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Trimester dependent preterm births in pregnancy with genital herpes

Research Article

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Abstract: Previous studies reported controversial results regarding the possible association of recurrent genital herpes during pregnancy with a higher risk of preterm birth/low birth weight in newborns. Thus, birth outcomes of mothers with prospective and medically recorded symptomatic recurrent genital herpes confirmed by serological examination and of mothers without genital herpes were compared in the population-based large data set of the Hungarian Case-Control Surveillance of Congenital Abnormalities. Our results showed that of 38,151 newborn infants, 86 (0.23%) had mothers with symptomatic recurrent genital herpes confirmed by serological examination during pregnancy. The rate of preterm births (14.0% vs. 9.2%) was higher in babies born to mothers with symptomatic recurrent genital herpes (OR with 95% CI: 1.7, 1.0-3.1) and this increase showed a trimester dependence with the highest rate in the third trimester (23.5%; OR with 95% CI: 2.6, 1.5-4.5). In conclusion, clinically diagnosed recurrent genital herpes during the third trimester of pregnancy associated with high risk for preterm birth.

Keywords: *Recurrent genital herpes • Gestational age at delivery • Preterm birth*

1. Introduction

Herpes simplex virus 1 (HSV-1) and Herpes simplex virus 2 (HSV-2) are known as human pathogens [1]. HSV-1 is normally associated with orofacial infections, whereas HSV-2 usually causes genital infections [2]. However, both viruses are capable of causing either genital or orofacial infections.

In 2003 more than 300 million women and 200 million men were infected with HSV-2 because HSV-2 spreads easily through sexual contact [3]. The infection often lasts for life and sporadically causes symptoms, including painful blisters that can burst and form ulcers. Approximately 22% of pregnant women are infected with HSV-2 and 2% of women acquire genital herpes during pregnancy [4]. However, genital herpes is undiagnosed in up to 90% of these pregnant women because they are asymptomatic or have subtle symptoms attributed to other vulvovaginal infections. These diagnostic problems explain that the diagnosis of genital herpes should be based on laboratory confirmation. However, it is necessary to differentiate primary and recurrent (due to the reactivation of disease) forms of genital herpes with clinical symptoms and confirmed by laboratory examinations, in addition to asymptomatic genital herpes based on laboratory screening.

Both symptomatic (clinical) and asymptomatic (subclinical) HSV-2 infection during pregnancy may be associated with several complications. Among them, an increased risk for preterm delivery/birth and low birth weight, i.e. small-for-gestational-age newborns was reported in some studies [5-7]. However, other studies did not find an association between genital herpes and preterm birth and/or low birth weight [8-11]. Thus, the aim of the study was to evaluate the association of *symptomatic recurrent genital herpes* (SRGH) in pregnant women with the risk of preterm births and low birth weight newborns in the population-based large data set of the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) between 1980 and 1996 [12].

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2. Material and Methods

The HCCSCA is based on the comparison of exposures during pregnancy in the mothers of cases with different congenital abnormalities and in the mothers of controls without any defect. Cases with congenital abnormalities are identified from the Hungarian Congenital Abnormality Registry [13] for the HCCSCSA. Control newborns were selected from the National Birth Registry of the Central Statistical Office for the HCCSCA. In general, two newborns were matched individually to each case according to sex, week of birth in the year when cases were born, and district of parents' residence.

Here only the so-called control newborn infants are evaluated because congenital abnormalities may have a more robust effect for birth outcomes than SRGH, and henceforth the term controls will not be mentioned.

There were *three sources of exposure (*maternal disorders and related drug treatments) and *other information:*

Medically recorded data

Mothers were asked, in an explanatory letter, immediately after the selection of newborns to send us the prenatal care logbook and other medical records (mainly discharge summaries of their deliveries) related to diseases and their treatment during the study pregnancy and their child's health condition in a prepaid envelope. 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, on average, seven times. The first visit was between 6 and 12 gestational weeks. The task of obstetricians in prenatal care clinics is to examine pregnant women and to ask laboratory examinations if these tests are necessary, in addition to record all pregnancy complications, maternal diseases and drug treatments during pregnancy in the logbook. Logbooks and other medical documents were sent back to mothers within 3 weeks.

