ORIGINAL ARTICLE

Anemia in pregnancy and its association with pregnancy outcomes in the Arctic Russian town of Monchegorsk, 1973–2002

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ABSTRACT

Objectives. The purpose of this study was to determine the prevalence of anemia in pregnancy in Monchegorsk, north-west Russia, and to analyse its association with birth weight and the risk of stillbirth and preterm birth.

Study design. A registry study based on the Kola Birth Registry.

Methods. A total of 24,525 women who gave birth in Monchegorsk between 1973 and 2002 and who had data on anemia in pregnancy in the Kola Birth Registry (KBR) were included in the study. For these women, data on maternal anemia, age, occupation, marital status, parity, smoking, alcohol, gestational age, birth weight, stillbirth and year of delivery were obtained from the KBR. Linear regression was used to study the effect of maternal anemia on birth weight. Logistic regression was used to estimate the effect of anemia on the risks of stillbirth and preterm birth, with adjustment for the above-mentioned characteristics. Crude and adjusted odds ratios (OR) were calculated.

Results. The prevalence of anemia increased from 43.7% in the 1970s to 89.8% in the beginning of the 2000s. Infants born to women with anemia were 48 grams (95% CI 36, 59) heavier than infants of non-anemic women. Women with anemia in pregnancy were less likely to have stillbirths (OR=0.68; 95% CI 0.52, 0.89) and preterm births (OR=0.66; 95% CI 0.58, 0.75) after adjustment for potential confounders.

Conclusion. The prevalence of anemia in pregnant women as defined by the KBR more than doubled during the 30-year period. Positive associations with birth weight and negative associations with the risk of stillbirth and live preterm birth were observed.

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INTRODUCTION

Anemia is one of the most common nutritional disorders in the world. According to the WHO's criteria, anemia is defined as a blood hemoglobin concentration lower than 120 g/l for non-pregnant women and lower than 110 g/l for pregnant women (1).

Every fourth person in the world is anemic, and among pregnant women this percentage reaches 42% (2). The prevalence of anemia varies both between and within countries. While the prevalence of anemia in pregnancy varies between 5% and 31% in developed nations (3–5), it may be as high as 90% in developing countries (6). In Russia, 20.8% of pregnant women are anemic according to the WHO database; however, no survey data from Russia were available, so this percentage was obtained using a regression equation with a low coefficient of determination (0.32), and thus should be accepted with caution (2). Moreover, given the size of the country and large economic and social variations between the regions, the WHO estimate may poorly reflect the situation in the Russian circumpolar areas. Our search for Russian studies published in international peer-reviewed journals using PubMed with “anemia,” “prevalence,” “pregnancy” and “Russia” as keywords resulted in 0 relevant hits, reflecting the need for evidence on the prevalence of anemia during pregnancy in Russia.

 Associations between anemia in pregnancy and pregnancy outcomes have been investigated in many studies. Levy et al., for example, observed that maternal anemia was an independent risk factor for preterm delivery and low birth weight (7). In China, low hemoglobin concentration was associated with increased risk for preterm birth, small-for-gestational-age foetuses and low birth weight (8). Women with anemia had infants who were at higher risk of having a low birth weight and foetal growth restrictions than infants born to non-anemic women (9). Anemia was also associated with a higher risk of stillbirth (10,11).

Many studies, however, have shown that the most favourable pregnancy outcomes occur when the mother’s hemoglobin level is below the recommended cut-off value for anemia. Malhotra et al., for example, observed that the mean birth weight was highest in babies with maternal hemoglobin concentration between 96 and 105 g/l (12). In a large study from the UK, the highest birth weight was associated with hemoglobin values between 86 and 95 g/l (13). The same study showed that the risk of preterm delivery was lowest among women with hemoglobin levels between 96 and 105 g/l. The same hemoglobin level was associated with the lowest risk of foetal death in the U.S. National Collaborative Perinatal Project (14).

Heterogeneity in the results may be partly explained by the methodological differences between studies. The most commonly used WHO definition of anemia is based only on hemoglobin level, which in uncomplicated pregnancy without iron supplements falls steeply from the time of conception until 20 weeks, due to differential increases in plasma volume and red cell mass. The hemoglobin level then remains constant until 30 weeks and rises slightly before birth (15). This normal process distorts the usual relationship between hemoglobin and iron deficiency in women who are not pregnant. It complicates comparisons between the studies because measurements were taken at different stages of pregnancy. This influenced both the prevalence estimates of anemia and associations with pregnancy outcomes because
of differences in the foetal growth at different stages of pregnancy (16). Moreover, anemia may be the result of not only insufficient dietary iron but also of infections, chronic inflammation or folic acid and vitamin B12 deficiencies, which themselves may be associated with pregnancy outcomes.

