Developmental Defects and Chromosomal Aberrations in Spontaneous Abortions and Stillbirths

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Abstract. The authors analysed 1488 cases of spontaneous abortions and stillbirths in Bratislava. They focused on the course of human embryogenesis and the chromosomal constitution. A high mean frequency rate of both developmental defects (14.4%) and chromosomal aberrations (33.6%) was revealed and both were found to be in close relation with the length of gestation. The most severe developmental defects occurred mostly in early stages of human embryogenesis, i.e. in the 1st trimester of gestation.

Key words: Spontaneous abortions and stillbirths — Developmental defects — Chromosomal aberrations

Introduction

Embryogenesis is a process of a multicellular organism arising from a single cell – zygote. In the group of organisms of higher complexity, including man, it is a highly complex, cascade like process. Each change in the plan at the very beginning or during its realisation will always cause a change in the quality of the final result, i.e. a new human being with an inborn developmental defect. In the human newborn population the incidence of inborn developmental defects is worldwide about 2% (Thorogood 1997) and they cause serious social, ethical, economical and medical problems, not only for the family but also for the whole community (Sever et al. 1993).

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The incidence of developmental defects and chromosomal aberrations in prematurely terminated pregnancies (spontaneous abortions and stillbirths) is much higher (Mikamo 1970, Kajii et al. 1980, Dejmek et al 1992, Vojtaššák et al. 1995, 1996), but information about the given period of human reproduction is still scarce.

In the present study, we analysed the proportion and the characteristics of developmental defects and chromosomal aberrations in spontaneous abortions and stillbirths in the region of Bratislava (Slovakia).

Materials and Methods

The material from 1488 spontaneous abortions and stillbirths was received from the 1st, 2nd and 3rd Department of Gynaecology and Obstetrics, School of Medicine, Comenius University (SMCU) and three other local hospitals in Bratislava during the period of 1992–1998 The biological material was transported in aseptic conditions to the Institute of Medical Biology SMCU, where the presence of embryonal and extraembryonal tissues, as well as the course of embryogenesis were defined by standard methods (Table 1) (Fujikura et al 1966, Dráč 1977, Fantel et al 1980) Two parallel samples of embryonal tissue were taken for *in vitro* cultivation and for pathological examination

Chromosomal slides were obtained by the direct imprint method (Simoni et al , 1986) or after short-term and long-term cultivations made by the "sandwich technique" (Bullerdiek et al 1979) in humidified atmosphere with 5% CO_2 in the air The following media were used RPMI 1640 (Sigma, USA), MAC SEVAC (ÚSOL Praha, Czech Republic) supplemented with 20% newborn calf serum (Ivanovice na Hané, Czech Republic) and antibiotics (G-PNC, Streptomycin, each 100,000 IU/l) according to Šubrt (1988) The slides were stained conventionally and by G-banding technique (Seabright, 1971)

Table 1. Morphological classification of spontaneous abortions and stillbirths (Fantel et al 1980)

IES	intact empty sac or anembryomole
RS	ruptured sac without embryonal structures
RSC	ruptured sac with umbilical cord, stump, yolk sac or amniotic membranes
DE	disorganised embryo
EF	embryo with focal anomalies
FF	fetus with focal anomalies
F	fragment – incomplete specimen consisting of decidua with trophoblastic material
IE	incomplete embryo
IF	incomplete fetus
EN	normal embryo
FN	normal fetus

Results

In 1488 spontaneous abortions and stillbirths we analysed 215 (14.4%) cases with disturbed embryogenesis, i e IES, DE, EF and FF were detected. (For abbreviations see Table 1). The most serious developmental defects (IES and DE) were found

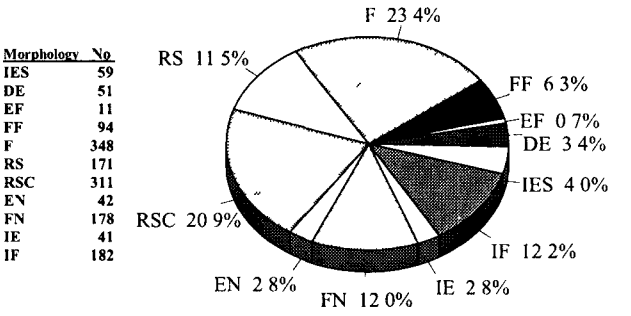


Figure 1. Morphological groups in 1488 examined spontaneous abortions and stillbirths

