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Reproductive outcome after exposure to surgery under anesthesia during pregnancy

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Abstract. The objective of the study was to examine the teratogenic potential of surgery under anesthesia during pregnancy in the large population-based dataset of the Hungarian Case-Control Surveillance of Congenital Abnormalities, 1980–1994. An analysis of cases with congenital abnormalities and matched healthy controls was performed. Of 35,727 pregnant women who had babies without any defects (control group), 73 (0.20%) had had operations under anesthesia. Of 20,830 pregnant women who had offspring with congenital abnormalities, 31 (0.15%) had operations with anesthesia. There was no higher rate of surgery under anesthesia in any congenital abnormality group. In addition, the case-control pair analysis did not show a significantly higher rate of surgery and anesthesia in the second and third months of gestation in any group of congenital abnormalities. A lower birth weight was found in healthy newborn infants born to mothers with surgery during pregnancy, however, it was explained by the subgroup with cervical incompetence often treated by cerclage which is of limited efficacy. Surgery under anesthesia does not appear to present teratogenic risk to the fetus.

Key words: Surgery during pregnancy – Anesthesia in pregnant women – Congenital abnormalities – Birth weight

Introduction

Because of instinctive protection of pregnant women and their babies surgical interventions during pregnancy cause anxiety to women and of their physicians. The large population-based dataset of the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) [3] seems to be appropriate to check the teratogenic potential of operations under anesthesia by comparing 35,727 healthy control infants with 20,830 cases with congenital abnormality, both being born between 1980 and 1994.

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Subjects and methods

The Hungarian Congenital Abnormality Registry (HCAR) is a national-based registry of cases with congenital abnormality [2]. Notification of malformed offspring is compulsory for physicians. After stillbirths and infant deaths due to congenital abnormality, pathologists send a copy of the obligatory autopsy findings to the HCAR. The recorded annual total prevalence of cases with congenital abnormality was 44 per 1000 informative offspring (liveborn infants, stillborn and selectively aborted fetuses) in the 1980s. Most major congenital abnormalities (about 88%) were notified to the HCAR between 1980 and 1994 [2].

The HCCSCA [3] included the following steps.

The first step was the *identification* of cases with congenital abnormality from the dataset of the HCAR. The majority of cases were notified to the HCAR within the first month (about 60%) or first 3 months (77%) of postnatal life [2]. *Cases* with isolated and unidentified multiple congenital abnormalities were included into the dataset of the HCCSCA. Mild defects such as a congenitally clicking hip, congenital inguinal hernia, hemangiomas, syndromes of known origin and minor anomalies were excluded.

The 2nd step was to ascertain appropriate *controls* for each case. Newborn infants without congenital abnormalities were matched by sex, birth week, and district of parents' residence from the national birth registry of the Central Statistical Office. Until 1988 2, and later 3 matched controls were selected for each case.

The 3rd step was *to obtain data.* A reply-paid questionnaire with an explanatory letter was promptly mailed to the parents. The questionnaire requested information on drugs taken, maternal diseases, pregnancy complications, unusual events (e.g., accident, surgery) and occupational exposures during pregnancy. Mothers were asked to send us the prenatal care logbook and every available medical document about their pregnancy. In cases, regional district nurses were asked to visit nonrespondent families and to obtain the necessary data. Thus, complete information was available on 82% (70% due to reply, 12% due to visit) of cases. The response rate for controls was 65%. District nurses did not participate in the evaluation of nonrespondent controls for ethical reason. In a previous study 200 control families with no response were visited at home and the distribution of pregnancy complications did not differ from the pattern of control pregnant women who responded.

The fourth step was the identification of operations. *Operations* were defined as *surgery* (laparatomy, e.g., appendectomy or transvaginal, e.g., cerclage or any other surgical intervention) under *general anesthesia* in *inpatient clinics.* Interventions under local anesthesia, e.g., chorion villous sampling or amniocentesis were excluded. Three *gestational time* intervals were defined: a) The 1st month of pregnancy. b) The 2nd and 3rd months of pregnancy when organogenesis is occurring. c) The 4th to 9th months of pregnancy. *Confounding factors,* as maternal age, birth order, pregnancy complications, e.g., proportion of threatened abortions and preterm births, maternal disorders and drug uses during pregnancy were noted. *Birth weight and gestational age* were only evaluated in controls and the data about liveborn infants born to mothers with or without surgery were compared.

