

## RESEARCH

# Chromosomal polymorphisms in assisted reproduction: an analysis of 942 cycles

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## Abstract

The use of intracytoplasmic sperm injection (ICSI) has recently increased worldwide. The live birth rate per ICSI cycle is low, and over half of infertile couples remain childless. Chromosomal polymorphisms are up to five times more common in couples with infertility compared to the general population. We aimed to investigate the association between chromosomal polymorphisms and reproductive outcomes in couples undergoing ICSI treatment. We analysed 942 ICSI fresh and frozen embryo transfer cycles in 697 women who underwent karyotyping analysis using Giemsa-Trypsin-Leishman banding prior to assisted conception at the Fertility Centre of Lanka Hospitals, Sri Lanka, between 2016 and 2018. The primary outcomes were pregnancy, miscarriage, and live birth rates. We compared outcomes according to the presence or absence of chromosomal polymorphism in females, males and couples. There were 294 pregnancies (31.2%) recorded in the study; 130 suffered a miscarriage (13.8%), 13 were ectopic pregnancies (1.3%) and 151 resulted in a live birth (16.0%). The evidence from univariable and multivariable analyses (adjusted for age, BMI, ovarian reserve and treatment type) did not confidently identify a difference in pregnancy, miscarriage or live birth rates between couples with no chromosomal polymorphisms compared to couples where the female, male or both partners were carriers of a chromosomal polymorphism. Further, we did not identify a clear association between the presence of chromosomal polymorphisms and reproductive outcomes compared to participants without chromosomal polymorphisms. Wide CIs precluded the identification of clinically meaningful associations.

## Lay summary

Infertility affects approximately one in eight couples worldwide. The use of intracytoplasmic sperm injection (ICSI), where the sperm is directly injected into an egg using a micromanipulator outside the body, has become particularly popular in recent years. However, the success rate remains low. In human cells, the genetic material is arranged in structures called chromosomes. Chromosomal polymorphism is a normal variation where the genetic material is arranged differently to the average individual and is more common in infertile couples compared to the general population. We analysed data from 942 ICSI cycles in 697 couples who underwent karyotyping analysis to assess the changes in chromosomes between 2016 and 2018. The pregnancy rate was 31.2%, with 16.0% of participants experiencing a live birth, while 13.8% of pregnancies resulted in a miscarriage and 1.3% were outside the womb cavity (ectopic). The evidence did not identify a clear association between the chromosomal polymorphism and the outcome of treatment.

**Key Words:** ► infertility ► assisted reproductive treatment ► chromosomal polymorphism ► pregnancy outcomes

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## Introduction

Infertility is common, affecting one in eight couples worldwide (ESHRE 2020). Assisted reproductive technology (ART), including *in vitro* fertilisation (IVF) and intracytoplasmic sperm injection (ICSI), is the mainstay treatment for couples with infertility. More than two million ART cycles are performed worldwide every year, and this number is steadily increasing (Mascarenhas *et al.* 2012, ESHRE 2022). The use of ICSI has become particularly popular in recent years, with double the number of cycles globally compared to conventional IVF (ESHRE 2018). However, the live birth rate per ICSI cycle remains relatively low (~30%) (HFEA 2016).

Chromosomal polymorphisms are normal variations that occur in 2–5% of the general population. They are usually found in the genetically inactive heterochromatic regions of chromosomes (Wyandt *et al.* 2017) and have no clear impact on phenotype (Brothman *et al.* 2006), although in many species chromosomal polymorphisms result in reduced fertility (Kirkpatrick *et al.* 2010). In humans, polymorphisms are also up to five times more common in couples with infertility compared to the general population (Xu *et al.* 2016). The presence of polymorphism affects spermatogenesis adversely and could be detrimental to the outcome of ICSI (Nakamura *et al.* 2001, Yakin *et al.* 2005). In addition, increased rates of recurrent miscarriages and other adverse obstetric outcomes have been associated with chromosomal polymorphism (Minocherhomji *et al.* 2009, Ahmet Okay *et al.* 2010, Pokale 2015).

Chromosomal polymorphism is described as the presence of variants in the heterochromatin region of the chromosome. The constitutive heterochromatin is the stable form present in the polymorphic variants. An increase or decrease of the heterochromatin region of the long arm of the chromosome constitutes heterochromatic segments (non-acrocentric). Chromosomal polymorphism may also manifest through increases in the length of the short arm of the chromosome (acrocentric) with a satellite stalk, satellite or a double satellite. Finally, the International System for Human Cytogenetic Nomenclature considers gene inversions [Inv(9)] to also fall within the definition of chromosomal polymorphism (Shaffer *et al.* 2013).

