

Evaluation of counselling for pregnant women exposed to potentially hazardous environmental factors

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Pregnancy outcomes of 546 women seeking advice for exposure to suspected dangerous environmental factors during pregnancy were analysed. Induced abortion was recommended to 58 women, and this advice was followed by 55 of them. An additional 24 pregnancies were interrupted. The rates of fetal death (spontaneous abortion, stillbirth and infant death) in the non-terminated pregnancies corresponded to national figures. The proportion of birth defects among the liveborn infants of women exposed to hazardous physical, chemical, microbial and maternal factors was 5/67 (7.5%), 11/120 (9.2%), 6/158 (3.8%) and 1/22 (4.5%), respectively. These figures did not differ significantly from the expected ones based on the Hungarian registered and estimated figures. Furthermore, a causal relation between the environmental factors and the defects could be excluded in all but one case in which there was exposure to a high dose of oestrogen.

Five thousand seven hundred and forty women, alone or accompanied by their male partner, came to our Genetic Counselling Clinic between 1973 and 1980. One thousand seven hundred and seventy-four of the women (30.9%) were already pregnant at consultation and 546 (9.5%) asked for advice owing to exposure, during a planned pregnancy, to environmental factors that were suspected to be teratogenic. The majority of these counsellees were referred to us by the medical staff providing them with prenatal care. This paper reports on follow-up of pregnancy outcomes in women seeking advice for exposure during pregnancy to environmental factors suspected of being dangerous.

MATERIAL AND METHOD

A questionnaire was sent to the 546 women who visited our Genetic Counselling Clinic in the period 1973–1980 because of exposure to potentially hazardous environmental factors during pregnancy. (The questionnaire was mailed about 9 months after the visit.) In 52 cases (9.5%) the address was wrong or had been changed. Counsellees who did not answer the first time, were asked again to fill out the questionnaire. Seventeen women did not respond, 3.4% of the counsellees with known address. Sixty-nine pregnant women who were lost had no newborns with registered congenital anomalies in the Hungarian Congenital Malformation Register (1) in the year following the visit. (This Registry has the personal data of index children and their parents.) Eventually 477 women returned completed questionnaires (Table I). Occasionally some

TABLE I
Material and distribution of pregnancy outcomes

Material	No	Per cent
Total sample	546	
Could not contact	52	69
No response	17	
Study sample		
Pregnancy outcome known	477	
Aborted (on advice)	55	79
Aborted (own decision)	24	
Fetal death	31	6.5
Livebirth	367	76.9
Infant death	5	1.4
Birth defect	23	6.3
Congenital anomaly	20	5.4
Severe congenital abnormality	10	2.7

pregnant women were exposed to more than one potential teratogen (e.g. an infection and a drug); in these cases only the seemingly more important factor was taken into consideration. When more than one drug was taken, each was evaluated separately (Table V). Available medical records (e.g. relating to X-ray or disease) or serological examinations (in infections) were used to confirm the reported exposure and the dose and time of any possible effect. In the case of exposure to chemicals, evaluation was based on the report of the women themselves.

As a second step the outcomes of the pregnancies were evaluated (Table I). Seventy-nine induced and 27 spontaneous abortions and one ectopic pregnancy were accepted on the basis of the questionnaires. Unfortunately, no fetuses were autopsied after termination of pregnancy or spontaneous abortion. A detailed necropsy record was requested and evaluated in 3 cases of stillbirth and 5 cases of infant death. The parents of 23 infants with birth defects were requested to return to

our Genetic Counselling Clinic with their children. The affected children were checked thoroughly by our consultant experts. Four families who could not come were visited in their homes. The condition of 339 children declared healthy by the parents was checked on the basis of data requested from competent district paediatricians. The medical information received in 308 cases (90.9%) and the reported data did not change the distribution of major congenital anomalies. Finally, the data of the Hungarian Congenital Malformation Register were checked.

