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Monitoring of risk factor/outcome combinations: a valuable supplement to birth defect monitoring

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Since the thalidomide disaster in the early sixties many birth defect monitoring systems and registries have been set up to detect changes in the frequencies of specific birth defects. The primary methods of monitoring have been the statistical analysis of data on birth prevalences and teratologic analysis. The yield of this monitoring effect has nevertheless been low when one considers the lack of etiologic factors detected in this way. We therefore propose an additional strategy involving (periodic) classification of all cases in a birth defect registry according to possible risk factors and notified anomalies coupled with a search for specific associations between risk factors and (patterns of) anomalies. We here present data showing the sensitivity of the method. Sensitivity was studied by looking at some already well known associations between risk factors and congenital anomalies in our registry involving 1850 cases. The associations studied were neural tube defects and maternal use of valproic acid, numerical chromosomal anomalies and advanced maternal age, gastroschisis and low maternal age, and autosomal recessive disorders and parental consanguinity. Each of these associations was apparent in the registry, suggesting that risk factor/outcome monitoring as described here is a potentially strong method for finding new etiologic factors in birth defects.

Introduction

Since the thalidomide disaster in the early sixties many birth defect monitoring systems and registries have been set up to detect changes in the occurrence of birth defects and their link to external factors [1]. Two methods of monitoring have prevailed, the statistical and the teratological approach [2]. The statistical approach involves periodic analysis of data on birth prevalences with different statistical techniques, such as observed/expected comparisons, CUSUM tech-

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nique, sets technique, moving window method, etcetera [3,4]. The teratologic approach involves the continuous scrutiny by experienced dysmorphologists of the population of newborns with congenital anomalies for unusual combinations of defects. An example of this approach is the monitoring of multimalformed infants [5]. Both methods have their pro's and con's, and they are most profitably combined [2]. The yield of this monitoring effort has nevertheless been low if one considers the lack of etiologic factors detected in this way [6]. As several teratogens have been detected in the meantime by clinical observation [7], one is tempted to conclude that the monitoring methods employed lack sufficient sensitivity. This is especially true when a birth defect caused by a relatively rare teratogen cannot be distinguished clinically from a much more common 'naturally occurring' defect. Under these circumstances the few additional cases remain hidden in the majority of 'normally' occurring cases. There is thus a need for additional methods of monitoring.

The approaches described above are examples of 'outcome monitoring'. Generally, an alternative procedure is monitoring of exposure. Examples of 'exposure monitoring' are measurements of air pollution or of received radiation dose. Exposure monitoring can only be applied to well known risk factors and for this very reason it is not suitable as a method for discovering new teratogens. Another possibility, however, is to search for the association of possible external factors and birth defects. This type of approach, which we call 'monitoring for risk factor/outcome combinations' or 'risk factor/outcome monitoring' for short, is usually adopted, for instance, in the screening of occupation data from cancer registries, but has not to the best of our knowledge been described in birth defect monitoring. The question arises whether it would not be beneficial to add this type of monitoring to the arsenal of birth defect monitoring techniques.

We came across risk factor/outcome monitoring when searching for possibly defect-related maternal medications in our local birth defects registry, which is part of the European Community's concerted action for the epidemiology of birth defects, EUROCAT [8]. Apart from the description of the anomaly/anomalies, the variables registered include the age of the parents, reproductive history, family history, consanguinity, occupation, illness during pregnancy, habitual exposure and drugs taken during pregnancy. To identify maternal medications which might be involved we produced lists in which all cases were first sorted according to the type of drug(s) used, and subsequently, within the subset of cases with the same maternal medication, according to the type of birth defect. In this way we noticed two cases of anencephaly after clomifene use, and subsequently another case of anencephaly after bromocriptin medication. These cases prompted us to report on the possible association of subfertility, ovulation induction and neural tube defects [9]. Since our report this association has been confirmed by several authors [10–14], although two other authors did not find the association [15,16].

Ovulation induction was reported in only 9 out of 1850 cases in the registry (at August 1, 1990). Apart from the 3 cases of neural tube defects there were 6 other congenital anomalies reported: microphthalmia, ventricular septal defect, cleft lip and palate, fibular aplasia, translocation Down syndrome and DiGeorge sequence.

The 3 cases in which neural tube defects and ovulation induction were association represented only a very small proportion of the total number of 112 cases of neural tube defects in the registry. Such a small contribution from a new possible risk factor to the large sample of 'naturally occurring' neural tube defects could hardly ever have been discovered by monitoring birth prevalences of neural tube defects. It is also noteworthy that we were able to discover this possible associated between ovulation induction and neural tube defects in spite of the fact that the registry asked only for information on maternal drug use during pregnancy and not before pregnancy. The information on ovulation induction was provided spontaneously by physicians supplying the information on the cases. Even under these circumstances we were able to register the signal.

