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Cohort profile: Anhui Maternal–Child Health Study in China

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ABSTRACT

Purpose The Anhui Maternal–Child Health Study (AMCHS) aims to examine determinants of reproduction, pregnancy and postpartum maternal and child health outcomes in Chinese women who received assisted reproductive technology (ART).

Study design and participants AMCHS is an ongoing cohort study starting from May 2017. AMCHS recruits participants from all couples who sought ART treatment in the First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China. The participants are interviewed to document baseline sociodemography, lifestyles, dietary intake and environmental exposure. Their clinical characteristics are obtained from hospital records. Samples of blood, follicular fluid and semen are collected at the clinic. Participants receive a standard long pituitary downregulation or a short protocol with an antagonist for the treatment. They are followed up from preconception to delivery, or discontinuation of ART treatment. Details of their children's health are documented through a questionnaire focusing on developmental status and anthropometry measurement.

Findings to date Until April 2021, AMCHS had recruited 2042 couples in the study. 111 women withdrew from the study and 19 failed to retrieve oocytes. Among the 1475 confirmed pregnancies, 146 had miscarriages or terminated their pregnancies, 9 had stillbirths and 263 were ongoing pregnancies. The implantation failure increased with maternal age; adjusted OR was 1.43 (95% CI 1.16 to 1.77) in the age of 31–35 years, 1.97 (95% CI 1.46 to 2.66) in 35–39 years and 6.52 (95% CI 3.35 to 12.68) in ≥40 years compared with those aged 20–30 years. Among the 1057 couples with successful ART who were followed up for delivering babies, 576 had their children examined at age 30–42 days, 459 at 6 months and 375 at 12 months.

Future plans The AMCHS will identify comprehensive risk factors for poor ART outcomes and explore potential interaction effects of multiple factors including sociopsychological aspects of environmental exposure, dietary intake and genetics on maternal and child health.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The Anhui Maternal–Child Health Study (AMCHS) is the first prospective reproductive cohort study conducted in Anhui, China, to examine factors influencing assisted reproductive technology (ART) risk and outcomes.
⇒ The study investigates various risk factors, including BioBank data for reproductive, pregnancy and child health outcomes over time.
⇒ The study includes and focuses on the paternal impact on adverse reproductive and pregnancy outcomes.
⇒ The cohort may potentially recruit more participants who are in high socioeconomic status (SES) so and the findings might not be generalised to couples in low SES.
⇒ The rate of lost-to-follow-up may rise with the cohort follow-up time, which could bring potential bias for the study findings.

INTRODUCTION

Infertility has increased in many populations and has been identified as a global public health priority.[1] The infertility rate has increased from 6.7% to 15.5% among women of reproductive age in the world over the past two decades,[2 3] and there are around 48 million infertile couples.[4] Infertility causes psychological distress, social stigmatisation, marital discord and heavy financial burden in families.[5–7] The median per-person cost of in vitro fertilisation (IVF) treatment is about US$38 015.[8]

Assisted reproductive technology (ART) is an effective solution for infertility. Globally, around 1.7%–4% of all births are born using ART.[9] While ART is important for infertility treatment, its outcomes vary with different ART procedures. In a cohort study of 631 singleton viable gestations at 19–36 weeks in Italy, Cavoretto *et al* found that thawed blastocyst transfers were associated with greater estimated fetal weight and birth weight versus fresh blastocyst transfers.[10] There is evidence that ART could markedly increase the incidence of pregnancy complications (eg, gestational diabetes mellitus (GDM), placenta previa, premature delivery) and poor neonatal outcomes (eg, stillbirth).[9 11–13] The reasons for adverse pregnancy outcomes remain unclear; however, there has been increasing research on whether infertility is caused by the technology of ART itself or by parental characteristics and their exposure to risk factors.[14–16]

Previous studies showed that unhealthy lifestyles including cigarette smoking and physical inactivity adversely affect ART outcomes such as low pregnancy rate, low live birth rate and miscarriage,[17 18] while IVF treatment increases the risk of GDM,[19] birth defects[20] and preterm birth compared with a natural pregnancy.[21] However, most studies have focused on maternal influences during pregnancy and the delivery process.[22–25] Few studies have simultaneously examined multiple risk factors, especially at a genetic level for adverse pregnancy outcomes of ART. Little is known about how much the characteristics of a male spouse contribute to the infertility and fewer studies have collected such data from both men and women during the preconception period.[26 27] Furthermore, current knowledge of risk factors for ART adverse outcomes are predominately derived from studies undertaken in high-income countries (HICs).[13 28–30] The findings of HICs' studies may not be applicable to those in low- and middle-income countries (LMICs), where the burden of infertility is higher.[2] Few prospective cohort studies have been undertaken in LMICs to assess risk factors among infertility couples who received ART and their prognosis.[31 32]