Statistical methods

For comparison of confounding factors, birth weight and gestation age, Student t and chi-square tests were used. The occurrence of operation under anesthesia in the total control group was compared with the figures for 24 congenital abnormality groups by gestational month and adjusted odds ratios (OR) and 95% confidence intervals (95% CI) for potential confounders (maternal age, pregnancy complications, maternal diseases, drug uses) were evaluated using ordinary logistic regression analysis. *Case-control pairs* were compared using McNemar test according to gestational months and the adjusted OR (with 95% CI) was calculated by a conditional logistic regression model. Cases were compared with one of their matched controls in each congenital abnormality group. In 92% of cases at least one of the matched controls was available. If 2 or 3 matched controls were available, only one control was selected randomly for any one case. Fisher's exact test was performed on analyses based on less than 5 cases. In addition a modified McNemar approach with two controls per case was also evaluated using the Mantel-Haenszel test.

Results

There were 35,727 control infants and 73 (0.20%) of their mothers had an operation under anesthesia during the pregnancy. During the study period there were 1,923,413 total births in Hungary, hence the controls represent 1.9% of the Hungarian newborn population. There were 20,830 cases of congenital abnormalities and in 31 (0.15%) instances mothers had had operation under anesthesia during the pregnancy. The difference in the occurrence of surgical intervention was not significant between cases and controls (Table 1).

Mean maternal age and birth order did not differ significantly between control and case groups (Table 1). The proportion of pregnancy complications, maternal acute and chronic diseases, traumas and the use of drugs were also similar in both groups.

The gestational age at the time of operation under anesthesia in the two study groups is shown in Table 2. The distribution of gestational months is similar in both groups ($\chi^2_8 = 4.85$; $p = 0.77$) with a peak at the 6th month. Cerlage for cervi-

Table 1. The occurrence of operations under anesthesia during pregnancy and confounding factors

	Controls		Cases				Difference
	No.	%	No.	%	OR	95% CI	*p*
Total number	35,727	–	20,830	–		referent	
Operation	73	0.20	31	0.15	0.73	(0.48 1.11)	0.14
Confounding factors							
Maternal age (yr; mean±S.D.)	26.0±4.7		27.1±5.8				0.33
Birth order (mean±S. D.)	1.68±0.81		1.69±0.71				0.98
Pregnancy complications							
Nausea, vomiting	3	4.1	3	9.7	1.72	(0.39 7.55)	0.50
Threatened abortion	20	27.4	14	45.2	1.20	(0.61 2.38)	0.56
EPH (edema, proteinuria, hypertension)	4	5.5	3	9.7	1.29	(0.32 5.20)	0.74
Cervical incompetence	44	60.3	20	64.5	0.78	(0.46 1.32)	0.35
Threatened preterm birth	12	16.4	6	19.4	0.86	(0.32 2.29)	0.76
Anemia	9	12.3	5	16.1	0.95	(0.32 2.84)	0.93
Maternal acute diseases							
Infectious diseases of Respiratory system	20	27.4	11	35.5	0.94	(0.45 1.97)	0.88
Urinary tract	5	6.8	1	3.2	0.34	(0.06 2.08)	0.31
Genital organ	3	4.1	6	19.4	3.43	(0.94 12.58)	0.06
Appendicitis	6	8.2	2	6.5	0.57	(0.13 2.46)	0.49
Maternal chronic diseases							
Hemorrhoid	6	8.2	2	6.5	0.57	(0.13 2.46)	0.49
Ovarian cysts	6	8.2	1	3.2	0.29	(0.05 1.69)	0.22
Trauma	8	11.0	4	12.9	0.86	(0.27 2.69)	0.80
More common drug uses							
Promethazine	31	42.5	12	38.7	0.66	(0.34 1.29)	0.23
Terbutalin	28	38.4	12	38.7	0.73	(0.37 1.45)	0.37
Diazepam	21	28.8	7	22.6	0.57	(0.24 1.35)	0.19
Allylestrenol	20	27.4	10	32.3	0.86	(0.40 1.83)	0.69
Drotaverine	19	26.0	7	22.6	0.63	(0.26 1.50)	0.30