Retrospective maternal information

A post-paid structured questionnaire together with lists of diseases and medicaments, in addition with a printed informed consent were also mailed to the mothers. The questionnaire requested information on pregnancy complications, maternal diseases and medicine (drug and pregnancy supplement) taken during pregnancy according to gestational months. In order to standardise the answers, mothers were asked to read the enclosed lists of diseases (including genital herpes) and medications as a memory aid before replying and to give a signature for the informed consent.

The period between birth and return of "information package" (questionnaire, logbook, discharge summary) was 5.2 $\pm$ 2.9 months.

Supplementary data collection

Regional nurses visited 200 non-respondent and 600 respondent control mothers at home in two validation studies [14,15] because the committee on ethics considered this follow-up to be disturbing to the parents of all healthy children. Regional nurses helped mothers to fill in the questionnaire, evaluated available medical records; in addition obtained data of lifestyle factors through an interview of mothers and fathers or other close relatives living together and the so-called family consensus was evaluated.

Thus, the necessary maternal and newborn data regarding exposures during pregnancy were available on 83.0% of mothers (81.3% from correspondence, 1.7% from visit).

The procedure of data collection in the HCCSCA was changed in 1997 since regional nurses visited and questioned all cases and controls; however, these data had not been validated at the time of this analysis. Thus, only the data set of 17 years between 1980 and 1996 is evaluated here.

Birth weight and gestational age at delivery were recorded in the discharge summary of mothers because all deliveries took place in inpatients obstetric clinics in Hungary during the study period. We calculated gestational age from the first day of the last menstrual period. The definition of preterm birth was less than 37 completed weeks (less than 259 days), while the definition of low birthweight was less than 2500 gram.

The definition of clinically recognized SRGH was the reactivation of genital herpes (grouped vesicles with progression rarely to ulceration and crusting, localized to a small area of external genitalia) from the previous lesions of genital organs in the study. After the clinical investigation of pregnant women by obstetricians at any visit in the prenatal care clinics, women with visible suspected genital herpes were referred to laboratory examination to confirm the existence of HSV-2 specific antibodies by serologic assay based on the HSV-2 glycoprotein G.

2.1. Statistical analysis of data

Statistical analyses were carried-out with the software SAS version 8.02 (SAS Institute Ins., Cary, North Carolina, USA). Chi square test was used for the evaluation of maternal variables. We calculated odds ratios (OR) and their 95% confidence intervals (CI) for categorical data, while Student t test for quantitative variables of birth outcomes. At the calculation of adjusted t

Table 1. Characteristics of pregnant women with or without SRGH.

Variables	Pregnant women without SRGH (N = 38,065)		Pregnant women with SRGH (N = 86)		Comparison	
	No.	%	No.	%		
Quantitative						
Maternal age (yr)						
24 or less	17,944	47.1	50	58.1		
25 – 29	12,863	33.8	22	25.6	$\chi^2_2 = 4.3$	p = 0.12
30 or more	7,258	19.1	14	16.3		
Mean ± S.D.	25.5±4.9		24.7±4.8		t = 1.5	p = 0.14
Birth order						
1	18,153	47.7	56	65.1	χ^2_1=10.4	p = 0.001
2 or more	19,912	52.3	30	34.9		
Mean ± S.D.	1.7±0.9		1.5±1.0		t = 1.9	p = 0.05
Categorical						
Unmarried	1,465	3.9	6	7.0	$\chi^2_1 = 2.3$	p = 0.13
Employment status						
Professional	4,342	11.4	11	12.8		
Managerial	10,109	26.6	25	29.1		
Skilled worker	11,671	30.7	19	22.1		
Semiskilled worker	5,766	15.2	17	19.8	$\chi^2_6 = 8.1$	p = 0.23
Unskilled worker	1,854	4.9	5	5.8		
Housewife	2,037	5.3	1	1.2		
Others, mainly students	2,286	6.0	8	9.3		

and OR, maternal age, birth order, employment status as indicator of socioeconomic status, were used as confounders.

