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No effect of human chorionic gonadotropin treatment due to threatened abortion in early pregnancy for birth outcomes

Research article

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Abstract: Human chorionic gonadotropin (HCG) is used parenterally for treatment of threatened abortions and repeated spontaneous abortion in pregnant women. No controlled epidemiological studies of preterm birth and low birthweight newborns in pregnant women with HCG treatment have been published while the results of animal investigations were controversial. The data of 97 pregnant women with HCG treatment in the second and third months of pregnancy due to threatened abortion and/or previous spontaneous abortion(s) was compared with the data of other 38,054 pregnant women in the population-based large data set of the Hungarian Case-Control Surveillance of Congenital Abnormalities. There was no difference in mean gestational age at delivery and birth weight, in addition the rate of preterm birth and low birthweight newborns. Parenteral HCG treatment in the early pregnancy due to threatened abortion did not associate with a higher risk for preterm births or low birthweight newborns. However, a higher occurrence of gestational diabetes was found in pregnant women with HCG treatment and there was a slight male excess among newborn infants ($p=0.06$).

Keywords: *Human chorionic gonadotropin • Pregnancy • Threatened abortion • Preterm birth • Low birthweight newborns*

1. Introduction

Human chorionic gonadotropin (HCG) is used parenterally for the treatment of female infertility due to anovulation and luteal phase deficiency or of threatened and repeated spontaneous abortion in pregnant women. This natural placental hormone is extracted from the urine of pregnant women with a light LH activity and its half-life is about 30 hours [1]. Previously two animal investigations showed a fetal weight reduction after HCG treatment in early pregnancy of mouse and rats [2,3], while parenteral HCG treatment in the rat produced some increase in weight of the newborns [4]. Human studies focused the possible association between abortion, congenital abnormality or multiple pregnancy rates and HCG treatment in early pregnancy [5-8], but birth weight and gestational age at delivery, in addition the rate of preterm births and low birthweight newborns were not evaluated in controlled epidemiological studies [9].

Thus we decided to check the controversial effect of HCG in pregnant women with threatened abortion for the fetal development based on birth weight and gestational age at delivery, in addition the rate of preterm birth and low birthweight in the data set of the HCCSCA [10]. Infertile women with preconceptional HCG treatment were excluded from the study because these data were incomplete in the HCCSCA and we wanted to evaluate a sample as homogeneous as possible.

2. Material and Methods

Newborn infants without birth defects born to mothers with or without HCG treatment as reference during pregnancy were compared. These newborn infants were ascertained from the National Birth Registry of the Central Statistical Office as controls for the HCCSCA. These newborn infants were controls in the HCCSCA and they were matched to every case with congenital abnormalities selected from the Hungarian Congenital Abnormality Registry [11] according to sex, week of

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Table 1. Characteristics of mothers with or without HCG treatment.

Maternal variables	Untreated (N = 38,054)		Treated (N = 97)		Comparison	
Quantitative	No.	%	No.	%		
Maternal age (yr)						
- 24	17,961	47.2	33	34.0		
25 – 29	12,846	33.8	39	40.2	$\chi^2_2 = 7.1$	p = 0.03
30 -	7,247	19.0	25	25.8		
Mean ± S.D.	25.4±4.9		26.8±4.6		t = 2.7	p = 0.006
Birth order						
1	18,141	47.7	68	70.1	$\chi^2_1 = 19.5$	p < 0.0001
2 or more	19,913	52.3	29	29.9		
Mean ± S.D.	1.7±0.9		1.4±0.6		t = 5.5	p < 0.0001
Categorical						
Unmarried	1,470	3.9	1	1.0	$\chi^2_1 = 2.1$	p = 0.15
Employment status						
Professional	4,330	11.4	23	23.7		
Managerial	10,104	26.6	30	30.9		
Skilled worker	11,660	30.6	30	30.9		
Semiskilled worker	5,774	15.2	9	9.3	$\chi^2_6 = 23.9$	p = 0.0005
Unskilled worker	1,859	4.9	0	0.0		
Housewife	2,036	5.4	2	2.1		
Other	2,291	6.0	3	3.1		

