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ORIGINAL ARTICLE



# Reproductive outcomes of infertile couples undergoing assisted reproductive technology who are carriers of chromosomal abnormalities: a retrospective cohort study

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**ABSTRACT**

**Background:** The aim of this study is to determine whether infertile couples who are carriers of chromosomal abnormalities have distinct cumulative clinical pregnancy and cumulative live birth rates among patients undergoing assisted reproductive technology (ART).

**Methods:** Design: A retrospective cohort study. Setting: Department of Reproduction and Infertility in Chengdu Women's and Children's Central Hospital.

**Patients:** A total of 112 couples were in the exposed group with chromosomal abnormalities, and 226 couples without chromosomal abnormalities were in the control group, totalling 338 cases enrolled from 1 January 2017 to 31 December 2020. The control group (infertile couples without chromosomal abnormalities) was 1:2 matched by female age, type of infertility (primary, secondary), and type of ART (IVF, ICSI, or IUI). The primary outcomes were cumulative clinical pregnancy rate and cumulative live birth rate.

**Results:** The results indicated that chromosome abnormalities did not lead to significant differences in primary outcomes. The overall cumulative clinical pregnancy rate and cumulative live birth rate were not statistically different between the two groups (74.8% vs. 81.6%, $p = .150$) and (65.4% vs. 69.1%, $p = .508$). Further analysis revealed that there was also no significant difference in cumulative miscarriage rate between the two groups (13.9% vs. 20.3%, $p = .213$).

**Conclusions:** There were no significant differences in the cumulative clinical pregnancy rate or cumulative live birth rate between infertile couples with or without chromosomal abnormalities.

**KEY MESSAGES**

- The prevalence of infertility is rising year by year worldwide.
- Carriers of chromosomal abnormalities undergoing ART have the similar cumulative clinical pregnancy rate or cumulative live birth rate.
- The data we analysed have a certain significance for clinical decision-making involving ART for couples with chromosomal abnormalities, and it provides a meaningful reference for patients and physicians in the selection of PGT.

**Abbreviations:** ART: assisted reproductive technology; PGT: preimplantation genetic technologies; IUI: intrauterine insemination; IVF: in vitro fertilization; ICSI: intracytoplasmic sperm injection; CVS: chorionic villus sampling; PCOS: polycystic ovary syndrome; AMH: anti-Müllerian hormone

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Chromosomal abnormalities; infertility; cumulative clinical pregnancy rate; cohort study; assisted reproductive technology

## Introduction

Infertility is a disease of the reproductive system that is defined as failure to achieve a clinical pregnancy within 12 months or more of regular unprotected sexual intercourse (clinical definition according to the World Health Organization (WHO) [1]. The prevalence of infertility is high around the world, and it is estimated that one in four couples are infertile [2]. The latest epidemiological investigation in China showed that among 10 742 women, the prevalence of infertility was 25.0% (2680/10 742) [3]. Data from infertility clinics have shown that 1.3% of partners have chromosomal abnormalities [4], which have been associated with infertility [5] and early abortions [6].

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However, few studies have examined whether couples who were carriers of chromosomal abnormalities undergoing assisted reproductive technology (ART) have a significantly different pregnancy rate and number of embryo transfer procedures performed. Preimplantation genetic technologies (PGTs) [7] are increasingly being used with *in vitro* fertilization (IVF). Genetic counselling and discussion of possible preimplantation genetic testing should be offered when a structural rearrangement (translocation, inversion, deletion, and insertion) is discovered in a parent. PGT is now able to differentiate inherited chromosome arrangements. Chromosomal testing is a routine screening test for infertile couples who have an indication for ART. For all carriers of chromosomal abnormalities, we provide genetic counselling. Some studies found out carriers of chromosomal abnormalities still having a chance of having normal children [8,9]. Even couples with unbalanced chromosomal abnormalities had a similar chance to have a healthy child as non-carrier couples, despite a higher risk of miscarriage [10].

Some IVF practitioners argue that PGT is not properly validated. They argue that current analyses are not sufficiently robust in that they are biased by the fact that clinics are motivated by the need to be seen to be innovating and by the income associated with charging patients for 'the latest' therapy [11]. PGT-A is considered a so-called 'add on' treatment without proper supporting evidence and that any such treatment not validated by RCTs. In the light of current no evidence whatsoever of the benefit of PGT some infertile patients who are carriers of chromosomal abnormalities refuse PGT after genetic counselling and request random selection of embryos when they seek ART. This research aims to determine whether the outcomes are different between couples who are carriers of chromosomal abnormalities and couples without chromosomal abnormalities among the ART population.