China is the largest and most populated LMIC in the world and around 15.5% of women are infertile (range 7.2%–26.7%),[33] which is higher than those in HICs (eg, 12% in the USA, 12.5% in the UK).[2 34] The cost of IVF and ART treatment is personally funded, with no government subsidy. Anhui, one of 34 provinces in China, is located in the mid-eastern region of China and consists of 61 million residents.[35] The rate of infertility in Anhui is 14.5%, which is close to the national level of 15.5%, and many families cannot have their children due to infertility. While there has been an increase in the number of infertile couples who take ART, there is little investigation in the factors of ART treatment and outcomes in Chinese women. To address these omissions, we have recently proposed and conducted the Anhui Maternal–Child Health Study (AMCHS). AMCHS is an ongoing prospective preconception cohort study of couples accepting ART treatment. Our cohort study aims to examine (1) comprehensive risk factors of early environment from maternal and paternal preconception to birth influencing the development of embryo and fetal health, (2) the impact of the interaction between multiple environments and genes on infants' growth and development, (3) the short-term and long-term implication of ART to the next generation compared with natural conceived pregnancy population and (4) the impact of adverse pregnancy on children health.

COHORT DESCRIPTION

Study design, setting and participants

Since May 2017, we have invited all infertile couples who received medically assisted reproduction through IVF-based technologies (ie, fresh or frozen IVF protocols, including intracytoplasmic sperm injection (ICSI)) in the First Affiliated Hospital of Anhui Medical University (AHMU), Hefei City, Anhui Province, China, to take part in AMCHS. Participants' recruitment in AMCHS is consecutive. The inclusion criteria for study participants are (1) couples who are receiving ART treatment for the first time and (2) those who have not accepted oocyte or sperm donation or intrauterine insemination.

At the beginning of the recruitment cycle, AMCHS research coordinators register sociodemographic information of eligible couples. To obtain consent from the participants, a fertility specialist would introduce the AMCHS to married couples who come to the clinic for IVF treatment consultations. Patients can fully consider from consultation to treatment. When married couples were both willing to participate in the study, they would sign an informed consent form. The discussion of the study and consent was carried out in a private room in the clinic. The couples would join in this cohort study for IVF treatment once they signed the consent form. We offered women free ultrasound monitoring throughout their IVF treatment as an incentive to taking part. Participants could withdraw at any time they wanted without giving any reasons, which would not affect their ongoing care. Researchers interviewed participants using a general health and risk factor questionnaire; these interviews were carried out in a private room in the clinic. Following participant consent, they also accessed participant's medical records, including cycle, pregnancy and delivery data, and took biological samples for long-term storage for solely medical research purposes.

From May 2017 to December 2020, we recruited 2198 eligible couples. The participants were interviewed for baseline assessment and their fasting blood samples were taken before commencing IVF treatment. Figure 1 shows the flow chart of the participants' recruitment and follow-up processes throughout the study. Participants are followed up from the study entry throughout their fertility care, pregnancy, birth (for those achieving pregnancy) and children (until 3 years old) or until they discontinue treatment or withdraw from the study. As of April 2021, 2042 couples have had IVF treatment, of which 1828 couples received embryo transfer surgery (figure 1). Among 1475 women who confirmed pregnancies, 138 suffered from abortion, 8 suffered from ectopic, 9 suffered from stillbirth, 263 were ongoing pregnancies and 1057 gave live birth to babies. There are 940 children followed up until delivery, 576 children completed the follow-up at age 30–42 days, 459 children completed the follow-up at age 6 months, 375 completed the follow-up at 12 months and 26 completed the follow-up at 36 months.