RESULTS

Induced abortion was recommended to 58 of the 546 women for the following reasons: proven rubella, varicella, and other infections in 32 cases (Table VII), chemicals (a drug or alcohol) in 11 cases (Table IV), mater-

TABLE II

Pregnancy outcome of women exposed to physical environmental factors and psychological stress during pregnancy

Physical factors	Number of pregnant	Method of diagnosis	Pregnancy outcome unknown	Induced abortion		Fetal death	Evaluated live births	Birth defect	
				indicated	done			No	per cent
Diagnostic X-ray (mainly abdominal)	82	Medical documentation	8	0	5	8	61	5	8.2
Therapeutic X-ray (malignant disease)	4	Medical documentation	0	4	4 (4)*	0	0	0	0
Mechanical trauma (mainly abdominal)	4	History	1	0	1	0	2	0	0
IUD	7	Medical documentation	0	0	1	3	3	0	0
Psychological stress	2	History	0	0	1	0	1	0	0
Total	99	—	9	4	12 (4)*	11	67	5	7.5

* The number of indicated induced abortions is shown in brackets

nal disease and its therapy in 11 cases (Table VIII) and radiotherapy in 4 cases (Table II). Our advice was followed by 55 women. However, an additional 24 women had their pregnancy interrupted; therefore the total figure of induced abortions was 79 cases (Table I).

For *spontaneous* abortion the reported birth rate of 6.8% was lower than the registered Hungarian value (13%). This may be an ascertainment bias since the recorded peak of spontaneous abortion occurs in about the 8th week of gestation in Hungary, and the majority of our counselees had passed this time. The stillbirth figure, 0.8%, corresponded to the

national value (0.8%). No anomalies were observed among the stillborns.

Out of 367 livebirths, five died within the infant period; the rate (1.36%) was lower than the national figure in the period studied (2.9%). The cause of death in these five cases was the very low birth weight: 800 g, 850 g, 900 g, 1180 g (with RDS) and 1450 g (in a twin), respectively. No congenital anomalies were observed in these autopsied dead infants. In 4 cases the reason for their visit to the Genetic Counselling Clinic was a suspected but unconfirmed rubella infection and in one case a mononucleosis.

TABLE III
Birth defects in newborns of women exposed to diagnostic X-rays

Defect	Current view of aetiology	Localisation of X-rays	Time of X-rays during pregnancy
Bilateral retinoblastoma	Gametic mutation	Gastric	4th week
Trisomy 13	Gametic non-disjunction	Cervical	4th week
Spina bifida cystica	Multifactorial	Chest	2nd week
Congenital inguinal hernia	Multifactorial	Cholecystography	4 times in 11th week
Congenital inguinal hernia	Multifactorial	Chest	15th week

In the following sections the various categories of environmental factors and their relation to birth defects observed in livebirths will be analysed.

Among the physical factors (Table II) diagnostic X-ray examinations were predominant (82.8%). Our estimate of the dose to which the fetus was exposed did not reach the threshold of teratological significant doses

accepted in Hungary (10 rads) in any case, thus we recommended to maintain the pregnancies. Nevertheless 5 pregnancies were terminated. Among the 61 live-borns birth defects occurred in five (8.2%). The details of these cases are presented in Table III; when all factors are considered a causal relation between the X-ray exposure and the defects seems highly improbable.

TABLE IV
Pregnancy outcome of women exposed to chemicals during pregnancy

Chemical factors	Number of pregnant women	Method of diagnosis	Pregnancy outcome unknown	Induced abortion		Fetal death	Evaluated live births	Birth defect	
				indicated	done			No	per cent
Alcoholic beverage	5	History	1	1	1 (1)*	0	3	1	(33.3)
Contraceptive pill	75	History	10	0	0	1	64	3	(4.7)
Drug	84	History	12	10	16 (9)*	8	48	7	14.6
Occupational exposition (radiation 2, infection 1, chemical 3)	6	History: 4 Medical documentation: 2	1	0	0	0	5	0	0
Total	170	—	24	11	17 (10)*	9	120	11	9.2