birth in the year when the cases were born, and district of parents' residence. There were three restrictions at the selection of cases with congenital abnormalities for the data set of the HCCSCA from the HCAR. On the one hand, only cases reported during the first three months after birth or pregnancy termination were selected because shorter time between the end of pregnancy and data collection increases the accuracy of information regarding pregnancy history without undue loss of power since 77% of cases were reported during this time window [11]. On the other hand, three mild congenital abnormalities (such as congenital dislocation of hip based on Ortolani click, congenital inguinal hernia, and large hemangiomas) were excluded from the data set of the HCCSCA. Finally CA-syndromes caused by major mutant genes and chromosomal aberrations were also excluded from the HCCSCA because they had preconceptional origin. In addition, newborn infants born from multiple pregnancies were excluded from this analysis of controls.

2.1. Exposure and confounder data were obtained from three sources

(1) Mothers were asked to send us the prenatal care logbook (including drugs prescribed by obstetricians), the discharge summary of delivery (including birth weight and gestational age), and all other medical records concerning the study pregnancy. Prenatal care was mandatory for pregnant women in Hungary (if somebody did not visit prenatal care, she did not get maternity grant and leave), thus nearly 100% of pregnant women visited prenatal care with a first visit of 6-12 weeks of gestation and with an average of 7 visits. Obstetricians in prenatal care are obliged to examine pregnant women and to record all pregnancy complications, maternal diseases and prescribed drugs particularly regarding pregnancy in the logbook. Logbooks and other medical documents were sent back to mothers within 3 weeks.

(2) A reply-paid questionnaire with an explanatory letter and lists of drugs and diseases was also sent to the mothers. The questionnaire requested information medicine (drug and pregnancy supplement) intakes, pregnancy complications and maternal diseases during pregnancy according to gestational months. To standardize the answers, mothers were asked to read the enclosed lists of medicines (including HCG) and diseases as a memory aid before they replied.

The average time between end of pregnancy and return of "information package" including questionnaire, prenatal logbook, etc was 5.2 ± 2.9 months with a limit of 3 and 12 months. In addition, 200 non-respondent mothers were visited at home by regional nurses, as part of a validation study [12] and they helped mothers

Table 2. Prevalence of pregnancy complications in pregnant women with or without HCG treatment.

Pregnancy complications	Untreated (N = 38,054)		Treated (N = 97)		Comparison	
	No.	%	No.	%	POR	95% CI
Threatened abortion*	6,463	17.0	77	79.4	5.0	3.3 – 7.4
Nausea, vomiting (excessive)**	3,863	10.2	6	6.2	0.6	0.3 – 1.3
Preeclampsia, eclampsia***	3,214	8.5	7	7.2	0.8	0.4 – 1.8
Threatened preterm delivery°	5,432	14.3	28	28.9	2.4	1.6 – 3.8
Placental disorders°°	587	1.5	5	5.2	3.5	1.4 – 8.6
Gestational diabetes°°°	267	0.7	3	3.1	4.5	1.4 – 14.4
Anemia, iron deficiency°°°	6,345	16.7	11	11.3	0.6	0.3 – 1.2

* *medically recorded vaginal bleeding and/or uterine contractions*
** *prospectively and medically recorded with treatment of antiemetic drugs*
*** *including pregnancy hypertension, oedema and albuminuria*
° *including medically recorded cervical incompetence*
°° *including placenta previa, premature separation of placenta, antepartum hemorrhage*
°°° *medically recorded*

to fill-in the same questionnaire and evaluated the data of available medical documents. The response rate of mothers was 82.6% and 0.4% of mothers were visited at home. Prenatal care logbooks were available in 93.8% of mothers evaluated.

