Is There an Association between Preconception Paternal X-ray Exposure and Birth Outcome?

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Diagnostic x-rays are performed commonly on men of reproductive age, yet little is known about the potential effects of these x-rays on the future unborn children of such men. This study examines the possibility that preconception diagnostic x-ray studies of fathers may adversely affect their newborns. The authors used prospectively collected data from the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) for 7,678 birth records for women who gave birth in the County of Avon, England, in 1991–1992. Birth weight, gestational age, and fetal growth of infants whose fathers received diagnostic x-ray examinations likely to deliver significant gonadal doses within one year prior to conception were compared with infants whose fathers did not receive such x-rays. The mean birth weight of babies of exposed fathers was 3,358 g compared with a mean of 3,437 g in the unexposed group (p = 0.055). A similar difference was noted for intrauterine growth, 3,374 g exposed versus 3,437 g unexposed (p = 0.078). The downward trend in birth weight and fetal growth (birth weight adjusted for gestational age) persisted despite control for infants’ sex and important parental variables such as age, height, race, education, occupational exposure, parity, and maternal smoking. Because medical x-rays are the largest controllable source of man-made ionizing radiation, more detailed study of the potential effect of paternal x-irradiation on progeny seems justified. Am J Epidemiol 1997;145:546–51.

Ionizing radiation is known to have detrimental effects on the reproductive systems of both males and females (1). In the United Kingdom, 12 percent of all exposure to ionizing radiation comes from man-made sources, 94 percent of which are medical radiologic procedures. It is estimated that 21 million radiologic examinations are performed in Britain each year (2). These radiologic examinations are evenly distributed among age groups, including those encompassing the major reproductive years (3). Fluoroscopic examinations account for approximately 6 percent of all x-rays, and such examinations contribute greatly to the genetically significant radiation dose received by the population (4).

The danger to the embryo and fetus of intrauterine ionizing radiation exposure is well documented (5). Atomic bomb studies show that children exposed to ionizing radiation in utero exhibit a linear dose-effect relation between exposure and several neurodevelopmental and growth abnormalities depending on the gestational age at exposure (6). Diagnostic x-rays are no longer performed routinely during pregnancy because of the risk of damage during critical periods of organogenesis (7). The effect on the fetus of preconception x-irradiation is less well described. Some studies of humans show an increased incidence of chromosomal abnormalities in offspring of mothers who received preconception diagnostic x-rays (8). Other studies suggest an association between preconception paternal exposure to diagnostic x-rays and infant leukemia (9).

Work in the past decade has increasingly suggested the potential importance of preconception paternal exposures to fetal growth and development. Mechanisms by which the father may contribute to birth outcomes include genetic and epigenetic phenomena (10). An important epigenetic phenomenon is genomic (gametic) imprinting, where the expression of a gene depends on whether it was transmitted by the mother or father. This parent-of-origin effect means there must be dif-
ferential (non-mutational) modification of deoxyribonucleic acid (DNA) at gametogenesis. There is evidence in the mouse (11, 12) that the imprint is differential methylation of DNA that occurs before or during gametogenesis and is erased between generations. Of particular interest in the present context is the fact that the insulin-like growth factor 2 (IGF2) gene is imprinted in both mouse and human, with only the paternally derived allele being active during fetal life (13, 14). IGF2 stimulates fetal growth. Fetal mice without the active paternal IGF2 allele are born small (13) and removal of the maternal silencing imprint by a nearby H19 deletion causes mice to be born large (15). Another gene of interest is the negative regulator of cell proliferation, p57\textsuperscript{KIP2}, which is imprinted, but here, the paternally derived allele is the silent one (16).

One effect of DNA damage by x-rays is to trigger cell "protection"/tumor suppressor responses such as increased p53 production that can suppress growth (17). This growth suppression by p53 may be effected through various mechanisms including transcriptional down-regulation of a number of genes. In somatic cells, at least, transcriptional regulators can induce sequence-specific demethylation (18). Perhaps in the germline, increases in p53 induced by x-rays might modify the imprint setting/DNA methylation of IGF2, p57\textsuperscript{KIP2}, or other imprinted genes involved in regulating growth. Kirk and Lyon (19) were able to induce dwarfism and several congenital anomalies in offspring of male mice irradiated with large doses of x-rays immediately prior to conception.

