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Maternal and neonatal outcomes of antenatal anemia in a Scottish population: a retrospective cohort study

Running headline: Maternal and neonatal outcomes of antenatal anemia

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Abstract

Introduction. Antenatal anemia is a major public health problem in the UK, yet there is limited high quality evidence for associated poor clinical outcomes. The objectives of this study were to estimate the incidence and clinical outcomes of antenatal anemia in a Scottish population.

Material and methods. A retrospective cohort study of 80 422 singleton pregnancies was conducted using data from the Aberdeen Maternal and Neonatal Databank between 1995 and 2012. Antenatal anemia was defined as haemoglobin $\leq 10\text{g/dl}$ during pregnancy. Incidence was calculated with 95% confidence intervals (CI) and compared over time using a chi-squared test for trend. Multivariable logistic regression was used to adjust for confounding variables. Results are presented as adjusted odds ratios (aORs) with 95% CI. *Results.* The overall incidence of antenatal anemia was 9.3 cases/100 singleton pregnancies (95%CI 9.1-9.5), decreasing from 16.9/100 to 4.1/100 singleton pregnancies between 1995 and 2012 ($p < 0.001$). Maternal anemia was associated with antepartum hemorrhage (aOR 1.26, 95%CI 1.17-1.36), postpartum infection (aOR 1.89, 95%CI 1.39-2.57), transfusion (aOR 1.87, 95%CI 1.65-2.13) and stillbirth (aOR 1.42, 95%CI 1.04-1.94), reduced odds of postpartum hemorrhage (aOR 0.92, 95%CI 0.86-0.98) and low birthweight (aOR 0.77, 95%CI 0.69 – 0.86). No other outcomes were statistically significant. *Conclusions.* This study shows the incidence of antenatal anemia is decreasing steadily within this Scottish population. However, given that anemia is a readily correctable risk factor for major causes of morbidity and mortality in the UK, further work is required to investigate appropriate preventive measures.

Key words

Anemia, pregnancy outcome, neonatal outcome, haemorrhage, postpartum infection

Abbreviations

AMND, Aberdeen Maternal and Neonatal Databank;

aOR, adjusted odds ratio;

APH, antepartum hemorrhage;

BMI, body mass index;
CI, confidence interval;
ICD-9, International Classification of Diseases 9;
MOH, major obstetric hemorrhage;
NICE National Institute for Health and Care Excellence
PPH, postpartum hemorrhage,

Key Message

Although the incidence of antenatal anemia is decreasing, there is evidence of poor outcomes like postpartum infection and stillbirth. Given anemia is an easily correctable risk factor; further work is required to generate robust evidence to inform clinical practice.

Introduction

Globally, the prevalence of anemia is 24.8% affecting 1.62 billion people (1). The most affected groups are women and children in Africa and South East Asia. The global prevalence in pregnancy in 2011 was estimated to be 38%. Whilst this has decreased from 43% in 1995, this still constitutes a significant public health problem in both low and high-income settings. The prevalence of maternal anemia in high-income countries was estimated to be 25% in 2011 (2).

According to UK guidelines (3), anemia in pregnancy is defined as hemoglobin <11g/dl in the first trimester, hemoglobin <10.5g/dl in the second and third trimester and hemoglobin <10g/dl in the postpartum period. In the UK, the absolute number of pregnant individuals with anemia at any one time is estimated to be 100,000(1). Recent observational data from a UK multicentre study of 2103 women estimated the prevalence of anemia to be higher at 24.4% (4). So, despite being simple to treat, the prevalence of anemia in pregnant women probably remains high in the UK.

There is evidence that anemia is a risk factor for adverse maternal and neonatal clinical outcomes such as low birthweight (5). A recent study of the maternal and neonatal outcomes of iron deficiency anaemia in Israel demonstrated an increased risk of Cesarean section, transfusion and a lower Apgar score (6). Despite this, prevalence of anemia remains high and there is a surprising lack of consistent high quality evidence with regards to other clinical

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outcomes, particularly maternal morbidities in high income settings similar to the UK. These shortcomings are problematic and have implications not only for compliance and acceptability of treatment, but also to define suitable public health interventions.

The Aberdeen Maternity and Neonatal Databank (AMND) has collected information on all deliveries in the Grampian region of Scotland for more than 60 years. High quality data on maternal hemoglobin and maternal and neonatal outcomes are available, thus making this an ideal resource to investigate further the outcomes of antenatal anemia. The aims of this current study were to estimate the incidence of antenatal anemia in the Grampian region of Scotland between 1995 and 2012, identify any trend over time and describe maternal and neonatal outcomes of antenatal anemia in this population.

Material and methods

This was a retrospective cohort study using data on singleton pregnancies recorded in the AMND between 1995 and 2012. The AMND Steering Committee approved the research protocol before data extraction took place. An access confirmation letter was received on 9th May 2014 with the reference SB/AMND14. Ethical approval was not required for secondary analysis of these anonymised data under the terms of operation of the AMND. The NHS Health Research Authority decision tool was used to verify that NHS research ethics committee approval was not required (7).