As an ongoing cohort study, AMCHS continues to recruit the participants and we conduct follow-up and interviews with the remaining couples in the cohort (figure 1). Initially, we planned to recruit 2000 couples for the outcome analysis and close the recruitment in June 2021. The sample size was considered according to the incidence of reproductive and pregnancy outcomes. The number of participants (n=2042) in the current dataset has shown enough study power for some outcomes based

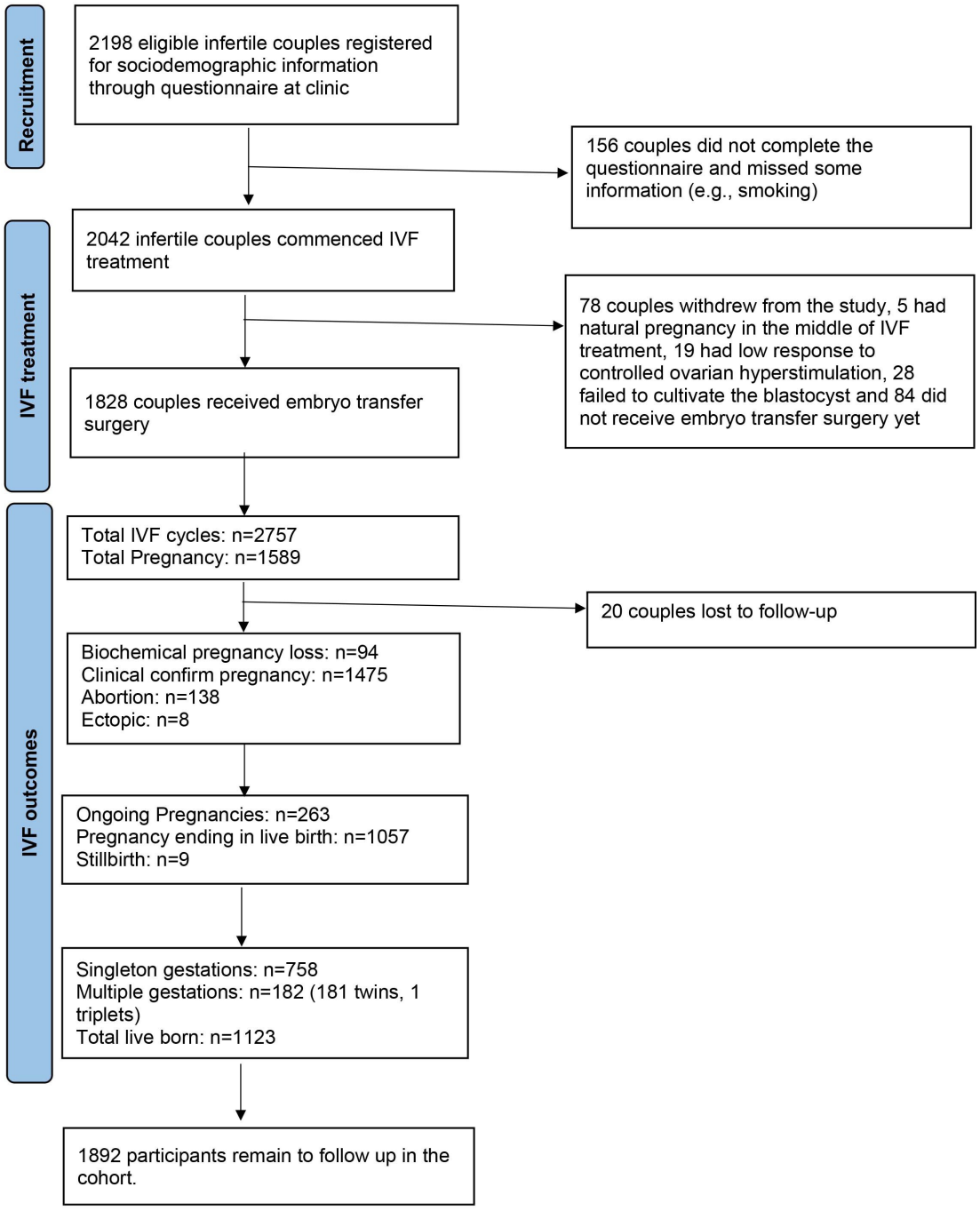

Figure 1 Flow chart for participants and updated outcomes in the follow-up of AMCHS. AMCHS, Anhui Maternal–Child Health Study; IVF, in vitro fertilisation.

on the formula of the cohort sample size, for example, current analysis for the impact of maternal age on implantation failure. From January to November 2021, AMCHS recruited and followed up 29 participants. The study powers for other complicated data analysis for rare outcomes will be ensured in ongoing recruitment and follow-up of the AMCHS cohort.

Patient and public involvement

Patients and the public involvement were considered, but neither are involved in the design, conduct, reporting or dissemination plans of our research.

