Conditions at Conception and Risk of Menstrual Disorders

Luc J. Smits,1 Wim N. P. Willemsen,2 Gerhard A. Zielhuis,1 and Piet H. Jongbloet1

In a case-control study, we evaluated the association of the risk of menstrual disorders with four periconceptional factors: short preceding interpregnancy interval (<6 months), low (≤19 years) or high (≥40 years) maternal age at conception, and month of conception. We divided 919 women who had visited a fertility clinic between 1991 and 1995 into three categories: cases (with mean menstrual cycle length ≥42 or ≤21 days, or a variation of ≥14 days between cycles, or amenorrhea, N = 294), controls (with cycles within a range of 25–35 days and variation ≤7 days, N = 520), and intermediates (N = 105). A self-administrable questionnaire was mailed, asking for information about maternal reproductive history and age, and potential confounders such as smoking, exercise, and level of education. Response (77%) differed little among cases, intermediates, and controls. We found elevated risks for short pregnancy intervals [adjusted odds ratio (OR) = 2.04; 95% confidence interval (CI) = 1.04–4.02] and advanced maternal age (OR = 3.24; 95% CI = 1.27–8.30) but not for low maternal age (OR = 0.58; 95% CI = 0.11–3.14) (cases vs controls). We found similar effects for intermediates vs controls. The distribution of month of conception did not differ much from controls for both cases and intermediates. The results indicate that conception after short pregnancy intervals or at advanced maternal age increases the risk of menstrual disorders in daughters. The precise etiology is unclear, but it may lie in the quality of the oocyte at conception.

(Epidemiology 1997;8:524–529)

Keywords: conception, menstrual disorders, case-control study, maternal age, seasons, birth intervals.

Menstrual cycle disorders can lead to considerable concern and form a major cause of infertility.1 Irregularity of menstruation is usually due to disturbances of the hypothalamic-pituitary-ovarian axis. Determinants of dysfunction of the hypothalamic-pituitary-ovarian axis include heavy exercise,2,3 smoking,4 undernutrition, and overnutrition.5 For the most part, however, the etiology of hypothalamic-pituitary-ovarian dysfunction (and thereby of irregular menstruation) is unknown.

In an earlier paper,6 we hypothesized that dysfunction of the ovaries may originate in early gestation, induced by a suboptimal maturational state of the oocyte at the time of ovulation ("preovulatory overripeness of the oocyte"). In animal research, specific malformations of the gonads were shown in specimens conceived from overripe eggs.7,8 Preovulatory overripeness of the oocyte is supposed to occur predominantly in situations in which the hormonal regulation of the menstrual cycle is disturbed. Such disturbances prevail during the postnatal period after a pregnancy9,10 and at low11,12 and advanced11,13 reproductive age. As there is evidence that the regularity of the menstrual cycle also varies throughout the year, probably under influence of the light-sensitive pineal hormone melatonin,14–16 the risk of preovulatory overripeness may fluctuate with it.

The idea that there are conditions within the natural reproductive span of a woman that are intrinsically unfavorable for pregnancy, even if she is otherwise (mentally, physically, and genetically) healthy, is far from new, yet it is gaining increased attention. Next to advanced maternal age, which has long been a known risk factor for various adverse reproductive outcomes,19–21 low maternal age (and especially teenage pregnancy) has been shown to increase the risk of unfavorable pregnancy outcomes, independently from associated determinants such as life-style, prepregnancy care, and prenatal care.22–24 The relation between short birth intervals and adverse pregnancy outcomes has often been thought to be confounded by the higher prevalence of preterm birth after short birth intervals, but this theory has been clouded by the finding that short pregnancy intervals have similar effects.25,26 Finally, the idea that there may be different risks associated with reproduction in different months throughout the year has been little acknowledged but has received recognition in relation to the occurrence of schizophrenia in offspring.27,28

From the 1Department of Medical Informatics, Epidemiology, and Statistics, University of Nijmegen, and 2Department of Obstetrics and Gynecology, Academic Hospital Sint Radboud, Nijmegen, The Netherlands.

