Fetal sex and preterm birth: are males at greater risk?

Jennifer Zeitlin1,4, Marie-Josèphe Saurel-Cubizolles1, Jaques de Mouzon2, Lucile Rivera3, Pierre-Yves Ancel1, Béatrice Blondel1 and Monique Kaminski1

1Epidemiological Research Unit on Perinatal and Women’s Health, U149 INSERM, Paris, 2FIVNAT Registry and Epidemiological Unit for Human Reproduction, U292 INSERM, Kremlin Bicêtre and 3Service de Protection Maternelle et Infantile, Conseil Général de Seine-Saint-Denis, France

4To whom correspondence should be addressed. E-mail: zeitlin@cochin.inserm.fr

BACKGROUND: The existence of a male excess among preterm births is interesting because it could shed light on the aetiology of preterm birth. Possible mechanisms are greater body weight, increased susceptibility to complications of pregnancy, sex-linked biochemical processes and earlier conception in the fertile cycle. METHODS: We measured the association between fetal sex and preterm birth in four original datasets, including a cohort of births after IVF, and 20 populations extracted from published birthweight references. The original samples were also analysed by mode of onset. RESULTS: There were more males among preterm and early preterm births than among term births in most populations, including IVF births (odds ratio: 1.09–1.24). No male excess was observed for two cohorts of black births, induced preterm births in the general population, and spontaneous onset births after IVF. CONCLUSIONS: The proportion of male births declines with increasing gestation, even when time of conception is known. This male excess appears to be strongest for spontaneous preterm births. Studying the sex ratio of preterm births by medical risk factors may clarify why the male excess is absent in some populations. The possibility that obstetric decision-making affects the sex ratio of indicated births must be considered.

Key words: IVF births/preterm birth/risk factors/sex ratio

Introduction

The greater mortality risks for males during pregnancy and infancy are well known. Boys have higher rates of fetal and neonatal mortality and are more vulnerable to long-term neurological and motor impairments after preterm birth (Khoury et al., 1985; Verloove-Vanhorick et al., 1994; Smith, 2000; Stevenson et al., 2000). In the past decade, several studies using large datasets have found an excess in the proportion of boys among preterm versus term births (McGregor et al., 1992; Cooperstock and Campbell, 1996; Astolfi and Zonta, 1999), building on earlier, less conclusive, research on this subject. The higher proportion of preterm births among males could contribute to an explanation for their higher mortality in infancy. However, the question of the male excess is interesting primarily because of the light that it could shed on the aetiology of preterm birth.

Several mechanisms have been proposed to explain why pregnancies carrying male fetuses could have a higher risk of preterm birth: (i) heavier average body weight which increases the probability of preterm labour (Hall and Carr-Hill, 1982; McGregor et al., 1992); (ii) a greater susceptibility to certain medical complications associated with preterm birth, such as pregnancy-induced hypertension or infection (Campbell et al., 1983; MacGillivray and Davey, 1985); and (iii) sex-linked biochemical processes, including labour promoted by estrogen production from androgen precursors or by interleukin-1 that may differ between male and female fetuses (Cooperstock and Campbell, 1996). Another explanation, which is not based on a greater male susceptibility to preterm birth, is that boys are more likely to be conceived in the beginning of the fertile period in contrast with girls who are associated with inseminations in the middle of the cycle (James, 1994, 2000).

This analysis explores the association between fetal sex and the risk of preterm birth in 24 populations of singleton births. We test for the presence of a male excess among all preterm births and early preterm births. The inclusion of births from the French National IVF Registry makes it possible to test for a male excess when time of conception is known with certainty. We undertook further analyses within four samples by mode of onset of the delivery. Explanations based on labour-inducing processes predict a greater male excess for spontaneous births while those positing a greater susceptibility to medical complications during pregnancy could lead us to expect a greater excess among induced preterm births.

Materials and methods

This analysis used data from four original data sources, one European and three French, as well as data extracted from published articles to explore the sex distribution of preterm versus term births. All analyses were undertaken using singleton pregnancies only. When possible,
stillbirths were excluded since the predominance of male fetuses among stillbirths was not the subject of this analysis.

