Self-poisoning during pregnancy as a model for teratogenic risk estimation of drugs

Disaster epidemiology

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Dilemmas

at the teratogenic risk estimation of drugs

1. Clinical trial programs of a drug under development cannot include pregnant women.

2. Results of experimental animal investigations cannot be extrapolated for pregnant women due to species differences.

Conclusion: the harsh reality is that human beings remain the ultimate test organism to detect teratogenic/fetotoxic drugs.

Dilemmas

at the teratogenic risk estimation of drugs

Postmarketing evaluation

3. Clinical observations /trials
   - case report – selection bias
   - clinical series – no appropriate control
   - RCT – no pregnant women

4. Epidemiological studies
   - Descriptive – not appropriate for identification of causes
   - Analytical – recall bias
     - small (clinical) doses
     - confounders

Conclusion: these postmarketing data are useful to predict human teratogenic risk but the extent of these predictions needs to be taken with caution in the clinical practice.

Disaster epidemiology

a) Natural catastrophes/circumstances

earthquake

high radon exposure

high altitude, etc.

b) Human-made catastrophes/circumstances

nuclear bomb (Hiroshima, Nagasaki)

nuclear plant accident (Chernobyl)

extreme occupational exposures

self-poisoning (suicide)

Suicide

Suicide attempt

age: young (17-19 yr)

sex: female excess (1 : 4)

psychiatric diseases: rare

Suicide mortality

advanced age (over 50 yr)

male excess (2.5 : 1)

frequent

Budapest Monitoring of Self-Poisoned Pregnant Women (1960-1993)

Department of Toxicological Internal Medicine, Korányi Hospital, Budapest (”Study hospital”).

“Catchment” region: Budapest and surrounding area (Pest county): 3 million people.

In general about 100 pregnant women attempted suicide in each year during the study period.

Budapest Monitoring of Self-Poisoned Pregnant Women (1960-1993)

Method:

1. **Sensitive blood pregnancy test in all women aged between 15 and 50 years**
2. **A signature for informed consent**
3. **Special antenatal care**
4. **Data collection in a personal card**

   Personal data.
   Lifestyle (alcohol, smoking, narcotics).
   Case history; History of previous pregnancies.
   History of study pregnancies; Self-poisoning: date and time (hour, minute); postconceptional fetal age; name, dose and administration route of chemicals (medicines); interval between intake of drugs and admission to the study hospital; antidotes.

Budapest Monitoring of Self-Poisoned Pregnant Women (1960-1993)

5. **Clinical evaluation of mothers**
   - Symptoms (e.g. duration of unconsciousness)
   - Blood level of drugs
   - Disease-process
   - Pregnancy outcome (termination of pregnancy, miscarriage)

6. **Follow-up of exposed children**
   - Birth outcomes (sex, gestational age, birth weight)
   - Congenital anomalies, particularly congenital abnormalities (CAs)
   - Postnatal development
   - School records
   - Psychometric examination
   - Behavioral examination

7. **Controls** - a) Sibs
   b) Matched controls

Estimation of severity of self-poisoning

1. **Blood concentration of drugs**

   however, it depends on time elapsed between self-poisoning and hospital admission, the effect of medical intervention in the ambulance car, treatment after admission to the study hospital (gastric lavage, antidotes, etc.).