The experience described above made us wonder whether our method of arrangement might have a more general application to the monitoring of birth defects. In this paper we report on a study on the sensitivity of risk factor/outcome monitoring in our own registry.

Materials and Methods

We studied sensitivity of monitoring of risk factors/outcome combinations by looking at some already well known associations between risk factors and congenital anomalies in the data of our registry (1850 cases at August 1, 1990). The associations studied were neural tube defects and maternal use of valproic acid [17], (numeric) chromosomal anomalies and advanced maternal age [18], gastroschisis and low maternal age [19], and autosomal recessive disorders and consanguinity [18]. All cases were arranged according to reported presence of the particular risk factor and according to the types of anomalies notified. Ordering of anomalies is based on their codes. Coding is according to the British Paediatric Association amendment of the International Classification of Diseases [20].

The aim of risk factor/outcome monitoring is the same as for other types of birth defect monitoring: finding suggestions of possibly relevant events that might lead to hypotheses concerning risk factors for congenital anomalies and that should be followed up in further studies. Such possibly relevant events may be termed alarms, as in other types of birth defect monitoring. Alarms should not be given unless the number of cases with the same anomaly and risk factor exceeds an integer N ($N \neq 0$), which depends among other things on a preset significance level α and has to be calculated for each situation. N represents the lowest non-zero integer for which

$$\sum_{n=0}^{N} P(n \text{ in } M) > (1-\alpha),$$

$P(n \text{ in } M)$ being the probability of n cases with the same particular anomaly in a list of M cases with a particular risk factor under the null-hypothesis of no

association. This probability depends on the prevalences of the particular anomaly and risk factor in the data set. In this study α was set at 0.05.

Results

The results are shown in Tables 1 and 2. There are 3 cases of neural tube defects among 7 with maternal valproate use (expected number 0.42), 2 cases of gastroschisis among 13 with low maternal age (expected number 0.07), 8 cases with chromosomal anomalies among 14 with advanced maternal age (expected number 1.48), and 4 cases with disorders classified as autosomal recessive disorders in McKusick's catalog of Mendelian phenotypes [21] among 12 with parental consan-

TABLE 1

Types of congenital anomalies in cases in which maternal use of valproate, extreme maternal age, or presence of parental consanguinity was reported [1]

Maternal valproate use		Maternal age below 19 years	
228.00	hemangioma's	270.82	hyperprolinemia I
741.05	spina bifida	741.05	spina bifida
741.90	spina bifida	742.08	encephalocele
741.93	meningomyelocele	745.20	tetralogy of Fallot
752.60	hypospadia	745.49	small VSD
752.60	hypospadia	750.51	pyloric stenosis
758.53	unbal. translocation	754.41	bowing long bones legs
		755.00	polydactyly
		755.24	rudimentary dig V
		756.71	gastroschisis
		756.71	gastroschisis [2]
		758.54	46,XX,8p+
Maternal age above 40 years		Parental consanguinity (3rd–5th degree)	
***.**	complex heart defect	279.21	Nezelof syndrome
***.**	complex heart defect	284.00	Fanconi anemia
745.20	tetralogy of Fallot	335.00	Werdnig-Hoffmann disease
749.29	cleft lip & palate	***.**	MR/MCA NOS, as in a previous sister
758.00	trisomy 21	***.**	MCA (a.o. hypopl. kidneys)
758.00	trisomy 21	753.11	infantile polycystic kidneys
758.00	trisomy 21	***.**	ASD, fibrosis of lung, growth retard.
758.00	trisomy 21	754.30	dysplasia of hip
758.00	trisomy 21	755.12	syndactyly 2nd–3rd toe
758.20	trisomy 18	755.12	same anomaly (twins)
758.20	trisomy 18	757.40	congenital alopecia + MCA
758.70	Klinefelter syndrome	757.40	congenital alopecia + MCA
754.50	pes equinovarus		(sib of previous case)
759.87	lysosomal anom. NOS		

[1] Cases are listed with the following information: ICD/BPA code, unless complex anomalies (***.**) and type of anomaly.
MCA = multiple congenital anomalies; MR = mental retardation; NOS = not otherwise specified.
[2] With micrognathia.