Address correspondence to: Luc J. Smits, Department of Medical Informatics, Epidemiology, and Statistics, University of Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.

This work was supported by Grant 900-561-064 from The Netherlands Organization for Scientific Research.

Submitted July 26, 1996; final version accepted February 5, 1997.

© 1997 by Epidemiology Resources Inc.
In this study, we tested the prediction that women with menstrual disorders were conceived more often after short pregnancy intervals (within 6 months after the end of a preceding pregnancy), or at low (≤19 years) or advanced (≥40 years) maternal age. We also evaluated whether they showed an unusual month-of-conception distribution.

Subjects and Methods

The study population comprised 919 women who had presented at the infertility clinic of an academic hospital in Nijmegen, the Netherlands, in the period 1991–1995. Subjects were selected on the basis of their medical files. We excluded those for whom there was no clear information about the menstrual cycle, whose reason for seeking help was not infertility, who came for re-fertilization, who had problems with cervical mucus, or whose medical file was not available during the selection period.

On the basis of self-reported contraception-free menstrual cycle characteristics at the first visit, we categorized the 919 eligible women into three groups: cases (with mean cycle length ≥42 days or ≤21 days, or a within-subject variation between cycles of 14 days or more, or amenorrhea); controls (with cycles within a range of 25–35 days and a within-subject variation between cycles of no more than 7 days); and intermediates (those who were neither case nor control). Thus defined, there were 294 (32%) cases, 520 (57%) controls, and 105 (11%) intermediates.

We sent two reminders, the last one enclosing a new copy of the questionnaire, and 105 (11%) intermediates. We sent two reminders, the last one enclosing a new copy of the questionnaire, and 105 (11%) intermediates.

We calculated odds ratios (ORs), crude and controlled for confounding, using unconditional logistic regression. We evaluated the following factors as potential confounders: respondent's age, physical exercise, Quetelet index, number of liveborn or stillborn siblings, cigarette smoking, and partner's education. In addition, in studying each determinant (be it maternal age at conception, pregnancy interval, or month of conception), we treated the remaining determinants as potential confounders. We evaluated confounding by adding one potential confounder at a time to the model; if the crude OR (or at least one of the dummies designating determinant status) was altered by 10% or more, we retained the factor in the model; otherwise, we excluded it. We excluded observations with unknown confounder values from analysis.

To study seasonality of conception, we first calculated the proportion of cases (or intermediates) for each month of conception. We assumed that, if different months of conception bore different risks, the pattern of proportions would have a sinusoidal form with a period of either 1 or 0.5 year, or a combination of both. We modeled the pattern by introducing factors referring to amplitude and shift into a logistic model.

Results

After up to three mailings, 701 of the 919 questionnaires were completed and returned. Owing to incorrect address information, 11 potential respondents never received any of the letters, so the actual response rate was 701/908 = 77%. Among the respondents, 219 (31%) were cases (among whom 47 were amenorrheic), 85 (12%) were intermediates, and 397 (57%) were controls. A comparison of these figures with their distribution in the original study population indicates that there was little differential response among study groups.

Table 1 presents sociodemographic, behavioral, and reproductive characteristics of the study group, by case/intermediate/control status. Cases and intermediates were generally younger than controls (mean difference = 1.5 years and 0.6 year, respectively) and born in more recent years. Cases more often had a high Quetelet index (≥30) and less often had 5 or more siblings.

