4.Diazepam

The very large doses of diazepam used for self-poisoning during pregnancy did not induce a higher rate of specific congenital abnormalities and intrauterine growth retardation. However, our experiences have shown the feasibility and benefits of self-poisoning model for the estimation of human teratogenic and fetotoxic risk of drugs

5.Nitrazepam

The very large doses of nitrazepam used for suicide attempt during pregnancy resulted in a very high rate of musculoskelatal CAs which may be connected with the disruption of protein metabolism in fetal mesenchyma. Our experiences have shown the feasibility and benefits of self-poisoning model for the estimation of human teratogenic and fetotoxic risk of drugs.

Discussion

In the past the incidence demographic characteristics and motivation of suicide during pregnancy were studied. There is an obvious sex and age difference between suicide mortality and suicide attempts. The majority of suicide attempters are young (peak in the 18-20 years old in our project), female (68% in the Budapest Registry), in general otherwise healthy (the proportion of psychiatric diseases was 3.3 % among self-poisoned pregnant women who delivered later live-born babies), although their lifestyle may reflect a self-harming behaviour including alcohol consumption and smoking, while suicide mortality occurs mainly in advanced age, in males and psychiatric problems are frequently revealed .

The number of attempted suicides increased significantly in the 20th century, up to the annual registered suicide attempt rate: 0.38% in Boston 1964-1992 and 0.23% in Budapest in the 1970s . In addition the proportion of self-poisoning showed a dramatic rise (90%) within suicide attempts . Thus recently the self-poisoning epidemic has resulted in a major socio-medical problem mainly in young females . It is good that the number of survivors after self-poisoning during pregnancy has increased significantly due to the more effective medical

treatment. However, the long term effects of self-poisoning including the teratogenic and mutagenic effects of drugs have become an important medical problem.

The timing of attempted suicides during pregnancy is very characteristic. Previous studies showed a peak in the third gestational month , and it was confirmed in the first and second period of our project. However, the data of the third period of the project based on the detection of self-poisoned pregnant women by a very sensitive pregnancy test indicated an earlier peak immediately after the recognition of pregnancy and related conflicts. The explanation of this discrepancy is the detection method of pregnancy. In the past pregnancy was diagnosed by bimanual gynecological examination after the second missed menstrual period. However, now we have a chance to recognize the pregnancy during or immediately after the first missed menstrual period due to the recent very sensitive pregnancy test which was used in the third period of our project. The incidence of early fetal loss of pregnancy is very high in general , but particularly in pregnant women with self-poisoning as our study showed. This phenomenon may explain the low rate of recorded miscarriages in the first and second periods of the project.

The major message of our project is the feasibility of the self-poisoning model during pregnancy for the evaluation of teratogenicity of drugs. Many drugs are subject to contraindications or special warnings because they have not been sufficiently studied during pregnancy or investigations in animals have revealed adverse teratogenic or fetotoxic effect . Data of self-poisoned pregnant women would provide an appropriate source of information for the better estimation of the potential teratogenic hazards of drugs during pregnancy.

There are many strengths of the self-poisoning model:

(1) This model shows an obvious similarity to animal investigations when large doses are administered once on a certain gestational day or during a relatively short period.

(2) These pregnant women are hospitalized, thus medically recorded prospective exposure data are available for the estimation of human teratogenicity of the drug studied.

(3) If we are able to show the lack of CAs after the use of very large doses of a drug during the critical period of CAs, it is an important argument against its teratogenicity.

(4) We have a chance to evaluate the dose – response relation which is an important criterion in experimental teratology but the uses of clinical doses of drugs are not appropriate for this estimation.

(5) Obviously the use of the daily clinical dose of a drug in 100 pregnant women is not equal to 1 pregnant woman with 100 fold higher dose of this drug due to the well-known thresholdeffect of teratogenic drugs.

However, the limitations of the self-poisoning model are also obvious:

(i) The number of pregnant women who attempted suicide in the critical

period of major CAs was fortunately relatively low. Thus only an international collaboration can achieve a higher number of self-poisoned pregnant women with *specific drugs* whit appropriate statistical power.