TABLE 2

Cross tabulations of investigated risk factors and pregnancy outcomes

Neural tube defects and maternal valproate use

Type of defect	Maternal valproate use			
	Reported		Not reported	
	n	%	*n*	%
Neural tube defects	3	42.9	109	5.9
Other	4	57.1	1734	94.1
Total	7	100.0	1843	100.0

Hypospadias and maternal valproate use

Type of defect	Maternal valproate use			
	Reported		Not reported	
	n	%	*n*	%
Hypospadias	2	28.6	86	4.7
Other	5	71.4	1757	95.3
Total	7	100.0	1483	100.0

Gastroschisis and low maternal age

Type of defect	Maternal age below 19			
	Reported		Not Reported	
	n	%	*n*	%
Gastroschisis *	2	15.4	8	0.4
Other	11	84.6	1839	99.6
Total	13	100.0	1.847	100.0

Chromosomal anomalies and advanced maternal age

Type of defect	Maternal age above 40			
	Reported		Not reported	
	n	%	*n*	%
Chromosomal anomalies	8	57.1	188	10.2
Other	6	42.9	1648	89.8
Total	14	100.0	1836	100.0

Classified autosomal recessive (AR) disorders and parental consanguinity

Type of defect	Consanguinity			
	Reported		Not reported	
	n	%	*n*	%
Classified AR disorders	4	33.3	67	3.6
Other	8	66.7	1771	96.4
Total	12	100.0	1838	100.0

* Excludes omphalocele.

guinity (expected number 0.46). (Expected numbers were calculated using the assumption of no association). In addition 2 cases of hypospadias were observed among the 7 with maternal valproate use (expected number 0.33). This association has been noticed before [22]. The 3 cases of congenital heart disease among 14 mothers over 40 are not remarkable as a comparable proportion (20%) of the registered children of mothers under 41 also have congenital heart defects. Apart from the 4 cases with a classified AR disorder [21] among the registered children from consanguineous parents (Nezelof syndrome, Fanconi anemia, Werdnig Hoffmann disease and infantile polycystic kidneys) there were 3 more cases with a probably autosomal recessive disorder among the remaining 8.

Table 3 shows N for the associations studied. The actual number of cases in this study exceeded the calculated N value in all cases.

TABLE 3

Number of cases to be exceeded (N) before an alarm should be given (see text for explanation)

Congenital Anomaly [1]		Risk factor		Number of cases to be exceeded (N) [2]
Type	Prevalence *	Type	Prevalence *	
NTD	112/1850	ovulation induction	9/1850	2
NTD	112/1850	valproate	7/1850	2
Hypospadias	88/1850	valproate	7/1850	1
Chromosomal abnormalities	196/1850	maternal age above 40	14/1850	4
Gastroschisis	10/1850	maternal age below 19	13/1850	1
Classified AR disorders	71/1850	parental consanguinity	12/1850	2

* Prevalence in dataset.

[1] AR = autosomal recessive; NTD = neural tube defect.

[2] With $\alpha = 0.05$.

Discussion

We considered the sensitivity of monitoring of risk factor/outcome combinations by examining some already well known associations in our registry of 1850 cases. All risk factors studied showed a significant association with a particular birth defect. This result might be based on a true risk factor/outcome relation or be due to preferential reporting of cases of interest to our registry. It is hard to see why advanced maternal age should lead to preferential reporting of chromosomal anomalies. Two of the 3 cases in which a neural tube defect was associated with maternal valproate use were notified before the appearance of the 1982 paper of Robert and Guibaud [23] who reported on the first series of cases. The association of gastroschisis and low maternal age is hardly known outside the group of teratologists. Most of the observed associations therefore cannot be explained by preferential reporting. On the contrary, our results strongly suggest that risk factor/outcome monitoring as described here is a potentially strong method for finding new etiologic factors in birth defects. It has been said that birth defects registries cannot compete with clinicians in finding new associations between risk factors and specific congenital anomalies. This may be true, as long as registers are only interested in the periodic analysis of birth prevalences. We feel that risk factor/outcome monitoring, just as the teratologic method, comes closer to the clinical approach, still having the advantage of a large data set, much larger than most clinicians can afford. A computer software system could produce most of these analyses relatively easily on a periodic basis for monitoring purposes. It is astounding that this simple, common sense procedure has not attracted more attention in birth defect monitoring.

