vascular function, metabolic syndromes and cancer.[8–13] Whether the elevated risks are attributable to parental characteristics related to infertility or to ART procedures warrants elucidation.

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The China National Birth Cohort (CNBC) study is a nationalwide birth cohort study involving 12 provinces and 30 medical centres, aiming to recruit 30 000 families receiving ART and 30 000 families with spontaneous pregnancies. As the primary study centre of the CNBC, Jiangsu centre initiated the establishment of the Jiangsu Birth Cohort (JBC), which is the subset of the CNBC, since April 2014 in three cities in Jiangsu (Nanjing, Suzhou and Changzhou). It was a family-based prospective study consisting of both ART-conceiving couples and naturally conceiving couples. The overarching goals of the JBC were to systematically assess the health and wellbeing among children conceived using ART as compared with those who were conceived spontaneously, and to clarify whether the elevated risks are attributable to parental characteristics related to infertility or to ART procedures, taking into consideration ART-related parental characteristics. In addition, the cohort was designed to facilitate the conduct of state-of-the-art 'omics' studies by collecting maternal, paternal and child biospecimens across the pre-, peri and postnatal stages, to systematically evaluate how environmental, genetic and clinical factors may influence birth outcomes and child health. The China National Birth Cohort (CNBC) study group was responsible for the data, and access may be granted upon the proposed projects being approved by the scientific committee consisting of senior researchers in the CNBC team.

Who is in the cohort?

The JBC study recruited both ART conceiving and spontaneously conceiving families at three major hospitals in Jiangsu, namely the Women's Hospital Affiliated to Nanjing Medical University (Nanjing), Suzhou Hospital Affiliated to Nanjing Medical University (Suzhou) and Changzhou Maternity and Child Health Care Hospital Affiliated to Nanjing Medical University (Changzhou). Owing to the great need of family-based studies in investigating intergenerational impacts of parental factors, the JBC was designed to collect both health-related information and biospecimens from the biological parents and offspring from both the ART conceiving and spontaneously conceiving families at ART clinics and obstetrics departments, respectively.

The JBC identified potential study participants among those who consulted for ART treatment at ART clinics. Eligible participants were Chinese residents of the pre-specified cities who were going to receive in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) treatment. Those who planned to conceive by sperm donation, oocyte donation or intrauterine insemination were excluded from recruitment. Upon identification, the couples were invited to participate in the JBC before their first egg retrieval cycle. On the other hand, the spontaneously conceiving couples were invited and recruited from obstetrics departments when they established health record profiles during early pregnancy (8–14 weeks of gestation). Eligible couples were Chinese residents who planned to have routine antenatal clinical examinations in the same hospital. Obstetricians or professional health workers explained the objectives, procedures, potential benefits and confidentialities of the study to all eligible families. Informed written consent was obtained from those who agreed to participate. The JBC provided each family with a membership card and a unique family ID for further follow-up. The participants could withdraw from the cohort at any time. The study was approved by the ethics committees of Nanjing Medical University and the participating hospitals.

Between April 2014 and June 2022, 11 330 eligible ART conceiving families and 28 306 eligible spontaneously conceiving families were identified. We invited 1000 ART conceiving families and 2000 spontaneously conceiving families annually, based on a convenience sampling method. As a result, 7618 ART and 14 996 spontaneously conceiving families agreed to participate. The participation rates were 95.2% for ART conceiving families and 93.7% for spontaneously conceiving families. Among recruited families, the mean age of ART couples was greater than that of spontaneously conceiving couples (women: 31.1 ± 4.3 years for ART vs 28.7 ± 3.8 years for spontaneous, $P < 0.001$; men: 32.5 ± 5.2 years for ART vs 30.1 ± 4.5 years for spontaneous conception, $P < 0.001$). Most of the participants were urban residents and had an education level of more than 12 years (Table 1).

