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ORIGINAL ARTICLE ***Reproductive epidemiology***

Follicle pool, ovarian surgery and the risk for a subsequent trisomic pregnancy

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STUDY QUESTION: Is there an association between trisomic pregnancy, a marker for decreased oocyte quality, and the reduced oocyte quantity that follows ovarian surgery?

SUMMARY ANSWER: Previous ovarian surgery is not associated with an increased risk for a subsequent trisomic pregnancy.

WHAT IS KNOWN ALREADY: Ovarian surgery diminishes the number of oocytes. The risk for a trisomic pregnancy is suggested to be higher in women with fewer oocytes, independent of their chronological age.

STUDY DESIGN, SIZE, DURATION: This is a matched case–control study. Cases are women with a confirmed trisomic pregnancy occurring between 1 January 2000 and 31 December 2010 regardless of pregnancy outcome and controls are women that had a live born child without a trisomy. In total, there were 8573 participants in the study; 1723 cases and 6850 controls.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Data were obtained from Danish medical registries. Matching criteria were maternal age and year of conception. Number of controls matched per case ranged from one to four. Among cases and controls with a trisomic pregnancy, 2.7% (46/1723) versus 2.5% (172/6850) had undergone ovarian surgery before pregnancy.

MAIN RESULTS AND ROLE OF CHANCE: History of ovarian surgery is not associated with a higher risk for a subsequent trisomic pregnancy (odds ratio = 1.00, 95% confidence interval 0.99–1.01). Subgroup analyses by indication of surgery and interval between ovarian surgery and pregnancy do not show an effect on trisomic pregnancy risk.

LIMITATIONS, REASONS FOR CAUTION: The medical registries used to select cases and controls did not contain information on surgical technique nor volume of ovarian tissue resected, previous trisomic pregnancy prior to the ovarian surgery or long-term use of oral contraceptives. Therefore, correction for these factors was not performed.

WIDER IMPLICATIONS OF THE FINDINGS: We did not confirm the hypothesis that ovarian surgery, a marker for decreased oocyte quantity, is related to trisomic pregnancy, a marker for decreased oocyte quality. This suggests that ovarian surgery, which has a direct reductive effect on the size of the follicle pool, may affect oocyte quality differently when compared with the reduction in follicle pool size due to ageing.

STUDY FUNDING/COMPETING INTEREST(S): The study was supported by grants from the Gratama Stichting, University of Groningen and the University Medical Center Groningen, The Netherlands. Ø.L. has within the last 3 years received honoraria for speeches in pharmacoepidemiological issues, not related to this study. The Department of Obstetrics and Gynaecology receives unrestricted educational grants from Ferring Pharmaceuticals. A.H. received a grant from ZonMW (i.e. National Dutch Scientific funding) for a RCT not related to this publication. Dr A.H. received speakers fee from MSD for an educational presentation. All other authors have no conflict of interest.

Key words: ovarian surgery / trisomic pregnancy / trisomy / oocyte pool / ovarian reserve

Introduction

Aneuploidy is the main cause of congenital birth defects and miscarriage (Hassold et al., 1996; Fritz et al., 2001; Boyd et al., 2011). The most common autosomal chromosomal aberrations are trisomy 13, 18 and 21 (Irving et al., 2011; Loane et al., 2013), which result from errors during meiosis. Maternal age is known as the major factor influencing the rate of meiotic errors, specifically meiotic non-disjunction (Hook, 1981; Fisch et al., 2003; Pellestor et al., 2003). The underlying mechanism of meiotic non-disjunction associated with ageing is unknown but multiple causal factors resulting in loss of sister chromatid cohesion, accumulation of environmental damage, hormonal change or a smaller oocyte pool (Nagaoka et al., 2012) are thought to be involved.

