Birth weight and age at menarche in patients with polycystic ovary syndrome or diminished ovarian reserve, in a retrospective cohort

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BACKGROUND: Few studies have investigated the association between subfertility in women and factors in early life such as birth weight and age at menarche, and most have produced contradictory results. In the present study, this association was investigated among women undergoing artificial reproductive techniques (ART), including IVF for reason of polycystic ovary syndrome (PCOS) or diminished ovarian reserve. Herein, PCOS included oligomenorrhea and at least one additional symptom such as hyperandrogenism, hirsutism or polycystic ovaries on ultrasound. In most patients this was concomitant with elevated serum LH levels. Diminished ovarian reserve was defined as receiving a donated oocyte or having a low response to ovarian hyperstimulation. METHODS: Among a retrospective cohort of 26 428 women diagnosed with subfertility between 1980 and 1995, three study groups and one reference group were defined using data from medical records. Women were included in the first group if diagnosed as having PCOS (n = 265). In order to define diminished ovarian reserve capacity, two groups were selected: (i) women receiving a donated oocyte (n = 98); and (ii) women having a low response (three follicles or less) to ovarian hyperstimulation in both their first and second IVF cycles (n = 351). Women with tubal obstruction formed the reference group (n = 957). In a logistic regression model, the effect of birth weight and age at menarche was examined. Information on both variables was obtained from mailed questionnaires. RESULTS: Birth weight did not differ significantly between the study groups and the reference group. However, PCOS patients were significantly older at menarche [OR 3.31 (2.18–5.04)]. Women receiving a donated oocyte and low responders were significantly younger at menarche [OR 2.67 (1.35–5.29) and OR 2.01 (1.26–3.20) respectively]. CONCLUSION: The fetal origins hypothesis, the association between intrauterine growth retardation and disease in adult life, could not be confirmed, though a relationship between timing of menarche and PCOS and a diminished ovarian reserve was identified. Further investigation of the effect of birth weight on fertility outcome in a prospective setting is strongly advised.

Key words: age at menarche/birth weight/diminished ovarian reserve/fetal origins/PCOS

Introduction

In recent years, infertility treatment has become one of the most pressing issues of modern health care. In the United States, up to 43% of women aged between 15 and 44 years have been estimated as having impaired fecundity, and 24% of them benefit from some kind of artificial reproductive technology (ART) (Wilcox and Mosher, 1993). Polycystic ovary syndrome (PCOS) and a diminished ovarian reserve contribute to subfertility among women. In order to identify women at risk of developing fertility-related problems, at a stage when more therapeutic options are open, early risk factors such as age at menarche and birth weight are being explored. Although the effect of age of menarche on PCOS is still unclear, PCOS is found in relation to premature pubarche, which in girls is defined as the appearance of pubic hair before the age of 8 years (Toscano et al., 1998; Ibanez et al., 2000; Rosenfield et al., 2000). Contradictory findings have been reported with regard to age at menopause, the final stage of ovarian follicle pool depletion. A young age (Cramer and Xu, 1996; Meschia et al., 2000), as well as an older age at menarche (Sherman...
et al., 1981; Frisch, 1987; Do et al., 1998) have been associated with a premature or young age at menopause. Most investigators however have failed to confirm any direct relationship between age at menarche and age at menopause (van Noord et al., 1997; Kato et al., 1998; Harlow and Signorello, 2000; Testa et al., 2001).

Birth weight, while being a crude indicator for intrauterine adverse conditions, has become a major factor to consider when investigating the aetiology of adult-onset disease. Over the past two decades a considerable amount of convincing evidence has been brought forward associating adverse intrauterine conditions with adult-onset disease, including high blood pressure and glucose intolerance (Barker, 1994). Impaired fetal growth as well as a higher weight at birth have both been reported as a factor in the aetiology of PCOS, as well as a diminished ovarian reserve (Cresswell et al., 1997a; b; Trelor et al., 2000; Michelmore et al., 2001).

The aim of the present study was to investigate the association between birth weight, age at menarche and participation in ART for reasons of PCOS or diminished ovarian reserve. For this purpose, access was acquired to a unique set of data from a retrospective cohort consisting of all women undergoing fertility treatment in the Netherlands between 1980 and 1995.