A recent systematic review of chromosomal polymorphism in assisted reproduction found an association with higher rates of miscarriage which was sex-dependent given the higher miscarriage rate observed in female carriers of chromosomal polymorphism compared to male carriers (Ralapanawe *et al.* 2022). The review did not find evidence related to chromosomal polymorphisms

having any adverse effects on rates of pregnancy, clinical pregnancy, ongoing pregnancy, preterm birth and live birth after IVF or ICSI, irrespective of whether the carrier was the female partner, the male partner or both. In addition, the systematic review called for further research to confirm the association between polymorphic variations in females and miscarriage and to strengthen the certainty of the evidence for other reproductive outcomes. We propose that if miscarriage rates are higher in patients with chromosomal polymorphism, it is reasonable to hypothesise that there could be a knock-on effect on other pregnancy outcomes. Here we explore the association between chromosomal polymorphisms and reproductive outcomes in couples undergoing ICSI treatment.

## Materials and methods

### Study design

This study retrospectively investigated couples undergoing karyotyping analysis followed by a cycle of ICSI treatment at the Fertility Centre of Lanka Hospitals Corporation Plc, Sri Lanka, from January 2016 to December 2018. Pregnancy outcomes were collected until November 2019.

We excluded couples undergoing treatment with donor gametes, with numerical or structural abnormalities in karyotyping or absence of karyotyping reports, poor follicular development, abnormal cleavage or blastocyst formation, freeze-all cycles and records where pregnancy outcomes had not been documented.

### Karyotype analysis

Karyotyping was performed on peripheral blood leukocytes. The standard laboratory protocol using Giemsa-Trypsin-Leishman banding was followed for all samples. Twenty metaphases were counted and analysed. Four to five karyotypes were analysed at a banding resolution of 550 $\times$ . The karyotyping results were reviewed by two analysts independently.

### Ovarian stimulation, ICSI and embryo culture

All female participants were stimulated with a long protocol using GnRH agonist 0.1 mg (triptorelin/Decapeptyl, Ferring GmbH, Wittland, Germany) combined with recombinant follicle-stimulating hormone (FSH) 150–450 IU (follitropin alfa/Gonal-f, Merck Serono, Modugno (BA), Italy) or a short protocol with GnRH antagonist 0.25 mg (cetorelix

acetate/Cetrotide, Baxter Oncology GmbH, Halle, Germany) combined with recombinant FSH 150–450 IU. After the evaluation of serum oestradiol level (1000–5000 pg/mL) on the tenth day, recombinant human chorionic gonadotrophin (hCG) 250 µg (choriogonadotropin alfa/Ovidrel, Merck, Serono S.p.A., Modugno (BA), Italy) was administered subcutaneously. Oocyte recovery was performed 35 h after the hCG injection. Following oocyte insemination with ICSI, embryos were cultured (Vitrolife Sweden AB, V.Frolunda, Sweden) for up to 3 days. All embryos with more than six cells were selected. Two embryos were transferred per fresh cycle, and the remaining embryos were vitrified. In women where a fresh transfer was not possible, we performed cryopreservation of all embryos and carried out frozen embryo transfer (FET) at a later date.

### Embryo transfer

Two cleavage-stage fresh embryos were transferred per cycle, and the remaining embryos were vitrified. Subsequent FET cycles involved warming and transfer at cleavage stage (six to eight cells) or further culture of embryos for 2 days until blastocyst formation.

### Outcomes and follow-up

Pregnancy was confirmed 2 weeks after embryo transfer (Serum  $\beta$  HCG >10 mIU/mL). The primary outcomes included pregnancy rate (gestational age 4–6 weeks), miscarriage rate (gestational age less than 12 weeks) and live birth rate (gestational age over 32 weeks). Outcome data were analysed per female, male and couple according to the presence or absence of chromosomal polymorphism. There were no missing data for demographic characteristics including age, BMI, FSH, luteinising hormone (LH), thyroid-stimulating hormone (TSH), free thyroxine (T4) and prolactin. The pregnancy rate refers to positive pregnancies for the cycles with embryo transfers. Miscarriage refers to pregnancy losses calculated from the total number of treatment cycles. Live birth rate refers to the total number of live babies from the total number of fresh and frozen embryo transfers.