## Materials and methods

This was a retrospective cohort study. The exposed group comprised infertile couples with chromosomal abnormalities. The control group comprised infertile couples without chromosomal abnormalities. Bias was due mostly to sampling error. To minimize the sampling error, we matched 1:2 data by female age, type of infertility (primary, secondary), and type of ART, namely, intrauterine insemination (IUI), IVF, or intracytoplasmic sperm injection (ICSI), was conducted. Including criteria was infertile patients who carriers of chromosomal abnormalities refuse PGT after genetic counselling and request random selection of embryos when they seek ART. A total of 4656 infertile couples came to our centre (Department of Reproduction and Infertility, Chengdu Women's and Children's Central Hospital) for ART in the past 3 years (1 January 2017 to 31 December 2020) and were followed-up with phone calls.

Authors had access to information by ID number in our medical record system that could identify individual participants during or after data collection.

### Ethics approval

This study was approved by the Ethics Committee of Chengdu Women's and Children's Central Hospital, and all data were irreversibly anonymized, assuring protection of all patients' information. Ethics approval number: No. B2019 [9].

### Data extraction

The International System for Human Cytogenetic Nomenclature (ISCN, 2016) [12], was used to define chromosomal abnormalities. Infertility was defined according to the WHO criteria. Outcomes were divided into groups by sex among couples with chromosomal abnormalities, and *t*-tests were used. Chromosomal testing is a routine screening method for infertile couples. Some infertile patients who are carriers of chromosomal abnormalities undergo PGT after genetic counselling, while some ask for random selection of embryos when they seek ART. After adequate communication, $>$100 couples (112/4656) who were carriers of chromosome abnormalities who came to our centre for ART refused PGT in the past 3 years (1 January 2017 to 31 December 2019). However, they were told that chorionic villus sampling (CVS) or amniocentesis should be performed.

Two separate members of our team collected the following data from the electronic database of our centre. The quantitative variables were based on common causes of infertility, and the following data were collected: medical record number, female age, male age, chromosome karyotypes, type of infertility, type of ART, endometriosis, immune infertility (positive for anti-sperm antibody, anti-ovarian antibody, anti-endometrium antibody, or anti-cardiolipin antibody), fallopian tube obstruction (diagnosed by hysterosalpingography or laparoscopic surgery), endometrial abnormality (diagnosed by hysteroscopy), polycystic ovary

**Table 1.** Parameters of data extraction.

| Parameters | Quantitative variables | Primary outcomes | Secondary outcomes |
|---|---|---|---|
| 1 | Medical record number | Cumulative clinical pregnancy rate | Cumulative miscarriage rate |
| 2 | Female age | Cumulative live birth rate | MII oocyte count |
| 3 | Male age | | Number of embryos |
| 4 | Chromosome karyotypes | | Number of good-quality embryos |
| 5 | Type of infertility | | |
| 6 | Type of ART | | |
| 7 | Endometriosis | | |
| 8 | Immune infertility | | |
| 9 | Fallopian tube obstruction | | |
| 10 | Polycystic ovary syndrome | | |
| 11 | Years of infertility | | |
| 12 | AMH value | | |
| 13 | Percentage of normal sperm | | |

ART, assisted reproductive technology; AMH, anti-Müllerian hormone.

syndrome (PCOS), years of infertility, anti-Müllerian hormone (AMH) value, percentage of normal sperm. The primary outcomes were cumulative clinical pregnancy rate, and cumulative live birth rate (after 28 weeks of gestation). Secondary outcomes were closely related to clinical outcomes, and the following data were collected: Cumulative miscarriage rate, MII oocyte count, number of embryos, and number of good-quality embryos (Table 1). Embryo grading was performed by the same team of two highly trained embryologists, whom with over 10 years of experience by guidelines for assisted reproduction in China [13]. The outcomes were defined based on the International Committee for Monitoring Assisted Reproductive Technology and the World Health Organization revised glossary of ART terminology 2009. 'Cumulative clinical pregnancy' was defined as the detection of a gestational sac *via* transvaginal ultrasonography including the cycle when fresh embryos were transferred, and subsequent frozen/thawed ART cycles. 'Cumulative live birth' was defined as the complete expulsion or extraction of the foetus from his/her mother, followed by breaths or other evidence of life, such as a heartbeat, umbilical cord pulsation, or definite movements of voluntary muscles including the cycle when fresh embryos were transferred, and subsequent frozen/thawed ART cycles. In China, $<$28 weeks is not considered a live birth. Live birth defined give live foetus after 28 weeks of gestation. Miscarriage: the spontaneous loss of a clinical pregnancy that occurs before 20 completed weeks of gestational age (18 weeks post fertilization) or, if gestational age is unknown, the loss of an embryo/foetus of $<$ 400 g [1]. Cumulative miscarriage rate: Number of miscarriages divided by number of clinical pregnancies. All clinically pregnant patients continued to visit our clinic for 12 weeks. All clinical pregnant patients had miscarried or given birth at the time of follow-up.

