Received: 6 June 2024 | Revised: 14 July 2024 | Accepted: 15 July 2024

DOI: 10.1002/ijgo.15828

GYNECOLOGY OBSTETRICS FIGO WILEY

CLINICAL ARTICLE

Gynecology

# Infertility following trisomic pregnancies: A nationwide cohort study

Satu Wedenoja[1,2,3,4] | Mika Pihlajamäki[1] | Mika Gissler[1,5,6,7] | Juho Wedenoja[8] | Hanna Öhman[9,10] | Seppo Heinonen[2] | Juha Kere[3,4,11] | Helena Kääriäinen[12] | Laura Tanner[13,14]

[1]Information Brokers, Finnish Institute for Health and Welfare, Helsinki, Finland
[2]Obstetrics and Gynecology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
[3]Stem Cells and Metabolism Research Program, University of Helsinki, Helsinki, Finland
[4]Folkhälsan Research Center, Helsinki, Finland
[5]Research Center for Child Psychiatry, University of Turku, Turku, Finland
[6]Region Stockholm, Academic Primary Health Care Center, Stockholm, Sweden
[7]Karolinska Institutet, Department of Molecular Medicine and Surgery, Stockholm, Sweden
[8]Department of Ophthalmology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
[9]Biobank Borealis of Northern Finland, Oulu University Hospital, Oulu, Finland
[10]Faculty of Medicine, University of Oulu, Oulu, Finland
[11]Department of Biosciences and Nutrition, Karolinska Institutet, Huddinge, Sweden
[12]Genomics and Biomarkers Unit, National Institute for Health and Welfare, Helsinki, Finland
[13]Department of Clinical Genetics, Helsinki University Hospital, Helsinki, Finland
[14]Department of Medical and Clinical Genetics, University of Helsinki, Helsinki, Finland

**Correspondence**
Satu Wedenoja, Folkhälsan Research Center, Haartmaninkatu 8, 00290 Helsinki, Finland.
Email: satu.wedenoja@helsinki.fi

## Abstract

**Objective:** To study whether gynecologic or reproductive disorders show association with trisomic conceptions.

**Methods:** This nationwide cohort study utilized the Registry of Congenital Malformations to identify women who had a trisomic pregnancy ($n=5784$), either with trisomy 13 (T13; $n=351$), trisomy 18 (T18; $n=1065$) or trisomy 21 (T21; $n=4369$) from 1987 to 2018. We used the Finnish Maternity cohort to match the cases to population controls ($n=34\,422$) on the age, residence, and timing of pregnancy. These data were cross-linked to the ICD-10 diagnoses of the national Care Registry for Health Care data on specialized health care in Finland during 1996 to 2019. Both inflammatory (ICD-10 diagnoses: N70–N77) and noninflammatory disorders of the genital tract (N80–N98) were studied. Crude odds ratios (ORs) with 95% CIs were calculated for associations between diagnoses and trisomic conceptions.

**Results:** The diagnosis of female infertility (N97) at any time was associated with trisomic conceptions (OR: 1.19, 95% CI: 1.08–1.32). In the subgroup analysis, this association was found for T18 (OR: 1.29, 95% CI: 1.03–1.61) and T21 (OR: 1.17, 95% CI: 1.04–1.32), but not for T13 (OR: 1.15, 95% CI: 0.75–1.72). When restricting the timing of the diagnosis of female infertility, an elevated OR was found only after the index pregnancy (OR: 1.81, 95% CI: 1.56–2.09). These increased odds for infertility after trisomic conceptions were observed both in women <35 years (T18 OR: 1.91, 95% CI: 1.21–3.00; T21 OR: 1.68, 95% CI: 1.31–2.14) and in women ≥35 years (T18 OR: 2.17, 95% CI: 1.40–3.33; T21 OR: 1.87; 95% CI: 1.47–2.39), but not after T13 conceptions.

**Conclusion:** Our observational data suggest a link between trisomic conceptions and subsequent diagnoses of infertility but do not demonstrate causality. These data implicate that partially similar mechanisms might predispose to trisomy and infertility, regardless of maternal age.

