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Article

Tetanus toxoid and congenital abnormalities

A.E. Czeizel*, M. Rockenbauer

Department of Human Genetics and Teratology, National Institue of Public Health — WHO Collaborating Centre for the Community Control of Hereditary Diseases, Budapest, Hungary

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Abstract

Objective: To study the human teratogenic potential of tetanus vaccination during pregnancy. *Methods:* Pair analysis of cases with congenital abnormalities and matched healthy controls was performed in the large population-based dataset of the Hungarian Case–Control Surveillance of Congenital Abnormalities, 1980–1994. *Results:* Of 35 727 pregnant women who had babies without any defects in the study period (control group), 33 (0.09%) were vaccinated with tetanus. Of 21 563 pregnant women who had offspring with congenital abnormalities, 25 (0.12%) had tetanus vaccination. This difference was not significant ($P = 0.39$). The case–control pair analysis confirmed the safety of tetanus vaccination during pregnancy, particularly in the second and third months of gestation, i.e. during the critical period for congenital abnormalities. *Conclusion:* Tetanus vaccination during pregnancy appears not be teratogenic to the fetus. Thus, there is no contraindication, if the use of tetanus toxoid is necessary during pregnancy.

Keywords: Tetanus vaccination; Pregnancy; Congenital abnormalities; Case-control analysis

1. Introduction

A couple visited our Genetic Counselling Clinic because their child was affected with severe multiple congenital abnormalities including microcephaly, anal atresia and micropenis. The mother was vaccinated by tetanus toxoid in the fourth week of gestation and later it was blamed as the cause of the multiple congenital abnormalities of the probandus. In addition, tetanus vaccination during pregnancy was the reason for induced abortion in two cases in Hungary during the 1980s [1]. There appears to be no evidence for the human teratogenic potential of tetanus vaccination during pregnancy [2,3], nevertheless, the use

*Corresponding author. Tel.: +36 1 2155773; fax: +36 2155773
E-mail: czeizel@oki.jaboki.hu

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of tetanus toxoid causes maternal anxiety and presents a difficult decision for physicians. The large population-based dataset of the Hungarian Case–Control Surveillance of Congenital Abnormalities (HCCSCA) [4] is appropriate to evaluate the teratogenic potencial of tetanus toxoid by comparing 35 727 healthy control infants and of 21 563 cases with congenital abnormality born between 1980 and 1994.

2. Materials and methods

The Hungarian Congenital Abnormality Registry (HCAR) is a national-based registry of cases with congenital abnormality [5]. Notification of malformed offspring is compulsory for physicians, mainly obstetricians (in Hungary practically all deliveries take place in hospital), pediatricians (who are working in the neonatal units of inpatient obstetric clinics and various inpatient and outpatient pediatric clinics) and experts at nine prenatal diagnostic centers in Hungary. In lethal cases (stillbirths and infant deaths due to congenital abnormalities), pathologists send a copy of the detailed autopsy record to the HCAR. Autopsy is obligatory in the case of infant deaths. The recorded annual total prevalence of cases with congenital abnormality was 35 per 1000 informative offspring (liveborn infants, stillborn and selectively aborted fetuses) during the study period and approximately 90% of major congenital abnormalities was reported to the HCAR.

The procedure of the HCCSCA [4] included the following steps.

The first step was the *identification* of cases from the dataset of the HCAR. The majority of cases was reported to the HCAR within the first quarter (77%) of postnatal life [5]. *Cases* with isolated and unidentified multiple congenital abnormalities were included in the dataset of the HCCSCA. Three mild defects such as congenital dislocation of hip based on Ortolani click (with an obvious overdiagnosis in Hungary due to neonatal orthopedic screening), congenital inguinal hernia (most experts do not consider it as congenital abnormality), hemangiomas (with a great difficulty to differentiate minor anomaly and congenital abnormality manifestation of this developmental disturbance on the basis of report), syndromes of known origin (e.g. Down syndrome) and minor anomalies (as hydrocele testis), were excluded.