The EUROPOP study

The European Program of Occupational Risks and Pregnancy Outcome (EUROPOP) was a European case-control study to explore the relationship between occupational risk factors and preterm birth (Saurel-Cubizolles et al., 1997). Data were from the Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Italy, The Netherlands, Poland, Romania, Russia, Scotland (UK), Slovenia, Spain and Sweden. Cases were all preterm singleton live and stillbirths between 22 and 36 completed weeks of gestation born in participating maternity hospitals. The control group included every 10th singleton live birth or stillbirth at ≥37 completed weeks of gestation over the same time period. Gestational age was based on obstetric estimates, derived from last menstrual period and ultrasound measures. These analyses used data on 5024 preterm and 8197 full-term singleton livebirths.

French National Perinatal Surveys (FNPS)

The French National Perinatal Surveys collect data on all births with a gestational age of ≥22 weeks or a birthweight of ≥500 g in France during a 1 week period with the aim of monitoring the evolution of indicators of perinatal health and medical practice (Fois-L’Helias and Blondel, 2000; Blondel et al., 2001). Data are collected through interviews with the mother and from medical records. Gestational age is based on the best estimate available in the medical records, including the results of ultrasound scans. The total sample of 26 011 singleton live births combined data from the national survey in 1995 (a week in February, n = 12 885) and the national survey in 1998 (a week in November, n = 13 126). Less than 1% of births had missing data on gestational age or sex (n = 246). The percentage preterm was 4.6%.

Seine-Saint-Denis Experimental Health Certificates (SSD Registry)

This database included all births that occur in the district (département) of Seine-Saint-Denis in France. It was constituted from 8th day health certificates (Certificats de Santé du 8ème jour), a certificate that must be filled out for each infant before the 8th day of life. The data used for this analysis included all live births that occurred between October 1998 and the end of December 1999. Sixty-three cases had missing gestational age and 29 data on fetal sex. The total sample numbers were 24 554 term and 1382 preterm singleton live births. The percentage preterm was 5.3%.

National IVF Registry: Fécodnation In Vitro National (FIVNAT)

FIVNAT was set up in January of 1986 and includes most French IVF centres (de Mouzon et al., 1993; Fécodnation In Vitro National, 1995). These centres participate in the registry on a voluntary basis. Data are collected using three forms: one for infertility diagnosis and the IVF cycle, one for thawed embryo transfers and one for obstetric and paediatric data. These forms are completed by each centre and centralized in the registry. Gestational age at birth was computed in theoretical weeks of amenorrhea by adding 14 days to the difference between the date of oocyte retrieval and the date of delivery (Fécodnation In Vitro National, 1995). The data used for these analyses were from 13 819 singleton live births resulting from IVF from the registry’s inception in 1986 until 1997. The preterm birth rate for this cohort was 8.4%.

Birthweight reference populations

Datasets were constructed from birthweight reference populations abstracted from published articles. A Medline search on combinations of the following key words ‘fetal/neonatal/birthweight’ and ‘references/norms/curves’ identified 54 articles with published birthweight reference standards. Data were abstracted from articles where the numbers of male and female births at each gestational age were given. For these samples, it was possible to calculate the ratio of males to females at each gestational age. All population-based samples were selected for the analysis and hospital-based samples were also included, with the exception of two samples that had <250 preterm births. Three articles contained data on several reference populations: in Canada (Arbuckle and Sherman, 1989), data were given for two distinct periods and in two US samples data were presented separately for white and black births (Amini et al., 1994; Roberts et al., 1996). A published article on birthweight and the risk of stillbirth in Scotland provided the number of live male and female births at each gestational age and was also included (Smith, 2000).

The 20 birthweight reference populations, abstracted from 18 published articles, are listed and referenced in Table I, which shows whether the sample is hospital- (H) or population- (P) based, the gestational ages included in the studies, the sample sizes for preterm and term births, and the percentage preterm. In general, these birth cohorts have large sample sizes since it is necessary for establishing birthweight percentiles (ranges: 650–91 000 preterm births and 4150–6 162 382 term births). With the exception of a population from Denver and Norway, all births were live births.

Exclusion criteria for the studies are specified in Table I. All studies eliminated infants with missing gestational age and birthweight and used various exclusion criteria for birthweight outliers. In most populations, only cases with missing data on birthweight or gestational age or those with extreme values for these variables were excluded. Many articles did not provide information on the percentage of cases excluded and none of the articles provided information on the sex ratio of excluded cases. Stricter exclusion criteria were used for the Swedish analysis where 20% of births were excluded to obtain a ‘healthy population’. In the earlier Scottish data sets, only legitimate births were included. Hospital samples are more likely to include higher risk populations. In the East Midland sample the authors excluded all in-utero transfers to minimize this bias. They also excluded pregnancies without a dating scan before 24 weeks as well as congenital anomalies. In the sample from the hospital in Cleveland, Ohio, however, both white and black births were high risk (15% preterm birth rate). These exclusion criteria and the gestational age limits affect the preterm birth rates, which ranged from 3 to 15%.