KEYWORDS
epidemiology, infertility, maternal age, risk factor, trisomy

**Funding information**
Päivikki ja Sakari Sohlbergin Säätiö; Juhani Ahon Lääketieteen Tutkimussäätiö

## 1 | INTRODUCTION

Human autosomal trisomies – characterized by a third chromosome instead of two – are among the most common causes of congenital birth defects and intellectual disability.[1] Their incidence and prevalence vary strongly depending on the maternal age. While around 20% of oocytes are aneuploid in women under 35 years of age, aneuploidy affects more than 50% of oocytes at advanced maternal age.[2] Up to 90% of fetuses with autosomal trisomies receive the extra chromosome from the mother.[3] Accordingly, the strong maternal age effect is seen for the prevalence of all survivable autosomal aneuploidies, namely trisomy 13 (T13), trisomy 18 (T18), and trisomy 21 (T21).[4]

Why advanced maternal age, defined as 35 years or older, results in an exponential increase in the rate of aneuploidy remains poorly understood.[2,5] In older women, age-dependent decay of meiotic mechanisms such as centromeric cohesion might trigger chromosomal non-disjunction.[6] However, around 1% to 5% of all clinically recognized pregnancies are trisomic even in women younger than 35 years.[2,7,8] Among them, aberrant crossing over or recombination of chromosomes might play a major role.[9] Moreover, environmental exposures such as smoking or defective folic acid metabolism might modulate the pathogenesis.[6,8,10–12]

Previous work has highlighted that some gynecologic or reproductive conditions such as low oocyte pool, infertility caused by anovulatory factor, recurrent pregnancy loss, and endometriosis increase the risk of trisomy.[13,14] However, evidence of an association between antral follicle pool or reproductive hormone levels with trisomic conceptions are lacking,[15] and chromosomal analysis of preimplantation embryos shows no association between anovulatory infertility and aneuploidy.[16] As for endometriosis, experimental models support increased formation of aneuploid oocytes, but clinical data are conflicting.[17–19] Whether diseases of female pelvic organs mediate the risk of trisomic conceptions remains largely unclarified.

We conducted a cohort study using population-based registry data collected over 30 years in Finland. We hypothesized that disorders of the female genital tract or pelvic organs, potentially having negative impact on fertility, might be associated with trisomic conceptions. Our secondary aim was to examine whether younger women, with a trisomic conception <35 years, differ from the older mothers in terms of their gynecologic and reproductive health.

## 2 | MATERIALS AND METHODS

This registry-based nationwide cohort study was approved by the Finnish Institute for Health and Welfare (THL/2295/5.05.00/2019) and by the Biobank Borealis (BB_2021_5001). Research was performed according to the approved guidelines. No informed consents were required from the study subjects specifically for this study, but were available for biobanking the samples, as defined in the regulations of the national Biobank Act (688/2012).

### 2.1 | Study population

Trisomic conceptions were identified from the national Registry of Congenital Malformations. We included all women whose fetuses or newborns received a diagnosis of T13, T18, or T21 during pregnancy or after birth between 1987 and 2018. These trisomic pregnancies resulted in either miscarriage, abortion, or live birth but data on the pregnancy outcome were not included in the analyses.

During the study period of 1987–2018, 34% of trisomic conceptions were diagnosed after miscarriage, abortion, or at birth, and 65% were diagnosed through the prenatal screening program offered as part of the routine antenatal care. During the study period, all pregnant women had been offered first-trimester ultrasound and second trimester morphology ultrasound as well as screening programs of that time (serum screening or combined screening) free of charge. Uptake of these prenatal screening tests has traditionally been high. Invasive testing (chorionic villus sampling or amniocentesis) had been offered for those with a positive screening result or a known carrier status of a genomic rearrangement but, after 1990s, were no longer solely based on advanced maternal age. All congenital anomalies, including those diagnosed prenatally, have been registered to the national Registry of Congenital Malformations and, if resulting in birth, also to the Medical Birth Registry.