### *Statistical analysis*

All data were entered into IBM SPSS Statistics 25. The statistical significance level was set at 0.05. Numerical variables were tested for their normality using the Kolmogorov–Smirnov test. Normally distributed variables are presented as the mean ± standard error of the mean and were compared using ANOVA. Continuous variables with non-normal distributions are expressed as the median and range and were compared using the nonparametric method (Kruskal–Wallis rank-sum test or Wilcoxon–Mann–Whitney test). Independent sample *t*-tests were used for continuous variables. Nominal variables are reported in the form of frequencies with percentages and were compared using the $\chi^2$ test or Fisher's exact test. The relationship between these factors and cumulative pregnancy rate/delivery of a healthy baby (baby-take home rate) was studied using conditional logistic regression, and the estimated odds ratios (ORs) and their 95% confidence intervals (CIs) are reported. Variables with *p* values $<$.1 in the univariate analysis were included in the multivariate stepwise logistic regression to explore the independent factors in predicting the pregnancy/delivery rate.

### *Patient and public involvement*

Patients were not involved in this study.

## Results

### *Baseline characteristics*

The baseline characteristics of the cases are shown in Table 2. Couples with chromosomal abnormalities were in the exposed group. The control group was matched by female age, type of infertility, and type of ART. Additionally, male age, endometriosis, and PCOS,

**Table 2.** Baseline characteristics of study population.

| Characteristic | Exposed group Cases ($N = 107$) | Control group Cases ($N = 223$) | $p$ value |
|---|---|---|---|
| Type of infertility | | | .616 |
| Primary | 65 (60%) | 129 (58%) | |
| Secondary | 42 (40%) | 94 (42%) | |
| Type of ART | | | |
| IVF | 79 (74%) | 162 (73%) | .953 |
| ICSI | 21 (20%) | 47 (21%) | |
| IUI | 7 (6%) | 14 (6%) | |
| Female age | 30 (23–40) | 30 (21–40) | .695 |
| Male age | 31 (23–51) | 31 (22–50) | .749 |
| Endometrium abnormality | 17 (16%) | 27 (12%) | .344 |
| Endometriosis | 10 (9%) | 16 (7%) | .493 |
| Immune infertility | 2 (2%) | 8 (4%) | .394[a] |
| Fallopian tube obstruction | 64 (60%) | 135 (61%) | .900 |
| PCOS | 22 (21%) | 45 (20%) | .936 |
| Year of infertility | 3.00 (1.00–18.00) | 3.00 (0.3–13) | .030[†] |
| AMH value | 3.42 (0.07–18.00) | 2.80 (0.06–18.00) | .323 |
| Percentage of normal sperm% | 2.5 (0–10) | 2.5 (0–9.7) | .469 |

Values are presented as median (range) or $n$ (%).
[†]$p < 0.05$.
[a]Using the result of Fisher's exact test.
ART: assisted reproductive technology; IVF: *in vitro* fertilization; ICSI: intracytoplasmic sperm injection; IUI: intrauterine insemination; AMH: Anti-Müllerian hormone.

among other variables, did not significantly differ between cases and controls.

### Types and numbers of chromosome anomalies

A total of 112 couples had chromosomal abnormalities. Among the couples, 66 of the carriers were male (59%), and 46 were female (41%). The types of abnormalities were divided into five categories: chromosome disorder/structural aberrations/chromosomal inversion (62/112); translocation (12/112); Robertsonian translocation (ROB, 4/112); and sex chromosome abnormalities (Table 3). The detailed list of karyotype is presented in Supplementary Material S1. We had excluded the sperm donor in both groups, 107 couples had chromosomal abnormalities and 223 couples had normal chromosomal were include in the analysis.

