Author's response to reviews

Title: Male gonadal dose of ionizing radiation delivered during X-ray examinations and monthly probability of pregnancy: a population-based retrospective study.

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Author's response to reviews: see over

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REPLY TO THE REVIEWERS

REVIEWER 1:

Major compulsory revisions

1°) The main limitation of this study are probably the retrospective recall of the reproductive history and covariates 50 years back – as well as recall of X-ray examinations many years back in time. While the latter is discussed in detail, little is mentioned about reproductive history except that there is some data to indicate that women can recall TTP in pregnancies leading to live births. But how is recall of infertile periods ? – probably far less reliable. Poor recall of infertile periods is indicated by a small number of such periods (<<10%). Recall of frequency of sexual intercourse during specific time periods back in time must also be very questionable. These issues might be discussed and commented upon in more detail.

Reply:

In our study, the length of the recall period for reproductive history and covariates is 15. For this duration, the quality of recall of time to pregnancy has been shown to be satisfactory if the attempt at pregnancy leads to a live birth (Joffe et al., Fertil Steril, 1993). There is no such validation study for unsuccessful attempts at pregnancy, but we preferred to include them because we considered that the potential bias induced by a poor quality of recall of these attempts would be preferable than the clear selection bias induced by their exclusion.

We added a specific paragraph on the quality of recall of TTP in the discussion: “Estimation of fecundity” (page 15-line 20):

“Time to pregnancy is considered to be well recalled by women over a 15-year period in the case of pregnancy attempts leading to a live birth (Joffe et al., AJE, 2005). The quality of recall of time of unprotected intercourse when the period of unprotected intercourse does not end with a pregnancy has not been studied to our knowledge. We had no information about the TTP of pregnancies that ended in miscarriages. Nonbirth outcomes like spontaneous abortions are commonly excluded from retrospective TTP studies, notably because there are doubts about the quality of recall of TTP for spontaneous abortions (Joffe et al., AJE, 2005). This exclusion implies the hypothesis that X-ray radiations would have the same effect on TTP for periods of unprotected intercourse leading to a spontaneous abortion and for those
leading to a live birth. The exclusion of unsuccessful attempts at pregnancy has been shown to limit the statistical power and bias TTP studies (Juul et al., Epidemiology, 2000) (Sallmen et al., Epidemiology, 2000) (Slama et al., Epidemiology, 2004). We considered that this potential bias was of more concern than the potential bias induced by a poor quality of recall of such unsuccessful periods of unprotected intercourse, and therefore chose to include them in the analysis."

We therefore also added a sentence on the quality of recall of specific covariates likely to influence TTP (page 16-line 14).

"Some covariates likely to influence TTP were not taken into account in the study. For example, the last contraceptive method used by the couple at the beginning of the unsuccessful attempts at pregnancy was not available."

Finally, we agree that the quality of recall of frequency of sexual intercourse over a 15-year period is likely to be poor. We therefore added a sentence on the quality of recall of specific covariates likely to influence TTP, and frequency of sexual intercourse in particular, in the discussion (page 19-line 10):

"Recall bias may also exist for adjustment factors, thus leaving residual confounding; the quality of recall of the frequency of sexual intercourse over a 15-year period, for instance, may be poor, as illustrated by the fact that there were 20% of missing data for this question."

2°) A table explaining important variables as pregnancy in spite of contraception, type of contraception, ect., would be helpful.

Reply:

An added figure (Figure 1) explains more precisely the creation of the cohort. It mentions the pregnancies which occurred while the woman was using a contraceptive method. Last method of contraception was unfortunately not collected for unsuccessful attempts at pregnancy; we mentioned that this variable could not be controlled for discussion (page 16-line 14). The final size of the population was 1110.

3°) A more clear description of the creation of the cohort, including response rates, would also be helpful (p11-line 5-18). It is not clear what happens with pregnancies that end in spontaneous abortions or stillbirths.

Reply:

The new Figure 1 also indicates the different outcomes of the achieved pregnancies or of the pregnancies attempts. It clearly highlights that no TTP was defined for spontaneous abortions and stillbirths.

We had no information about TTP of pregnancies that ended in miscarriages or still-births. As mentioned in the revised discussion (see page 15-line 25 and the reply to the first question), there is no validation study for the quality of recall of TTP of attempts at pregnancy ending
with miscarriages, which are therefore commonly excluded. We made the hypothesis that X-rays had the same effect on TTP whatever the outcome of the pregnancy. In other words, we made the hypothesis that if X-ray radiations increased TTP, this effect would not be limited to pregnancies that ended in a spontaneous abortion. Such an approach, consisting in excluding spontaneous abortions from the analysis of TTP, and including unsuccessful attempts at pregnancy, was recently recommended in a review article on the retrospective TTP design (Joffe et al., AJE, 2005).

4°) The effect of X-ray radiation on testis function is expected to be transient, unless severe effects on stem cells or/and Sertoli cells occur. The latter is unlikely at medical X-ray examinations. Therefore it can be questioned whether the approach using cumulative doses is the most relevant? Should be discussed. If at all possible with the retrospective data, the fecundability during 1-2 years after exposure would be more interesting to examine. If not possible it should be stressed that the transient effect would not be chosen design.

Reply:

It is not obvious to us that an effect of X-ray radiation on testis function is most likely transient, even at low doses. The literature is sparse on this issue. As mentioned with more details page 5-line 8, one of the very few studies that described the effects of X-ray radiations on sperm cells indicated that spermatogenies A were also affected. The gonadal dose corresponding to a reduction by 50% in the number of type A spermatogonia was estimated to be about 100 mGy (Clifton et al., J Androl, 1983). The fact that type A spermatogonia, the germinal cells of the testis, seem sensitive to X-ray radiation indicates a possible long-term effect of gonadal exposure to ionizing radiation. Thus, the long term effect of X-ray exposure of the testis is worth being studied.