We used data from the Finnish Maternity Cohort (FMC) held by the Biobank Borealis to assemble a control group of women without a diagnosis of trisomy in their pregnancy. The FMC cohort is a nationwide collection of serum samples taken from pregnant women for routine screening of congenital infections during the latter part of the first trimester or the early weeks of the second trimester.[20] We selected a maximum of six control subjects for each woman with a trisomic conception, and matched the controls on age, residence, and timing of the pregnancy. The age of the control subjects was identified on the index date. Residence was either the same town or county in Finland. Timing of the pregnancy was noted as the calculated conception date based on the first trimester screening date and was assigned to be not more than 2 months different from that of the women with trisomic pregnancies. Altogether, we found six matched controls for 5698 (99%) of all 5784 cases. Because we did not want to exclude the remaining cases in our patient series, we accepted five matched controls for 11 cases, four controls for 18, three controls for 15, two controls for 20, and only one control for 22 cases. To find matched controls, we accepted two different pregnancies from six women to serve as controls for different trisomic conceptions. These controls were utilized in subgroup analyses of T13, T18 or T21, but all individuals (cases and controls) were counted only once at the whole series level analyses.

### 2.2 | Diagnoses of gynecologic disorders

Initial case selection was based on the diagnosis of a trisomic conception. Matched controls were selected based on the absence of a diagnosis of trisomy in their pregnancy. Thereafter, the study women were linked based on their personal identification numbers to the national Care Registry for Health Care that involves all diagnoses related to the specialized healthcare, either inpatient admission or outpatient clinic contact. We utilized data spanning 1996 to 2019, when diagnoses were coded according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) as described by the WHO. Data covered inpatients admissions, and from 1998 onwards, also outpatient visits.

For the primary analysis, both inflammatory diseases of female pelvic organs (ICD-10 diagnoses: N70–N77) and noninflammatory disorders of the genital tract (N80–N98) were studied for the whole study series. We calculated the number of women with each diagnosis at any time. Second, we studied the diagnoses that were associated with trisomic conceptions in subgroups of women with T13, T18, or T21 conceptions, and their respective controls. Third, we tested whether the associated diagnoses were coded before or after the index pregnancy, and whether they showed association with trisomic conception among younger (<35 years) or older (≥35 years) women of the study series.

### 2.3 | Statistical analysis

We characterized women with trisomic conceptions and control women by case–control groups (T13, T18 or T21), and by different age groups. The cases and controls were matched on the age, residence, and timing of pregnancy, while no other confounders were available. All comparisons were two-valued (yes, no) and the outcome variables were two-valued. We used chi-square test with Yates correction to compare trisomic conceptions with controls regarding gynecologic diagnoses and calculated crude odds ratios (ORs) and 95% CIs. Each diagnosis was assessed independently among cases and controls. The statistical significance was set at *P* values less than 0.05, and two-tailed *P* values were used. The analyses were conducted using the Graph Pad version 10.1.1 (GraphPad Software, LLC).

## 3 | RESULTS

We detected a total of 6042 trisomic conceptions in Finland between 1987 and 2018. For building up the study series, we excluded 258 trisomic conceptions, of which 198 were recurrent trisomic pregnancies occurring in 99 women and 60 were conceptions for which no matched controls could be found from the Biobank data.

**TABLE 1** Characteristics of women with trisomic conceptions and matched controls in Finland between 1987 and 2018.

| Characteristic | No. (%) Women with trisomic conception[a] (*n* = 5784) | Control women[b] (*n* = 34 422) |
|---|---|---|
| Trisomy 13 (T13) | 351 (6.1) | 2088 (6.1) |
| Trisomy 18 (T18) | 1065 (18.4) | 6331 (18.4) |
| Trisomy 21 (T21) | 4369 (75.6) | 26 009 (75.6) |
| Maternal age, years | | |
| <25 | 433 (7.5) | 2594 (7.5) |
| 25–29 | 855 (14.8) | 5130 (14.9) |
| 30–34 | 1288 (22.3) | 7724 (22.4) |
| 35–39 | 1888 (32.6) | 11 313 (32.9) |
| 40– | 1320 (22.8) | 7661 (22.3) |

[a]Includes one individual with a combined trisomy 13 and 21.
[b]Includes six individuals, whose two different pregnancies were used as controls.

