SMALL-FOR-GESTATIONAL-AGE NEWBORNS OF FEMALE REFINERY WORKERS EXPOSED TO NICKEL

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Abstract

Objectives: It has not yet been established whether exposure to nickel (Ni) compounds may cause reproductive toxicity. The objective of this study was to investigate whether women employed under conditions of nickel exposure in early pregnancy were at elevated risk of delivering a newborn small-for-gestational-age (SGA).

Materials and Methods: A register-based study of a well defined population. Data on pregnancy outcome and maternal occupation were obtained from the Kola Birth Registry. Each birth record was assigned a Ni exposure rating category according to maternal occupation at the time of becoming pregnant. Nickel exposure assessment was based on determining the water-soluble Ni subfraction of respirable aerosol fraction obtained by personal monitoring, and/or on measurements of urine Ni concentration. The reference population were the delivering women with background exposure level. The study population consisted of 22,836 births (> 27 weeks of gestation) and the SGA infants were defined as below the 10th percentile birth weight for gestational age in the source population. Multiple logistic regression was used to analyze the association of the outcome with the assigned exposure rating category.

Results: The adjusted odds ratio for Ni-exposed women for giving birth to an SGA newborn was 0.84 (95% CI: 0.75–0.93).

Conclusions: We found no adverse effect of maternal occupational exposure to water-soluble Ni in the first part of pregnancy on the risk of delivering an SGA newborn without trisomy. The finding does not exclude a possibility that exposure throughout pregnancy might produce such an effect.

Key words: Fetal growth retardation, Nickel, Small-for-gestational-age infant, Registry, Russia

INTRODUCTION

It has not yet been established whether exposure to nickel (Ni) compounds may cause reproductive toxicity [1] as defined by the European Commission [2]. This reflects the paucity of both animal and human evidence. In Europe, it is only in Russia that the number of women workers employed at Ni refineries is large enough to conduct epidemiological investigations of pregnancy outcome. The largest Ni refinery in the European part of Russia is located in the borough of Mončegorsk where thorough assessments of exposure to Ni, cobalt and other industrial hazards have been carried out [3–5].

The recently reported studies in Mončegorsk did not reveal an elevated risk of spontaneous abortions [6] or malformations of the genital organs [7] in the newborns of women occupationally exposed to Ni in early pregnancy, compared to the non-exposed women. A developmental concern is plausible since Ni does cross the placental barrier [5,8]. Animal studies indicate that Ni tetracarbonyl...
and water-soluble Ni salts are toxic to the newborn [1]. A metal related to nickel in its production is cobalt (Co). Urine concentrations of both metals reflect primarily airborne exposures to water-soluble Ni and Co(II) salts [4,9]. However, in view of the relatively short half-life (24 hours) for Ni in urine and its elimination from serum [10], cumulative exposure may not be a factor of particular concern for exposures to water-soluble Ni. As regards Co exposure, there is no human evidence for effects on fertility and fetal development but oral and inhalation animal studies with water-soluble Co(II) salts suggest that they may be of concern [11,12]. 

Low birth weight is causally associated with neonatal and perinatal mortality, and linked to an unfavourable development of the infant. The main determinants are poor fetal growth and short gestation, and the former increases the risk of the latter. Preterm infants are more likely to be small relative to their gestational age after premature rupture of membranes [13]. When the growth rate of the fetus does not reach its full potential, an intrauterine growth restriction (IUGR) follows, which is a condition that cannot be reversed through therapy [14]. IUGR is associated with antenatal and postnatal morbidity and survival [14], and is mainly due to decreased uterine blood flow [16] or an impaired placental function [14], placental dysfunction [15] or poor placental growth [16]. The regulation of fetal growth is a complex and multifactorial process, including maternal and environmental factors [17] as well as intrinsic fetal conditions [16,18]; the interaction of these factors adds to the complexity [17]. It is known that the newborns of multiparous women are less likely to be small for gestational age [19]. For women who deliver a small infant, the probability of this being repeated in the next pregnancy is high [20]. The newborns in multiple pregnancies also tend to be small [21]. On a population basis, small-for-gestational-age (SGA) is a common surrogate of IUGR [13]. An SGA infant is usually defined as a neonate with a birth weight lower than the 10th percentile for gestational age [18,21]. In other words, the SGA fetus has not reached its expected size. 