Materials and methods

The cohort
Information for this study was extracted from data available from the OMEGA Project, a nationwide cohort of 26,428 women diagnosed with subfertility in all 12 IVF clinics in The Netherlands between January 1980 and January 1995. The main aim of the OMEGA study was to investigate the late health effects of hormonal stimulation due to ART (Klip et al., 2001). Medical information on subfertility diagnosis and subfertility treatment was obtained by trained research assistants from medical records which were provided by all the participating IVF centres. Additional information on self-reported risk factors was extracted from the questionnaires mailed to all women who were alive and traceable in January 1997. Of 25,323 questionnaires posted to these women, a total of 16,284 was completed and returned. Detailed information on the cohort and methods of data collection has been described elsewhere (Klip et al., 2001).

Selection of study groups
For the purpose of the present study, three patient groups and one reference group were selected from women enrolled in the OMEGA database with completed questionnaires. Information from the medical records was used for primary selection.

Women were included in the first patient group if diagnosed as having PCOS (n = 265), the criteria for which varied from centre to centre. However, in all centres diagnostic criteria for PCOS included oligomenorrhoea and at least one additional symptom such as hyperandrogenism, hirsutism or polycystic ovaries on ultrasound. In most patients this situation was concomitant with elevated serum LH levels.

Two different patient groups were defined with regard to diminished ovarian reserve capacity. The first group comprised all women who had received an embryo conceived by donated oocytes (n = 98). The second group comprised women who had a low response to adequate ovarian hyperstimulation in both their first and second IVF cycles (n = 351). A low response was defined as three or less follicles at oocyte retrieval, or cancellation of the stimulation cycle due to low response. The reference group consisted of women whose only cause of subfertility was tubal obstruction, assuming that intrauterine growth retardation and hormonal factors do not play a prominent role in this specific cause of subfertility (n = 957).

Women diagnosed with any additional cause of subfertility, other than the causes which were considered for inclusion, were excluded. After the primary selection, the following women were excluded: those diagnosed with cancer; those treated with radiation therapy or chemotherapy; those diagnosed with any chromosomal or genetic defect such as fragile X or Turner syndrome (Sherman, 2000; Abir et al., 2001; Birkebaek et al., 2002); or those who were exposed to diethylstilbestrol (DES) in utero. Furthermore, all women with infections or surgery on the reproductive organs were excluded, with the exception of the tubal operations as carried out in the reference group. Information on causes of subfertility, IVF treatment and date of first attending a fertility clinic was obtained from the medical records. Information on whether participants were part of a multiple gestation, their mother’s age at the time of birth, weight at birth, date of birth, birth order, country of birth, age at menarche, current height and weight, smoking habits and education level were taken from the mailed questionnaires. Participants were asked to report age at menarche as the exact calendar year of first menstruation, or exact age at first menstruation, or, if they could not recall the precise age or year, to choose between the categories under 12 years, 12–14 years, or over 14 years. The questionnaires provided no information on the gestational age of the participants.

Statistical analysis
Logistic regression analysis was performed to estimate the difference in birth weight and age at menarche between the individual groups, simultaneously correcting for relevant confounders. Potential confounders were added to the logistic regression model and then subsequently removed from the model in order of least significance. The significance level of Wald statistics to include a variable as confounder was set at P = 0.2. Odds ratios (OR) were considered significant if the P-value of the Wald statistics was ≤ 0.05 and the 95% confidence interval (CI) of the OR did not include the value 1. Individual cases with missing data on any of the items included in the logistic regression model were automatically excluded from the analysis. Logistic regression analysis was also performed to estimate OR for the characteristic of having a missing value for birth weight between individual groups and the reference group. Data were analysed using SPSS.9 for Windows.

The effect of birth weight was examined as a continuous as well as a categorical variable. In the latter case, birth weight was categorized as lighter or heavier than 2.5 kg (low birth weight) or as lighter or heavier than 1.5 kg (very low birth weight). These categories were analysed using SPSS.9 for Windows.

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In order to distinguish between extremes in age at menarche, a categorical variable was used for analysis. Education level was used as an indicator for socioeconomic status. Participants could choose between seven levels of increasing education levels ranking from no education up to university. These categories were pooled into three categories of: no education and primary school; high school and vocational training; or college, university and higher. Country of birth was categorized as Europe and North America or other. For the analysis, a categorical variable on smoking was used: never smoked; or ever smoked. Current height and body weight were used to calculate the body mass index (BMI) as: body weight (kg)/height² (cm).

