Fertility is not altered in young adults born small for gestational age

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Submitted on April 25, 2010; resubmitted on June 20, 2010; accepted on June 23, 2010

BACKGROUND: The intrauterine environment may have a lifelong impact on individuals’ health. However, results on the relationship between birth size and gonadal function are conflicting, and it remains unknown whether reproductive function is altered in adults born small for gestational age (SGA). The aim of the present study was to compare the fertility of young adults from the general population, born either SGA or appropriate for gestational age (AGA).

METHODS: There were 579 adults born SGA (birthweight under the 10th percentile) who were compared with 703 subjects of the same age (age 29.4 ± 4.1 years) born AGA (birthweight between 25th and 75th percentiles). They fulfilled a questionnaire focusing on the first attempt to give birth, to have a measure of the time to pregnancy and an estimation of the fecundability (the monthly pregnancy probability), two relevant indicators of fertility at the couple level. Ratios of fecundability between AGA and SGA subjects were adjusted for known fertility factors (age, smoking, reproductive history) and for socioeconomic status.

RESULTS: Time to pregnancy was comparable in the two groups: 5.7 ± 8.0 versus 6.6 ± 10.5 months in AGA and SGA, respectively (P = 0.31), in women and 5.1 ± 7 versus 6.0 ± 9 months in AGA and SGA, respectively, in men (P = 0.53). The adjusted ratios of fecundability comparing SGA to AGA subjects were not significant: HR = 0.91 [0.68;1.21] (P = 0.5) in women and HR = 0.95 [0.67;1.74] (P = 0.82) in men.

CONCLUSION: When studied in young adults from the general population, fertility is not reduced in those born SGA.

Key words: SGA / human fertility / epidemiology / fetal programming

Introduction

The intrauterine environment may have a lifelong impact on individuals’ health. Epidemiological studies have shown that individuals born small for gestational age (SGA) are at increased risk of developing insulin resistance (IR), cardiovascular disease and metabolic syndrome (MS) as adults (Barker et al., 1993). Other endocrine axes, such as the hypothalamic-pituitary-gonadal axis, have also been implicated. However, results on the association between birth size and gonadal function are conflicting. Disorders such as hypospadias, cryptorchidism and reduced gonadal function have been found in males born SGA, along with a smaller testicular volume and decreased testosterone level after puberty, and an increased serum follicle-stimulating hormone (FSH) level in infancy, of boys born SGA (Cicognani et al., 2002; Ibanez et al., 2002c). In contrast, others have not find significant differences in gonadal function between boys born SGA and those born appropriate for gestational age (AGA; Jensen et al., 2007; Kerkhof et al., 2009). Elevated serum levels of inhibin B in men born SGA have been reported (Allvin et al., 2008). However, no relationship between birthweight and male infertility has been found (Ozturk et al., 2001). In adolescent girls born SGA, several anomalies have been reported: ovarian hyporesponse to FSH, subclinical hyperandrogenism (adrenal and/or ovarian origin), reduced ovulation rate and reduced uterine and ovarian sizes (Ibanez et al., 2000a, b, 2002a, b, 2003). However, these results have not been confirmed by others (Hernandez et al., 2006; Sadrzadeh et al., 2003). In young women (22 years of age) born SGA, we did not find any indication of hyperandrogenism based on clinical and hormonal profiles (Jaquet et al., 1999). Recently, in a large data set of families of women with polycystic ovarian syndrome, no associations were found between birthweight and hyperandrogenism or oligomenorrhea (Legro et al., 2010). This literature review shows that there are controversies concerning the association between birth size and gonadal function in both men and women. Moreover, most of the studies have been performed in adolescents and have evaluated the biological or morphological profiles of subjects born SGA. It is still unknown whether reproductive anomalies exist into adulthood for those born SGA. Fertility is the main outcome of the reproductive function. Therefore, the
aim of the present study was to investigate the fertility of a population-based sample of young adults, either women or men, born SGA, who were followed-up prospectively and compared with a control group of young adults born AGA.

**Subjects and methods**

The design of this community-based cohort of young adults, aimed at investigating the long-term consequences of being born SGA, has been detailed elsewhere (Meas et al., 2010). Briefly, subjects were recruited in a population-based registry of the metropolitan area of the city of Haguenau in North-east France. This registry included all the pregnancies occurring in the maternity unit of the city hospital, from 1971 to 1985. The SGA group includes singleton subjects with birthweight below the 10th percentile for sex and gestational age according to the local growth standard curves. The AGA group is made of singleton subjects with birthweights between the 25th and the 75th percentiles and who were the first babies in the registry born immediately after a subject born SGA.