The following maternal and lifestyle factors have repeatedly been reported to be associated with IUGR: maternal smoking [13,17,19,22,23], moderate and heavy alcohol consumption [24], intrauterine infections [25], low maternal birth weight [17], low maternal body height [22], body weight [17], and body mass index (BMI) [13,19,22]. Furthermore, IUGR is more common among female infants [21]. The risk of being born SGA has also been associated with maternal substance abuse [23], medication use [20], age [13,22], solvent exposure [20], malnutrition [26], ethnicity [19], low socioeconomic status/education [22,23], medical complications [21] including pre-eclampsia [22] and hypertension/toxemia [13,19,22], and some illnesses [27]. Working in a standing position during pregnancy [28], previous induced abortions [29], and environmental exposure to toxic substances and air pollutants might also have an impact [21,30]. Congenital defects, such as genital, gastrointestinal and chromosomal anomalies, have consistently been found in association with SGA [18,20,31,32]. 

In the present study, the aim was to assess whether women occupationally exposed during pregnancy to elevated levels of water-soluble Ni at the Mončegorsk Ni refinery complex (see below) were at a higher risk of delivering an SGA newborn than those not so exposed, in the borough of Mončegorsk, Russia.

**MATERIAL AND METHODS**

**Context**

The borough of Mončegorsk is located in the Kola Peninsula in north-western Russia [33]. The population (66,200 in 1995) has been exposed to large emissions of sulphur dioxide, dust, nickel, cobalt and copper from the local Ni, Co and Cu refineries (collectively referred to as the Ni-refinery complex) [34]. In the period of 1973–97, as much as 42.5% of the delivering women in the population were employed at the Ni company [35]. The refinery operates 24 hours a day, on a three-shift basis. As revealed by workplace exposure data, the highest urinary Ni concentrations were found in the matte roasting, anode casting, and electro-refining departments [3]. The refining processes at different departments of this refinery were outlined previously [3,4].

The maternal care and benefits have been described elsewhere [7,33]. The regular practice during the study period...
was that all pregnant women were advised to visit a gynaecologist before 12 weeks of pregnancy. Women performing heavy or hazardous jobs were to be transferred to another work post as soon as the pregnancy had been confirmed (A. Vojtov, personal communication). In Russian regulations, a spontaneous abortion has been defined as a delivery before 28 weeks of pregnancy (and birth weight < 1000 g and length < 35 cm), where the fetus is without life or survives less than 168 hours.

The Kola Birth Registry
In the present study, the source of data was the Kola Birth Registry (KBR) [7,33]. The KBR includes detailed data about live births, as well as stillbirths in at least 28 weeks’ gestation, by residents of Mončegorsk giving birth over the period of 1973 through 2003. The registry included also information about maternal occupation and workplace during pregnancy, compiled from the clinical records. The registered gestational age was obtained from the delivery records. We have previously provided a comprehensive account of the history, content, data collection and data quality of the KBR [33,35]. The data about the workplace and the smoking habit were supplemented with questionnaire-reported information [6,36].

Ni exposure and pregnancy outcome classification and analysis
Quantitative analyses of air and urine samples for Ni and other metals and metalloids that were performed during the observation period of 1995–2001 were used to characterize exposure. The quarterly stationary air quality measurements carried out since 1980, combined with the knowledge based on company records that the refinery operations remained materially unchanged since the 1960s, ensure that the measurements reflect also past exposures. The following general categories were assigned to each birth record in the KBR according to maternal occupation at the onset of pregnancy: background exposure, low exposure, and high exposure [7]. The assigned job-specific exposure ratings for the different job categories may be obtained from the authors. For non-Ni refinery workers, the recorded occupations were used as an evidence of solvent exposure [7], and the urinary Ni measurements in associated projects during the study period [5], as an index of Ni body burden. Details of the in-plant exposure assessment, exposure classification, and assignment of exposure rating category to each study participant were reported previously [3,4,7].

The SGA infants were defined as those with birth weight below the 10th percentile birth weight for gestational age. The distribution of birth weight amongst all singleton deliveries in the period of 1973–2003 in Mončegorsk was used to determine the 10th percentile birth weight for each integer week of gestation from 28 to 40 weeks. The infants born at 41 and 42 weeks were included in the 40-week group in the distribution analysis. The 10th percentile was determined sex-specifically for the newborns with gestational age of at least 37 weeks (birth frequencies < 37 weeks were considered to be too low for sex-specific determination). A total of 25,258 singleton births were registered during the study period, and of these, the birth weight was missing in seven records and an additional six were pseudohermaphrodites or the sex could not be determined. The gestational age and birth weight distributions are presented in Table 1. The study population was selected from the remaining 25,245 newborns (i.e. the source population) based on the following a priori-defined inclusion criteria: (1) born in the period of 1973–2001, which excluded 1194 births from the analysis; (2) mother residing in Mončegorsk at the onset of pregnancy, which excluded an additional 958; (3) registered gestational age of 28–42 (this excluded 132); (4) maternal workplace and job registered (excluded 98); (5) no diagnosis of chromosomal aberrations (trisomies 13, 18 and 21, and Turner’s syndrome) at birth (this excluded 27). After excluding the ineligible births, the study population consisted of 22,836 newborns.