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Results

The general characteristics of the study population are listed in Table I. The reference group had a mean birth weight of 3323 g, while the mean birth weights of PCOS patients, women receiving an embryo from a donated oocyte and low responders were 3311 g, 3318 g and 3293 g respectively. The mean birth weight of girls born during the early 1970s in The Netherlands was 3352 g (Voorhorst et al., 1990). Of all participants, 27% failed to report a birth weight. There were no statistical differences between study groups and the reference group in availability of self-reported birth weights (Table II).

Women with PCOS were younger at their first visit to a fertility clinic and had a higher BMI compared to the reference group. The differences of 2 years in age at first visit and 2.0 points in BMI were both significant (P < 0.0001) and were included in the final logistic regression model. Furthermore, women receiving an embryo from oocyte donation and low responders were more likely to have a low education level. This effect was significant, and hence educational level was included in the final logistic regression model.

No significant association was found between PCOS and birth weight. The OR (95% CI) of PCOS associated with mean birth weight was 0.91 (0.71–1.17). In the reference group, 711 women reported a birth weight, 92 had a low birth weight, and nine had a very low birth weight. From the 200 reported birth weights in the PCOS group, 27 were low and none was very low. The OR (95% CI) for PCOS associated with a low birth weight, defined as <2500 g, was 0.88 (0.53–1.48).

However, patients diagnosed with PCOS had a significantly older age at menarche. At the time of menarche, 26% of the PCOS patients versus 13.8% in the reference group were aged over 14 years. The OR associated with an age at menarche over 14 years compared with 12–14 years was 3.31 (2.18–5.04).

A diminished ovarian reserve was not significantly associated with birth weight. Sixty women receiving an embryo from a donated oocyte reported a birth weight. With birth weight as a continuous variable, the OR (95% CI) for receiving an embryo from a donated oocyte reported a birth weight. With birth weight as a continuous variable, the OR (95% CI) for receiving an embryo from a donated oocyte was 1.02 (0.67–1.55). For low birth weight (n = 6) and very low birth weight (n = 1) these values were 0.75 (0.31–1.85) and 1.15 (0.14–9.66) respectively. For the low responders (243 reported birth weights), the OR (95% CI) associated with mean birth weight was 0.93 (0.73–1.19). The OR associated with low birth weight (n = 39) and very low birth weight (n = 2) were 1.12 (0.70–1.80) and 0.44 (0.08–2.32) respectively.

Table I. General characteristics of the study population selected from the OMEGA study cohort with completed questionnaires by subfertility diagnosis. Participants with more than one subfertility diagnosis were excluded.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference group (n = 957)</th>
<th>PCOS (n = 265)</th>
<th>Oocyte donation (n = 98)</th>
<th>Low responders (n = 351)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (g)</td>
<td>3323 ± 669</td>
<td>3311 ± 677</td>
<td>3318 ± 675</td>
<td>3293 ± 658</td>
</tr>
<tr>
<td>Age at 1st visit to fertility clinic (years)</td>
<td>31 ± 4.7</td>
<td>29 ± 3.9</td>
<td>33 ± 4.5</td>
<td>33 ± 4.8</td>
</tr>
<tr>
<td>Age at 1st IVF (years)</td>
<td>32 ± 3.8</td>
<td>-</td>
<td>-</td>
<td>35 ± 3.9</td>
</tr>
<tr>
<td>Age at time of study (years)</td>
<td>38 ± 4.9</td>
<td>35 ± 4.5</td>
<td>38 ± 4.4</td>
<td>40 ± 4.3</td>
</tr>
<tr>
<td>BMI at time of study (kg/m²)</td>
<td>23.8 ± 3.8</td>
<td>25.8 ± 5.3</td>
<td>24.1 ± 3.8</td>
<td>24.6 ± 4.7</td>
</tr>
<tr>
<td>Mother’s age at delivery (years)</td>
<td>29 ± 6.1</td>
<td>29 ± 6.5</td>
<td>29 ± 6.4</td>
<td>30 ± 6.3</td>
</tr>
<tr>
<td>Mother’s age time of study (years)</td>
<td>67 ± 8.2</td>
<td>64 ± 8.4</td>
<td>67 ± 8.0</td>
<td>70 ± 8.0</td>
</tr>
<tr>
<td>Age at menarche (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤11 years</td>
<td>12 (115)</td>
<td>15.5 (41)</td>
<td>20.9 (18)</td>
<td>19.0 (65)</td>
</tr>
<tr>
<td>12–14 years</td>
<td>74 (709)</td>
<td>58.5 (155)</td>
<td>58.1 (50)</td>
<td>70.6 (242)</td>
</tr>
<tr>
<td>&gt;15 years</td>
<td>13.8 (132)</td>
<td>26 (69)</td>
<td>20.9 (18)</td>
<td>10.5 (36)</td>
</tr>
<tr>
<td>Country of birth (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe or North America</td>
<td>92.8 (883)</td>
<td>90.5 (237)</td>
<td>92.6 (75)</td>
<td>92.3 (322)</td>
</tr>
<tr>
<td>Other</td>
<td>7.2 (69)</td>
<td>9.5 (25)</td>
<td>7.4 (6)</td>
<td>7.7 (27)</td>
</tr>
<tr>
<td>Education (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>27.2 (260)</td>
<td>40.3 (106)</td>
<td>37 (30)</td>
<td>32.5 (114)</td>
</tr>
<tr>
<td>Middle</td>
<td>51.9 (495)</td>
<td>47.1 (124)</td>
<td>46.9 (38)</td>
<td>45.5 (160)</td>
</tr>
<tr>
<td>High</td>
<td>20.9 (119)</td>
<td>12.5 (33)</td>
<td>16 (13)</td>
<td>21.9 (77)</td>
</tr>
<tr>
<td>Birth order (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First child</td>
<td>30.2 (281)</td>
<td>31.7 (82)</td>
<td>44.9 (44)</td>
<td>31.6 (108)</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