A first visit took place between 1994 and 2001, and 886 subjects born AGA and 734 subjects born SGA were recruited. As expected, the number of deaths in newborns was significantly higher in the SGA group. Reasons for non-participation at this stage have been previously reported (Leger et al., 1997). Among the participants, only the proportion of women was significantly greater. Birthweight did not significantly differ between SGA and AGA individuals who agreed or did not agree to participate.

Data presented in this study were collected between April 2005 and December 2008. Among 1620 eligible subjects for the prospective follow-up, 1308 (593 SGA and 715 AGA) agreed to participate in the prospective follow-up visit between 2005 and 2008 (participation rate: 80.7%) (Meas et al., 2010, Fig. 1). We compared the 1308 subjects who participated in the second visit with the 312 non-participant subjects at the time of the second observation. BMI was also comparable in the non-participants (SGA: 24.9 ± 4.9 versus AGA: 23.9 ± 4.3 kg/m²) and participants (SGA: 24.2 ± 5.2 versus AGA: 24.0 ± 4.3 kg/m²).

Subjects attended a medical visit at the municipality hospital of the city of Haguenau. Three trained nurses recorded information about medical history. Body weight was measured with a portable scale and height with a wall-mounted stadiometer. Weight for height was assessed as BMI (kg/m²). IR was also assessed by homeostatic model assessment—insulin resistance (HOMA-IR) measurements.

During the visit, subjects completed a self-administered questionnaire. The questionnaire included information on age at the start of the conception attempt, previous or current reproductive problems, use of contraceptive methods before the occurrence of pregnancy, reproductive history and any use of medical assistance for conception. The women were asked about their age of menarche, the length and regularity of their menstrual cycles without treatment, any history of any gynecological disorders, any history of obstruction of fallopian tubes, surgery or diseases and the results of their last pap smear. They were also asked about their partners with regard to any known causes of infertility or surgical sterilization.

The men were interviewed about any history of mumps after puberty, testicular damage, surgery for cryptorchidism, inguinal hernia, varicocele, testicular torsion, genital infection (Chlamydia, gonocoque, cystitis, prostatite, epididymite), testicular trauma, thyroid disease, diabetes or any other medical disease. They were also asked about their partners with regard to any known causes of infertility or operations for obstruction of fallopian tubes.

Thus, the questionnaire concerned their whole reproductive life. It was similar for women and men, except that questions asked to men...
concerned the pregnancies of their partner. The questionnaire then focused on the first attempt at pregnancy, whether it was successful or not, in order to have a measure of the time to pregnancy (TTP) that was accurate and comparable between subjects. Time to pregnancy, which is the duration of time with unprotected intercourse (ending or not in a pregnancy), is a relevant fertility indicator in epidemiological studies (Joffe, 1997); it is directly linked with the fecundability which is the monthly probability of pregnancy (Spira, 1998). Of course, TTP could only be studied in couples who had attempted to become pregnant. We have also recorded any issue relating to the pregnancy: miscarriage, ectopic pregnancies, stillborn or abortion.

The study protocol was reviewed and approved by the ethical committee of the Saint-Louis Medical School at the Paris Diderot, University of Paris, and all participants gave written consent.

Statistical methods

The characteristics of AGA and SGA subjects were compared with χ² and Student’s t-tests. Cumulative probability curves of pregnancy were estimated using Kaplan–Meier methodology. TTP and fecundability were analyzed using regression models adapted to discrete survival duration, particularly the Cox discrete time model (Scheike and Jensen, 1997). These methods provide ratios of fecundability (hazard ratios) between AGA and SGA subjects adjusted for known fertility factors (age and smoking at the time of conception attempt and reproductive history: for example menstrual disorders, obstruction of fallopian tubes, mumps with testicular damage, cryptorchidism) and for socioeconomic status.

Results

The mean gestational age did not differ between the AGA and SGA groups (39.4 for AGA and SGA subjects). There were also no significant differences between the proportion of preterm births (3.4% for AGA and 4.5% for SGA) and the sex distribution (gender M/F 47%/53% in the AGA group versus 45%/55% in the SGA group).