### Statistical analysis

Baseline characteristics and outcome data were described with proportions for binary data or means with S.D. or median and interquartile range for continuous variables, as appropriate. The rates of the reproductive outcomes

were plotted graphically using proportions and 95% CIs. Complete case analysis was adopted. Logistic regression models were fitted to estimate the unadjusted and adjusted odds ratio for confounding variables including age, BMI, FSH, LH and type of treatment (fresh vs frozen). All statistical analyses were done using Stata Statistical Software (Release 16, TX, USA).

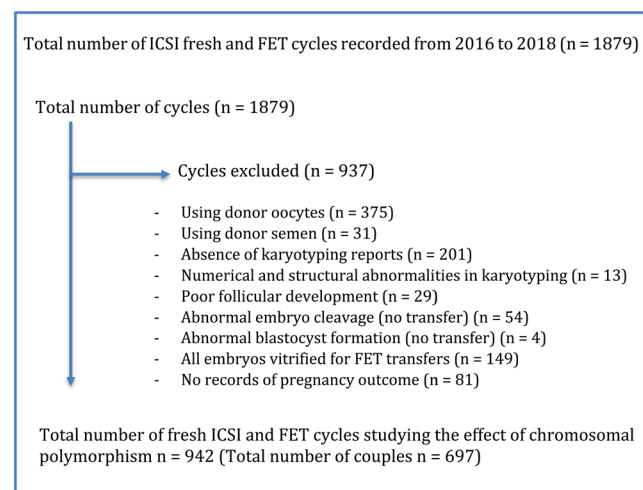
### Ethical consideration

The ethics committee of Lanka Hospitals Corporation PLC granted permission for the use of the patient record data database following the review of the study protocol.

### Results

There were 1879 ICSI and FET cycles performed at the Fertility Centre during the study period. In total, 937 fresh ICSI and FET cycles were excluded from the analysis due to the use of donor gametes, absence of karyotyping reports, numerical and structural abnormalities in karyotyping, poor follicular development, abnormal cleavage and blastocyst formation, embryo vitrification without subsequent transfer and records without pregnancy outcomes. [Figure 1](#) shows the data selection process. There were 149 participants who underwent long ( $n = 114$ ) or short ( $n = 35$ ) protocol stimulation and did not proceed with FET due to hyperstimulation or any other factors but went on to have FET at a later date. In total, 942 treatment cycles (548 fresh ICSI cycles and 394 FET cycles) from 697 couples were included in the study.

[Table 1](#) contains baseline characteristics of the study population. Supplementary Table 1 (see section on



**Figure 1** Flow chart of data selection process.

**Table 1** Baseline characteristics of the study population ( $n = 942$ ). Data are presented as  $n$  (%) or as mean  $\pm$  S.D.

Characteristics	Values
Age	34 $\pm$ 4.1
BMI	24 $\pm$ 3.8
FSH	6.5 $\pm$ 1.8
LH	5.8 $\pm$ 2.7
Treatment type	
ICSI cycles	
Long agonist	407 (43.2)
Short antagonist	141 (15)
FET cycles	
Cleavage stage transfers (day 3)	219 (23.2)
Blastocyst stage transfers (day 5)	175 (18.6)
Oocytes retrieved	15.5 $\pm$ 8.2
Mature oocytes	15.0 $\pm$ 8.2
Fertilised oocytes	11.2 $\pm$ 7.4
Cleavage embryos (day 3)	7.5 $\pm$ 5.1
Chromosomal polymorphism	
Females with polymorphism	150 (15.9)
Males with polymorphism	200 (21.2)
Couples with polymorphism	144 (15.3)
Couples without polymorphism	448 (47.6)

FET, frozen embryo transfer; FSH, follicle-stimulating hormone; ICSI, intracytoplasmic sperm injection; LH, luteinising hormone.

supplementary materials given at the end of this article) contains types of chromosomal polymorphic variants present in female and male participants in the study population.

From the 942 cycles analysed, in 144, both partners were carriers of polymorphisms (15.3%); in 150, only the female partners were carriers of polymorphisms (15.9%); in 200, only the males were carriers of polymorphisms (21.2%); and in 448 cycles, neither partner carried a polymorphism (47.6%).