It is indisputable that the number of antral follicles available for maturation decreases with ovarian aging (Faddy and Gosden, 1996); the number of oocytes steadily decreases by ovulation, atresia and apoptosis (Baker, 1963) and menopause occurs when the number drops below a critical value (Faddy and Gosden, 1996). The link between ovarian ageing and increased rates of aneuploid oocytes is explained by the so-called oocyte pool hypothesis, which states that with a lower number of oocytes a selection of suboptimal oocytes for ovulation occurs more frequently, resulting in higher risk of aneuploidy (Warburton, 1989). According to this hypothesis, pregnancy outcome is better predicted by ovarian age parameters, irrespective of the chronological age. Indeed, increased risk for a trisomic pregnancy in cases of fewer oocytes, independent of chronological age, has been described before (Brook et al., 1984).

Not only physiological ageing decreases follicle numbers, but also iatrogenic damage such as ovarian surgery (Garcia-Velasco and Somigliana, 2009; Benaglia et al., 2010; Berlanda et al., 2013) leads to a smaller follicle pool. In a small study, women with surgical removal of one of their ovaries were more likely to have a child with Down syndrome later in life when compared with non-operated controls (Freeman et al., 2000). Our research group has previously found an association between trisomic pregnancy and history of ovarian surgery prior to pregnancy in subfertile women treated with IVF (Haadsma et al., 2010). However, the results of this latter study cannot be generalized to the fertile population.

Therefore, the aim of our present study is to determine the effect of ovarian surgery on the risk for a subsequent trisomic pregnancy based on general population data with a large sample size. The hypothesis is being tested at populational level, that is, it includes normal fertile women with spontaneous pregnancies, as well as infertile women pregnant via assisted reproductive techniques (ART). In this study, trisomy is taken as a parameter for oocyte quality, that is, an underlying parameter of non-disjunction, and ovarian surgery as a model for reduced oocyte quantity or reduced size of follicle pool and we expect these two parameters to be positively correlated (less quantity indicating less quality) independent of chronological age. We hypothesized that women who have undergone ovarian surgery have an increased risk for a trisomic pregnancy later in life.

Materials and Methods

Study design and participants

We performed a matched case–control study based on data from nationwide Danish medical registries. All women with a confirmed trisomic pregnancy between 1 January 2000 and 31 December 2010 registered at the Hospital Discharge Register and at the Cytogenetic Central Register were selected as cases. We excluded trisomic pregnancies of women born in Greenland and Faroe Islands or any countries outside Denmark. Trisomies 13, 18 and 21 confirmed by karyotyping were included, regardless of the pregnancy outcome (termination, intrauterine death, still born or live born child) to avoid underestimation of the risk. Trisomic pregnancies with translocations as the underlying mechanism or pregnancies with oocyte donation were excluded. Controls were women who had a live born child without a trisomy in the same birth period as cases. Cases and controls were selected irrespective of surgery status. Matching criteria were maternal age and year of conception. The indication of ovarian surgery in cases and controls was derived from ICD-10 codes (International classification of diseases, 10th revision). Those included: malignancies of the female genital tract (DC53.0–57.9); benign neoplasm of ovary (DD27.0–27.9); benign neoplasm of other and unspecified female genital organs (DD28.0–28.9); neoplasm of uncertain or unknown behavior of female genital organs (DD39.0–39.9); polycystic ovary syndrome (PCOS) (DE28.2); salpingitis and oophoritis (DN 70.0–70.9) other female pelvic inflammatory diseases (DN73.0–73.9); endometriosis (DN80.0–80.9); non-inflammatory disorders of the ovary, fallopian tube and broad ligament (DN83.0–83.9); extra-uterine pregnancy (DO00.0–00.9).