Values in parentheses are numbers of patients.

*Mean age at first visit to fertility clinic.

For the comparison of low responders with the reference group, the mean age at time of first IVF cycle was used instead of age at first visit to fertility clinic.

BMI = body mass index.

Table II. Results of the logistic regression analysis estimating odds ratios (OR) for the variable missing birth weight between study groups

<table>
<thead>
<tr>
<th>Study group</th>
<th>Not reporting birth weight OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>PCOS</td>
<td>0.84 (0.58–1.22)</td>
<td>0.37</td>
</tr>
<tr>
<td>Oocyte donation</td>
<td>1.05 (0.60–1.83)</td>
<td>0.86</td>
</tr>
<tr>
<td>Low responders</td>
<td>1.01 (0.74–1.37)</td>
<td>0.95</td>
</tr>
</tbody>
</table>

There were no statistical differences between study groups and the reference group in availability of self-reported birth weights.

*Adjusted for age at menarche, education level, age at time of study, country of birth and birth order.
Women with a diminished ovarian reserve were significantly younger at the time of their menarche. In women receiving a donated oocyte, the OR associated with a menarchal age of 11 years and younger was 2.67 (1.35–5.29) compared with 12–14 years. In the low responders group, the OR was 2.01 (1.26–3.20). At the time of menarche, 12% of the reference group versus 20.9% of women receiving a donated embryo and 19% of the low responders were aged less than 11 years.

The results of the logistic regression analyses of the main determinants and other variables in the final logistic regression model are listed in Table III.

### Discussion

In a subfertile population seeking fertility treatment, birth weight was not related to the risk of PCOS or to diminishing ovarian reserve. An older age at menarche, however, was related to a greater risk of PCOS, whereas a young age at menarche was significantly associated with strong indicators of a diminished ovarian reserve.

The present finding that birth weight was unrelated to PCOS seems to be at variance with previously published findings. However, studies reporting a positive association between low birth weight and PCOS were conducted in a specific group of young girls who had not only a low birth weight but also premature pubarche and hyperandrogenism (Ibanez et al., 2000). It is very likely that this may be a highly selected subgroup of patients with PCOS features, which is quite different from the majority of PCOS patients in a subfertile population. The association with birth weight might be restricted to this specific subpopulation. In contrast, given the retrospective nature of the present study and the international disagreement on the definition of PCOS, patient selection herein might have been too heterogeneous to draw conclusions as to the effect of birth weight on PCOS.

In the present study population, diminished ovarian reserve was not related to birth weight, and this was not in accordance with the present authors’ previous findings. In a twin study, a positive association was found between a high birth weight and a premature menopause before the age of 40 years (Trelor et al., 2000). In that study, twin sisters with premature menopause were significantly heavier compared to their non-affected twin sisters. the mean difference in birth weight being 307 g (P = 0.05).