The second step was to ascertain appropriate *controls* for each case. Two newborn infants without congenital abnormalities were matched to every case according to gender, birth week, and district of parents' residence from the national birth registry of the Central Statistical Office.

The third step was to obtain *exposure data*. Reply-paid questionnaires with explanatory letters were mailed immediately after the notification to the parents of the cases and of the matched controls. The questionnaire requested information on drugs taken, maternal diseases, pregnancy complications, unusual events (e.g. accident, surgery, vaccination) and occupational exposures during gestation according to gestational weeks, as well as data on employment, social class, and family history. Furthermore, mothers were requested to send the *prenatal care logbook* and every medical document concerning their diseases during pregnancy and the defects of children. In the group of cases, regional district nurses were asked to visit non-respondent families and to obtain the necessary data. Thus, complete information was available on 81% (69% due to reply, 12% due to visit) of cases. The response rate for matched controls was 65%. District nurses did not participate in the evaluation of non-respondent matched controls for ethical reasons.

The fourth step was the evaluation of tetanus vaccination. The *source of information* was differentiated into three groups: (i) only data from prenatal care logbook (prenatal care physicians are obliged to record all events during pregnancy in the logbook) and/or other medical documents; (ii) only data from questionnaire; and (iii) concordant data from both medical documents and questionnaire. *Gestational time* was calculated from the first day of last menstrual period and three time intervals were considered: (i) First month of pregnancy. This time period is before the critical period for development of congenital abnormalities because approximately the first 2 weeks of gestation are before conception and the second 2 weeks involve the pre- and implantation period with 'all or nothing' rule, i.e. only liveborn

infants and very early fetal deaths, but not congenital abnormalities may occur. (ii) The second and third months of gestation involve the most sensitive, the so-called critical period for *major* congenital abnormalities. (iii) Fourth to ninth months of gestation. *Confounding factors,* such as maternal age, birth order, pregnancy complications as the proportion of threatened abortions and preterm births, acute and chronic maternal disorders and drug uses, were also evaluated.

The fifth step was the *statistical analysis of data* using the STATA statistical software. First, the occurrence of confounding factors and gestational time distribution of tetanus vaccination was compared between the case and control groups using χ^2 and Student's t-test. Second, the frequency of tetanus vaccination in the total control group as referent was compared with the figures of 24 congenital abnormality groups by gestational time periods and adjusted odds ratios (OR) with 95% confidence interval (95%CI) for potential confounders were evaluated in an ordinary logistic regression model. Third, the data of *case–control pairs* were compared using the McNemar test according to gestational time periods and the adjusted OR with 95%CI were calculated by the conditional logistic regression model. Cases were compared with one of their matched controls in each congenital abnormality group. In 95% of cases at least one of the matched controls was available. Fisher's exact test was performed on analyses based on cases numbering < 5.

3. Results

Of the controls consisting of 35727 healthy infants, 33 (0.09%) had mothers with tetanus vaccination during pregnancy. The study period contained 1923413 total births in Hungary, hence the group of controls represents 1.9% of the Hungarian newborn population. Of 21563 cases with congenital abnormality, 25 (0.12%) had mothers who received tetanus vaccination during pregnancy. The difference in the occurrence of tetanus vaccination was not significant between cases and controls (Table 1).

The sources of information concerning tetanus vaccination showed a similar pattern of distribution in the control and case groups, approximately half of tetanus toxoid use being medically documented.

Among confounding factors, maternal age and birth order did not differ between the two groups. The proportion of threatened abortions was higher in the control group. Threatened preterm birth and all but one maternal disorder showed a similar number of occurrences in the case and control groups. The exception was excessive nausea–vomiting, which had a higher rate in the control group. The reason for tetanus vaccination, e.g. accident was mentioned in 80% of cases and in 88% of controls. Among the most commonly used drugs, only allylestrenol treatment occurred more frequently in the case group.

The time of tetanus vaccination according to months of gestation (Table 2) was similar in the two study groups ($\chi^2_8 = 2.9$; $P = 0.95$). The maximum was found in the second month followed by the third month, i.e. in the critical period of congenital abnormalities.