A multiple logistic regression analysis was conducted, with the presence or absence of SGA as the dichotomous outcome. The association between the categories of exposure to water-soluble Ni and the pregnancy outcome was adjusted for factors that were selected a priori based on literature reports of consistent relevant associations and
in a sub-analysis of boys only. Preterm (28–36 weeks) SGA vs. preterm non-SGA newborns were subject to a separate sub-analysis (including also sex as a covariate). In post-hoc sub-analyses, only the newborns of women employed at the Ni refinery complex (see Table 3) were considered, and in another one, those of employed women only.

The level of significance was set at 5%. Wald statistics was used to test the equality of the coefficients for the exposed and non-exposed groups. Given that 9.9% of the infants

availability of data from the KBR. The following were selected: first delivery (yes/no); regular maternal exposure to solvents at work (yes/no); maternal age > 34 years (yes/no) [21]; maternal height; smoking (yes/no); previous induced abortions (yes/no); and obvious signs of alcohol abuse in pregnancy (yes/no). Considering the potential for residual confounding, an analysis was also run without smoking in the model. Before the onset of the study, we also decided to adjust for the presence of one or more genital defects in Table 1.

**Table 1. Gestational age (GA) and birth weight (BW) distributions of births in the source and study populations in Mončegorsk**

<table>
<thead>
<tr>
<th>Weeks of gestation</th>
<th>N°</th>
<th>Proportion of births (%)</th>
<th>BW range (grams)</th>
<th>BW &lt; 10th percentile</th>
<th>N°</th>
<th>Proportion of births (%)</th>
<th>n &lt; 10th percentile BW</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>51</td>
<td>0.20</td>
<td>800–2 100</td>
<td>&lt; 900</td>
<td>46</td>
<td>0.19</td>
<td>3</td>
</tr>
<tr>
<td>29</td>
<td>34</td>
<td>0.13</td>
<td>870–2 300</td>
<td>&lt; 1 000</td>
<td>29</td>
<td>0.13</td>
<td>2</td>
</tr>
<tr>
<td>30</td>
<td>63</td>
<td>0.25</td>
<td>360–2 600</td>
<td>&lt; 1 000</td>
<td>57</td>
<td>0.25</td>
<td>3</td>
</tr>
<tr>
<td>31</td>
<td>56</td>
<td>0.22</td>
<td>600–2 500</td>
<td>&lt; 1 100</td>
<td>56</td>
<td>0.25</td>
<td>4</td>
</tr>
<tr>
<td>32</td>
<td>95</td>
<td>0.38</td>
<td>1 000–2 600</td>
<td>&lt; 1 300</td>
<td>86</td>
<td>0.38</td>
<td>8</td>
</tr>
<tr>
<td>33</td>
<td>123</td>
<td>0.49</td>
<td>1 100–3 500</td>
<td>&lt; 1 500</td>
<td>109</td>
<td>0.48</td>
<td>9</td>
</tr>
<tr>
<td>34</td>
<td>146</td>
<td>0.58</td>
<td>950–3 700</td>
<td>&lt; 1 600</td>
<td>126</td>
<td>0.55</td>
<td>9</td>
</tr>
<tr>
<td>35</td>
<td>204</td>
<td>0.81</td>
<td>800–3 800</td>
<td>&lt; 1 700</td>
<td>188</td>
<td>0.82</td>
<td>17</td>
</tr>
<tr>
<td>36</td>
<td>422</td>
<td>1.67</td>
<td>1 220–4 300</td>
<td>&lt; 2 000</td>
<td>398</td>
<td>1.74</td>
<td>37</td>
</tr>
<tr>
<td>37 Boys</td>
<td>426</td>
<td>1.69</td>
<td>1 500–4 000</td>
<td>&lt; 2 350</td>
<td>377</td>
<td>1.65</td>
<td>34</td>
</tr>
<tr>
<td>Girls</td>
<td>378</td>
<td>1.50</td>
<td>1 200–5 300</td>
<td>&lt; 2 300</td>
<td>339</td>
<td>1.48</td>
<td>26</td>
</tr>
<tr>
<td>38 Boys</td>
<td>1 175</td>
<td>4.65</td>
<td>1 300–4 800</td>
<td>&lt; 2 600</td>
<td>1 039</td>
<td>4.55</td>
<td>88</td>
</tr>
<tr>
<td>Girls</td>
<td>1 085</td>
<td>4.30</td>
<td>1 500–4 750</td>
<td>&lt; 2 550</td>
<td>962</td>
<td>4.21</td>
<td>89</td>
</tr>
<tr>
<td>39 Boys</td>
<td>1 610</td>
<td>6.38</td>
<td>2 000–4 800</td>
<td>&lt; 2 850</td>
<td>1 403</td>
<td>6.14</td>
<td>140</td>
</tr>
<tr>
<td>Girls</td>
<td>1 485</td>
<td>5.88</td>
<td>1 450–5 000</td>
<td>&lt; 2 700</td>
<td>1 277</td>
<td>5.59</td>
<td>108</td>
</tr>
<tr>
<td>40 Boys</td>
<td>7 466</td>
<td>29.57</td>
<td>1 400–5 650</td>
<td>&lt; 2 950</td>
<td>6 906</td>
<td>30.24</td>
<td>728</td>
</tr>
<tr>
<td>Girls</td>
<td>7 333</td>
<td>29.05</td>
<td>1 700–5 400</td>
<td>&lt; 2 950</td>
<td>6 830</td>
<td>29.90</td>
<td>675</td>
</tr>
<tr>
<td>41 Boys</td>
<td>1 087</td>
<td>4.31</td>
<td>2 250–5 100</td>
<td>&lt; 2 850</td>
<td>948</td>
<td>4.15</td>
<td>43</td>
</tr>
<tr>
<td>Girls</td>
<td>1 008</td>
<td>4.00</td>
<td>2 300–5 000</td>
<td>&lt; 2 850</td>
<td>883</td>
<td>3.87</td>
<td>45</td>
</tr>
<tr>
<td>42 Boys</td>
<td>471</td>
<td>1.87</td>
<td>2 500–5 150</td>
<td>NA^d</td>
<td>432</td>
<td>1.89</td>
<td>14</td>
</tr>
<tr>
<td>Girls</td>
<td>387</td>
<td>1.53</td>
<td>2 300–4 800</td>
<td>NA^d</td>
<td>347</td>
<td>1.52</td>
<td>14</td>
</tr>
<tr>
<td>43</td>
<td>122</td>
<td>0.48</td>
<td>2 550–4 950</td>
<td>NA^d</td>
<td>Not included</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>18</td>
<td>0.07</td>
<td>2 700–4 300</td>
<td>NA^d</td>
<td>Not included</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>3</td>
<td>0.01</td>
<td>3 200–3 950</td>
<td>NA^d</td>
<td>Not included</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>25 245</td>
<td>100</td>
<td>22 836</td>
<td>100</td>
<td>2 096 (9.18%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