(ii) In addition most pregnancies are terminated after attempted suicide

in early pregnancy, and we were not able to evaluate CAs of fetuses in these pregnancies. However, the investigation of the embryo will be possible after the use of the so-called abortion pills (misepristone + misoprostol) in the future.

(iii) Frequently more than one drug was used for self-poisoning and it is

not easy to differentiate the effect of different drugs. However, there are appropriate statistical methods to differentiate their effect. In addition there is a low chance that one drug can neutralize the teratogenic effect of another drug. On the other hand we know several examples for the teratogenic interaction of different drugs .

(iv) Many drugs get probably never or only very rarely used for self

-poisoning.

(v) It would be ideal to estimate the effective dose of drugs; however,

we know the administered dose, but the effect of drugs depends on the time interval between the intake and medical treatment, and on the efficacy of medical intervention. However, the clinical symptoms of self-poisoned patients may help us to estimate the severity of intoxication.

(vi) Pregnant women who attempted suicide had a lower socioeconomic

status therefore they cannot represent the pregnant population in large.

(vii) In addition several pregnant women who attempt suicide are already

on medication, smoke cigarettes, or consume alcohol, and self-poisoning itself is frequently combined with alcohol abuse. Thus the rate of these lifestyle factors in self-poisoned pregnant women was much higher than in the Hungarian pregnant population in large.

(viii) Extremely difficult to find appropriate controls for this very specific

high risk pregnant women and for their exposed children. However, our experiences regarding sib controls are good.

(ix) Another problem is connected with the methodology. Unfortunately it

showed some differences in the three periods of our project due to the experiences obtained the ongoing study and available financial sources. As far as we know the data of similar projects have not been published. Thus it would be necessary to describe a protocol for this approach.Last but not least the study of these self-poisoned pregnant women raises some ethical (voluntary participation) and political (e.g. racial) problems, however, such projects of this high risk subpopulation may provide medical and social help for them, e.g. we organized a special antenatal care for our self-poisoned pregnant women.

Nevertheless, the self-poisoning model seems to be a third, more effective,human approach for the evaluation of drug teratogenicity beyond clinical and analytical epidemiological studies. This third approach was previously called "experimental" epidemiology but it does not sound well in the human being. We prefer the term *disaster epidemiology* when extraordinary natural catastrophes, e.g. earthquake and human-made disasters such

Hiroshima/Nagasaki nuclear bomb attacks , Chernobyl nuclear plant accident , accidents in chemical industry such in Seveso or Bophal offer a special opportunity to study the association between disorders, e.g. CAs and specific environmental agents. Self-poisonings may be classified as continuous and not rare events in the human-made disaster epidemiology.

Previously we published the general results of the three periods of our self-poisoned pregnant women project. However, only homogeneous and sufficiently large study groups of self-poisoned pregnant women using the same drug and their appropriate controls can help us at the teratogenic evaluation of different drugs. We are planning to do it in the near future in our 394 exposed children born to mothers who attempted suicide with the commonly used drugs. Pregnancy outcomes following poisonous mushroom intoxication during pregnancy were published previously .

In the past we examined the frequency of chromosomal aberrations (mutations) in the blood of self-poisoned pregnant women and non-pregnant people . The self-poisoning model seemed to be a unique approach for the examination of the long term effect of germinal mutagenic effect of drugs and other chemicals in the offspring of self-poisoned persons .

The point is that our Hungarian self-poisoning project in pregnant women and the Swedish CA-registry showed that drug intoxication during pregnancy due to attempted suicide is appropriate for the evaluation of teratogenic effect of large doses of drugs and other chemicals, therefore it would be necessary to utilize the benefits of disaster epidemiology. We suggest therefore establishing an *international monitoring system of self-poisoned pregnant women* (e.g. under the umbrella of the EMEA in Europe or of the CDC in USA) based on the following arguments:

(1) All self-poisoned pregnant women need special medical-toxicological care in specialised inpatient clinics. Thus these pregnant women are cared for in *a limited number of specialised hospitals* (we were lucky that Budapest and its surroundings, including 3 million people had also one hospital for these patients), thus their ascertainment is not difficult.