For the families enrolled up to 30 June 2020 (5061 ART families and 12 793 spontaneous conception families), we have completed data from their entry throughout their fertility care (for ART families), pregnancy, birth and at 1 year after childbirth when 1-year-old health examination was performed (Figure 1). Among the ART participants, 90 did not undergo oocyte retrieval, 407 had retrieval but not a transplanted embryo. A total of 4564 couples completed 7154 embryo transplant cycles (IVF or ICSI), among which three were excluded due to loss to follow-up, 2475 ended in implantation failure and 725 pregnancies were only chemically detected by a beta human chorionic gonadotropin (β-hCG) blood test but not clinically visualised on ultrasound (biochemical pregnancy loss) (Figure 1). Among the remaining 3951 ultrasound-confirmed pregnancies, 79 ended in ectopic loss, 555 ended in miscarriage, 45 ended in induced abortion, 12 ended in stillbirth and 3260 successful pregnancies resulted in 3980 live births (Figure 1). Among the 12 793 spontaneous conception families enrolled at early pregnancy (8–14 weeks of gestation), 147 were excluded due to loss to follow-up or withdrawal (Figure 1). The remaining 12 647 families reported pregnancy outcomes, among which 12 410 pregnancies resulted in 12 500 live-born infants, 106 ended in miscarriage, 103 in induced abortion and 27 in stillbirth (Figure 1).

Detailed newborn characteristics were shown in Table 2. Among all the live-birth pregnancies, ART conceiving pregnancies have higher incidence of preterm birth than spontaneously conceiving pregnancies (18.1% vs 4.2%). Among the 3980 ART conceiving and 12 500 spontaneously conceiving live births, ART conceiving live births were more likely to have low birthweight (18.1% vs 2.9%).

The JBC had seven neonatal deaths and three child deaths among the 3980 ART-conceived live births, and six neonatal deaths and six child deaths among the 12 500 spontaneously conceiving live births. The postnatal follow-up for the families enrolled up to 30 June 2020 has been completed, with 3238 ART conceived and 9964 spontaneously conceived infants being assessed by telephone at 42 days after birth; 3237 ART conceived and 8993 spontaneously conceived infants were assessed by telephone at 6 months after birth. One year after birth, 3318 ART conceived infants and 9026 naturally conceived infants visited the child health care clinic for health examination, with follow-up rate reaching 83.6%

Table 1. Baseline characteristics of couples enrolled in the Jiangsu Birth Cohort[a]

Characteristic	ART conceiving (*n*=7618)	Spontaneously conceiving (*n*=14 996)	*P*
Study centre			
Nanjing	2815 (37.0)	6506 (43.4)	<0.001
Suzhou	3451 (45.3)	4910 (32.7)	
Changzhou	1352 (17.7)	3580 (23.9)	
Residence			
Urban	7023 (92.2)	11 530 (76.9)	<0.001
Rural	589 (7.7)	3416 (22.8)	
Unknown	6 (0.1)	50 (0.3)	
Household income (CNY)			
<50,000	391 (5.1)	997 (6.6)	<0.001
50 000–100 000	1965 (25.8)	3467 (23.1)	
100 000–200 000	2874 (37.7)	6248 (41.7)	
≥200 000	2382 (31.3)	3978 (26.5)	
Unknown	6 (0.1)	306 (2.0)	
Maternal age (years)			
Mean ± SD	31.1 ± 4.3	28.7 ± 3.8	<0.001
<25	237 (3.1)	1658 (11.0)	<0.001
25–30	2752 (36.1)	7839 (52.3)	
30–35	3136 (41.2)	4319 (28.8)	
≥35	1493 (19.6)	1169 (7.8)	
Unknown	0	11 (0.1)	
Maternal BMI (kg/m^2)			
Mean ± SD	22.5 ± 3.2	21.3 ± 3.0	<0.001
<18.5	575 (7.5)	2271 (15.1)	<0.001
18.5–24.0	4786 (62.8)	10 220 (68.2)	
24.0–28.0	1584 (20.8)	1919 (12.8)	
≥28.0	471 (6.2)	494 (3.3)	
Unknown	202 (2.7)	92 (0.6)	
Maternal education (years)			
≤12	2147 (28.2)	2054 (13.7)	<0.001
>12	5468 (71.8)	12 894 (86.0)	
Unknown	3 (0.0)	48 (0.3)	
Paternal age (years)			
Mean ± SD	32.5 ± 5.2	30.0 ± 4.5	<0.001
<25	126 (1.7)	970 (6.5)	<0.001
25–30	2185 (28.7)	6748 (45.0)	
30–35	3126 (41.0)	4874 (32.5)	
≥35	2177 (28.6)	2269 (15.1)	
Unknown	4 (0.0)	135 (0.9)	
Paternal education (years)			
≤12	1961 (25.7)	1894 (12.6)	<0.001
>12	5656 (74.3)	12 253 (81.7)	
Unknown	1 (0.0)	849 (5.7)	

ART, assisted reproductive technology; BMI, body mass index; SD, standard deviation

[a] Figures are number (%) or mean ± SD.

in ART conceived infants and 72.3% in spontaneously conceived infants (Figure 1).