^a Number of newborns. Not including unisex and pseudohermaphrodite newborns and newborns with records lacking birth weight data (13 records).

^b 40–42 weeks of gestation were collapsed into one category.

^c The 10th-percentile cut-off as determined from the distribution of all births for 1973–2003 (5th column).

^d Not applicable.
were expected to be born SGA, the univariate statistical power to detect an odds ratio of 1.3 or higher was at least 95%. The power was calculated using StatCalc, EpiInfo, version 3.3.2, and the multiple logistic regression analyses were carried out using SAS statistical software, version 9.1. The Regional Ethics Committee of Northern Norway, the Norwegian Data Inspectorate and the regional health administration of the Murmanskaja Oblast approved the setting up and use of KBR for epidemiological studies.

RESULTS

There were 2096 (9.2%) newborns defined as SGA, of these 47.7% were girls. Of the 1925 women delivering an SGA infant, 171 gave birth to more than one infant (8.8%). The 20,740 births in the reference group corresponded to deliveries by 15,894 women; of these 879 gave birth to an SGA infant. 51% of the deliveries were by nulliparous women. As presented in Table 2, the mothers of 10.6% of the SGA and 13.0% of the reference infants were employed during pregnancy at jobs with Ni exposure above the background level. A higher proportion of SGA infants were born by women who were known to be smokers and/or abused alcohol than in the reference group. Previous induced abortion was more prevalent among mothers in the reference group. Considering the workplace, the highest proportion of SGA infants was born by women who were not employed (11.8%). SGA distribution by maternal workplace and exposure rating categories is presented in Table 3.

The unadjusted odds ratio (OR) of an SGA birth per unit increase in exposure category was 0.79 (95% CI: 0.68–0.91) and the adjusted OR was 0.84 (0.75–0.93). The sequential removal of maternal height and previous induced abortions (models 2 and 3, respectively) from the full model (model 1) did not change the parameter estimate for Ni-exposure (Table 4). This indicated that these factors were expected to be born SGA, the univariate statistical power to detect an odds ratio of 1.3 or higher was at least 95%. The power was calculated using StatCalc, EpiInfo, version 3.3.2, and the multiple logistic regression analyses were carried out using SAS statistical software, version 9.1. The Regional Ethics Committee of Northern Norway, the Norwegian Data Inspectorate and the regional health administration of the Murmanskaja Oblast approved the setting up and use of KBR for epidemiological studies.