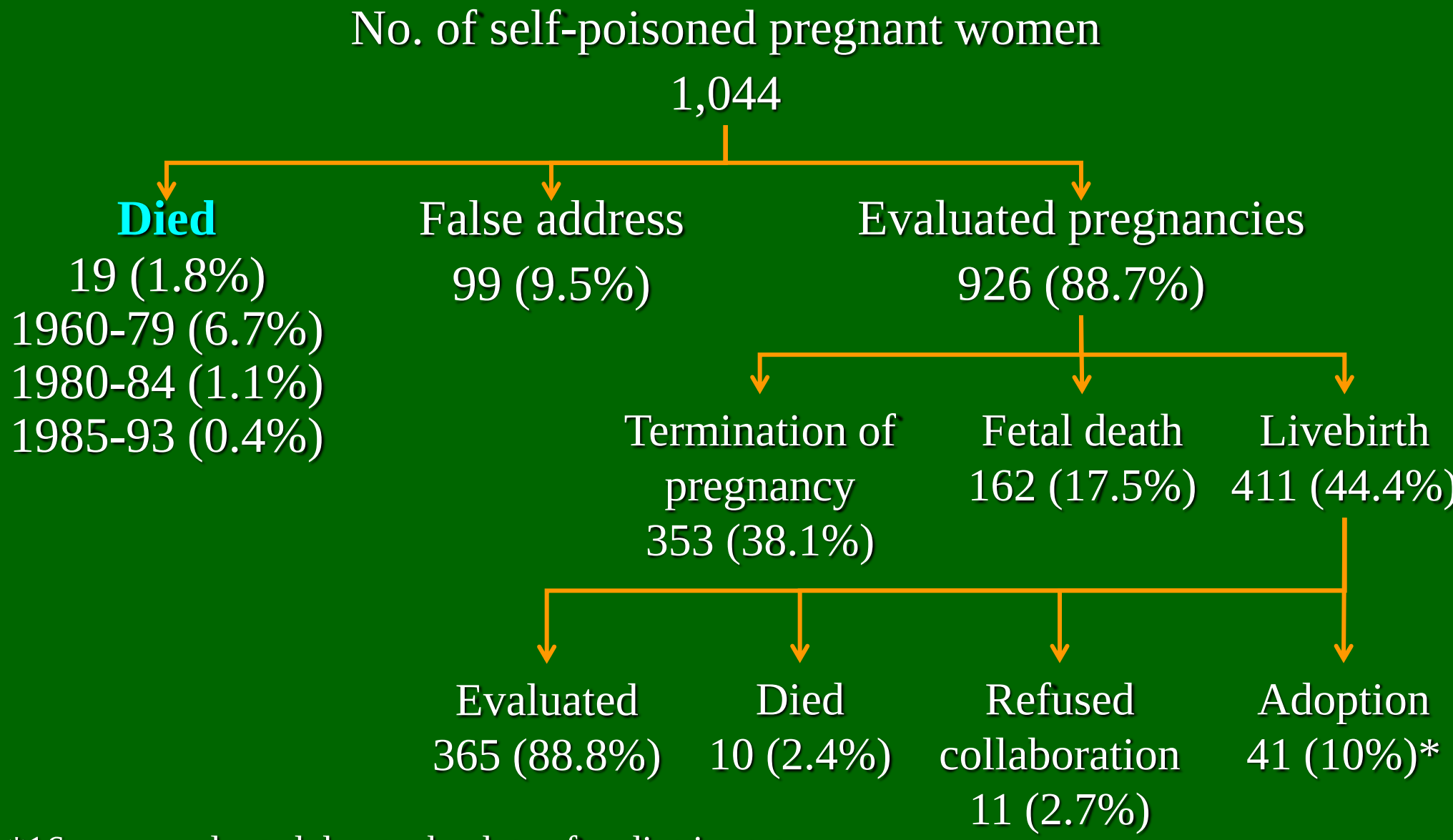
2. **Information of mothers regarding the number of drug tablets used for self-poisoning.**

3. **Clinical symptoms.**

Classification of severity of self-poisoning

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 artificial respiration
Very severe	life-threatening: unconsciousness more than 2 days and/or uremia or multiorgan failure
Fatal	

Total data set (1960-1993)



*16 were evaluated due to the data of pediatric status

Characteristics of case mothers

Variables	Self-poisoned pregnant women		Hungarian pregnant women	
Quantitative	**Mean**	**S.D.**	**Mean**	**S.D.**
Maternal age	**23.1**	**5.7**	**25.4**	**4.9**
(19 year or less, %	**32.1**		**8.6**	
Birth order	**1.4**	**0.9**	**1.7**	**0.9**
Categorical	**%**		**%**	
Unmarried	**58.0**		**4.9**	
Socioeconomic status				
High	**19.7**		**38.0**	
Medium	**37.5**		**30.6**	
Low	**42.8**		**31.4**	
Smokers	**42.0**		**18.9**	
Regular drinkers	**15.2**		**0.6**	

Time of self-poisoning, in addition number of fetal losses and livebirths (between 1960 – 1993)

Fetal development (lunar month)	Self-poisoning		Fetal loss			Livebirth
	No.	%	Chemical pregnancy No.	Miscarriage No.	Induced abortion No.	No.
I.	213	37.9	111	3	73	12
II.	128	22.8	3	6	94	15
III.	71	12.6	0	5	30	28
IV.	40	7.1	0	4	5	26
V.	30	5.3	0	0	1	27
VI.	28	5.0	0	0	0	21*
VII.	23	4.1	0	0	0	18*
VIII.	22	3.9	0	0	0	4*
IX-X.	7	0.4	0	0	0	2
Total	562	100.0	114	18	203	178