Statistical methods

Descriptive statistics were used to compare differences between cases and controls and to test whether they were matched adequately. To test the hypothesis that women with a history of ovarian surgery have an increased risk for having a trisomic pregnancy, analyses were performed with generalized estimating equations (GEEs), assuming a fixed non-zero correlation within clusters consisting of cases and their matched controls (exchangeable correlation structure). Subgroup analyses were performed to assess the risk of trisomic pregnancy depending on the indication that led to surgery and the influence of the interval between ovarian surgery and pregnancy. Intervals below the 25th percentile were categorized as short interval; intervals above the 75th percentile were categorized as large interval. Intervals in between the 25th percentile and the 75th percentile were categorized as intermediate. The categorization was conducted to determine whether surgery would affect ovary function particularly just after surgery (short interval) or whether the negative effects of surgery would appear only later in time. Stratified analyses for different age groups were made by categorizing age in the following percentiles: below 25th percentile, above 75th percentile and the interval in between percentile 25th and 75th. The relationship between intervals and probability of trisomic pregnancy was explored by spline regression using Stata LC version 11 (Statacorp. College Station, TX, USA). The probability of having a trisomic pregnancy was calculated for each of the interval time points between surgery and pregnancy. A figure was created to visualize the curve of probability when connecting all the interval time points. A P-value of <0.05 was considered significant. Analyses were performed using the IBM Statistical Package for the Social Sciences software, version 20 (Supplier: IBM Corporation. Armonk, NY, USA).

Results

Table I shows characteristics of cases and controls in the study. In total, 8573 women were included in our study. Controls were 6850 and cases 1724; 1 case could not be matched to controls, 12 controls did not have a match, 1679 cases were matched with 4 controls, 40 cases with 3 controls, 2 cases with 2 controls and 1 case with 1 control. Among the trisomic pregnancies 7.5% (129/1723) were trisomy 13 cases, 19.7% (340/1723) were trisomy 18 cases and 72.8% (1254/1723) were trisomy

Table I Description of women in the study population.

	Total (n = 8573)	Cases (n = 1723)	Controls (n = 6850)	Value of P
Age at conception[1]	8573	34.6 ± 5.5	34.5 ± 5.4	0.82
Ovarian surgery	218	46 (2.7%)	172 (2.5%)	
Indication of ovarian surgery	190	41 (2.4%)	149 (2.2%)	0.77
Benign neoplasm	70	12/41 (29.3%)	58/149 (38.9%)	
Endometriosis	45	13/41 (31.7%)	32/149 (21.5%)	
Non-inflammatory disorders	54	11/41 (26.8%)	43/149 (28.9%)	
Other reasons[2]	21	5/41 (12.2%)	16/149 (10.7%)	
Age at ovarian surgery[1]	218	29.2 ± 6.5	28.2 ± 6.5	0.36
Interval between surgery and pregnancy	218			0.35
Interval between surgery and pregnancy[1]	218	6.8 ± 5.3	8.1 ± 6.8	0.02
Short interval (<P25th)	54	14/46 (30.4%)	40/172 (23.3%)	
Intermediate interval (p25–p75)	109	21/46 (45.7%)	88/172 (51.2%)	
Large interval (>P75th)	54	11/46 (23.9%)	43/172 (25.0%)	
Mode of conception[3]	8573			0.01
Spontaneous	8064	1599 (92.8%)	6464 (94.4%)	
IUI	110	32 (1.9%)	78 (1.1%)	
ART[4]	399	92(5.3%)	307 (4.5%)	

Mixed models analyses were performed for the description of the data.
IUI, intrauterine insemination.
[1]Mean (years) ± (SD).
[2]Other reasons: extra-uterine pregnancy, salpingitis and oophoritis, PCOS, malignancies of the female genital tract, benign neoplasm of the other and unspecified female genital organs and other female pelvic inflammatory diseases.
[3]One participant from the control group was missing information on mode of conception.
[4]ART includes: IVF, ICSI, frozen embryo transfer and testicular sperm aspiration, testicular sperm extraction and percutaneous epididymal sperm aspiration.

