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Iron deficiency anemia: Pregnancy outcomes with or without iron supplementation

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ABSTRACT

Objective: To estimate the efficacy of iron supplementation in anemic pregnant women on the basis of occurrence of pregnancy complications and birth outcomes.
Methods: Comparison of the occurrence of medically recorded pregnancy complications and birth outcomes in pregnant women affected with medically recorded iron deficiency anemia and iron supplementation who had malformed fetuses/newborns (cases) and who delivered healthy babies (controls) in the population-based Hungarian Case-Control Surveillance System of Congenital Abnormalities.
Results: Of 22 843 cases with congenital abnormalities, 3242 (14.2%), while of 38 151 controls, 6358 (16.7%) had mothers with anemia. There was no higher rate of preterm births and low birth weight in the newborns of anemic pregnant women supplemented by iron. However, anemic pregnant women without iron treatment had a significantly shorter gestational age at delivery with a somewhat higher rate of preterm births but these adverse birth outcomes were prevented with iron supplementation. The rate of total and some congenital abnormalities was lower than expected and explained mainly by the healthier lifestyle and folic acid supplements. The secondary findings of the study showed a higher risk of constipation-related hemorrhoids and hypotension in anemic pregnant women with iron supplementation.
Conclusion: A higher rate of preterm birth was found in anemic pregnant women without iron treatment but this adverse birth outcome was prevented with iron supplementation. There was no higher rate of congenital abnormalities in the offspring of anemic pregnant women supplemented with iron and/or folic acid supplements.

Introduction

Anemia is defined as a hemoglobin value below the lower limits of its normal range. However, anemia is not a disease but a sign similar to fever and very common in pregnant women. The symptoms of anemia are caused by tissue hypoxia such as fatigue, lightheadedness, weakness, and exertional dyspnea [1].

Iron deficiency is a leading cause of anemia in many parts of the world and particularly in Hungary. Iron is an essential element in the production of hemoglobin for the transport of oxygen to tissues and in the synthesis of enzymes that are required to use oxygen for the production of cellular energy [2]. Iron deficiency anemia detected in early pregnancy is associated with a lower energy and iron intake, resulting in an inadequate gestational weight gain over the whole pregnancy, and a greater than two-fold increase in the risk of preterm delivery [3,4]. On the other hand, most studies indicated a U-shaped curve relationship between the maternal hemoglobin concentrations, i.e., anemia according to the trimesters of pregnancy. Thus the risk of preterm delivery was approximately doubled in pregnant women with moderate-to-severe anemia during the first and second trimesters, while this relationship was reversed during the third trimester: anemia (low hemoglobin) associated with a decreased risk of preterm births [5–11]. A similar U-shaped association was found between anemia in different trimesters and the rate of low birth weight newborns [12–16]. High hemoglobin levels often correlate clinically with increased risk of pre-eclampsia and suggest failure of the plasma volume to expand [2].

The aim of the study was to check the efficacy of iron supplementation during pregnancy in anemic pregnant women

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on the basis of incidence of pregnancy complications and birth outcomes of their newborns in the population-based data set of the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) [17].

Materials and methods

Cases were selected from the data set of the Hungarian Congenital Abnormality Registry (HCAR), 1980–1996 [18]. Diagnosis of structural birth defects, i.e., congenital abnormalities (CAs), was based on the compulsory notification of physicians from birth until the end of the first postnatal year to the HCAR, and on autopsy reports because autopsy was mandatory for all infant deaths. Since 1984, fetal defects diagnosed in prenatal diagnostic centers with or without termination of pregnancy have also been included in the HCAR. The total (birth + fetal) prevalence of cases with CA diagnosed from the second trimester of pregnancy through the age of 1 y was 35 per 1000 informative offspring (live-born infants, stillborn fetuses, and electively terminated malformed fetuses) in the HCAR, 1980–1996, and about 90% of major CAs were recorded in the HCAR during the 17 y of the study period [19].

Controls were defined as newborn infants without any CA, and they were selected from the National Birth Registry of the Central Statistical Office for the HCCSCA. In most years two controls were matched to every case according to sex, birth week, and district of parents' residence.

