Pregnancy complications and birth outcomes in pregnant women with viral infections: a population-based study

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Abstract

Objective: The aim of the present study was to estimate the effect of viral infections on the development of pregnancy complications and on birth outcome. Design: A population-based retrospective study. Setting and Population: 57,231 control pregnancies (without any birth-defects) were analysed in The Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA). Methods: Associations between viral infection exposures in the 1st trimester of pregnancy and pregnancy complications and birth outcomes were analysed using the non-exposure group as reference, adjusting for maternal age, highest education, and maternal tobacco use. Main Outcome Measures: Quantitative variables such as mean maternal age, birth weight and gestational age and categorical variables like pregnancy complications were evaluated in the group of viral infections and control mothers. Results: In total, 2,238 cases with maternal viral infections during pregnancy were identified in the HCCSCA (influenza: 2,016, enterovirus: 48, herpes simplex: 28, hepatitis B: 22, varicella-zoster: 14, respiratory syncytial virus: 11 and unspecified virus infections: 104). The incidences of threatened abortion (OR: 1.3, 95% CI: 1.2-1.5), threatened preterm birth (OR: 1.4, 95% CI: 1.1-1.7) and anaemia (OR: 1.4, 95% CI: 1.3-1.6) were higher in the mothers of cases. The risk of gestational diabetes was lower in the group of viral infections (OR: 0.4, 95% CI: 0.23-0.9). No significant differences have been detected in preterm birth, birth weight or IUGR between the infected and the control groups. Conclusions: The findings of this study suggest that viral infections during pregnancy do not exert a deleterious effect on birth outcomes.

1. Introduction

The recent outbreak of COVID-19 pneumonia, caused by SARS-CoV-2 virus, has highlighted the role of viral infections during pregnancy as well.[1-3] The importance of these diseases will probably increase as we face growing risks of pandemics, which may affect the pregnant mother and the foetus[4].

Viral infections during pregnancy raise several clinical challenges including adverse pregnancy outcomes and birth defects in the offspring.[5] Previous studies have shown that SARS during pregnancy may result in spontaneous miscarriage, preterm delivery, and intrauterine growth restriction.[6]

Other maternal viral infections (e.g. cytomegalovirus, hepatitis B, herpes simplex, influenza, rubella, varicella zoster) have also been found to affect foetal development.[4,7,8] However, the results of these studies are conflicting.

The Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) is one of the largest case-control data sets of birth defect surveillance in the world.[9] The total number of control new-borns (without any congenital anomaly) in this database is 57,231.

The aim of the present study was to estimate the effect of viral infections on the development of pregnancy complications and on birth outcome, using the data set of the HCCSCA.

2. Patients and methods

The Hungarian Congenital Abnormality Registry (HCAR)

The HCAR was established in 1962 as the first national-based registry of congenital anomalies (CAs) in the world.[10] Reporting of patients as cases with CA to the HCAR is mandatory for physicians from birth until the end of the first postnatal year.

The Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA)

Cases with CAs in the HCAR were enrolled to the HCCSCA if they met all the following selection criteria: (a) Reported to the HCAR within 3 months after birth or elective termination of pregnancy, (b) Did not have any of three mild CAs (dislocation of the hip, congenital inguinal hernia and large haemangioma) and (c) Did not have CA-syndromes caused by gene mutations or chromosomal aberrations with preconceptional origin.

Controls were defined as new-born infants without CAs and they were matched to cases according to sex, birth week, and district of parents' residence. These controls were selected from the National Birth Registry of the Central Statistical Office based on case lists for each quarter of the years from the HCCSCA. In general, 2 controls were selected for each malformed new-born. If controls were twins, only one of them was randomly selected for the HCCSCA. In addition, if selected controls had any CA, these infants were excluded from the group of controls.

The HCCSCA was established in 1980. The collection of data was changed in 1997, slightly modifying the structure of the HCCSCA also. All data collected in the HCCSCA between 1980 and 2009 were unified into a validated single database that is now open for examination. This dataset of the HCCSCA is evaluated in this paper.