3. Results

The number of births was 2,146,574 in Hungary between 1980 and 1996, while the number of evaluated newborn infants was 38,151, i.e. 1.8% of all births in the study period. Of the 38,151 newborns, 228 (0.60%) had mothers with the diagnosis of genital herpes during the study pregnancy.

Of 228 mothers, 88 (38.6%) had prospectively and medically recorded genital herpes during the study pregnancy confirmed by recorded serologic assay in the prenatal maternity logbook. Genital herpes was mentioned by 109 mothers without medical record in the logbook, they were excluded from the study because in general the type (first occurrence and recurrent) and the time (according to gestational months) of genital herpes were not mentioned in this retrospective self-reported maternal information, in addition the validity of these diagnoses is low. Medically recorded genital herpes without serologic examination was found in 33 pregnant women, they were also excluded from the study. In the remaining 88 mothers, two had primary genital herpes. These mothers were also excluded from this analysis because partly two subjects do not allow an epidemiological analysis, partly we wanted to evaluate a group of SRGH as homogeneous as possible. Thus finally 86 (0.23%) newborn infants born to mothers with prospectively and medically recorded SRGH confirmed by serological examination were evaluated.

The maximum of SRGH occurred in the fifth gestational month (17.4%), followed by the sixth (16.3%) and second-third gestational (14.0% and 14.0%) months in the mothers. The occurrence of SRGH was rare in the last two months of gestation. Of these 86 newborns, one mother was affected with two SRGH during the study pregnancy (in the second and fifth months, the first manifestation was evaluated).

Table 1 summarizes the basic characteristics of mothers with SRGH or without SRGH as reference. Mothers with SRGH were somewhat younger with a significantly lower mean birth order due to the larger proportion of primiparae. The proportion of unmarried pregnant women was somewhat but not significantly larger in pregnant women with SRGH. The distribution of maternal employment status did not show differences between mothers with or without SRGH.

Table 2. Mean birth weight and gestational age at delivery, in addition the rate of low birthweight newborns and preterm birth in babies born to mothers without SRGH as reference and with SRGH.

	Mothers							
	without SRGH		with		Comparison			
Variables	(N = 38,065)		(N = 86)		unadjusted		adjusted	
Quantitative	Mean	S.D.	Mean	S.D.	t=	p=	t=	p=
Birth weight, g*	3276	511	3163	534	2.0	0.04	1.2	0.24
Gestational age, wk**	39.4	2.0	38.9	2.5	1.6	0.12	1.9	0.06
Categorical	No.	%	No.	%	OR (95% CI)		OR (95% CI)	
Low birthweight*	2,158	5.7	9	10.5	1.9 (0.9 – 3.9)		1.5 (0.6 – 3.6)	
Preterm birth**	3,484	9.2	12	**14.0**	1.6 (0.9 – 3.0)		**1.7 (1.0 – 3.1)**	

**adjusted for maternal age, birth order, maternal employment status and gestational age*
***adjusted for maternal age, birth order and maternal employment status*
Bold numbers show significant association

Table 3. Mean birth weight and gestational age at delivery, in addition the rate of low birthweight newborns and preterm birth in babies born to mothers with SRGH according to trimester of the study pregnancy compared to the birth outcome of pregnant women without SRGH shown in Table 2.

