Vol.2, No.8, 945-950 (2010)
doi:10.4236/health.2010.28140

A possible association between cervical erosion in pregnant women and congenital abnormalities in their children—a population-based case-control study

Ferenc Bánhidy[1], Nándor Ács[1], Erzsébet H. Puhó[2], Andrew E. Czeizel[2]*

[1]Second Department of Obstetrics and Gynecology, Semmelweis University, School of Medicine, Budapest, Hungary
[2]Foundation for the Community Control of Hereditary Diseases, Budapest, Hungary; *Corresponding Author: czeizel@interware.hu

Received 25 February 2010; revised 24 March 2010; accepted 25 March 2010.

ABSTRACT

Objective to study the possible association between erosion of cervix in pregnant women (ECP) and structural birth defects, *i.e.* congenital abnormalities (CA) in their offspring. Study design: Comparison of cases with CA and all matched controls without any CA born to women with prospectively and medical record ECP in the population-based large data set of the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA). Results: HCCSCA contained 22,843 cases and 38,151 matched controls, the informative offspring of 40 (0.18%) case mothers and the newborns of 25 control mothers (0.07%) with ECP were compared and the higher risk for total CA (adjusted OR with 95% CI: 2.7, 1.6-4.4) was found explained by the higher risk of 9 cases with hypospadias (OR with 95% CI: 4.5, 2.1-9.7) and 10 cases with cardiovascular CAs (OR with 95% CI: 3.4, 1.6-7.1), particularly with conotruncal CAs. Conclusions: An unexpected possible association of ECP with higher risk for hypospadias and conotruncal cardiovascular CAs was found and these findings are considered as signals that need confirmation or rejection

Keywords: Erosion of Cervix in Pregnant Women; Birth Outcomes; Congenital Abnormalities; Hypospadias; Cardiovascular Malformations

1. INTRODUCTION

The objective of our project entitled "Possible association of maternal diseases during pregnancy with adverse birth outcomes" is conducting a systematic analysis all recorded maternal diseases in the population-based large data set of the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) [1]. The preliminary analysis of Erosion of Cervix in Pregnant Women (ECP) showed an unexpected association with high rate of total structural birth defects, *i.e.* Congenital Abnormalities (CAs), thus it was necessary to evaluate the specific CAs in detail. The medical term for cervical erosion is cervical ectopy because the cells at the os of the cervix changes from the squamous cells normally found at this region to columnar cells and this pathological condition gives a red and eroded appearance [2]. To our best knowledge the possible association of ECP with CAs in their children has not been checked or reported in controlled epidemiological studies [3] thus the results of our case-control study based on the HCCSCA [4] are presented here.

2. MATERIALS AND METHODS

2.1. Subjects

Cases with CA were selected from the Hungarian Congenital Abnormality Registry (HCAR) [5] for the HCCSCA. Notification of cases with CA is mandatory for physicians from the birth until the first birthday to the HCAR and most CAs are reported by obstetricians (in Hungary practically all deliveries take place in inpatient obstetric clinics and birth attendants are obstetricians) or paediatricians (working at neonatal units of inpatient obstetric clinics as well as of various general and special inpatient and outpatient paediatric clinics). Autopsy during the study period was obligatory for all infant deaths and was performed in about 80% of stillborn fetuses. Pathologists sent a copy of the autopsy report to the HCAR if defects were identified in stillborn fetuses or infant deaths. Fetal defects diagnosed by prenatal diagnostic centres with or without elective termination of pregnancy have also been reported to the HCAR

Copyright © 2010 SciRes.

since 1984. The recorded total (birth + fetal) prevalence of cases with CA diagnosed from the second trimester of pregnancy through the age of one year was 35.0 per 1000 *informative offspring* (live-born infants, stillborn fetuses and electively terminated malformed fetuses) in the HCAR, 1980-1996.

Controls were identified and selected from the National Birth Registry of the Central Statistical Office for the HCCSCA. Controls were defined as newborn infants without CA and in general two controls were matched with every case according to sex, birth week and district of parents' residence.

2.2. Collection of Exposure Data and Confounding Factors

2.2.1. Medically Recorded Prospective Data

Mothers were asked to send us the prenatal maternity logbook and other medical records (mainly discharge summaries) regarding their diseases and related treatments during the study pregnancy. 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, 7 times. The task of obstetricians was to record all pregnancy complications, maternal diseases (such as cervical erosion) and related drug prescriptions in the prenatal maternity logbook.