The current consensus is that the primary cause of anemia in pregnancy is plasma volume expansion, which is not associated with adverse pregnancy outcomes in developed countries, where undernutrition, iron and folate deficiencies among non-pregnant women are rare (16). Russian women, however, are at high risk of iron deficiency (17). Russia’s political and economic transition during the 1990s was characterized by the impoverishment of a major part of the population. The proportion of preterm births in northern Russia during this period increased to more than 5%, and the average birth weight decreased to 3.3 kg (18).

The crisis of the 1990s was followed by a considerable economic growth, which began in 1999 and was characterized by an increase in Russia’s GDP by an average of 6–7% every year. Given that the relationship between unfavourable social circumstances and anemia is well established (19,20), the prevalence of anemia in pregnancy might have varied across periods of recent Russian history. Inconsistency in the findings from previous research on the association between anemia and pregnancy outcomes warrants further study, particularly in areas with a mean birth weight below 3.3 kg (16), which, combined with almost non-existent information on anemia in pregnancy in Russia, makes northern Russia an optimal setting for research.

This study aims to investigate the prevalence of anemia in pregnant women in the town of Monchegorsk, north-west Russia, from 1973 through 2002, and to analyse associations between maternal sociodemographic factors and anemia in pregnancy, as well as associations between maternal anemia and birth weight, stillbirth and preterm birth.

MATERIAL AND METHODS

Setting
Monchegorsk is a small town in the Murmansk oblast situated on the Kola peninsula, north of the Arctic Circle. It is an important centre of nickel and copper production and is one of the most polluted towns in Russia (21). According to the all-Russian Census of 1989, the size of the population in Monchegorsk was 68.6 thousand. Since then, the population has been steadily decreasing, dropping to 52.2 thousand in 2002, which was the last year of the study period.

Study design and sample
This is a registry-based study. All data were obtained from the Kola Birth Registry (KBR). The KBR was initiated in 1997 after the publication of the Chashchin et al. paper, which showed a twofold increase in spontaneous abortions and a threefold increase in congenital malformation among infants whose mothers worked at the nickel refineries in Monchegorsk (22). The KBR was originally designed to study the association between occupational exposures and reproductive health. Data on all births from 1973 were obtained from general medical journals, the Monchegorsk hospital gynecology journals and delivery department journals, and were retrospectively entered into a computerized database. The KBR is an extensive source of information about mothers, infants and the factors that may
influence pregnancy outcomes. The validity of the medical documentation from these sources was recognized as sufficient for epidemiological investigations (23–25). The registry contains data on 25,156 births from the 22nd gestational week in the town of Monchegorsk from 1973 through 2002. All 24,712 women with available data on anemia in pregnancy were included in the calculation of the prevalence of anemia. Women with multiple pregnancies (n=172) or with missing data on age (n=3), gestational age (n=6) and birth weight (n=6) were excluded from other analyses (Fig. 1).

**Variables**

Maternal anemia is registered in the KBR as a dichotomous variable and is defined as hemoglobin concentration below 120 g/l in any trimester of pregnancy. There are no data on the type of anemia in the KBR, so it is assumed that the overwhelming majority of cases are iron deficiency anemia. The prevalence of anemia over time was presented in 5-year periods, except the first and the last ones, which logically correspond to periods of late Soviet and Russian history: 1973–1979, 1980–1984, 1985–1989, 1990–1994, 1995–1999 and 2000–2002. Maternal age was divided into 5 groups: <20 years, 20–24 years, 25–29 years, 30–34 years and 35 years or older. Marital status was recorded as either married or unmarried, based on the official registration. Three groups were used for parity: 1st birth, 2nd birth and ≥3rd birth. By occupation, all women were divided into 6 groups, using modified categories from the International Standard Classification of Occupations (ISCO): (1) managers, professionals and technicians (ISCO groups 1–3); (2) clerks and service employees (ISCO groups 4–5); (3) skilled workers (ISCO groups 6–8); (4) elementary occupations (ISCO group 9); (5) housewives, unemployed, students; and (6) unknown. Tobacco smoking and alcohol consumption were recorded as dichotomous variables. Stillbirth and preterm birth were documented as dichotomous variables. Preterm birth was defined as gestational age below 37 completed weeks. Stillbirth was defined according to the 4 signs of life used in the standard WHO definition, which was adopted by Russia in 1993 (26).