Data Collection

Data about maternal lifestyle factors, maternal diseases and drug intake during pregnancy was obtained via three sources:

1. *Prospective, medically recorded data.* Mothers were requested to send the prenatal maternity logbook and every medical record concerning their diseases during the study pregnancy. Prenatal care was mandatory for pregnant women, thus nearly 100% of them attended prenatal care, on average 7 times between the 6^{th}gestational week and delivery. The task of obstetricians in prenatal care was to record all maternal diseases and medicinal products used by women during the study pregnancy in the logbook.

2. *Retrospective, maternal self-reported information.* A structured questionnaire and a printed informed consent were also mailed to the mothers of cases and controls. It comprised questions regarding maternal diseases and related drug treatments, pregnancy supplements. Mothers were asked to read the enclosed list as a memory aid before they filled-in the questionnaire and signed the informed consent.

3. *Supplementary data collection* . After 1996 regional nurses made home visits to all cases and controls. They helped mothers collect their medical records and fill in the questionnaire. The collection procedure was impugned by one mother in 2002 alluding to concerns of data privacy. The activity of the HCCSCA was stopped when the legal procedure started in 2003 and the HCCSCA could continue its work again only in 2005.

The following data are available for each case and control pregnancy: CA(s), gender, maternal age, paternal age, birth year/month/date, birth weight, gestational age, area of mother's living, birth order, mother's and father's qualification, employment status and type of employment, mother's marital status, outcome of previous pregnancies, maternal diseases during pregnancy (according to pregnancy months), drug intake during pregnancy (according to pregnancy months), mother's smoking habits and alcohol consumption patterns.

Evaluation of cases with viral infections

The presence of congenital anomalies may affect pregnancy outcome, therefore cases with birth defects were excluded from the present study. Thus, viral infections during the 57,231 control pregnancies were analysed.

Data were eligible for evaluation in the case of the following diseases: influenza, hepatitis B, varicella-zoster, herpes simplex, enterovirus, respiratory syncytial virus and unspecified viral infections.

Since the first trimester is critical for the development of several pregnancy complications the effects of the above-mentioned infections occurring during the first 3 months were analysed separately.

Statistical Analysis

Quantitative variables such as mean maternal age, birth weight and gestational age were evaluated by Student's t test. Chi square test was used for the evaluation of birth order and employment status. For categorical variables like pregnancy complications adjusted odds ratios (OR) with 95% confidence intervals (CI) were estimated. A multivariable conditional logistic regression model was used to compare maternal risk factors of cases with controls. Among confounding factors maternal age (continuous variable), birth order (parity) (2 vs. 1, 3+ vs. 1) and employment status (skilled/semiskilled worker vs. professional/managerial, unskilled worker/other vs. professional/managerial) as an indicator of socio-economic status were considered.[11]

3. Results

In total, 2,238 cases with maternal viral infections during pregnancy were identified in the HCCSCA between 1980 and 2009 (3.9% of the 57,231 liveborn infants). Of these new-borns, 1,153 cases were detected with infections during the 1st trimester. The detailed numbers of specific viral infections identified were as follows: influenza (2,016), enterovirus (48), herpes simplex (28), hepatitis B (22), varicella-zoster (14), respiratory syncytial virus (11) and unspecified virus infections (104). Live births in Hungary between 1980 and 2009 were 3,009,303, thus 57,231 pregnancies represented 1.9% of all Hungarian births.

General characteristics of the participants

Socio-demographic data of cases and controls are presented in Table 1. Maternal age was slightly higher in the control group as compared to infected mothers (26.2±5.1 vs. 25.8±4.7 years). The distribution of maternal employment status indicated a higher socioeconomic status of case mothers. The proportion of managerial mothers was 26.1% (N=585) in the group of cases and 19.2% (N=10,533) in the control group, while that of unskilled mothers were 1.9% (N=44) in the infected group, and 3.6% (N=1,967) in controls. No significant differences were found in birth order (primiparous women among cases: 1,276 (57.0%) vs. 48,801 (54.9%) in the control group). A highly significant difference between the two study groups has been found in maternal smoking. The proportion of smoker mothers was 15.9% in the group of viral infections while 8.7% in the control group.