Questionnaire survey

Both female and male participants completed a baseline questionnaire survey. The questionnaire includes sociodemographic information (eg, date of birth, sex, educational level, occupational class, income and residential area), lifestyle questions (eg, smoking habits, alcohol consumption, dietary intake, tea and coffee drinking habits and physical activities), environmental exposures (eg, passive smoking or indoor air pollution), reproductive history, medical history, medication history and family history. We assessed mental health via questionnaires of

Chinese Perceived Stress Scale (0–40), Centre for Epidemiologic Studies Depression Scale (0–60), Self-Report Anxiety Scale (20–80) and sleep quality (Pittsburgh Sleep Quality Scale (0–20)).

We include a questionnaire recording ART medications and pregnancy complications at later visits during each per trimester. To investigate newborn health, we use questionnaires to document food diaries of newborn in food frequency questionnaires including intakes of dietary supplements, mothers' feeding practices, breast milk frequency, sleep patterns in Brief Infant Sleep Questionnaire, anthropometry of infant, medical history and medication history.

Data collection and follow-up of the cohort

The AMCHS is designed to examine exposures from preconception period throughout once per trimester of pregnancy (for those achieving pregnancy), and up to labour and delivery. Ultrasound monitoring of ovarian response was offered as an integral part of the cycle. When the number of mature oocytes met the requirement of IVF/ICSI, couples would be arranged to retrieve oocytes and sperm. Laboratory technicians in the IVF laboratory collected follicular fluid, sperm and seminal plasma. The fasting blood used to test for pregnancy was collected after 2 weeks of embryo transfer surgery. When a positive pregnancy test was obtained, pregnant women were invited to the reproductive centre at gestational weeks 4, 24, 32 for a questionnaire interview and blood sample collection. Medical records at gestational weeks 4, 24, 32 about gestational clinical information were also accessed. The baseline questionnaire and mental health questionnaires are used at each visit.

During the birth admission, maternal blood, and cord blood and tissue were collected by the nursery midwife. The child was examined at ages 30–42 days, 6 months, 1-year and 3-year-olds (during early childhood). At age 30–42 days, 6 months, 12 and 36 months after giving birth, mothers were approached by phone for a questionnaire interview and provided information about clinical physical examination at the local community hospital.

Electronic questionnaires were used for data collection. The original questionnaire data were encrypted and saved to the cloud every day. Quality control staff used prewritten programmes to check the reliability and logic of the data. Results would feed back to the research coordinators on the same day for verification and correction. When missing and unreasonable data occurred, our research coordinators would correct them through face-to-face interviews for participants, by telephone or by checking the electronic medical record system (figure 1).

Outcomes measures

We collected data from the interview questionnaires, extracted medical information from a fertility clinic and delivery records from hospital. Blood samples and follicular fluid were collected from the female partner. Sperm and seminal plasma samples were collected from the male partner. A sample of cord blood and tissue was collected from the newborn.

Electronic medical record abstraction: cycle, pregnancy and delivery data

The AMCHS team abstracted clinical medical records during each individual fertility treatment cycle and throughout follow-up (up to the birth of an infant for those achieving pregnancy). Research coordinators abstracted clinical information in the First Affiliated Hospital of AMHU to ascertain the outcome of each cycle, including physician assigned infertility diagnosis, infertility medical history, blood pressure, body mass index (BMI), medication regimen; hormone at HCG (human chorionic gonadotropin) day, luteal phase support after IVF, scoring for fertilisation, embryo culture and transfer, biochemical pregnancy (with β-hCG measurements), clinical pregnancy (with ultrasound assessment) and relevant data. Antenatal and neonatal hospital medical records were also accessed. During the study period, antenatal, intrapartum and postpartum events were captured from hospital medical records or phone interviews.

The AMCHS Biobank

Blood samples were obtained from female partners at several times during the periods of preconception to delivery and from the male partner at preconception. We also collected blood samples from cord blood and tissue at birth. The collection of blood samples from couples to their babies enable us to explore any heredity influences and detect any potential biomarkers for disease aetiology. Follicular fluid, sperm and seminal plasma were collectedto evaluate the quality of gametes, which could be the key factors of IVF outcomes.