Three sources of exposure data and confounding factors

1) *Prospective information of medical doctors.* Mothers were asked to send us the prenatal maternity logbook and other medical records, particularly discharge summaries in an explanatory letter. Prenatal care was mandatory for pregnant women in Hungary (if somebody did not visit a prenatal care clinic, she did not receive a maternity grant and leave); thus, nearly 100% of pregnant women visited prenatal care clinics, on average, seven times during their pregnancies. The first visit was between the 6th and 12th gestational week when obstetricians recorded all pregnancy complications, maternal diseases, and related drug prescriptions in the prenatal maternity logbook. In addition there are laboratory examinations including blood sugar, hemoglobin level, red blood cell count, and hematocrit measurement in pregnant women in the first visit in prenatal care clinics.
2) *Retrospective self-reported maternal information.* A structured questionnaire, along with a list of drugs and pregnancy supplements, diseases, plus a printed informed consent form were mailed to the mothers immediately after the selection of cases and controls. We also asked mothers to give a signature for informed consent form.

The mean ± SD time elapsed between the birth or pregnancy termination and the return of the "information package" (questionnaire, logbook, etc) in our prepaid envelope was 3.5 ± 1.2 and 5.2 ± 2.9 mo in the case and control groups, respectively.

3) *Supplementary data collection.* Regional nurses were asked to visit all non-respondent case mothers and to help mothers to fill in the questionnaire; in addition, they evaluated available medical records and obtained data regarding the lifestyle (smoking and drinking habits, elicit drugs during the study pregnancy) through a cross interview of mothers and their male partners or other relatives living together, and the results of "family consensus" were recorded. Regional nurses could not visit all non-respondent control mothers due to the decision of the committee on ethics; thus, only 200 non-respondent and 600 respondent control mothers were visited at home by regional nurses as part of two validation studies [20,21] using the same method as in non-respondent case mothers.

Here the 17 y data of the HCCSCA between 1980 and 1996 are evaluated because the data collection has been changed since 1997 (all mothers are visited by regional nurses), and this part of the data set has not been validated until now.

The necessary information was available in 96.3% of cases (84.4% from reply to the mailing, 11.9% from the nurse visit) and in 83.0% of the controls (80.9% from reply, 2.1% from visit). An informed consent form was signed by 98% of mothers.

The diagnostic criteria of anemia in the study

The normal hemoglobin level is for adult female is 14.0 ± 2.0 g/dL [22]. However, if the previously mentioned definition of anemia, i.e., "hemoglobin value below the lower limits of normal range not explained by the state of dehydration" [1] is accepted, 20–60% of pregnant women will be found to be anemic at some time during the pregnancy [23]. Thus the Centers for Disease Control and Prevention defined anemia in pregnancy as a hemoglobin level below 11 g/dL in the first and third trimesters and below 10.5 g/dL in the second trimester [24]. In Hungary the diagnosis of anemia was based on the previously mentioned laboratory examinations including hemoglobin level, red blood cell count, and hematocrit measurement in pregnant women during the first visit in the prenatal care clinic. Thus the diagnostic criterion of anemia was prospectively and medically recorded anemia in the prenatal maternity logbook by obstetricians in the study. If anemia was mentioned only by mothers in the questionnaire, these pregnant women were excluded from the study due to the unreliable/subjective nature of this information in general without mentioning the onset and other characteristics of anemia.

Gestational time was calculated from the first day of the last menstrual period. Beyond birth weight (g) and gestational age at delivery (wk), the rate of low birth weight (<2500 g) and preterm births (<37 wk) as adverse birth outcomes were analyzed on the basis of discharge summaries of inpatient obstetric clinics. The critical period of most major CAs is in the second and third gestational months; it explains that this time window is used as the critical period of CAs in this study [25].

Pregnancy complications were evaluated only in prospectively and medical recorded data in the prenatal maternity logbook, while the occurrence of maternal diseases was analyzed on basis of both medically recorded data and maternal information.

Related drug treatments and use of pregnancy supplements, particularly folic acid/folic acid containing multivitamins and iron products, were also evaluated. In Hungary, only one kind of folic acid tablet was available during the study period and it contained 3 mg. The available iron supplements included 50 (10 mg elementary Fe^{2+}), 70, and 100 mg ferrous sulfate in one tablet. Multivitamins, more exactly the combination of micronutrients, contain folic acid (but at a low dose between 0.1 and 1.0 mg) and iron.

Among other potential confounding factors, maternal age, birth order, and marital and employment status as indicators of socio-economic status [26], were evaluated.