Some limitations of the current analysis should be considered. One potential source of bias was self-reported birth weights. Many women in the Netherlands choose to deliver at home with the aid of qualified midwives; hence, there is a high level of dependency on self-reported birth weights. International studies have shown that self-reported birth weights in women aged less than 40 years correlate highly with birth-certificate values, with coefficients between 0.75 and 0.83 (Troy et al., 1996; Sanderson et al., 1998). The present authors’ experience with a similar study population is that among 140 interviewed women in the age range of 25–55 years, 85% reported the correct birth weight (data unpublished). Thus, reported birth weights can be considered as fairly accurate. Moreover, it can be assumed that there is no difference in recollection between the reference group and the case groups as they were all selected from the same cohort of women who visited a clinic with fertility-related problems.

Another limitation of the present study was that no information was available on gestational age, which is another
Birth weight, age at menarche and ovarian function

potential confounding variable. Infants born prematurely often have lower birth weights compared with infants born at term, although this low birth weight could be appropriate for the given gestational age. On the other hand, infants with a birth weight in the normal range might be small for their gestational age.

A strong association was found between a diagnosis of PCOS and an experience of first menstruation after the age of 14 years. Although premature pubarche has been shown to be related to PCOS, the effect of age at menarche remains unclear (Helm et al., 1995; Toscano et al., 1998; Ibanez et al., 2000; Rosenfield et al., 2000). The present findings may, however, have been affected by recall bias. Very irregular menstruation with a long time span between two successive menstrual cycles in adolescence might affect the precise recollection of first menstruation. However, given the impact of the first menstruation in a young girl’s life, it can be assumed that the effect of recall bias is minimal, particularly for women with a very early or very late age at menarche. As very few data on age at menarche were missing (1.0%), there was not expected to be any significant effect of missing data on age at menarche.

Extreme cases of oligomenorrhea, however, might present themselves as primary amenorrhea or late-onset menarche with an otherwise completed sexual development (Dramusic et al., 1997). It was also shown that the receipt of an embryo conceived by donated oocytes, as well as having a low response to ovarian stimulation, were significantly linked to a younger age at menarche. The association between age at menarche and age at menopause, the final stage of ovarian depletion, remains controversial. A young age at menarche, as well as an older age, have been reported as risk factors for early menopause (Sherman et al., 1981; Frisch, 1987; Cramer and Xu, 1996; Do et al., 1998; Meschia et al., 2000). However, in many cases investigators found no association between these two fertility parameters (van Noord et al., 1997; Kato et al., 1998; Harlow and Signorello, 2000; Cooper et al., 2001; Testa et al., 2001). The present data suggest that women with a menarchal age of less than 12 years are 2-fold more likely to respond inadequately to stimulation, and 2.6-fold more likely to have subfertility problems requiring an oocyte donation. The discrepancy between the present findings and those of previous reports might be due to the chosen definition of ovarian depletion. Age at menopause may be an inaccurate estimator of depletion of ovarian reserve. Age at menopause is a retrospective diagnosis, whilst menopausal transition is a gradual process that takes 10–15 years. Hence, pinpointing a date can be extremely difficult, especially when it is also taken into account that many women use oral contraceptives or hormone replacement therapy during this period of life. A low response to stimulation in two successive IVF cycles as well as a lack of any response, however, are considered direct estimates of diminished ovarian reserve (Hughes et al., 1989). The prospective follow-up of the OMEGA study population has shown that, indeed, women with a low response to ovarian hyperstimulation are more likely to become post-menopausal at a younger age (de Boer et al., 2002), and this finding has been supported by other recent studies (Nikolaou et al., 2002)

Assuming that inadequate responses to hyperstimulation and menopause have the same underlying mechanisms, the present findings would indicate that an ‘early start’ leads to an ‘early end’.

The present data indicate that a low education level is significantly associated with fertility treatment due to a diminished ovarian reserve. This is in accordance with previously published findings, where a low educational level was seen to be frequently correlated with subfertility (Wulff et al., 1997; Akre et al., 1999).

In summary, the results of this large analysis suggest that there is no clear close relationship between birth weight and the fertility disorders PCOS and limited ovarian reserve. Possible minor effects, if present, may have been obscured due to the retrospective nature of the study. However, in order to reveal subtle effects of birth weight on fertility, then additional accurate prospective studies are required.

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