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Ergotamine treatment during pregnancy and a higher rate of low birthweight and preterm birth

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What is already known about this subject

- Previously the association between oral ergotamine treatment during pregnancy and gestational age, birthweight, the frequency of preterm birth and low birthweight has not been studied.
- Ergotamine is a drug that is not used frequently nowadays.

What this study adds

- The association between low birthweight and/or preterm birth and ergotamine treatment may be connected with ergotamine-induced vasoconstriction in the placenta of pregnant women.
- The pharmacological model used in this study could be used to evaluate the placental effects of other drugs.

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Aims
Previously the association between oral ergotamine treatment during pregnancy and gestational age at delivery, birthweight, the rate of preterm birth and low birthweight has not been studied.

Methods
Newborn infants without congenital abnormalities born to mothers with or without ergotamine treatment during pregnancy were evaluated in the population-based data set of the Hungarian Case-Control Surveillance of Congenital Abnormalities between 1980 and 1996.

Results
Of 38 151 newborn infants with medically recorded gestational age and birth weight, 77 were born to mothers who had received ergotamine treatment during pregnancy. A statistically significant decrease was found in the mean gestational age (0.7 weeks) and birth weight (196 g) among exposed relative to unexposed infants, though these differences were not obstetrically significant. However, there was a significant increase in the proportion of low birthweight newborns (16.4% *vs.* 5.7%) and preterm births (16.4% *vs.* 9.2%) after the use of ergotamine during pregnancy. The effect of ergotamine was more obvious in male newborn infants, particularly after treatment in the third trimester.

Conclusions
The association between low birthweight and/or preterm birth and ergotamine treatment may be connected with the effect of ergotamine on the placenta of pregnant women.

Introduction

Ergotamine is an ergot alkaloid that acts as a vasoconstrictor in many vascular beds, but the precise effect of different doses of ergot alkaloids on the placental vasculature of humans is not known [1]. Uterine bleeding mainly after delivery and miscarriage was frequently treated with ergotamine. Ergotamine or ergotamine in combination with other drugs were also used for the treatment of migraine [2]. Previously we found an association between ergotamine use during the second and third gestational month and neural-tube defects [3, 4].

As far as we know the possible association between ergotamine treatment during pregnancy and gestational age at delivery and birth weight, and also the rate of preterm birth and low birthweight newborns has not been studied. There were 38 151 liveborn infants without congenital abnormalities in the population-based Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) [5] between 1980 and 1996. Therefore we decided to evaluate the birth outcomes of these newborn infants born to mothers with or without ergotamine treatment during pregnancy.

Methods

Newborn infants without congenital abnormalities were selected from the National Birth Registry of the Central Statistical Office for the HCCSCA. Only newborns without congenital anomalies were included in the study because congenital anomalies may have an effect on gestational age as well as birthweight.

Exposure and confounder data were collected from three sources. (i) A reply paid questionnaire with an explanatory letter and a list of medicinal products (including ergotamine) and diseases was mailed immediately after the selection of newborn infants to their parents. The questionnaire requested information on medicinal (drug and pregnancy supplements) intake, pregnancy complications, and maternal diseases during pregnancy, according to gestational months. To standardize the answers, mothers were asked to read the enclosed lists of medicinal products and diseases as a memory aid before they replied. The average time interval between end of pregnancy and questionnaire return was 5.2 ± 2.9 months. (ii) Mothers were also asked to send their antenatal care logbook, discharge summary of delivery including birthweight and gestational age and all other medical records concerning their pregnancy. (iii) Regional nurses visited and questioned 200 nonrespondent mothers [6]. They helped to fill in the questionnaire and they evaluated the available antenatal logbooks, discharge summaries, etc. The necessary exposure data were available for 83.0% (82.6% from reply, 0.4% from visit) of mothers and the antenatal care logbook was available for 93.8% of the women.

Two ergotamine containing medicinal products were evaluated. For ergotamine tartrate (Ergam®, Richter), the recommended use was 25 drops two or three times daily which corresponded to 0.6 mg ergotamine. The oral tablet of Kefalgin® (Richter) contained 0.2 mg ergotamine tartrate, 60 mg caffeine, 150 mg aminophenazone and 5 mg belladonna leaf extract. Two tablets are recommended first followed by one tablet 30 min later, and the maximum daily intake is six tablets.