Statistical analysis

SAS version 8.02 (SAS Institute Inc, Cary, NC, USA) was used for statistical analyses of data. First, the main maternal variables were evaluated in case and control pregnant women using Student's *t* test for quantitative analysis, while χ^2 test for categorical variables at the comparison of pregnant women with or without anemia as reference. The prevalence of other maternal diseases and drug intakes during pregnancy, in addition to pregnancy complications, were compared between the group of case and control mothers with anemia using odds ratios (OR) with 95% confidence intervals (CI). In the next step, birth outcomes of control newborns without CA were compared in the groups of mothers with or without anemia. Cases with CA were excluded from this analysis because CAs may have a more drastic effect for birth outcomes as anemia. At the calculation of adjusted *t* value for gestational age at delivery and OR for the rate of preterm birth, maternal age, and employment status, in addition to birth order were considered as confounders, while the calculation of adjusted *t* for birth weight and OR for the rate of low birth weight newborns, gestational age at delivery was added to the previously mentioned confounders. Finally, we compared the occurrence of anemia during the study pregnancy in specific CA groups of cases and in their all matched controls, and adjusted OR with 95% CI were evaluated in conditional logistic regression models.

Results

Of 22 843 cases with CA, 3242 (14.2%), while of 38 151 controls without CA, 6358 (16.7%) had mothers with medically recorded anemia in the prenatal maternity logbooks in the data set of the HCCSCA. Of 3242 cases mothers with anemia, 1999 (61.7%), and of 6358 control mothers with anemia, 4444 (69.9%) were specified as iron deficiency anemia. Hereditary spherocytosis was recorded only in two pregnant women; megaloblastic anemia was not found in Hungarian pregnant women during the study period. The rest of the pregnant women with anemia had unspecified anemia, but practically all were considered to be iron deficiency anemic due to iron supplementation (Table 1). Of 3242 case mothers, 210 (6.5%) and of 6358 control mothers, 363 (5.7%) were not treated with iron.

Different iron derivatives were used in 94% of anemic pregnant women; however, about 60% of pregnant women without anemia had a similar iron supplementation (Table 1). The use of folic acid was also much more frequent in control and case

Table 1
Occurrence of pregnancy supplementation

Pregnancy supplements	Case mothers				Control mothers			
	Without anemia (N = 19 601)		With anemia (N = 3242)		Without anemia (N = 31 793)		With anemia (N = 6358)	
	No.	%	No.	%	No.	%	No.	%
Iron	11 710	59.7	3032	93.5	20 776	65.3	5995	94.3
Calcium	1472	7.5	331	10.2	2837	8.9	746	11.7
Folic acid	9019	46.0	2260	69.7	16 207	51.0	4568	71.8
Vitamin B6	1673	8.5	340	10.5	3371	10.6	715	11.2
Vitamin D	5137	26.2	964	29.7	8443	26.6	1707	26.8
Vitamin C	747	3.8	165	5.1	1340	4.2	345	5.4
Vitamin E	1167	6.0	251	7.7	1878	5.9	409	6.4
Multivitamins	1157	5.9	173	5.3	2038	6.4	471	7.4

mothers with anemia than in women without anemia. There was no difference in the use of folic acid-containing multivitamins among the study groups. However, it is worth mentioning the generally higher rate of all kinds of different supplementations in pregnant women with anemia.

Anemia was diagnosed in general during the first visit in prenatal care clinics due to the laboratory blood examination of pregnant women. Thus the peak of anemia diagnoses was in the third gestational month in both case and control mothers followed by the second gestational month. After the third gestational month, there was a decreasing trend of anemia, practically without the diagnosis of anemia after the seventh gestational month. However, the time of anemia diagnoses reflects the time of blood examination and not the onset of anemia in these gestational months.

The main characteristics of mothers with or without anemia as reference are shown in Table 2. The mean maternal age was somewhat lower due to the higher proportion of the young age group (19 y or less). The mean birth order and the distribution of maternal employment status as indicator of socioeconomic status did not show a characteristic pattern.

The data of lifestyle were evaluated based on the so-called family consensus in pregnant women visited at home. Of 2640 case mothers visited at home, 396 (15.0%) had medically recorded anemia, and among them, 54 (13.6%) smoked during the study pregnancy. Of 2244 case mothers without anemia, 526 (23.4%) were smokers. A similar trend was seen in 800 control mothers visited at home. Among them, 114 (14.5%) were recorded as anemic and 15 (12.9%) smoked during the study pregnancy, while of 684 control mothers without anemia, 137 (20.0%) had a smoking habit during the study pregnancy. The drinking habit was also evaluated but the rate of regular drinkers was about 1% in all subsamples.

The occurrence of maternal diseases is shown in Table 3. In general the incidence of acute disease groups was higher in pregnant women with anemia compared to pregnant women without anemia, although these differences were not significant. Among chronic diseases, three (in fact, two) showed some association with maternal anemia. The constipation-related hemorrhoids certainly had a role in the origin of maternal anemia. The higher prevalence of hypotension in anemic pregnant women is noteworthy.