(2) Self-poisoned patients are thoroughly examined, thus drug concentrations in blood, symptoms and treatments are medically recorded, making the most important *prospective data* available.

(3) The *high rate of TOP* after self-poisoning during pregnancy can be decreased by an appropriate teratological counselling regarding the drugs used for suicide attempt and thorough ultrasound scanning during pregnancy considering the expected CAs in the fetus. On the other hand, most embryos would be appropriate for embryopathological examination after the TOP using the abortion pills.

(4) Quantitative estimates of exposures can be judged based on the level of drugs in the blood, the severity of clinical symptoms, etc. therefore we have an opportunity to estimate a *dose-response relation*, and finally to determine the teratogenic threshold dose of drugs.

(5) A more deeper and reliable knowledge regarding the teratogenic effect of certain drugs gained by self-poisoning model may help us in general *to estimate better their risk in the origin of expected specific CAs*. Thus well-directed ultrasound scanning in the second trimester can identify, or can exclude these CAs after the early use of clinical doses of teratogenic drugs, and to protect the life of several fetuses without CA, instead of the present frequent TOP.

(6) *Self-poisoned pregnant women at high risk* need special medical care regarding the fate of the study pregnancy and their further life. This international monitoring system may contribute to solve this socio-medical task as well.

(7) An extra goal is to obtain the data of general health, mental and behavioral development of these children, to understand better the human fetotoxic, including neurotoxic effect of drugs (Lendvay and Czeizel, 1989). An effort would be necessary also to provide a special socio-medical help for these *high risk children*.

(8) Offspring of exposed children would offer a special opportunity to estimate *reproductive fitness in the third generation*, again similar to the animal reproductive investigations. Thus this international monitoring system would be an adequate and unique approach to evaluate the human mutagenic effect of drugs in the stored DNA samples of exposed children.

(9) Finally this international monitoring system of self-poisoned pregnant women may stimulate and contribute to the research and *prevention of suicidal behaviour* (Bertolote and Fleischmann, 2005).

In conclusion our experiences have shown the feasibility and benefits of self-poisoning model within the disaster epidemiology for the estimation of human teratogenic risk of drugs and other chemicals

Publications

1. 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
J Gidai, N Ács, F Bánhidy, and AE Czeizel
Toxicology and Industrial Health, Feb 2008; vol. 24: pp. 29 - 39.

2. A study of the teratogenic and fetotoxic effects of large doses of chlordiazepoxide used for self-poisoning by 35 pregnant women
J Gidai, N Ács, F Bánhidy, and AE Czeizel
Toxicology and Industrial Health, Feb 2008; vol. 24: pp. 41 - 51.

3. An evaluation of data for 10 children born to mothers who attempted suicide by taking large doses of alprazolam during pregnancy
J Gidai, N Ács, F Bánhidy, and AE Czeizel
Toxicology and Industrial Health, Feb 2008; vol. 24: pp. 53 – 60

4. A study of the effects of large doses of medazepam used for self-poisoning in 10 pregnant women on fetal development
J Gidai, N Ács, F Bánhidy, and AE Czeizel
Toxicology and Industrial Health, Feb 2008; vol. 24: pp. 61 - 68.

5. Self-poisoning during pregnancy as a model for teratogenic risk estimation of drugs
AE Czeizel, J Gidai, D Petik, G Timmermann, and EH Puhó
Toxicology and Industrial Health, Feb 2008; vol. 24: pp. 11 - 28.

Self-poisoning during pregnancy

as a unique model for teratogenic risk estimation of large doses of benzodiazepin-derivatives

PhD Thesis- book

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Pécs, 2008.

INTRODUCTION

The clinical trials of a drug under development in general cannot include pregnant women. Thus, only the results of experimental animal investigations are available to evaluate teratogenic risk before the marketing of drugs. It would be ideal to identify teratogens with screening tests in lower organisms and to prevent their contact with the human population. However, we are far from this optimal situation because the screening systems are imperfect and these results cannot be extrapolated for pregnant women due to species differences. Thus the harsh reality is that the human being remains the ultimate test organism to detect teratogenic drugs.

