*Original Article*

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# Systematic analysis and evaluation of chromosome aberrations in major birth defects associated with infertility

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**SUMMARY** Previous studies have indicated an elevated risk of infertility in certain birth defects, including congenital heart disease (CHD), hypospadias, cryptorchidism, and disorders of sexual development (DSD). Although the identification of chromosomal abnormalities or chromosomal aberrations (CAs) is crucial for the diagnosis of these conditions, the assessment of CAs in these disorders remains unclear, and few large-scale studies have been conducted at multiple centers. The aim of the current study was to systematically evaluate the prevalence of CAs in CHD, hypospadias, cryptorchidism, and DSD. Studies reporting CAs in these birth defects were retrospectively analyzed from 1991-2023, using online databases such as PubMed and Google scholar as well as preprints and references from related literature. Comprehensive screening, data acquisition, and systematic assessments of the identified literature were performed. Ultimately, searches yielded a total of 7,356 samples from 14 published articles on CHD, 298 hypospadias cases from 4 published articles, 1,681 cryptorchidism cases from 4 published articles, and 2,876 DSD cases from 7 published articles. Carrier rates of CAs varied widely among these studies and conditions. A retrospective analysis revealed that CHD was associated with the highest carrier rate (26%) for CAs, followed by DSD (21%), hypospadias (9%), and cryptorchidism (5%). A subtype analysis of CAs indicated a higher prevalence of numerical abnormalities among the reported cases. Therefore, considering CAs in birth defects associated with infertility is imperative. This provides a foundation for the further clinical implementation of chromosomal screening and enhancing high-risk screening for individuals in the real world.

***Keywords*** chromosomal aberration, birth defects, infertility

## 1. Introduction

Birth defects are a physiological or structural abnormality at birth that can arise from various factors, including developmental defects, infection, and heredity. Approximately 6% of newborns worldwide are affected by birth defects, ranging from treatable cases to severe conditions that significantly impact lifelong health (*1*). This issue has become a crucial determinant of population quality, particularly as several countries have experienced a significant decline in birth rates over the past few decades. In China, for example, the birth rate has noticeably decreased from 14‰ to 6.8‰ since 2000, accompanied by a decline in fertility and a changing profiling of major birth defects (*2*). Birth defects such as congenital heart disease (CHD) and hypospadias are associated with infertility (*2*), uncovering factors contributing to reduced fertility rates. In addition, disorders that affect the endocrine and reproductive systems such as androgen insensitivity syndrome (AIS) (*3*), a common disorder of disorders of sex development (DSD), may also have significant impacts on fertility. Chromosomal aberrations (CAs), consisting of numerical and structural chromosome abnormalities, are a common characteristic of severely clinical consequences such as spontaneous abortion, death, and birth defects (*4,5*). CAs are also associated with disorders of reproductive and sexual development (*5,6*). Numerical CAs, mainly including aneuploidy, are caused by chromosome segregation errors in mitosis, whereas structural CAs in the form of chromosomal fragments, rearrangements, chromosomal translocations, and heterozygous deletions are the result of DNA damage and arm-level chromosome gain or loss (*7,8*). Despite many studies focusing on the identification of associated genes using whole-exome sequencing, there remains a lack of multicenter studies on CAs. Therefore, the aim of the current study was to systematically assess the prevalence of CAs in these four birth defects that affect fertility, offering fundamental insights for the future clinical

implementation of chromosomal screening.

## 2. Literature search strategies and analytical methods

### 2.1. Search strategies

This systematic review was conducted following the PRISMA guideline (*9*). PubMed and Google scholar were used to search for articles published between 1991 and 2023 by two authors with the keywords "chromosome aberrations", "chromosomal disorder", "congenital heart disease", "hypospadias", "cryptorchidism", and "disorders of sex development". In addition, the references of the articles were reviewed to identify potentially relevant studies and ensure comprehensive coverage of the relevant literature. Only English-language literature was considered for analysis. Two reviewers independently evaluated the eligibility of the articles based on the following criteria: (a) assessment of the association between these types of birth defects and CAs; (b) availability of original data from randomized controlled trials, non-randomized controlled clinical trials, prospective and retrospective cohort studies, and case-control studies; and (c) the incidence of CAs for which data were available or could be obtained from the given data. Potentially eligible studies were excluded if they were: (a) conference papers or editorials; (b) case reports and case series; (c) repetitions and literature with missing or insufficient information, and (d) articles published before 1990. A full-text review was subsequently conducted for data extraction from all remaining studies. The name of the first author, year of publication, source, sample size, and number of CAs were recoded for each included study. In cases where a consensus could not be reached on study eligibility, a third reviewer was consulted.