We compared the characteristics of families enrolled in the present study with the general population, using data obtained from the National Maternal Near Miss Surveillance System (NMNMSS) of Jiangsu province, which to some extent could represent the general population of Jiangsu province,[14] and from the ART clinics of the three above-mentioned hospitals in Jiangsu, with women in the NMNMSS database between 2014 and 2019. Spontaneously conceiving women included in the JBC study had a similar mean age but a higher level of education. There was no significant difference in neonatal sex, whereas the incidences of preterm birth (gestational age <37 weeks), low birthweight (birthweight <2500 g) and macrosomia (birthweight ≥4000 g) in the JBC study were lower as compared with the NMNMSS database (Supplementary Table S1, available as Supplementary data at *IJE* online). When compared with the overall couples who received treatments between 2015 and 2022 in ART clinics of the three above-mentioned hospitals, the ART couples included in the JBC study showed similar mean age and maternal body mass index (BMI), but were more likely to have a higher level of education (Supplementary Table S2, available as Supplementary data at *IJE* online).

How often have they been followed up?

Once enrolled, the ART couples were followed through the whole fertility treatment procedure including oocyte pick-up (ART Visit 1), embryo transplantation (ART Visit 2), blood β-hCG test (ART Visit 3) and ultrasound scan to confirm pregnancy status (ART Visit 4) (Figure 2). The ART couples were asked to complete standardized and structured questionnaires and they donated biological samples including blood, urine, follicular fluid, sperm and seminal plasma with the follow-up. The clinical data were collected from medical records (Figure 2). Women who showed negative pregnancy