Pregnancy complications and birth outcomes

Among medically recorded pregnancy complications the incidences of threatened abortion (OR: 1.3, 95% CI: 1.2-1.5), threatened preterm birth (OR: 1.4, 95% CI: 1.1-1.7) and anaemia (OR: 1.4, 95% CI: 1.3-1.6) were higher in the mothers of cases than in the mothers of matched controls. On the contrary, the risk of gestational diabetes was lower in the group of viral infections as compared to control mothers (OR: 0.4, 95% CI: 0.23-0.9). Detailed data are shown in Table 2. In the case of pregnancy complications, no differences have been found between the specific virus groups and the viral infection group in general. The only exception was a significantly higher risk of preeclampsia in the influenza group as compared to control mothers (OR: 1.3, 95% CI: 1.0-1.8, $p<0.05$).

Data on pregnancy outcome measures are presented in Table 3. Events during the 1st trimester may play a pivotal role in the proceedings of the whole pregnancy, as it was mentioned before. Therefore, pregnancy outcome results with a history of a viral infection during the first three months are also given. No significant differences have been detected in foetal birth weight or the prevalence of IUGR between the infected and the control groups. Preterm birth measures (birth before the completed 37th week or birth weight under 2,500 grams) also did not differ significantly between the two study groups. The only significant difference was the somewhat longer gestational age detected among infected mothers as compared to the control group (39.4±2.0 vs. 39.3±1.9 weeks). All pregnancy outcome results in the group of 1st trimester virus infection were

congruent with results in the complete infected group. Among specific viral infections a significantly lower birth weight (2985.7±585.9 vs. 3297.4±521.0, $p<0.05$) and shorter gestational age (38.1±1.4 vs. 39.3±1.9, $p<0.05$) have been found in the case of mothers with hepatitis B as compared to the control group. None of the other pathogens resulted in specific alterations in pregnancy complications or birth outcomes different from virus infections in general.

4. Discussion

The aim of the present study was to investigate the association of maternal viral infections during pregnancy with pregnancy complications and delivery outcomes. The results are based on the comparison of mothers of cases and uninfected controls.

The major findings of our study are that viral infections during pregnancy are associated with higher incidences of threatened miscarriage, threatened preterm delivery and anaemia. On the contrary the risk of gestational diabetes was decreased in infected mothers. Gestational age was longer in the infected group as compared to controls. Birth weight and the risk of preterm birth or IUGR did not differ significantly between the two study groups. Hepatitis B infection during pregnancy was associated with shorter gestational age and lower birth weight.

Miscarriage occurs in about 20% of pregnancies and may result in severe psychological and physiological issues for the patient. A thorough analysis of the available literature has found that influenza infection was associated with an elevated risk of spontaneous abortion, while the effect of hepatitis B and herpes simplex virus remained controversial.[12] Our data also support the potential deleterious effects of viral infections on the incidence of threatened miscarriage. However, the database of the HCCSCA is not suitable for analysing miscarriage data since it only contains records of preterm and term new-borns.

Preterm birth affects approximately 12-15% of pregnancies and in more than 50% of the cases no risk factors are known. Chronic hepatitis B virus infection was found to increase the risk of preterm labour and birth in pregnant women.[13,14] Increased rates of preterm birth are also reported in pregnant patients hospitalized with influenza virus infection, however, the limited amount of data does not permit firm conclusions.[15,16] In our dataset we were not able to confirm an elevated risk of preterm delivery in mothers suffering from virus infections during pregnancy. A shorter gestational age and lower birth weight was verified only in the case of hepatitis B infection; however, these alterations did not reach the limits of preterm birth. On the other hand, the prevalence of threatened preterm labour (preterm uterine contractions or ultrasonographic signs exhibited by the cervix and lower uterine segment) was increased significantly among mothers with viral infections. The pathomechanism of viral infections in inducing preterm birth is still debated. Viral infections of the placenta may act as a factor sensitizing women to intrauterine bacterial infection, resulting in an inflammatory response to even low concentrations of bacteria.[17] Intrauterine bacterial infection may then lead to preterm uterine contractility.