Distribution of drugs used for self-poisoning

Drugs	No. of liveborn babies
Diazepam	112
Phenobarbitals	40
Nitrazepam	36
Meprobamate	27
Chlordiazepoxide	25
Promethazine	23
Valeriana + phenobarbital	20
Promethazine + glutethimide + amobarbital	15
Glutethimide	10
Amobarbital	7
Aminophenazone + phenacetin + caffeine	4
Medazepam	3
Barbital + aminophenazone	3
Others (in two or one pregnant woman)	46
Total	391*

*several pregnant women used more than one drug

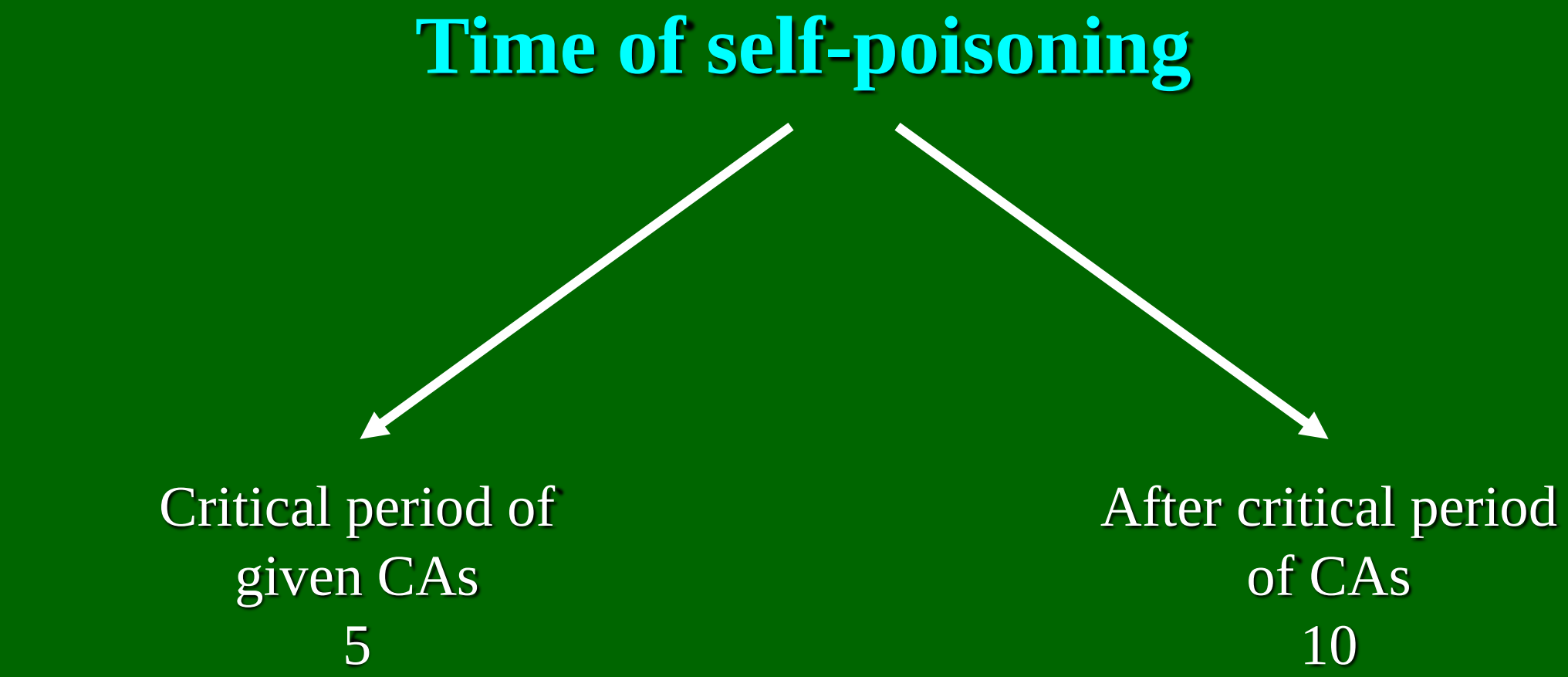
Controversial estimation of teratogenic potential of diazepam

- U.S. and Finnish studies in 1975 showed an association between diazepam and orofacial clefts (cleft lip + palate and posterior cleft palate).
- Laegreid et al. (1987-1992) delineated a benzodiazepine embryofetopathy (with a cardinal symptom of orofacial clefts).
- In Hungary we were not able to detect any teratogenic effect of diazepam and other benzodiazepines after the use of the usual clinical doses.
- Some other studies (e.g. in the USA) resulted only in negative findings.