Variables	SRGH in first trimester (No. = 30)				SRGH in second trimester (No. = 39)				SRGH in third trimester (No. = 17)			
Quantitative	Mean	S.D.	t=	p=	Mean	S.D.	t=	p=	Mean	S.D.	t=	p=
Birth weight, g*	3348	535	0.4	0.72	3147	524	1.6	0.11	3112	447	1.1	0.28
Gestational age, wk**	39.5	2.3	0.4	0.69	39.2	2.5	0.5	0.59	**38.7**	2.1	2.3	**0.03**
Categorical	No.	%	OR	95% CI	No.	%	OR	95% CI	No.	%	OR	95% CI
Low birthweight*	1	3.3	0.4	0.0 - 4.3	5	12.8	1.4	0.7 – 5.6	3	17.7	3.0	0.9 – 7.5
Preterm birth**	2	6.7	0.8	0.2 - 3.3	6	15.4	1.7	0.9 – 3.0	4	**23.5**	**2.6**	**1.5 – 4.5**

**adjusted for maternal age, birth order, maternal employment status and gestational age*
***adjusted for maternal age, birth order and maternal employment status*
Bold numbers show significant associations

The incidence of pregnancy complications did not show significant difference between pregnant women with or without SRGH. Only the higher rate of threatened preterm delivery in pregnant women with SRGH was near to the level of significance (20.9% vs. 14.3%, OR with 95% CI: 1.6, 0.9-2.7).

Acute and chronic maternal diseases did not show significant difference between mothers with and without SRGH.

Among frequently used drugs, some antimicrobial drugs, such as ampicillin (10.5% vs. 6.9%) and sulfamethoxazole+trimethoprim (cotrimoxazole) (5.8% vs.1.2%) had a more frequent use in the mothers with SRGH. Acyclovir was not used in pregnant women SRHG during the study period.

Mean gestational age at delivery and birth weight, in addition the rate of preterm births and low birthweight newborns are shown in Table 2. Sex ratio did not show difference between babies born to mothers with or without SRGH (OR with 95% CI: 0.8, 0.5-1.2), thus birth outcomes are not reported separately in male and female newborns. Mean gestational age was 0.5 week shorter in the mothers with SRGH compared to mothers without SRGH. The rate of preterm births was significantly higher in the newborns of mothers with SRGH compared to the newborns of pregnant women without SRGH. The shorter gestational age was reflected in birth weight, it was smaller by 113 grams in the newborns of pregnant women with SRGH. Thus the rate of low birthweight newborns was also higher but this difference was not significant.

Finally we evaluated birth outcomes according to the SRGH in different trimesters of the study pregnancies as well (Table 3). There was an obvious time trend, the second trimester associated with a shorter gestational age and with a higher rate of preterm births, however, the shortest gestational age and the highest rate of preterm births occurred after SRGH during the third trimester. Mean birth weight and the rate of low birth weight newborns showed a similar trend, but these figures did not reach the level of significance if they were adjusted for gestational age.

4. Discussion

Our study showed a statistical significant association between maternal SRGH and the rate of preterm births (14.0% vs. 9.2%) and that a higher rate of preterm birth can be explained by SRGH in the second and mainly in the third trimester of pregnancy.

HSV infection of the genital tract is one of the most common viral sexually transmitted infections/diseases [16-19], most caused by HSV-2 but can be caused by HSV-1 as well. Women are more likely to become infected than men, with positive correlation to the number of sexual partners. About 5% of reproductive-aged women reported a history of genital herpes in our periconception clinic [20] and it corresponded to the figure found in other countries [1,2]. However, between 4.2% (in England and Wales) and 27.1% (in the USA) of the female populations have antibodies to HSV-2 [21].

The diagnosis and classification of genital herpes infection/disease is not an easy task. *Symptomatic (clinical)* manifestation of genital herpes needs confirmation by laboratory assays. Of course, the diagnosis of *asymptomatic (subclinical)* genital herpes infections is based on laboratory examination with culture or polymerase chain reaction test of HSV-2 in genital lesion and/or type-specific glycoprotein G-based serologic testing. The later was used in the study. Antibodies to HSV-2 develop during the first several weeks after infection and persist indefinitely. The antibody response to HSV-2 is distinguishable from HSV-1 because the surface glycoprotein G differs in size and epitope content between HSV-1 and HSV-2. Thus serologic assay is appropriate for the diagnosis HSV-2 infection on the basis of HSV-2 glycoprotein G (gG2) [22].