The study series involved 5784 women with a laboratory-confirmed diagnosis of T13, T18, or T21 in their fetus or newborn between 1987 and 2018. The control series involved 34 422 women matched on age, residence, and timing of pregnancy.

Table 1 shows the characteristics at the time of the index pregnancy. Of these women, 2576 (44.6%) with a trisomic conception and 15 448 (44.8%) of controls were under 35 years at the time of the index pregnancy. Of trisomic conceptions, 4369 (75.6%) were associated with T21, 1065 (18.4%) with T18, and only 351 (6.1%) with T13.

### 3.1 | All gynecologic diagnoses

We first studied all gynecology-specific codes at any time before or after the index pregnancy (Table S1). To this end, we included only the diagnoses that had been detected in at least five women with trisomic conceptions (either T13, T18 or T21). We observed an increased OR (1.19, 95% CI: 1.08–1.32) for female infertility (ICD-10 diagnosis group of N97) among cases. In the subgroup analysis, N97 diagnosis showed association with T18 (OR: 1.29, 95% CI: 1.03–1.61) and T21 (OR: 1.17, 95% CI: 1.04–1.32) conceptions, but not for T13 (OR: 1.15, 95% CI: 0.75–1.72) (Table 2).

We also found inverse comorbidity for some disorders. Diagnoses of menstrual pain (N94) and female genital prolapse (N81) at any time yielded decreased odds in women with trisomic conceptions. However, results were null when assessed in the subgroups of T13, T18, and T21, and in the respective controls (Table S1).

### 3.2 | Secondary analyses

We further studied the association between female infertility and trisomic conceptions regarding the time of the N97 diagnosis and the age of the women.

TABLE 2 Association of female infertility (N97) with trisomic conceptions among women who were pregnant in Finland between 1987 and 2018.

| Measure | No. (%) with N97 diagnosis: Women with trisomic conception[a] (*n* = 5784) | Control women[b] (*n* = 34 422) | OR | 95% CI | *P* value |
|---|---|---|---|---|---|
| All | 472 (8.2) | 2387 (6.9) | 1.19 | 1.08–1.32 | <0.001 |
| Subgroups | | | | | |
| Trisomy 13 | 30 (8.5) | 157 (7.5) | 1.15 | 0.75–1.72 | 0.57 |
| Trisomy 18 | 102 (9.6) | 480 (7.6) | 1.29 | 1.03–1.61 | 0.03 |
| Trisomy 21 | 340 (7.8) | 1752 (6.7) | 1.17 | 1.04–1.32 | 0.01 |

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Includes one individual with a combined trisomy 13 and 21.

[b]Includes six individuals, whose two different pregnancies were used as controls in different subgroups.

TABLE 3 Association of female infertility (N97) with trisomic conceptions after the index pregnancy among women who were pregnant in Finland between 1987 and 2018.

| | No. (%) with N97 diagnosis: Women with trisomic conception[a] (*n* = 5784) | Control women[b] (*n* = 34 422) | OR | 95% CI | *P* value |
|---|---|---|---|---|---|
| All | 245 (4.2) | 822 (2.4) | 1.81 | 1.56–2.09 | <0.001 |
| Subgroups | | | | | |
| Trisomy 13 | 14 (4.0) | 54 (2.6) | 1.57 | 0.85–2.85 | 0.19 |
| Trisomy 18 | 55 (5.2) | 165 (2.6) | 2.04 | 1.48–2.77 | <0.001 |
| Trisomy 21 | 176 (4.0) | 603 (2.3) | 1.77 | 1.49–2.10 | <0.001 |
| Women < 35 years at the time of the index (trisomic/control) pregnancy | | | | | |
| All | 121 (4.7) | 433 (2.8) | 1.71 | 1.39–2.10 | <0.001 |
| Subgroups | | | | | |
| Trisomy 13 | 8 (4.3) | 32 (2.8) | 1.52 | 0.72–3.20 | 0.41 |
| Trisomy 18 | 26 (5.6) | 84 (3.0) | 1.91 | 1.21–3.00 | 0.007 |
| Trisomy 21 | 87 (4.5) | 317 (2.7) | 1.68 | 1.31–2.14 | <0.001 |
| Women ≥ 35 years at the time of the index (trisomic/control) pregnancy | | | | | |
| All | 124 (3.9) | 389 (2.1) | 1.92 | 1.57–2.36 | <0.001 |
| Subgroups | | | | | |
| Trisomy 13 | 6 (3.7) | 22 (2.3) | 1.63 | 0.69–3.99 | 0.44 |
| Trisomy 18 | 29 (4.8) | 81 (2.3) | 2.17 | 1.40–3.33 | <0.001 |
| Trisomy 21 | 89 (3.6) | 286 (2.0) | 1.87 | 1.47–2.39 | <0.001 |