2.2.2. Retrospective Maternal Information

A structured questionnaire together with informed consent was also mailed to the mothers immediately after the selection of cases and controls.

The period between birth or elective termination of pregnancy and return of "information package" (logbook, questionnaire, informed consent, etc.) in our prepaid envelop was 3.5 ± 1.2 and 5.2 ± 2.9 months for cases and controls, respectively.

2.2.3. Supplementary Data Collection

Regional nurses were asked to visit all non-respondent mothers of cases at home, and they helped mothers to fill-in the same questionnaire, evaluated available medical documents, in addition obtained data regarding lifestyle (smoking, drinking, drug use) through a personal interview of mothers and their close relatives living together. Regional nurses visited only 200 non-respondent and 600 respondent control mothers as part of two validation studies [6,7], as the ethics committee considered that this follow-up would be disturbing to the parents of healthy children. Regional nurses used the same method as in non-respondent case mothers.

Finally necessary data were collected for 96.3% of cases (84.4% from reply, 11.9% from visit) and for 83.0% of controls (81.3% from reply, 1.7% from visit). Informed consent was signed and returned by 98.4% of mothers. The name and address of children without signed informed consent were deleted in the HCCSCA. The procedure of data collection in the HCCSCA was changed in 1997 such that 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.

2.3. Definition of ECP and their Diagnostic Criteria

Erosion without mention of cervitis and cervitis-endocervitis with mention of erosion are two different specified codes in the International Classification of Diseases (ICD-WHO) [8], pregnant women with these diagnoses were included to the study. Thus pregnant women 1) with ectropion of cervix, 2) with cervical incompetence, dysplasia, leukoplakia, laceration, stricture, stenosis, mucous polyp of cervix and 3) with the inflammatory diseases of female pelvic organs frequently associated with cervitis and related erosion were excluded from the study.

Two groups of ECP were differentiated: 1) previously known and documented erosion which existed in the study pregnancy, and 2) erosion diagnosed at the time of their visit in the prenatal care clinic by obstetrician and confirmed by colposcopic examination. Thus ECP was medically recorded in the prenatal maternity logbook. If PAP smear showed atypical cells, cervical biopsy was performed and women with precancerous condition were also excluded from the study.

The gestational age was calculated from the first day of the last menstrual period. Both birth weight and gestational age at delivery were medically documented in the discharge summary of mothers after delivery.

Among confounding factors, maternal age, birth order, marital and employment status as indicator of socioeconomic [9], other maternal diseases and medication (drugs and pregnancy supplements) were considered.

2.4. Statistical Analyses

The data of the study were analyzed by the software package SAS version 8.02 (SAS Institute Ins., Cary, North Caroline, USA). The characteristics of case and control mothers were compared using Student t test for quantitative and chi square statistics or odds ratios (OR) with 95% confidence interval (CI) for categorical variables. The prevalence of ECP was compared in mothers of cases with different CA groups and their all matched controls, and adjusted OR with 95% CI were evaluated in a conditional logistic regression model.

3. RESULTS

Of 22,843 cases with CA, 40 (0.18 %) had mothers with

Copyright © 2010 SciRes.

ECP, while of 38,151 controls, 25 (0.07%) were born to pregnant women affected with ECP. The diagnosis of ECP was based on colposcopic examination and prospectively (at the first visit between the 6th and 10th gestational weeks in the prenatal care clinics) medically recorded in the prenatal maternity logbook. Thus the onset of ECP was considered to be before conception or in early pregnancy. Of 40 case mothers, 13 (32.5) had the diagnosis of ECP with cervitis, while of 25 control mothers, 4 (16.0%) had the similar combined diagnosis.

Table 1 summarizes the most important maternal variables. Mean maternal age and birth order in mothers with ECP did not differ significantly from the figures of the reference sample. The proportion of unmarried women was somewhat higher in pregnant women with ECP. Control pregnant women with ECP showed a higher socioeconomic status on the basis of their employment status than case pregnant women with ECP. The use of folic acid during pregnancy was higher in control mothers particularly affected with ECP than in case mothers. A similar trend was seen in the use of multivitamins as well. However, these differences did not reach the level of significance due to the limited number of affected pregnant women.

Of 2,640 case mothers visited at home, 5 (0.19%) had ECP and 3 (60.0%) were smoker during the study pregnancy. Of 2,635 mothers without ECP, 575 (21.8%) smoked. Of 800 control mothers visited at home, 152 (19.0%) smoked during the study pregnancy, only one smoker had the diagnosis of ECP.