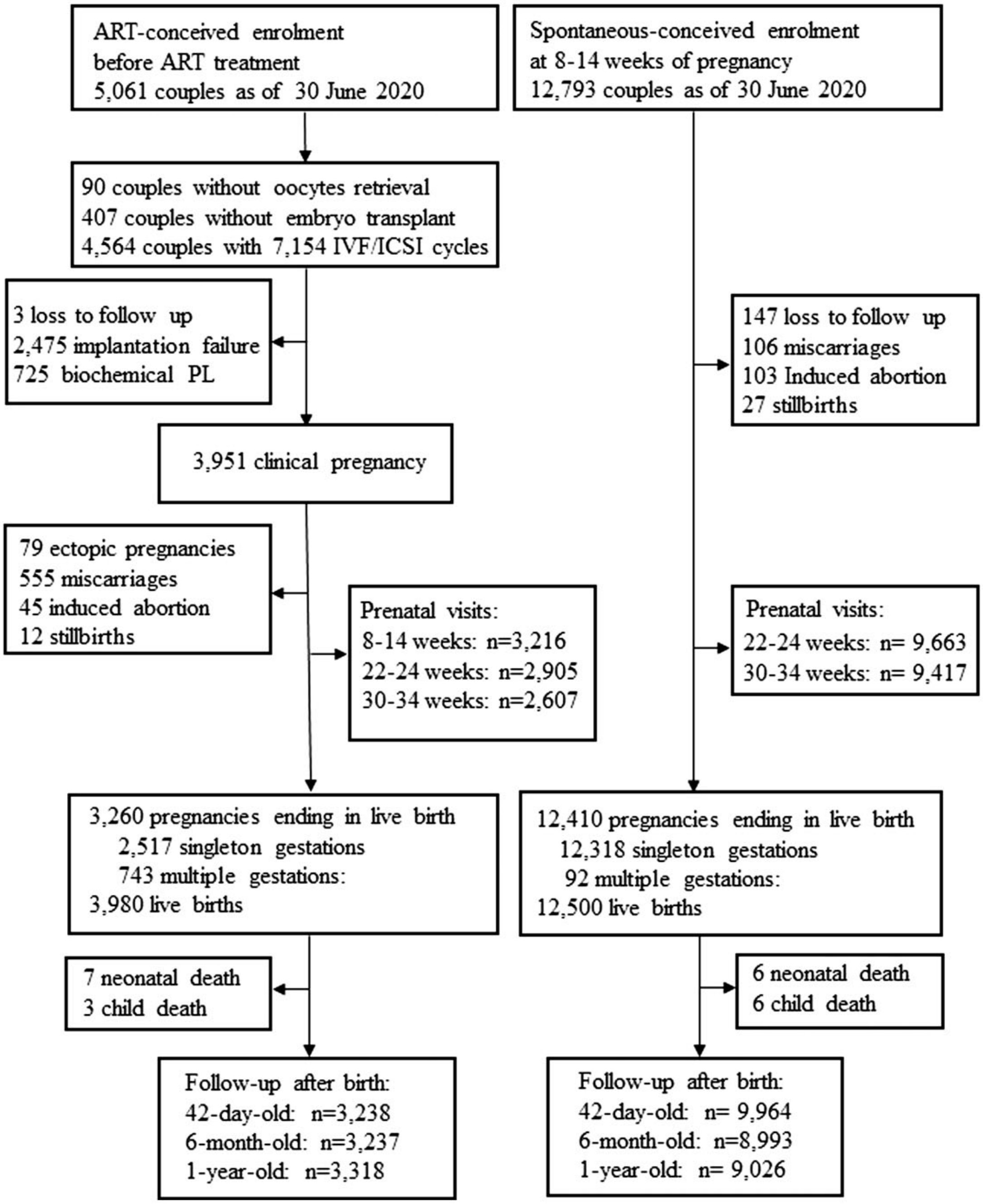

Figure 1. Flow chart of the Jiangsu Birth Cohort. [a]The follow-up status was reported for 5061 ART families and 12 793 spontaneous conception families enrolled before 30 June 2020. ART, assisted reproductive technology; IVF, in-vitro fertilization; ICSI, intracytoplasmic sperm injection; PL, pregnancy loss

results, biochemical pregnancy or early abortion usually entered next embryo transfer cycle or egg retrieval cycle, which were followed afterwards (Figure 2).

Spontaneously conceiving couples were recruited during early pregnancy (8–14 weeks of gestation) at obstetrics clinics. Baseline information and blood and urine specimens were collected from both the biological mother and father. The clinical data were collected from medical records (Figure 2). Thereafter, all ART and spontaneous pregnancy couples were followed with the same protocol. They were seen at another two antenatal care visits, once during mid-pregnancy (Antenatal Visit 1: 22–26 weeks of gestation), and again during late pregnancy (Antenatal Visit 2: 30–34 weeks of gestation). During these visits, questionnaire surveys were conducted and blood and urine samples from women were collected. Detailed clinical data including physical examination, clinical tests and pregnancy complications (i.e. gestational diabetes mellitus, hypertensive disorder complicating pregnancy) were extracted from medical records (Figure 2). During parturition (Delivery Visit), pregnancy complications and birth outcomes (i.e. premature delivery, birthweight and birth defects) were collected from medical records. Infants were examined as newborns at obstetrics clinics and their anthropometric parameters were measured (Figure 2).

During the postnatal period, mothers were interviewed by telephone approximately 42 days after birth (Postnatal Visit 1) and 6 months after birth (Postnatal Visit 2) to complete a structured questionnaire collecting data on infants' feeding

Table 2. Newborn characteristics of the Jiangsu Birth Cohort[a]

Newborn characteristic	ART conceiving	Spontaneously conceiving	*P*
Number of pregnancies	3260	12 410	
Number of live births	3980	12 500	
Gestational age (weeks)			
Mean ± SD	38.0 ± 2.2	39.1 ± 1.5	<0.001
<37	588 (18.1)	518 (4.2)	<0.001
≥37	2665 (81.7)	11889 (95.8)	
Unknown	7 (0.2)	3 (0.0)	
Sex			
Male	2190 (55.0)	6485 (51.9)	<0.001
Female	1788 (44.9)	6008 (48.1)	
Unknown	2 (0.1)	7 (0.0)	
Birthweight (g)			
Mean ± SD	3049.3 ± 644.4	3354.4 ± 454.5	<0.001
<2500	721 (18.1)	364 (2.9)	<0.001
2500–4000	3015 (75.8)	10852 (86.8)	
≥4000	238 (6.0)	892 (7.1)	
Unknown	6 (0.1)	392 (3.1)	

ART, assisted reproductive technology; SD, standard deviation.
[a] Figures are number (%) or mean ± SD.