### 2.2. Data analysis

Both a common-effect model and random-effects model were used to provide pooled estimates of the incidence of these four birth defects. The common-effect model assumes uniformity of the true effect across studies, while the random-effects model accounts for substantial variation in effect sizes by incorporating it into the standard errors. While we are confident in the comprehensiveness of our search strategy, not all conducted studies may have been included. The random-effects model addresses this by assuming that our sample is representative of all existing studies, including those that may not have been published or completed. For each complication of interest, the pooled incidence was computed along with a 95% confidence interval (CI). The $I^2$ statistic was used as an indicator of study heterogeneity. The $I^2$ statistic was reported for each pooled estimate as a measure of study heterogeneity, with values of $p \geq 0.100$ and $I^2 \leq 25.0\%$ indicating good homogeneity between studies and an $I^2$ greater than 50% suggesting substantial study heterogeneity. Event rates were calculated in R with the metafor package (*10*).

## 3. Results

### 3.1. Summary of the systematic literature search

Figures 1-4 depict the PRISMA diagrams illustrating the systematic literature retrieval process for CHD, hypospadias, cryptorchidism, and DSD, respectively. Table 1 provides a summary of the outcomes documented in the included publications concerning these conditions. All studies included in the analysis were published between 1991 and 2023.

For CHD, a total of 622 records were included in the initial search after removing duplicate articles (Figure 1). Ultimately, 14 publications met the inclusion criteria, and 7,356 cases were included. The incidence of CAs ranged from 9-59%.

For hypospadias, the initial search resulted in 297 records after removing duplicate articles (Figure 2). Ultimately, 4 publications met the inclusion criteria, and 298 cases were included. The incidence of CAs ranged from 4-12%.

For cryptorchidism, a total of 275 records were included in the initial search after removing duplicate articles (Figure 3). Ultimately, 4 publications met the inclusion criteria, and 1,681 cases were included. The incidence of CAs ranged from 3-8%.

For DSD, a total of 67 records were included in the initial search after removing duplicate articles (Figure 4). Eventually, 7 publications met the inclusion criteria, and 2,876 cases were included. The incidence of CAs ranged widely from 10-43%.

### 3.2. Incidence of CAs

The combined results of the incidence of CAs in CHD, hypospadias, cryptorchidism, and DSD was also calculated (Table 1). Fourteen studies reported CAs in CHD, resulting in a total of 1,204 CA events out of 7,356 included cases. The total pooled incidence of CAs for CHD was 26% (95% CI, 19-34%, $I^2 = 97\%$; Figure 5).

For hypospadias, a total of 26 CAs were detected in 298 included cases. The overall pooled incidence of CAs for hypospadias was 9% (95% CI, 6-13%, $I^2 = 19\%$; Figure 6).

Four studies reported CAs in the context of cryptorchidism, with a total of 78 CA events in 1,681 included cases. The total pooled incidence of CAs for cryptorchidism was 5% (95% CI, 3-7%, $I^2 = 83\%$; Figure 7).

For DSD, four studies reported CAs, resulting in 567 CA events out of 2,876 included cases. The total pooled incidence of CAs for DSD was 21% (95% CI, 14-31%, $I^2 = 97\%$; Figure 8).