AMND data were collected from the University of Aberdeen Maternity Hospital, which is a tertiary maternity hospital for the NHS Grampian region and the only maternity unit for the city of Aberdeen. It is the only hospital in the area serving a defined geographical population with approximately 5000 births per year. Data were collected from the first antenatal visit through to the postpartum period. The methods used for data entry, coding and internal validation of the AMND have been described previously (8-10). Coders that have undergone training from clinicians extract pregnancy related events and clinical outcomes from medical records using International Classification of Diseases 9 (ICD-9) codes. Data entry, storage and retrieval are subject to regular internal validation checks by comparison of the database with original patient medical records. Clinical epidemiologists carry out verification. The dataset has a low inconsistency rate of 0.014%, which has been cited in other studies using this database (9).

Within the databank, antenatal anemia has been defined since 1995 as hemoglobin of $\leq 10\text{g/dl}$ at booking and information on maternal anaemia was available coded as a categorical variable on this basis. This definition was based on the consensus of the AMND clinical advisory group. The exposed cohort was defined as those with hemoglobin $\leq 10\text{g/dl}$ as per AMND definition and will be referred to as those with antenatal anemia throughout this article. Antenatal anemia was identified at any time prior to birth.

Smoking status and ethnicity were defined based on maternal self-report at first booking. The Scottish Index of Multiple Deprivation (SIMD) was used as a measure of socioeconomic status and the WHO classification of obesity was used to define body mass index (BMI) (12). Diabetes in this study was defined as women with pre-existing diabetes and did not include gestational diabetes.

Pre-specified maternal outcomes investigated were as follows: Gestational hypertension, defined as new arterial hypertension in a pregnant woman after 20 weeks gestation without the presence of protein in the urine (ICD 9 code 642.3 and 642.4); postpartum infection (ICD 9 codes 670.0-679.4 [major puerperal infection], 672.0-672.04 [pyrexia of unknown origin] and 675.0-675.94 [infection of the breast and nipple]); pre-eclampsia, defined as the presence of gestational hypertension and more than 300mg or urinary protein in a 24 hour collection (ICD 9 codes 642.5 and 642.8); eclampsia, defined clinically as generalised seizures in a pregnancy with severe hypertension and proteinuria (ICD 9 code 642.6); antepartum hemorrhage (APH)(ICD 9 641.9); postpartum hemorrhage (PPH) defined as blood loss at delivery $\geq 500\text{ml}$ (11), and derived from the reported clinical estimate of blood loss at delivery; major obstetric hemorrhage (MOH) derived similarly based on the definition of blood loss at delivery $\geq 2000\text{ml}$ (11); maternal death and transfusion.

Pre-specified neonatal outcomes investigated were as follows: stillbirth; neonatal unit admission; preterm delivery defined as gestational age at birth of less than 37 weeks; low birthweight defined as a birthweight less than 2500g; very low birthweight defined as a birthweight less than 1500g and early neonatal death

Data exclusions were applied to remove abortions, multiple pregnancies and pregnancies occurring after 2012. Multiple pregnancies were excluded for ease of analysis and interpretation as other UK cohort studies have similarly done so (13) on the basis that the

incidence of anemia and other outcomes such as delivery blood loss may be higher due to the proportionately higher iron requirements in multiple pregnancies (14).

Statistical analysis

The incidence of anemia and clinical outcomes were calculated as rates with 95% confidence intervals. The trend in the incidence of anemia was examined using the chi-squared test for trend. Continuous variables were summarised as mean (where normally distributed) and median (where the distribution was not normal). Categorical variables were summarised as frequencies and percentages. Univariable logistic regression analysis was used to compare the outcomes between exposed and unexposed women. These results are presented as odds ratios with 95% confidence intervals. Multivariable logistic regression was used to adjust each outcome for known confounding variables. Factors with pre-existing evidence from the literature suggesting they were potential confounders were included in the main model. These included age, parity, smoking status, ethnicity, socioeconomic status and BMI. They were all included in the analysis as categorical terms as there was pre-existing evidence of non-linear association with the continuous categorical variables. Co-morbidities which were hypothesised to be possible confounders were incorporated into the model in a forward stepwise manner in ascending order of the odds ratio. Co-morbidities which statistically significantly affected the fit of the model ($p < 0.05$) on likelihood ratio testing were included. Those that did not contribute significantly to the fit of the model were excluded. The final model was adjusted for age, parity, smoking status, ethnicity, socioeconomic status, BMI and chronic kidney disease. Data completeness was assessed by summary and descriptive statistics. All statistical analyses were carried out using STATA 13, 2013: Stata Statistical Software: Release 13 (StataCorp., College Station, TX, USA).

Results

The database contained information on 82 545 pregnancies between 1995 and 2012. Exclusions were applied to abortions ($n=205$ pregnancies), multiple pregnancies ($n=1541$) and pregnancies after 2012 ($n=377$). The final total study population included 80 422 pregnancies (Figure 1). Of these 7475 pregnancies had antenatal anemia and 72 947 were uncomplicated by this over the 18-year period.

The overall incidence of anemia in the study population was 9.3/100 singleton pregnancies (95% confidence interval (CI) 9.1 to 9.5). The incidence of anemia decreased from the highest recorded incidence of 16.9/100 singleton pregnancies in 1996 to 4.1/100 singleton pregnancies

in 2012 ($p < 0.001$) (Figure 2). The median gestation at the time of measurement of booking hemoglobin was nine weeks (interquartile range 8-12 weeks; mean 10.6, SD 5.31 weeks). Within the exposed group, antenatal anemia was identified in the first trimester in 4854 pregnancies (65%), the second trimester in 1911 pregnancies (26%) and in the 3rd trimester in 317 pregnancies (4%). The gestation at the time of booking hemoglobin measurement was missing in 393 pregnancies (5%).