Table 2. Characteristics of the mothers of SGA and non-SGA infants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Non-SGA Frequency (%)</th>
<th>SGA Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of births</td>
<td>20 740</td>
<td>2 096</td>
</tr>
<tr>
<td>Low nickel exposure</td>
<td>1 526 (7.4%)</td>
<td>146 (7.0%)</td>
</tr>
<tr>
<td>High nickel exposure</td>
<td>1 167 (5.6%)</td>
<td>75 (3.6%)</td>
</tr>
<tr>
<td>Occupational solvent exposure</td>
<td>579 (2.8%)</td>
<td>83 (4.0%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>50 (0.2%)</td>
<td>4 (0.2%)</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>10 372 (50.0%)</td>
<td>1 252 (59.7%)</td>
</tr>
<tr>
<td>Previous induced abortion(s)</td>
<td>8 658 (41.8%)</td>
<td>665 (31.7%)</td>
</tr>
<tr>
<td>Age &lt; 16 years</td>
<td>23 (0.1%)</td>
<td>3 (0.1%)</td>
</tr>
<tr>
<td>Age &gt; 34 years</td>
<td>1 159 (5.6%)</td>
<td>127 (6.1%)</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>909 (4.4%)</td>
<td>91 (4.3%)</td>
</tr>
<tr>
<td>First visit to the gynaecologist before 12 weeks of pregnancy</td>
<td>9 246 (44.9%)</td>
<td>771 (37.5%)</td>
</tr>
<tr>
<td>Alcohol abuse in pregnancy</td>
<td>73 (0.4%)</td>
<td>39 (1.9%)</td>
</tr>
<tr>
<td>Tobacco smoking during pregnancy</td>
<td>204 (1.0%)</td>
<td>62 (3.0%)</td>
</tr>
<tr>
<td>Pre-gestational diabetes</td>
<td>28 (0.1%)</td>
<td>0</td>
</tr>
<tr>
<td>Mean body height [cm]</td>
<td>162 f</td>
<td>160 f</td>
</tr>
<tr>
<td>Mean calendar year of birth</td>
<td>1 986</td>
<td>1 984</td>
</tr>
<tr>
<td>Number of women</td>
<td>15 894</td>
<td>1 925</td>
</tr>
</tbody>
</table>

* 9 records lacking information. 1 record lacking information.
  156 (0.8%) records lacking information. 37 (1.8%) records lacking information.
  Data described previously [35]. 1 1256 (6.1%) records lacking information and one excluding outlier.
  169 (8.1%) records lacking information.
In the sub-analysis including only the preterm births, the OR for SGA in the exposed groups was 0.61 (0.31–1.20), while in the post-hoc analyses, the OR was 0.80 for the Ni refinery group and 0.83 when the newborns of unemployed/housekeeping mothers were excluded.

Table 4. Adjusted odds ratios (OR) and Wald confidence limits (CL) for SGA infants and nickel exposure during pregnancy.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Parameter Estimate</th>
<th>Model 1&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Model 2&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Model 3&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CL</td>
<td>OR</td>
<td>95% CL</td>
</tr>
<tr>
<td>SGA-Newborn</td>
<td>-0.18</td>
<td>0.84</td>
<td>0.75–0.93</td>
<td>0.82</td>
</tr>
</tbody>
</table>

<sup>a</sup> The probability of an SGA birth was modelled. Test for trend across three exposure categories.

<sup>b</sup> Adjusted for previous induced abortions, nulliparity, maternal solvent exposure, maternal height, maternal age > 34, maternal smoking and maternal alcohol abuse. The Hosmer-Lemeshow Goodness-of-Fit (HLGF) Test indicated a good model fit (p = 0.23). The association of predicted probabilities of spontaneous abortion and observed responses, denoted by gamma, was 0.29.

<sup>c</sup> Maternal height was removed from model 1 because of missing values (see Table 2). HLGF-test: p = 0.001, which suggested poor fit. Gamma = 0.21.

<sup>d</sup> Previous induced abortions removed from model 2 (correlated with nulliparity (Pearsons coefficient = 0.51) and 29% of the variation in induced abortion was explained by the other covariates included in the model). Better fit was achieved: HLGF-test: p = 0.79 and Gamma = 0.22.