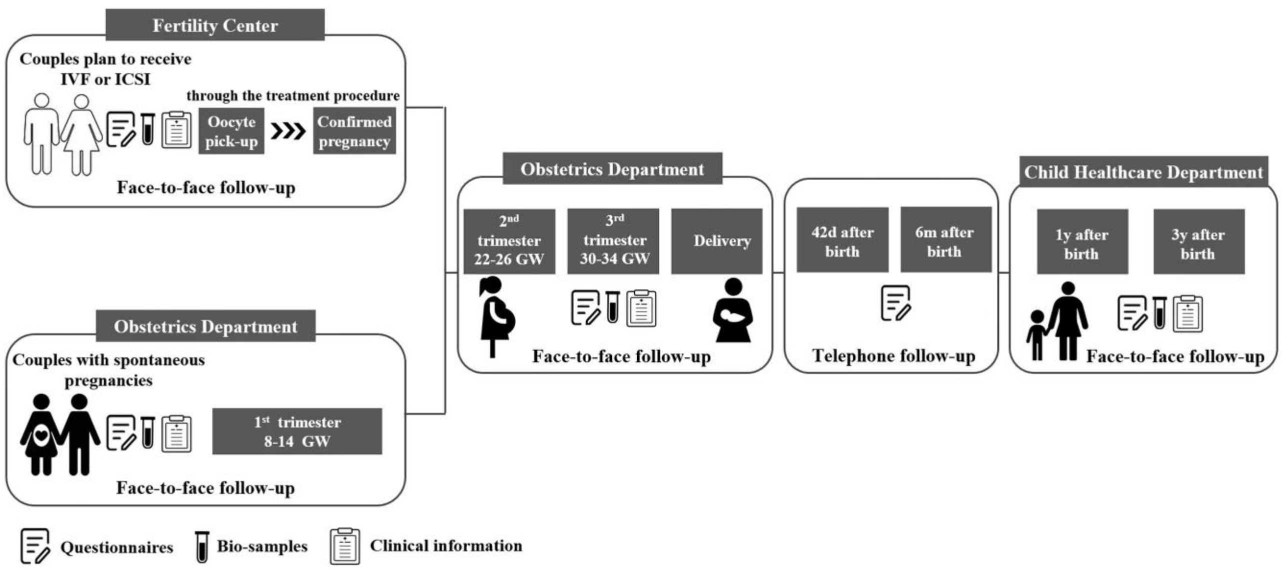

Figure 2. The recruitment and follow-up in the Jiangsu Birth Cohort. IVF, in-vitro fertilization; ICSI, intracytoplasmic sperm injection; GW, gestational week

patterns, sleep patterns and diseases. When children reached the ages of 1 year (Postnatal Visit 3) and 3 years (Postnatal Visit 4), they would be invited along with their mothers to visit the child health care department at the hospital where they were born. The hospitals would offer physical examinations, anthropometric measurement and neurodevelopment assessments (Figure 2).

What has been measured?

Once enrolled, women and their partner were asked to complete the standardized and structured questionnaires by face-to-face interview covering their demographic and socioeconomic data, lifestyle and behavioural traits (i.e. smoking, alcohol consumption and physical activity), occupational exposure, reproductive history and disease and medication history (Table 3). All couples were asked to complete a self-administered Food Frequency Questionnaire (FFQ) to access their habitual dietary habits during the past 1 month. The 20-item Centre for Epidemiologic Studies Depression Scale (CES-D), 10-item Perceived Stress Scale (PSS-10) and a 20-item Self-rating Anxiety Scale (SAS) captured their mental health status.[15–17] The Pittsburgh Sleep Quality Scale was used to evaluate maternal sleep quality (Table 3).[18] During antenatal visits (one during 22–26 weeks of gestation, and one during 30–34 weeks of gestation) information on the mother's lifestyle, behavioural traits, health and diseases and medication during pregnancy was collected at the two visits (Table 3).

