VERSITA

Cent. Eur. J. Med. • 9(6) • 2014 • 802-806
DOI: 10.2478/s11536-013-0347-2

Central European Journal of **Medicine**

Fetal growth promoting effect of hydroxyethylrutoside in pregnant women

Research Article

Éva Pósfai*[1], Andrew E. Czeizel[1], Ferenc Bánhidy[3]

1 Foundation for the Community Control of Hereditary Diseases, Budapest, Hungary

2 Second Department of Obstetrics and Gynecology, Semmelweis University, School of Medicine, Budapest, Hungary

Received 29 June 2013; Accepted 27 November 2013

Abstract: Objective. To evaluate the effect of hydroxyethylrutoside (HER) for fetal development because this flavonoid derivate drug is frequently used in pregnant women for the treatment of vascular diseases. Method. Comparative analysis of exposure (HER treatment) during pregnancy in the newborn infants without any defects born to mothers with or without HER treatment in the population-based Hungarian Case-Control Surveillance System of Congenital Abnormalities. Main outcomes measures were gestational age at delivery, birth weight, pre- and post-term birth, low and large birth weight. Results: Of 38,151 newborn infants, 1,143 (3.0%) were born to mothers with oral HER treatment. The mean birth weight of newborn infants born to mothers with HER was 115 grams larger and is associated with a lower rate of low birth weight and a higher rate of large birth weight. Conclusions. Oral HER treatment during pregnancy associates with a fetal growth promotion effect.

Keywords: *Hydroxyethylrutoside • Pregnancy • Birth weigh • Gestational age at delivery • Low birthweight • Preterm birth • Fetal growth promotion • Population-based study*

1. Introduction

At the evaluation of drug treatments during pregnancy, in general their teratogenic, i.e. structural birth defect inducing effect is highlighted. In 1998 we attempted to evaluate the effect of drugs on birth weight and gestational age in the population-based Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) between years 1980-1991 [1] and found that hydroxyethylrutoside (HER) had the most obvious fetal growth promoting effect. Recent studies have shown the biological effect of flavonoids and semiflavonoids for the human body [2,3] . Rutoside, a flavonoid derivate [4], later became a medicinal product like HER [5,6] because it can reduce microvascular permeability and erythrocyte aggregation, improve microcirculation and microvascular perfusion, has antioxidant properties and anti-inflammatory capacity, and therefore protects the vascular endothelium using the treatment of venous insufficiency and related disorders [2, 5-7].

Varicose veins in lower extremities [8] and hemorrhoids [9] are frequent pathological conditions in pregnant women, therefore are treated frequently by HER [10,11]. The efficacy of this treatment was evaluated in the Cochrane Database as well [12-14]. In Hungary HER is one of the most frequently used drug during pregnancy therefore the aim of this study was to analyze the HER effect for fetal development in a detailed analysis of the larger population-based data set of the HCCSCA [15].

2. Material and methods

The data set of the HCCSCA is based on the comparison of cases with congenital abnormalities and their matched controls. Cases are selected from the

* *E-mail: evaposfay@gmail.com*

Hungarian Congenital Abnormality Registry (HCAR), the function and results of the HCAR were reported previously in detail [16]. Controls were selected from the National Birth Registry of the Central Statistical Office for the HCCSCA on the basis of case lists for each quarter of the years. Controls were defined as newborn infants without congenital abnormality. In general two controls were matched to every case according to sex, birth week in the year when the case was born, and district of parents' residence [15]. In this analysis only controls are evaluated because congenital abnormalities have a more robust effect for birth outcomes as HER.

An explanatory letter was mailed to mothers immediately after the selection of cases and controls to ask them to send us for 4 weeks the prenatal maternity logbook with the discharge summary of their delivery (in Hungary practically all deliveries take place in inpatient obstetric clinics, and birth attendants are obstetricians) and other medical records concerning their diseases during the study pregnancy. In addition a structured questionnaire and a printed informed consent form were also mailed to the mothers. The questionnaire helped us to evaluate the socio-demographic data of mothers [15].

The mean ± S.D. time elapsed between the birth and the return of the "information package" (discharge summary, logbook, informed consent form) in our prepaid envelope was 5.2 ± 2.9 months in the control group [15] . Our co-workers visited 200 non-respondent and 600 respondent control mothers to obtain or to check the necessary data in two validation studies [17,18]. Overall, the necessary information was available on 83.0% of the controls (81.3% from reply, 1.7% from visit) [18]. The procedure of data collection in the HCCSCA was changed in 1997, and the recent data had not been validated at the time of the analysis [15].

The gestational age was calculated from the first day of the last menstrual period, and birth weight and gestational age were analyzed on the basis of discharge summary of deliveries.

