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# THE HAZARDS OF FETAL EXPOSURE TO DRUG COMBINATIONS

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## Introduction

It is generally accepted that the offspring of epileptic mothers has a higher risk of congenital anomalies. ( 1 ). Amongst others, teratogenic activity of anti-epileptic drugs has been suggested as a causative mechanism, since more congenital anomalies have been found among infants of treated epileptic mothers, than in the offspring of untreated epileptic mothers. ( 2 ). When the number of congenital anomalies was established according to the individual anti-epileptic drugs, conflicting results were obtained. ( 3, 5).

Recently, we investigated combinations of anti-epileptic drugs with respect to the occurrence of congenital anomalies.

Firstly, we were wondering whether combinations of PHB with other drugs cause more congenital anomalies than expected from the individual drugs.

Secondly, we were interested in DPA and CBZ, of wich drugs relatively few data are available because of their recent introduction.

## Abbreviations

PHB = phenobarbitone
DPH = phenytoin
PMD = primidone
DPA = dipropylacetate
CBZ = caramazepine
SUL = sulthiame
ESX = ethosuximide
BDZ = benzodiazepines
ACA = acetazolamide

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Materials and methods

The population studied consists of women visiting the outpatients' clinics of the "Instituut voor Epilepsiebestrijding" in the Netherlands.

In all women the onset of epilepsy was before pregnancy. All deliveries have been taken place in hospitals, and the neonates have been routinely examined by local pediatricians. From 1972 onwards data concerning congenital anomalies have been registrated shortly after birth. Later detected anomalies of congenital origin are not included in the results.

Results

The outcome of 184 pregnancies in 120 women is given in Table I. All 14 pregnancies without drug treatment resulted in the delivery of live-born infants, one of them with congenital anomalies. (Table II)

Out of 151 live-born exposed infants, 15 cases of congenital anomalies (9,9 %) have been found. Included are three infants with severe dysmorphic features at birth and later obvious mental retardation. (Table III).

Table IV shows the number and relative risk of congenital anomalies according to the individual anti-epileptic drugs. Only after exposure to PHB or DPH significantly more congenital anomalies have been found.

From the 7 possible combinations of PHB with one of the other anti-epileptic drugs, only the numbers of PHB + DPH, PHB + DPA, and PHB + CBZ were adequate to analyse.

Combined exposure to PHB + DPH is not accompanied with significantly more congenital anomalies (observed 7; expected 4.4). (Table V).
Considerably more congenital anomalies have been found when PHB + DPA had been given, than when given separately (observed 8; expected 2.2). (Table VI).
Also more congenital anomalies have been observed when PHB and CBZ had been given combined (observed 7; expected 3.3). (Table VII).

Table I: Outcome of 184 pregnancies in 120 women after the onset of epilepsy.