### Clinical outcomes

Our statistical results show that there were no significant differences in primary outcomes among those with chromosomal abnormalities compared with those without. The overall cumulative clinical pregnancy rate was nearly the same between the two groups (74.8% vs. 81.6%, $p = .150$). The overall cumulative live birth rate was also nearly the same between the two groups (65.4% vs. 69.1%, $p = .508$, Table 4). Statistical analysis of the secondary clinical outcomes showed that there were no statistically significant differences

**Table 3.** Karyotype of carriers with various chromosomal abnormalities.

| Karyotype | Male | Female | Total |
|---|---|---|---|
| Inversion(inv) | 32 | 30 | 62 |
| Translocation(t) | 7 | 5 | 12 |
| Robertsonian translocation (rob) | 2 | 2 | 4 |
| Sex abnormalities | | | |
| 46, X, inv (Y) | 16 | | 20 |
| 47, XYY | 1 | | |
| 47, XXX | | 1 | |
| 47, XY, +mar | 2 | | |
| Mosaic | 3 | 11 | 14 |
| Total | 63 | 49 | 112 |

**Table 4.** Primary clinical outcomes.

| Characteristic | Exposed group %($n$/$N$) | Control group %($n$/$N$) | $p$ value |
|---|---|---|---|
| Cumulative clinical pregnancy rate | | | |
| Overall | 74.8% (80/107) | 81.6% (182/223) | .150 |
| IVF | 78.5% (62/79) | 87.0% (141/162) | .087 |
| ICSI | 76.2% (16/21) | 83.0% (39/47) | .520[a] |
| IUI | 28.6% (2/7) | 14.3% (2/14) | .574[a] |
| Cumulative live birth rate | | | |
| Overall | 65.4% (70/107) | 69.1% (154/223) | .508 |
| IVF | 68.4% (54/79) | 74.1% (120/162) | .352 |
| ICSI | 71.4% (15/21) | 68.1% (32/47) | .783 |
| IUI | 14.3% (1/7) | 14.3% (2/14) | 1.000[a] |

Values are presented as % ($n$/$N$).
[a]Using the result of Fisher's exact test.

in cumulative miscarriage rate, MII oocyte count, embryo count, good-quality embryo count, or number of embryo transfer procedures performed (Table 5). Analysis by gender in couples with chromosomal abnormalities showed that there were no statistically significant differences in both primary outcomes and secondary outcomes (Table 6).

### Univariate analysis of the primary outcomes

One-way ANOVA showed that assisted reproduction techniques, fallopian tube obstruction, AMH, and female age had effects on the cumulative clinical pregnancy rate. Only assisted reproduction techniques and female age had effects on the cumulative live birth rate (Supplementary Material S2).

### Multivariate analysis of the primary outcomes

Multivariate analysis of primary outcomes was performed by logistic regression. The method was to input all the included factors into the model and calculate the $p$ value after adjustment. In the single-factor analysis, male and female age, type of infertility, fallopian tube obstruction, and AMH had $p < .1$, but after regression analysis after including all factors in the model, only female age and type of infertility had

**Table 5.** Secondary clinical outcomes.

| Characteristic | Exposed group $n = 105$ | Control group $n = 209$ | $p$ value |
|---|---|---|---|
| Cumulative miscarriage rate | 13.9% (11/79) | 20.4% (37/181) | .213 |
| MII oocyte count | 14 (2–36) | 14 (1–42) | .781 |
| Embryo count | 5 (0–15) | 5 (0–20) | .547 |
| High quality embryo count | 2 (0–15) | 2 (0–17) | .974 |
| Number of embryo transfer procedures performed | 1 (0–5) | 1 (0–5) | .017* |

Values are presented as median (range).
*$p < .05$.

**Table 6.** Analysis by gender in couples with chromosomal abnormalities.

| Outcomes | Male | Female | $p$ value |
|---|---|---|---|
| Cumulative clinical pregnancy rate | 46 (73.0%) | 34 (77.3%) | .618 |
| Cumulative live birth rate | 41 (65.1%) | 29 (65.9%) | .929 |
| Cumulative miscarriage rate | 13.3 (6/45) | 14.7 (5/34) | 1.000* |
| MII oocyte count | 14.30 ± 7.194 | 14.77 ± 7.919 | .758[a] |
| 2PN | 9 (0–24) | 8 (1–32) | .791 |
| Embryo count | 6 (0–14) | 5 (0–15) | .176 |
| High quality embryo count | 2 (0–11) | 2 (0–15) | .619 |
| Number of embryo transfer procedures performed | 1 (0–5) | 1 (0–3) | .626 |

*Values are presented as mean ± standard deviation, median (range) or $n$ (%).
[a]In the male chromosomal abnormalities carrier group and female chromosomal abnormalities carrier group, this variable follows a normal distribution, $p$ value is calculated using Student's $t$-test.