In general, the incidence of medically recorded other pregnancy complications again was higher in mothers with anemia compared to mothers without anemia (Table 4). However, it is worth evaluating mainly control pregnant women with anemia

Table 2
Characteristics of mothers with or without anemia (as reference)

Variables Quantitative	Case mothers				Control mothers			
	Without anemia (N = 19 601)		With anemia (N = 3242)		Without anemia (N = 31 793)		With anemia (N = 6358)	
	No.	%	No.	%	No.	%	No.	%
Maternal age, y								
19 or less	2075	10.6	431	13.3	2669	8.4	608	9.6
20–29	13 376	68.2	2217	68.4	22 976	72.3	4626	72.8
30 or more	4150	21.2	594	18.3	6148	19.3	1124	17.7
Mean, SD	25.6 ± 5.3		24.9 ± 5.1		25.5 ± 4.9		25.3 ± 4.7	
Birth order								
1	9119	46.5	1589	49.0	15 131	47.6	3078	48.4
2 or more	10 482	53.5	1653	51.0	16 662	52.4	3280	51.6
Mean, SD	1.9 ± 1.2		1.8 ± 1.0		1.7 ± 0.9		1.7 ± 0.9	
Categorical								
Unmarried	1144	5.8	125	3.9	1245	3.9	227	3.6
Employment status								
Professional	1692	8.6	285	8.8	3641	11.5	782	12.3
Managerial	4358	22.2	739	22.8	8511	26.8	1754	27.6
Skilled worker	5575	28.4	926	28.6	10 058	31.6	1850	29.1
Semiskilled worker	3584	18.3	613	18.9	5020	15.8	1141	17.9
Unskilled worker	1509	7.7	267	8.2	1837	5.8	350	5.5
Housewife	2082	10.6	324	10.0	1976	6.2	378	5.9
Others	801	4.1	88	2.7	750	2.4	103	1.6

Table 3
Occurrence of maternal diseases

Maternal diseases	Case mothers				Control mothers			
	Without anemia (N = 19 601)		With anemia (N = 3242)		Without anemia (N = 31 793)		With anemia (N = 6358)	
	No.	%	No.	%	No.	%	No.	%
Acute disease groups								
Influenza—common cold	4117	21.0	771	23.8	5715	18.0	1298	20.4
Respiratory system	1797	9.2	316	9.7	2898	9.1	554	8.7
Digestive system	183	0.9	38	1.2	231	0.7	41	0.6
Urinary tract	1292	6.6	296	9.1	1846	5.8	453	7.1
Genital organs	1287	6.6	302	9.3	2280	7.2	525	8.3
Others	911	4.6	212	6.5	1505	4.7	376	5.9
Chronic diseases								
Diabetes mellitus	138	0.7	18	0.6	205	0.6	24	0.4
Epilepsy	79	0.4	16	0.5	84	0.3	6	0.1
Migraine	468	2.4	96	3.0	590	1.9	118	1.9
Essential hypertension	1388	7.1	224	6.9	2300	7.2	380	6.0
Hypotension	391	2.0	149	4.6	899	2.8	366	5.8
Phlebitis-thrombophlebitis	52	0.3	19	0.6	109	0.3	37	0.6
Varicose veins	258	1.3	74	2.3	445	1.4	121	1.9
Hemorrhoids	606	3.1	192	5.9	1222	3.8	402	6.3
Constipation	326	1.7	140	4.3	530	1.7	269	4.2
Others	283	1.4	71	2.2	422	1.3	108	1.7

because fetal defects may have some association with pregnancy complications (e.g., placental disorders) in case mothers. Threatened abortion and preterm delivery, in addition to severe nausea-vomiting and polyhydramnios, were recorded more frequently in control pregnant women with anemia.

In the next step, the prevalence of pregnancy complications was evaluated in 214 anemic control pregnant women without iron treatment, in 1579 anemic control pregnant women with iron supplementation, in 4419 anemic control pregnant women with iron + folic acid supplementation, and in 149 anemic control pregnant women with folic acid supplementation (Table 5). The prevalence of severe nausea-vomiting was the lowest after iron + folic acid supplementation and the highest in untreated anemic pregnant women. However, other pregnancy complications did not show significant differences among these subgroups.

There was no significant difference in the distribution and frequency of other drug uses between women with and without anemia.