Among maternal diseases, the prevalence of haemorrhoids was higher both in case mothers (10.0% vs. 3.5%) and control mothers (12.0% vs. 4.3%) with ECP compared to pregnant women without ECP. The incidence of threatened preterm delivery (22.5% vs. 11.4% in case and 44.0% vs. 14.3% in control mothers) and anaemia (32.5% vs. 14.2% in case and 28.0% vs. 16.7% in control mothers) was much higher in pregnant women with ECP.

Allylestrenol, diazepam, promethazine and terbutaline were used for the prevention/treatment of threatened preterm delivery therefore these drugs showed a higheruse in pregnant women with ECP compared to pregnant women without ECP as reference (**Table 2**). However, clotrimazole and other antifungal drugs were also used more frequently by pregnant women with ECP. Only allylestrenol treatment occurred more frequently in

Table 1. Maternal characteristics

Maternal variables Quantitative	Case mothers without with ECP (N = 22,803)		(N = 40)		Control mothers without with ECP (N = 38,126)		(N = 25)		Comparison of case and control mothers with ECP
Maternal age, yr.	No.	%	No.	%	No.	%	No.	%	p =
– 19	2,501	11.0	5	12.5	3,277	8.6	0	0.0	
20 – 29	15,564	68.3	29	72.5	27,583	72.3	19	76.0	0.21*
30 –	4,738	20.8	6	15.0	7,266	19.1	6	24.0	
Mean, S.D.	25.5 ± 5.3		24.5 ± 4.6		25.5 ± 4.9		25.8 ± 4.3		0.33**
Birth order (parity)									
1	10,690	46.9	18	45.0	18,196	47.7	13	52.0	0.72*
2 or more	12,133	53.1	22	55.0	19,930	52.3	12	48.0	
Mean, S.D.	1.9 ± 1.1		1.9 ± 1.5		1.7 ± 0.9		1.8 ± 1.0		0.27**
Categorical	No.	%	No.	%	No.	%	No.	%	
Unmarried	1,264	5.5	5	12.5	1,470	3.9	2	8.0	0.50**
Employment status									
Professional	1,973	8.7	4	10.0	4,419	11.6	4	16.0	
Managerial	5,093	22.3	4	10.0	10,256	26.9	9	36.0	
Skilled worker	6,489	28.5	12	30.0	11,901	31.2	7	28.0	
Semiskilled worker	4,191	18.4	6	15.0	6,157	16.1	4	16.0	0.12**
Unskilled worker	1,770	7.8	6	15.0	2,187	5.7	0	0.0	
Housewife	2,400	10.5	6	15.0	2,353	6.2	1	4.0	
Others	887	3.9	2	5.0	853	2.2	0	0.0	
Pregnancy supplements									OR 95% CI
Iron	14,716	64.5	26	65.0	26,751	70.2	20	80.0	0.8 0.5 – 1.3
Folic acid	11,259	49.4	20	50.0	20,758	54.4	17	68.0	0.7 0.4 – 1.7
Multivitamins	1,327	5.8	3	7.5	2,506	6.6	3	12.0	0.6 0.2 – 2.7

*chi-square test; **Student t-test

Copyright © 2010 SciRes.

control mothers than case mothers with ECP.

The birth outcomes of control newborns without CA are presented in **Table 3** because CAs in cases may have a more drastic effect for gestational age and birth weight than ECP. There was no significant difference in these variables of controls born to mothers with or without ECP.

The estimation regarding the possible association of ECP with the risk of different CAs including at least 3 cases is shown in **Table 4**. The total rate of CAs showed a higher risk explained by the higher risk of hypospadias in 9 cases and cardiovascular CAs in 10 cases. The minor anomaly manifestation of hypospadias, *i.e.* coronal type was excluded in the HCAR. The distribution of cardiovascular CAs was the following: transposition of great vessels 1, tetralogy of Fallot 3, ventricular septal defect 3, congenital stenosis of aortic valve 1, persistent ductus arteriosus 1, unspecified 1.

4. DISCUSSION

Our population-based case-control study showed a higher risk of hypospadias, and cardiovascular CAs in the children of women with ECP. Transposition of great vessels, tetralogy of Fallot, and certain part of ventricle septal defects can be combined in the group of conotruncal defects [10], and of 10 cases with cardiovascular CAs, 7 belonged to this group.