<sup>e</sup> Pertains to model 1.
DISCUSSION

The multiple analyses confirmed the univariate association between the level of occupational Ni exposure and the odds of an SGA infant (OR = 0.8 ± 0.1). The OR is a good estimate of the relative risk when the prevalence of the outcome is less than 15%. It was advantageous that the data about most of the known relevant confounding factors were available, and that the prospective nature of recording the data registered in the KBR excluded a possibility of recall and information bias concerning these factors. If the finding of our study was distorted due to the confounding factors not adjusted for, these factors must have been independently and causally associated with SGA and with working in non-Ni-exposed jobs. The factors consistently reported in association with SGA, that were not adjusted for in our analysis, were maternal BMI and hypertension. BMI as a covariate adjusts for healthy babies who were naturally small due to genetic determinants. However, since the maternal weight registered in the KBR was measured when the woman was already pregnant, and the maternal weight gain is associated with fetal growth, we decided instead to include maternal height in the model. Despite the relatively large proportion of missing values for maternal height, no changes were observed in the parameter estimates of Ni exposure and the covariates when height was excluded from the model. Furthermore, there is no apparent reason why the non-exposed women should have been shorter than the exposed ones. Thus, the intrinsic maternal height did not appear to have confounded the results. Only four (0.2%) of the mothers of the SGA newborns were diagnosed with pre-pregnancy hypertension, and three of them were in the exposed groups. A previous SGA by the same mother does not constitute an independent risk factor and, therefore, was not considered a potential confounder.

The KBR contains information about apparent alcohol abuse in pregnancy [35], which is a rather unique feature. The covariates such as nulliparity, solvent exposure, high maternal age, smoking and alcohol abuse showed the expected positive direction of association with the outcome. Solvent exposure may have been under-adjusted, since only the jobs with a high likelihood of regular high-level exposure were denoted as exposed in the analyses [7]. With regard to previous induced abortions as a risk factor for an SGA infant, the reported findings have been inconsistent [29]. An explanation for the higher prevalence of previous induced abortion in our reference group might be that this practice was more common among healthy workers (see below) and a delivery in the following pregnancy might indicate that the pregnancy was planned.

Two congenital defects that have been reported in association with SGA are undescended testicle(s) and hypospadias [32]. In a previous investigation, we found no association between Ni exposure and these conditions [7]. We then decided not to adjust for SGA in the analysis because the two defects may precede SGA. With this argument in mind, we added the two defects as a covariate in a sub-analysis of boys in the present study. They were found to be associated with the risk of SGA (OR = 2.02 (1.13, 3.62)) and, as expected, including this factor in the model did not change the odds ratio for Ni exposure (0.83 (0.72, 0.96)). Thus, adjusting for SGA would not have changed the results of the previous study. More recently, we have shown that there was no apparent risk of a self-recognized spontaneous abortion and the assigned Ni exposure [6]. Otherwise, a tendency to miscarriage could have explained a lower risk for SGA among the Ni-exposed workers.

IUGR is a result of the factors that operate throughout pregnancy, but especially during the first two trimesters [15]. Smith et al. found that a suboptimal growth in the first trimester tends to manifest itself at birth [37]. Fetuses exposed only in the last trimester tend to be of low weight, but of normal length [15]. In the Russian Federation, as in the former Soviet Union, gravid women were obliged by law to go on a leave after 30 weeks of pregnancy. Furthermore, a pregnant woman performing a job that could be potentially hazardous to the fetus had the right to be temporarily transferred to another job. However, the transfer was not granted before a diagnosis of pregnancy had been confirmed by the gynecological polyclinic (A. Vojit, personal communication). In our study population, the mode, mean and the median gestational age at the first visit to the gynecologist was 8, 14
and 12 weeks, respectively. Thus, presumably none of the women in the assigned exposure categories who delivered after 30 weeks’ gestation were exposed throughout pregnancy, and some of them not beyond the first 2–3 months of pregnancy. Cumulative exposure is presumably not a factor of particular concern for exposures primarily to water-soluble Ni, since the half-life of appearance of Ni in urine and of its elimination from serum is about 24 hours [10]. Hence, in our study population, the duration of exposure during pregnancy was perhaps not long enough to assess the effect of Ni exposure throughout pregnancy. To shed light on the impact of exposure duration, we included a posteriori the gestational age (GA) at the first visit to the gynecologist in model 1, but it did not affect the OR of the exposure variable (0.83). The most premature newborns were delivered in the weeks around the time of obligatory pregnancy leave. Thus, we can assume that they remained in the same exposure group almost throughout their gestation. However, a post hoc analysis revealed that 0.8% of the newborns in the group with background exposure weighed 1500 g or less, compared to 0.7% and 0.3% in the low and high exposure groups, respectively.