The birth outcomes of newborn infants without CA born to mothers with anemia did not show an adverse pattern (Table 6). There was no difference in sex ratio between the two study groups. The mean gestational age at delivery was the same; thus, the rate of preterm births was also similar. There was no real difference in the mean birth weight; therefore, the rate of low birth weight newborns also did not show significant difference in the newborns of anemic and non-anemic pregnant women. There was no difference in the rate of post-term births, i.e., 42 wk or more gestational wk (10.3% versus 10.1%) and large newborns, i.e., over 4000 g birth weight (7.2% versus 7.6%) in control mothers with and without anemia. (The latter data are not shown in Table 6.)

However, it is worth making a comparison of anemic control pregnant women without and with iron supplementation (Table 7). There was 0.4 wk shorter mean gestational age in 214 anemic pregnant women without iron supplementation and 33 g larger mean birth weight compared to 1576 anemic pregnant women with iron treatment. The rate of preterm birth was lower in the treated subgroup than in the untreated subgroup (but somewhat higher than in the group of pregnant women with anemia in Table 6). The rate of low birth weight newborns was higher but not significantly in untreated anemic pregnant women compared to iron-treated anemic pregnant women.

In addition, the birth outcomes of newborn infants born to anemic pregnant woman treated with iron + folic acid or folic acid alone can also be evaluated (Table 7). The longest mean

Table 4
Incidence of other pregnancy complications

Pregnancy complications	Case mothers				Comparison of cases with or without anemia OR with 95% CI	Control mothers				Comparison of controls with or without anemia OR with 95% CI
	Without anemia (N = 19 601)		With anemia (N = 3242)			Without anemia (N = 31 793)		With anemia (N = 6358)		
Threatened abortion	2925	14.9	572	17.6	**1.2 (1.1–1.3)**	5284	16.6	1226	19.3	**1.2 (1.1–1.3)**
Nausea-vomiting, severe	1404	7.2	338	10.4	**1.5 (1.3–1.7)**	3040	9.6	815	12.8	**1.4 (1.3–1.5)**
Preeclampsia-eclampsia	560	2.9	110	3.4	1.2 (0.9–1.5)	947	3.0	211	3.3	1.1 (0.9–1.3)
Gestational hypertension	5	0.0	0	0.0	—	9	0.0	4	0.1	2.2 (0.7–7.2)
Gestational diabetes	98	0.5	22	0.7	1.4 (0.9–2.2)	199	0.6	30	0.5	0.8 (0.5–1.1)
Placental disorders*	227	1.2	69	2.1	**1.9 (1.4–2.4)**	500	1.6	93	1.5	0.9 (0.7–1.2)
Polyhydramnios	161	0.8	50	1.5	**1.9 (1.4–2.6)**	146	0.5	45	0.7	**1.5 (1.1–2.2)**
Oligohydramnios	27	0.1	6	0.2	1.3 (0.6–3.2)	13	0.0	1	0.0	0.4 (0.1–2.9)
Threatened preterm delivery†	2114	10.8	492	15.2	**1.5 (1.3–1.6)**	4378	13.8	1069	16.8	**1.3 (1.2–1.4)**

Bold numbers show significant associations
* Includes placenta previa, premature separation of placenta, and antepartum hemorrhage.
† Includes cervical incompetence as well.

Table 5
Incidence of pregnancy complications of control mothers without treatment and with iron and/or folic acid treatment

Pregnancy complications	Treatment											
	No (N = 214)		Iron (N = 1576)			Folic acid (N = 149)			Iron + folic acid (N = 4419)			Total (N = 6358)
	No.	%	No.	%	OR (95% CI)	No.	%	OR (95% CI)	No.	%	OR (95% CI)	No.
Threatened abortion	39	18.2	295	18.7	1.0 (0.7–1.5)	32	21.5	1.2 (0.7–2.1)	860	19.5	1.1 (0.8–1.5)	1226
Nausea-vomiting, severe	48	22.4	238	15.1	**0.6 (0.4–0.9)**	24	16.1	0.7 (0.4–1.1)	505	11.4	**0.4 (0.3–0.6)**	815
Preeclampsia-eclampsia	8	3.7	46	2.9	0.8 (0.4–1.7)	7	4.7	1.3 (0.5–3.6)	150	3.4	0.9 (0.4–1.9)	211
Gestational hypertension	1	0.5	1	0.1	0.1 (0.0–2.2)	0	0.0	—	2	0.1	0.1 (0.0–1.1)	4
Gestational diabetes	2	0.9	7	0.4	0.5 (0.1–2.3)	1	0.7	0.7 (0.1–8.0)	20	0.5	0.5 (0.1–2.1)	30
Placental disorders*	3	1.4	15	1.0	0.7 (0.2–2.3)	1	0.7	0.5 (0.0–4.6)	74	1.7	1.2 (0.4–3.8)	93
Polyhydramnios	4	1.9	10	0.6	0.3 (0.1–1.1)	0	0.0	—	31	0.7	0.4 (0.1–1.1)	45
Oligohydramnios	0	0.0	0	0.0	—	0	0.0	—	1	0.0	—	1
Threatened preterm delivery†	28	13.1	230	14.6	1.1 (0.7–1.7)	20	13.4	1.0 (0.6–1.9)	792	17.9	1.5 (0.9–2.2)	1069