Ergotamine exposure was evaluated in five different ways. (i) The source of information: data from the antenatal care logbook (obstetricians are obliged to record all prescribed drugs for women concerning pregnancy-related complications and diseases in the logbook and/or other medical records, mainly discharge summary); data from the questionnaire (including drugs used for treatment of diseases unrelated to pregnancy prescribed by general practitioners or other physicians; in addition, drugs taken by the personal choice of pregnant women); concordant data from both medical records and questionnaire. (ii) The route of administration: both ergotamine products were administered orally. (iii) Dose and (iv) duration of treatment. (v) Gestational age was calculated from the first day of the last menstrual period. The definition of preterm birth was <37 completed weeks (<259 days). Thus term births occurred from 37 to less than 42 completed weeks (259–293 days). The definition low birthweight was less than 2500 g (up to, and including 2499 g).

Maternal age, birth order, marital and employment status, acute and chronic maternal diseases, pregnancy supplements and other drug uses were evaluated as confounders. In addition, the possible association between pregnancy complications and gestational age was analyzed.

The statistical analysis was based on the SAS version 8.02 statistical software package (SAS Institute Inc., Cary, North Carolina, USA). The quantitative variables (e.g. maternal age) were analyzed by Student's *t*-test, while the chi square test was used for categorical variables. The possible association between pregnancy complications, maternal diseases, other frequently used drugs during pregnancy and ergotamine treatment was checked by crude prevalence odds ratio (POR) and 95% confidence interval (95% CI). For the comparison of mean birthweight and gestational age between exposed and unexposed groups crude and adjusted Student's *t*-test was used. To evaluate preterm birth and low birthweight newborns crude and adjusted POR with 95% CI

Table 1
Distribution of treatment according to gestational months

Ergotamine products		Gestational months 1	2	3	4	5	6	7	8	9	Total
Ergotamine drops	*n*	10	7	7	5	3	3	7	4	9	55
	%	18.2	12.7	12.7	9.1	5.5	5.5	12.7	7.3	16.4	100
Kefalgin®	*n*	10	6	3	1	1	1	0	0	0	22
	%	45.5	27.3	13.6	4.5	4.5	4.5	0.0	0.0	0.0	100

were calculated. Multiple logistic regression was used to adjust for the confounding factors.

Results

During the study period there were 2 146 574 births in Hungary. Hence 38 151 subjects represented 1.8% of the births. Of 38 151 liveborn infants, 55 (0.14%) had mothers who were treated orally with drops of ergotamine, while 22 (0.06%) had mothers who received Kefalgin® tablets during pregnancy. The mean daily dose of ergotamine drops was 1.5 mg and the mean daily dose of Kefalgin® was 0.3 mg. The duration of their treatment showed a wide spectrum from 1 day to 7 months. The mean duration of ergotamine drops and Kephalgin® treatment was 3.2 and 2.1 months, respectively.

Of the 55 treated with ergotamine drops and the 22 receiving Kefalgin® treatment, 47 (85.5%) and 20 (90.9%) had their use medically recorded, respectively. The remainder was reported by the mothers.

Table 1 shows the onset of treatment according to gestational month. The peak for ergotamine treatment was in the first month and this may reflect preconceptional treatment. The last month had the second highest frequency of ergotamine treatment. When these data regarding the birth outcome are evaluated, we have to consider three facts: (a) The gestational age is calculated from the first day of the last menstrual period. Thus pregnant women are not pregnant in the first 2 gestational weeks, while during the third and fourth gestational weeks the transportation of zygotes in the Fallopian tube and implantation of blastocysts in the uterus occur. However, both zygotes and blastocyst are comprised of stemcells explaining the all-or-nothing effect rule, i.e. any insult results in either very early loss or no ill effects on the pregnancy at all. (b) The real fetal growth does not occur in normal pregnancies before 18 completed gestational weeks of pregnancy. Thus all ergotamine exposures that occurred in pregnant women before the second trimester of pregnancy should not be considered as relevant exposures regarding birth weight. (c) The duration of treatment showed a wide spectrum and we used the previously mentioned mean values in our calculations.