A higher risk of threatened preterm delivery was recorded in women with ECP but it did not associate with a higher risk of preterm births on the contrary of the somewhat shorter gestational age. Thus there was an overdiagnosis of threatened preterm delivery or its treatment was very effective. The higher rate of anaemia can be explained partly by the higher rate of haemorrhoids.

The crucial point of the study is the diagnostic validity of ECP. Our study design excluded pregnant women with secondary erosion due to the inflammatory diseases of genital organs. However, about half of case and control mothers with ECP were treated by antimicrobial drugs, thus the infectious origin of ECP cannot be excluded in some pregnant women.

Table 2. Frequently used drugs in pregnant women with ECP.

Drugs	Case mothers without ECP (N = 22,803)		Case mothers with ECP (N = 40)		Control mothers without ECP (N = 38,126)		Control mothers with ECP (N = 25)		Comparison of case and control mothers with ECP
	No.	%	No.	%	No.	%	No.	%	OR 95% CI
Allylestrenol	3,472	15.2	9	22.5	5,346	14.0	11	44.0	0.5 0.3 – 0.9
Clotrimazole	1,627	7.1	14	35.0	3,070	8.1	7	28.0	1.3 0.7 – 1.7
Diazepam	2,737	12.0	9	22.5	4,126	10.8	4	16.0	1.4 0.8 – 2.9
Econazole, fluconazole, natamycin, nystatin	248	1.1	6	15.0	408	1.1	4	16.0	0.9 0.3 – 3.4
Metronidazole	383	1.7	5	12.5	565	1.5	5	20.0	0.7 0.2 – 2.9
Metronidazole + miconazole*	572	2.5	4	10.0	843	2.2	3	12.0	0.8 0.1 – 3.3
Promethazine	3,638	16.0	10	25.0	6,019	15.8	6	24.0	1.0 0.7 – 1.4
Terbutaline	2,340	10.3	10	25.0	3,988	10.5	6	24.0	1.0 0.7 – 1.5

Table 3. Birth outcomes of newborn infants without defects born to women with and without ECP (the latter group as reference).

Variables	Pregnant womenwithout ECP (N = 38,126)		with ECP (N = 25)		Comparison (adjusted)
Quantitative	Mean	S.D.	Mean	S.D.	p =
Gestation age at delivery (wk)	39.4	2.1	39.1	2.1	0.12*
Birth weight (g)	3,276	511	3,237	586	0.49**
Categorical	No.	%	No.	%	OR (95% CI)
Preterm births (less than 37 completed gestational week)	3,494	9.2	2	8.0	0.9 (0.6-1.8)*
Low birthweight newborns (less than 2500 g)	2,165	5.7	2	8.0	1.2 (0.7-2.9)**

*adjusted for maternal age, birth order and maternal socio-economic status; **adjusted for maternal age, birth order, maternal socio-economic status and gestation age

Copyright © 2010 SciRes.

Table 4. Estimation of possible association of maternal ECP with different CAs in their offspring compared to the occurrence of ECP during the study pregnancy in case and control mothers.

Study groups	Grand total N	Pregnancy No.	%	OR	95% CI**
Controls	38,151	25	0.07	Reference	
Cases with					
Cardiovascular CAs*	4,480	10	0.22	**3.4**	**1.6 – 7.1**
Undescended testis*	2,052	3	0.15	2.2	0.7 – 7.4
Hypospadias*	3,038	9	0.30	**4.5**	**2.1 – 9.7**
Clubfoot*	2,424	3	0.12	1.9	0.6 – 6.3
Poly/syndactyly*	1,744	3	0.17	2.6	0.8 – 8.7
Other CAs	9,105	12*	0.13	1.7	0.8 – 3.9
Total	22,843	40	0.18	**2.7**	**1.6 – 4.4**

*isolated CAs; **spina bifida with hydrocephalus, atresia of external auditory canal with absence of auricle, anotia, tracheal stenosis, cleft lip, cleft lip + cleft palate, oesophageal atresia, anal atresia, cystic kidney, torticollis, multiple CA: ventricular septal defect + cleft palate + undescended testis, multiple CA: branchial cyst + rectal atresia + clubfoot; *** adjusted OR for maternal age (< 20 yr vs. 20-29 yr vs. 30 yr or more), and employment status (professional-managerial-skilled worker vs. semiskilled worker-unskilled worker-housewife vs. others), birth order (first delivery vs. one or more previous deliveries), and ECP drug treatments(as a dichotomous variable); Bold numbers show significant associations.