The potential for exposure misclassification was a shortcoming of our study, like in most studies involving exposure classification based on job function. An advantage was that the information about the woman’s occupation at the time of conception was available, and that it was not subject to recall bias for it was recorded during the woman's first visit to the gynaecologist. Furthermore, compared to investigations where exposure levels are based solely on the information about occupation or workplace, this study has the strength that assessments of job-related personal exposures and biological monitoring were conducted at the production departments. Maternal urinary Ni concentration can be considered a fetal exposure index since it is proportional to her serum Ni level, and Ni is known to cross the placenta. The water-soluble Ni aerosol sub-fraction most strongly correlates with body fluid levels [3,4,38]. The major potential for misclassification concerns the occupations with periodic or possible exposure, especially in the exposure window around conception and early pregnancy. In women with occupations that involve occasional work in the exposed areas, the exposure levels can have been under- or overestimated, as the information about the actual work tasks and their duration was available only for the women who also took part in the questionnaire study mentioned above [36]. Thus, for the women in these types of jobs, we know little about staying in the exposed areas at work. Furthermore, it is likely that a number of individuals in occupations involving daily exposure may have been unexposed during a part of the period before pregnancy leave, due to holidays, sick leave, etc., which would have diluted a true effect in our study.

Misclassification of workplaces with background exposure and of corresponding job titles is not likely because this information was recorded as well during pregnancy. Thus, a misclassification of Ni exposure cannot explain the finding of our study, as the highest proportions of SGA were born to women not employed or employed outside the refinery plants (Table 3).

Although the KBR contains information about the occupation of all subjects in our study, we had a very limited insight into what exposures the occupations outside the metal refineries could involve in the past, especially 20 to 30 years ago. Any workplace exposure relevant to SGA births in the unexposed group would have influenced the result towards a no-effect finding. It is likely that some of the women who were employed outside the Ni refinery complex could have been exposed to such factors. However, the regulations on the right to be transferred from a potentially hazardous job and on the pregnancy leave were non-differential between Ni refinery workers and other workers.

Another plausible explanation for the low odds ratio found in our study is a healthy-worker effect [39]. Interestingly, the highest proportion of SGA births was observed among the women who were unemployed or homemakers (11.8%). The only workplace group with an SGA proportion above 10% was that with a low exposure in the construction, repair, supply and service departments (11.4%) (see Table 3). Since in the post-hoc sub-analyses the employer and employment did not change the direction of the calculated OR, differences due to workplace regulations and employment status do not appear likely.
Furthermore, the low OR values support the assumption that a healthy-worker bias may have occurred and might be associated with the choice of work and/or change of occupation. The relatively high wages offered in the Ni-production made these jobs attractive. By legislation, every person was to be medically examined before he/she could start a new job, and would not be given the job if his/her health condition were not good enough for the position. Every worker employed at an enterprise, such as the Ni refinery, had to have a medical examination every year [40]. Workers who have acquired a chronic disease, injury, or poor health were then likely to be transferred from occupations that were hazardous or physically demanding. Annually, 10–20 women in the refineries were advised to change their job for health reasons [7]. In such cases, a job change would mean a transfer to less hazardous/demanding jobs and departments of the refinery. However, such job changes were voluntary for non-occupational diseases, and rather unlikely for Ni-production workers, as they would bring about a decrease in their salary.

The 10th percentile cut-off point as a definition of an SGA infant has been commonly adopted [13,19,23,24]. The advantage of identifying the cases based on the distribution in the reference population, rather than on a fixed, sex-specific birth weight for gestational age, is that the percentile cut-off does not consider the effects of the potential determining factors that are, or might be, population-dependent (such as maternal height, weight, age and ethnicity). Information about the distribution of birth weight by gestational age in Russia or Russian regions is not available, except for the data from the KBR of Mončegorsk. The sex-specific distribution was used because girls tend to be overrepresented among the smallest newborns [21], as revealed by the sex-specific 10th percentile for birth weight among the term infants in our study. Nevertheless, we considered the available study population too small to determine with sufficient precision the sex-specific cut-off for births at less than 37 weeks' gestation (Table 1). Thus, boys were slightly overrepresented in the SGA births included in the analysis (54.4% vs. 52.3% in the reference group). However, pre-mature births constituted a mere 4.4% of all cases, and the misclassification of SGA would be non-differential between the exposed and non-exposed mothers.