21 cases. There were 278 live born trisomic pregnancies (16.1%) and 1445 (83.9%) terminations, intrauterine deaths/stillborn. The average (±SD) maternal age at conception was 34.5 years (±5.4), ranging from 16 to 47 years and there was no significant difference in the average age between cases and controls. There were 218 women with a history of ovarian surgery before pregnancy. Among these, 9 women had a biopsy, 82 had an excision of pathological tissue in the ovary, 77 had an ovarian resection, 15 had an ovarian excision and 30 had an excision of ovary and a salpinx. Data on the type of ovarian surgery was missing for five women. Women who did not have ovarian surgery and women who had ovarian surgery after pregnancy were included in the reference group labeled 'no surgery'. The average age at surgery was 28.4 years (±6.46), ranging from 13.7 to 43.5 years and the difference of 1 year between cases and controls was not significant. The three most prevalent indications for surgery were benign neoplasm, endometriosis and non-inflammatory disorders. The mean interval between ovarian surgery and the subsequent pregnancy was 7.82 years; 25th and 75th percentiles were 2.20 and 12.92 years, respectively. Interval range for cases varied from 0.15 to 20.61 years; for controls from 0.05 to 27.75 years and controls had on average a 1.3 years longer interval when compared with cases. The majority of women included in this study conceived spontaneously, but intrauterine insemination (IUI) and ART were also observed (see Table I). Cases and controls differed significantly by mode of conception and interval between surgery and pregnancy. Results did not change when sensitivity analyses were performed by restricting the analyses to trisomy 21 cases and their controls, or when selecting only spontaneous pregnancies. Table II shows results for the comparison between women who underwent ovarian surgery before pregnancy and women who did not. Overall, there was a 1.1% difference in proportions for trisomic pregnancies between groups. A history of

Table II Odds ratio for the trisomic pregnancy associated with ovarian surgery.

	Total (n = 8573)	OR and 95% CI for the risk of trisomic pregnancy
No surgery	8355	*Reference group
Ovarian surgery	218	1.001 [0.988–1.014]
Indication of ovarian surgery		
Benign neoplasm	70	0.993 [0.971–1.016]
Endometriosis	45	1.018 [0.991–1.045]
Non-inflammatory disorders	54	0.992 [0.961–1.025]
Interval between surgery and pregnancy		
Short interval (<P25th)[1]	54	1.019 [0.981–1.039]
Intermediate interval (p25th–p75th)	109	0.999 [0.981–1.017]
Large interval (>P75th)	54	0.997 [0.972–1.021]

[1]One case was not matched.

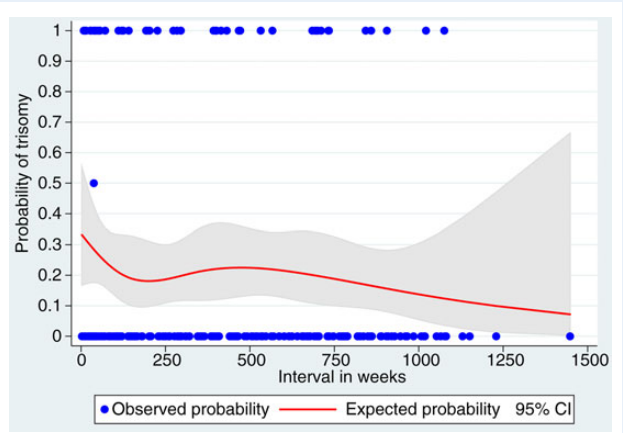

Figure 1 The probability for a trisomic pregnancy in women according to interval between ovarian surgery and pregnancy. Spline regression is a technique to investigate non-linear relationships between a determinant and an outcome. We used restricted cubic spline regression, which means that the probability of having a trisomic pregnancy was calculated for multiple intervals between surgery and pregnancy. The regression lines for each interval were connected with smoothed transitions, resulting in a curve visually representing the probability of trisomy as a function of interval between surgery and pregnancy. The dots at the top represent time intervals for cases and the dots below for the controls. The middle dot is a case and control with the same time interval. The continuous line is the expected probability and the dark area, the 95% CI. There was a trend suggesting that the shorter the interval between ovarian surgery and pregnancy, the higher the probability for a trisomic pregnancy, but this was not statistically significant.

ovarian surgery was not statistically significantly associated with a higher risk for a subsequent trisomic pregnancy. Subgroup analyses with the selection of women who had surgery due to benign neoplasm, endometriosis or non-inflammatory disorders did not change the results. Neither a short interval between surgery and pregnancy nor a longer interval had an effect on the risk for a trisomic pregnancy when compared with the reference group. There was a trend indicating that the shorter the interval between ovarian surgery and pregnancy, the higher the probability for a trisomic pregnancy, but no significant difference was found (Fig. 1). When we stratified for groups of younger than 31 years, older than 39 years and between 32 and 39 years of age (percentiles 25th, 75th and in between 25th and 75th) the results did not change. We have performed additional sensitivity analyses regarding interval between surgery and pregnancy. Results did not change when excluding the large interval or when excluding the short interval group. Adjusting for mode of conception and age at surgery also showed no difference between groups.