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Includes one individual with a combined trisomy 13 and 21.

[b]Includes six individuals, whose two different pregnancies were used as controls in different subgroups.

We found no association between trisomic conceptions and female infertility before the index pregnancy (Table S2). Instead, 245 (4.2%) individuals with a trisomic conception and 822 (2.4%) controls had a subsequent diagnosis of female infertility, corresponding to an adjusted OR of 1.81 (95% CI: 1.56–2.09) in the whole series (Table 3). In the subgroup analysis, the highest OR of 2.04 (95% CI: 1.48–2.77) arose after T18 conceptions, while OR of 1.77 (95% CI: 1.49–2.10) was observed after T21 conceptions, and results were null after T13 conceptions (OR: 1.57, 95% CI: 0.85–2.85) (Table 3).

We then studied the diagnoses of N97 in women according to the age groups. Subsequent diagnoses of female infertility (N97) were associated with trisomic conceptions both in women <35 years at the index pregnancy (OR: 1.71, 95% CI: 1.39–2.10) and in those ≥35 years at the index pregnancy (OR: 1.92, 95% CI: 1.57–2.36). These associations were observed both after T18 and T21 but not after T13 conceptions (Table 3).

We did not study N97 subdiagnoses (N97.0 to N97.9) in detail because many women received several different N97 subdiagnoses and relative distribution of subdiagnoses was highly similar among cases and controls (Table S3).

## 4 | DISCUSSION

This population-based study demonstrates an association between trisomic conceptions and subsequent diagnoses of female infertility. The odds of infertility after trisomic conceptions were elevated by more than 80% in the whole series. Remarkably, this association appeared also in younger women, who were <35 years at the time of the trisomic pregnancy. Moreover, we found no similar associations for other gynecologic or reproductive disorders. Although these observational data cannot prove causality, this study suggests that similar mechanisms might predispose to trisomic conceptions and infertility, in both younger and older women.

A main strength of our study is the large population-based series of 5784 women and 34 422 matched controls. Unlike many other studies on human trisomic conceptions, we had a significant number of 2576 women <35 years at the time of the index pregnancy with trisomy. This allowed us to link diagnoses of female infertility also to younger women, for whom no major risk factors for trisomic pregnancies have been demonstrated so far.[21] Since the Finnish national healthcare system is responsible for all prenatal screening tests and maternal care, and coding of the disorders have been consistently performed during several decades, we are likely to have all laboratory-confirmed trisomic conceptions and clinical diagnoses of infertility here. Because of the publicly funded maternity care, equal accessibility to the prenatal screening guaranteed by law, and high uptake of prenatal screening as well as strict uniform criteria for invasive procedures, our data is highly representative of the Finnish population. As an additional strength, control population was adjusted on maternal age, residence, and timing of pregnancy, potentially excluding major environmental or time-dependent exposures, if any, to trisomy or infertility.