There were 294 pregnancies (overall pregnancy rate 31.2%; ICSI pregnancy rate 24.3% (133/548); FET 40.9% (161/394) recorded in 942 cycles in the study); of which, 130 suffered a miscarriage (overall miscarriage rate 13.8%; ICSI miscarriage rate 11.3% (62/548); FET 17.2% (68/394)), 13 had an ectopic pregnancy (1.3%; ICSI 1.5% (8/548);

FET 1.3% (5/394)) and 151 had a live birth (overall live birth rate 16.0%; ICSI live birth rate 11.5% (63/548); FET 22.3% (88/394)). The total number of participants with chromosomal polymorphic variants was 494 (52.4%), while 448 (47.6%) did not exhibit any of the polymorphic variants. Table 2 shows details of pregnancy, miscarriage and live birth rates according to the presence or absence of chromosomal polymorphism.

Table 3 presents the unadjusted and adjusted odds ratios for factors influencing the rates of pregnancy, miscarriage and live birth. We found no association between chromosomal polymorphisms and these reproductive outcomes.

Figure 2 shows the point effect estimates and respective CIs for outcomes of pregnancy, miscarriage and live birth for the whole cohort and for females, males and couples with polymorphism.

## Discussion

In this analysis, we found no evidence of a difference in pregnancy, miscarriage or live birth rates between participants without polymorphisms and in those where one or both partners were carriers of chromosomal polymorphisms. This was observed in the unadjusted univariate analysis and multivariate analysis adjusted for age, BMI, ovarian reserve markers and treatment type. Although some of our point estimates suggest a clinically important impact, the CIs were wide and crossed the line of no effect.

In this study, some participants did not proceed with FET due to hyperstimulation or other factors and underwent FET instead. A small proportion of outcome data on pregnancy, miscarriage and live birth were missing or not reported and were not included in the study. The study sample was large, but we cannot rule out a type II error. The attrition or loss to follow-up rate were low, and we were able to adjust the result for potential confounders.

**Table 2** Pregnancy, miscarriage and live birth rates of carriers and non-carriers of chromosomal polymorphism.

Polymorphism	$n$	Pregnancy rate (%)	Miscarriage rate (%)	Live birth rate (%)
Females, males or couples with polymorphism	494	156 (31.6)	73 (14.8)	79 (16.0)
Females with polymorphism	150	36 (24)	19 (12.7)	16 (10.7)
Males with polymorphism	200	68 (34)	28 (14)	38 (19)
Couples with polymorphism	144	52 (36.1)	26 (18.1)	25 (17.4)
Couples without polymorphism	448	138 (30.8)	57 (12.7)	72 (16.1)
Total	942	294 (31.2)	130 (13.8)	151 (16.0)