For the analysis, a subset of studies was defined that were population based with minimal exclusion criteria. This subset included 10 birthweight reference populations plus the three original population-based datasets.

Analysis

The analysis contrasted the sex distribution by preterm and term status. The association between male sex and the risk of preterm birth was expressed as an odds ratio (OR) with female sex as the reference category. OR were also calculated for early preterm births, defined as births before 33 weeks of gestation. Data on early preterm births were available for all but four of the birth cohorts. χ2-tests for trend were done for the proportion male with rising gestational age up until term. We used random effects meta-analysis to estimate a combined measure of the association between fetal sex and preterm birth in the 24 populations as well as the extent to which subgroups explained heterogeneity in the pooled estimate. The latter analysis relates study co-variates to the outcome, assuming a normal distribution for the residual errors with both a within-study and an additive between-studies component of variance. The within-study variance (SE) was derived from each study and the overall variance...
Table I. Populations of singleton live births from published articles

<table>
<thead>
<tr>
<th>Location, year</th>
<th>Reference</th>
<th>Hospital (H) or population (P) sample</th>
<th>GA (range)</th>
<th>Preterm n</th>
<th>Term n</th>
<th>% preterm</th>
<th>Exclusion or inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denver, Colorado, USA, 1948–1961</td>
<td>Labchenco et al. (1966)</td>
<td>H (one centre)</td>
<td>24–42</td>
<td>1485</td>
<td>4150</td>
<td>NAb</td>
<td>Hospitalized preterm and all live term white births. Gross pathological conditions and missing GA excluded (7%)</td>
</tr>
<tr>
<td>Aberdeen, Scotland, 1948–1964</td>
<td>Thomson et al. (1968)</td>
<td>P</td>
<td>32–42</td>
<td>2575</td>
<td>43 786</td>
<td>5.6</td>
<td>Legitimate births only. Missing GA (10%). Macerated stillbirths and congenital anomalies excluded</td>
</tr>
<tr>
<td>Cleveland, Ohio, USA 1975–1992</td>
<td>Amini et al. (1994)</td>
<td>H (one centre)</td>
<td>24–44</td>
<td>White 3941</td>
<td>Black 3911</td>
<td>Black 20 983</td>
<td>Excluded if discordance between estimated GA and Dubowitz score &gt;2 weeks (7.4%)</td>
</tr>
<tr>
<td>Aberdeen, Scotland 1979–1983</td>
<td>Campbell et al. (1993)</td>
<td>P</td>
<td>32–42</td>
<td>653</td>
<td>13 566</td>
<td>4.6</td>
<td>None mentioned</td>
</tr>
<tr>
<td>Italy, 1984–1985</td>
<td>Parazzini et al. (1991)</td>
<td>P</td>
<td>28–42</td>
<td>64 842</td>
<td>1 101 591</td>
<td>5.6</td>
<td>None mentioned</td>
</tr>
<tr>
<td>Canada, 1986</td>
<td>Arbuckle and Sherman (1989)</td>
<td>P</td>
<td>25–42</td>
<td>18 333</td>
<td>335 170</td>
<td>5.2</td>
<td>Excluded birthweights &lt;5000 g or &gt;5000 g</td>
</tr>
<tr>
<td>East Midlands, UK, 1986–1991</td>
<td>Wilcox et al. (1993)</td>
<td>H (3 centres)</td>
<td>24–42</td>
<td>2983</td>
<td>40 624</td>
<td>7.2</td>
<td>Excluded if no scan 24 wks (7.5%), congenital anomalies and in-utero transfers</td>
</tr>
</tbody>
</table>

aTwo populations included stillbirths, as noted in inclusion criteria.

bTerm births were only included up to 1955.