Maternal demographic and medical characteristics are summarised in Table 1. There was a low proportion of missing data ($< 3\%$) for ethnicity, smoking and deprivation. BMI data was missing in approximately 6% of cases in both women with and without antenatal anemia. The women with antenatal anemia were slightly younger, of higher parity and more affluent than those without antenatal anemia. Maternal co-morbidities that were hypothesised to affect both exposure and outcome were assessed in each group and are summarised in Table 2. Diabetes was the most common co-morbid condition followed by chronic kidney disease. All other co-morbid conditions were rare in both women with and without antenatal anemia. There was a significantly higher proportion of women with chronic kidney disease in the exposed group.

Maternal outcomes are shown in Table 3. The most common maternal outcome was PPH with an overall incidence of 26.3/100 singleton pregnancies (95%CI 26.0-26.6). The incidence of PPH was significantly lower in the group with anemia compared to the comparison group (21.8% compared to 26.8%). APH was the second most common maternal outcome at 11.6/100 singleton pregnancies (95%CI 11.4-11.8). The incidence of APH was higher in the group with anemia. Similarly, the incidence of MOH and transfusion were higher in the group with anemia. After adjustment for known confounding variables and chronic kidney disease, the odds of PPH were 8% lower in those with anemia compared to the unexposed group (aOR 0.92, 95%CI 0.86-0.98 $p = 0.007$). In contrast, the adjusted odds of maternal transfusion (aOR 1.87, 95%CI 1.65-2.13); APH (aOR 1.26, 95%CI 1.17-1.36); and MOH (aOR 1.19, 95%CI 0.91-1.56) were higher in the anemia group, although MOH was not significantly higher. After adjustment, the odds of postpartum infection (aOR 1.89, 95%CI 1.39-2.57) and pre-eclampsia (aOR 1.20, 95%CI 1.05 - 1.38) were higher in those with anemia compared to the unexposed group.

Neonatal outcomes are shown in Table 4. The most common neonatal outcome was special care baby unit (SCBU) or neonatal intensive care unit (NICU) admission with an incidence of 14.9/100 singleton pregnancies (95%CI 14.5-15.02). After adjustment, the odds of having a

stillborn baby were significantly higher in women with anemia compared to the unexposed group (aOR 1.42; 95%CI 1.04-1.94, $p=0.027$). The odds of low birthweight were significantly lower amongst the anemia group (aOR 0.77, 95%CI 0.69-0.86). There were no significant differences in any of the other neonatal outcomes.

The power of the study to detect different odds ratios as statistically significant was assessed using the most common and least common study outcomes, PPH and maternal death respectively. The lowest odds ratio detectable as statistically significant for the total sample size of 80 422 pregnancies would be 9.7 for maternal death and 1.1 for postpartum hemorrhage.

Discussion

The overall incidence of antenatal anemia in pregnancy was 9.3 per 100 women with singleton pregnancies and decreased over time in this Scottish population. Anemia was associated with a significantly increased risk of maternal APH and transfusion but with a significantly reduced risk of PPH. The odds of postpartum infection were significantly higher in those with anemia. Anemia was associated with significantly lower odds of low birthweight, but higher odds of stillbirth.

The main strengths of this study were its large size and comprehensive population data. This allowed simultaneous analysis of maternal and neonatal clinical outcomes of antenatal anemia. The retrospective cohort design gave the opportunity to evaluate the temporal trends in antenatal anemia in this stable population using routine high quality data. However, a variety of data limitations have implications for the interpretation of the findings. The use of routine data meant that information such as the use of iron supplementation during pregnancy, for example, was not available to fully explore the association between anemia and clinical outcomes. The AMND definition of anemia as hemoglobin $\leq 10\text{g/dl}$ was problematic for a number of reasons. Firstly, this definition is lower than UK National Institute for Health and Care Excellence (NICE) guidelines, which use $<11\text{g/dl}$ in the first trimester, 10.5g/dl after the second trimester and $<10\text{g/dl}$ in the postpartum period. Thus, the

identified incidence in this study could be lower than that would have been identified using NICE criteria (3), and the results should be interpreted as the outcomes of more severe anemia on this basis. The lack of continuous data on hemoglobin measurements meant a more nuanced interpretation of the association between different severities of anemia and outcomes was not possible. Furthermore, although this study was large, it was not sufficiently powered to reliably detect significant differences for rare outcomes such as maternal death and eclampsia. As the study was carried out in a Scottish population without significant ethnic mix, it may not be generalisable to the rest of the UK.

The incidence of antenatal anemia based on this study was lower than other UK estimates. Another UK cross-sectional survey (4) identified a prevalence of 15-30% compared to 9% in this study. This difference has to be interpreted cautiously given the difference in hemoglobin cut-offs used to define antenatal anemia between the studies. Other possible reasons for differences in the observed incidence are differences in the study populations. This study with a predominantly rural Scottish population may not directly compare to more ethnically diverse urban populations.