* The number of indicated induced abortions is shown in brackets

One hundred and seventy pregnant women visited us because of exposure to suspected teratogenic chemicals (Table IV). Among the 5 women who consumed alcohol during pregnancy, one could be regarded as an alcohol addict, and for her termination of pregnancy was suggested and performed. Of the remaining 4 women, 3 indulged occasionally in large amounts of alcohol and one consumed moderate amounts of alcohol several times before the pregnancy was evident. These women wanted their pregnancies and they were encouraged to continue them. The women who mentioned moderate alcohol consumption gave birth to a 2800 g boy with tracheal stenosis. Seventy-five women took contraceptive pills during the periconceptual period. Among the 64 liveborn babies who

were evaluated, three had defects: a 2500 g girl with intrauterine growth retardation showed a significant somatic retardation in her later post-natal life, too; a boy with predisposition for dislocation of the hip, and a girl with haemangioma. Another 84 pregnant women took 191 different drugs (Table V). In 10 cases termination of pregnancy was recommended (Table VI): 9 women followed this advice. An additional 7 women also had an induced abortion. Among 48 livebirths, evaluated birth defects occurred in 7 (14.6%). Three mothers of these children had received an oestrogen-progesterone combination. One, who had been given 20 ampoules of Limovanil® (oestradiol benzoate 2.5 mg and progesterone 12.5 mg) for the purpose of abortion gave birth to a boy

TABLE V
Pregnancy outcome of women exposed to drugs

Drug	Number of pregnant women	Number of birth defect
Analgetics	13	0
Antihistaminics	16	0
Anticonvulsants	3	0
Anti-inflammatory	24	1*
Antimicrobials	18	2*
Sedatives	53	1
Tranquilizers	6	0
Cardiotonics, vasodilators	10	1
Sex hormones	30	3
Other hormones	16	0
Others	2	0
Total	191	8

* The same child

TABLE VI
Data of pregnant women to whom termination of pregnancy was recommended on the basis of drug consumption

Case number	Drug	Amount	Time (week)	Remarks
368/1978	chloramphenicol metronidazole	2 g/day 1 g/day	4—5th	Threatened abortion Kidney X-rays Nephrolithiasis
774/1978	diazepam chlordiazepoxide barbital	400 mg once 400 mg once 40 g once	4th	Suicide attempt
1120/1978	nitrazepam phenobarbital oestradiol progesterone	1 mg/day 200 mg/day 75 mg/day 150 mg/day	0—8th 4—6th	60 years old diabetic husband Cholecystography and ventricular X-ray 15 times. Attempted abortion
1232/1978	meprobamate diazepam valeric acid phenobarbital chlordiazepoxide	0.6 g/once 15 mg/once 3 g once 3 g once 1.5 g once	0—8th 6th	Epilepsy Suicide attempt
1561/1979	valeric acid phenobarbital	5 g once 5 g once	14th	Suicide attempt
1850/1979	oxytetracycline codeine unknown others	1620 mg/day 60 mg/day “many”	1—2nd	Symptoms of poisoning
1948/1979	phenytoin	300 mg/day	0—8th	Epilepsy, operated for arachalnoide cyst
1094/1980	phenmetrazine HCl oxytetracycline diethylstilboestrol-dipropionate	100 mg/day 2160 mg/day 40 mg once	5—8th 8th	Pneumonia Attempted abortion
1110/1980	oestradiol progesterone	10 mg/day 50 mg/day	3—4th	Psoriasis, hormonal pregnancy test
1544/1980	oestradiol progesterone thioridazine trimipramine	30 mg/day 150 mg/day 125 mg/day 75 mg/day	3—4th 0—10th	Attempted abortion Severe depression. ABO incompatibility

with limb reduction (unilateral, terminal transverse type fingers), and the other two, who received Limovan® (ethynyl oestradiol 0.01 mg and pregnenolone 10 mg) as a hormonal pregnancy test, gave birth to a boy with predisposition for dislocation of the hip and a girl with haemangioma. Of the additional

4 cases, 3 had mild anomalies: congenital inguinal hernia (meprobamate), predisposition for dislocation of the hip (co-trimoxazole), and haemangioma (prednisolone, penamecillin, oxytetracycline, nalidixic acid and terbutaline). The women had used clinical doses of these drugs in the 2nd and 3rd months of pregnancy.