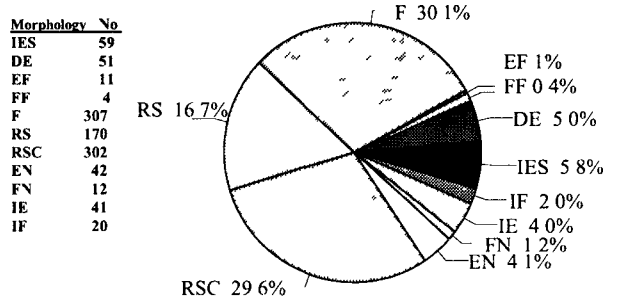


Figure 2. Morphological groups in the 1st trimester of gestation in 1019 examined spontaneous abortions

only in the first trimester of gestation. IES – anembryomoles, with the presence of extraembryonal tissues only, were found in 4% (59) of cases and DE with the presence of undifferentiated mass of embryonal cells only, in 3.4% (51) of cases. Less severe forms of developmental defects could be considered as equivalents of inborn developmental defects in newborns. These included the groups of embryos (EF) and fetuses (FF) with focal anomalies, with the frequency rate of 0.7% (11) and 6.3% (94), respectively (Figs. 2 and 3).

The incidence of particular morphological groups differs in relation to the length of gestation. As expected, IES and DE were found only in the 1st trimester with rates of 5.8% (59) and 5% (51), respectively (Fig. 2). The group of FF had a frequency rate of 0.4% (4) in the 1st trimester and of 20.4% (83) in the second trimester (Fig. 3)

The cultivation success was 65% (969) of the total of 1488 cases The most common chromosomal aberration observed was trisomy (48.1%), followed by triploidy (20.9%) and monosomy X (17.2%).

Of the 30 successfully karyotyped IES, we detected a chromosomal aberration

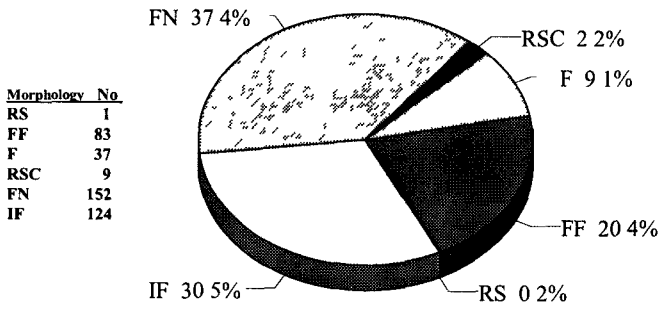
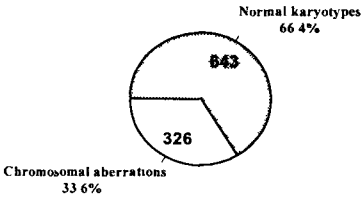


Figure 3. Morphological groups in the 2nd trimester of gestation in 406 examined spontaneous abortions



Morphology	No.
structural aberrations	10
mosaic abnormal/abnormal	4
mosaic normal/abnormal	22
monosomy X	56
trisomy of autosomes	157
3n	68
4n	7
monosomy of autosomes	2

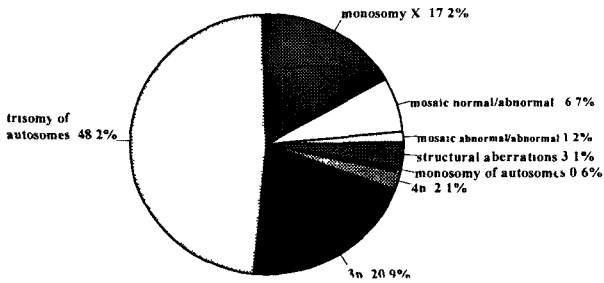


Figure 4. Karyotypes in 1488 examined spontaneous abortions and stillbirths

in 13 (43 3%) cases. There were trisomies (4), polyploidies (3) and mosaics (6) (Table 1) In the group of DE, of the 35 successfully karyotyped cases, there were 17 (48.6%) cases with normal karyotype. The most frequent chromosomal aberration present in this group was trisomy (77 8%) (Table 1). The cultivation of EF and FF material was successful in 72 (62.1%) cases Normal karyotype was found in 69.4% and chromosomal aberration in 30 6% of cases. The most frequent chromosomal aberration was trisomy, detected in 54 5% of cases.

Discussion

In comparison with the incidence of birth defects in newborns (2%), we detected a seven times higher frequency rate of developmental defects (14 4%) in spontaneous

abortions and stillbirths (Fig. 1). This information, however, has only approximative value with regard to the fact that the greater part of the samples analysed was not complete and so not fully informative (70%) (F, RS, RSC, IE and IF). The actual incidence of developmental defects in spontaneous abortions and stillbirths can be assumed to be much higher.

According to the length of gestation, the relative rate of individual types of developmental defects varied. In the 1st trimester (1019 cases) IES represented 5.8% and DE 5% of cases (Fig. 2). The equivalents of birth defects had a frequency rate of only 1% in EF and 0.4% in FF. Logically, in the 2nd trimester, only FF were present, yet their frequency rate amounted to 20.4% (Fig. 3). This is by 5% more than in a previous study (Vojtaššák et al. 1995) and ten times more than in newborns.