GA = gestational age; NA = not available.
Table II. Percentage male by preterm status and odds ratios (OR) for preterm birth associated with male sex

<table>
<thead>
<tr>
<th>Data source</th>
<th>Term % male (n)</th>
<th>All preterm births (&lt;37 weeks) % male (n) OR 95% CI</th>
<th>Early preterm births (&lt;33 weeks) % male (n) OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>EUROPOP, 1994–1997</td>
<td>52.1 (8197)</td>
<td>55.4 (5024) 1.14 1.06–1.22</td>
<td>55.8 (1375) 1.15 1.04–1.30</td>
</tr>
<tr>
<td>FNPS, 1995–1998</td>
<td>51.0 (24 583)</td>
<td>54.2 (1182) 1.13 1.01–1.27</td>
<td>53.2 (186) 1.09 0.82–1.14</td>
</tr>
<tr>
<td>SSD Registry, 1998–1999</td>
<td>51.1 (24 552)</td>
<td>54.5 (1370) 1.14 1.03–1.27</td>
<td>52.1 (292) 1.04 0.83–1.31</td>
</tr>
<tr>
<td>FIVNAT Registry, 1986–1997</td>
<td>51.3 (12 652)</td>
<td>53.4 (1167) 1.09 0.96–1.23</td>
<td>53.3 (229) 1.08 0.83–1.14</td>
</tr>
</tbody>
</table>

Birthweight reference populations
- Denver, 1948–1961 50.6 | 55.4 | 1.22 1.08–1.37 |
- Aberdeen, 1948–1964 51.4 | 55.3 | 1.17 1.08–1.27 |
- Scotland, 1973–1979 51.7 | 54.2 | 1.10 1.05–1.16 |
- Glasgow, 1975–1979 51.2 | 53.6 | 1.10 1.15–1.19 |
- Norway, 1967–1998 51.0 | 55.8 | 1.21 1.19–1.22 |
- Canada, 1975–1992 (white) 50.4 | 48.8 | 0.94 0.87–1.00 |
- Germany, 1976–1985 50.9 | 53.7 | 1.12 1.00–1.26 |
- Sweden, 1977–1981 50.8 | 55.4 | 1.20 1.16–1.25 |
- Aberdeen, 1979–1983 51.5 | 56.8 | 1.24 1.06–1.45 |
- Scotland, 1980–1996 51.2 | 54.9 | 1.16 1.13–1.19 |
- Italy, 1984–1985 51.3 | 53.6 | 1.09 1.08–1.11 |
- France, 1984–1988 50.9 | 51.8 | 1.04 0.99–1.09 |
- Canada, 1986 51.0 | 55.6 | 1.21 1.17–1.24 |
- East Midlands, UK 1986–1991 51.1 | 54.0 | 1.12 1.04–1.21 |
- Connecticut, 1988–1993 (white) 51.0 | 54.4 | 1.14 1.10–1.19 |
- Connecticut, 1988–1993 (black) 51.0 | 49.9 | 0.97 0.90–1.04 |
- Australia, 1991–1994 51.3 | 55.0 | 1.16 1.14–1.19 |
- Canada, 1994–1996 51.1 | 54.9 | 1.16 1.14–1.19 |

CI = confidence interval.

was estimated by an iterative procedure, using an estimate which was based on restricted maximum likelihood. Analyses were done using the meta and metareg commands in STATA v6.0.

Further analyses were undertaken according to whether the birth was spontaneous or induced in the EUROPOP sample and the three French datasets. The category of induced births includes induced deliveries and Caesarean sections before the onset of labour. The comparison group was all term births. In the EUROPOP study and the French national perinatal surveys, >99% of all births had information on mode of onset. In the Seine-Saint-Denis registry, however, 8.5% of the births had missing information on mode of onset. Missing data were more frequent in preterm deliveries (11.4 versus 8.4%), but did not differ by sex (8.5% for pregnancies with boys versus 8.7% for pregnancies with girls). For the FIVNAT registry, 7% of the births have missing information on the onset of labour. Missing data are not more frequent among preterm versus term births (6.9 and 7.0% respectively), nor among pregnancies with male or female fetuses (7.2 and 6.8% respectively).

Results

Table II displays male births as a percentage of total births for term, preterm and very preterm births as well as corresponding OR for male sex in 24 populations of singleton births. Sample sizes for the birthweight reference populations are presented in Table I. Almost everywhere, there was a higher percentage of males among preterm compared with term births. OR in 20 out of the 24 populations ranged from 1.09 to 1.24. This excess risk translated into preterm birth rates 0.5–1% higher for boys versus girls as, for example, in Norway in 1967–1998 (4.8% for girls and 5.8% for boys), Canada in 1986 (4.7 and 5.6%), Italy in 1984–1985 (5.3 and 5.8%), France in 1995–1998 (4.3 and 4.9%), Scotland in 1980–1996 (5.5 and 6.3%), Australia in 1991–1994 (4.9 and 5.6%), and in Canada in 1994–1996 (5.4 and 6.2%).