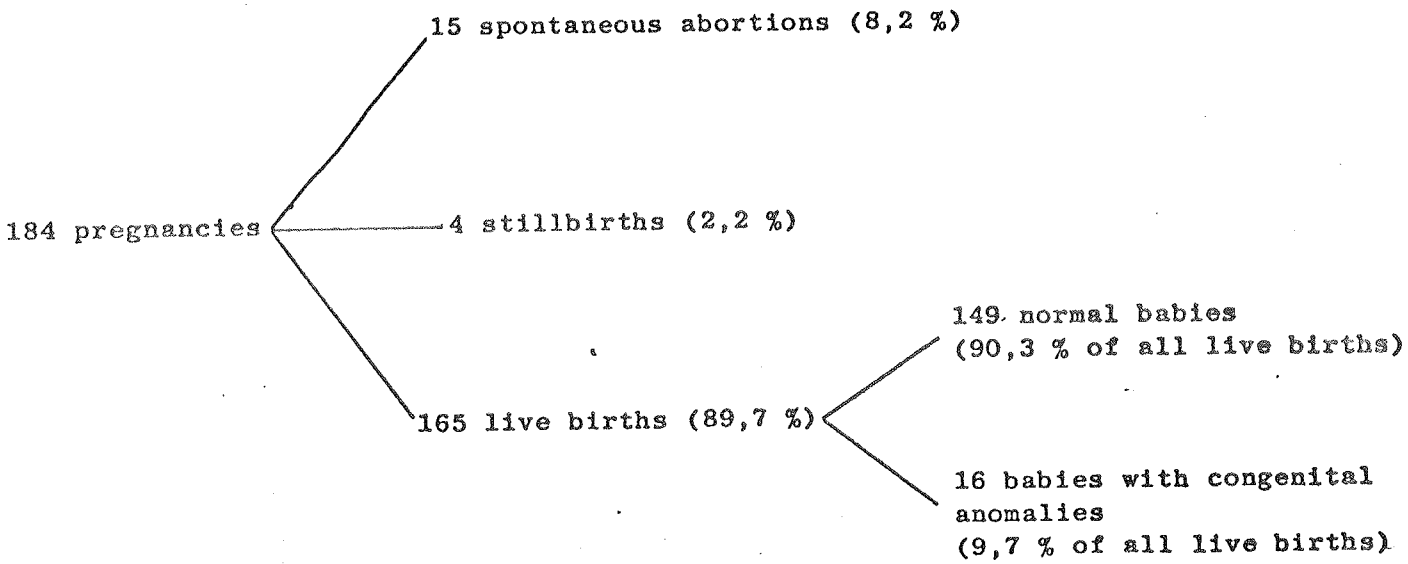


Table II. Outcome of 184 pregnancies and prenatal exposure to anti-epileptic drugs.

| exposure to anti-epileptic drugs | number | spontaneous abortions | stillbirths | live births | |
|---|---|---|---|---|---|
| | | | | congenital anomalies | normal |
| yes | 170 | 15 | 4 | 15 | 136 |
| no | 14 | -- | -- | 1 | 13 |

Table III. Congenital anomalies and anti-epileptic drugs.

(the numbers refer to the daily dose during the first trimenon of pregnancy)

| | PHB | DPH | PMD | DPA | CBZ | ESX | BDZ | M/F** |
|---|---|---|---|---|---|---|---|---|
| 1. CHD * | 250 | 100 | 750 | | | | | F |
| 2. CHD anomalies of the great vessels | 150 | 200 | | 1200 | 800 | | | F |
| 3. CHD (septum defect) | 75 | 75 | 375 | | | | | F |
| 4. CHD (tetralogy of Fallot) | | | | 1800 | | | | F |
| 5. CHD Mesenterium commune Intracranial hemorrhage | 50 | 200 | | 900 | 1800 | | | M |
| 6. Dysmorphy Mental retardation | 75 | 150 | | | | | | M |
| 7. Dysmorphy Mental retardation | 150 | | | 1500 | 600 | | | M |
| 8. Dysmorphy Mental retardation | 150 | | | 1500 | 600 | | | M |
| 9. Cleft lip | 150 | 300 | | 600 | 800 | | | F |
| 10. Cleft lip Cleft palate | 150 | 300 | | 900 | 600 | | | M |
| 11. Duplication of the right ureter | | 300 | | 900*** | 900 | | 75 | M |
| 12. Club feet | 100 | | | | | 1000 | | F |
| 13. Ptosis | | 270 | 90 | | | | | M |
| 14. Agenesis of the lacrimal ducts **** | 60 | | | 900 | 1000 | | | M |
| 15. Downs'syndrome | 150 | | | 2400 | | | | F |

*) CHD = congenital heart disease
**) M/F = male/female
***) dipropylacetamide, not included in statistical analysis
****) imipramine also prescribed during the first trimenon of pregnancy

Table IV: Incidence and relative risk of congenital anomalies (C.A.) in live-born infants according to maternal anti-epileptic drug use.

| Exposure to (alone or with other drugs ! ) | N exposed | N C.A. | % C.A. | relative risk of C.A. |
|---|---|---|---|---|
| any anti-epileptic drug | 151 | 15 | 9,9 | (1.00) |
| PHB | 65 | 12 ($p<0.01$)* | 18,5 | 1.9 |
| DPH | 51 | 9 ($p<0.05$)** | 17,7 | 1.8 |
| PMD | 23 | 3 | 13,0 | 1.3 |
| DPA | 65 | 9 | 13,9 | 1.4 |
| CBZ | 74 | 8 | 10,8 | 1.1 |
| SUL | 2 | - | - | - |
| ESX | 39 | 1 | 2,6 | 0.3 |
| BDZ | 10 | 1 | 10,0 | 1,0 |
| ACA | 3 | - | - | - |