Ionizing radiation is capable of inducing a wide spectrum of cellular, molecular, biochemical, and hormonal abnormalities. It is therefore reasonable to examine the potential effect of ionizing radiation on fetal growth mediated through the father. In this study, we investigated the association between paternal diagnostic medical x-ray exposure prior to conception and subsequent fetal growth. Because medical x-rays represent the bulk of controllable man-made exposure to ionizing radiation, the identification of possible detrimental effects on fetal growth from paternal exposures could have important influence on decisions involving elective radiologic procedures in men and family planning.

MATERIALS AND METHODS

The sample for this study is drawn from the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC), which has been previously described (20). Briefly, ALSPAC is a prospective, longitudinal study of a geographic cohort of children beginning during pregnancy and continuing to age 7 years. The study was designed to identify environmental, social, psychologic, and genetic factors associated with fetal, infant, and child health. Extensive self-administered questionnaires, abstracted medical records, biologic samples, and direct examination of children provide a unique body of health information for analysis.

Participants in ALSPAC were recruited from among all pregnant women who lived in three health districts of the County of Avon, England, and whose expected dates of delivery fell between April 1, 1991 and December 31, 1992. Over 80 percent of eligible women chose to participate, resulting in 14,893 pregnancies initially enrolled. Women were approached at booking. If they enrolled in the study, they were encouraged to invite their partners to participate as well. Each woman was sent two questionnaires that inquired about diagnostic x-ray exposure: one questionnaire for the woman to complete and the other for her partner to complete. Of these questionnaires, 12,471 were returned by women who were still pregnant, and 8,650 were returned by the partners. From the latter returned questionnaires, we excluded partners who did not answer any of the questions on x-ray exposure and partners who were not the father of the infant by maternal report. The cohort was further restricted to singleton live births, leaving 7,678 birth records for analysis.

The exposure variable was generated from an item on the partner's questionnaire asking about specific medical x-ray studies performed any time within 12 months preceding conception. Dates of examination were not requested, so it was not possible to determine the precise timing of procedures within the 12-month interval with respect to the time of conception. Only those procedures with a high likelihood of gonadal exposure were chosen for analysis. These included abdominal x-rays, barium studies of the upper and lower gastrointestinal tract, intravenous pyelograms, and pelvis and hip x-rays. Head and neck films, limb films, and chest films were not considered likely to result in significant gonadal exposures. Lumbar spine films were not differentiated in the questionnaire from other back films and were included with the studies without significant gonadal exposure.

Estimates of gonadal x-ray dose received from these procedures vary from a mean of 4.40 mGy (0.44 rad) for hip or pelvis studies to 0.07 mGy (0.007 rad) for lumbar spine studies (21). The actual dose received by individual patients may, however, vary by up to three orders of magnitude depending on differences in radiographic technique, individual body habitus, and equipment type (2). Thus, actual individual doses cannot be determined from historical data. For this reason, exposures were combined into a single categorical variable of "exposed" versus "nonexposed." The non-
exposed category consisted of the group of fathers who received no x-rays within one year prior to conception and fathers who received only x-rays distal to the gonads. The exposed group was all fathers who had studies of the abdominal or pelvic areas.

Potential maternal and paternal self-reported occupational exposures to ionizing radiation were captured from additional questionnaire items. Occupational exposures considered for mothers and fathers included medical, dental, scientific, and laboratory-related exposures, as well as nuclear power production exposures. Paternal exposures were grouped as either total lifetime exposures or exposures within one year of conception of the birth under study. Maternal occupational exposures were grouped only as total lifetime exposures.

The main outcome variables were birth weight, gestational age, and fetal growth (birth weight adjusted for gestational age). Birth weight was collected from the mothers and recorded in grams. Gestational age was calculated from the estimated date of confinement and the actual birth date. Sex ratio of infants and rates of preterm delivery (delivery before 37 weeks gestation) were also examined. Secondary independent variables were included in the analysis based on their potential impact on these outcome measures. Maternal and paternal height in centimeters, and maternal and paternal age at birth were treated as continuous variables. Maternal and paternal race (white vs. nonwhite), along with maternal parity and gravidity, maternal smoking during pregnancy, and maternal alcohol use during pregnancy were considered and treated as dichotomous variables. Maternal and paternal educational status were analyzed using a four-level categorical variable consistent with the British educational system. Sex of the infant was also included. Variables which failed to reduce variance in birth weight residuals by a minimum p value of 0.15 were dropped from the analysis.