Plasma and blood cell samples were separated from the blood via centrifugation for 10 min at a relative centrifugal force of 3000 g at 4°C. Plasma was stored at a −80°C refrigerator, and the blood cell was stored at −20°C refrigerator. Cord blood and tissue were stored at 4°C after a temporary delivery in the operation room and then transferred to a 20°C refrigerator within 24 hours. Seminal plasma was centrifuged before it was subpackaged. Finally, the sperm (1 mL) and seminal plasma (2 mL) were stored in a nitrogen canister in a −80°C refrigerator. Follicular fluid was collected more than 5 mL on average. After being centrifuged, the subpackage was stored in an −80°C refrigerator.

The overview of data collection and timepoint of AMCHS are shown in table 1 and table 2.

Data presentation and statistical analysis

Data were presented as mean (SD) for continuous variables and as number (percentage) for categoric variables. The continuous variables include age, BMI, depression symptoms, anxiety symptoms, stress symptoms, sleep quality, follicle-stimulating hormone, luteinising hormone, oestradiol. The categorical variables include district (city, country, countryside). Education

Table 1 Data collected during the preconception and pregnancy period of the AMCHS

Data variable	Preconception period		Pregnancy period		
	Male	Female	Visit 1 (4 weeks)	Visit 2 (24 weeks)	Visit 3 (32 weeks)
Socioeconomic status*	√	√			
Lifestyles†	√	√	√	√	√
Environmental exposure	√	√	√	√	√
Physical activities	√	√	√	√	√
Nutritional dietary	√	√	√	√	√
Health condition‡	√	√	√	√	√
Sleep, mood and psychological scale§	√	√	√	√	√
Physician assigned infertility diagnosis	√	√			
Reproductive history		√			
Indications for IVF/ICSI treatment	√	√			
Outpatient preoperative routine examination before the cycle	√	√			
Semen Parameter	√				
ART medication regimen		√			
Luteal phase support after IVF		√			
Scoring for fertilisation		√			
Hormone at HCG day		√			
Embryo culture and transfer		√			
Ultrasound scan of pregnancy			√	√	√
Blood (fasting)	√	√	√	√	√
Follicular fluid		√			
Sperm	√				
Seminal plasma	√				

*Socioeconomic data include educational level, occupation and family income.
†Lifestyle questions include smoking status, alcohol consumption, tea and coffee drinking habits.
‡Health condition include blood pressure, BMI, medical history, medication history, IVF treatment history, pregnancy complication during pregnancy period, menstrual history.
§Sleep, mood and psychological scale consists of 10-item Perceived Stress Scale, Self-Report Depression Scale, Self-Report Anxiety scale and Pittsburgh Sleep Quality Scale. The validity and reliability of Chinese version of above questionnaires have been verified.[36 43]
AMCHS, Anhui Maternal–Child Health Study; ART, assisted reproductive technology; BMI, body mass index; HCG, human chorionic gonadotropin; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilisation.

level (under secondary, secondary, high school, college/university, postgraduate), annual household income (<¥50 000/year, ¥50 000–¥100 000/year, 100 000–200 000/year, ¥200 000–¥300 000/year, >¥300 000/year), occupation (officers, technician, clerk, business and service personnel, agriculture, forestry, animal husbandry, fishery and water conservation personnel, production and shipping equipment operators and related personnel, solider, other practitioners who are inconvenient to be classified, unemployed), smoking status (active smoking, passive smoking), tubal status (normal, abnormal), sexual abstinence (normal, abnormal), infertility type (primary infertility, secondary infertility), antral follicle counting (0, 1–5, 6–10, 11–15, >15) and sperm volume (normal, abnormal). Multivariate adjusted regression models were used to examine the adverse outcomes in relation to baseline exposure variables. All analyses were performed using SPSS V.26.0 (IBM, Armonk, New York, USA).

FINDINGS TO DATE

As this AMCHS is an ongoing cohort study, which will recruit more participants and will have a longer time to follow-up, our initial findings are limited in the followings.