For ART couples, the core clinical data were collected from medical records at ART clinics, including a multiple hormone examination for women before ART procedure, a semen quality examination for men, detailed infertility diagnosis, embryo type, embryo score and detailed protocol of ART treatment (Supplementary Table S3, available as Supplementary data at *IJE* online). After the pregnancy, clinical data were available for ART-treated and spontaneously conceiving women, such as complete blood count, urinalysis,

Table 3. Summary of collected data from the questionnaires and medical records and collected biological samples during baseline, antenatal and postanal follow up.

Characteristics	Time points				
Baseline and antenatal follow-up	**Before ART cycle**	**8-14 weeks**	**22-26 weeks**	**30-34 weeks**	**Delivery**
Maternal questionnaire					
Demographic and Socioeconomic data	A	S			
Occupational exposure	A	S			
Indoor air pollution	A	S			
Pet feeding	A	S			
Smoking and passive smoking	A	S	SA	SA	
Alcohol consumption	A	S	SA	SA	
Tea consumption	A	S	SA	SA	
Coffee and caffeinated beverage consumption	A	S	SA	SA	
Physical activity	A	S	SA	SA	
Food frequency questionnaire	A	S	SA	SA	
Micronutrient supplements	A	S	SA	SA	
Self-rated health status	A	S			
Menstruation history	A	S			
Reproductive history	A	S			
Diseases history	A	S			
Pittsburgh sleep quality scale	A	S	SA	SA	
Self-Rating Anxiety Scale	A	S	SA	SA	
Center for Epidemiologic Studies Depression Scale	A	S	SA	SA	
10-item Perceived Stress Scale	A	S	SA	SA	
Paternal questionnaire	A	S			
Demographic and Socioeconomic data	A	S			
Occupational exposure	A	S			
Indoor air pollution	A	S			
Pet feeding	A	S			
Smoking and passive smoking	A	S			
Alcohol consumption	A	S			
Tea consumption	A	S			
Coffee and caffeinated beverage consumption	A	S			
Physical activity	A	S			
Hot bath habit	A	S			
Food frequency questionnaire	A	S			
Micronutrient supplements consumption	A	S			
Self-rated health status	A	S			
Diseases history	A	S			
Pittsburgh sleep quality scale	A	S			
Self-Rating Anxiety Scale	A	S			
Center for Epidemiologic Studies Depression Scale	A	S			
10-item Perceived Stress Scale	A	S			
Medical record					
Complete blood count		SA	SA	SA	SA
Urinalysis		SA	SA	SA	SA
Blood biochemical examination		SA	SA	SA	SA
Physical examination		SA	SA	SA	SA
Obstetric examination		SA	SA	SA	SA
Blood pressure		SA	SA	SA	SA
Thyroid function test		SA	SA	SA	
Pregnancy complication		SA	SA	SA	SA
Fetal heart monitoring		SA	SA	SA	SA
Fetal ultrasound examination		SA	SA	SA	SA
Birth outcome					SA
Biological sample					
Follicular fluid	A				
Sperm and seminal plasma	A				
Maternal peripheral blood	A	S	SA	SA	SA
Maternal urine	A	S	SA		
Paternal peripheral blood	A	S			
Paternal urine	A	S			
Maternal feces		SA		SA	
Meconium					SA
Placenta, cord blood,					SA
Amniotic fluid					SA

(continued)

Table 3 (continued)

Characteristics	Time points			
Postnatal follow-up	**42 days**	**6 months**	**1 year**	**3 years**
Child Questionnaires				
Anthropometric parameters	SA	SA	SA	SA
Breastfeeding	SA	SA	SA	SA
Dietary and supplements intake	SA	SA	SA	SA
Bowel habits			SA	SA
Sleeping	SA	SA	SA	SA
Outdoor exercise			SA	SA
Symptoms and diagnosis	SA	SA	SA	SA
Medication	SA	SA	SA	SA
Neurodevelopment assessment				
BSID-III			SA	SA
GDS			SA	SA
Medical record				
Ophthalmology examination			SA	SA
Dental eruption and oral examination			SA	SA
Physical examination			SA	SA
Hemoglobin			SA	SA
Biological sample				
Children's fingertip blood			SA	SA
Children's feces			SA	SA