Ectopic pregnancies ( $n = 13$ , 1.3%) were excluded from the miscarriages

**Table 3** Unadjusted and adjusted odds ratio for pregnancy, miscarriage and live birth rates.

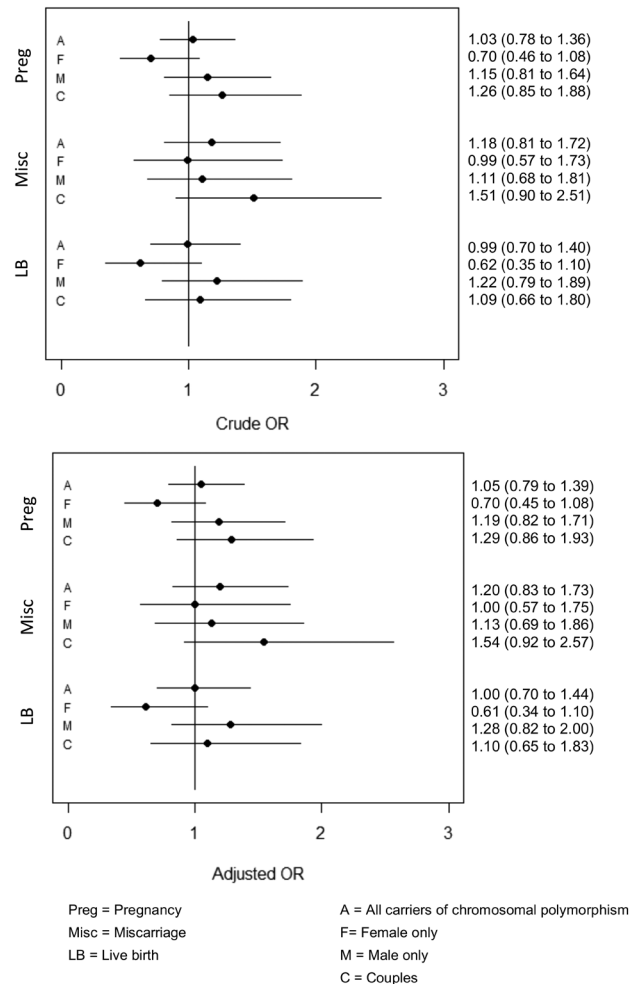
Outcome	Unadjusted OR		Adjusted OR	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Pregnancy				
Females, males or couples with polymorphism	1.03 (0.78–1.36)	0.79	1.05 (0.79–1.39)	0.73
Females with polymorphism	0.70 (0.46–1.08)	0.11	0.70 (0.45–1.08)	0.10
Males with polymorphism	1.15 (0.81–1.64)	0.42	1.19 (0.82–1.71)	0.34
Couples with polymorphism	1.26 (0.85–1.88)	0.23	1.29 (0.86–1.93)	0.21
Miscarriage				
Females, males or couples with polymorphism	1.18 (0.81–1.72)	0.36	1.20 (0.83–1.73)	0.32
Females with polymorphism	0.99 (0.57–1.73)	0.98	1.00 (0.57–1.75)	0.99
Males with polymorphism	1.11 (0.68–1.81)	0.65	1.13 (0.69–1.86)	0.60
Couples with polymorphism	1.51 (0.90–2.51)	0.11	1.54 (0.92–2.57)	0.09
Live birth				
Females, males or couples with polymorphism	0.99 (0.70–1.40)	0.97	1.00 (0.70–1.44)	0.95
Females with polymorphism	0.62 (0.35–1.10)	0.10	0.61 (0.34–1.10)	0.10
Males with polymorphism	1.22 (0.79–1.89)	0.35	1.28 (0.82–2.00)	0.27
Couples with polymorphism	1.09 (0.66–1.80)	0.71	1.10 (0.65–1.83)	0.71

The reference category is no chromosomal polymorphism in either partner. OR, odds ratio.

Our findings are consistent with existing literature summarised in our previous systematic review of observational studies (Ralapanawe *et al.* 2022). The review suggested that there was a paucity of evidence on whether polymorphic variation in individuals (males or females) or couples adversely affects the chance of a pregnancy, miscarriage and live birth following ICSI, except for miscarriage in the presence of chromosomal polymorphism in females. However, nine studies in the systematic review involved participants of Chinese origin, and extrapolation to other cohorts may not be appropriate.

The existing literature is conflicting, with some authors reporting that chromosomal polymorphisms are associated with adverse reproductive outcomes (Xiaobin *et al.* 2012, Cheng *et al.* 2017), while others have identified no such association (Hong *et al.* 2011, Liang *et al.* 2014, Song *et al.* 2017). It is possible that our study may have been underpowered to detect any differences. Further, a small adverse effect of chromosomal polymorphisms upon reproductive outcomes may exist for some populations but not others. There is a need for additional prospective studies evaluating the association between chromosomal polymorphisms and reproductive outcomes in patients of multiple ethnicities.

Finally, future research should investigate whether there is an adverse effect from specific high-risk chromosomal polymorphisms on reproductive outcomes. There is evidence that specific types of polymorphisms including non-acrocentric and Yqh in male patients may exhibit a particularly strong association with reproductive outcomes (Yakin *et al.* 2005, Sipek Jr *et al.* 2014, Xu *et al.*



**Figure 2** Confidence intervals of unadjusted and adjusted odds ratios of pregnancy, miscarriage, and live birth of female, male and couple with chromosomal polymorphism.

2016). It remains unclear, however, whether these high-risk polymorphisms are associated with adverse outcomes following ART.

#### Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/RAF-21-0116>.

#### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartialities of the research reported.

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#### Author contribution statement

M S B R and I G were responsible for defining the research question; M S B R, S L G and I G conceptualised and designed the work; M S B R and S L G were responsible for the data acquisition; M J P, M S B R, S L G, and I G performed the statistical analysis; S L G assisted in the design of the figures and tables, and in the manuscript preparation; All authors including N K assisted with interpretation of the findings; M S B R drafted the manuscript. P M and I G revised the final manuscript. All authors revised the manuscript critically for important intellectual content and gave final approval of the version to be published. A C is the guarantor.

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