Theoretically 3 causes are worth differentiating in the origin of ECP: 1) Trauma, however, it is not likely during early pregnancy. 2) Topical chemicals (e.g. spermaticidal contraceptive creams) were not used by these pregnant women. 3) The high level of estrogens in the body during pregnancy.

At the evaluation of the possible association between ECP and higher risk of hypospadias and conotruncal defects, the effect of ECP itself, the causes of ECP, related drug treatments, other confounders and chance effect should be considered.

The direct effect of ECP for the organogenesis of embryo/fetus does not seem to be plausible.

The causes of ECP may have some association with higher risk of CAs. Our previous study showed an association of acute pelvic inflammatory diseases with 4.2-folds higher risk of atrial septal defect, type II [11], however, this type of cardiovascular CA did not occur in the study. Estrogens may have some teratogenic effect in particular circumstances. A higher risk of hypospadias was found in pregnant women exposed to an elevated estrogen intake from drugs or such dietary sources as milk or soy [12]. This hypothesis was supported by an experimental study in mice, showing that supraphysiological doses of synthetic estrogen during pregnancy induce hypospadias in 50% of the male fetuses [13]. Some epidemiological studies indicated a causal association between sex hormones, particularly oral contraceptives and cardiovascular CAs [14] but other studies did not confirm this association [15]. Obviously this possible association may occur only in women and/or fetuses with special genetic predisposition both for ECP and CAs triggered by these hormonal factors.

The teratogenic potential of clotrimazole, metronidazole, metronidazole+miconazole, econazole, nystatin, natamycin, fluconazole was checked in the previous studies based on HCCSCA and these drugs did not show an association with higher risk of hypospadias and cardiovascular CAs [16]. The drugs used for the treatment of threatened preterm delivery such as diazepam [17] and promethazine [18] did also not show any association with a higher risk of hypospadias and cardiovascular CAs in the data set of the HCCSCA, in addition in 112 and 32 pregnant women who attempted suicide with large doses of diazepam [19] and promethazine [20], respectively. However, allylestrenol had some association with a higher risk of hypospadias [21], but this hormone was used more frequently by control mothers than by case mothers with ECP and at the calculation of adjusted OR was considered.

The effect of other and unknown confounders may also be important, finally the chance effect cannot be excluded in multiple testing. The association of ECP with cardiovascular CAs and hypospadias is significant, but the small numbers of cases and controls greatly reduced the robustness of these associations.

The strengths of the study are 1) population-based large data set of the HCCSCA including 65 pregnant women with prospectively and medically recorded ECP based on colposcopic examination in ethnically homogenous European (Caucasian) people. 2) The matching of cases and controls, 3) in addition most confounders such as other maternal diseases and related treatments are known. 4) The good validity of CA diagnoses due to the medically reported cases to the HCAR which were checked by a paediatrician and medical geneticist [5], in addition new information from recent medical examinations and the questionnaire was helpful to ex-

Copyright © 2010 SciRes.

clude cases with misdiagnosed CA or to correct the CA diagnosis in the HCCSCA [4].

However, our data set also has serious weaknesses. 1) ECP is a symptom and not a clinical entity. The study design excluded secondary ECP due to microbial origin, however, the use of antimicrobial drugs questioned the diagnostic criteria of ECP in the study. 2) In general data were not available regarding the possible electro- or cryocautery and diathermy in pregnant women with ECP.

The unexpected findings of our study would need a biologically plausible explanation. Our hypothesis is based on a special genetic predisposition in pregnant women with a much higher sensitivity for the high level of estrogens during pregnancy. This higher level of estrogens explains the common occurrence of cervical erosion in pregnant women and may associate with a higher risk of hypospadias and conotruncal cardiovascular CA in their offspring.

In conclusion, our population-based case-control study showed an association of ECP in early pregnancy with a higher risk for hypospadias and conotruncal cardiovascular CAs. These findings are considered only as a signal and further studies are needed to confirm or reject these associations.

5. ACKNOWLEDGEMENTS

This study was partly sponsored by a generous grant from Richter Gedeon Pharmaceuticals Ltd., Budapest, Hungary.

REFERENCES

[1] Czeizel, A.E., Ács, N., Bánhidy, F. and Vogt, G. (2006) Possible association between maternal diseases during pregnancy and congenital abnormalities. In: Engels, J.V., Ed. *Birth defects*: *New research*. NOVA Science Publisher, New York, 55-70.