HER as Venoruton® (Novartis) is a registered drug containing a mixture of semisynthetic flavonoids: 7-mono-O-(β-hydroxyethyl)-rutoside (monoHER) and structurally related hydroxyethylrutosides (HERs). HER tablets for oral treatment contain 300 mg and 500 mg. The recommended daily oral treatment is 3 times 300 mg or 2 times 500 mg for 3-5 weeks [19].

Among confounders, maternal age, parity (birth order), marital and employment status as indicator of socioeconomic status [18], maternal diseases, other drug uses, folic acid were evaluated.

Data of the study were evaluated statistically by the software package SAS version 8.02 (SAS Institute Inc., Cary, North Caroline, USA). Chi-square test was used for categorical variables, while Student t-test for quantitative variables. The rate of pre- or post-term birth, and low and large birth weight in the newborns of pregnant women with or without HER treatment were compared, and adjusted OR with 95% CI were calculated using a conditional logistic regression model.

3. Results

The total number of births in Hungary was 2,146,574 during the study period between 1980 and 1996. Thus the 38,151 live-born controls without defects represented 1.8% of all Hungarian births, and among those controls, 1,143 (3.0%) were born to mothers treated orally with HER.

Of 1,143 control mothers, 666 (58.3) had medical recorded HER treatment in the prenatal maternity logbook. The doses of oral HER treatment was daily 900-1000 mg in most pregnant women, while the mean duration of treatment was 4.8 months. About 20% of women started HER treatment before conception and they continued it during pregnancy. The peak of the new onset treatments was the fifth and the sixth month in these pregnant women.

Table 1 shows the basic characteristics of mothers with HER treatment and without HER treatment as reference. The mean maternal age and birth order was higher in pregnant women with HER treatment. There was no significant difference in the marital and employment status of pregnant women with or without HER treatment.

Eight hundred mothers were visited at home and only 27 had HER treatment. Of these 27 pregnant women, 9 (33.3%) were smokers. In the 773 women without HER use, 154 (19.9%) were smokers.

There was no difference in the incidence of pregnancy complications (e.g. threatened abortion and preterm birth) and acute diseases between pregnant women with or without HER treatment. Of 1,143 pregnant women with HER, 6 had gestational diabetes. Among chronic diseases, the prevalence of varicose veins in lower extremities (51.3% vs. 0.7%), hemorrhoid (8.8% vs. 0.4%) and phlebitis-thrombophlebitis (2.8% vs. 0.3%) was higher in mothers with HER treatment than in pregnant women without HER treatment.

Only 2 mothers continued their acenocoumarin (Syncumar^{R}) treatment after the diagnosis of pregnancy. Heparin treatment was recorded in some pregnant women but most frequently Rutascorbin^{R} (rutoside + ascorbic acid) was used (23.2%), whilst this rate was only 0.8% in untreated mothers. Other frequently used

drugs did not show significant difference between pregnant women with or without HER treatment.

Table 2 summarises the birth data of newborn infants born to pregnant women with or without HER treatment. The mean gestational week was 0.1 week longer, and it associated with a marginal reduction in the rate of preterm births. The mean birth weight was 115 gram larger and it is associated with a lower rate of low birth weight and higher rate of large birth weight in newborns.

This analysis was repeated based only on medically recorded HER treatment in the prenatal maternity logbook and similar associations were found. The

Table 1. Maternal characteristics of pregnant women with oral HER treatment and without HER treatment as reference

Variables	Pregnant women			
	without oral HER treatment		with oral HER treatment	
Quantitative	(N=37,008)		(N=1,143)	
	No.	%	No.	%
Maternal age (yr)				
19 or less	3,248	8.8	29	2.5
20 – 29	26,892	72.7	710	62.1
30 or more	6,868	18.6	404	35.3
Mean ± S.D.	25.4 ± 4.9		27.9 ± 4.9	
Birth order				
1	17,953	48.5	256	22.4
2 or more	19,055	51.5	887	77.6
Mean ± S.D.	1.7 ± 0.9		2.2 ± 1.1	
Categorical	No.	%	No.	%
Unmarried	1,439	3.9	33	2.9
Employment status				
Professional	4,262	11.5	161	14.1
Managerial	9,977	27.0	288	25.2
Skilled worker	11,528	31.2	380	33.2
Semiskilled worker	5,986	16.2	175	15.3
Unskilled worker	2,117	5.7	70	6.1
Housewife	2,300	6.2	54	4.7
Others	838	2.3	15	1.3

Table 2. Birth outcomes of newborn infants born to mother with oral HER treatment and without HER treatment as reference