Whilst other studies suggest the incidence of anemia is persistently high, this study points to a steady decline in the prevalence of antenatal anemia in a UK population. There are a number of possible reasons for this observed decline. This may be related to improved diagnosis and treatment; however, the main limitation of this study is that treatment effects could not be controlled for. Dietary improvements and micronutrient supplementation could also account for the decline. Figure 2 highlights that there was a very steep decline between 1998 and 2001. The UK government introduced bread and flour regulations for a mandatory minimum iron level for flour in 1998 (15) which may have also contributed to this reduction. Other studies in pregnant Danish women have shown the prevalence of antenatal anemia to be 25% in women not taking iron supplements and up to 3% in those taking supplements (16).

Although APH is one of the most common clinical outcomes associated with anemia, this association has not been widely studied. This study found a statistically significant increased risk of APH in those with antenatal anemia and which has not been found in previous studies

(17, 18). The majority of antenatal anemia was diagnosed in the first trimester. This suggests that the temporal association is such that anemia preceded APH in the majority of cases and is therefore more likely to contribute to APH than APH contributing to anemia. However, this observed association has to be interpreted with caution, as the exact time of APH was not available to confirm this. It is an important limitation that antenatal anemia was identified at any time prior to birth and that it is not possible to distinguish between those who had anemia treated in the first trimester from those who did not. Therefore it was not possible to tell those who had antenatal anemia that was resolved prior to delivery and those where anaemia persisted throughout most of the pregnancy. We may have underestimated the risks due to persisting anemia on this basis.

The odds of PPH being lower in the exposure group are out of keeping with findings in the literature. Whilst the evidence for mild or moderate levels of anemia with PPH are less clear, it has been found in previous studies that severe anemia is associated with an increased risk of PPH (19, 20). The association observed in this analysis may be explained by treatment effects not controlled for in the analysis such as iron supplementation and active management of the third stage of labour in women known to have antenatal anemia. However, in pregnancies with antenatal anemia, the observed increased odds of major obstetric hemorrhage, defined, as blood loss greater than 2000 ml did not achieve statistical significance.

Postpartum infection was found to be significantly associated with antenatal anemia. A previous case-control study of the AMND population also found anemia to be a significant predictor of maternal sepsis (21). This has major implications for research and clinical practice as sepsis has been highlighted as a leading cause of maternal deaths in the UK (22). The significant association between anemia and stillbirth was also found in a London-based cohort (14). However, the main limitation in that study was the high proportion of missing data (35%) on variables such as ethnicity, smoking status and deprivation, which are known to be significant confounders. Establishing the association between anemia and stillbirths is important because the UK has the third highest rates of stillbirth in Europe (23). The stillbirth rate in Scotland is 4.7/1000 births and in 30% of cases the cause is unknown.

Whilst a recent systematic review and meta-analysis (5) suggests that low birthweight is an adverse outcome associated with anemia, this study, in contrast, suggested the odds of low birthweight are reduced at a hemoglobin of $\leq 10\text{g/dl}$. This association may be spurious as it was

not possible to correct for treatment effects in this analysis. An alternative explanation recently raised is that, in well-nourished populations, what is classified as mild anemia may be physiologically appropriate plasma volume expansion due to pregnancy (24) that may not be associated with adverse clinical outcomes. It is thought contemporaneous assessment of iron status and haematocrit are required to distinguish between iron deficiency anemia and physiological anemia. This unexpected association with low birthweight, along with that of PPH, could be explained by residual unknown confounders that could not be accounted for in this study.

In conclusion, this study suggests that the incidence of antenatal anemia is declining in this Scottish population. It provides clear evidence of some associated poor outcomes, in particular, maternal postpartum infection, maternal transfusion and stillbirth. Given that anemia is a readily correctable risk factor for these clinical outcomes, which are a major cause of morbidity and mortality in the UK, further work is required to investigate the association between antenatal anemia and clinical outcomes in order to develop more effective strategies to further reduce the incidence of antenatal anemia.

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References

1. World Health Organisation (WHO). Worldwide prevalence of anaemia 1993-2005; WHO global database on anaemia 2008. Available online at: http://www.who.int/vmnis/publications/anaemia_prevalence/en/ (accessed 8 August 2014)
2. Stevens G, Finucane M, De-Regil L, Paciorek C, Flaxman S, Branca F, et al. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995–2011: a systematic analysis of population-representative data. *Lancet Global Health* 2013;1: e16–25.
3. National Institute for Health and Care Excellence (NICE) 2008. Clinical Guideline 62, Antenatal Care: routine care for the healthy pregnant woman. RCOG Press.
4. Barroso F, Allard S, Kahan BC, Connolly C, Smethurst H, Choo L, et al. Prevalence of maternal anaemia and its predictors: a multi-centre study. *Eur J Obstet Gynecol Reprod Biol.* 2011;159:99-105.
5. Haider BA, Olofin I, Wang M, Spiegelman D, Ezzati M, Fawzi WW, et al. Anaemia, prenatal iron use, and risk of adverse pregnancy outcomes: systematic review and meta-analysis. *BMJ.* 2013;346:f3443.
6. Drukker L, Hants Y, Farkash R, Ruchlemer R, Samueloff A, Grisaru-Granovsky S. Iron deficiency anemia at admission for labor and delivery is associated with an increased risk for Cesarean section and adverse maternal and neonatal outcomes. *Transfusion.* 2015;55:2799-2806..
7. Medical Research Council UK/NHS Health Research Authority Ethics Decision Tool 2014. Available online at <http://www.hra-decisiontools.org.uk/ethics/>: (accessed 1 February 2014).
8. Bhattacharya S, Townend J, Bhattacharya S. Recurrent miscarriage: Are three miscarriages one too many? Analysis of a Scottish population-based database of 151,021 pregnancies. *Eur J Obstet Gynecol Reprod Biol.* 2010;150:24-7.
9. Bhattacharya S, Campbell DM. The incidence of severe complications of preeclampsia. *Hypertens Pregnancy.* 2005;24:181-90.
10. Humphrey T, Tucker JS. Rising rates of obstetric interventions: exploring the determinants of induction of labour. *J Public Health (Oxf).* 2009;31:88-94.