Discussion

A history of ovarian surgery was not associated with a higher risk of a subsequent trisomic pregnancy, independent of the indication of surgery or the interval between ovarian surgery and pregnancy.

Animal studies support the hypothesis that ovarian surgery may have an effect on oocyte quantity and quality. Female mice had an earlier and increased incidence of aneuploid embryos after unilateral ovariectomy (Brook *et al.*, 1984). Nevertheless, evidence in women is conflicting. A previous study ($n = 4795$) looking at the relation between ovariectomy and trisomic pregnancy resulting in spontaneous abortion found no effect of surgery [odds ratio (OR) = 1.5, 95% confidence interval (CI) 0.4–3.9]) (Warburton and Kline, 2001). Levels of anti-Mullerian hormone (AMH), FSH and inhibin B or sonographic antral follicle count (AFC), all parameters of the size of the follicle pool, were not statistically associated with trisomic losses in some studies (Kline *et al.*, 2004, 2011; Grande *et al.*, 2014), while in other studies, women with trisomic pregnancies showed evidence for depletion of the follicle pool as indicated by elevated FSH levels (Van Montfrans *et al.*, 1999, 2002). All of these previously cited studies as well as this current study are based on the same underlying mechanism: indicators of ovarian follicle pool size and their association to aneuploidy rates, irrespective of chronological age.

Strengths of the current study are the sample size and the majority of clusters having four controls per case, as well as inclusion of all pregnancies irrespective of outcome (termination, intrauterine death, still born or live born child) and different modes of conception (spontaneous, IUI or different ART methods). The selection of more than four controls per case would have minimal effect on statistical power (Rothman, 1986). The statistical method of our choice (GEE) enabled good estimates of ORs, expressed in small CIs, that is, a more accurate estimate. Additionally, the method accounts for dependency of the matching between case and controls. This explains the risk of 1.02 for trisomy for the group that had surgery due to endometriosis even though the differences in proportions were 10.2% between cases and controls. In all analyses, despite the absence of differences in *P*-values among statistical methods, the risk was higher when using an independent type of analysis (e.g. logistic regression), but this effect was diminished when taking into account the clustering and the dependent matching structure.

The medical registries used to select cases and controls have limitations, for example they did not contain information on surgical technique or volume of ovarian tissue resected, for which we could not control in the analyses. Nevertheless, the indication of surgery can be regarded as a predictor of the amount of tissue necessary to be resected. Surgical techniques such as cystectomy are usually minimally invasive, whereas resection of endometriomas generally requires a far greater amount of tissue to be removed. In our study, the indications of surgery and the most prevalent ICD codes that required more tissue to be removed [endometriosis (DN80.0–80.9)] did have a higher proportion of trisomic cases compared with the indications that needed less tissue removed, but the difference was not statistically significant. It has been argued that different surgery procedures have different effects on ovarian volume and the oocyte pool (Var *et al.*, 2011). Moreover, other confounding factors, such as previous trisomic pregnancy prior to ovarian surgery and subsequent pregnancy (De Souza *et al.*, 2009) or long-term use of contraceptives in the period between surgery and pregnancy, that could have an effect on the quantity of oocytes (Nagy *et al.*, 2013) could not be corrected for.

Women who have undergone ovarian surgery before pregnancy represented 2.57% (220/8573) of the total study population. One can argue that comparison groups are not proportional in the number of participants, nevertheless, case–control studies should not include subjects based on exposure (in this study, surgery prior to pregnancy) and ovarian surgery is a rather uncommon event. Therefore, the population at risk was impossible to predict due to study design.