A, ART-conceived; S, spontaneous-conceived; ART, assisted reproductive technology; BSID-III, Bayley Scales of Infant Development, 3rd Edition; GDS, Gesell Development Scale.

blood biochemical examination, obstetric complications, prescribed medication and adverse pregnancy outcomes (for example miscarriage and stillbirth) (Table 3; and Supplementary Table S4, available as Supplementary data at *IJE* online). After delivery, the birth outcomes with detailed obstetric data (i.e. birthweight, birth defects, delivery mode) were extracted from medical records (Table 3).

All couples' peripheral blood and urine samples were collected at enrolment. Follicular fluid, sperm and seminal plasma were collected from ART-treated couples on the day of oocyte pick-up. During mid and late pregnancy, peripheral blood was collected repeatedly from women. The amniotic fluid, cord blood, meconium and placental tissue were also collected at delivery (Table 3). The urine samples were stored at −20 °C and other biospecimens stored at −80 °C, before being retrieved and thawed for assays.

All cohort children were offered free child health examinations from infancy to early childhood, as scheduled. Approximately 42 days after delivery, mothers received telephone requests to complete questionnaires that covered a broad range of items about their children including anthropometric parameters, breastfeeding, dietary and supplements intake, behaviour traits and sleep quality, diseases, injuries and medication usage (Table 3). Six months after delivery, mothers were followed one more time via telephone. Then cohort children were invited to visit the child health care clinic at ages 1 and 3 years along with their mothers. During each clinic visit, physical examination, clinical examinations and blood test were conducted (Table 3). Trained health professionals examined and evaluated children's neurodevelopment using standardized tools (Gesell Development Scale, GDS; Bayley Scales of Infant and Toddler Development, Version-III, Bayley-III) at the ages of 1 and 3 years (Table 3).[19,20] The children's fingertip blood and feces samples were collected at their 1-year and 3-year clinic visits (Table 3).

All data collection and management were based on the Cloud Based Cohort Management System for the JBC (CBCMS-JBC, a computerized system specially designed for the project). CBCMS-JBC has three main modules: participants management, questionnaire setting and quality control, and web-based questionnaire survey. All follow-up data interaction was performed in real time. For data safety, only authorized staff have access to the system. The system has unique features designed for the tablet-based questionnaire survey, for example several built-in functions to avoid missing items and to minimize logic errors during data entry. The data that pass the standardized evaluation were de-identified and cloud-based stored.

What has it found? Key findings and publications

To date, the JBC study has assessed the differences in health and wellbeing between children born after ART versus those born after spontaneous pregnancies. We first compared the incidence of total birth defects (including both major and minor defects) between ART children and naturally conceived children, and found that ART confers an increased risk for birth defects in offspring (13.9% vs 7.0%). Mediation analysis demonstrated that twinning accounted for 31.1% of the risk of ART-associated birth defects. Our findings highlight the importance of further evaluating the safety of ART approaches, including the number of embryo transfer.[21] In a pilot whole-genome sequencing study of 202 ART trios and 205 naturally conceived trios, we reported that the children conceived via ART carried 4.59 more germline *de novo* mutations than their counterparts who were born after spontaneous pregnancy. Further, we have associated the accumulation of non-coding functional *de novo* mutations, particularly paternally derived ones, with the increased risk of congenital heart disease in children.[22] Using whole-genome sequencing data, we additionally estimated leukocyte telomere length (LTL) in both parents and offspring. Our data showed that infants born after ART had shorter initial LTL than spontaneously conceived offspring, independently of parental LTL and other confounders. Moreover, our study demonstrated that the shortened LTL was attributable to the transfer of blastocyst-stage embryos.[23] In the investigation characterizing the features and the determinants of the gut microbiome in ART newborns, we observed reduced gut microbiota α-diversity and declined Bacteroidetes relative abundance in ART neonates, which was largely driven by specific ART treatments. Following up these neonates for 6 months after their births, we further demonstrated the effects of gut microbiome composition on infant rapid weight gain.[24]

In aetiological studies of children's neurodevelopment evaluated by the Gesell Development Scale or Bayley-III, we reported a strong association between antenatal corticosteroid exposure and an increased risk of infants being non-competent in cognitive development at 1 year of age, providing new information when weighing the benefits and potential risks of maternal antenatal corticosteroid administration.[25] In addition, we identified environmental pollution (exposure to $PM_{2.5}$[26] and titanium[27] antenatally), maternal dietary pattern[28] and maternal mild hypothyroidism[29] as influencing factors for offspring's neurodevelopment at 1-year-old follow-up.