The main limitation of our study was that this registry-based analysis was unable to count miscarriages or medical abortions before the diagnosis of trisomy. Notably, more than 35% of early miscarriages are explained by an abnormality in the number of chromosomes.[22] Furthermore, most trisomic embryos are likely to be miscarried soon after conception,[23] and our series included only those trisomic pregnancies that received the genetic diagnosis. Moreover, data on gynecologic diagnoses were available only from 1996 onwards. Because we could not assess the time needed to get pregnant for the index pregnancy of our study, we cannot exclude the association between primary infertility and trisomic conceptions in our series. As for infertility diagnoses, we were able to find only those who sought help for infertility and received the diagnosis. The low number of women diagnosed with a trisomic conception and subsequent infertility, and highly similar infertility rates in women under 35 years and older, suggests that younger women were more likely to seek fertility testing than older women. An additional limitation is that our series included no data on the duration of infertility, number of conceptions before the infertility diagnosis, or conception method. Moreover, many of the pregnancies with trisomies were terminated, and we cannot rule out effects of abortion on subsequent pregnancies. However, no data supports the link between medical abortions and chances of getting pregnant in the future.[24,25] Although we had no data on parental balanced chromosomal translocations, causing 4% to 5% of trisomic conceptions and predisposing to infertility,[26,27] or confounders such as smoking,[10] their influence is likely to be minor at the level of the whole series.

Infertility affects around 15% of all couples, and one of the major etiological factors is advanced maternal age.[28] In this study, diagnoses of female infertility at any time appeared in 8.2% of women with trisomic conceptions and were more common than the rate of 6.9% in the controls. These figures are lower than the self-reported lifetime subfertility of 16% in Finland,[29] but in line with the findings that less than half of infertile women seek infertility treatments.[30] Although both T18 and T21 conceptions were associated with subsequent diagnoses of infertility, case counts were too low and confidence intervals too wide for T13 to examine this association independently. It is therefore possible that similar association could be observed for T13 with a larger patient cohort. Since no other human aneuploidies than T13, T18 and T21 were studied here, and all but laboratory-confirmed diagnoses of trisomy were lacking, the magnitude of association between female infertility and previous trisomic conceptions remains obscure.

Aneuploidy in oocytes is the leading cause of infertility.[31] On the other hand, previous studies found no association between non-oocyte related etiologies of infertility and aneuploidies.[32] One of the major obstacles in studies of female infertility and the risk of trisomic conceptions is that they share advanced maternal age as a major risk factor. Moreover, couples seeking infertility treatments may not be representative of the general population and some nondisjunction events can be increased among them.[8] Our study setting and results are noteworthy for several reasons. First, this study was registry-based analysis that involved national data on all trisomic conceptions and infertility diagnoses. Second, we had a significant number of women <35 years, who showed increased odds for future infertility after trisomic conceptions similarly to observations in older women. Third, no other pregnancy complications such as recurrent pregnancy losses, being associated with an increased aneuploidy rate,[32] were associated with trisomic conceptions in our series. Therefore, our results are novel and raise a possibility that some women have an age-independent genetic predisposition to trisomic conceptions and infertility. This finding is supported by the observations that prior aneuploid pregnancies are, age-independently, increasing the risk of future aneuploid conceptions.[32,33] In agreement with this, specific altered recombination patterns show association with maternal meiotic errors and some of them are age-independent.[34] Moreover, several genetic loci have been linked to the risk of chromosomal nondisjunction for T21,[35] and mitotic errors resulting in trisomic conceptions are rare but age-independent.[36] That we found no association between primary infertility and trisomic conceptions may be related to the fact that information on the time elapsed to get pregnant for the first time were missing and infertility diagnoses were available only from 1996 onwards.

## 5 | CONCLUSIONS

Our study implicates chromosomal non-disjunction resulting in human trisomies as a possible culprit for some cases of subsequent female infertility. These data suggest that not only the small risk of recurrent trisomy,[37] but also the possibility of infertility, are worth mentioning in the setting of genetic or clinical counseling of couples after trisomic pregnancies. Collectively, these data suggest that some mechanisms of trisomic conceptions are age-independent and might decrease the chances of getting pregnant in the future. As this was an epidemiological study, a large multicenter prospective trial will be needed to confirm the findings of this study.

### AUTHOR CONTRIBUTIONS

Satu Wedenoja, Mika Gissler, Seppo Heinonen, Juha Kere and Laura Tanner: Conceived, designed, and directed the study. Satu Wedenoja and Laura Tanner: Acquired funding. Satu Wedenoja, Mika Pihlajamäki, Mika Gissler, Juho Wedenoja and Hanna Öhman: Acquired and analyzed the data. Satu Wedenoja, Mika Pihlajamäki, Mika Gissler, Helena Kääriäinen and Laura Tanner: Wrote the draft of the article. All authors reviewed and revised the article. All authors read and approved the final article.