The effect of exposure on birth weight was first examined using means of the unadjusted data. The difference in the means was evaluated by a standard two-tailed t-test (22). Using multivariate models including other independent variables known to predict birth weight, an analysis of x-ray exposure was performed in multivariate linear regression (22). In such a model, the estimated effect of x-ray exposure can be interpreted as the difference between means adjusted for these other factors. Subgroup analyses were performed adjusting for educational status, parental race, and occupational exposure, but these variables were not required in the final regression. A similar procedure was used for intrauterine growth by including linear and squared gestational age in the multivariate regression model, and for gestational age in days. Sex ratios of exposed versus nonexposed infants as well as frequency of preterm delivery in exposed versus nonexposed babies were also examined using the chi-square test (22). The effect of paternal exposure to chest x-ray studies without other studies likely to deliver significant gonadal doses during the year prior to pregnancy was used as an additional control. Finally, x-ray examinations preceding the one year prior to the pregnancy under consideration were examined in similar fashion for effect on birth outcome.

In all analyses, a statistically significant finding is one for which the appropriate statistic has a two-sided p value of 0.05 or less (22).

**RESULTS**

Table 1 shows the characteristics of the mothers and fathers by father’s exposure category. There were no notable differences likely to confound the results of the analysis. Mean unadjusted birth weight of infants born to unexposed fathers was 3,437 g compared with a mean of 3,358 g for infants born to exposed fathers. This difference of 79 g decreased slightly after controlling for sex of infant, maternal parity, maternal and paternal height, and maternal smoking during pregnancy, and remained statistically nonsignificant (table 2). The difference in mean birth weight between infants of exposed and nonexposed fathers lessened when nonwhite parents were excluded from the analysis, but the nonsignificant trend toward lower birth weight remained evident. Further subgroup analysis excluding maternal and paternal medical occupational exposure as well as occupational radiation exposure showed persistent but smaller differences in mean adjusted birth weights in infants of exposed fathers.

Fetal growth, defined as birth weight adjusted for gestational age, showed a similar decrease in infants of x-ray-exposed fathers (3,374 g) compared with nonexposed fathers (3,437 g). This decrease persisted after adjustment for infants’ sex, maternal parity, maternal and paternal height, and maternal smoking during pregnancy. It also remained evident after excluding nonwhite parents and various occupational exposures of both the mother and the father, and controlling for parental education level. All differences failed to meet the statistical significance criterion used here.

Mean gestational age was found to be 280 days in infants of unexposed fathers compared with 279 days in infants of exposed fathers. This slight nonsignificant difference remained after adjustment for maternal age and sex of the infant, both with and without nonwhite parents. No difference was found in the rate of preterm delivery in infants born to exposed vs. nonexposed fathers, though only ten of the 172 babies...
of x-ray-exposed fathers in the analysis cohort were premature. Sex ratios were the same in infants born to x-ray-exposed fathers compared with nonexposed fathers. No reduction or significant difference in birth weight or intrauterine growth was found in infants born to fathers who had only chest x-rays during the year prior to pregnancy \((n = 288, \text{mean unadjusted birth weight } = 3,474 \text{ g})\) compared with infants born to fathers who received neither chest x-rays nor x-rays with gonadal exposure prior to pregnancy \((n = 7,266, \text{mean unadjusted birth weight } = 3,435 \text{ g})\). Finally, no significant reduction in birth weight, intrauterine growth, or gestational age was found in infants born to fathers exposed to diagnostic x-rays any time before one year prior to conception \((n = 1,190, \text{mean unadjusted birth weight } = 3,394 \text{ g})\) compared with infants born to nonexposed fathers \((n = 6,004, \text{mean unadjusted birth weight } = 3,424 \text{ g})\).