Bold numbers show significant associations.
* Includes placenta previa, premature separation of placenta, and antepartum hemorrhage.
† Includes cervical incompetence as well.

gestational age and lowest rate of preterm births were found after iron + folic acid supplementation in anemic pregnant women, but the mean birth weight was lower and the rate of low birth weight newborns was higher than in the group of anemic pregnant women with folic acid alone treatment. Thus folic acid may have a more obvious effect for birth weight and the rate of low birth weight newborns than iron.

Table 8 shows the risk of 25 different CA groups in the offspring of women with anemia compared to their matched controls without CA born to mothers with anemia. There was no higher risk in the group of total CAs and in any specific group of CAs. In fact, adjusted OR with 95% CI was lower in the total CA group and 12 specific CA groups. We attempted to evaluate these associations only in women with recorded anemia in the second and/or third gestational months, i.e., critical period of most major CAs, again without any association. The adjusted OR with 95% CI was 0.78, 0.71–0.85 in the total group of CAs, and was also lower in three specific CA groups. The lowest risk was found in the CA of ears but based on only 10 cases. The lower risk of undescended testis cannot be evaluated because the critical period of this CA is during the last gestational months. However, the somewhat lower risk of cardiovascular CAs needs further studies because this CA group is the most frequent among the major CAs.

Discussion

We examined the efficacy of iron supplementation during pregnancy in anemic pregnant women regarding the incidence of their pregnancy complications and birth outcomes of their newborn infants. The newborns of pregnant women with early diagnosis of anemia but without iron treatment had a significantly shorter gestational age at delivery and somewhat higher rate of preterm births. However, this higher rate of preterm birth was not found in newborn infants of anemic pregnant women with iron supplementation during the first trimester of pregnancy. The incidence of pregnancy complications was higher in anemic pregnant women particularly among case mothers. Only severe nausea-vomiting was reduced by iron treatment in anemic pregnant women. A higher rate of CAs was not found in the offspring of pregnant women with anemia; in fact, the total rate of CAs and some specified CAs were lower. The secondary finding of the study was that pregnant women with anemia treated by iron supplements showed a healthier lifestyle and more consciousness of medical care.

The prevalence of anemia during the study pregnancy was 14.2% and 16.7% in case and control mothers in the study, respectively, i.e., a higher figure was recorded in control mothers. The origin of anemia was iron deficiency in most pregnant women.

As the classical study of Scott and Pritchard [27] showed, the iron stores in healthy women are marginal at best due to the menstrual blood loss (25–30 mL) in every female cycle. However, pregnancy presents substantial demands on iron balance above and beyond what is saved by 9 mo of amenorrhea. Thus the usual diet in general cannot supply this large demand of iron; therefore, supplementation of iron is necessary during pregnancy [28].

Table 6
Birth outcomes of newborns without defects (controls) born to pregnant women with anemia or without anemia

Birth outcomes	Pregnant women				Comparison			
	Without (N = 31 793)		With anemia (N = 6358)		Crude		Adjusted	
	Mean	SD	Mean	SD	*t*	*P*	*t*	*P*
Quantitative								
Gestational age (wk)	39.4	2.0	39.4	2.2	1.5	0.13	1.6*	0.10
Birth weight (g)	3275	513	3278	500	0.3	0.74	0.2†	0.81
Categorical	No.	%	No.	%	OR (95% CI)		OR (95% CI)	
Preterm birth	2919	9.2	577	9.1	0.99 (0.90–1.08)		0.97 (0.88–1.07)*	
Low birth weight	1850	5.8	317	5.0	**0.85 (0.75–0.96)**		**0.85 (0.74–0.99)**†	

Bold numbers show significant associations.
* Adjusted for maternal age, birth order, and maternal socio-economic status.
† Adjusted for maternal age, birth order, maternal socio-economic status, and gestational age.