### FUNDING INFORMATION

This study received funding from Päivikki and Sakari Sohlberg Foundation and Juhani Aho Foundation for Medical Research.

### CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

### DATA AVAILABILITY STATEMENT

Data available on request from the authors.

### ORCID

*Satu Wedenoja* https://orcid.org/0000-0003-0212-4851

### REFERENCES

1. Hassold TJ, Jacobs PA. Trisomy in man. *Annu Rev Genet*. 1984;18:69-97.
2. Gruhn JR, Zielinska AP, Shukla V, et al. Chromosome errors in human eggs shape natural fertility over reproductive life span. *Science*. 2019;365:1466-1469.
3. Hassold T, Hunt P. To err (meiotically) is human: the genesis of human aneuploidy. *Nat Rev Genet*. 2001;2:280-291.
4. Elmerdahl Frederiksen L, Ølgaard SM, Roos L, et al. Maternal age and the risk of fetal aneuploidy: a nationwide cohort study of more than 500 000 singleton pregnancies in Denmark from 2008 to 2017. *Acta Obstet Gynecol Scand*. 2024;103:351-359.
5. Fragouli E, Alfarawati S, Spath K, et al. The origin and impact of embryonic aneuploidy. *Hum Genet*. 2013;132:1001-1013.
6. Herbert M, Kalleas D, Cooney D, Lamb M, Lister L. Meiosis and maternal aging: insights from aneuploid oocytes and trisomy births. *Cold Spring Harb Perspect Biol*. 2015;7:a017970.
7. Hassold T, Chiu D. Maternal age-specific rates of numerical chromosome abnormalities with special reference to trisomy. *Hum Genet*. 1985;70:11-17.
8. Nagaoka SI, Hassold TJ, Hunt PA. Human aneuploidy: mechanisms and new insights into an age-old problem. *Nat Rev Genet*. 2012;13:493-504.
9. Lamb NE, Sherman SL, Hassold TJ. Effect of meiotic recombination on the production of aneuploid gametes in humans. *Cytogenet Genome Res*. 2005;111:250-255.
10. Coppedè F. Risk factors for down syndrome. *Arch Toxicol*. 2016;90:2917-2929.
11. Antonarakis SE, Skotko BG, Rafii MS, et al. Down syndrome. *Nat Rev Dis Primers*. 2020;6:9.
12. Cuckle H, Benn P. Review of epidemiological factors (other than maternal age) that determine the prevalence of common autosomal trisomies. *Prenat Diagn*. 2021;41:536-544.
13. Gianaroli L, Magli MC, Cavallini G, et al. Predicting aneuploidy in human oocytes: key factors which affect the meiotic process. *Hum Reprod*. 2010;25:2374-2386.
14. Shahine LK, Marshall L, Lamb JD, Hickok LR. Higher rates of aneuploidy in blastocysts and higher risk of no embryo transfer in recurrent pregnancy loss patients with diminished ovarian reserve undergoing in vitro fertilization. *Fertil Steril*. 2016;106:1124-1128.
15. Warburton D, Dallaire L, Thangavelu M, Ross L, Levin B, Kline J. Trisomy recurrence: a reconsideration based on North American data. *Am J Hum Genet*. 2004;75:376-385.
16. Weghofer A, Munne S, Chen S, Barad D, Gleicher N. Lack of association between polycystic ovary syndrome and embryonic aneuploidy. *Fertil Steril*. 2007;88:900-905.
17. Mansour G, Sharma RK, Agarwal A, Falcone T. Endometriosis-induced alterations in mouse metaphase II oocyte microtubules and chromosomal alignment: a possible cause of infertility. *Fertil Steril*. 2010;94:1894-1899.
18. Juneau C, Kraus E, Werner M, et al. Patients with endometriosis have aneuploidy rates equivalent to their age-matched peers in the in vitro fertilization population. *Fertil Steril*. 2017;108:284-288.
19. Yan N, Yuan X, Huang S, Jie H, Wang J, Yuan Y. Ovarian endometrioma increases the embryo aneuploid rate: an analysis of 7092 biopsied blastocysts from fertile monogenetic disease carriers. *BMC Womens Health*. 2023;23:244.
20. Gissler M, Surcel HM. Combining health register data and biobank data. *Stat J IAOS*. 2012;28:53-58.
21. Hassold T, Hunt P. Maternal age and chromosomally abnormal pregnancies: what we know and what we wish we knew. *Curr Opin Pediatr*. 2009;21:703-708.
22. Savva GM, Morris JK, Mutton DE, Alberman E. Maternal age-specific fetal loss rates in Down syndrome pregnancies. *Prenat Diagn*. 2006;26:499-504.
23. Bray IC, Wright DE. Estimating the spontaneous loss of Down syndrome fetuses between the times of chorionic villus sampling, amniocentesis and livebirth. *Prenat Diagn*. 1998;18:1045-1054.
24. Atrash HK, Hogue CJ. The effect of pregnancy termination on future reproduction. *Baillieres Clin Obstet Gynaecol*. 1990;4:391-405.
25. Thorp JM Jr, Hartmann KE, Shadigian E. Long-term physical and psychological health consequences of induced abortion: review of the evidence. *Obstet Gynecol Surv*. 2003;58:67-79.
26. Witters G, Van Robays J, Willekes C, et al. Trisomy 13, 18, 21, Triploidy and Turner syndrome: the 5T's. Look at the hands. *Facts Views Vis Obgyn*. 2011;3:15-21.
27. Morin SJ, Eccles J, Iturriaga A, Zimmerman RS. Translocations, inversions and other chromosome rearrangements. *Fertil Steril*. 2017;107:19-26.