- Accepted Article
11. RCOG. Postpartum Haemorrhage Prevention and Management. Royal College of Obstetricians and Gynaecologists Green-top Guideline 52. 2009;
 12. WHO. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation. . WHO Technical Report Series. Geneva: World Health Organisation, 2000.
 13. Little MP, Brocard P, Elliott P, Steer PJ. Hemoglobin concentration in pregnancy and perinatal mortality: A London-based cohort study. *Am J Obstet Gynecol.* 2005;193:220-6.
 14. Ben Miled S, Bibi D Fau - Khalfi N, Khalfi N Fau - Blibech R, Blibech R Fau - Gharbi Y, Gharbi Y Fau - Castalli R, Castalli R Fau - Khrouf N, et al. Iron stocks and risk of anemia in twins. *Arch Institut Pasteur Tunis.* 1989;66:221-41.
 15. UK Government. Bread and Flour Regulations 1998. Statutory Instrument No 141.
 16. Milman N. Prepartum anaemia: prevention and treatment. *Ann Hematol.* 2008;87:949-59.
 17. Makrides M, Crowther CA, Gibson RA, Gibson RS, Skeaff CM. Efficacy and tolerability of low-dose iron supplements during pregnancy: a randomized controlled trial. *Am J Clin Nutr.* 2003;78:145-53.
 18. Ziaei S, Norrozi M, Faghihzadeh S, Jafarbegloo E. A randomised placebo-controlled trial to determine the effect of iron supplementation on pregnancy outcome in pregnant women with haemoglobin ≥ 13.2 g/dl.[Erratum appears in *BJOG.* 2007 Oct;114(10):1311 Note: Dosage error in published abstract; MEDLINE/PubMed abstract corrected]. *BJOG.* 2007;114:684-8.
 19. Rush D. Nutrition and maternal mortality in the developing world. *Am J Clin Nutr.* 2000;72:212S-40S.
 20. Combs CA, Murphy EL, Laros RK, Jr. Factors associated with postpartum hemorrhage with vaginal birth. *Obstet Gynecol.* 1991;77:69-76.
 21. Acosta CD, Bhattacharya S, Tuffnell D, Kurinczuk JJ, Knight M. Maternal sepsis: a Scottish population-based case-control study. *BJOG.* 2012;119:474-83.
 22. Knight M, Kenyon S, Brocklehurst P, Neilson J, Shakespeare J, Kurinczuk JJ (Eds), et al. Saving Lives, Improving Mothers' Care - Lessons learned to inform future maternity care

from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009–12. Oxford: National Perinatal Epidemiology Unit, University of Oxford, 2014.

23. Europeristat. Health and Care of Pregnant Women and Babies in Europe in 2010. In: J. Zeitlin, European Perinatal Health Report. European Commission Directorate for Health and Consumers.
24. Brion M-JA, Leary SD, Smith GD, McArdle HJ, Ness AR. Maternal anemia, iron intake in pregnancy, and offspring blood pressure in the Avon Longitudinal Study of Parents and Children. *Am J Clin Nutr.* 2008;88:1126-33.

Figure 1: Flow diagram of exclusion criteria and final study sample. Hb, hemoglobin.

See attached figure 1.