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**Figure 1. Sampling frame.**
Before 1993, only heartbeat, breathing and/or screaming were counted as a sign of life; stillborns with a gestational age below 28 weeks were classified as abortions, and so were live born infants who did not survive 7 days (24). Birth weight measured in grams was used as continuous variable.

Statistical analysis

Bivariate analyses of continuous and nominal variables were performed using Student’s unpaired t-tests and Pearson’s chi-squared tests, respectively. Associations between anemia and maternal biological and sociodemographic characteristics, as well as the effects of anemia on stillbirth and preterm birth were studied using multiple logistic regression analysis. Given that the studied pregnancy outcomes were rare, odds ratios (OR) can be considered adequate estimates of relative risks. Independent effect of maternal anemia on birth weight was studied by multiple linear regression analysis, with adjustment for potential confounders. Additional adjustment was made for gestational age to separate the effect of anemia on infant growth from its effect on preterm delivery. For both ORs and regression coefficients, 95% confidence intervals (CI) were calculated. In order to separate the effects of anemia on stillbirth from its effects on preterm delivery and foetal growth, stillbirths were excluded from the analyses of preterm birth and birth weight. However, in order to make the study comparable with studies which did not make this exclusion (for example, 13), we repeated the analyses and included stillbirths. The reference group for each variable was selected in accordance with what was considered to be the most favourable group. All statistical analyses were performed using SPSS version 15.0 for Windows.

The study was approved by the Ethical Committee of Northern State Medical University (Arkhangelsk, Russia) in March 2009.

RESULTS

The prevalence of maternal anemia increased from 43.7% in the 1970s to 89.8% between 2000 and 2002. The most notable increase occurred during the 1990s (Fig. 2).

Figure 2. Prevalence of maternal anemia registered in the KBR from 1973 through 2002, by time periods.
The characteristics of the women included in the analysis and the overall prevalence of anemia across all groups are presented in Table 1. The age of the mothers ranged from 13 to 46 years. The proportion of teenage mothers over the study period was 11.4%. The overall proportion of women 35 years or older was 5.5%. Only 3.5% were housewives, unemployed or students. Occupational status was unknown for 11.6% of the women. A very small proportion of women consumed alcohol or smoked during pregnancy (0.4% and 0.9%, respectively). More than half of the women (51.3%) were primiparae. At the time of delivery, 86.3% of the women were married. The highest prevalence of anemia was observed among unmarried and unemployed women, housewives, students and women with unknown occupation (Table 1).

Table 1. Sample characteristics and the prevalence of anemia with 95% confidence intervals (CIs).

| Age | n | % | n of women with anemia | Prevalence, % | 95% CI |
|-----|---|---|------------------------|--------------|--------|
| < 20 | 2797 | 11.4 | 1599 | 57.2 | 55.3-59.0 |
| 20-24 | 9705 | 39.6 | 5405 | 55.7 | 54.7-56.7 |
| 25-29 | 7214 | 29.4 | 4129 | 57.2 | 56.1-58.4 |
| 30-34 | 3449 | 14.1 | 1996 | 57.9 | 56.2-59.5 |
| ≥ 35 | 1360 | 5.5 | 791 | 58.2 | 55.5-60.8 |

| Occupation | n | % | n of women with anemia | Prevalence, % | 95% CI |
|------------|---|---|------------------------|--------------|--------|
| Managers, professionals, technicians | 5488 | 22.4 | 3139 | 57.2 | 55.9-58.5 |
| Clerks, service employees | 6705 | 27.3 | 3557 | 53.0 | 51.9-54.2 |
| Skilled workers | 5849 | 23.8 | 3232 | 55.3 | 54.0-56.5 |
| Elementary occupations | 2782 | 11.3 | 1529 | 55.0 | 53.1-56.8 |
| Housewives, unemployed, students | 863 | 3.5 | 602 | 69.8 | 66.6-72.7 |
| Unknown | 2838 | 11.6 | 1861 | 65.6 | 63.8-67.3 |