*) compared with the total exposed group excluding all PHB-exposed infants

**) compared with the total exposed group excluding all DPH-exposed infants

Table V. Incidence of congenital anomalies (C.A.) in live-born infants according to combined or separate exposure to PHB and DPH.

| Exposure to (alone or with other drugs ! ) | N exposed | N C.A. | % C.A. | |
|---|---|---|---|---|
| PHB + DPH | 28 | 7 | 25 | |
| PHB (without DPH) | 37 | 5 | 14 | N.S. |
| DPH (without PHB) | 23 | 2 | 9 | |

Table VI. Incidence of congenital anomalies (C.A.) in live-born infants according to combined or separate exposure to PHB and DPA.

| Exposure to (alone or with other drugs ! ) | N exposed | N C.A. | % C.A. | |
|---|---|---|---|---|
| PHB + DPA | 19 | 8 | 42 | |
| PHB (without DPA) | 46 | 4 | 9 | $X_2^2 = 21,71$ *) $p < 0.001$ |
| DPA (without PHB) | 46 | 1 | 2 | |

*) significantly different from expected, in favour of an association between exposure to PHB + DPA and congenital anomalies.

Table VII. Incidence of congenital anomalies (C.A.) in live-born infants according to combined or seprate exposure to PHB and CBZ.

| Exposure to (alone or with other drugs ! ) | N exposed | N C.A. | % C.A. | |
|---|---|---|---|---|
| PHB + CBZ | 28 | 7 | 25 | |
| PHB (without CBZ) | 37 | 5 | 14 | $X_2^2 = 9.50$ * $p < 0.01$ |
| CBZ (without PHB) | 46 | 1 | 2 | |

*) significantly different from expected, in favour of an association between exposure to PHB + CBZ and congenital anomalies.

Discussion

Infants prenatally exposed to PHB or DPH showed more congenital anomalies than infants exposed to other anti-epileptic drugs. These results seem to be in contrast with, for instance, those reported by Shapiro et. al. ( 3 ). In an even larger population of infants born to epileptic mothers, he did not find any association of PHB or DPH with congenital anomalies. However, as Visser et.al. already has pointed out, it is necessary to know the proportion of infants not exposed to any of these drugs, in particular when comparing drugs with possibly the same teratogenic mechanism. ( 5 ). Besides, in our study probably more infants have been exposed to PHB combined with other - recently introduced - drugs.

In infants exposed to CBZ or DPA we did not observe significantly more congenital anomalies, and therefore it would be tempting to suppose that these drugs - in particular CBZ - are relatively safe, corresponding with earlier reports. ( 4 ). However when DPA or CBZ were combined with PHB, much higher rates of congenital anomalies were found, than expected from the analysis of the individual drugs.

These issues raise the question whether not only the individual drugs, but also specific drug combinations can be responsible for the higher rate of congenital anomalies in the offspring of epileptic mothers. It has to be considered that seemingly safe drugs still can have teratogenic properties when given in specific combinations.

Because of a considerable overlap in exposure to the individual anti-epileptic drugs, it is impossible to determine from our findings which combination of drugs is primarily related to teratogenesis. For example, out of 8 infants with congenital anomalies after exposure to PHB + CBZ, 7 had also been exposed to DPA ! Moreover, prescribing specific combinations of drugs can be related to other teratogenic factors. Therefore, a multifactorial analysis of possible causes of congenital anomalies has to be done.

Anyhow, the issues obtained from this rather small population of exposed

infants, indicate the necessity to investigate the teratogenic activity not only of any anti-epileptic drug, but also of combinations of them, in experimental as well as in clinical studies.

Meanwhile, the association of prenatal exposure to anti-epileptic drugs with congenital anomalies remains just an association, and only has a signal-function.

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