Table 2. Time of operation under anesthesia and types of surgical interventions

Gestation month	Control			Cases		
	No.	%	Operation	No.	%	Operation
I	6	8.2	Appendectomy 3 Trauma-fracture 2 Ovarian cystectomy	2	6.5	Trauma-fracture Curettage (uterus bicornis)
II	5	6.8	Appendectomy 2 Trauma-fracture Laparoscopy Polyp removal	2	6.5	Appendectomy Cholecystectomy
III	8	11.0	Ovarian cystectomy 3 Trauma-fracture 2 Appendectomy Breast cyst removal Palmar cyst removal	2	6.5	Trauma-fractures Oophorectomy for right dermoid cyst
IV	6	8.2	Trauma-fractures 3 Hemorrhoidectomy 2 Ovarian cystectomy	2	6.5	Trauma-fracture Cerclage
V	10	13.7	Cerclage 8 Hemorrhoidectomy Ovarian desmoid cystectomy	3	9.7	Cerclage 2 Appendectomy
VI	23	31.5	Cerclage 23	8	25.8	Cerclage 7 Myomectomy
VII	10	13.7	Cerclage 9 Bartholin's cystectomy	6	19.3	Cerclage 4 Breast cyst removal Ovarian cystectomy
VIII	4	5.5	Cerclage 4	5	16.1	Cerclage 5
IX	1	1.4	Paraurethral cystectomy in vagina	1	3.2	Trauma-fracture
Total	73	100.0	Cerclage 44 Trauma 8 Appendectomy 6 Hemorrhoidectomy 3 Ovarian cystectomy 6 Others 6	31	100.0	Cerclage 19 Trauma 4 Appendectomy 2 Others 6

cal incompetence was most frequent operation followed by surgery for trauma and appendicitis. The type of surgical interventions was similar in the group of controls and cases ($\chi^2_3 = 0.18$; $p = 0.98$).

Of 24 congenital abnormality groups evaluated, only seven consisting of 2 or more cases are shown in Table 3. The absolute risk was low. There was no higher rate of operation in any of the congenital abnormality groups studied.

The McNemar test for case-control pairs did not indicate a significant difference in the surgical intervention rate during the whole of pregnancy or in the second and third months of gestation.

The mean birth weight was lower in newborn infants of control mothers who had an operation than in the group of control mothers who did not (Table 4). However, this difference can be explained by the subgroup of mothers with surgery for cervical incompetence ($t = -2.52$; $p = 0.01$). Thus, mean birth weight was somewhat but not significantly higher in the control subgroup of mothers who had an operation other than cervical incompetence than in the group of controls who had no op-

Table 3. Occurrence of operation under anesthesia according to gestation month in the total control and 7 congenital abnormality groups

Study groups	Gestation months																Grand total
	I				II–III				IV–IX				Total				
	No.	%	OR	95% CI	No.	%	OR	95% CI	No.	%	OR	95% CI	No.	%	OR	95% CI	
Total controls	6	0.17	Referent		13	0.36	Referent		54	0.15	Referent		73	0.20	Referent		35,727
Isolated CAs																	
Cardiovascular CAs	0	0.00	–	–	1	0.03	0.8	0.1–6.5	8	0.20	1.8	0.8–3.9	9	0.23	1.2	0.6–2.4	3,969
Cystic kidney	0	0.00	–	–	1	0.85	7.4	1.0–56.7	1	0.85	7.4	1.0–56.7	2	1.71	4.4	0.6–32.7	117
Hypospadias	0	0.00	–	–	2	0.07	4.2	0.8–21.8	2	0.07	0.5	0.1–2.2	4	0.15	0.6	0.2–1.8	2,726
Undescended testis	0	0.00	–	–	0	0.00	–	–	3	0.16	1.3	0.4–4.3	3	0.16	0.8	0.2–2.5	1,862
Club foot	1	0.04	3.9	0.4–33.6	0	0.00	–	–	1	0.04	0.4	0.1–2.9	2	0.09	0.5	0.1–1.9	2,242
Other isolated CAs	1	0.01	1.1	0.1–9.8	0	0.00	–	–	7	0.08	0.7	0.3–1.6	8	0.09	0.5	0.2–1.0	8,443
Multiple CAs	0	0.00	–	–	0	0.00	–	–	3	0.20	0.7	0.1–3.5	3	0.20	0.5	0.1–2.1	1,471
Total CAs	2	0.01	0.8	0.1–4.1	4	0.02	0.5	0.1–1.9	25	0.12	1.1	0.7–1.8	31	0.15	0.8	0.5–1.2	20,830