The evaluation of HCG treatment was based on ten approaches: (1) Source of information (i) prospective data from medical records only; (ii) retrospective self-reported maternal information from the questionnaire only; and, (iii) concordant data from both medical records and questionnaire. (2) Type of treatment: HCG alone and HCG plus other drugs. (3) The route of administration: In Hungary three kinds of HCG (Choriogonin®, Richter, and Choragon®, Ferring 1500 or 5000 IU, in addition Profasi®, Serano, 2000 or 5000 IU per ampoule) were available for parenteral treatment. (4-5) Dose and duration of HCG treatment. (6) Gestational age was calculated from the first day of the last menstrual period, while the onset of HCG treatment was evaluated according to months. (7) Pregnancy complications. (8) Confounding factors such as maternal age, birth order, socioeconomic and marital status, maternal disorders and other medicine intakes. (9) Lifestyle factors. Smoking was evaluated on the basis of number of daily cigarettes. Four groups of pregnant women were differentiated according to the drinking habit during the study pregnancy: abstinents (never drink), occasional drinkers (to drink from once during pregnancy to once a week), regular drinkers (more than one drink per week) and daily drinkers (to drink once or more per day). (10) Birth weight and gestational age, and the rate of low birthweight infants (<2,500 g) and preterm birth (<37 weeks or less than 259 days) as primary outcome variables.

2.2. Statistical analysis

Statistical analysis was performed using the software package SAS version 8.02 (SAS Institute Ins., Cary, North Caroline, USA). At the comparison of pregnant women with or without HCG treatment as reference during the study pregnancy, Student t-test was used for quantitative and chi square test for categorical variables. At the comparison of mean gestational age at delivery and birth weight adjusted Student t-test was used. During the analysis of the preterm births, low birthweight newborns, in addition pregnancy complications and medicine intakes, we used unconditional logistic regression model to compare the treated group with the untreated group, and adjusted prevalence odds ratio (POR) with 95% confidence interval (CI) were evaluated. At the calculation of adjusted POR birth order, maternal age, employment status as an indicator of socio-economic status, maternal diseases and other medicine uses were used as confounders.

3. Results

Of 38,151 mothers, 139 (0.36%) were treated by HCG parenterally. The study period contained 2,146,574 total births in Hungary, thus our study sample represented 1.8% of Hungarian births. In general, the recommended protocol was followed in the treatment of women with repeated or threatened abortion, i.e. first 10,000 IU of HCG followed by twice 5000 IU per week until the 14th gestation week.

The first month HCG treatment occurred in 37 pregnant women, this group may reflect the preconceptional use of HCG due to infertility, and HCG treatment was not continued after the recognition of

Table 3. Use of pregnancy supplements by mothers with or without HCG treatment.

Pregnancy supplements	Untreated (N = 38,054)		Treated (N = 97)		Comparison	
	No.	%	No.	%	POR	95% CI
Iron	26,693	70.2	81	83.5	2.2	1.3 - 3.7
Calcium	3,571	9.4	12	12.4	1.4	0.7 - 2.5
Folic acid	20,706	54.4	69	71.1	2.1	1.3 - 3.2
Vitamin B6	4,074	10.7	12	12.4	1.2	0.6 - 2.2
Vitamin D	10,125	26.6	25	25.8	1.0	0.6 - 1.5
Vitamin C	1,659	4.4	19	19.6	5.3	3.2 - 8.8
Vitamin E	2,265	6.0	22	22.7	4.6	2.9 - 7.5
Multivitamins	2,498	6.6	11	11.3	1.8	0.9 - 3.4
Others or unspecified vitamins	4,664	12.3	12	12.4	1.0	0.6 - 1.9

pregnancy, thus these pregnant women were excluded from the study. The onset and/or time of HCG treatment were not specified in five pregnant women, they were also excluded from the study. Thus, finally 97 mothers were evaluated, the onset of HCG treatment was in the second month of gestation in 60 (61.9%) and third month of gestation in 37 (38.1%) pregnant women

Of these 97 mothers, 95 (97.9%) had medically recorded HCG treatment in the prenatal care logbook or discharge summary of hospitalized pregnant women. Nobody used HCG alone.