**Table 1. Summary of study characteristics and CA carrier results in the included studies**

| Diseases | PMID | Authors (Year published) | Incidence (%) | N | Sample size |
|---|---|---|---|---|---|
| CHD | 12797095 | Allan *et al*. (1991) | 16 | 77 | 467 |
| | 36011280 | Okashah *et al.* (2022) | 59 | 16 | 27 |
| | 35169781 | Atli *et al.* (2021) | 22 | 5 | 23 |
| | 34988127 | Zhang *et al*. (2021) | 26 | 279 | 1,089 |
| | 34098741 | Chelliah *et al*. (2021) | 46 | 37 | 80 |
| | 18512234 | Rosa *et al*. (2008) | 14 | 29 | 204 |
| | 33345990 | Mustafa *et al*. (2020) | 37 | 80 | 217 |
| | 33247990 | Tomotaki *et al*. (2021) | 56 | 25 | 45 |
| | 32371943 | Qiu *et al*. (2020) | 20 | 48 | 235 |
| | 30558042 | Cai *et al*. (2018) | 13 | 19 | 146 |
| | 30133550 | Luo *et al*. (2018) | 39 | 140 | 362 |
| | 25497206 | Stoll *et al*. (2015) | 9 | 354 | 4,005 |
| | 24145389 | Trevisan *et al*. (2013) | 17 | 50 | 298 |
| | 1590238 | Smythe *et al*. (1992) | 28 | 45 | 158 |
| | Current study | | 26[a] | 1,204 | 7,356 |
| Hypospadias | 12394752 | Moreno-Garcia *et al*. (2002) | 7 | 7 | 100 |
| | 29473028 | González *et al*. (2018) | 4 | 2 | 49 |
| | 1514208 | Yabumoto *et al*. (1992) | 12 | 16 | 131 |
| | 1686509 | Yamaguchi *et al.* (1991) | 6 | 1 | 18 |
| | Current study | | 9[b] | 26 | 298 |
| Cryptorchidism | 12394752 | Moreno-Garcia *et al*. (2002) | 3 | 26 | 916 |
| | 1686509 | Yamaguchi *et al.* (1991) | 5 | 4 | 83 |
| | 8738627 | Sasagawa I *et al*. (1996) | 4 | 7 | 160 |
| | 32293821 | Sharifi N *et al*. (2020) | 8 | 41 | 522 |
| | Current study | | 5[a] | 78 | 1,681 |
| DSD | 34036105 | Benchikh *et al*. (2021) | 15 | 154 | 1,005 |
| | 29581155 | Kohva *et al*. (2018) | 37 | 204 | 550 |
| | 22644991 | Öcal *et al*. (2012) | 27 | 78 | 285 |
| | 32282607 | Dhamankar *et al*. (2020) | 23 | 7 | 30 |
| | 29996319 | Yi P *et al*. (2018) | 43 | 23 | 53 |
| | 36419940 | Man E *et al*. (2023) | 11 | 68 | 607 |
| | 27754965 | Ganie *et al*. (2016) | 10 | 33 | 346 |
| | Current study | | 21[a] | 567 | 2,876 |

PMID, PubMed Unique Identifier; CAs, chromosomal abnormalities or chromosomal aberrations; N, number; CHD, congenital heart disease; DSD, disorders of sexual development; [a], incidence was calculated based on a random effects model; [b], incidence was calculated based on a common effect model.