Gestational diabetes mellitus (GDM) affects 1-22% of all pregnancies globally, depending on the population and diagnostic criteria used.[18] It is largely associated with severe pregnancy complications like prenatal morbidity, preterm labour, dystocia, etc. In our dataset GDM was found to be significantly less frequent among mothers affected by viral infections as compared to the control group. Regarding this finding we were not able to identify substantive publications in the literature. In the background of the development of GDM, the role of many cytokines and other immunological factors have been investigated.[19] Pro-inflammatory cytokines and other inflammatory markers have been shown as predictors of diabetes.[20,21] We only hypothesize that viral infections may alter the activity of some anti-inflammatory cytokines resulting in a protection against insulin resistance. On the other hand, this finding of ours may also be incidental since the number of investigated cases is relatively low (8 in 2,238 infected mothers vs. 458 in 54,993 controls).

In most countries of the world, the prevalence of anaemia in pregnancy is over 20%.[22] It has been associated with prematurity, low birth weight, hypertensive disorders and adverse pregnancy outcomes.[23,24] In our study viral infections during pregnancy were associated with a significantly elevated prevalence of maternal anaemia as compared to uninfected control mothers. We were unable to find significant data in the literature,

that could explain this relatedness. In non-pregnant individuals autoimmune haemolytic anaemia has been reported in a number of viral infections.[25] Moreover, parvovirus infection has been associated with red cell aplasia.[26] In infants a mild viral infection was found to induce a significant decrease in haemoglobin that may persist for 14 to 30 days and may be difficult to distinguish from iron deficiency.[27] In a rodent model it was suggested that viruses may trigger autoantibody-mediated anemia by activating macrophages through gamma-interferon production.[28] On the other hand, anaemia may also act as a causative factor, enhancing susceptibility of pregnant mothers to viral infections.[29]

A further interesting finding of our study is that maternal smoking was significantly more frequent among mothers affected by viral infections as compared to the uninfected control group. Smoking is a well-established risk factor of various infections,[30]therefore, this finding is not surprising. However, it is worth mentioning that although maternal smoking is associated with unfavourable pregnancy outcome,[31,32] this correlation could not be verified in the present study.

The strengths of our study are related to the large population-based data set of the HCCSCA in an ethnically homogeneous Hungarian (Caucasian) population. Pregnancy complications, gestational age and birth weight can be estimated with high accuracy since data were medically recorded. This study included all viral infections during pregnancy and these exposure data were based on multiple sources including prenatal maternity logbooks which provided prospective medically recorded data. Exposure time and potential confounders were also documented.

However, there are also some limitations of our study. The major weakness of our dataset is that the diagnosis of viral infections was based on reported data without serological evidence of the virus infection. Maternal smoking data were based partly on retrospective maternal information burdened by recall bias.[33] A previous validation study of our group showed the low reliability of retrospective maternal self-reported information regarding smoking and alcohol drinking during pregnancy.[34] Another weakness of our study is that only cases born between 1980 and 2009 were evaluated, thus the results of the recent decade could not be analysed in this field.

In conclusion the findings of this study suggest that viral infections during pregnancy do not exert a deleterious effect on birth outcomes. The incidences of threatened miscarriage threatened preterm birth and maternal anaemia are higher in pregnancies affected by viral infections. The incidence of gestational diabetes is lower after viral infections during pregnancy. Maternal smoking is more frequent in pregnancies with viral infections.

Contribution to authorship

N.A. played a pivotal role in creating the database of the HCCSCA. D.S., B.P., R.C. and B.L. contributed to conception, design, data interpretation, and approval of the version to be published. D.S. and N.A. conducted the data analyses and wrote the manuscript. B.P., R.C. and B.L. reviewed the manuscript.

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Conflict of interest statement

The authors declare no conflict of interest.

Ethics statement

Data collection for the HCCSCA was begun in 1980. Ethics approval was not required at that time.

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