Of 24 congenital abnormality groups evaluated, six consisted of two or more cases (Table 3). No congenital abnormality group had a higher rate of tetanus vaccination than that of the total control group. Evaluating tetanus vaccination in the second and third months of gestation, i.e. during the critical period of embryonic development, there was no difference between the total control and case groups.

The appropriate analysis for case–control pairs is the McNemar test (Table 4). Adjusted odds ratios showed no differences in maternal tetanus vaccination during the whole pregnancy for any congenital abnormality. In addition, the use of tetanus toxoid did not show a significant difference in the second and third months of gestation.

4. Discussion

Tetanus toxoid is an inactivated *Clostridium tetani* toxin and is administrated intramuscularly or subcutaneously to induce active immunity to tetanus. This paper evaluated tetanus vaccination during pregnancy in mothers with offspring affected with congenital abnormalities and their matched unaffected controls. Our results indi-

Table 1
The occurrence of tetanus vaccination during pregnancy, source of information, and confounding factors

Variables	Cases		Controls		Difference P value
	No.	%	No.	%	
Total number	21 563		35 727		
Tetanus vaccination	25	0.12	33	0.09	0.39
Source of information					
Medically documented	12	48.0	16	48.5	
Only questionnaire	13	52.0	17	51.5	0.97
Confounding factors					
Maternal age, year (mean, S.D.)	26.9	5.3	25.7	5.2	0.56
Birth order (mean, S.D.)	1.80	1.08	1.94	1.14	0.52
Threatened abortion	1	4.0	5	15.2	0.03
Threatened preterm birth	3	12.0	5	15.2	0.73
Maternal disorders (> 1 in each group)					
Anemia	2	8.0	7	21.2	0.17
Nausea, vomiting, excessive	0	0.0	5	15.2	0.04
Infectious diseases of					
respiratory system	3	12.0	11	33.3	0.06
urinary tract	0	0.0	2	6.1	0.21
genital organ	2	8.0	1	3.0	0.40
Varicositas, phlebitis	0	0.0	4	12.1	0.07
Accident	20	80.0	29	87.9	0.41
Drug uses (> 2 in each group)					
Allylestrenol	8	32.0	1	3.0	0.04
Noraminophenazine	2	8.0	5	15.2	0.41
Terbutaline	1	4.0	4	12.1	0.28
Dimenhydrinate	1	4.0	3	9.1	0.45
Penamecillin	3	12.0	3	9.1	0.42
Promethazine	1	4.0	5	15.2	0.17
Diazepam	2	8.0	6	18.2	0.27

cated that tetanus vaccination was not teratogenic.

The benefits of the HCCSCA's dataset were the large population-based cohort, 58 pregnant women receiving tetanus vaccination, and the matching of cases with congenital abnormalities and their controls. However, there were also drawbacks. The dataset was based on retrospective information of women concerning tetanus vaccination for 52% of controls and cases. There is no complete ascertainment: approximately 10% of major congenital abnormalities was unreported and complete information was available on 81% of cases. The response rate of control mothers

Table 2
Distribution of tetanus vaccination according to gestational months

Groups	Gestational months									
	I	II	III	IV	V	VI	VII	VIII	IX	Total
Cases No.	3	5	5	2	2	4	2	2	0	25
%	12.0	20.0	20.0	8.0	8.0	16.0	8.0	8.0	0.0	100.0
Controls No.	4	8	5	4	1	3	4	3	1	33
%	12.1	24.3	15.2	12.1	3.0	9.1	12.1	9.1	3.0	100.0

Table 3
Occurrence and adjusted odds ratios (OR) with 95% confidence interval (CI) of tetanus vaccination grouped by gestational months (CA, congenital abnormality)