A plea for risk factor/outcome monitoring implies that registries should record not only birth defects but also possible risk factors, as completely and as correctly as possible. The fact that the method may work even when data are incomplete – as shown in the case of ovulation induction – is comforting, but should not divert attention from the fact that incompleteness of data leads to postponement of warnings. The recording of risk factors should allow for the inclusion of potentially, but not already established, risk factors as well as for the inclusion of established risk factors. Use of drugs, occupation, habitual exposures and illnesses before or during pregnancy should be considered as potential risk factors/unless proven otherwise. The registration of already known risk factors is needed in order to be able to restrict further analysis to cases of unknown etiology.

Notwithstanding the increased sophistication and sensitivity of risk factor/outcome monitoring there are some drawbacks. First, unknown types of risk factors cannot be monitored. Risk factor/outcome monitoring therefore cannot replace birth prevalence or teratologic monitoring, and all 3 methods should be applied in parallel. Secondly, as with other types of monitoring, and even more so, false alarms are to be expected (their number depending on α and the number of possible associations monitored). Notification of the scientific community, the authorities or general public of the existence of an association between a possible risk factor and a birth defect should therefore be postponed until (a) supporting evidence has been obtained from other sources, including case-control studies or other analytical methods and (b) other explanations, such as preferential reporting, have been excluded.

Conclusion

Monitoring of risk factor/outcome combinations is a sensitive method for birth defect monitoring and should be added to the arsenal of already existing methods.

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References

1 Dukes MNG. Monitoring birth defects. Int J Risk Safety Med 1991;2:237–238.
2 Congenital malformations worldwide. A report from the International Clearinghouse for Birth Defects Monitoring Systems. Amsterdam, New York, Oxford: Elsevier, 1991.
3 Barbujani G. A review of statistical methods for continuous monitoring of malformation frequencies. Eur J Epidemiol 1987;3:67–77.

4 Lie RT, Vollset SE, Botting B, Shoerven R. Statistical methods for surveillance of congenital malformations: when do the data indicate a true shift in the risk that an infant is affected by some type of malformation. Int J Risk Safety Med 1991;2:289–300.
5 Mastroiacovo, P. An ICBDMS collaborative study: monitoring multimalformed infants. Int J Risk Safety Med 1991;2:255–270.
6 Erickson JD. The International Clearinghouse for Birth Defects Monitoring Systems: Past, present and future. Int J Risk Safety Med 1991;2:239–248.
7 Sever JL, Brent RL, eds. Teratogen Update. Environmentally induced birth defects risks. New York: Alan R. Liss Inc, 1986.
8 Eurocat Working Group. Surveillance of congenital anomalies. Years 1980–1986. Department of Epidemiology. Brussels: Catholic University of Louvain, 1989.
9 Cornel MC, Ten Kate LP, Dukes MNG et al. Ovulation induction and neural tube defects. Lancet 1989;i:1386.
10 Cuckle H, Wald N. Ovulation induction and neural tube defects. Lancet 1989;ii:1281.
11 Czeizel A. Ovulation induction and neural tube defects. Lancet 1989;ii:167.
12 Karabacak OR, Kuror C, Celiloglu M. Ovulation induction and neural tube defects. Lancet 1989;ii:1391–1392.
13 Milunsky A, Derby LE, Jick H. Ovulation induction and neural tube defects. Teratology 1990;42:593.
14 Robert E, Pradat E, Laumon B. Ovulation induction and neural tube defects: a registry study. Reprod Toxicol 1991;5:83–84.
15 Mills JL, Simpson JL, Rhoads GG et al. Risk of neural tube defects in relation to maternal fertility and fertility drug use. Lancet 1990;336:103–104.
16 Rosa F. Ovulation induction and neural tube defects. Lancet 1990;336:1327.
17 Lammer EJ, Sever, LE and Oakley GP. Teratogen update: valproic acid. Teratology 1987;35:465–473.
18 Vogel F, Motulsky AG. Human Genetics. Problems and approaches. 2nd ed. Berlin, Heidelberg, New York: Springer-Verlag, 1986.
19 Torfs C, Curry C, Roeper P. Gastroschisis. J Pediatr 1990;116:1–6.
20 British Pediatric Association. Classification of diseases (A paediatric supplement compatible with the ninth revision of the WHO International Classification of Diseases, 1977), 1979.
21 McKusick VA. Mendelian inheritance in man. Catalogs of autosomal dominant, autosomal recessive and X-linked phenotypes. 8th ed. Baltimore and London: The Johns Hopkins University Press, 1988.
22 Lindhout D. Teratogenesis in maternal epilepsy. New aspects of prevention. Thesis, Amsterdam, 1985.
23 Robert E, Guibaud P. Maternal valproic acid and congenital neural tube defects. Lancet 1982;ii:937.