Study participants and characteristics

Online supplemental table 1 shows baseline characteristics of AMCHS women and men. Most of the couples were from the urban areas with a household income of ¥50 000 to ¥1 00 000 (RMB) per year. Of 2042 women, the average age at the time of enrolment was 31.1 years old (SD 4.6) (range 20–48 years), with the majority being in the age group 30–40 years (50.4%), 60.8% are educated ≥college and 26.5% are working in office. While 5.1% of women smoked or used to smoke before pregnancy, 61.5% were exposed to passive smoking, and about one-third of women consumed alcohol. The majority of women (57.4%) had a normal prepregnancy BMI (18.5–<23.9 g/m^2) (the mean

Table 2 Data collected at the postdelivery period of the AMCHS

Data variable	Delivery	Visit 1 30–42 days	Visit 2 6 months	Visit 3 12 months	Visit 4 36 months
Interviews and self-administered questionnaires*		√	√	√	√
Medical records†	√				
Anthropometry measurement‡	√	√	√	√	√
Biosample collection					
Maternal blood	√				
Cord blood	√				
Cord tissue	√				

Medical records are for antenatal, intrapartum and postpartum events of mothers and infants. Anthropometry is for children. The data of postdelivery period is for children.
*Interviews and self-administered questionnaires focused on the child's developmental status include food diaries, Food Frequency Questionnaires, intakes of dietary supplements, mothers' feeding practices, breast milk frequency, Brief Infant Sleep Questionnaire, medical history, medication history and physical activities.
†Medical records include gender of infant, number of gestations, type of delivery, Apgar score, and congenital diseases.
‡Anthropometry measurement includes height, weight, and head circumference.
AMCHS, Anhui Maternal–Child Health Study.

BMI was 22.5 kg/m^2 (SD 3.1)). 6.1% of women suffered anxiety, but 36.7% of women suffered from depression. None of the women had any sleeping problems. Approximately four-fifths of women had a female infertility factor as their primary diagnosis. The main reason for infertility in these women was tubal factors (56.7%). 85.7% women never had a history of pregnancy, and 85.7% of women had never given birth. Of 291 women who used to have a pregnant history, very few participants had a history of hypertension or GDM. Of 1004 women who completed questions about pregnancy history, the rates of caesarean section history, adverse pregnancy history, artificial abortion were 47.1%, 44.4%, 63.6%, respectively, which are both higher than the average rate in China.[36–38]

Of 2042 men, the average age at the time of enrolment was 32.5 years old (SD 4.6) (range 22–57 years), and 55.8% were in the age group of 30–40 years. 65.1% of male participants are educated ≥college, and 26.2% are working in business and service personnel. 54.3% smoked or used to smoke, more than 80% were exposed to passive smoking and 63.3% consumed alcohol. The percentage of normal BMI (18.5–<23.9 kg/ m^2) in men is the highest (%) (the mean BMI was 24.5 kg/ m^2 (SD 3.3)). 27.9% of men suffered from depression, 4.6% had anxiety and 0.1% had a sleeping problem. 33.8% had a male factor as their primary infertility diagnosis, with the main reason being abnormal progressive motility (37.7%).

Cycle endpoints

1828 couples have been examined for a total of 2757 cycles during the follow-up time. These cycles resulted in 1589 pregnancies, of which 5.9% (n=94) were only chemically detected by a β-hCG blood test and not clinically visualised on ultrasound (biochemical losses) (figure 1).

Among these 1475 ultrasound-confirmed pregnancies, 9.4% ended in spontaneous abortion before 20 gestational weeks, 0.58% ended in preterm birth, 9 pregnancies ended in stillbirth (loss in or after 20 weeks) (figure 1).

Table 3 Associations of female age with implantation failure: AMCHS

Age (years)	Participants All	Implantation failure (%)		Model 1 OR	95% CI	P value	Model 2 OR	95% CI	P value
20–29 (group 1)	852	314	36.9	Ref		<0.001	Ref		<0.001
30–34 (group 2)	675	303	44.9	1.43	1.16 to 1.77	0.001	1.39	1.11 to 1.75	0.005
35–39 (group 3)	237	124	52.3	1.97	1.46 to 2.66	<0.001	1.65	1.20 to 2.30	0.002
≥40 (group 4)	58	46	79.3	6.52	3.35 to 12.68	<0.001	4.99	2.47 to 10.08	<0.001

Model 1: adjusted for district (city, country, countryside), education level (under secondary, secondary, high school, college/university, postgraduate) and annual household income (<¥50 000/year, ¥50 000–¥100 000/year, ¥100 000–¥200 000/year, ¥200 000–¥300 000/year, >300 000/year).
Model 2: adjusted for male age, district (city, country, countryside), education level (under secondary, secondary, high school, college/university, postgraduate), annual household income (<¥50 000/year, ¥50 000–¥100 000/year, ¥100 000–¥200 000/year, ¥200 000–¥300 000/year, >¥300 000/year), anxiety, depression, stress, tubal status (normal, abnormal), endometrium status (normal, abnormal), follicle counting (0, 1–5, 6–10, 11–15, >15), female infertility type (primary infertility, secondary infertility), follicle-stimulating hormone, luteinising hormone, oestradiol sexual abstinence (normal, abnormal), antral sperm volume (normal, abnormal), sperm concentration (normal, abnormal) and sperm progressive motility (normal, abnormal).
AMCHS, Anhui Maternal–Child Health Study.