28. Sharma R, Biedenharn KR, Fedor JM, Agarwal A. Lifestyle factors and reproductive health: taking control of your fertility. *Reprod Biol Endocrinol*. 2013;11:66.
29. Malin M, Hemminki E, Räikkönen O, Sihvo S, Perälä ML. What do women want? Women's experiences of infertility treatment. *Soc Sci Med*. 2001;53:123-133.
30. Terävä AN, Gissler M, Hemminki E, Luoto R. Infertility and the use of infertility treatments in Finland: prevalence and socio-demographic determinants 1992-2004. *Eur J Obstet Gynecol Reprod Biol*. 2008;136:61-66.
31. Charalambous C, Webster A, Schuh M. Aneuploidy in mammalian oocytes and the impact of maternal ageing. *Nat Rev Mol Cell Biol*. 2023;24:27-44.
32. Kort JD, McCoy RC, Demko Z, et al. Are blastocyst aneuploidy rates different between fertile and infertile populations? *J Assist Reprod Genet*. 2018;35:403-408.
33. Munné S, Sandalinas M, Magli C, Gianaroli L, Cohen J, Warburton D. Increased rate of aneuploid embryos in young women with previous aneuploid conceptions. *Prenat Diagn*. 2004;24:638-643.
34. Oliver TR, Feingold E, Yu K, et al. New insights into human nondisjunction of chromosome 21 in oocytes. *PLoS Genet*. 2008;4:e1000033.
35. Chernus JM, Allen EG, Zeng Z, et al. A candidate gene analysis and GWAS for genes associated with maternal nondisjunction of chromosome 21. *PLoS Genet*. 2019;15:e1008414.
36. Antonarakis SE, Avramopoulos D, Blouin JL, Conover Talbot C Jr, Schinzel AA. Mitotic errors in somatic cells cause trisomy 21 in about 4.5% of cases and are not associated with advanced maternal age. *Nat Genet*. 1993;3:146-150.
37. Warburton D. The effect of maternal age on the frequency of trisomy: change in meiosis or in utero selection? *Prog Clin Biol Res*. 1989;311:165-181.


## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Wedenoja S, Pihlajamäki M, Gissler M, et al. Infertility following trisomic pregnancies: A nationwide cohort study. *Int J Gynecol Obstet*. 2024;00:1-7. doi:10.1002/ijgo.15828