The characteristics of the mothers are shown in Table 2. Mean maternal age was lower in the group receiving ergotamine drops than in the untreated pregnant women. A similar difference was not seen when comparing the Kefalgin® treated with the untreated group. Mean birth order and marital status were similar in the exposed and unexposed groups. Semiskilled pregnant women used ergotamine drops more frequently during pregnancy.

Table 3 summarizes the occurrence of pregnancy complications. The prevalence of threatened abortions and particularly of placental disorders was greater in the ergotamine drops group compared with the Kefalgin® treated group. All the five pregnant women with placental disorders had placenta previa with antepartum haemorrhage and ergotamine drop treatment in the last month of pregnancy, and four had a Caesarean section. Kefalgin® treatment was more frequent in women with excessive nausea and vomiting during pregnancy.

There was no difference in the prevalence of acute maternal disorders between the exposed and unexposed groups. Among chronic maternal diseases, migraine showed a predominance in the exposed groups as a main indication for ergotamine treatment.

The distribution and occurrence of other frequently used drugs were similar in exposed and unexposed groups. Among pregnancy supplements, folic acid showed a higher use in the group exposed to ergotamine (72.7%) than in the unexposed (54.4%) group (POR with 95% CI 2.2; 1.2, 4.0).

The distribution of gestational age at delivery and birth weight in the ergotamine exposed and unexposed groups is shown in Table 4. Mean gestational age was shorter by 0.7 weeks after the use of ergotamine drops during pregnancy (adjusted $t = 2.5$, $P = 0.01$). The mean birthweight was also lower by 196 g (adjusted $t = 2.1$, $P = 0.04$) in the newborn infants born to mothers with ergotamine treatment during pregnancy than in the

Table 2
Maternal characteristics in the untreated (i.e. no ergotamine drops or Kefalgin® tablet treatment) and treated groups

Maternal variables	Untreated ($n = 38\,074$)		Ergotamine ($n = 55$)		Comparison		Kefalgin® ($n = 22$)		Comparison	
	Mean	SD	Mean	SD	*t*	*P*	Mean	SD	*t*	*P*
Quantitative										
Maternal age (years)	25.5	4.9	24.2	3.7	2.5	0.02	25.3	3.8	0.2	0.86
Birth order	1.7	0.9	1.7	0.8	0.4	0.70	1.9	0.9	0.9	0.40
Categorical	*n*	%	*n*	%	POR	95% CI	*n*	%	POR	95% CI
Unmarried	1 469	3.9	2	3.6	0.9	0.2, 3.9	0	0.0	–	–
Employment status										
Professional	4 349	11.4	3	5.5	0.4	0.1, 1.4	1	4.5	0.4	0.1, 2.7
Managerial	10 117	26.6	12	21.8	0.8	0.4, 1.5	5	22.7	0.8	0.3, 2.2
Skilled worker	11 667	30.6	15	27.3	0.8	0.5, 1.5	8	36.4	1.3	0.5, 3.1
Semiskilled worker	5 765	15.1	16	29.1	2.3	1.3, 4.1	2	9.1	0.6	0.1, 2.4
Unskilled worker	1 852	4.9	5	9.1	2.0	0.8, 4.9	2	9.1	2.0	0.5, 8.4
Housewife	2 037	5.4	0	0.0	–	–	1	4.6	0.8	0.1, 6.3
Others	2 287	6.0	4	7.3	1.2	0.4, 3.4	3	13.3	2.5	0.7, 8.4