In four samples, the confidence interval for the OR included one. For the first of these, the FIVNAT registry, the OR was within the lower limit of effects observed in other populations: 1.09. For the other samples, however, a hospital-based sample in France in 1984–1988, and samples of black births (one population-based and one hospital-based) from Cleveland and Connecticut, OR were notably lower: 1.04 0.94, 0.97. For a Canadian population in 1972 the OR is 1.05 although the confidence interval does not include one.

The male excess existed for early preterm birth in most samples; OR associated with early preterm birth were almost identical to those within the whole sample. Two exceptions are the French National Perinatal Surveys and the Seine-Saint-Denis Registry where the OR for early preterm birth were lower than the OR for all preterm births and were not significantly different from 1.

Figure 1 plots the percentage of male births by gestational age group starting with the group 33–36 weeks gestation. We omitted early preterm births since this information is not

CI = confidence interval.
available for all samples, and is presented in Table II. Figure 1 illustrates a common pattern of decreasing proportions of male births with increasing gestational age. The trend was significant in all samples with OR for male sex significantly greater than 1. The data from the sample of IVF births also adhere to this pattern (large diamond-shaped plots) and the declining percentage of boys with gestational age was significant ($\chi^2$-test for trend, $P < 0.001$). This trend was also significant for the Canadian 1972 sample ($P < 0.001$) and the French 1988 sample ($P < 0.001$), the two samples with lower OR for the association between fetal sex and preterm birth. In contrast, the trend was not significant for the samples of black births (presented as dashed lines)

A combined estimate of the association between male sex and preterm birth from the 24 studies was calculated using random effects meta-analysis. The combined measure was 1.12 (1.09–1.15) and was highly significant. The test for heterogeneity was significant ($P < 0.0001$). Two populations of black births contributed significantly to the observed heterogeneity ($Z = -4.542, P < 0.0001$); if these two populations were excluded, the combined measure was 1.14 (1.11–1.17). The test for heterogeneity remained significant ($P < 0.0001$). The combined estimate for the subgroup of population-based studies with minimal exclusions was similar to the overall estimate: 1.13 (1.10–1.17). Whether the studies had significant versus minimal exclusions did not contribute to an explanation of the heterogeneity. For early preterm births, the combined estimate was 1.14 (1.10–1.18).

Table III presents results by mode of onset using the four datasets where this information was available. The risk of preterm birth associated with carrying a male fetus was higher for spontaneous preterm births in the three samples of naturally conceived births (OR: 1.17 for EUROPOP; OR: 1.29 for the French National Perinatal Surveys; OR: 1.29 for the Seine–Saint-Denis registry). In fact, male sex was not significantly related to the risk of induced preterm birth in any of these samples. In contrast, the opposite pattern emerges from the sample of IVF births: the excess risk associated with male sex was apparent only in induced preterm deliveries and there was no excess of boys among spontaneous preterm births.

The analysis of early preterm births in Table III showed that for the two French samples (National Perinatal Surveys and the SSD Registry), the overall OR associated with male sex (shown in Table II) represented an average of a strong association with spontaneous preterm births and none for induced preterm births. In these samples, about one-half of early preterm births were induced. In the FIVNAT sample, a male excess was evident—although not statistically significant—for spontaneous early preterm births.

Discussion

Males have a greater risk of being born before term in a wide range of populations across time and space. OR associated with male sex were between 1.09 and 1.24 in 21 out of 24 populations. Results of other studies on this topic from New England, Aberdeen and Italy are within this range [calculated crude OR: 1.16, 1.20 and 1.11 respectively (Hall and Carr-Hill, 1982; McGregor et al., 1992; Astolfi and Zonta, 1999)] as are those from studies including fetal sex as a co-variate in risk factor analyses [adjusted OR of 1.10 and 1.28 (van den Berg and Oechsli, 1984; Shiono and Klebanoff, 1986)]. The combined estimate of the OR for preterm birth from the 24 birth cohorts is 1.12 (1.09–1.14). Large sample sizes provide high precision for individual estimates and there is significant heterogeneity in this association over a relatively narrow range of values.