Secondly, infections caused by HSV are defined clinically, but mainly serologically as *primary and secondary infections.* The cellular targets of HSV are epithelial cells of skin and mucosa, in addition neurons. During the primary infections in the skin and/or mucosa caused by sexual contact with infected partners, HSV enters into sensory and autonomic neurons, through the axons that extent to the location of the lesions. Once HSV is in the neuron nucleus, it can be latent for the entire life of the host [1,2]. However, physical or emotional stress can reactivate HSV which transport back through the axon to the original point of entry, and shed in the genital area inducing clinical symptoms, i.e. disease, though it may be also asymptomatic. The reactivation of HSV may occur despite the presence of the immune response followed the primary infections. Almost 100% of women with HSV-2 infection have symptomatic or asymptomatic recurrent genital herpes throughout their lives [23,24]. Thus the clinical diagnosis without laboratory confirmation showed poor sensitivity in some previous studies [26,27]. In general SRGH is caused by HSV-2 because the frequency of genital reactivation is much less with HSV-1 which rarely recurs symptomatically or asymptomatically after the first year of infection [27,28].

The secondary findings of our study showed a somewhat lower maternal age with a larger proportion of primiparous and unmarried pregnant women with SRGH.

Our study showed a clinically important increase in the rate of preterm births after SRGH during the third trimester. The gestational age specific birth weight groups did not show a significant retardation, thus the lower birth weight and higher rate of low birthweight were mainly connected with the shorter gestational age at delivery. Thus our results may explain the previously found controversial association between SRGH and higher risk for preterm birth because this association is trimester dependent. The available data make clear that antibodies alone cannot prevent infection and SRGH, this fact explain the failure of genital herpes vaccine [3]. The question is whether this preterm birth inducing effect in pregnant women with SRGH is associated with the direct effect of HSV-2, indirect effect of maternal symptoms, physical or emotional stress which can reactivate SRGH or with depressed immunological status in the last gestational months of pregnant women.

In addition pregnant women can spread HSV-2 to their newborns and neonatal herpes sometimes kills them. This infection in general is acquired via the birth canal, but rare cases of intrauterine infections by HSV-2 have been described [29-39]. The rare transplacental HSV-2 infection may occur in less than 5% of primary infections [40], it may induce a typical spectrum of structural fetal/birth defects, i.e. congenital abnormalities between 6th and 14th weeks of gestation [41-43]. Our previous case-control study did not show a higher risk of congenital abnormalities in the offspring of pregnant women with recurrent genital herpes [44].

The strengths of HCCSCA are that this large population-based data set included 86 pregnant women with SRGH in ethnically homogeneous European sample. These pregnant women had prospective and medically recorded diagnosis of SRGH confirmed by serological examination, exposure time and confounding factors were known. In addition birth weight and gestational age at delivery were medically recorded, thus the diagnoses of preterm births and low birthweight newborns had a good validity.

The limitations of our study are connected partly with the diagnosis of SRGH (if SRGH did not occur during the visit in prenatal care clinics, serologic examination was not requested), partly the weaknesses of our data set (e.g. the lack of virologic examination in most pregnant women). These circumstances explain the low prevalence of SRGH in the study. Further weakness of our study is the lack of data regarding maternal smoking as confounder in the total data set. Our previous validation study showed the low reliability of retrospective maternal self-reported information regarding smoking during pregnancy [45], therefore these data were collected only in a minor part of the data set based on the home visit. Of these 800 pregnant women, 152 (19%) smoked during pregnancy which corresponded well to the figure of smoking among Hungarian pregnant women. In addition the smoking habit cannot modify the trimester dependent preterm birth risk.

In conclusion, our study showed an association between SRGH during the second and mainly in third trimester of pregnancy and a higher risk for preterm births.

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