Figure 1: Flow Diagram of Exclusion Criteria and Final Study Sample

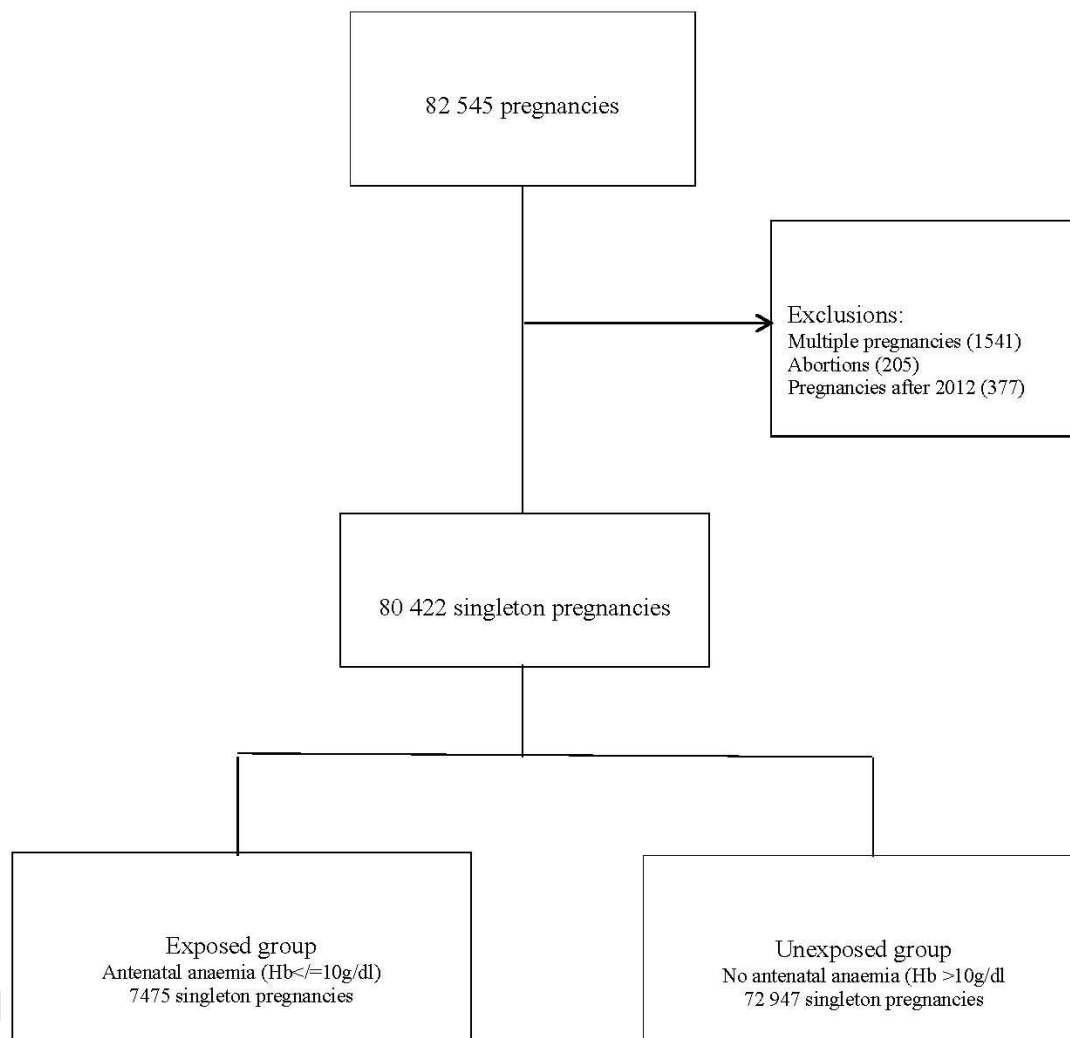


Figure 2. Incidence of antenatal anemia in the Grampian Region, Scotland from 1995-2012.

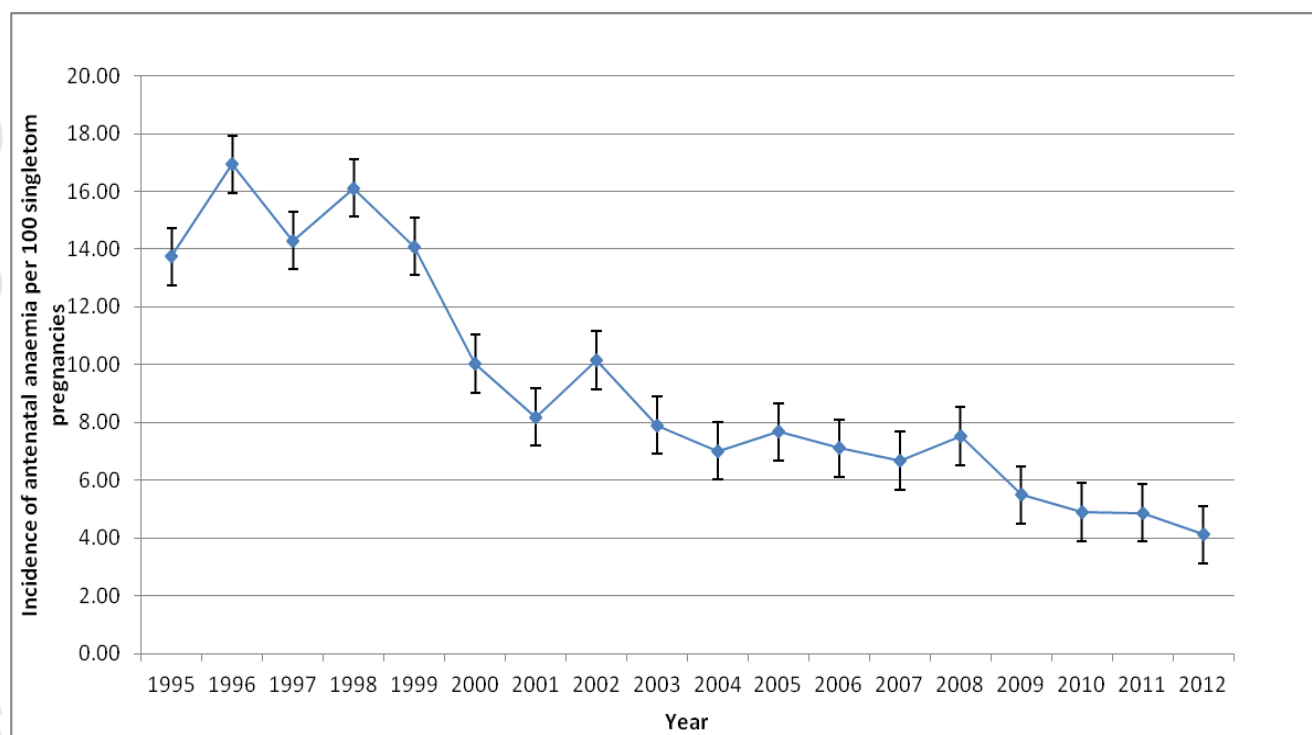


Table 1. Baseline characteristics of the study population. Hb, haemoglobin; BMI, body mass index.