After the marketing of drugs, two kinds of post-authorisation data are used for the estimation of their teratogenic potential . The first group of data are obtained through case reports, clinical case series and randomized controlled trials. However, case reports are burdened by serious selection bias, clinical case series usually have no appropriate controls, and there are serious barriers to perform randomized controlled trials in pregnant women. The second group of data is connected with analytical epidemiological studies and/or registry/surveillance/monitoring systems.However, the possible association between the low clinical doses of drugs and structural birth defects: congenital abnormalities (CAs) is modified by confounders, it is difficult to restrict recall bias by comparison of mothers with affected children and mothers with healthy babies, and in general there is no chance to estimate the dose-response relation. These postmarketing data are useful to predict human teratogenic risk of drugs but the extent of these predictions must be regarded with caution in the medical practice.

Pregnant women, who attempt suicide by taking large doses of drugs and do survive, may represent a unique model to study teratogenicity, fetotoxicity and mutagenicity of chemical compounds . We use the term *self-poisoning* for this kind of attempted suicide . Previously mainly case reports of drug overdosages and suicides during pregnancy as a

component of maternal mortality have been published. The possible association between drugs used for self-poisoning and CAs in case series and CA registries were rarely evaluated.

Our experiences in the Budapest registry of self-poisoned patients were good, therefore we recommend establishing an *international registry of self-poisoned pregnant women*. Here we describe in brief the history of our activity in this field, the methodology, and present the baseline data of our materials to demonstrate the strengths and weaknesses of this approach in the evaluation of teratogenic potential of drugs and estimate the teratogenic and fetotoxic effects of large doses of five benzodiazepine derivatives (alprazolam, medazepam, chlordiazepoxide, diazepam, nitrazepam)

MATERIALS AND METHODS

Subjects

The study region included Budapest, the capital of Hungary and the surrounding area containing about three million people. All self-poisoned persons in this region were admitted to the Department of Toxicological Internal Medicine, Korányi Hospital, Budapest (henceforth „study hospital"). The objective of our project was to identify pregnant women among self-poisoned females and to evaluate the effect of large doses of drugs on the fetal development in their *exposed children*. Gestational age was calculated from the first day of the last menstrual period; however, we used the term *postconceptional pregnancy age* estimated from the first day of the third week of the first lunar (28 days) gestational month, i.e. from the speculative day of conception.

First period of the project: a retrospective ascertainment of self-poisoned pregnant women

The admission records and medical files of all female patients in the study hospital between 1960 and 1979 were reviewed in 1980. All pregnant women with self-poisoning were identified and their personal, lifestyle, medical and particularly self-poisoning data in the study pregnancy were recorded on their personal file. Later our coworker visited these

pregnant women at home to elucidate their pregnancy outcome, to obtain the data of their exposed child born from the study pregnancy based on the medical records (discharge summaries of their deliveries, etc.) and to invite these mothers with their children for a medical and psychometric examination between 1981 and 1983 to our institute.

The second period of the project: a continuous ascertainment of self-poisoned pregnant women

A psychologist visited the study hospital every second day between 1980 and 1984 and contacted all females between the age of 15 and 50 years to identify pregnant women on the basis of case history and missed menstrual cycle through a personal interview and the pregnancy of these women was confirmed by a gynecologist. The data of self-poisoned pregnant women were obtained in the personal file. Later the psychologist visited these mothers at home to elucidate their pregnancy outcome and to obtain the personal and medical data of exposed children on the basis of available medical documents (discharge summary of delivery, medical records of pediatrician, etc.), in addition the cognitive and behavioral development of exposed children were tested.

The third period of the project: a continuous ascertainment of pregnant women by a sensitive pregnancy test screening in all self-poisoned women between 15 and 50 years

A pregnancy test (based on the blood level of beta hCG) was performed in blood samples taken for the measurement of drugs used for self-poisoning at the admission to the study hospital in all reproductive aged women from 1985 until 1993. Each pregnant woman had the personal file including the necessary data obtained by our coworkers. Later one of our two coworkers visited these pregnant women at home to elucidate their pregnancy outcome, to obtain the data of exposed children and to invite these mothers with their exposed child (and their other children) to our institute for a medical and cognitive-behavioral examination between 8 and 12 postnatal months. All missing exposed children were visited at home by the pediatrician of our staff.