Pregnancy Interval

One hundred forty cases, 57 intermediates, and 280 controls were born from nonfirst maternal pregnancies, of which 128 cases, 56 intermediates, and 253 controls provided sufficient information to allow calculation of the length of the preceding pregnancy interval. Pregnancy interval varied with the outcome of the previous pregnancy; median intervals were 19 months after a livebirth, 12 months after a stillbirth, and 5 months after a miscarriage. The median pregnancy interval after livebirths with lactation was shorter (18 months) than the median interval after livebirths without lactation (23 months), which might be explained by the tendency of lactating women to omit contraception, thereby increasing the risk of an unplanned pregnancy.
TABLE 1. Sociodemographic, Behavioral, and Reproductive Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Cases (N = 219)</th>
<th>Intermediates (N = 85)</th>
<th>Controls (N = 397)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>49.3</td>
<td>47.1</td>
</tr>
<tr>
<td>≥30</td>
<td>51.7</td>
<td>52.9</td>
</tr>
<tr>
<td>Gravida</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulli</td>
<td>75.8</td>
<td>77.6</td>
</tr>
<tr>
<td>1 or higher</td>
<td>24.2</td>
<td>22.4</td>
</tr>
<tr>
<td>Year of birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1962</td>
<td>41.1</td>
<td>47.1</td>
</tr>
<tr>
<td>≥1962</td>
<td>58.9</td>
<td>52.9</td>
</tr>
<tr>
<td>Quetelet index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>21.1</td>
<td>21.2</td>
</tr>
<tr>
<td>≥20</td>
<td>67.0</td>
<td>71.7</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>40.2</td>
<td>41.4</td>
</tr>
<tr>
<td>No</td>
<td>59.8</td>
<td>58.6</td>
</tr>
<tr>
<td>Unknown (No.)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Physical exercise &gt;7 hr week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>89.5</td>
<td>95.3</td>
</tr>
<tr>
<td>Yes</td>
<td>10.5</td>
<td>4.7</td>
</tr>
<tr>
<td>Education of partner</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>30.7</td>
<td>26.8</td>
</tr>
<tr>
<td>Middle</td>
<td>33.5</td>
<td>37.8</td>
</tr>
<tr>
<td>High</td>
<td>35.8</td>
<td>35.4</td>
</tr>
<tr>
<td>Unknown (No.)</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Number of siblings (liveborn or stillborn)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>26.5</td>
<td>25.6</td>
</tr>
<tr>
<td>1-4</td>
<td>55.5</td>
<td>48.8</td>
</tr>
<tr>
<td>≥5</td>
<td>18.0</td>
<td>25.6</td>
</tr>
<tr>
<td>Unknown (No.)</td>
<td>13</td>
<td>14</td>
</tr>
</tbody>
</table>

The upper parts of Tables 2A and 2B present adjusted ORs for pregnancy interval in cases and intermediates. Controls provide denominator values for the ORs for both cases and intermediates. Because observations were scarce in the category of 1–3 months, both in cases (4) and in intermediates (0), we pooled the 1–3 month and 4–6 month categories. For both cases and intermediates, we observed elevated ORs: 2.04 [95% confidence interval (CI) = 1.04–4.02] and 2.38 (95% CI = 1.03–5.52), respectively.

We performed two checks of the sensitivity of these ORs to the accuracy of pregnancy interval calculation. First, we restricted the analysis to those women who had provided information on the term date of their birth (92%), and second, we restricted the analysis to women whose mothers assisted them in filling out the questionnaire (67%). Neither restriction resulted in a notable change in the ORs. Also, restriction to women whose preceding sibling was liveborn (whether breastfed or not) did not change the results.

MATERNAL AGE

Maternal age was unknown in 19 respondents. The lower parts of Tables 2A and 2B present adjusted ORs for maternal age in cases and intermediates. Again, controls provide denominator values for the ORs for both cases and intermediates. In both cases and intermediates, elevated ORs were seen for maternal age ≥40 years (3.24 and 1.82, respectively). We saw no increase in ORs for maternal age <20 years.

Notably, the effect of maternal age was confounded by pregnancy interval. Without control for pregnancy interval, ORs for low maternal age were higher, and those for high maternal age were lower, indicating that the decline of the occurrence of short birth intervals with increasing age is stronger in cases and intermediates than in controls.