Study groups	First month		Second–third months			Fourth–ninth months		Total			Grand total
	No.	%	No.	%	OR (95% CI)	No.	%	No.	%	OR (95% CI)	No.
Total control	4	0.01	13	0.04	Referent	16	0.04	33	0.09	Referent	35 727
Isolated CAs											
Neural-tube defects	0	0.00	1	0.09	0.8 (0.0–16.0)	1	0.09	2	0.17	1.5 (0.3–8.8)	1160
Poly/syndactyly	0	0.00	1	0.06	1.8 (0.2–13.8)	3	0.19	4	0.25	2.1 (0.6–6.9)	1573
Cardiovascular CAs	1	0.03	0	0.00	–	3	0.08	4	0.10	1.1 (0.4–3.2)	3969
Clubfoot	0	0.00	1	0.04	1.4 (0.2–10.4)	2	0.09	3	0.13	1.5 (0.5–5.0)	2242
Other CAs	2	0.02	6	0.06	1.6 (0.6–4.2)	2	0.02	10	0.10	1.0 (0.5–2.0)	10 415
Multiple CA	0	0.00	1	0.05	1.1 (0.1–9.1)	1	0.05	2	0.09	0.5 (0.1–3.8)	2204
Total	3	0.01	10	0.05	1.2 (0.5–2.8)	12	0.06	25	0.12	1.1 (0.6–1.9)	21 563

was lower, however, a complementary study did not show a significant difference in the distribution of pregnancy complications including surgery and vaccination between respondent and 200 non-respondent families. Finally, a drawback was the small number of cases in the subgroups of congenital abnormalities, while this was a large dataset, the rare event of interest and subgroup analysis generated concerns about sample size. Thus, the number of pregnant women with tetanus vaccination in the second and third months of gestation was relatively small (13 control and 10 case mothers) due to the rare indication of tetanus vaccination during pregnancy.

There is a question as to whether there is any epidemiological evidence of an association between tetanus toxoid and spontaneous abortions [6]. Unfortunately the dataset was not appropriate for the evaluation of spontaneus abortion. Congenital abnormalities were not increased among children of 337 women who received immunization with tetanus toxoid during the first 4 lunar months of pregnancy or in children of 853 women immunized with tetanus toxoid anytime during pregnancy [7]. Studies in experimental animals (e.g. rats) suggested that immunization during pregnancy with tetanus toxoid was unlikely to increase the risk of congenital abnormalities [8,9]. Nevertheless, according to Friedman and Polifka [3], the available data were insufficient to state that there was no risk. However, our analysis did not indicate any teratogenic effect of tetanus toxoid during pregnancy. Thus, we rejected the hypothesis that the multiple congenital abnormalities in the probandus was caused by tetanus vaccination during the pregnancy of her mother.

Table 4
Results of McNemar analysis of case-control pairs and adjusted odds ratios (OR) with 95% confidence interval (CI) of tetanus vaccination during pregnancy. (The data of subgroups of the second–third month of gestation are shown in brackets)

Congenital abnormality (CA) groups	Case–control pairs				Whole pregnancy			Second–third months	
	No–No	Yes–No	No–Yes	Yes–Yes	No.	OR	(95% CI)	OR	(95% CI)
Neural-tube defect	990 (993)	2 (1)	2 (0)	0 (0)	994	0.6	(0.1–5.8)	3.0	(0.1–73.7)
Poly/syndactyly	1452 (1456)	4 (1)	1 (0)	0 (0)	1457	1.6	(0.3–8.1)	1.5	(0.1–26.0)
Cardiovascular CAs	3641 (3644)	3 (0)	1 (0)	0 (0)	3645	1.8	(0.3–12.1)	–	–
Clubfoot	2028 (2031)	3 (1)	3 (2)	0 (0)	2034	1.3	(0.3–6.8)	0.6	(0.1–7.4)
Other isolated CAs	9549 (9559)	9 (5)	9 (3)	0 (0)	9567	0.9	(0.4–2.3)	1.6	(0.4–6.1)
Multiple CAs	2003 (2004)	2 (1)	2 (2)	0 (0)	2007	0.5	(0.0–6.5)	0.6	(0.0–9.8)

The effect of tetanus immunization during pregnancy may protect against neonatal tetanus of infants [10–12].

In conclusion, there is no contraindication to use tetanus vaccination during pregnancy.

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