$p < .05$, with the other factors having $p > .05$ (Supplementary Material S3).

## Discussion

The prevalence of infertility is rising year by year worldwide. The latest epidemiological investigations have shown the prevalence of infertility to be 25% in China [3]. Chromosomal abnormalities are associated with infertility [5] and may be the major recognized genetic cause of recurrent miscarriage [14]. Our study indicated that the primary outcomes (cumulative clinical pregnancy rate and cumulative live birth rate) were not affected by chromosome abnormalities without PGT in the comparison of the two groups. The miscarriage rate of two groups was no statistic difference too. Because of the small amount of miscarriage, we use it as a secondary outcome. This study found that the number of embryo transfer procedures performed was lower after ICSI in the exposed group, which may be associated with a greater proportion of chromosomal abnormalities in male.

Although male age and normal sperm percentage did not affect the primary outcomes (cumulative clinical pregnancy rate and cumulative live birth rate), male age was highly correlated with fertilization and embryo count. Although there has been a significant decline in the fertility of both men and women globally, although there has been a significant decline in the fertility of both men and women globally, intracytoplasmic sperm injection (ICSI), the problem caused by the male factor is partially solved. One study showed the normal sperm morphology rate <4% significantly increased the total fertilization failure rate but did not affect the clinical or neonatal outcomes [15].

Genetic counselling and discussion of possible preimplantation genetic testing should be offered when a structural rearrangement (translocation, inversion, deletion, or insertion) is discovered in a parent. Because of these limitations, confirmation of preimplantation genetic testing–structural rearrangement results by means of chorionic villus sampling (CVS) or amniocentesis should be offered [16]. However, the evidence suggests that universal use of PGT-A is premature. We know that the technology is imperfect: PGT-A can erroneously call euploid embryos aneuploid [17] and we do not know what to do with apparently mosaic embryos [18]. Blockeel et al. showed that preimplantation genetic screening does not increase the implantation rates after IVF-intra-cytoplasmic sperm injection in women with repeated implantation failure [19]. Some studies have failed to show improvements in live birth rates for women younger than 37 years of age [20–22], so it seems unlikely that the added complexity and cost of this intervention can be justified in younger patients. An economic analysis of preimplantation genetic testing for aneuploidy by polar body biopsy in woman of advanced maternal age showed that PGT-A greatly increased the cost and suggested that patients and doctors need to be aware of the high-cost implications of applying PGT-A [23].

Embryo selection with preimplantation genetic testing may improve pregnancy outcomes after initial

embryo transfer. However, it remains uncertain whether PGT improves the cumulative live-birth rate as compared with conventional IVF. This study will support some evidence to confirm that PGT is not properly validated for carriers of chromosomal abnormalities. Previous studies in carriers of chromosomal abnormalities showed they were just as high as to have a healthy child as non-carrier couple. This study in couples undergoing ART has the similar conclusions. The data we analysed have a certain significance for clinical decision-making involving ART for couples with chromosomal abnormalities, and it provide a meaningful reference for ART population, fertility experts, and genetic counsellors for risk evaluation, selecting the most appropriate ART as well as management and treatment.

### *Limitations of this study*

This was a retrospective cohort study. Bias was due mostly to sampling error. To minimize the sampling error, we 1:2 matched the data by female age, type of infertility, and type of ART. The data source is from a single centre, the sample size is small, and the data do not include PGT. We need to further expand the sample size.

## Conclusion

There were no significant differences in cumulative clinical pregnancy rate and cumulative live birth rate between carriers of chromosomal abnormalities and non-carrier couples in infertile couples undergoing ART.

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## Author contributions

L.C. and F.W. involved in design and conduct of the study, data analysis, drafting the manuscript. Y.L. involved in supervised data analysis, and revised the manuscript. M.L. involved in the design and conducted the study, checked data extraction and validated the final version for submission. All authors approved the final manuscript and agreed to be accountable for all aspects of the work.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

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## Data availability statement

The data that support the findings of this study are available from Chengdu Women's and Children's Central Hospital, but restrictions apply to the availability of these data, which were used under licence for the current study and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission from the Ethics Committee of Chengdu Women's and Children's Central Hospital.

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