After applying the inclusion criteria, the 10th percentile birth weight in the study population ended up being the same as the 10th-percentile cut-off in the source population in all strata except for the boys born at 40 weeks' gestation (Table 1). However, the latter was the expected result of collapsing 40–42 weeks' gestation while determining the 10th percentile for the 40 weeks' study stratum. Thus, the percentiles were probably not far off from the true distribution (third column from the left in Table 1). Furthermore, the 10th percentiles for birth weight were not higher than those reported for other populations; rather on the lower side in the 37–40 weeks' strata [41,42]. An issue of more concern in our study was the precision of the recorded birth weight measurements. The recorded birth weight tended to be rounded off to the nearest 50 or 100 g, which made the distribution less continuous. The concern involves the births around the cut-off, since some of the births that were defined as non-SGA would have been below the 10th percentile if the birth weight measurements/record had been more precise. The clustering around the nearest 50 or 100 g explains why the proportion of SGA to non-SGA infants was 9.2% instead of the expected 9.9% that a larger study population with measurements to the nearest gram would have yielded.

The gestational age based solely on the date of the last menstruation tends to overestimate pregnancy duration by 7–10 days [43]. Ultrasound has been commonly in use in Mončegorsk from the early 90s, and together with the menstrual date has been applied since then to establish the gestational age. However, the annual proportions of SGA in the 1980s were not higher than in the 1990s. The highest annual proportion was noted in 1978 (16.4%). Furthermore, the staff at the delivery ward in Mončegorsk sometimes recorded a range of weeks, for example 36–37, when the 37th week of gestation was not completed. This should have been registered in the registry as 36 weeks, but it has come to our attention that rounding up occurred routinely. Such overestimations must have led to
required a more stringent alpha level in the statistical tests [45], and hence it should not have influenced the conclusions of this study. The validity and reliability of the data were discussed previously [7,33,36].

To sum up, the study revealed some of the challenges in trying to assess the effect of a single-exposure component in pregnancy when the duration of exposure may be of concern, especially when the compound has a short half-life in the body. On the other hand, to ensure the proper development of the fetus under such circumstances, legislation that regulates job change and sick leave in pregnancy seems warranted, as practised in the Soviet Union and in the Russian Federation.

CONCLUSIONS

We found no adverse effect of maternal occupational exposure to water-soluble Ni in the first part of pregnancy on the risk of delivering a chromosomally normal SGA newborn. However, the finding does not exclude a possibility that exposure throughout pregnancy might produce such an effect.

ACKNOWLEDGEMENTS

The Kola Birth Registry and the present study were supported by the Mončegorsk Municipal Environment Fund; the Norwegian Foreign Ministry; the Norwegian Ministry of Health, through the Barents Health Programme; the Ontario Workplace Safety and Insurance Board (Canada); the Norwegian Research Council; and the Nickel Producers Environmental Research Association (USA).

The authors acknowledge the valuable assistance of Aleksandr V. Vojtov, head doctor at the Gynecological Polyclinic in Mončegorsk, Natalja P. Romanova of the Northwest Public Health Research Centre, St. Petersburg, the staff of the Kola Research Laboratory for Occupational Health in Kirovsk, the medical staff of the Kola Mining and Metallurgical Company (Russia), and of Yngvar Thomassen at Statens Arbeidsmiljøinstitutt (Norway).

a downward skewing of the gestational age-specific distributions of birth weight, and thereby to some incorrect borderline inclusions and exclusions, compared to the true 10th percentile. As mentioned above, the potential misclassification of cases due to the recording and registration procedures would be independent of exposure. However, a non-differential misclassification would dilute a true effect of exposure towards a non-adverse finding in our study.

When SGA is considered as a proxy for IUGR, the 10th percentile as a conventional approximation on a population basis tends to overestimate the incidence of IUGR [18,21], especially among term births [44], and is the source of misclassification of true IUGR cases in the group of preterm births before 32 weeks’ gestation [18]. Thus, the newborns at > 36 weeks’ gestation, who were truly below the 10th percentile but defined as non-SGA due to the reasons discussed above, most probably were not the IUGR births. Furthermore, a truly increased risk of IUGR due to Ni exposure would be attenuated towards a no-risk finding when using the conventional SGA as a proxy. However, both the odds ratio for the exposure in our study and its precision (narrow confidence interval) suggest that an elevated risk of IUGR among the newborns in our exposed groups was not likely.

Another advantage of our study design was that the mothers of both the cases and controls were residing in the same area and, therefore, had similar environmental background exposures. The population of Mončegorsk has also been highly homogenous both in the socio-economic and ethnic terms. Furthermore, since the KBR covers the whole population of the borough, and relatively few records (0.4%) were lacking the job/workplace data, the external validity of the results may be considered high. However, as presented in the Results, 23% of the mothers of children in the reference group and 9% of mothers of SGA infants contributed more than one newborn to the study, which may violate the assumption of independent outcomes. On the other hand, the inclusion criteria were non-differential in terms of exposure. According to Sharma, no sophisticated tests are available to verify this. If the assumption had been violated, it would have
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