Characteristic	Exposed (antenatal anemia) Hb \leq 10g/l n=7475 n (%)	Unexposed (no antenatal anemia) Hb $>$ 10 n=72 947 no (%)	<i>p-value</i>
Maternal age (years)	Mean 28.2	Mean 29.2	<0.001
≤ 20	710 (9.50)	3873 (5.31)	
21-29	3505 (46.89)	32 601 (42.32)	
30-39	3053 (40.84)	34 431 (47.20)	
40-49	204 (2.73)	2017 (2.77)	
≥ 50	0 (0.00)	2 (0.00)	
Missing	3 (0.04)	23 (0.03)	
Parity			<0.001
0	2778 (37.16)	36 176 (49.59)	
1-3	4454 (59.59)	35 709 (48.95)	
> 3	243 (3.25)	1056 (1.45)	
Missing	0 (0.00)	6 (0.01)	
Ethnicity			<0.001
White	6829 (91.36)	67 321 (92.29)	
Black, Asian and minority ethnic groups	583 (7.80)	5155 (7.07)	
Missing	63 (0.84)	471 (0.65)	
Smoking Status			<0.001
Smokers	2114 (28.28)	19 074 (26.15)	
Non-smokers	5195 (69.50)	52 302 (71.70)	
Missing	166 (2.22)	1571 (2.15)	
Scottish Index of Multiple Deprivation			<0.001
First decile (most deprived 10%)	1111 (14.86)	12 690 (17.40)	
Second decile	1041 (13.93)	11 762 (16.12)	
Third decile	1009 (13.50)	11 809 (16.19)	
Fourth decile	467 (6.25)	5379 (7.37)	
Fifth decile	661 (8.84)	6124 (8.40)	
Sixth decile	679 (9.08)	6342 (8.69)	
Seventh decile	445 (5.95)	3669 (5.03)	
Eight decile	731 (9.78)	5511 (7.55)	
Ninth decile	48 (6.5)	3523 (4.83)	
Tenth decile (least deprived 10%)	705 (9.43)	4308 (5.91)	
Missing	140 (1.88)	1830 (2.51)	
BMI	Median (23.5)	Median (24.5)	<0.001
Underweight ($<18.5\text{kg/m}^2$)	305 (4.08)	1604 (2.20)	
Normal ($18.5\text{-}24.9\text{kg/m}^2$)	4283 (57.30)	36 142 (49.55)	
Overweight ($25\text{-}29.9\text{kg/m}^2$)	1689 (22.6)	19 172 (26.28)	
Obese ($\geq 30\text{ kg/m}^2$)	767 (10.26)	11 818 (16.20)	
Missing	431 (5.77)	4205 (5.77)	

Table 2. Baseline co-morbidities in the study population. Hb, haemoglobin.

Co-morbidity	Exposed (antenatal anemia) Hb \leq 10g/l n=7475 n (%)	Unexposed (no antenatal anemia) Hb>10 n=72 947 n (%)	<i>p-value</i>
Chronic kidney disease			
Yes	23 (0.31)	226 (0.31)	0.975
No	7452 (99.69)	72 721 (99.69)	
Missing	0 (0.00)	0 (0.00)	
Diabetes			
Yes	64 (0.86)	522 (0.72)	0.173
No	7411 (99.14)	72 425 (99.28)	
Missing	0 (0.00)	0 (0.00)	
Splenomegaly			
Yes	2 (0.03)	9 (0.01)	0.273
No	7473 (99.97)	72 938 (99.99)	
Missing	0 (0.00)	0 (0.00)	
Cirrhosis			
Yes	2 (0.03)	21 (0.03)	0.637
No	7473 (99.97)	72 926 (99.97)	
Missing	0 (0.00)	0 (0.00)	
Organ transplant			
Yes	7 (0.09)	6 (0.01)	<0.001
No	7468 (99.91)	72 941 (99.99)	
Chronic lung disease			
Yes	4 (0.05)	20 (0.03)	0.179
No	7471 (99.95)	72 927(99.97)	
Missing	0 (0.00)	0 (0.00)	
Rheumatological disease			
Yes	2 (0.03)	5 (0.01)	0.133
No	7473 (99.97)	72 942 (99.99)	
Missing	0 (0.00)	0	

Table 3. Maternal clinical outcomes among women with antenatal anemia.