Table 3
Prevalence of pregnancy complications

Pregnancy complications	Untreated ($n = 38\,074$)		Ergotamine drops ($n = 55$)		Comparison		Kefalgin® ($n = 22$)		Comparison	
	n	%	*n*	%	POR	95% CI	*n*	%	POR	95% CI
Threatened abortion	6491	17.1	16	29.1	**2.0**	**1.1, 3.6**	5	22.7	1.4	0.5, 3.9
Nausea, vomiting (excessive)	3856	10.1	7	12.7	1.3	0.6, 2.9	6	27.3	**3.3**	**1.3, 8.5**
Preeclampsia*, eclampsia	3215	8.4	5	9.1	1.1	0.4, 2.7	1	4.6	0.5	0.1, 3.8
Threatened preterm delivery	5444	14.3	11	20.0	1.5	0.8, 2.9	5	22.7	1.8	0.7, 4.8
Placental disorders**	587	1.5	5	9.1	**6.4**	**2.5, 16.1**	0	0.0	–	–
Anaemia	6337	16.6	14	25.5	1.7	0.9, 3.1	5	22.7	1.5	0.5, 4.0

**Including pregnancy hypertension, oedema and proteinuria; **including placenta previa, premature separation of placenta, antepartum haemorrhage; Bold numbers show significant association.*

newborns of unexposed women. The proportion of preterm births (16.4% *vs.* 9.2%) was 1.8-times larger in the exposed group (adjusted POR 1.9; 95% CI 1.0, 4.0). The proportion with low birthweight (16.4% *vs.* 5.7%) was 2.9 fold larger in the exposed groups (adjusted POR with 95% CI 2.8; 1.2, 6.5).

The sex of newborns can modify mean birth weight. The difference in mean birth weight between male and female newborns was 118–139 g in Hungary during the years of the study period. There was no significant difference in the male : female ratio between exposed (37 : 18; 67.3%) and unexposed (24 762 : 13 334; 65.0%) ergotamine drop groups ($P = 0.72$). The higher proportion of males is explained by the fact that these newborns who acted as controls were matched to cases with congenital abnormalities which have a male predominance due to the high rate of defects in male genitalia, such as hypospadias and undescended testis.

The mean birth weight was 245 g lower in males and this significant reduction was in agreement with the 3.7 times higher rate of low birthweight newborns (Table 5). The mean gestational age was 1 week shorter in males and it was reflected in a 2.6 higher rate of preterm births. The mean birth weight difference (106 g) and gestational age (0.3 weeks) did not show a significant difference between females born to treated and untreated

Table 4
Distribution and mean (±SD) gestational age at delivery and birth weight in newborn infants born to mothers with or without treatment with ergotamine drops

	Gestational age (weeks)						Exposed				Unexposed			
	<36		37–41		>42		Total		Gestational age (weeks)		Total		Gestational age (weeks)	
Birth weight (g)	Yes	No	Yes	No	Yes	No	number	%	Mean	SD	number	%	Mean	SD
<2499	6	1277	3	830	0	51	9	16.4	35.0	3.4	2158	5.7	35.6	3.2
2500–3499	3	2181	26	19 160	2	1468	31	56.4	38.8	1.8	22 809	59.9	39.1	1.8
>3500	0	29	14	10 760	1	2340	15	27.3	40.5	1.5	13 129	34.5	40.7	1.2
Total number	9	3487	43	30 750	3	3859	55	100.0	38.7	2.7	38 096	100.0	39.4	2.0
%	16.4	9.2	78.2	80.7	5.5	10.1	100.0				100.0			
Mean	2162	2484	3247	3 323	3440	3615	3080				3 276			
SD	549	436	481	429	185	485	629				511			

Table 5
Mean birth weight and gestational age at delivery (±SD), the rate of low birthweight newborns and preterm births in males and females born to mothers with or without treatment with ergotamine drops

	Birth weight (g)						Gestational age (weeks)						Low birthweight newborns					Preterm births				
	Treated		Untreated		Comparison		Treated		Untreated		Comparison		Treated		Untreated		Comparison	Treated		Untreated		Comparison
Study groups	Mean	SD	Mean	SD	*t*	*P*	Mean	SD	Mean	SD	*t*	*P*	*n*	%	*n*	%	POR (95% CI)	*n*	%	*n*	%	POR (95% CI)
Male	3079	693	3324	513	**2.1**	**0.03**	38.4	3.1	39.4	2.0	1.9	0.06	6	16.2	1232	5.0	**3.7 (1.5, 8.8)**	7	18.9	2062	8.3	**2.6 (1.1,5.8)**
Female	3081	489	3187	494	0.9	0.36	39.0	1.7	39.3	2.1	0.4	0.66	3	16.7	926	7.0	2.7 (0.8, 9.2)	2	11.1	1425	10.7	1.0 (0.2,4.5)
The onset of treatment after:																						
first trimester	2961	681	3276	511	**2.6**	**0.01**	38.3	3.0	39.4	2.0	**2.0**	**0.05**	6	19.4	2161	5.7	**4.0 (1.6, 9.7)**	6	19.4	3490	9.2	**2.4 (0.9,5.8)**
second trimester	2781	740	3276	511	**3.0**	**0.007**	37.9	3.5	39.4	2.0	1.9	0.07	6	30.0	2161	5.7	**7.1 (2.7, 18.4)**	5	25.0	3491	9.2	**3.3 (1.2,9.1)**