Exposure data

The dose and effect of drugs used for self-poisoning were estimated (i) on the information obtained from self-poisoned pregnant women in the study hospital in the second and third period, while at the home visit in the first period of the project regarding the name

and number of tablets used for self-poisoning and the following clinical symptoms, (ii) drug levels in their blood measured in the study hospital, and (iii) the clinical severity of intoxication on the basis of symptoms, duration of unconsciousness, etc. recorded in the medical files of self-poisoned pregnant women.

The severity of self-poisoning was defined into five categories: mild (no comatose condition at or after admission), moderate (comatose condition or unconsciousness at or after admission), severe (unconsciousness longer than 1 day after admission and/or need for artificial respiration), very severe (life-threatening, i.e. unconsciousness more than 2 days with severe complications such as uremia or multiorgan failure) and fatal (the fetuses of these pregnant women could not be evaluated in our project) outcome.

All self-poisoned pregnant women were asked to sign a consent form (after the home visit in the first period and before discharge in the second and third period of the project) regarding voluntary participation in the study and permission for follow-up home visits and examination of their children.

Main outcomes measures

First *pregnancy outcomes* were evaluated and classified into five groups. The data of (i) miscarriages (early and intermediate fetal death), (ii) stillbirth (late fetal death, its definition was 26 or more pregnancy week at the onset of the project and we insisted on this definition until the end of the project) and (iii) livebirths were medically recorded because all deliveries and recognized miscarriages took place in inpatients maternity clinics in Hungary. (iv) The termination of pregnancy (TOP) was accepted on the information of self-poisoned mothers. Finally we used the term (v) chemical pregnancy based on the positive pregnancy test without any later clinical symptoms of pregnancy in the third period of the project. Only one ectopic pregnancy was diagnosed among our self-poisoned pregnant women in the third period of the project, this woman was included in the groups of miscarriages. The elective terminations of pregnancy after the prenatal diagnosis of fetal defects was introduced in the 1980s in Hungary, but this pregnancy outcome did not occur in our material.

The discharge summaries (including birth weight and gestational age, and visible CAs) of all stillborn fetuses and live-born babies were available at the home of mothers or we obtained their copies from the hospital where mothers delivered their fetuses or newborns.

Exposed children were evaluated from four different aspects:

1. CAs. Live-born exposed children had a thorough medical examination in the first and third period of the project by our staff, while maternal information and pediatric records were evaluated in the second period of the project. The autopsy records were available and evaluated in deceased children and stillborn fetuses because autopsy was obligatory in infant deaths and usual in stillborn fetuses. The so-called *minor anomalies* were defined as unusual morphologic features that are of no serious medical consequence to the patient . Minor anomalies of exposed children were examined in the first period of the project, and they were evaluated thoroughly on the basis of the protocol list of minor anomalies in the third period of the project. However, in general minor anomalies were not mentioned in the available medical records during the second period of the project.

At the evaluation of CAs, isolated and multiple CAs were differentiated. The definition of multiple CA was a concurrence of 2 or more CAs or at least one CA with 2 or more minor anomalies in the same person affecting at least 2 different organ systems .

2. *Intrauterine fetal growth retardation.* The data of medically recorded birth weight and pregnancy age of live-born exposed children were used for the calculation of pregnancy age specific birth weight compared with Hungarian developmental standard . Intrauterine fetal growth retardation seemed to be the most sensitive indicator of fetoxic effect of drugs . In addition, the rate of preterm births and low birthweight newborns were also evaluated.

3. The *cognitive development* of exposed children was measured by the Budapest Developmental Test which is appropriate for the estimation of cognitive development from the infant age and our children were classified into 4 groups (i) above mean (111-120 IQ, mean 115), (ii) mean (90-110 IQ, mean 100), (iii) under mean (80-89 IQ, mean 85) and (iv) very low (70-79 IQ, mean 75). Some other cognitive tests were used due to the wide age spectrum (1-21 years) in the first period of the project , but because we evaluated the results of the Budapest Development Test during all the three periods of the project, in general these results are shown. Of course, a special attention was paid for the detection of

exposed children with *mental retardation* (MR). At the diagnosis of MR, the accepted international recommendations (less than 70 IQ, etc) were followed . Most exposed children with MR were diagnosed previously and confirmed in our project. Some exposed children with suspected new diagnosis of MR in our project had a longer follow-up to confirm or exclude the diagnosis of MR.