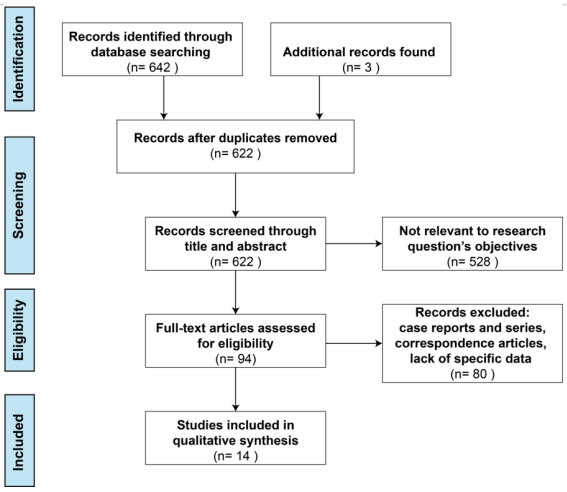


**Figure 1. PRISMA flowchart of a systematic literature search for CHD.**

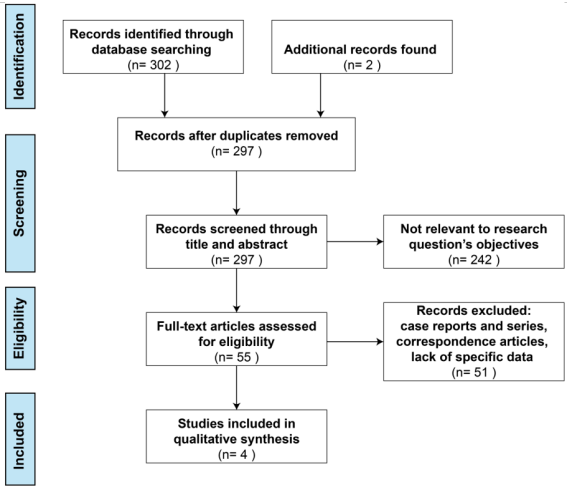


**Figure 2. PRISMA flowchart of a systematic literature search for hypospadias.**

### 3.3. Subtypes of CAs in fertility-related birth defects

Table 2 shows the subtypes of CAs detected in four birth defects affecting fertility, excluding cases without specific subtypes of CAs. As shown in the table, there was a higher frequency of autosomal chromosome

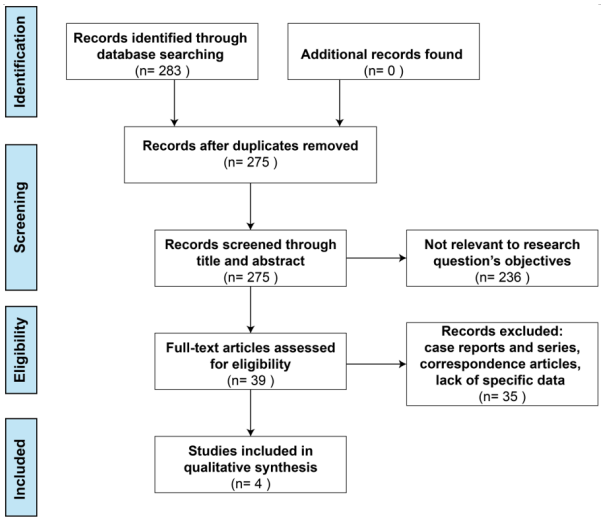


**Figure 3. PRISMA flowchart of a systematic literature search for cryptorchidism.**

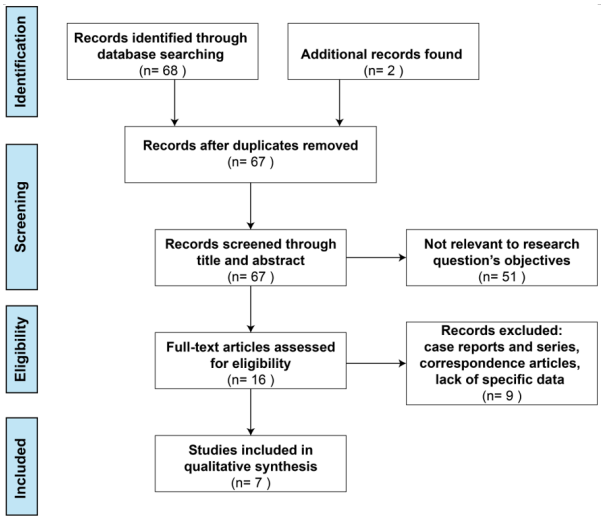


**Figure 4. PRISMA flowchart of the systematic literature search for DSD.**

abnormalities in CHD cases compared to sex CAs (94.80% *vs.* 5.20%, respectively). Among autosomal CAs in CHD cases, numerical abnormalities constituted the majority (70.65%), with trisomy 21 and trisomy 18 being the most common subtypes of CAs, accounting for 40.96% and 22.70%, respectively. In contrast to CHD, there was a higher incidence of sex CAs in patients with DSD, with 92.59% of cases exhibiting numerical abnormalities. Notable subtypes of CAs in DSD included Turner syndrome, Klinefelter syndrome, and mixed gonadal dysgenesis, respectively accounting for 37.04%, 26.10%, and 29.45%.