The chromosomal analysis revealed that 33.6% of the samples analysed had a chromosomal aberration. The most frequent form was autosomal trisomy (48.2%), almost one half of all cases. The next frequent chromosomal aberrations were triploidy (20.9%) and monosomy X (17.2%). The incidence of chromosomal anomalies in a single morphological group is shown in Table 2.

In IES cases, we detected chromosomal anomalies in 43.3% of cases (13 of 30 karyotyped cases). The most frequent chromosomal anomaly was autosomal trisomy (13.3%). Surprisingly, we observed an extremely high frequency rate of mosaics (16.7%). In a study of 59 karyotyped anembryomoles, Vojtaššák et al. (1996) detected a lower mean frequency rate of chromosomal anomalies (35.6%). According to the mechanisms of origin, they recognised two separate forms of IES, a primary and a secondary one. Concerning secondary IES, the same frequency rate of chromosomal anomalies was identified (43.5%) as in the present study.

DE represents the second group of severe lesion of embryogenesis, and we detected 51.4% chromosomal anomalies in this group (Table 2). The most frequent chromosomal aberration in this group was autosomal trisomy (40%), followed by triploidy (8.6%).

We detected only a small number of EF in our study (11) with a low cultivation success, and therefore the presented results have only limited informative value. Nevertheless, in three of them (50%) a chromosomal anomaly was detected: two autosomal trisomies and one monosomy X.

In the group of FF (66 cases), we detected a chromosomal anomaly in 28.8%, representing twice the frequency detected in a previous study (Vojtaššák et al. 1995) , i.e. 12.1%, and a 15 times higher rate than the incidence in newborns (2%). Again, the most frequent chromosomal anomaly was autosomal trisomy (15.2%). We detected sporadically also cases of monosomy X (1.5%), triploidy (3%), structural aberrations (3%) and mosaics (4.5%).

Generally speaking, every third developmental defect is caused by a specific chromosomal anomaly. The spectrum is wider than in newborns and the attempts to create a specific syndromology have failed because the phenotypic expression of specific chromosomal anomaly is more variable in the time of early intrauterine development than in newborns.

Table 2. Morphological groups of 1488 spontaneous abortions and stillbirths and their karyotypes (969)

Morphological group	Total No.	Karyotyped	row %	Normal karyotype	row %	Trisomy of autosomes	row %	Trisomy of gonosomes	row %	Monosomy of autosomes	row %	Monosomy of gonosomes	row %	3n	row %	4n	row %	Structural aberrations	row %	Mosaic normal/abnormal	row %	Mosaic normal/abnormal	row %
Ies	59	30	3.1	17	56.7	4	13.3	0	0	0	0	0	0	2	6.7	1	3.3	0	0	5	16.7	1	3.3
RS	171	97	10.0	56	57.7	27	27.8	0	0	2	2.1	2	2.1	4	4.1	1	1.0	2	2.1	3	3.1	0	0
DE	51	35	3.6	17	48.6	14	40.0	0	0	0	0	1	2.9	3	8.6	0	0	0	0	0	0	0	0
EF	11	6	0.6	3	50.0	2	33.3	0	0	0	0	1	16.7	0	0	0	0	0	0	0	0	0	0
FF	94	66	6.8	47	71.2	10	15.2	1	1.5	0	0	1	1.5	2	3.0	0	0	2	3.0	3	4.5	0	0
F	348	198	20.4	130	65.7	24	12.1	2	1.0	0	0	7	3.5	24	12.1	2	1.0	1	0.5	6	3.0	2	1.0
RSC	311	215	22.2	109	50.7	54	25.1	2	1.8	0	0	30	14.0	15	7.0	1	0.5	1	0.5	2	0.9	1	0.5
EN	42	22	2.3	6	27.3	1	4.5	0	0	0	0	3	13.6	12	54.5	0	0	0	0	0	0	0	0
FN	178	146	15.1	132	90.4	5	3.4	1	0.7	0	0	1	0.7	1	0.7	1	0.7	3	2.1	2	1.4	0	0
IE	41	30	3.1	16	53.3	3	10.0	0	0	0	0	7	23.3	3	10.0	0	0	1	3.3	0	0	0	0
IF	182	124	12.8	110	88.7	7	5.6	0	0	0	0	3	2.4	2	1.6	1	0.8	0	0.0	1	0.8	0	0
Total	1488	969	65.1	643	66.4	151	46.3	6	1.8	2	0.6	56	17.2	68	20.9	7	2.2	10	3.1	22	6.7	4	1.2

Spontaneous abortions contain a high concentration and wide spectrum of developmental defects, which in one half of them are caused by a specific chromosomal aberration as the most frequent etiological factor observed. The etiology of the other defects is still mostly unrecognised. The frequency of developmental defects in this period of human reproduction is 10 to 15 times higher than in newborns. It could thus be an optimal source of information for the study of human embryogenesis.

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