| Marital status | n | % | n of women with anemia | Prevalence, % | 95% CI |
|----------------|---|---|------------------------|--------------|--------|
| Married | 21172 | 86.3 | 11828 | 55.9 | 55.2-56.5 |
| Unmarried | 3353 | 13.7 | 2092 | 62.4 | 60.7-64.0 |

| Parity | n | % | n of women with anemia | Prevalence, % | 95% CI |
|--------|---|---|------------------------|--------------|--------|
| 1st birth | 12573 | 51.3 | 7083 | 56.3 | 55.5-57.2 |
| 2nd birth | 9176 | 37.4 | 5263 | 57.4 | 56.3-58.4 |
| ≥ 3rd birth | 2776 | 11.3 | 1574 | 56.7 | 54.9-58.5 |

| Tobacco smoking | n | % | n of women with anemia | Prevalence, % | 95% CI |
|-----------------|---|---|------------------------|--------------|--------|
| No | 24303 | 99.1 | 13788 | 56.7 | 56.1-57.4 |
| Yes | 222 | 0.9 | 132 | 59.5 | 52.9-65.7 |

| Alcohol consumption | n | % | n of women with anemia | Prevalence, % | 95% CI |
|---------------------|---|---|------------------------|--------------|--------|
| No | 24418 | 99.6 | 13873 | 56.8 | 56.2-57.4 |
| Yes | 107 | 0.4 | 47 | 43.9 | 34.9-53.4 |

| Time periods | n | % | n of women with anemia | Prevalence, % | 95% CI |
|--------------|---|---|------------------------|--------------|--------|
| 1973-1979 | 5929 | 24.2 | 2579 | 43.5 | 42.2-44.8 |
| 1980-1984 | 5389 | 22.0 | 2379 | 44.1 | 42.8-45.5 |
| 1985-1989 | 5531 | 22.6 | 3089 | 55.8 | 54.5-57.2 |
| 1990-1994 | 3379 | 13.8 | 2142 | 63.4 | 61.8-65.0 |
| 1995-1999 | 2618 | 10.7 | 2224 | 85.0 | 83.6-86.3 |
| 2000-2002 | 1679 | 6.8 | 1507 | 89.8 | 88.3-91.2 |
| Total | 24525 | 100.0 | 13920 | 56.8 | 56.1-57.4 |

*Totals may not be equal to 100.0% due to rounding.
*Calculated using Wald method.
In crude analysis, women aged 25 years or older, women who were housewives or students, who were unemployed, unmarried or whose occupation was unknown were more likely to be anemic in pregnancy than the reference groups. Women who drank alcohol during pregnancy were less likely to have anemia. There was a clear increase in the odds of anemia over time. After adjustment for all studied variables, women who smoked were less likely to have anemia, as well as women who worked as clerks and service employees. Women who gave birth to a second baby were more likely to have anemia compared to primiparous women. The association between time periods and anemia remained strong after adjustment for other variables (Table II).