Characteristics of 97 HCG treated mothers during pregnancy and the other 38,054 pregnant women as reference are shown in Table 1. The mean maternal age was higher in HCG treated mothers because the proportion of women over 25 years old was larger. However, the mean birth order was lower due to the much larger proportion of first birth order. This variable included only previous birth outcomes, but not spontaneous abortions. The higher proportion of professional and managerial women in the treated group is noteworthy.

There was no difference in the prevalence of acute maternal diseases such as influenza, common cold, diseases of respiratory and digestive systems, urinary tract, genital organs and others during the study pregnancy between the HCG treated and reference pregnant women. Among chronic maternal disorders, epilepsy, diabetes mellitus and others were evaluated, but we did not find significant differences in their occurrence of mothers with or without HCG treatment.

Among pregnancy complications (Table 2), the recorded occurrence of threatened abortions was nearly 80% in HCG treated group as the main indication of HCG treatment. The indication of HCG treatment in other HCG treated pregnant women may be previous spontaneous abortion, because it was mentioned by 50 mothers. Thus the recorded threatened abortion was connected with a previous abortion at least in the half of our pregnant women. The threatened preterm deliveries, placental disorders and gestational diabetes occurred also more frequently in the HCG treated than in the untreated mothers. However, of 28 pregnant women with threatened preterm delivery, 14 had also threatened abortion. Of 5 pregnant women with placental disorders, all had threatened preterm delivery and one was recorded with threatened abortion as well. The possible association between gestational diabetes and the indication of HCG treatment is unexpected thus noteworthy.

Of course, drugs used for the treatment of threatened abortion in Hungary such as allylestrenol (33.0%), diazepam (15.5%), drotaverine (21.6%), magnesiums (18.6%), promethazine (30.9%) were found more frequently in HCG treated pregnant women. The higher use of aminophylline (16.5%), dexamethasone (13.4%) and terbutaline (18.6%) may be connected with the treatment of threatened preterm delivery. Clomiphene treatment in the first gestational month occurred in 7 pregnant women and it indicated their infertility followed by HCG treatment in early pregnancy.

Four pregnancy supplements: vitamin E and C, iron and folic acid were used more frequently by HCG treated mothers (Table 3). The use of vitamin E is a popular treatment for infertile women in Hungary.

The main findings of the study are summarized in Table 4. The male excess was more obvious in the newborn infants of treated mothers than the babies of HCG untreated mothers and the difference was near to the level of significance (p=0.06). There was no difference in the rate of preterm births, in addition of low birthweight newborns, and these findings were in agreement with similar mean birth weight and gestational age at delivery. At the calculation of adjusted

Table 4. Characteristics of newborn infants born to mothers with or without HCG treatment.

Variables	Treated (N = 97)		Untreated (N = 38,054)		Adjusted	
Categorical	No	%	No	%	POR	95% CI
Male	72	74.2	24,727	65.0	1.54	0.98 - 2.44
Preterm birth	9	9.3	3,487	9.2	1.19	0.59 – 2.36
Low birth weight	7	7.2	2,160	5.7	1.48	0.68 – 3.21
					Adjusted	
Continuous	Mean	S.D.	Mean	S.D.	t	p
Birth weight	3,278	571	3,276	511	0.4	0.67
Gestational age	39.3	2.1	39.4	2.0	0.8	0.40

t for mean birthweight, gestational age was considered as confounder.

The mean birthweight and mean gestational age at delivery were analyzed separately in boys and girls, but differences related to HCG treatment were not found.

4. Discussion

The results of the study showed that parenteral HCG treatment in the second and third gestational months of pregnancy mainly due to threatened abortion and/or previous spontaneous abortion(s) did not associate with a higher risk for preterm births and low birthweight newborns.