Bold numbers show significant associations.

mothers. Therefore there was no difference in the rate of low birthweight newborns and preterm births between the two study groups. However, it is necessary to note the lower number of treated females.

We evaluated ergotamine exposure in pregnant women after the first trimester and particularly after the second trimester as relevant exposures (Table 5). The most obvious reduction in mean birth weight (495 g) and increase (7.1 fold) in the rate of low birthweight newborns were found if ergotamine treatment started after the second trimester. A significant but less obvious effect was observed in the group of pregnant women who started ergotamine treatment after the first trimester.

The analysis of gestational age and specific birth weights indicated intrauterine growth retardation, though the gestational age was also shorter in the treated group.

The data for Kefalgin® were similar to the findings with ergotamine drops but less obvious, probably due to the much lower dose of ergotamine. Mean gestational age (39.0 weeks) was shorter, while birth weight (3183 g) was smaller, in addition the proportion of preterm births (13.3%) and low birthweight newborns (9.1%) was larger in the exposed than in unexposed group. The number of newborns was too low for further analyses.

Discussion

Treatment with ergotamine drops during pregnancy was associated with a shorter gestational age (0.7 weeks) and lower birth weight (196 g). However, this statistically significant difference is not really an obstetrically significant difference. However, the 1.8 times higher proportion of preterm births and 2.9 times higher rate of low birthweight seem to be more important but these figures were based only on nine newborns. This association was found only in male newborn infants and it was obvious (495 g birth weight reduction and 7.1 fold increase in the rate of low birthweight newborns) due to treatment with ergotamine drops after the second trimester of pregnancy. In addition there was a dose-dependent effect because ergotamine drops (daily dose 1.5 mg) had a greater effect on birth outcomes than Kefalgin® (with daily dose of 0.3 mg ergotamine).

The benefits of the HCCSCA are (i) it is population-based, (ii) the data set is large and included 77 newborn infants born to mothers receiving ergotamine treatment, (iii) it is ethnically homogeneous (European-Caucasian), (iv) birth weight and gestational age were recorded, and (v) most pregnant women had medically recorded (i.e. prospective) ergotamine treatment. This dataset also has drawbacks: (i) ergotamine is considered a teratogenic drug in humans, and therefore it was used rarely during pregnancy in Hungary, (ii) the response rate of women was 83%. However, a previous validation study did not indicate significant differences in drug use between mothers with and without response [6], (iii) the identification of ergotamine treatment was based on maternal self-reporting in 9–14% of pregnant women. Ergotamine products were prescribed for migraine by other physicians and these pregnant women did not mention this during antenatal care, (iv) the average time interval between the end of pregnancy and questionnaire return was 5.2 ± 2.9 months. Elsewhere we have shown that maternal data are reliable [6] and this time interval did not modify the medically recorded data, (v) most women treated with ergotamine also used other medicinal products. However, there was no difference in the distribution and occurrence of other drugs between exposed and unexposed pregnant women, (vi) no information was obtained regarding smoking and alcohol consumption in the total data set because of the low validity of these data during pregnancy in Hungary [7], although smoking has a well-known birth weight reduction effect [8, 9]. However, the proportion of smokers during pregnancy (19.5%) was known in the home visit subsample of 200 control women and this corresponded to the Hungarian population figure [10]. Thus we supposed that there was no significant difference in the rate of smokers in the exposed and unexposed subgroups, and (vii) most birth weights and gestational age at delivery were medically recorded. However, while birth weight is a reliable birth outcome endpoint, the gestational age at delivery and at the time of drug ingestion was based on the last menstrual period which is not reliable. Ultrasound scanning can be used to improve the accuracy of gestational age, but it was rarely performed in our pregnant women during the study period. However, we suppose that this error was the same in the exposed and unexposed groups.