According to the selection criteria, subjects born SGA were lighter (2627 ± 298 versus 3366 ± 276 g), shorter (47.7 ± 2 versus 50.3 ± 1 cm) and thinner (11.6 ± 1.1 versus 13.3 ± 0.8 kg/m²) at birth than subjects born AGA. Characteristics of the subjects are given according to gender in Table 1.

In women

There were 704 women who participated in the study, and 690 answered the fertility questionnaire (participation rate: 98%, Fig. 1). Of these, 415 women (61%) have attempted at least once to conceive; the percentage was comparable in the SGA and AGA groups (39.4 for AGA and SGA subjects). There were also no significant differences between the proportion of preterm births (3.4% for AGA and 4.5% for SGA) and the sex distribution (gender M/F 47%/53% in the AGA group versus 45%/55% in the SGA group).

The menstrual cycle length was similar between SGA and AGA women (for women with regular cycles, the length was 28.3 ± 2.1 days for SGA versus 29.1 ± 1.7 days for AGA, P = 0.08, and for women with irregular cycles, the length was 58.2 ± 55 days for SGA versus 58.8 ± 53 days for AGA, P = 0.94).

There were 358 women who succeeded in becoming pregnant: 8 had failed and 37 were still trying at the time of the interview. The mean TTP among periods ending in a delivery, and the fecundability were similar in AGA and SGA women (Table 1). Cumulative probability curves of pregnancy were almost the same in SGA and AGA women (Fig. 2a).

In men

A total of 604 men participated in the study, and 592 answered the fertility questionnaire (participation rate: 98%, Fig. 1). Of these, 231 men (40%) have at least one time tried for their partners to conceive; the percentage was significantly reduced in the SGA group (35%) compared with the AGA group (43%) (P = 0.03). There were 21 questionnaires were not completed so that the analysis of TTP was based on 210 men. Of these, 184 men succeeded in fathering a child, 4 failed and 22 were still trying at the time of the interview. The mean TTP among periods ending in a delivery and the fecundability were similar in AGA and SGA men (Table 1). Cumulative probability curves of pregnancy were almost the same between SGA and AGA men (Fig. 2b).

In men and women

There was no significant link between TTP and birthweight: the relationship between TTP and birthweight (expressed in standard deviation for gender and gestational age either in women or men) was linear with a slope not significantly different from 0 (P = 0.30 in women and P = 0.08 in men). Similarly, there was no significant relationship between TTP and IR, as assessed by HOMA-IR, in both genders (P > 0.60).

Discussion

The results of this study show no evidence of any association between birthweight and fertility at adulthood both in women and in men. This lack of association is not related to a lack of statistical power, because the sample size makes it possible to detect, with a power of 80%, a difference of 5% in women and 7% in men in the monthly probability of pregnancy. This corresponds to a hazard ratio around 1.3. Moreover, in our sample, the fecundability of the women and men born SGA is similar to that generally observed in the general population of a similar age, which is about 25–30% (Ferrari et al., 2007).

Finally, subjects born SGA did not differ with those born AGA in terms of history of reproductive disorders or subfertility treatment during the pregnancy attempt or in number of pregnancies carried by themselves or the partner.

Previous results on the relationship between low birthweight and gonadal dysfunction are conflicting. Some authors have reported an alteration of gonadal functions in subjects born SGA (Francois et al., 1997; Ibanez et al., 2002a, b, 2003), whereas others have found no relationship with birthweight (Jensen et al., 2007; Legro et al., 2010).
However, most of the data are based on small sample sizes and highly selected subjects. Moreover, the studies have been based on morpho-
logical or hormonal modifications, but little is known about fertility in adults born SGA. Our study supports the hypothesis that the dis-
orders previously described during childhood and adolescence do not have major consequences in terms of fertility of young adults.

Yet, fertility is the relevant measure of reproductive function from the point of view of patients and of clinicians as well. Consequently, this study focused on TTP. Moreover, the use of retrospective data to determine TTP in epidemiological studies has proved to be reliable, when asking for a current or recent pregnancy (Olsen et al., 1998).

Some authors have also reported an association between IR and gonadal dysfunction in subjects born SGA (Ibanez et al., 2002a). In this Haguenau cohort, we have found that subjects born SGA are more insulin resistant and have a significantly higher prevalence of MS in comparison with those born AGA (Jaquet et al., 2005; Meas et al., 2010). However, the present results, in line with others (Legro et al., 2010), did not show evidence of any relation between IR, measured by HOMA-IR index, and reduced fertility in the SGA group.