Outcome	Exposed antenatal anemia Hb \leq 10g/dl n=7475 n (%)	Unexposed no antenatal anemia Hb $>$ 10g/dl n=72 947 n (%)	Unadjusted OR (95%CI)	Adjusted OR ^a (95%CI)
Antepartum hemorrhage				
Yes	1057 (14.14)	8235 (11.29)	1.29(1.21-1.39)	1.26 (1.17-1.36)
No	6418 (85.86)	64 712 (88.71)	1 ^b	1 ^b
Missing	0 (0.0)	0 (0.0)		
Postpartum hemorrhage $>$ 500ml				
Yes	1628 (21.78)	19 516 (26.75)	0.76 (0.72 - 0.81)	0.92 (0.86-0.98) p=0.007
No	5804 (77.64)	52 923 (72.55)	1 ^b	1 ^b
Missing	43 (0.58)	508 (0.70)		
Major obstetric hemorrhage ($>$ 2000ml)				
Yes	63 (0.84)	597 (0.82)	1.02 (0.90-1.36)	1.19 (0.91-1.56)
No	7369 (98.58)	71 842(98.49)	1 ^b	1 ^b
Missing	43 (0.58)	508 (0.70)		
Transfusion				
Yes	338 (4.52)	1887 (2.59)	1.78 (1.58-2.01)	1.87 (1.65-2.13)
No	7137 (95.48)	71 060 (97.41)	1 ^b	1 ^b
Missing	0 (0.0)	0 (0.0)		
Gestational hypertension				
Yes	556 (7.44)	7030 (9.64)	0.75 (0.69 -0.82)	0.96 (0.87-1.06) ^c
No	6919 (92.56)	65 917(90.36)	1 ^b	1 ^b
Missing	0 (0.0)	0 (0.0)		
Pre-eclampsia				
Yes	295 (3.95)	3037 (4.16)	0.94 (0.84 -1.07)	1.20 (1.05-1.38)
No	7180 (96.05)	69 910 (95.84)	1 ^b	1 ^b
Missing	0 (0.0)	0 (0.0)		
Eclampsia				
Yes	3 (0.04)	49 (0.07)	0.60 (0.19-1.92)	0.77 (0.24-2.51)
No	7472 (99.96)	72 651 (99.93)	1 ^b	1 ^b
Missing	0 (0.0)	0 (0.0)		
Postpartum infection				
Yes	56 (0.75)	279 (0.38)	1.97 (1.47-2.63)	1.89 (1.39-2.57)
No	7419 (99.25)	72 668(99.62)	1 ^b	1 ^b
Missing	0 (0.0)	0 (0.0)		
Maternal death				
Yes	1 (0.01)	5 (0.01)	1.95 (0.22-16.71)	2.07 (0.22-19.36)
No	7474 (99.99)	72942 (99.99)	1 ^b	1 ^b
Missing	0(0.0)	0(0.0)		

^a adjusted for age, parity, smoking status, ethnicity, socioeconomic status, body mass index and chronic kidney disease.^b baseline comparison group.^c no longer significant on multivariable analysis.

Hb, hemoglobin; OR, odds ratio; CI, confidence interval.

Table 4. Neonatal clinical outcomes among women with antenatal anemia.

Outcome	Exposed antenatal anemia Hb \leq 10g/dl n=7475 n (%)	Unexposed no antenatal anemia Hb>10g/dl n=72 947 n (%)	Unadjusted OR (95% CI)	Adjusted OR ^a (95% CI)
Neonatal Outcomes				
Stillbirth				
Yes	59 (0.79)	403 (0.55)	1.43 (1.09-1.88)	1.42 (1.04-1.94) p=0.027
No	7413 (99.17)	72 476 (99.35)	1 ^b	1 ^b
Missing	3 (0.04)	68 (0.09)		
Preterm delivery (<37 weeks)				
Yes	540 (7.22)	5252 (7.20)	1.00 (0.92-1.10)	0.97 (0.88-1.07) p=0.554
No	6 935 (92.78)	67 683 (92.78)	1 ^b	1 ^b
Missing	0 (0.00)	12 (0.02)		
LBW <2500g				
Yes	393 (5.26)	4622 (6.34)	0.82 (0.74-0.91)	0.77 (0.69–0.86)
No	7078 (94.69)	68 301 (93.6)	1 ^b	1 ^b
Missing	4 (0.05)	24 (0.03)		
VLBW<1500g				
Yes	75 (1.00)	891 (1.22)	0.82 (0.65-1.04)	0.81 (0.62-1.06)
No	7386 (98.94)	72 032 (98.75)	1 ^b	1 ^b
Missing	4 (0.05)	24 (0.03)		
SCBU/NICU admission				
Yes	1097 (14.79)	10 783 (14.86)	0.99(0.93 -1.06)	1.01 (0.94-1.09)
No	6305 (85.02)	61 630 (84.96)	1 ^b	1 ^b
Missing	14 (0.19)	131 (0.18)		
Early neonatal death				
Yes	26 (0.35)	244 (0.33)	1.04 (0.7-1.56)	1.17 (0.76-1.79)
No	7390 (99.65)	72 300 (99.66)	1 ^b	1 ^b
Missing	0 (0.0)	0 (0.0)		

^aadjusted for age, parity, smoking status, ethnicity, socioeconomic status, body mass index and chronic kidney disease.

^b Baseline comparison group .

LBW: low birthweight; VLBW: very low birthweight; SCBU/NICU: special care baby unit/neonatal intensive care unit.