At present, preterm birth is a major problem in obstetrics, accounting for 70% of perinatal mortality and nearly half of long-term neurologic morbidity [11, 12]. In Hungary, the prevalence of preterm births is extremely high, at approximately 9% of all livebirths [13].

Schon *et al.* [14] found a reduction in fetal weight in the offspring of pregnant mice, rats and rabbits after oral ergotamine treatment. Hughes & Goldstein [15] hypothesized that ergotamine produces vasocontriction in the fetus and subsequent congenital abnormalities, but the rate of preterm birth and low birthweight has not been reported.

The proportion of low birthweight infants was larger than the proportion of preterm births after ergotamine

treatment in our study. We may suppose that this was due to intrauterine fetal growth retardation which is associated with a higher occurrence of preterm births, caused by the effect of ergotamine in the placenta. The higher sensitivity of male fetuses to the effect of ergotamine needs further explanation and/or studies.

In conclusion, a shorter mean gestational age and smaller mean birth weight, in addition to a higher rate of low birthweight newborns and preterm births, were found after ergotamine treatment during pregnancy, particularly in male fetuses and after ergotamine treatment in the third trimester. These associations might be explained by the effect of ergotamine on the placenta.

Competing interests: None declared.

References

1 Benke S, Schild HO, eds. Ergot alkaloids. Handbook of Experimental Pharmacology, Vol. 49. Springer Verlag, Berlin 1978.

2 Diamond S. Migraine headache prevention and management. Marcel Dekker, New York-Basel, 1990.

3 Czeizel AE. Teratogenicity of ergotamine. J Med Genet 1989; 26: 69–71.

4 Ács N, Bánhidy F, Puhó EH, Czeizel AE. A possible dose-dependent teratogenic effect of ergotamine. Reprod Toxic 2006; 22: 551–2.

5 Czeizel AE, Rockenbauer J, Siffel CS, Varga E. Description and mission evaluation of the Hungarian Case-Control Surveillance of Congenital Abnormalities. Teratology 2001; 63: 176–85.

6 Czeizel AE, Petik D, Vargha P. Validation studies of drug exposures in pregnant women. Pharmacoepidemiol Drug Safety 2003; 12: 409–16.

7 Czeizel AE, Petik D, Puhó E. Smoking and alcohol drinking during pregnancy. The reliability of retrospective maternal self-reported information. Cent Eur J Public Hlth 2004; 12: 179–83.

8 Lowe CR. Effects of mothers' smoking on birth weight of their children. Br Med J 1959; ii: 673–6.

9 Nahum GG, Stanislaw H. Hemoglobin, altitude and birth weight: does maternal anemia during pregnancy influence fetal growth? J Reprod Med 2004; 49: 297–305.

10 Czeizel AE, Vitéz M, Kodaj I, Lenz W. Smoking during pregnancy and congenital limb deficiency. Br Med J 1994; 308: 1473–6.

11 McCormick MC. The contribution of low birth weight to infant mortality and childhood morbidity. N Engl J Med 1985; 312: 82–90.

12 Hack M, Fanaroff AA. Outcomes of extremely immature infants – a perinatal dilemma. N Engl J Med 1993; 329: 1649–50.

13 Bjerkedahl T, Czeizel AE, Hosmer DW. Birth weight of single livebirths and weight specific early neonatal mortality in Hungary and Norway. Pediat Perinat Epid 1989; 3: 29–40.

14 Schon H, Leist KH, Ganwiler J. Single day treatment of pregnant rats with ergotamine. (Abstract). Teratology 1995; 11: 32A.

15 Hughes HE, Goldstein DA. Births defects following maternal exposure to ergotamine, beta blockers, and caffeine. J Med Genet 1988; 25: 396–9.