Am. J. Hum. Genet. 66:1680–1683, 2000

Report

Women with a Reduced Ovarian Complement May Have an Increased Risk for a Child with Down Syndrome

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Advanced maternal age is the only well-established risk factor for trisomy 21 Down syndrome (DS), but the basis of the maternal-age effect is not known. In a population-based, case-control study of DS, women who reported surgical removal of all or part of an ovary or congenital absence of one ovary were significantly more likely to have delivered a child with DS than were women who did not report a reduced ovarian complement (odds ratio 9.61; 95% confidence interval 1.18–446.3). Because others have observed that women who have had an ovary removed exhibit elevated levels of FSH and similar hallmarks of advanced maternal age, our finding suggests that the physiological status of the ovary is key to the maternal-age effect. In addition, it suggests that women with a reduced ovarian complement should be offered prenatal diagnosis.

Although advanced maternal age is a well-established risk factor for trisomy 21 Down syndrome (DS) (MIM 190685), much remains to be learned about the basis of the maternal-age effect. For example, the question of whether the chronological age of the mother or the physiological age of the ovary is more important has both biological and clinical relevance. If oocyte depletion with advancing age is the basis of the maternal-age effect, as is suggested by Warburton (1989), then women who have a reduced number of oocytes for other reasons might have an increased risk for a conception with trisomy 21. In this regard, it is not unusual for women to have ovarian surgery for a variety of conditions, and, because of associated infertility, a number of these women become candidates for in vitro fertilization (IVF) (Khalifa et al. 1992). The present study of the ovarian status of women who have had a child with DS provides clues to the nature of the maternal-age effect and suggests a risk factor that may be of clinical importance to a significant number of women.

This work is part of an ongoing population-based, case-control study of trisomy 21 in Atlanta. During 1989–1998, live-born infants with trisomy 21 were ascertained with the assistance of the Metropolitan Atlanta Congenital Defects Program (MACDP) of the Centers for Disease Control and Prevention (Edmonds et al. 1981). Of the 372 live-born infants with DS, 267 were enrolled in the study (participation rate 72%). In addition, the MACDP randomly selected 576 unaffected, live-born control infants from the same population. These infants were selected in proportion to the expected number of total births at each hospital. The parents of 347 of the control infants enrolled in the study (60% participation rate). Institution-approved informed consent was obtained from each participant. For all DS cases, DNA extracted from blood samples from the parent(s) and child was used to determine the parent and meiotic stage of origin of the chromosomal error (Lamb et al. 1996; Yang et al. 1999). A questionnaire—covering demographic factors, environmental exposures, and medical, reproductive, and family history—was administered to the parents of case and control infants. Mothers were asked whether, prior to the date of conception of the case or control infant, they had ever had an ovary removed. If they reported a history of ovarian surgery, we sought medical records to verify the details. Because various types of surgery were reported and one woman had no surgery but only congenital absence of one ovary (table 1), we designated the entire group as having a reduced ovarian complement (ROC).

Received December 17, 1999; accepted for publication February 7, 2000; electronically published March 24, 2000.

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0002-9297/2000/6605-0022$02.00

Table 1

Profile of ROC Cases and Controls

Subject[a]	Origin of Nondisjunction[b]	Maternal Age at Birth of Proband (years)	Maternal Age at Ovarian Surgery	Menstrual Cycle Length (d)[c]	Clinical Description
C152	Control	25	24	28	Unilateral salpingo-oophorectomy for tubal pregnancy
D461	MMI	39	Not applicable	28	Congenital absence of right ovary and tube detected at cesarean delivery of proband
D571	MMI	32	17	28	Oophorectomy for 9094-gm ovarian cyst
D602	MMI	32	30	32	Left oophorectomy for 120-cm^2 cyst involving entire left ovary
D611	MMII	28	23	28	Bilateral cystectomies for endometriosis; removal of one half of left ovary and one third of right
D698	MMI	36	23	25	Surgery for infertility: laparoscopy, reduction in size of both ovaries and removal of obstructing tissue from tubes
D852	MMI	33	31	30	Right salpingo-oophorectomy for hemorrhagic corpus luteal cyst
D942	MMI	31	14	28	Left salpingo-oophorectomy for benign teratoma; 1-cm wedge biopsy of right ovary

[a] C = control subject; D = case patient.

[b] MMI = maternal meiosis I; MMII = maternal meiosis II.

[c] Mean cycle length for control mothers without ROC, 28.6 ± 2.68 d; mean cycle length for case mothers without ROC, 28.19 ± 2.27 d.