Birth outcomes	Newborn infants				Comparison	
	without maternal oral HER treatment (N=37,008)		with maternal oral HER treatment (N=1,143)			
Quantitative	Mean	S.D.	Mean	S.D.	t=	p=
Gestational age (wk)*	39.4	2.1	39.5	1.8	1.9	0.06
Birth weight (g)**	3,272	511	**3,387**	495	4.7	**<0.0001**
Categorical	No.	%	No.	%	OR	95%CI
Preterm births (less than 37 wk) *	3,425	9.3	71	6.2	0.74	0.51-0.98
Low birth weight (2500 g or less)**	2,129	5.8	38	**3.3**	**0.61**	**0.42-0.83**
Post term births (more than 42 wk)*	667	1.8	18	1.6	1.22	0.96-1.55
Large birth weight (4000g or more) **	2,742	7.4	130	**11.4**	**1.33**	**1.15-1.60**

**adjusted for maternal age, parity, employment status, maternal vascular diseases, related drug treatments and folic acid use*
*** adjusted for maternal age, parity, employment status, maternal vascular diseases, related drug treatments, folic acid use and gestational age*
Bold numbers show significant associations

comparison of birth outcomes of pregnant women with HER with or without gestational diabetes did not show significant difference due to the small number (six) of pregnant women with gestational diabetes.

Finally we evaluated male and female newborn infants separately. Both 714 males (39.4 vs. 39.6 wk) and 429 females (39.3 vs. 39.5 wk) born to mothers with HER treatment had 0.2 weeks longer gestational age. However, the mean birth weight difference was larger in males (3,460 vs. 3,319 = 141 g) than in females (3,266 vs. 3,184 = 82 g). The decrease in the rate of preterm birth was somewhat stronger in males (5.0% vs. 8.5% = 3.5 %) than in females (8.2% vs. 10.8% = 2.6%) while the reduction of low birth weight was stronger in females (3.7% vs. 7.1% = 3.4%) than in males (3.1% vs. 5.0% = 1.9%).

4. Discussion

The objective of our study was to evaluate the impact of HER treatment for fetal development and larger birth weight was found in newborn infants born to mothers with HER treatment and it is associated with the lower rate of low birth weight and higher rate of large birth weight.

Thus our study confirmed the fetal growth promotion effect of oral HER treatment found in our previous "screening" paper [1] in a detailed analysis of larger material. This fetal effect may be connected with the general vascular effect of HER [6,7] in the placenta.

Previously causal association of diseases such as varicose veins of lower extremities [8] and haemorrhoids [9], i.e. the reason of HER treatment, with birth outcomes was not found. The frequency of drugs used for the treatment of varicose veins of lower extremities, phlebitis and hemorrhoids, in addition other drugs was similar in pregnant women with or without HER treatment.

Among other confounders, higher maternal age and parity with larger birth weight may be important but these variables were considered at the calculation of adjusted p value. Socioeconomic status of mothers based on their employment status was also considered as confounder though it did not show difference between pregnant women with or without HER treatment.

Smoking seems to be important in the origin of intrauterine growth restriction and/or preterm birth [21] and a higher rate of smokers was found in mothers with HER treatment than in the reference sample. However, our study showed a somewhat longer gestational age and larger birth weight in the newborn infants of mothers with HER treatment.

In general the effect of drugs for fetal growth is neglected, but our study shows a possible association of HER with larger birth weight, therefore its use may be useful after the diagnosis fetal growth restriction in the second half of pregnancy. However, the possible teratogenic effect of HER in the second and/or third gestational month was reported recently [22,23] .

The strengths of HCCSCA can be explained by the population-based large data set including 1,143 pregnant women with oral HER treatment in the ethnically homogeneous Hungarian (Caucasian) people; medically recorded gestational age at delivery and birth weight; available data for potential confounders.

However, this data set also has limitations. HER treatment was based on retrospective maternal information in 41.7% of pregnant women, however, our validation studies showed the reliability of maternal information [17,18]. In addition, we evaluated separately only medically recorded HER treatment as a golden standard [24]. In addition, lifestyle factors, such as smoking habits were known only in a subsample of mothers visited at home. However, these data were collected through a cross interview with mothers and their close family members [17,18], excluding the very unreliable retrospective maternal information [25]. The gestational age was calculated from the first day of the last menstrual period and it was checked on the basis of birth weight and gestational age from the discharge summary of deliveries. Recently the gestational age can be calculated exactly in IVF cycles, or by comparing LMP with CRL in the first trimester. However ultrasound scanning was not used frequently during the study period and/or recorded in our dataset.

In conclusion, oral HER treatment in pregnant women is associated with a fetal growth promotion effect, thus the fetal effect of flavonoid derivative drugs needs further studies.

Ackowledgement

The authors thank Erzsébet H. Puhó for her help in the statistical analysis of data.

Conflict of interest statement

Authors state no conflict of interest.