The studies on hypospadias and cryptorchidism yielded limited information on karyotype patterns, with sex CAs accounting for 69.23% and 60.26%, respectively; numerical abnormalities were the major subtype. In the context of sex chromosome numerical abnormalities in hypospadias and cryptorchidism, Klinefelter syndrome was the predominant type,

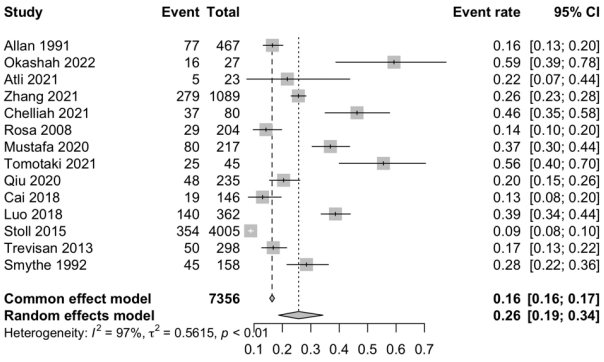


**Figure 5. Forest plot and pooled analysis of CA events in CHD**

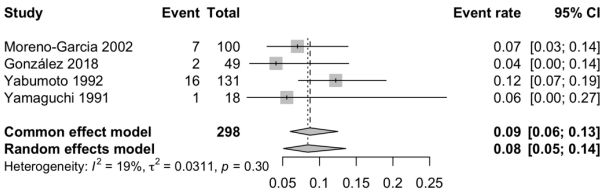


**Figure 6. Forest plot and pooled analysis of CA events in hypospadias.**

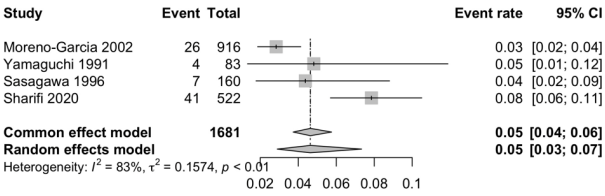


**Figure 7. Forest plot and pooled analysis of CA events in cryptorchidism.**

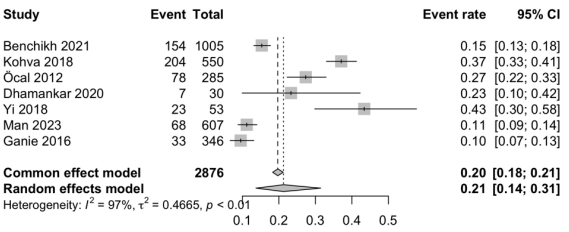


**Figure 8. Forest plot and pooled analysis of CA events in DSD.**

respectively accounting for 19.23% and 51.28%.

## 4. Discussion

Over the past two decades, there have been significant advancements in prenatal diagnosis technology, coinciding with notable shifts in the profiling of birth defects. CHD and hypospadias, both of which increase the risk of infertility, have progressively emerged as the major birth defects (*2*). CAs represent a common genetic cause of birth defects, exhibiting considerable diversity in samples across different regions for CHD, hypospadias, cryptorchidism, and DSD (Table 1). However, there has been a lack of a systematic assessment of the impact of CAs on these four birth defects, and a dearth of