4. The *behavioral scale* of exposed children was also estimated by the Behavioral Style Questionnaire, Home test, and Drawing Test in the second, and by the Behavioral Style Questionnaire in the third period of the project. Exposed children were classified into four groups: (i) normal, (ii) mild, (iii) moderate and (iv) severe behavioral deviation. The details of these methods were described previously . Behavioral scale was not measured in the first period of the project, but mothers informed us on the severe behavioral (criminal) deviation of 3 exposed children.

Controls

The previous and subsequent child(ren) of self-poisoned pregnant women were used as *sib controls*. However, several self-poisoned pregnant women were primiparous without previous and later child, in addition some women attempted suicide in two or more pregnancies, thus we found exposed sibs as well. Thus our study design included an *exposed child – matched unexposed sib control pair analysis* as well. If exposed children had more than one sib, one sib was selected for the exposed child-matched unexposed sib control pair analysis on the basis of same sex and next birth year. If exposed children had no sibling, one previous or subsequent child of self-poisoned pregnant women with TOP or fetal death (chemical pregnancy, miscarriage or stillbirth) was selected as controls on the basis of three matching criteria: same age (±1 year) and employment status (high, medium, low) of self-poisoned pregnant women, in addition the same sex of children. These sib controls had the same medical and cognitive-behavioral examination as exposed children; however, the dropout rate was larger.

Finally we evaluated the data of 38,151 newborns without CAs from the data set of the Hungarian Case-Control Surveillance of Congenital Abnormalities, 1980-1996 (Czeizel et al., 2001), as a *reference* sample representing 1.8% of all Hungarian births.

The *statistical analysis* was based on SAS version 8.02 statistical software package (SAS Institute, Cary, NC.). The quantitative variables of self-poisoned pregnant women were evaluated by Student t test while categorical variables with chi square test. The prevalence at birth of CAs and MR in the exposed children and in their sib controls were compared and odds ratio (OR) with 95% confidence interval (CI) were calculated by an unconditional multiple logistic regression model. At the evaluation of exposed child – matched unexposed sib control pairs, the conditional multiple logistic regression model was used.

RESULTS

1. Alprazolam

Of 30 pregnant women who used alprazolam for suicide attempt, 10 delivered live-born babies. The doses of alprazolam were between 7.5 and 100 mg with a mean of 27 mg. Of 10 exposed children, 6 were born to mothers who attempted suicide between the 3rd and 12th postconceptional week. Of 10 exposed children, 2 had congenital abnormalities. One of them was a multiple congenital abnormality including atypical gastroschisis and minor anomalies. The association of this defect and 30 mg alprazolum used for self-poisoning on the 14the postconceptional week cannot be excluded. Another child was affected with mild pectus excavatum, but the time of suicide attempt and the critical period of this CA did not overlap. Of 12 sibs, one had congenital abnormality, thus the rate of congenital abnormalities did not show significant difference between exposed children and their sibs. The mean birth weight and pregnancy age, in addition cognitive status and behavioral scale of exposed children did not indicate the fetotoxic, including neurotoxic effect of large doses of alprazolam.

2. Medazepam

Of 835 pregnant women, 32 (3.8%) used medazepam with or without other drugs for self-poisoning and 10 delivered live-born babies. The dose of medazepam ranged between 60 and 500 mg with a mean of 276 mg, and 8 suicide attempts occurred between the 4th and 12th postconceptional weeks. Of 10 exposed children, 1 was affected with congenital inguinal hernia, while of their 13 sibs, also 1. There was no intrauterine growth retardation, lower cognitive status and more frequent behavioral deviation in the children born to mothers who attempted suicide with medazepam during pregnancy.