References

[1] Czeizel AE, Toth M: Birth weight, gestational age and medications during pregnancy. Int J Gynaecol Obstet 1998;60(3): 245-249

[2] Galati G, Sabzevari O, Wilson JX, O'Brien PJ: Prooxidant activity and cellular effects of the phenoxyl radicals of dietary flavonoids and other polyphenolics. Toxicology 2002;177(1): 91-104

[3] Jacobs H, van der Vijgh WJ, Koek GH, Draaisma GJ, Moalin M, van Strijdonck GP, et al.: Characterization of the glutathione conjugate of the semisynthetic flavonoid monoHER. Free Radic Biol Med 2009;46(12): 1567-1573

[4] Rusznyak S, Szent-Györgyi A: Vitamin P: Flavonals as vitamins. Nature 1936;138: 27

[5] Kienzler JL, Sallin D, Schifflers MH, Ghika A: Pharmacokinetics of mono-3'- and mono-4'-0-(beta-hydroxyethyl)-rutoside derivatives, after single doses of Venoruton powder in healthy volunteers. Eur J Clin Pharmacol 2002;58(6): 395-402

[6] Wadworth AN, Faulds D: Hydroxyethylrutosides. A review of its pharmacology, and therapeutic efficacy in venous insufficiency and related disorders. Drugs 1992;44(6): 1013-1032

[7] Petruzzellis V, Troccoli T, Candiani C, Guarisco R, Lospalluti M, Belcaro G, et al.: Oxerutins (Venoruton): efficacy in chronic venous insufficiency – a double-blind, randomized, controlled study. Angiology 2002;53(3): 257-263

[8] Banhidy F, Acs N, Puho EH, Czeizel AE: Varicose veins of lower extremities in pregnant women and birth outcomes. Cent Eur J Public Health 2010;18(3): 161-168

[9] Bánhidy F, Ács N, Puhó HE, AE. C, : Possible association of materanal hemorrhoid with congenital abnormalities in their children: a population-based case-control study. Balkan J Med Genet 2010;2010; 13: 23-33

[10] Bergstein NA: Clinical study on the efficacy of O-(beta-hydroxyethyl)rutoside (HR) in varicosis of pregnancy. J Int Med Res 1975;3(3): 189-193

[11] Wijayanegara H, Mose JC, Achmad L, Sobarna R, Permadi W: A clinical trial of hydroxyethylrutosides in the treatment of haemorrhoids of pregnancy. J Int Med Res 1992;20(1): 54-60

[12] Young GL, Jewell D: Interventions for varicosities and leg oedema in pregnancy. Cochrane Database Syst Rev 2000(2): CD001066

[13] Quijano CE, Abalos E: Conservative management of symptomatic and/or complicated haemorrhoids in pregnancy and the puerperium. Cochrane Database Syst Rev 2005(3): CD004077

[14] Bamigboye AA, Smyth R: Interventions for varicose veins and leg oedema in pregnancy. Cochrane Database Syst Rev 2007(1): CD001066

[15] Czeizel AE, Rockenbauer M, Siffel C, Varga E: Description and mission evaluation of the Hungarian case-control surveillance of congenital abnormalities, 1980-1996. Teratology 2001;63(5): 176-185

[16] Czeizel AE: First 25 years of the Hungarian congenital abnormality registry. Teratology 1997;55(5): 299-305

[17] Czeizel AE, Petik D, Vargha P: Validation studies of drug exposures in pregnant women. Pharmacoepidemiol Drug Saf 2003;12(5): 409-416

[18] Czeizel AE, Vargha P: Periconceptional folic acid/multivitamin supplementation and twin pregnancy. Am J Obstet Gynecol 2004;191(3): 790-794

[19] Borvendég J. Gyógyszer compendium. (Hungarian),. Budapest: Havas MediMedia Információs KFT,. 2000

[20] Puho E, Metneki J, Czeizel AE: Maternal employment status and isolated orofacial clefts in Hungary. Cent Eur J Public Health 2005;13(3): 144-148

[21] Czeizel AE, Puho EH, Langmar Z, Acs N, Banhidy F: Possible association of folic acid supplementation during pregnancy with reduction of preterm birth: a population-based study. Eur J Obstet Gynecol Reprod Biol 2010;148(2): 135-140

[22] Vogt G, Puho E, Czeizel AE: A population-based case-control study of isolated ocular coloboma. Ophthalmic Epidemiol 2005;12(3): 191-197

[23] Paput L, Banhidy F, Czeizel AE: Association of drug treatments in pregnant women with the risk of external ear congenital abnormalities in their offspring: a population-based case-control study. Congenit Anom (Kyoto) 2011;51(3): 126-137

[24] Rockenbauer M, Olsen J, Czeizel AE, Pedersen L, Sorensen HT: Recall bias in a case-control surveillance system on the use of medicine during pregnancy. Epidemiology 2001;12(4): 461-466

[25] Czeizel AE, Petik D, Puho E: Smoking and alcohol drinking during pregnancy. The reliability of retrospective maternal self-reported information. Cent Eur J Public Health 2004;12(4): 179-183