Table 4. Mean birth weight and gestation age, as rate of low birth weight and preterm birth in healthy control infants born to mothers after operation under anesthesia during pregnancy

Variables	Operation			Without operation	Difference	
	Cervical incompetency	Others	Total		Test	*p*
Total number	44	29	73	35,654		
Birth weight (g; mean; S.D.)	2,971 ± 645	3,361 ± 407	3,132 ± 588	3,276 ± 528	$t = 2.28$	0.023
<2500 g (No., %)	6 13.6	0 0.0	6 8.2	2,016 5.9	$\chi_1^2 = 0.36$	0.549
Gestation age (week; mean, S.D.)	38.6 ± 2.5	39.8 ± 1.5	39.1 ± 2.2	39.4 ± 2.1	$t = 1.11$	0.265
<38 weeks (No., %)	8 18.2	4 13.8	12 16.4	4,976 14.0	$\chi_1^2 = 0.91$	0.340

eration during pregnancy ($t = 0.87$; $p = 0.39$). The rate of low birth weight was also higher ($\chi_1^2 = 5.24$; $p = 0.02$) in the subgroup of control mothers who had an operation for cervical incompetence.

Discussion

This paper compares surgical intervention rates under anesthesia during pregnancy in the mothers of babies with congenital abnormality and in matched control mothers with a normal baby.

The frequency of surgical interventions was somewhat lower in the case group than in the control group. Thus, the teratogenic effect of surgery and/or anesthesia can be excluded and this statement is confirmed by the detailed analysis of congenital abnormality groups.

The teratogenic effect of surgery and anesthesia have only been studied relatively rarely. Brodsky [1] analysing five reports, found no link between congenital abnormality and surgery under anesthesia during early pregnancy. This finding supported the results of experimental investigations [4]. Individual reports of appendectomy during pregnancy were reviewed by Mazze and Källen [7]. Källen and Mazze [5] evaluated 2,252 births following first trimester operations and found 6 offspring with a neural-tube defect. Of 572 pregnant women who underwent surgery at 4–5 weeks of gestation, 5 had offspring with neural-tube defects. They stated that if there is a causal relationship to any factor in surgery the absolute risk "could be 8–10 times, or even more for a neural-tube defect". Of our 31 pregnant women who had babies with a congenital abnormality, one had a neural-tube defect after surgery in the sixth month of gestation, though there were 1,161 cases of neural-tube defects in our dataset. (This one case explains that this group of congenital abnormalities was not shown in Table 3.) Only 5 and 2 mothers in the control and case groups, respectively, had operations during the second month (week 5–8) of gestation. Mazze and Källen [6] evaluated reproductive outcome after anesthesia and operation (excluding obstetrical operations, e.g., cerclage) in 5,405 cases of the Swedish registry. A higher rate of congenital abnormality and still-

birth was not found, but the number of infants with a birth weight below 1,500 g was increased with a relative risk of 2.2 (1.8–2.8). The Swedish registry study of 778 pregnant women who had an appendectomy did not show any increase in the number of malformed infants and stillborn fetuses, but a decrease was found in mean birth weight of 78±24 g. In our study the mean birth weight was lower and the rate of low birth weight was higher in healthy *control* infants born to mothers after operation under anesthesia during pregnancy. This was due to the inclusion of pregnant women who had the only moderately successful procedure of cerclage for cervical incompetence. Pregnant women who had other operations (mainly laparotomies) had babies with a somewhat higher birth weight and longer gestation age, but these differences were not significant.

Our study shows a lower rate of operation under anesthesia during pregnancy than in other countries [6]. This may reflect the reluctance of Hungarian physicians to perform surgery during pregnancy. The rate of appendectomy during pregnancy was one in 936 in Sweden and one in 5,955 in Hungary.

In conclusion, operations under anesthesia during pregnancy apparently need not be avoided on grounds of teratogenic hazards.

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