A strength of our study is that it was designed on a community basis with men and women recruited from a maternity registry without any medical particularities. The participation rate was high at the second visit, and similar in the SGA and AGA groups. Few differences were observed between the participating subjects and those lost to follow-up. Therefore, selection biases are likely very limited. Moreover, there was a priori no link between fertility and those lost to follow-up, because loss to follow-up occurred before the age at which fertility troubles may arise. Finally, our cohort was appropriate to explore fertility because the mean age of the subjects at the time of the questionnaire was 29.4 years. This was sufficient for them to have already attempted to have a first pregnancy since the mean age at pregnancy, in France, was 29.3 years for women in 2003 (Blondel et al., 2006).

### Table I  Characteristics of the study population according to birthweight and gender.

<table>
<thead>
<tr>
<th></th>
<th>AGA</th>
<th>SGA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>374</td>
<td>316</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>29.5 (4.2)</td>
<td>29.5 (4.1)</td>
<td>0.98</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.2 (4.7)</td>
<td>23.7 (5.5)</td>
<td>0.24</td>
</tr>
<tr>
<td>Smoking at the time of pregnancy attempt (no. %)</td>
<td>78 (21%)</td>
<td>83 (26%)</td>
<td>0.1</td>
</tr>
<tr>
<td>History of reproductive disorders (no. %)*</td>
<td>113 (30%)</td>
<td>99 (31%)</td>
<td>0.75</td>
</tr>
<tr>
<td>Women having attempted to conceive</td>
<td>218 (59%)</td>
<td>197 (63%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Subfertility treatment during the attempt (no. %)</td>
<td>18 (8%)</td>
<td>18 (9%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Number of pregnancies (no. %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>74 (38%)</td>
<td>79 (46%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>91 (47%)</td>
<td>69 (40%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>17 (9%)</td>
<td>15 (9%)</td>
<td></td>
</tr>
<tr>
<td>≥4</td>
<td>12 (6%)</td>
<td>10 (6%)</td>
<td></td>
</tr>
<tr>
<td>Time to conception** (months)</td>
<td>5.7 (8.0)</td>
<td>6.6 (10.5)</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>329</td>
<td>263</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>29.8 (4.0)</td>
<td>29.4 (4.2)</td>
<td>0.27</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.9 (3.7)</td>
<td>24.9 (5.0)</td>
<td>0.95</td>
</tr>
<tr>
<td>Smoking at the time of pregnancy attempt (no. %)</td>
<td>104 (32%)</td>
<td>102 (39%)</td>
<td>0.07</td>
</tr>
<tr>
<td>History of reproductive disorders*** (no. %)</td>
<td>27 (8%)</td>
<td>26 (9%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Partners having attempted to be pregnant (no. %)</td>
<td>142 (43%)</td>
<td>89 (35%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Subfertility treatment during the attempt (no. %)</td>
<td>12 (9%)</td>
<td>5 (6%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Number of pregnancies of the partner (no. %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>63 (53%)</td>
<td>32 (44%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>45 (38%)</td>
<td>33 (45%)</td>
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<tr>
<td>3</td>
<td>5 (4%)</td>
<td>3 (4%)</td>
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<tr>
<td>≥4</td>
<td>5 (4%)</td>
<td>5 (7%)</td>
<td></td>
</tr>
<tr>
<td>Time to conception** (months)</td>
<td>5.1 (7)</td>
<td>6.0 (9)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Data are expressed by mean (SD) or number (%). P-value for bivariate t-tests or χ².
AGA, appropriate for gestational age; SGA, small for gestational age.
*Menstrual disorders (mainly), obstruction of fallopian tubes.
**Among attempts ending in a pregnancy.
***Mumps with testicular damage, cryptorchidism.
In conclusion, our results may be interpreted as an absence of reduced fertility in young adults born SGA, when studied in the general population.

**Acknowledgements**

The authors are grateful to C. Trabant, M. Grasser and S. Wendling for their nursing skills and to the nursing staff who performed medical and biological tests.

**Conflict of interest:** T.M., S.D. and J.B. have nothing to disclose. C.L.M. has received lecture fees from Eli Lilly, Novo Nordisk and Pfizer.

**Funding**

This study was supported by a grant from the Agence Nationale de la Recherche (ANR-06-Physio 037), from INSERM (COSSEC 2007) and by a research grant from Pfizer France.

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