MONTH OF CONCEPTION

For our assessment of seasonality of conception, we excluded all respondents who were born from first pregnancies, because the month of first conception is strongly related with month of parental marriage, and cases and intermediates were born more often from first pregnancies. Marriage is usually not evenly distributed across the year, and we did not know the date of parental marriage.

TABLE 2A. Risk of Menstrual Disorders by Preceding Pregnancy Interval and Maternal Age at Conception, Cases vs Controls

<table>
<thead>
<tr>
<th>Cases N</th>
<th>Controls N</th>
<th>OR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-6</td>
<td>22</td>
<td>24</td>
<td>2.04</td>
</tr>
<tr>
<td>&gt;6t</td>
<td>97</td>
<td>210</td>
<td>1</td>
</tr>
</tbody>
</table>

TABLE 2B. Risk of Menstrual Disorders by Preceding Pregnancy Interval and Maternal Age at Conception, Intermediates vs Controls

<table>
<thead>
<tr>
<th>Preceding pregnancy interval (months)</th>
<th>Intermediates N</th>
<th>Controls N</th>
<th>OR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-6</td>
<td>11</td>
<td>24</td>
<td>2.38</td>
<td>1.03–5.52</td>
</tr>
<tr>
<td>&gt;6t</td>
<td>39</td>
<td>210</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Maternal age at conception (years)

| ≥19                                  | 1               | 6           | 0.70| 0.08–6.52 |
| 20–25                                | 7               | 34          | 0.85| 0.32–2.21 |
| 26–35†                               | 34              | 146         | 1   |
| 36–39                                | 4               | 37          | 0.50| 0.16–1.56 |
| ≥40†                                 | 4               | 11          | 1.82| 0.50–6.55 |

* Controlled for respondent's age, smoking, physical exercise, Quetelet index, number of siblings, month of conception, partner's education, month of birth, and maternal age or preceding pregnancy interval.
† Referent category.
In Figure 1, proportional month-of-conception distributions are given for cases and intermediates, with controls as a reference. Best fitting curves are drawn in the same figure. Despite their reasonable fit [8.38, degrees of freedom (df) = 9, P = 0.50 for cases; and 10.72, df = 9, P = 0.30 for intermediates], best fitting curves were statistically compatible with a straight line (P = 0.78 and P = 0.59, respectively).

Because inaccuracies in the information on the term date of the respondent's birth may have led to misclassification of month of conception, we re-analyzed the data including only those patients who gave information on the term date of birth (cf analysis of pregnancy interval). This re-analysis did not change the results materially in cases or in intermediates. Another re-analysis, restricted to those respondents whose mothers had assisted in filling out the questionnaire, also did not change the results.

Discussion

The results of this study indicate that conception after short pregnancy intervals or at high maternal age increases the risk of menstrual disorders in the offspring. They also indicate that the risk of menstrual disorders is not associated with month of conception or with low maternal age at conception.

These results are partly consistent with the hypothesis we have described earlier, which states that conception in conditions associated with maternal endocrine irregularities may lead to preovulatory overripeness of the oocyte.6 The hypothesis is based on direct evidence from animal experimentation and indirect evidence from observational human research. Overripeness of the oocyte has been observed in diverse animal species after artificial and non-artificial delays of ovulation and has been shown to affect fertilizability, implantation rates, and embryonic malformation rates.8,35-41 In humans, conceptions during irregular menstrual cycles are at higher risk of leading to malformed embryos42-44 and, more generally, conditions in which cycle irregularity is more prevalent are associated with increased rates of adverse reproductive outcome.19-21,23,25,26 Fertilization of pre- and postovulatory overripeness of the oocytes is a result of a dysfunction of the interplay between the hypothalamic-pituitary-ovarian axis the observed relations are connected with.

The hypothesis predicts effects on ovarian function. Irregularity of menstruation, however, is generally the result of a dysfunction of the interplay between the constituents of the hypothalamic-pituitary-ovarian axis. As we did not discriminate between different etiologic categories, we cannot be sure what part of the hypothalamic-pituitary-ovarian axis the observed relations are connected with.