Short-term effects are also worth being studied, as mentioned by the reviewer. Unfortunately, the size of the groups of exposed men were too small in our study: when we considered doses delivered the year before the beginning of the period of unprotected intercourse, there were 5 periods of unprotected intercourse with a gonadal dose between 5 and 10 mGy, and 9 with a dose above 10 mGy for the first month of unprotected intercourse; thus, confidence intervals were rather large. We added a sentence (page 18-line 4) stating that:

“We could not study the short-term effect of exposure to ionizing radiation (e.g. in the year before the beginning of the period of unprotected intercourse) because of a too small number of exposed men.”

5°) Truncations bias may be a concern because data were collected in spring 2000 and couples that discontinued contraception in June 1999 were included thus only leaving 6-12 months of follow-up for couples included during late Spring 1999.

Reply:

It is true that truncation may have induced an over-representation of short TTP at the end of the study period.
As a check, we estimated the monthly Hazard Ratios (HR) of pregnancies for unprotected intercourse that started between 1985 and December 1997. The results did not change, as shown in the tables below:

Our final model:

<table>
<thead>
<tr>
<th>Male gonadal dose (mGy)</th>
<th>n</th>
<th>%</th>
<th>HR</th>
<th>95% CI</th>
<th>p values</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>No X-ray examination</td>
<td>491</td>
<td>48.0</td>
<td>1.03</td>
<td>0.80</td>
<td>1.31</td>
<td>0.54</td>
</tr>
<tr>
<td>0.01-0.20</td>
<td>321</td>
<td>31.4</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.21-2.00</td>
<td>101</td>
<td>9.9</td>
<td>0.86</td>
<td>0.59</td>
<td>1.26</td>
<td>0.27</td>
</tr>
<tr>
<td>2.01-5.00</td>
<td>55</td>
<td>5.4</td>
<td>1.32</td>
<td>0.81</td>
<td>2.15</td>
<td></td>
</tr>
<tr>
<td>5.01-10.00</td>
<td>24</td>
<td>2.3</td>
<td>1.38</td>
<td>0.68</td>
<td>2.80</td>
<td></td>
</tr>
<tr>
<td>&gt; 10.00</td>
<td>31</td>
<td>3.0</td>
<td>1.44</td>
<td>0.73</td>
<td>2.86</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1023</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

After exclusion of attempts at pregnancy that started after 1997:

<table>
<thead>
<tr>
<th>Male gonadal dose (mGy)</th>
<th>n</th>
<th>%</th>
<th>HR</th>
<th>95% CI</th>
<th>p values</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>No X-ray examination</td>
<td>465</td>
<td>50.2</td>
<td>0.99</td>
<td>0.75</td>
<td>1.30</td>
<td>0.96</td>
</tr>
<tr>
<td>0.01-0.20</td>
<td>285</td>
<td>30.7</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.21-2.00</td>
<td>82</td>
<td>8.9</td>
<td>0.93</td>
<td>0.59</td>
<td>1.46</td>
<td></td>
</tr>
<tr>
<td>2.01-5.00</td>
<td>48</td>
<td>5.2</td>
<td>0.98</td>
<td>0.57</td>
<td>1.69</td>
<td></td>
</tr>
<tr>
<td>5.01-10.00</td>
<td>20</td>
<td>2.2</td>
<td>1.13</td>
<td>0.49</td>
<td>2.62</td>
<td></td>
</tr>
<tr>
<td>&gt; 10.00</td>
<td>27</td>
<td>2.9</td>
<td>1.38</td>
<td>0.65</td>
<td>2.95</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>927</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This was stated in the discussion (page 16-line 7):

"Since only a 9 to 12 months period extended from the end of the study period to the time of the interview, short TTP were over-represented among the periods of unprotected intercourse started at the end of the study period (Joffe et al., AJE, 2005). This truncation might entail a bias in the case of time trends in exposure. As a check, we restricted the analysis of Table 2 to periods of unprotected intercourse started between 1985 and December 1997. The HR of pregnancy associated with a dose above 10 mGy was 1.38 (95%CI: 0.65-2.95, n=27), very similar to the HR among the whole population, making any bias due to truncation unlikely."

**Minor essential revisions**

*Table 1: N=1057 does not correspond to the number mentioned in the legend and in the text (n=1109).*

Reply:

N=1257 corresponds to the number of X-ray examinations delivered to the partners during the window of exposure, whereas 1109 corresponds to the number of couples. To make this distinction clearer, we replaced "n" in the first line of table 1 by "number of X-ray examinations".
**Minor essential revisions**

*The authors should discuss the magnitude of the effect which the study is powered to detect – especially with regards to doses over 10 mGy.*

**Reply:**

An estimation of power is relevant if there is no bias in the study; this is unlikely to be the case here given the potential bias for classification of exposure. Assuming no bias, we can however estimate the power of our study using simulations based on the log-rank statistic (Baird et al., AJE, 1986).

In our study sample, there were 31 observations with a gonadal dose above 10 mGy, and 321 in the reference group. If we considered these 31 observations as the exposed group, then the whole sample that would include 20% of exposed observations would be constituted by about 120 observations in the unexposed group. The probability to detect a decrease of fecundability from 0.30 to 0.15 (a hazard ratio of 0.5), assuming a significance level of 0.05, was about 70% (Baird et al., AJE, 1986).

We indicated (page 20-line 6) that:

“Assuming no bias, the probability to detect a decrease in fecundability by 50% for men exposed to a gonadal dose above 10 mGy was about 70% for a significance level of 0.05 (Baird et al., AJE, 1986).”

**References:**