Table 7
Birth outcomes of newborns without defect (i.e., controls) born to anemic pregnant women without treatment and with iron treatment, in addition to folic acid and iron + folic acid and treatment

Birth outcomes	Treatment									
	Without (N = 214)		With iron (N = 1576)		Comparison adjusted		With folic acid (N = 1567)		With iron and folic acid (N = 1567)	
	Mean	SD	Mean	SD	*t*	*P*	Mean	SD	Mean	SD
Quantitative Gestational age (wk)	38.9	2.3	39.3	2.1	**2.2**[*]	**0.03**	39.4	2.0	39.5	2.0
Birth weight (g)	3234	545	3267	482	0.1[†]	0.91	3348	470	3282	505
Categorical	No.	%	No.	%	OR (95% CI)		No.	%	No.	%
Preterm birth	32	15.0	168	10.7	**0.67 (0.44–0.99)**[*]		14	9.4	363	8.2
Low birth weight	16	7.5	70	4.4	0.73 (0.35–1.55)[†]		5	3.4	226	5.1

Bold numbers show significant associations
[*] Adjusted for maternal age, birth order, and maternal socio-economic status.
[†] Adjusted for maternal age, birth order, maternal socio-economic status, and gestational age.

Previous studies showed a higher risk of preterm births and low birth weight newborns [2–16], in addition to stillbirth [29] in pregnant women with iron deficiency anemia. The reason that maternal anemia during the first and second trimesters is associated with an increased risk of preterm delivery/birth is not known [2]; only three hypotheses were generated, as follows: 1) hypoxia in the placenta and fetus; 2) increased oxidative stress in iron-deficient women cannot be neutralized by endogenous or dietary antioxidants; 3) reduced immune function due to iron deficiency associates with a higher risk of infection with increased production of inflammatory cytokines, secretion of corticotropin-releasing hormone, and production of prostaglandin [30]. However, these consequences of iron deficiency anemia can be prevented with appropriate iron treatment as our study indicated.

Our findings can be explained by the following three suppositions/facts: 1) most pregnant women may have mild anemia; 2) nearly all were treated with iron and it may be effective; 3) anemic women are considered a high-risk group of pregnant women with a higher standard of preconceptional and prenatal care and a healthier lifestyle. Recent meta-analyses of available data showed also that mild and/or treated iron deficiency anemia may be associated with little harm to either pregnant women or the fetus [1,31,32].

There were three secondary findings of the study that need attention. The first is the association of anemia with constipation-related hemorrhoids. This observation can be explained by the well-known association between constipation and hemorrhoids, frequently bleeding in our pregnant women. The cause of the so-called new-onset "pregnancy constipation"

Table 8
Estimation of risk for congenital abnormalities (CAs) in informative offspring of anemic pregnant women compared to matched control newborns without defect born to mothers with anemia

Study groups	Grand total No.	Entire pregnancy				II ± III mo			
		No.	%	OR[*] 95% CI		No.	%	OR[*] 95% CI	
Controls	38 151	6358	16.7	Reference		2022	5.3	Reference	
Isolated CAs									
Neural-tube defects	1203	195	16.2	0.7	0.6–0.9	61	5.1	1.0	0.7–1.4
Cleft lip ± palate	1374	190	13.8	0.7	0.6–0.9	78	5.7	1.2	0.8–1.6
Cleft palate only	601	86	14.3	0.8	0.5–1.0	28	4.7	0.8	0.4–1.3
Oesophageal atresia/stenosis	217	23	10.6	0.5	0.3–0.9	5	2.3	0.4	0.1–1.0
Congenital pyloric stenosis	241	45	18.7	0.8	0.5–1.4	19	7.9	1.6	0.7–3.4
Intestinal atresia/stenosis	153	19	12.4	0.9	0.5–1.8	4	2.6	0.5	0.1–1.9
Rectal/anal atresia/stenosis	220	21	9.6	0.5	0.3–0.9	3	1.4	0.3	0.1–1.0
Renal a/dysgenesis	126	14	11.1	0.8	0.3–1.9	5	4.0	0.8	0.2–3.7
Obstructive urinary CAs	343	40	11.7	1.0	0.6–1.6	18	5.3	1.6	0.7–3.6
Hypospadias	3038	432	14.2	0.8	0.7–0.9	128	4.2	0.9	0.7–1.2
Undescended testis	2051	263	12.8	0.6	0.5–0.8	74	3.6	0.5	0.4–0.7
Exomphalos/gastroschisis	238	38	16.0	0.9	0.5–1.6	9	3.8	0.5	0.2–1.1
Microcephaly, primary	109	15	13.8	0.8	0.3–2.2	2	1.8	0.1	0.0–1.2
Hydrocephaly, congenital	314	43	13.7	0.6	0.4–0.9	12	3.8	0.4	0.2–1.0
Eye CAs	99	11	11.1	0.4	0.1–1.2	4	4.0	0.9	0.2–4.1
Ear CAs	354	52	14.7	0.6	0.4–0.9	10	2.8	0.2	0.1–0.5
Cardiovascular CAs	4479	603	13.5	0.8	0.7–0.9	159	3.6	0.7	0.6–0.9
CAs of genital organs	123	15	12.2	1.0	0.4–2.2	5	4.1	1.0	0.3–3.7
Clubfoot	2424	361	14.9	0.8	0.7 –0.9	93	3.8	0.7	0.5–1.0
Limb deficiencies	548	91	16.6	0.9	0.6–1.2	31	5.7	1.0	0.6–1.8
Poly/syndactyly	1744	258	14.8	0.8	0.6–0.9	76	4.4	0.8	0.6–1.0
CAs of musculo-skeletal system	516	105	20.4	1.0	0.7–1.4	46	8.9	1.1	0.7–1.7
Diaphragmatic CAs	243	27	11.1	0.6	0.3–1.0	7	2.9	0.5	0.2–1.2
Other isolated CAs	736	102	13.9	1.0	0.8–1.3	27	3.7	1.0	0.6–1.7
Multiple CAs	1349	193	14.3	0.7	0.6–0.9	55	4.1	0.7	0.5–1.0
Total	22 842	3240	14.2	0.77	0.73–0.81	959	4.2	0.78	0.71–0.85