Exactly how preovulatory overripeness of the oocyte would lead to menstrual disorders remains speculative. The aforementioned experiments on amphibia and fish

![FIGURE 1. Month-of-conception distribution of cases and intermediates, and best-fitting curve. Upper curves = cases/(cases + controls); lower curves = intermediates/(intermediates + controls).](image-url)
showed a spectrum of abnormalities of gonadal development, ranging from complete absence or asymmetrical development of the gonads to normal-appearing gonads with reduced numbers of germ cells. This finding would correspond to the small size and low follicular content of the ovaries in patients with idiopathic premature ovarian failure (a condition associated with secondary amenorrhea), although the latter could also be due to an increased rate of attrition of a normal initial number of germ cells. Conceivably, overripeness of the oocyte not only leads to morphologic but also nonviable (biochemical) disturbances, and thus it might, for instance, be involved in the increase of ovarian androgen production in women with polycystic ovaries.

Subgroup analysis indicated that menarcheal age of the subjects acted as an effect modifier. Adjusted ORs for short pregnancy intervals in women with menarcheal ages of ≥15 years were 9.24 (95% CI = 1.46–57.89) for cases vs controls, and 10.91 (95% CI = 1.06–112.44) for intermediates vs controls. ORs for maternal age did not depend much on the subject's menarcheal age. Furthermore, ORs appeared to depend on whether a subject ever had experienced a pregnancy: adjusted ORs for short preceding pregnancy intervals in women who had been pregnant at least once were 3–5 times as high as those in nulligravid (OR = 6.42; 95% CI = 1.48–27.94 for cases vs controls; and OR = 6.11; 95% CI = 0.87–42.54 for intermediates vs controls). Again, no modification seemed present with maternal age as a determinant. It is unclear to us how to interpret these cases of apparent effect modification.

This study has some potential limitations. First, measurement of cycle characteristics was based primarily on routine medical interviews. Despite the possibility of in-person questioning, this method may not be completely reliable, because women who subjectively experience their cycles as being regular tend to overestimate their regularity, and where cycles increase in length or variability, the ability to make accurate estimations may decrease. It is unlikely, however, that the degree or direction of the inaccuracy is related to the study determinants, so that the effect may be a bias toward the null.

Second, in spite of the fact that the information needed to calculate determinant status mainly consisted of objective data such as birth dates, some of the information asked for in the questionnaire, especially dates of maternal miscarriages and stillbirths (needed to determine pregnancy intervals) and the term date of the subject's delivery, may have been more difficult to recover and therefore may be subject to inaccuracy. To reduce inaccuracies, we added the categories “do not know” and “could not ascertain” to questions asking for such information and treated these categories as missing values in the analyses. Furthermore, two-thirds of all respondents, equally distributed among the study groups, reported maternal assistance in filling out the questionnaire. Restriction of the analysis to this subgroup did not lead to different results, nor did restriction to respondents who gave information on the term date of birth. Also, exclusion of respondents who were conceived after routine medical interviews, despite the possibility of maternal assistance in filling out the questionnaire, especially dates of maternal miscarriages and stillbirths (needed to determine status mainly consisted of objective data such as birth dates), some of the information asked for in the questionnaire, especially dates of maternal miscarriages and stillbirths (needed to determine pregnancy intervals) and the term date of the subject's delivery, may have been more difficult to recover and therefore may be subject to inaccuracy. To reduce inaccuracies, we added the categories “do not know” and “could not ascertain” to questions asking for such information and treated these categories as missing values in the analyses. Furthermore, two-thirds of all respondents, equally distributed among the study groups, reported maternal assistance in filling out the questionnaire. Restriction of the analysis to this subgroup did not lead to different results, nor did restriction to respondents who gave information on the term date of birth. Also, exclusion of respondents who were conceived after