3. Chlordiazepoxide

Of 1044 self-poisoned pregnant women, 88 (8.4%) used chlordiazepoxide with or without other drugs for suicide attempt and 35 delivered live-born. The dose of chlordiazepoxide ranged between 20 and 300 mg with a mean of 117 $\pm$ 86 mg. Of 35 exposed children, 7 (20.0%) were affected with congenital abnormalities, while of their 22 sibs, 4 (18.2%). Thus there was no significant difference between the rate of congenital abnormalities in exposed children and in their sib controls. Of 17 pregnant women who attempted suicide between the 4th and 12th postconceptional week, 4 delivered live-born babies affected with congenital abnormality, namely atrial septal defect type II, complex defect of respiratory system, mild pyelectasis due to the stenosis of ureteropelvic junction, and congenital inguinal hernia. Further 3 children had hypospadias (glandular type), fetal alcohol syndrome and unrecognized multiple congenital abnormality including talipes equinovarus and 4 minor anomalies. The pregnancy age specific mean birth weigh indicated intrauterine fetal growth retardation and this association was confirmed by the dose-response relation, in addition by the higher rate of low birthweight newborns. The cognitive status and behavioral scale of exposed children did not indicate the fetotoxic, including neurotoxic effect of large doses of chlordiazepoxide.

4. Diazepam

Of 1044 self-poisoned pregnant women, 229 (21.9 %) used diazepam with or without other drugs for suicide attempt and 112 delivered live-born. The dose of diazepam ranged between 25 and 500 mg, however, most frequently 100 mg was used. Of 112 exposed

children, 15 (13.4 %) were affected with congenital abnormalities, while of their 112 matched sibs, 8 (7.1 %) (OR with 95% CI: 2.0, 0.8-5.0). Of 36 pregnant women who attempted suicide between the 4th and 12th postconceptional week, 5 (13.9%) delivered live-born babies affected with congenital abnormality, namely undescended testis in 2 exposed children, congenital dysplasia of the hip, talipes equinovarus, and congenital inguinal hernia 1-1 exposed child. The time of critical period of these defects and suicide attempts during pregnancy did not overlap. The mean pregnancy age and mean birth weigh were similar in exposed children and their sibs

5.Nitrazepam

1,044 pregnant who attempted suicide during pregnancy with drugs between 1960 and 1993, 107 (10.3%) used nitrazepam for suicide attempt and 43 delivered live-born. The mean dose of nitrazepam was 204 mg. Of 43 exposed children, 13 (30.2%) were affected with congenital abnormalities, while of their 29 sib controls, 3 (10.3%) (OR with 95% CI: 2.6, 1.0-7.3). Of 9 isolated CAs, 7 were musculoskeletal, while of 4 multiple CA, all had talipes equinovarus, deformation type and some minor anomalies. The mean pregnancy age was shorter.

Conclusion

1.Alprazolam

The very large doses of alprazolam used for self-poisoning during pregnancy did not result in a significantly higher rate of congenital abnormalities, however, the number of self-poisoned pregnant women were also 10 and the association of one multiple congenital abnormality with large dose of alprazolum cannot be excluded. The findings of the study did not show the fetotoxic including neurotoxic effect of very large dose of alprazolam. Finally our experiences have shown the feasibility and benefits of self-poisoning model for the estimation of human teratogenic and fetotoxic risk of drugs.

2.Medazepam

The very large doses of medazepam used for self-poisoning during pregnancy did not result in a higher rate of CAs, though 8 mothers attempted suicide during the critical period of major congenital abnormalities. The findings of the study did not show the fetotoxic including neurotoxic effect of very large dose of medazepam. Finally our experiences have shown the feasibility and benefits of self-poisoning model for the estimation of human teratogenic and fetotoxic risk of drugs

3. Chlordiatepoxide

The very large doses of chlordiazepoxide used for suicide attempts during pregnancy did not induce a higher rate of specific congenital abnormalities. However, a possible association between chlordiazepoxide and cardiovascular malformations cannot be excluded. On the other hand our self-poisoning model showed the fetotoxic effect of very large dose of chlordiazepoxide because dose dependent intrauterine growth retardation was observed. Finally our experiences have shown the feasibility and benefits of self-poisoning model for the estimation of human teratogenic and fetotoxic risk of drugs