### Table II. Results of multiple logistic regression of anemia by maternal characteristics and time periods.

| Characteristic                        | Crude OR | 95% CI     | Adjusted OR* | 95% CI     |
|---------------------------------------|----------|------------|--------------|------------|
| **Age (years)**                       |          |            |              |            |
| < 20                                  | 1.06     | 0.98-1.16  | 0.93         | 0.84-1.02  |
| 20-24                                 | 1.0      | Reference  | 1.0          | Reference  |
| 25-29                                 | 1.07     | 1.00-1.13  | 1.06         | 0.98-1.13  |
| 30-34                                 | 1.10     | 1.01-1.18  | 1.02         | 0.93-1.12  |
| 35+                                   | 1.10     | 0.99-1.24  | 1.02         | 0.89-1.16  |
| **Occupation**                        |          |            |              |            |
| Managers, professionals, technicians  | 1.0      | Reference  | 1.0          | Reference  |
| Clerks, service employees             | 0.85     | 0.79-0.91  | 0.87         | 0.80-0.94  |
| Skilled workers                       | 0.92     | 0.86-0.99  | 1.08         | 0.99-1.17  |
| Elementary occupations                | 0.91     | 0.83-1.00  | 0.94         | 0.85-1.04  |
| Housewives, unemployed, students      | 1.73     | 1.48-2.02  | 0.95         | 0.79-1.14  |
| Unknown                               | 1.43     | 1.30-1.57  | 0.90         | 0.80-1.00  |
| **Marital status**                    |          |            |              |            |
| Married                               | 1.0      | Reference  | 1.0          | Reference  |
| Unmarried                             | 1.31     | 1.22-1.41  | 0.95         | 0.87-1.03  |
| **Parity**                            |          |            |              |            |
| 1st birth                             | 1.0      | Reference  | 1.0          | Reference  |
| 2nd birth                             | 1.04     | 0.99-1.10  | 1.11         | 1.04-1.19  |
| ≥ 3rd birth                           | 1.02     | 0.93-1.10  | 1.05         | 0.95-1.17  |
| **Tobacco smoking**                   |          |            |              |            |
| No                                    | 1.0      | Reference  | 1.0          | Reference  |
| Yes                                   | 1.12     | 0.86-1.46  | 0.67         | 0.49-0.93  |
| **Alcohol consumption**               |          |            |              |            |
| No                                    | 1.0      | Reference  | 1.0          | Reference  |
| Yes                                   | 0.60     | 0.41-0.87  | 0.82         | 0.53-1.27  |
| **Time periods**                      |          |            |              |            |
| 1973-1979                             | 1.0      | Reference  | 1.0          | Reference  |
| 1980-1984                             | 1.03     | 0.95-1.11  | 1.02         | 0.94-1.09  |
| 1985-1989                             | 1.64     | 1.53-1.77  | 1.62         | 1.50-1.74  |
| 1990-1994                             | 2.25     | 2.06-2.45  | 2.31         | 2.12-2.52  |
| 1995-1999                             | 7.33     | 6.51-8.26  | 7.83         | 6.92-8.85  |
| 2000-2002                             | 11.38    | 9.64-13.44 | 12.17        | 10.26-14.44|

*Adjusted for the variables in the table.
Stillbirths and live preterm births constituted 1.0% and 4.6%, respectively, of all births from available data on anemia registered in the KBR. Women with anemia were less likely to have either stillbirths (0.8% vs. 1.2%, p=0.001) or live preterm births (3.7% vs. 5.7%, p<0.001). Moreover, their babies were on average 82 g heavier than babies born to non-anemic mothers (p<0.001).

In multivariable analysis, women who had anemia during pregnancy had about a 50% lower risk of stillbirth and live preterm birth compared to non-anemic women. Adjustment for other variables only marginally changed the estimates. In contrast, the effect of maternal anemia on birth weight became much less pronounced after an adjustment was made for gestational age (Table III). Repeating our analyses without the exclusion of stillbirths yielded similar results for both preterm birth (OR=0.62, 95% CI 0.55, 0.70) and birth weight (49 g, 95% CI 37, 61).

**DISCUSSION**

In this large registry-based study we observed an increase in the prevalence of anemia in pregnancy in Monchegorsk from 43.7% in the 1970s to 89.8% at the beginning of the 2000s. Anemia was more likely to be recorded for women having their second delivery and less likely among women employed as clerks and service employees. Anemia was less likely among smokers as well. The results also suggest that maternal anemia as defined in the registry is inversely associated with the risk of stillbirth and live preterm birth, and is positively associated with foetal growth.

The main strength of this study is the use of the registry, which contains the data on nearly all births in Monchegorsk during a 30-year period. This minimizes the risk of random error and selection bias. Moreover, the large size of the registry and the small amount of missing data for most variables used in the study allow even small effects of the studied characteristics on anemia and small effects of the latter on pregnancy outcomes to be estimated. At the same time, the validity of the study depends on the quality of the data available from the KBR, and therefore the results should be interpreted cautiously, taking into account the limitations of the registry.

The data on maternal anemia were missing for 444 women (1.8%). Although this proportion is low, the women with missing data had a much higher proportion of adverse

| Table III. Effect of anemia in pregnancy on stillbirth, preterm birth and birth weight. |
|-----------------------------------------------|
| Stillbirth | Preterm birth | Birth weight difference, g<sup>a,b</sup> |
| Crude OR (95% CI) | Adjusted OR (95% CI) | Crude OR (95% CI) | Adjusted OR (95% CI) | Crude | Adjusted |
| Anemia | | | | (95% CI) | (95% CI) |
| No | 1.0 | 1.0 | 1.0 | 1.0 | 0 | 0 |
| Yes | 0.65 (0.50-0.84) | 0.68 (0.52-0.89) | 0.64 (0.57-0.72) | 0.66 (0.58-0.75) | 82 (68-95) | 48 (36-59) |

<sup>a</sup>Stillbirths excluded.