[2] Gabbe, S.G., Niebyl, J.R. and Simpson, J.L. (2001) Obstetrics: Normal and problem pregnancies. 4th Edition, Churchill Livingstone, New York.

[3] Shepard, T.H. and Lemire, R.J. (2004) Catalog of Teratogenic Agents, 11th Edition. Johns Hopkins University Press, Baltimore.

[4] Czeizel, A.E., Rockenbauer, M., Siffel, C. and Varga, E. (2001) Description and mission evaluation of the hungarian case-control surveillance of congenital abnormalities, 1980-1996. *Teratology*, **63(5)**, 176-185.

[5] Czeizel, A.E. (1997) First 25 years of the hungarian congenital abnormality registry. *Teratology*, **55(5),** 299-305.

[6] Czeizel, A.E., Petik, D. and Vargha, P. (2003) Validation studies of drug exposures in pregnant women. *Pharmacoepid Drug Safety*, **12(5),** 409-416.

[7] Czeizel, A.E. and Vargha, P. (2004) Periconceptional folic acid/multivitamin supplementation and twin pregnancy. *American Journal of Obstetrics and Gynecology*, **191(3),** 790-794.

[8] WHO. (2007) International classification of disease. 10th revision, Wold Health Organization, Geneva

[9] Puho, E., Métneki, J. and Czeizel, A.E. (2005) Maternal employment status and isolated orofacial clefts in Hungary. *Central European Journal of Public Health*, **13(3)**, 144-148.

[10] Adams, F.H., Emmanouilideas, G.C. and Riemenschneider, T.A. (1989) Heart disease in infants, children and adolescents. Williams and Wilkins, Baltimore.

[11] Ács, F., Bánhidy, F., Puho, H.E. and Czeizel, A.E. (2008) Possible association between acute pelvic inflammatory disease in pregnant women and congenital abnormalities in their offspring? A population-based case-control study. *Birth Defects Research* (*Part A*), **82(8),** 563-570.

[12] Sharpe, R.M. and Skakkeback, N.E. (1993) Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? *Lancet*, **341(8857),** 1392-1395.

[13] Kim, K.S., Torres, C.R. Jr, Yucel, S., *et al*. (2004) Induction of hypospadis in a murine model by maternal exposure to synthetic estrogens. *Environmental Research*, **94,** 267-275.

[14] Janerich, D.T., Dugan, J.M., Standfast, S.J. and Strite, L. (1977) Congenital heart disease and prenatal exposure to exogenous sex hormeones. *British Medical Journal*, **1(6068),** 1058-1060.

[15] Bracken, M.B. (1990) Oral contraception and congenital malformations in offspring: A review and meta-analysis of the prospective studies. *Obstetrics & Gynecology*, **76(3),** 552-557.

[16] Czeizel, A.E. (2009) The estimation of human teratogenic/fetotoxic risk of exposures to drugs on the basis of Hungarian experience: a critical evaluation of clinical and epidemiological models of human teratology. *Expert Opinion on Drug Safety*, **8(3)**, 283-303.

[17] Czeizel, A.E., Erős, E., Rockenbauer, M., Sørensen, H.T. and Olsen, J. (2003) Shortterm oral diazepam treatment during pregnancy—A population-based teratological case-control study. *Clinical Drug Investigation*, **23,** 451-462.

[18] Bártfai, Z., Kocsis, J., Puhó, H.E. and Czeizel, A.E. (2008) A population-based case-control study of promethazine use during pregnancy. *Reproductive Toxicology*, **25(2)**, 276-285.

[19] Gidai, J., Ács, N., Bánhidy, F. and Czeizel, A.E. (2008) No association found between use of very large doses of diazepam by 112 pregnant women for a suicide attempt and congenital abnormalities in their offspring. *Toxic Indust Health*, **24**, 29-39.

[20] Petik, D., Ács, N., Bánhidy, F. and Czeizel, A.E. (2008) A study of the potential teratogenic effects of large doses of promethazine in 32 self-poisoned pregnant women. *Toxic Indust Health*, **24(1-2)**, 87-96.

[21] Czeizel, A.E. and Huiskes, N. (1988) A case-control study to evaluate the risk of congenital anomalies as a result of allylestrenol therapy during pregnancy. *Clinical Therapeutics*, **10**, 725-739.

Copyright © 2010 SciRes.