The benefits of the HCCSCA are: (i) national-based; (ii) large data set which includes 97 babies without birth defects born to mother with HCG treatment during the second and third gestational months of pregnancy due to threatened and/or previous abortion; (iii) in an ethnically homogeneous (European-Caucasian) population; (iv) HCG treatment was medically recorded in nearly all mothers; (v) the data of confounding factors were available; and, (vi) birth weight and gestational age at delivery were medically recorded.

However, this data set also has drawbacks: (i) The complete prevalence of previous miscarriages was not known, but 52% of our pregnant women reported on previous spontaneous abortion. This figure seems to be a minimal value due to the possibility of underreporting. The characteristics of our pregnant women were in agreement with this estimation because they were older with a lower birth order. These findings can be explained by previous unsuccessful pregnancies, namely spontaneous abortions. (ii) We attempted to obtain information regarding infertility treatment both from the prenatal logbook and questionnaire, but we estimate an underascertainment in this variable. Our plan was to exclude women with sterility and subfertility from this study, however, 7 women with clomiphene and a higher rate of vitamin E treatment showed that a certain part of our HCG treated pregnant women may have difficulties to achieve conception. (iii) The response rate was 83%, but the prevalence of drugs used during the study pregnancy did not show differences in the respondent and non-respondent mothers [12]. (iv) The proportion of smokers and alcohol drinkers was not known in the total data set due to the unreliable retrospective maternal information [13]. However, the proportion of smokers was 21% in non-respondent control mothers visited at home, similar to the figure of pregnant population in large (about 20%). There was no difference in the proportion of occasional, regular and daily drinkers between HCG treated and untreated mothers. (v) Birth weight and gestational age at delivery were medically recorded as we mentioned previously. However, while birth weight is a reliable birth outcome endpoint, the gestational age at delivery and at the time of drug ingestions were based on last menstrual period which is not reliable. Recently ultrasound scanning can help 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 calculation error was the same in the exposed and unexposed groups.

The previous clinical study of Caspi et al [8] showed an increase in female infants born to 110 pregnant women following induction of ovulation by gonadotropins. This finding was not confirmed by our study, in fact we found a male excess, which needs some discussion. The male excess is characteristic for controls in the data set of the HCCSCA due to the larger proportion of congenital abnormalities in males such as hypospadias and undescended testis and the so-called control newborn infants were matched to cases according to sex. However, the newborns of HCG treated pregnant women had some male excess compared with the newborns of HCG untreated mothers. This finding may be connected with the miscarriage preventive effect of HCG because an obvious male excess was found in early fetal death. Further studies are needed whether our finding is a

chance effect or HCG-related association.

Our previous studies did not show any association between vitamin E and C, in addition iron and folic acid and preterm birth [14].

Experimental animal investigations showed controversial results regarding birth outcomes after HCG treatment during pregnancy. Hultquist and Engfeldt [4] gave HCG injections in the rat and found some increase in the weight of newborn infants. Whether this size increase was due to the reduction in number of fetuses per litter was not evident. Bussi et al [3] reported a reduced fetal weight in rats after the use of high dose (320 IU sc) of human recombinant FSH. Sakai and Endo [2] also found a reduction in fetal weight in mice after intraperitoneal treatment with 2.5, 5.0 or 10.0 IU HCG. The question is that these findings were direct effect of HCG treatment or the secondary consequences of increased litter number.

The major finding of our study is that pregnant women with reported threatened abortions and/or previous spontaneous abortions and parallel HCG treatment did not have higher risks for preterm birth or low birthweight newborns. This is partially understandable because the fetal growth including weight is obvious after the 18th gestational week and HCG treatment occurred in the second and third gestational months. In addition, this finding is good news because there is no higher rate of preterm birth in pregnant women with threatened and/or previous abortions after HCG treatment in early pregnancy.

The unexpected higher risk for gestational diabetes in pregnant women with threatened abortions and HCG treatment is worth studying.

In conclusion, parenteral HCG treatment due to threatened abortion and/or previous spontaneous abortion(s) in the second and third months of pregnancy did not associate with a higher risk for preterm births or low birthweight newborns.

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