**Table 2. The distribution of types of chromosome abnormalities in four birth defects**

| Classification | CHD | | Hypospadias | | Cryptorchidism | | DSD | |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % |
| Autosomal chromosome abnormalities | 1,111 | 94.80 | 8 | 30.77 | 31 | 39.74 | 42 | 7.41 |
| Numerical abnormalities | 828 | 70.65 | 1 | 3.85 | 6 | 7.69 | 5 | 0.88 |
| Trisomy 18 | 266 | 22.70 | 1 | 3.85 | 1 | 1.28 | 0 | 0.00 |
| Trisomy 21 | 480 | 40.96 | 0 | 0.00 | 1 | 1.28 | 1 | 0.18 |
| Trisomy 13 | 75 | 6.40 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 |
| Others | 7 | 0.60 | 0 | 0.00 | 4 | 5.13 | 4 | 0.71 |
| Structural abnormalities | 170 | 14.51 | 1 | 3.85 | 25 | 32.05 | 37 | 6.53 |
| Translocations | 21 | 1.79 | 1 | 3.85 | 8 | 10.26 | 16 | 2.82 |
| Duplications | 6 | 0.51 | 0 | 0.00 | 1 | 1.28 | 0 | 0.00 |
| Deletions | 103 | 8.79 | 0 | 0.00 | 1 | 1.28 | 3 | 0.53 |
| Inversions | 3 | 0.26 | 0 | 0.00 | 13 | 16.67 | 18 | 3.17 |
| Ring-chromosome | 3 | 0.26 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 |
| Chromosomal polymorphisms | 9 | 0.77 | 0 | 0.00 | 2 | 2.56 | 0 | 0.00 |
| Others | 25 | 2.13 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 |
| Not classified* | 113 | 9.64 | 6 | 23.08 | 0 | 0.00 | 0 | 0.00 |
| Sex chromosome abnormalities | 61 | 5.20 | 18 | 69.23 | 47 | 60.26 | 525 | 92.59 |
| Numerical abnormalities | 34 | 2.90 | 7 | 26.92 | 46 | 58.97 | 525 | 92.59 |
| Klinefelter syndrome | 2 | 0.17 | 5 | 19.23 | 40 | 51.28 | 148 | 26.10 |
| Turner syndrome | 30 | 2.56 | 0 | 0.00 | 6 | 7.69 | 210 | 37.04 |
| Triple X syndrome | 2 | 0.17 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 |
| Mixed gonadal dysgenesis | 0 | 0.00 | 2 | 7.69 | 0 | 0.00 | 167 | 29.45 |
| Structural abnormalities | 1 | 0.09 | 0 | 0.00 | 1 | 1.28 | 0 | 0.00 |
| Deletions | 0 | 0.00 | 0 | 0.00 | 1 | 1.28 | 0 | 0.00 |
| Inversions | 1 | 0.09 | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 |
| Not classified* | 26 | 2.22 | 11 | 42.31 | 0 | 0.00 | 0 | 0.00 |
| Total (excluded ambiguous) | 1,172 | 100 | 26 | 100.00 | 78 | 100.00 | 567 | 100.00 |

N, number; CAs, chromosomal abnormalities or chromosomal aberrations; CHD, congenital heart disease; DSD, disorders of sexual development.
*The studies provided only the autosomal or sex CA information in cases but no further detailed information about the subtype of CAs.

multicenter studies examining CAs persists. As a result, our focus was directly on these four birth defects, all of which could potentially affect fertility in adulthood. A systematic evaluation of the prevalence of CAs and their subtypes in these disorders was performed.

Results revealed a high incidence of CAs in genomes associated with fertility-related diseases. The respective prevalence of CAs in CHD, hypospadias, cryptorchidism, and DSD was 26%, 9%, 5% and 21%, with CHD exhibiting the highest prevalence and cryptorchidism the lowest. CAs can result in severe phenotypes, such as CHD and DSD. CAs are categorized into numerical and structural abnormalities based on the mechanisms of chromosome segregation errors or DNA damage (*7,8*). Numerical CAs were the predominant anomalies observed in cases of CHD, cryptorchidism, and DSD, respectively accounting for 73.55%, 66.67%, and 93.47%. Numerical CAs typically involve deviations in the number of chromosomes from the normal karyotype due to misallocation during mitosis or cell division blockage. Numerical CAs mainly include aneuploidy, triploidy, and tetraploidy in humans. Given that systemic triploidy is usually fatal for humans, triploid fetuses typically result in eventual abortion (*11*). Aneuploidy, characterized by the gain or loss of chromatid or chromosome regions, represents the primary form of numerical CAs in clinical settings, contributing to conditions such as trisomy 21, trisomy 18, and Turner syndrome, which were found to be prevalent in CHD and DSD cases. In cases of CAs related to CHD, numerical abnormalities were frequently observed in euchromosome, accounting for 70.65%. And in DSD cases of CAs, the vast majority (92.59%) involved the sex chromosomes.

Numerical CAs of DSD are frequently associated with conditions such as Turner syndrome, Klinefelter syndrome, Triple X syndrome, Jacob's syndrome, mixed gonadal dysgenesis, and chimerism. Turner syndrome represents the most prevalent sex-related CAs and is the major genetic cause of primary amenorrhoea in women. Its typical karyotype is 45,X, but variations can include karyotypes such as 45,X/46,XX, 45,X/46XY, and 45,X/47,XXX (*12*). Clinical presentations often include a short stature, gonadal insufficiency, primary or secondary amenorrhea, infertility, micrognathia, low-protruding ears, a short neck, and elbow ectropion (*13,14*). Klinefelter's syndrome usually manifests with a chromosomal karyotype of 47,XXY, and variants can include karyotypes such as 48,XXXY, 49,XXXXY, and 46,XY/47,XXY (*15*). Patients may exhibit a tall stature, narrow shoulders, wide hips, sparse body hair, gynecomastia, small testes, androgen deficiency, learning disabilities, and delayed speech development (*13*). In Triple X syndrome with a karyotype 47,XXX, patients may clinically exhibit increased height and an elevated risk of learning disabilities, delayed speech, language, and motor skills development, weak muscle tone, behavioral and emotional difficulties, seizures,