TABLE VII
Pregnancy outcome of women allegedly exposed to microbial factors during pregnancy

Microbial factors	Number of pregnant women	Method of diagnosis	Pregnancy outcome unknown	Induced abortion		Fetal death	Evaluated livebirth	Birth defect	
				indicated	done			No	per cent
Cytomegalovirus	3	CMV specified IgM: 1	0	1	2 (1)*	0	1	0	0
"Influenza"	19	History and clinical symptoms	0	0	1	0	18	0	0
Hepatitis	4	Clinical symptoms	0	0	0	1	3	1	(33.3)
Herpes genitalis	7	Clinical symptoms	1	0	1	0	5	1	(20.0)
Herpes simplex	12	Clinical symptoms	2	0	0	0	10	0	0
Syphilis	1	Serologically excluded	0	0	0	0	1	0	0
Mononucleosis	1	Serologically	0	0	0	0	1	0	0
Mumps	12	Serologically in 8 cases	2	1	3 (1)*	0	7	0	0
Rubellavirus exposure or/and disease	157	Serologically in 17 cases	25	17	19 (16)*	8	105	4	(3.8)
Toxoplasmosis	10	Serologically in 4 cases	1	4	4 (4)*	1	4	0	0
Vaccination (cholera)	1	History	0	0	0	0	1	0	0
Chickenpox	12	Clinical symptoms in 9 cases	0	9	9 (9)*	1	2	0	0
Total	239	—	31	32	39 (31)*	11	158	6	3.8

* The number of indicated induced abortions is shown in brackets

The 7th case, a girl with cleft lip and palate and lacrimal atresia was born to a woman who took ampicillin and acetylsalicylic acid during the 9th to 11th weeks of pregnancy.

Among the infectious factors to which 239 women were exposed, rubella was most prevalent (65.7%) (Table VII). Termination of pregnancy was recommended only for rubella infection with seroconversion and for chickenpox with clinical symptoms. (Previously, our position had been the same for cases of toxoplasmosis proven by serological methods.) For one case of serologically confirmed cytomegalovirus infection (a woman who had previously given birth to a microcephalic mentally deficient child) and one case of mumps infection (social factors), the indication for induced abortion was based primarily on other factors. Among the 158 evaluated live-borns, birth defects occurred in 6. Four of them were delivered by rubella-protected women. Since these defects were Down syndrome, perinatal brain injury, syndactyly, and multiple abnor-

malities (auricular anomaly, bronchial stenosis, thymus hyperplasia, strabismus) that did not correspond to the congenital rubella syndrome, a cause-effect relation could be excluded. This was also the case for a possible relation between potential exposure of one woman to hepatitis virus (husband) during pregnancy and the congenital inguinal hernia in her son. A girl with aortic stenosis was born by Caesarean section to a woman with a genital herpes infection.

Thirty-eight women presented themselves because of potentially hazardous maternal factors (Table VIII). Termination of pregnancy was recommended in 11 cases for medical reasons, and was performed in 10. One woman with severe heart disease and thrombophlebitis who was treated with oral anticoagulants and other drugs did not want her pregnancy terminated despite our warning; she

TABLE VIII

Pregnancy outcome of women with potential hazardous material diseases during pregnancy

Material factors	Number of pregnant women	Pregnancy outcome unknown	Induced abortion		Fetal death	Evaluated livebirth	Birth defect	
			indicated	done			No	per cent
Tuberculosis	2	1	0	0	0	1	0	0
Haematologic	2	0	0	0	0	2	0	0
Diabetes mellitus	8	0	3	3 (3)*	0	5	0	0
Hepatic disease	4	2	0	0	0	2	0	0
Thyroid disease	10	2	2	2 (2)*	0	6	0	0
Heart disease	4	0	2	1 (1)*	0	3	1	(33.3)
Kidney disease	8	0	4	5 (4)*	0	3	0	0
Total	38	5	11	11 (10)*	0	22	1	(4.5)

* The number of indicated induced abortions is shown in brackets

gave birth to a child with multiple abnormalities including valvular heart defect (without specification) and anal atresia. One pregnant woman had an induced abortion against our advice. It is noteworthy that fetal death did not occur in any of the cases.

DISCUSSION

The principles and some statistics of our "information-guidance type" genetic counselling have been published previously (2). According to the results presented here, after being warned, 95% of pregnant women exposed to hazardous environmental factors terminated their pregnancies owing to the high risk of the fetus. In 419 pregnant women the suspected hazard of environmental factors was not a real or a significant one, therefore we recommended them to maintain their pregnancies and in 94% of these cases our advice was followed.