[*] OR adjusted for maternal age and employment status, birth order, and folic acid use in the first trimester.

mainly in the third and fourth gestational months is the common oral iron therapy during pregnancy, which may exacerbate constipation [33,34].

The second finding is the association of anemia and hypotension; the question is whether they have common or independent origin.

The third unexpected finding is the lower risk of some CA. Obviously anemia is not a teratogenic agent, but anemia cannot prevent CAs. However, beyond the healthier lifestyle the primary preventive effect of folic acid and folic acid containing multivitamin for neural-tube defect and some other CAs may explain the lower prevalence at birth of cardiovascular CAs [35–37], although the parallel use of folic acid supplementation in the first trimester was considered a confounder at the calculation of adjusted OR. However, multivitamins and others supplements, e.g., iron, may also contribute to this beneficial effect. Previously we showed that the combination of iron and a high dose of folic acid (about 6 mg) was able to reduce significantly the total (birth + fetal) prevalence of cases with Down syndrome [38].

The strengths of the HCCSCA are the population-based and large data set including 9600 pregnant women with prospectively and medically recorded anemia in an ethnically homogeneous Hungarian (Caucasian) population. Additional strengths include the matching of cases to controls without CAs; medically recorded pregnancy complications, gestational age at delivery, and birth weight; available data of potential confounders. Finally, the diagnosis of medically reported CAs was checked in the HCAR [18] and later modified, if necessary, on the basis of recent medical examination within the HCCSCA [17].

The major weakness of our study are: 1) The study is connected with the diagnosis of anemia, although it was based on the results of laboratory examination but in general the hemoglobin and hematocrit values and/or the number of red blood cells were not recorded in the prenatal maternity logbooks or they were not copied from the available medical documents; thus, we cannot estimate the severity and types (mycro-, normo-, macrocytic anemia). 2) The time of anemia diagnoses was recorded but not the true onset of anemia in the prenatal maternity logbook. 3) After the first diagnosis of anemia during the study pregnancy followed by iron treatment, it was difficult to evaluate the course of anemia, i.e., laboratory findings. 4) Many pregnant women without recorded anemia were also supplemented by iron; thus, the causal effect of iron for the treatment of iron deficiency anemia could not be estimated. 5) We were not able to evaluate the occurrence of miscarriages in the study pregnancy. 6) The occurrence of maternal smoking as a confounder was not known in the total data set. Our previous study showed the low validity of retrospective maternal self-reported information regarding smoking and alcohol drinking during pregnancy [39]; therefore, these data were collected only in a minor part of the data set of the HCCSCA based on the cross interview of women and their family members at the home visit. Of 2640 case mothers, 580 (22.0%), while of 800 control mothers, 152 (19.0%) smoked during pregnancy, which corresponded well to the figure of smoking among Hungarian pregnant women [40]. The differentiation of these pregnant women with or without anemia showed that mothers with anemia had a lower rate of smoking habit during the study pregnancy.

The main message of our study is that anemia, likely in most pregnant women due to iron deficiency, with iron supplementation, does not pose a risk for pregnant women and their fetuses. Thus there are significant benefits to birth outcomes for pregnant women who were anemic and took an iron supplement.

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