The cases in this report are those for which DNA studies were sufficiently complete to provide information on parent and stage of origin. Because all ROC cases were found to be the result of maternal meiotic nondisjunction, we included in the statistical analysis only the 189 maternal cases; that is, we omitted cases of paternal, mitotic, or unknown origin. Of the 347 control subjects who agreed to participate, 329 had completed interviews at the time of this report. Because of the small number of subjects with ROC among cases and controls, the asymptotic χ^2 distribution of test statistics used by the conventional logistic regression may not hold. Therefore, we used conditional exact inference to estimate exact odds ratios (OR) and 95% confidence intervals (CI) while adjusting for maternal age (seven age groups [in years]: <15, 15–19, 20–24, 25–29, 30–34, 35–39, and ⩾40) and maternal race (white or other [other includes 83% black]). The adjusted exact OR and 95% CI were estimated by means of LOGXACT software (Cytel 1996).

Table 1 provides details on each mother with ROC including seven cases (7/189) and one control (1/329). A significantly greater number of mothers of infants with DS (7/189) reported ROC than did mothers of control infants (1/329). The adjusted OR was 9.61 (95% CI 1.18–46.3).

Brook et al. (1984) were the first to suggest that a unilateral oophorectomy (ULO) could be a risk factor for DS. Observing that mice with a ULO had a premature onset of cycle irregularity and an early rise in aneuploidy, they concluded that the risk for DS is determined by the distance in time from the menopause (physiological age) rather than the chronological age of the mother and that the number of follicles limits the reproductive life span. Similarly, Warburton (1989) suggested that, if oocyte depletion is the major factor in age-related nondisjunction in humans, women who have had a trisomic conception at a young age might exhibit signs of early oocyte depletion, such as premature menopause.

Since the original report in mice, other studies have reported evidence of decreased reproductive fitness in women with a ULO. Many changes seen in these women are also seen with advancing maternal age in women with two ovaries. For example, higher FSH (Khalifa et al. 1992; Backer et al. 1999), lower estrogen (Lass et al. 1997), and shorter menstrual cycles (Hardy and Kuh 1999), hallmarks of advanced maternal age, have also been associated with ULO. These similarities suggest that age-related changes may be a matter of physiological rather than chronological age. There is evidence from IVF procedures that compensatory follicle growth occurs after ULO. Some studies have found that the number of follicles retrieved from women with one ovary

is similar to the number obtained from women with two ovaries (Alper et al. 1985; Hornstein et al. 1989), while others have reported that the number of retrievable follicles is decreased after ULO but is still more than half the number expected in women with two ovaries (Diamond et al. 1984; Boutteville et al. 1987). This compensatory follicle recruitment and growth may further contribute to a shorter reproductive life span in women with ULO (Cramer et al. 1995; Hardy and Kuh 1999).

Although many reports describe the reproductive status of women with ULO, no other studies, known to us, discuss the incidence of aneuploidy in these women. However, two recent reports have indicated that women who have had an aneuploid conceptus exhibit elevated serum FSH (van Montfrans et al. 1999; Nasseri et al. 1999). The present report of increased aneuploidy with ROC suggests that the physiological status of the ovary—and, more specifically, the number of follicles—may be a key factor in maternal meiotic nondisjunction. Whether, in turn, oocyte depletion is due to the passage of time or to maternal factors such as ROC or environmental exposures may be individually determined.

Our findings are consistent with the limited oocyte pool hypothesis proposed by Warburton (1989), which states that an oocyte in a suboptimal state of development could become the dominant follicle because of the small number of oocytes available in older women. An oocyte of this type might be more likely to exhibit chromosome nondisjunction. The challenge still remains to determine exactly how a depleted oocyte pool could lead to recruitment of an oocyte destined to undergo nondisjunction when meiosis resumes.

Finally, in addition to providing key information about the maternal-age effect, our findings, if confirmed, have important clinical implications, because they suggest that women with less than two intact ovaries because of surgery or congenital anomalies should be offered prenatal testing for chromosome abnormalities.

Acknowledgments

This report was supported by National Institutes of Health (NIH) contract NO1 HD92907 and NIH grant PO1 HD32111. We thank the participating families and acknowledge the General Clinical Research Center at Emory University for preparation of lymphoblastoid cell lines (PHS-NIH-MO-1-RR00039).

Electronic-Database Information

The URL for data in this article is as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for DS [MIM 190685])

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