Another important point is the correctness of counselling. During the study period, the Hungarian registered birth prevalence for congenital abnormalities was about 4% and the theoretically acceptable figure would be between 6–8% (5). The 365 pregnant women for whom pregnancy continuation was recommended and who have known pregnancy outcomes and gave birth to children, 20 (5.5%) had a malformed liveborn. This observed figure corresponds to the expected one of congenital abnormalities in the Hungarian population. The birth prevalence of severe

congenital abnormalities was 2.7% and this also fits well with the expected 3% rate. Furthermore the observed rates of different types of pre- and postnatal mortality did not exceed the national figures in 419 pregnant women where the maintenance of pregnancy was suggested and the pregnancy outcomes were known.

Of course, it would be better to use the record linkage than to organize a follow-up study. At present, however, the efficacy of record linkage has not reached the adequate level. On the one hand new congenital anomalies were not found. On the other hand, only seven congenital anomalies were registered from 20 known cases (35%). The completeness of reporting is better in the severe congenital anomalies, because out of 10, seven were notified.

According to Hungarian regulations, a 10% risk of severe and untreatable congenital anomalies without the possibility of prenatal diagnosis may be a medical indication for induced abortion before the 12th week of gestation. Such a risk could be anticipated in therapeutic X-ray of malignant diseases; in pregnant women with IUD in utero (though the teratogenic risk has not been confirmed); in alcoholic pregnant women who consumed large amounts of alcohol during pregnancy; in six drug groups such as androgens; antifolic acid derivatives; cytostatics; synthetic oestrogens; certain anticonvulsants like hydantoin, trimethadione and valproic acid derivatives; and dicou-

marol derivatives; rubella infection with seroconversion and chickenpox with clinical symptoms (though recent studies have demonstrated a fetal risk under 10%). The use of contraceptive pills during the periconceptional period entails only less than 1% risk increase if any (6, 8, 4). The oestrogens may increase the risk of limb reduction malformations threefold, from 0.04% to 0.12% (4). Thus a cause-effect relation could not be excluded in the case in which Limovanil® was administered to induce abortion. Thus the question may be raised whether or not the genetic advice given to the women exposed to Limovanil® was wrong. We believe that we can safely deny this, because the increase of specific risk (at most 0.1%) is individually negligible.

Of the 58 women to whom termination was recommended, three did not follow our advice. One aborted spontaneously (the 1561/1979 case in Table VI); one gave birth to a child with multiple congenital abnormalities (the case was mentioned among the women exposed to maternal factors); and one with rubella virus infection proved by seroconversion in the 8th–10th weeks of pregnancy, had a normal baby.

The efficacy of "official" advice concerning the potentially hazardous environmental factors during pregnancy seems to be good. The random risk, however, is a permanent Damocles' sword for the counsellor. It partly explains the defensive attitude of clinicians in the judgement of

potential teratogens. (In Hungary Law protects the counsellor versus the rare occurrence of random risk.) Another problem is the sketchy teratological knowledge of physicians. Finally, in Hungary the restriction of the previous liberal Abortion Law in 1974 also modified the consideration of potentially hazardous environmental factors during pregnancy. The rate of induced abortion for medical indication increased from 2.7% in 1970–1973 to 15.9% in 1979–1980. Analysis of this significant increase showed that the reason for about 40% of these cases was not well grounded from the teratological point of view and that clinicians have great difficulty in evaluating the significance of human teratogenic exposures (3). The difference means the loss of about 4000 planned pregnancies per year.

CONCLUSION

Follow-up of women seeking advice at a genetic counselling clinic because of exposure to potentially hazardous environmental factors during pregnancy is important because it provides an evaluation of the counselling and yields information on the effect of environmental factors that is difficult to gather. Our data support the recent epidemiological observations which suggest that the majority of potentially hazardous environmental factors are not true teratogens (7). These observations might lessen the fears of pregnant women

concerning the possible dangerous consequences of potential teratogens and this may be a great help because all pregnant women are exposed to some environmental factors.

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