Time and severity of self-poisoning with diazepam, number of livebirths and congenital abnormalities

Fetal development (lunar month)	Livebirth No.	Mild-moderate	Severe-very severe	Congenital abnormalities
I.	9	1	8	1
II.	11	5	6	4
III.	18	2	6	0
IV.	12	7	5	2
V.	15	9	16	1
VI.	16	8	8	2
VII.	13	7	5	3
VIII.	11	1	17	2
IX-X.	7	0	7	0
Total	112	40	72	15
%	100.0	35.7	64.3	13.4

Evaluation of 15 exposed children with CAs



Evaluation of 15 exposed children with CAs

Severity

- Isolated CAs
  - Mild
  - Severe
- Multiple CAs
  - FAS (fetal alcohol syndrome)
  - Unrecognised syndrome

	Mild	Severe	FAS (fetal alcohol syndrome)	Unrecognised syndrome
Exposed	10	1	2	2
	cong.inguinal hernia 3 undescended testis 2 talipes equinovarus 2 cong.dislocation of hip 1 ventricular septal defect (spontaneous closure) 2 hypospadias, glandular 1	pyloric stenosis		Talipes equinovarus, lowbroad nasal bridge, gingivobuccal frenulum rectus diastasis Torticollis, high-arched palate, gingivobuccal frenulum, rectus diastasis
Controls	6	2	0	1
	cong.inguinal hernia 2 undescended testis torticollis talipes equinovarus syndactyly	transposition of great vessels cong.arthrogryposis		(cleft lip + palate, complex cardiovascular CA, hypospadias)

Conclusion: no teratogenic effect (e.g. orofacial clefts)

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- In Hungary we were not able to detect any teratogenic effect of diazepam and other benzodiazepines after the use of the usual clinical dates.
- Some other studies (e.g. in the USA) resulted only in negative findings.
- Now we can show that 38 pregnant women who attempted suicide with very high dose of diazepam during the critical period of orofacial clefts had no liveborn babies with these CAs.

Possible explanation

Diazepam was used in psychiatric patients in the mentioned U.S. and Scandinavian studies while diazepam was used for the treatment of threatened abortion of pregnant women without any psychiatric diseases in Hungary.

Confirmation

Our recent study showed that panic disorder can induce CAs (mainly cleft lip ± palate) which can be prevented by diazepam.

		Diazepam	
		–	+
Panic	**–**	**Referent**	**1.1 (0.7 – 1.5)***
disorder	**+**	**3.1 (1.4 – 6.9)***	**1.5 (0.7 – 3.2)***

*adjusted OR with 95% CI

Conclusion

The previously found teratogenic effect of diazepam may be associated with underlying maternal diseases, lifestyle and/or other confounders.

Components of Tardyl®, a frequently used medicinal product for insomnia

Tardyl®	Dose
Amobarbital	125 mg
Glutethimide	125 mg
Promethazine	7.5 mg

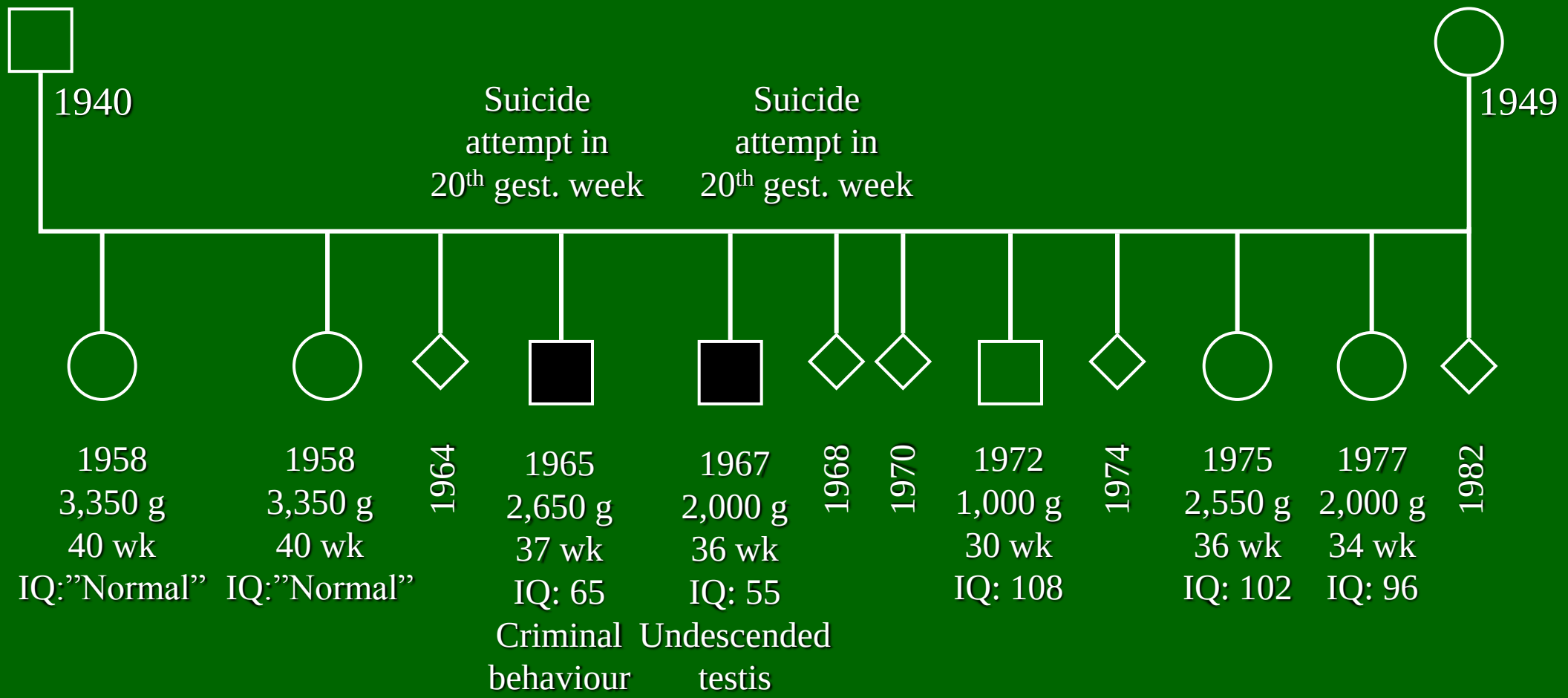
Large doses of these components had no teratogenic effect