The risk associated with fetal sex for early preterm births is of a similar magnitude. Two exceptions are the French samples from the late 1990s, where the OR for early preterm births are lower and not significantly different from 1. In all but two populations, the proportion of male births declines with gestational age up until ~40 weeks gestation.

These data sources come from Europe and North America over the last 50 years. The 20 birthweight reference populations were selected from all referenced articles that provided data to calculate the percentage of male births at each gestational age. These studies used varying exclusion criteria. Overall, exclusions on medical and social criteria were likely to result in a healthier population of births. However, limiting the analysis to birth samples with minimal exclusions did not change the overall association between fetal sex and preterm birth.

The risk of preterm birth was not affected by fetal sex for the two populations of black births included in this analysis: neither OR was significantly different from 1 and the overall trend with gestational age was not significant. This corroborates findings from a previous study that found a 7.2% excess of males among white singleton preterm births versus only a 2.8% excess among black singleton births in a New England sample of births (Cooperstock and Campbell, 1996). To explain their finding, the authors hypothesize that the causes of preterm birth in high-risk black populations, such as infection or pre-eclampsia, could be sex independent. They conclude that a labour-inducing mechanism influenced by fetal sex hormones is most likely responsible for the male excess among preterm births and that this excess would be most ‘epidemiologically evident’ in women at low risk of preterm birth (Cooperstock and Campbell, 1996). This interpretation is consistent with rates of preterm births observed in the sample from Connecticut, where the preterm birth rate is much lower for whites than blacks (5.4 versus 11.6%), but not with the sample from the...
Cleveland, Ohio hospital where preterm birth rates are identical for white and black births (15.1 and 15.7% respectively). No further information is available on the medical risk factors associated with preterm birth in this hospital; analyses to see if these differ by race would be needed in order to confirm or reject the hypothesis put forth by Cooperstock and Campbell.

Births from the French registry of IVF births were included in this analysis to test the theory that boys have a greater probability of being conceived earlier in the fertile cycle. Support for this theory comes from studies of other mammalian species and small studies on the sex of human offspring and the cycle day of natural insemination (James, 1994, 2000). We posited that if the excess of males was due solely to a difference in the timing of conception, it should disappear completely in IVF births for which the moment of conception is known with certainty for both sexes. This does not appear to be the case in the overall population of IVF births. Although the association between fetal sex and preterm birth is of lesser magnitude, the same population trends between the proportion of male births and gestational age are observed.

Our analyses of spontaneous versus induced onset of delivery in the four original data sets were intended to shed further light on underlying mechanisms. A greater male excess for spontaneous onset preterm births would add support to an explanation based on labour-inducing processes associated with fetal sex, whereas a greater male excess among medically indicated preterm births would favour an explanation based on a greater male susceptibility to certain complications of pregnancy, such as hypertension or growth restriction. A Scottish study from the early 1980s previously documented a higher proportion of males in spontaneous versus induced preterm births, leading the authors to posit that the labour-inducing effects of fetal sex hormones or the effects of fetal weight were most likely causal mechanisms (Hall and Carr-Hill, 1982). One limit of analyses based on mode of onset is that they do not separate out preterm births associated with preterm premature rupture of membranes (PROM). These can have either a spontaneous or medically decided onset, depending on how the PROM was managed.

An excess of males in preterm births following spontaneous onset of labour was clearly observed in the EUROPOP sample and the two French population-based samples. No significant excess was present for induced births. These results favour an explanation based on a labour-inducing mechanism. Our results for the IVF sample are not in line with the three other samples, however. An excess of males is not apparent among spontaneous IVF preterm births—the excess of males is observed only for induced births. While it is possible that there may be different medical risk factors associated with spontaneous and induced preterm birth in IVF and naturally conceived births, these conflicting results raise the question of how to interpret the sex ratio of deliveries with a medically decided onset.

To draw conclusions about the natural sex ratio from these results, we must assume that medical decisions do not affect the sex ratio. While fetal sex is unlikely to determine the decision to terminate a pregnancy before term, it is related to birthweight, which is a key parameter in these decisions. For instance, obstetric decision-making could have the effect of attenuating the natural sex ratio of indicated preterm births if single sex reference curves were used for the diagnosis of intrauterine growth restriction. Results from the two French population-based samples from the late 1990s provide some support for this possibility. No male excess is observed for early preterm births—in contrast to almost all other birth samples. Almost half of all early preterm births result from a medical decision to induce delivery and the low OR for male sex reflects an average of a strong male excess for spontaneous preterm births and no male excess for induced preterm births.