Our present results do not confirm the findings from two other studies on this subject. One previous case–control study, including a small number of women that underwent ovarian surgery (seven cases and one control), reported an OR of 9.61 (95% CI 1.18–446.3) for trisomic pregnancy in women who have undergone previous ovarian surgery; that is surgical removal of all or part of the ovary or congenital absence of one ovary (Freeman *et al.*, 2000). The sample size of the previous study (Freeman *et al.*, 2000) was small, hence possibly an overestimation of the effect size was shown. Our study with a robust sample size does not confirm these results. Our research group has previously found, in subfertile women who had undergone IVF, an association between trisomic pregnancy and a history of ovarian surgery prior to pregnancy [OR = 3.3 95% CI (1.0–10.5)] (Haadsma *et al.*, 2010). We did not find similar results in the present study, in which we have analyzed the data within a general population, and not only in subfertile women who had undergone IVF. Appropriate analyses with only IVF women in this study were not possible, because the matching structure would be lost.

Our results may be explained by the hypothesis that the natural reduction of ovarian reserve by aging and the iatrogenic effect of surgery could represent different mechanisms of depletion of the oocyte pool. In a meta-analyses, AMH levels decreased by 40% (−1.13 ng/ml; 95% CI −0.37 to −1.88) after excision of ovarian endometriomas; the effect was still present in studies in which age was not a significant confounder (age ≤40 years), but no effect of surgery was found for AFC (Raffi *et al.*, 2012). Furthermore, there may also be a compensatory effect of the non-operated ovary on total ovarian function over time. Women who had gone through unilateral oophorectomy had more follicles and oocytes at time of IVF stimulation than the ipsilateral ovary of women with both ovaries, suggesting a compensatory follicular recruitment of the remaining ovary (Khan *et al.*, 2014). The previous study (Khan *et al.*, 2014) does not consider the interval between surgery and IVF treatment, but, if there is a time effect for recovery of the remaining ovary, then the highest risk for a trisomic pregnancy would be expected to be within the short interval between surgery and pregnancy. An effect of surgery only in the short interval could mean that the non-operated ovary could be compensating as a long-term response to the lack of tissue in the operated ovary; an effect of surgery only in the long interval could mean that the compensating function of the other ovary exhausts over time. Our data show this higher risk for a shorter interval (Fig. 1), although risks did not differ statistically.

The lowest risk period for a women to have a trisomic pregnancy is not around menarche (Hunt and Hassold, 2010) when oocytes are expected to be 'young' and in great quantity; there is a higher risk for trisomy for pregnancies of 15-year olds than for 18-year olds. Additionally, only the quantity may not be enough either; there was no fertile window extended for women with PCOS in a recently published study (Kalra *et al.*, 2013). The quantity of oocytes for the PCOS population was higher when compared with women with tubal factor infertility only up to 40 years of age, but in older women there was no difference. Moreover, the correlation between quality and quantity may not be linear and loss of ovarian tissue could become more critical over time as the other remaining follicles ages, but this is not what we have found with our age category data analyses.

Finally, our study indicates that an intervention, such as ovarian surgery, that has a direct reductive effect on the size of the follicle pool, influences the relation of oocyte quantity and quality differently compared with the reduction in follicle pool size due to ageing. In summary, our findings indicate that ovarian surgery is not associated with a higher risk of a subsequent trisomic pregnancy. Women with a history of ovarian surgery prior to pregnancy may not be regarded to be at higher risk for a trisomic pregnancy.

Authors' roles

This study has been designed by A.A.H., M.L.H., A.P., Ø.L., H.G. and A.H. Execution was performed by T.C.H., A.A.H., M.L.H., A.P., Ø.L., H.G. and A.H. Analyses were performed by T.C.H., M.L.H., H.G. and A.H. Manuscript drafting was performed by T.C.H., M.L.H., J.A.L., H.G. and A.H. Critical discussion was performed by all authors.

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Conflict of interest

Ø.L. has within the last 3 years received honoraria for speeches in pharmacoepidemiological issues, not related the this study. A.H.:

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