**DISCUSSION**

We did not find a statistically significant difference in any of three major birth outcomes between infants of x-ray-exposed fathers and x-ray nonexposed fathers. The fact that the decreases in birth weight, gestational age, and fetal growth were robust in the face of controlling for a number of confounders is, however, a provocative finding. If the exposure variable had been more precise, it is possible that reductions in birth weight and fetal growth would have been

<table>
<thead>
<tr>
<th>Outcome category</th>
<th>Exposed fathers</th>
<th>Unexposed fathers</th>
<th>Difference* in means</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Mean (g) (SE)</td>
<td>No.</td>
<td>Mean (g) (SE)</td>
</tr>
<tr>
<td>Unadjusted birth weight</td>
<td>172</td>
<td>3,358 (40)</td>
<td>7,546</td>
<td>3,437 (6)</td>
</tr>
<tr>
<td></td>
<td>164</td>
<td>3,315 (39)</td>
<td>7,146</td>
<td>3,388 (7)</td>
</tr>
<tr>
<td>Adjusted birth weight†</td>
<td>172</td>
<td>3,374 (34)</td>
<td>7,546</td>
<td>3,437 (5)</td>
</tr>
<tr>
<td>Intrauterine growth§</td>
<td>164</td>
<td>3,334 (34)</td>
<td>7,146</td>
<td>3,387 (6)</td>
</tr>
</tbody>
</table>

* Mean birth weight of infants of unexposed fathers less mean birth weight of infants of exposed fathers.
† SE, standard error.
‡ Birth weight adjusted for infant's sex, maternal smoking during pregnancy, parity, and maternal and paternal height.
§ Birth weight adjusted using linear and quadratic terms for gestation in days.
¶ Birth weight adjusted for gestational age and infant's sex, maternal smoking during pregnancy, parity, and maternal and paternal height.

more substantial or would have followed a dose response curve. For example, the birth weights of infants whose fathers had x-rays more than one year prior to conception were no different from birth weights of infants of unexposed fathers. This suggests that the important exposure interval may be immediately prior to conception within a single cycle of spermatogenesis. Documenting precise individual doses and time within 3 months of conception might demonstrate a significant relation. Even if this were the case, it would be important to question whether the suggestive association might be due to x-ray exposure per se or to some difference in paternal health for which x-ray exposure might be a surrogate. The failure to find a birth weight decrement in infants of fathers who underwent chest x-ray in the year prior to conception, suggesting illness or cigarette smoking, argues against this and further strengthens the hypothesis that x-ray exposure to the father's gonads specifically represents a risk to his offspring.

The persistence of slightly reduced birth weights with paternal x-ray exposure adds support to the growing literature that suggests that preconception paternal health and exposure status may have measurable impact on pregnancy outcome. Because diagnostic x-rays will continue to be widely utilized, knowledge of possible detrimental effects on reproductive outcomes is of practical importance. For years, mothers have been routinely cautioned about the dangers of x-ray exposure during pregnancy. This standard of practice evolved over time as the dangers of low dose x-irradiation were defined. For example, several studies (23–26) that demonstrated an increase in childhood leukemia in offspring exposed to prenatal diagnostic x-ray were required to supplant the older conclusion of no additional risk based on finding of no excess leukemia in infants exposed in utero to the atomic bomb blast (27). Perhaps fathers should also be concerned about the dangers of x-ray prior to attempts to conceive, but several careful positive studies are required.

This is a questionnaire study and is therefore subject to response bias. The ALSPAC study is unusual in its broad scope and projected time frame. Over 80 percent of mothers in the geographic cohort and almost 70 percent of their partners responded to the questionnaires that generated the data for this study. We were unable to find any effect of maternal or paternal education, a good surrogate for social class, on our main results. Further, because we failed to find a difference in the group of infants whose fathers had chest x-rays versus infants of nonexposed fathers, this argues against the small decrement in birth weight in infants of exposed fathers being the result of reporting bias alone. Nonetheless, studies designed to examine this question specifically would be necessary to determine whether paternal preconception x-ray exposure does affect birth weight, fetal growth, or gestational age.

Additional work to investigate the effects of paternal x-rays on birth outcomes could be based on more detailed questionnaires of prospective fathers in family planning and obstetric clinics. Important information to gather would include precise timing of x-ray exposure prior to conception, medical indication for diagnostic x-ray, results of x-ray procedures, number of films taken, and duration of fluoroscopy. This would refine the exposure variables by permitting precise
definition of the timing of x-rays with respect to the period of spermatogenesis prior to conception, identification of potential health conditions that might confound results, and determination of more precise individual dose information. The potential public health impact of this issue and the suggestive results of our study seem to justify more detailed study of this hypothesis.

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REFERENCES