On the other hand, an excess of males among indicated preterm births could occur if heavier babies were more likely to be considered above the threshold where the adverse consequences of continued pregnancy outweigh those associated with preterm birth. This would be more likely to occur for closely monitored pregnancies and for moderate preterm births. This is the case for the IVF births: about half of preterm IVF births result from a medical decision, in contrast with a third for naturally conceived births, and the excess of males

Table III. Percentage male by preterm status and odds ratios (OR) for preterm birth associated with male sex, by mode of onset

<table>
<thead>
<tr>
<th></th>
<th>Term births</th>
<th>Preterm</th>
<th>Early preterm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% male (n)</td>
<td>% male (n)</td>
<td>% male (n)</td>
</tr>
<tr>
<td>EUROPOP Study</td>
<td>52.1 (8197)</td>
<td>56.0 (3384)</td>
<td>54.0 (1627)</td>
</tr>
<tr>
<td>French National</td>
<td>51.0 (759)</td>
<td>57.3 (417)</td>
<td>48.4 (89)</td>
</tr>
<tr>
<td>Perinatal Surveys (FNPS)</td>
<td>51.1 (784)</td>
<td>57.3 (444)</td>
<td>51.1 (152)</td>
</tr>
<tr>
<td>Seine–Saint-Denis Registry (SSD)</td>
<td>51.3 (579)</td>
<td>51.6 (508)</td>
<td>55.7 (85)</td>
</tr>
<tr>
<td>FIVNAT Registry</td>
<td>56.0 (1144)</td>
<td>55.8 (658)</td>
<td>1.17 (1.03–1.33)</td>
</tr>
<tr>
<td></td>
<td>Spontaneous OR (95% CI)</td>
<td>Induced OR (95% CI)</td>
<td>Spontaneous OR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>1.08–1.20</td>
<td>1.08–1.20</td>
<td>1.03–1.33</td>
</tr>
<tr>
<td></td>
<td>1.00–1.43</td>
<td>1.00–1.43</td>
<td>1.09–1.45</td>
</tr>
<tr>
<td></td>
<td>0.04–1.80</td>
<td>0.04–1.80</td>
<td>0.05–1.85</td>
</tr>
<tr>
<td></td>
<td>1.00–1.53</td>
<td>1.00–1.53</td>
<td>1.00–1.55</td>
</tr>
</tbody>
</table>

CI = confidence interval.
for induced IVF births is evident only among preterm births after 33 weeks of gestation.

Although the results of analyses by mode of onset provide most support for a labour-inducing mechanism, the possibility that medical decisions could affect the sex ratio of preterm births prevents us from completely rejecting the other hypotheses. For instance, in the absence of medical decisions to induce delivery, would we find no excess of males among IVF births, as posited by the early conception hypothesis? Similarly, could induction practices in naturally conceived populations make it impossible to observe a male excess among those infants whose delivery is medically decided?

In conclusion, these results provide strong evidence that boys are more likely to be born before term. This effect is observed in a wide range of populations, is evident among early preterm births, and appears to be strongest for spontaneous preterm births. To shed light on the mechanisms underlying this effect, and in particular to clarify the reasons that no male excess is evident in certain groups of preterm births, future analyses should explore the sex ratio of preterm births by aetiology, for both spontaneous and induced deliveries. The possibility that obstetric decision-making affects the sex ratios of induced births needs to be taken into consideration when analysing the sex ratios of births by mode of onset.

Acknowledgements

The EUROPOP study was financed by the European Union BIOMED project BMH1-CT94-1041. The authors wish to thank the members of the EUROPOP group. The French National Perinatal Surveys were partly funded by the Ministry of Health (Direction générale de la santé). The Seine-Saint-Denis experimental birth certificates are financed by the Conseil Général de la Seine-Saint-Denis. The authors wish to thank the maternal and child protection services for their collaboration. French National Registry on IVF is organized as a collaboration between the FIVNAT association and U292, INSERM and is partly funded by the pharmaceutical industry (Laboratoire Organon) and the French Ministry of Health.

References


Submitted on April 2, 2002; accepted on May 31, 2002