Main findings of exposed children born to pregnant women who attempted suicide with Tardyl® during pregnancy and of their exposed sibs

	Exposed children (N=27)		Unexposed sibs (N=46)		Comparison	
Categorical	No.	%	No.	%	OR	95% CI
Congenital abnormalities	2	7.4	2	4.4	1.8	0.2 – 13.9
Mental retardation	8	29.6	0	0.0	27.6	3.3-232.4
Quantitative	Mean	S.D.	Mean	S.D.	p =	
Birth weight (g)	2,883	55	2,895	67	0.94	
Pregnancy age (wk)	36.4	2.8	36.8	2.9	0.79	
Estimated						
Cognitive status (IQ)	AM M	UM MR	AM M	UM MR	p=	
No.	3 7	4 8	4 12	4 0	0.38	
IQ (mean ± S.D.)	82.2 ± 20.0		100.0 ± 9.7		0.04	
Behavioral scale	N +	++ +++	N +	++ +++	p=	
No.	4 4	3 5*	9 6	1 0	0.03	

*5 mentally retarded children

Pregnancy history of mothers who attempted suicide by Tardyl® in two pregnancies



Conclusions

Large doses of Tardyl® associated with a high risk (OR with 95% CI: 27.6, 3.3-232.4) of mental retardation.

This association shows the importance of drug interactions (e.g. glutethimide) because the components of Tardyl® separately did not induce mental retardation.

Tardyl® is the first known mental retardation induced drug.

Strengths of self-poisoning model

1. Large doses are administrated once on a certain day of pregnancy.
2. These pregnant women are hospitalized and medical data are available.
3. We can estimate the effective dose of drugs used for self-poisoning.
4. We can use the well-known dose-effect correlation: if very high doses of a given drug during the critical period do not induce CA – it is an important argument against the teratogenic potential of the drug.
5. We can evaluate other variables of reproductive toxicology (intrauterine growth retardation, mental and behavioral development, chromosomal aberrations, second generation).

Limitations of self-poisoning model

1. High proportion of early fetal loss.
2. Many pregnancies are terminated (but the recent use of abortion pills may help evaluate embryos).
3. Thus the number of liveborn infants born to mother who attempted suicide during the critical period of CAs is limited.
4. In general more than one drug is used for self-poisoning.
5. Several pregnant women who attempt suicide smoke cigarettes, consume alcohol, etc.

Recommendations

to establish an international monitoring system of self-poisoned pregnant women

1. It is feasible (self-poisoned persons are cared in specialized inpatient clinics).
2. Self-poisoned patients are thoroughly examined and we can estimate the exposure doses of drugs.
3. Self-poisoned pregnant women are at high risk, therefore they need special medical care.
4. This model would be the most effective epidemiological approach to evaluate the teratogenic and mutagenic effect of drugs in human beings.
5. This international monitoring system may stimulate and contribute the research and prevention of suicidal behaviours.