<sup>b</sup>Additionally adjusted for gestational age.
pregnancy outcomes: stillbirths and live preterm births constituted 5.4% and 22.4%, respectively, compared with 1.0% and 4.6% among women with known data on anemia (p<0.001 for both comparisons). Infants born to these women were on average 455 g lighter (p<0.001) than those born to women with available data. Women with no data on anemia were more likely to be registered as smokers (4.7% vs. 0.9%, p<0.001) and alcohol drinkers (4.5% vs. 0.4%, p<0.001). Given that the prevalence of smoking as well as alcohol consumption in the KBR are greatly underestimated, that is, only heavy smokers and alcohol abusers are registered (25,27), the women with missing data on anemia may represent the most disadvantaged group, and selection bias cannot be excluded.

Anemia in the KBR is registered based on a hemoglobin concentration below 120 g/l as a dichotomous variable. This cut-off value is 10 g/l higher than the level recommended by the WHO (1). Moreover, the KBR does not provide information about the point during pregnancy when maternal anemia was diagnosed. Given that even in uncomplicated pregnancy, hemoglobin concentration falls during the first 20 weeks due to a greater increase in plasma volume compared to red blood cell mass, it is questionable whether this condition can be defined as anemia, because the total red cell mass and total hemoglobin actually increase during pregnancy (13,28,29). Although the hemoglobin level during the first trimester is a good predictor of iron deficient anemia, which can be associated with adverse pregnancy outcomes (30), it is difficult to separate iron deficiency from the natural decrease in hemoglobin concentration caused by plasma volume expansion later in pregnancy. Therefore, additional measurements can be taken to diagnose iron deficiency, such as serum ferritin and mean corpuscular volume (MCV), but their predictive power falls if the prevalence of anemia is low (30,31). Moreover, serum ferritin is an acute phase reactant, and can produce spurious results in women with inflammation. The optimal predictor of maternal anemia seems to be MCV (32). It has also been suggested that in situations when MCV is ≥85 femtoliters, the level of hemoglobin commonly accepted as an indicator of anemia should be considered optimal (28). Thus, the main limitation of this study is the diagnosis of maternal anemia based only on hemoglobin concentration, without specifying when measurements were taken. A very liberal cut-off point of 120 g/l used in the KBR led to an overestimation of the prevalence of anemia in the population. As a result, many women were classified as anemic when it was likely that they were not.

This may at least partly explain why the prevalence of anemia in Monchegorsk greatly exceeds the corresponding data from Germany (3), Belgium (4) and Denmark (5), and why it is close to what has been reported from developing countries (6). In spite of the overestimation due to a more liberal definition of anemia, the same definition had been used for all data; therefore, the increase in the prevalence of anemia during the 30-year period is likely an accurate observation. The most pronounced increase occurred in the 1990s after the collapse of the Soviet Union, and might be associated with impoverishment of the majority of the population. At
the same time, the prevalence of anemia continued to increase during the early 2000s, even after the economic situation began to improve. This may lead to speculation that general economic indicators poorly reflect individual well-being, but may also suggest that other factors, such as improvement in diagnostics or registration over time might have contributed to the observed pattern.

Nutrition status plays a key role in the development of anemia (30). We observed a higher prevalence of anemia among unemployed and unmarried women, along with students and housewives, that is, women from the most economically disadvantaged categories. However, these associations did not remain significant after adjustments for other variables were made, suggesting that the population of Monchegorsk was rather homogenous by socio-economic standards, which is possible given that the majority of the working-age population is employed in the same industry.

Women who were having their second birth had slightly higher odds of being registered as anemic. One can speculate that a short time period between first and second pregnancies may be a partial explanation for this finding, but the information available from the KBR does not permit us to test this hypothesis. Smoking women were 50% less likely to be recorded as having anemia compared to non-smoking women. Smokers have a higher hemoglobin concentration than non-smokers, and the difference increases with the greater the number of cigarettes smoked due to the increased level of carbon monoxide in the smoker's bloodstream (33). Given that the prevalence of smoking, alcohol and drugs are greatly underestimated (25,27) in the study population, the observed 50% greater likelihood of anemia among non-smokers is plausible.