There have been 1057 live births, of which 117 need to be followed up. The remaining 940 pregnancies resulted in 1123 live births: 758 singletons and 363 multiples (181 pairs of twins, one set of triplets). To date, the overall live birth rate per initiated cycle is 38.3% (n=940/2757), and the live birth rate among cycles achieving pregnancy is 71.6% (n=1057/1475) (figure 1).

Data analysis for the impact of female age on implantation failure

This paper has shown our preliminary analysis examining the impact of maternal age on implantation failure based on the current follow-up data in AMCHS. Table 3 shows number and percentage of participants and implantation failure across four age groups, and adjusted OR for implantation failure according to maternal age. The rate of implantation failure significantly increased with age. After adjustment for district, education and family income, OR of implantation failure in women aged 30–34 years was 1.43 (95% CI 1.16 to 1.77), 1.97 (95% CI 1.46 to 2.66) in 35–39 years and 6.52 (95% CI 3.35 to 12.68) in ≥40 years compared with those aged 20–29 years. Further adjustment analysis for including clinical variables did not substantially change these ORs (see model 2 in table 3).

Strengths and limitaions of AMCHS

The AMCHS is the first prospective reproductive cohort study conducted in Anhui, China. The main strengths of AMCHS are the data collected based on couples from preconception period to 3 years of child. This allows us to evaluate the influence of specific sensitive windows towards reproductive and pregnancy outcomes, which are less possible to observe in most pregnancy cohorts.[26 27] We investigate a variety of risk factors for reproductive, pregnancy and child health outcomes. The in-person collection of multiple biospecimens from women, men and their child is over an extended time, enabling us to explore the relationship between risk factors and endpoints of interest at the molecular and genetic level. Using standardised questionnaires, our experienced interviewers have collected rich data from May 2017 to April 2021 and clinical abstraction from electricity medical records, which allows us to examine lifestyle, nutritional, environmental exposure, mental status of infertile couples and provided us with comprehensive covariate data. The resourceful data allow us to explore multiple interactions among risk factors. Furthermore, we highly focus on the paternal impact on adverse reproductive and pregnancy outcomes as the decline of sperm quality of male accounts for 30%–50% of infertility factors[39] and contribute to miscarriage.[40] This is often ignored in most pregnancy cohort studies.[26 27]

The study has limitations. First, the AMCHS cohort study was set up in only one hospital in Anhui province, which may lack external validation. While there have been more than 523 medical institutions approved to carry out human reproductive-assisted technologies across China,[41] we will set up a collaboration with other similarly designed maternal–child cohort studies from different provinces to enlarge the sample size by combining data sources to increase our study external validation. Furthermore, the majority of participants in the AMCHS cohort come from Hefei and 76.5% participants lived in urban areas. They were well-educated and had a higher socioeconomic status and nutrition status, but were less physically active compared with rural residents. Thus, caution should be exercised in generalising our findings to the whole Anhui province. As an ongoing cohort study, we will recruit more participants, particularly from rural areas to examine some specific factors (eg, indoor air pollution) associated with ART adverse outcomes. Second, although the participants' involvement is easy to sustain when they are in the middle of treatment for live birth, 11.1% (117/1057) of families that gave birth to babies are lost to follow-up, and after their babies' birth 6.6% (62 of 940) families withdrew from the study. Although the current withdrawal rate in our study is similar to those in HICs,[28 42] it may increase with the follow-up time. We will take all measures to maintain the cohort members in the follow-up as many as possible and examine the effect of those lost to follow-up on the cohort study findings.

COLLABORATIONS

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Contributors The research protocol was designed by YC. YC and RC set up the concept of this manuscript. JY drafted the manuscript and carried out the data analysis under RC supervision. CL, XP, XX and F-BT helped to collect the database and performed the data quality control. WZ and RK revised the manuscript. YC is responsible for the overall content as guarantor. All authors made comments and revisions on the manuscript and approved the final version.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by the ethics committee of Anhui Medical University (20160270).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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