What are the main strengths and weaknesses?

This study has several notable strengths. First, the family-based study involves both ART-treated pregnancies and spontaneous pregnancies, and therefore enables the comparison of maternal and child health consequences between ART conceiving and spontaneously conceiving populations and furthers the assessment of determinants of pregnancy outcomes and child health. Second, the JBC prospectively and repeatedly collects multidimensional health information as well as biospecimens from parents and offspring, which facilitates investigation into sensitive windows in early life. Particularly, the involvement of the father provides opportunities for analysing DNA trios (i.e. mother, father and offspring). Third, in addition to regular blood and urine samples, placental tissues, and cord blood are also collected. Follicular fluid, sperm and seminal plasma samples are collected from the ART population. The collected biospecimens are a rich resource for studies on gene-environment interactions and provide cues for explorations of molecular and cellular mechanisms. Fourth, the availability of data on preconception health and biospecimens collected provide us with a unique opportunity to evaluate the early life environmental, behaviour and psychology status factors comprehensively and precisely.

Weaknesses of the cohort include the fact that families with spontaneous conception are enrolled during early pregnancy rather than preconceptionally. Therefore, adverse pregnancy outcomes in early pregnancy, e.g. early miscarriage, are not recorded in the cohort. The high prevalence of adverse pregnancy outcomes among ART-treated women has been well studied and demonstrated. Thus, this cohort is established with the main aim to assess health and wellbeing in children born after different conception approaches. We cannot exclude the possibility that subfertile couples are included in the spontaneous conception cohort, as the infertility-related diagnoses and time to conception were not investigated among them. It might cause underestimation of the relative risk (RR) of adverse health outcomes in children born after ART, if there is any, when comparing with those born to spontaneously conceiving families. In addition, families participating in the JBC were mainly from urban areas and on average from higher socioeconomic groups, particularly the ART families. The JBC offers a breadth of measurements throughout pregnancy and infancy, but risk of misclassification of baseline data due to self-reporting must be considered in some cases. Particularly infertile couples, but not those who are in good reproductive status, might be more likely to report potential exposures such as family history. However, mothers were unaware of future health/disease status in the offspring, which most likely resulted in non-differential misclassification. Additionally, the main exposure of interest, ART treatment, is classified precisely.

Can I get hold of the data? Where can I find out more?

De-identified data are available to investigators with projects that fall within the policy and overall aim of the JBC, through collaborative agreements. Applicants must submit a formal proposal and a completed application form of the project to [cnbc@njmu.edu.cn]. Further information can be found on the study website [http://jbc-cnbc.njmu.edu.cn/] or through email to [cnbc@njmu.edu.cn]. Enquiries regarding data availability should be directed to Dr Zhibin Hu [zhibin_hu@njmu.edu.cn].

Members of the collaborative group of the China National Birth Cohort

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Ethics approval

The study was approved by the ethics committees of Nanjing Medical University [NJMUIRB (2014)248].

Data availability

See Can I get hold of the data? above.

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

Z.H. and H.S. conceived of the study and were in charge of overall direction and planning. Z.H., H.S., J.D., Y.X., Y.L. and H.M. designed the study. C.L., W.W., M.C., J.L. and J.S. conducted the data and sample collection. Y.L., D.J. and Y.J. drafted the protocol. Y.J. Y.Z. and J.C. performed data quality control and analysis. Z.H., H.S., J.D., Y.L. Y.X., H.M. and G.J. interpreted the data and revised the manuscript. Z. H. and H.S. obtained funding for the establishment of the cohort. All the authors gave final approval of the version to be published.

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Conflict of interest

None declared.

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