Our findings are in line with several studies which have shown that maternal anemia is inversely associated with a lower risk of stillbirth (34) and preterm birth, and that it is positively associated with birth weight (13,35). However, a number of studies have revealed an increased risk of low birth weight (7–9,12,36), preterm birth (7,8,36) and stillbirth (10,11) associated with anemia in pregnancy. The results of past studies greatly depend on the definition of anemia, the time when hemoglobin was measured and potential confounders used for adjustment. Several large studies have reported a U-shaped association between hemoglobin concentration and adverse pregnancy outcomes, with the lowest prevalence of low birth weight and preterm birth in the group of women who had the lowest hemoglobin values in pregnancy, between 95 and 105 g/l; values at these levels can be classified as anemia according to the WHO definition (12,13,37).

The mechanisms behind the effects of maternal anemia on adverse pregnancy outcomes are still unclear. Low maternal hemoglobin and iron deficiency may induce foetal hypoxia, maternal and foetal stress or an increase in the synthesis of the corticotrophin-releasing hormone (CRH), which in turn is associated with preterm labour (29). Moreover, iron deficiency may increase the risk of maternal infection, which is the main risk factor for preterm birth. Maternal anemia may also increase foetal cortisol production, which is known as an inhibitor of foetal growth (29,38).
On the other hand, high levels of hemoglobin have been consistently shown to be a risk factor for adverse pregnancy outcomes. Insufficient physiological expansion of the plasma volume during pregnancy which leads to higher levels of hemoglobin has been shown to be an independent risk factor for low birth weight and preterm birth (39). This can caused by increased blood viscosity, insufficient placental blood flow and increased risk of thromboembolism in placental blood vessels, resulting in intrauterine growth restriction or preterm birth (28). Iron supplementation in non-anemic women may actually increase the risk of poor pregnancy outcomes, further supporting evidence of the deleterious effects of high hemoglobin levels on pregnancy outcomes (32,40). Moreover, increased levels of hemoglobin in pregnancy are associated with an increase in the incidence of hypertension and pre-eclampsia, which are known to be associated with both foetal growth restriction and preterm delivery (28). Other indicators, such as high levels of ferritin during the third trimester of pregnancy have also been shown to increase the risk of preterm delivery (32).

It is likely that the anemic group in the KBR was a heterogeneous group, which consisted of some truly anemic women. However, the majority of the group was made up of women with normal hemoglobin levels by the WHO definition (>110 g/l) and women with hemoglobin levels above 95 g/l, that is, women with the lowest risk of adverse pregnancy outcomes (13,28). On the other hand, our non-anemic reference group consisted of women with a hemoglobin level of 120 g/l or higher, the level which has been shown to considerably increase the incidence of maternal hypertension and pre-eclampsia (41). High levels of hemoglobin may also increase the risk of preterm birth and low birth weight, even in the absence of pregnancy-induced hypertension or pre-eclampsia (38).

Combined with the evidence from other studies outlining the deleterious effect of high hemoglobin values on pregnancy outcomes, one may speculate that the associations observed in this study may be largely attributed to the definition used in the KBR. This also underlines the danger for other studies based on the same database which consider maternal anemia as a confounder. Adjustment for the invalid variable may introduce bias instead of controlling for it.

We suggest avoiding dichotomization of women into anemic and non-anemic by the criteria used in the KBR both in research and practice. In future studies, we recommend using hemoglobin concentration in each trimester of pregnancy as a continuous variable. Given that even relatively low levels of hemoglobin do not necessarily indicate anemia, other indications such MCV should be considered.

Conclusions

Our findings suggest that in Monchegorsk, the prevalence of anemia in pregnancy as registered in the KBR more than doubled between 1973 and 2002, from levels which were already high. However, maternal anemia is associated with lower risk of stillbirth and live preterm birth, and is positively associated with foetal growth. These findings should be interpreted cautiously, given the unconventional definition of anemia used by the KBR. Further studies should avoid dichotomization of anemia, indicate the period of pregnancy during which measurements were taken and use hemoglobin as a continuous variable, preferably in combination with MCV.
Anemia and pregnancy outcomes in Monchegorsk, Russia

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