and renal abnormalities (*14,15*). However, some cases of Jacob's syndrome may not present with any discernible phenotypic abnormalities. Jacob's syndrome is characterized by a karyotype of 47,XYY. Clinically, patients with this syndrome typically have an increased height, an elevated risk of learning disabilities, delayed development of speech, language, and motor skills, dystonic weakness, hand tremors, seizures, asthma, scoliosis, as well as behavioral and emotional difficulties (*14,15*). Similar to triple X syndrome, certain cases of Jacob's syndrome may present without noticeable phenotypic anomalies.

45,X/46,XY is a mixed gonadal hypoplasia syndrome characterized by a wide range of clinical phenotypes, spanning from females with Turner syndrome to phenotypically normal males with genital abnormalities and a short stature. Gonadal function appears to be adequate for spontaneous puberty in most 45,X/46,XY males. The etiology of its development is yet to be fully understood, although a widely accepted hypothesis suggests that it results from the nondisjunction or structural rearrangement of the Y chromosome during either fertilized egg division or early embryonic cell division (*16*). During mitosis, a delayed separation or rearrangement of the Y chromosome can generate three distinct cell lineages, 45,X, 46,XY, and 47,XYY, with trisomic cells often being lost in subsequent divisions, while 45,X and 46,XY cells are more likely to persist. During the segregation of sister chromatids of the Y chromosome, a break may occur in the palindrome or inverted repeat region, followed by a homologous exchange of sister chromatids, leading to structural abnormalities of the Y chromosome if this process is disrupted.

Structural CAs encompass a variety of alterations, such as deletions, duplications, inversions, translocations, insertions, isochromosomes, ring chromosomes, and chromosomal polymorphisms. Although not the primary form of CAs in fertility-related birth defects, chromosomal structural abnormalities account for 33.33% of CAs in cases of cryptorchidism. Chromosomal polymorphisms are minor structural aberrations in human chromosomes, primarily occurring in regions with highly repetitive DNA sequences but not in coding regions. Generally considered to have no clinical effects, these polymorphisms tend to emerge in highly repetitive sequences with no transcriptional activity. However, a recent study has suggested that chromosomal polymorphisms within the heterochromatin region could potentially lead to abnormalities during chromosome division and gamete production, ultimately resulting in abnormal embryonic development (*17*). Nevertheless, such chromosomal polymorphisms are rarely associated with fertility-related birth defects, accounting for only 0.77% of CAs in individuals with CHD and 2.56% of CAs in individuals with cryptorchidism. Such chromosomal polymorphisms were not found in the other two disorders. The most recent data on the impact of chromosomal polymorphisms on the reproductive outcomes of couples undergoing intracytoplasmic sperm injection (ICSI) treatment, based on 929 fresh and frozen embryo transfer cycles involving 692 women, did not reveal any disparities in reproductive outcomes between carriers and non-carriers of any type or number of chromosomal polymorphisms (*18*).

This retrospective analysis may be limited by the limited data available in the included literature. First, the analysis is influenced by the inclusion of studies with small sample sizes rather than large cohort populations. Second, the exclusion of certain articles due to unavailable or incomplete data could result in the omission of important studies.

The current study aimed to investigate the connections between fertility-related birth defects and CAs. Despite the reduced emphasis on chromosomal analysis, guidelines still recommend its utilization. The results of this study highlight its effectiveness in studying reproductive disorders. In addition, chromosome analysis in individuals diagnosed with reproductive diseases plays a significant role in the expanding field of preimplantation genetic diagnosis (PGD).

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*Conflict of Interest*: The authors have no conflicts of interest to disclose.

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