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ORIGINAL ARTICLE

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Malformations in newborn: results based on 30940 infants and fetuses from the Mainz congenital birth defect monitoring system (1990–1998)

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Abstract Prevalence rates of birth defects in the Federal Republic of Germany are informative to assess the general background risk of having a child with a birth defect. They provide basic figures to determine temporal and regional prevalence trends, to evaluate and initiate preventive measures and to initiate research projects. To avoid observer, definition and collection bias, active monitoring systems are required. Data collected in the active monitoring system of the Mainz Birth Defects Registry are presented. From 1990–1998, 30940 live-births, stillbirths and abortions underwent standardized physical and sonographic examinations. Anamnestic data were collected from prenatal care records, maternity files and hospital records. Major malformations were diagnosed in 2144 (6.9%) and mild errors of morphogenesis in 11104 (35.8%) of all infants. Risk factors associated with the occurrence of major malformations were identified by comparing anamnestic data from infants with and without major malformations. Using multivariate regression models, statistically significant associations were established for 9 risk factors. Causally related risk factors were parents or siblings with malformations, parental consanguinity, more than 3 minor errors of morphogenesis in the proband, maternal diabetes mellitus and ingestion of antiallergic drugs in the first trimester of pregnancy. Conjunctional risk factors were polyhydramnios, oligohydramnios and gestational age <32 weeks at birth. Using these risk factors, populations at risk for the occurrence of major malformation can be identified.

Keywords Malformation · Congenital birth defect

Introduction

Major birth defects are diagnosed in four (passive surveillance systems) to eight per cent (active surveillance systems) of infants. Malformations are the single leading cause of infant mortality in the western hemisphere. Children with birth defects account for about one third of all pediatric admissions [15, 28]. Optimal treatment and prevention of congenital malformations as well as adequate care of these children and counseling of their families are essential tasks of pediatrics.

In more than 60 per cent of cases the etiology of congenital birth defects is not known and primary prevention is impossible. In about 20 per cent the causes are monogeneous defects, in 5–10 per cent chromosome aberrations and in 2–10 per cent virus infections [11, 33].

Epidemiological data about congenital malformations is of vital importance for scientific research on pathomorphogenesis, for prevention and public health education.

In this study we analyzed a population based birth cohort to identify prevalence rates of major and minor malformations. In addition, we attempted to establish prevalence odds ratios to determine risk factors for congenital malformations.

Objectives, Methods and Probands

The Mainz birth defect monitoring system, the ‘‘Mainz Model” was launched in 1990. Its basic goals are summarized in Table 1. Surveillance systems for congenital malformations provide numerical data (e.g. prevalence figures), analyze epidemiological data (e.g. risk factors for congenital birth defects), establish and verify preventive measures (e.g. periconceptional folic acid), and provide quality control (e.g. sensitivity of prenatal ultrasound examinations).

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Table 1 Requirements of birth registries

- Registration of time trends (early warning system)
- Registration of regional trends (cluster)
- Contribution to malformation research
- Approaches to determining causality
- Approaches to prevention
- Instrument of quality control
- Planning of governmental health measures

Table 2 Objectives of the Mainz birth registry

- Complete and continuous registration
- Registration of all types of malformations
- Objective registration criteria
- Inclusion of livebirths, stillbirths and abortions
- Anamnestic data 6 weeks before birth
- Population based registration
- Exact definitions of the malformations
- Standardized examination procedure
- Qualified and specially trained investigators
- Prospective study design
- Accordance with data protection rules and professional secrecy

The complete and continuous registration of birth defects in livebirths, stillbirths and abortions is the basis to identify temporal and/or regional trends of prevalence. All types and combinations of birth defects have to be registered in order to avoid selection bias while recognizing new malformations and frequency fluctuations of known defects. Objective registration criteria are required to avoid external influences (e.g. press or television reports on specific malformations), thus ensuring the identification of true increases or clusters. Data about the pregnancies should be collected several weeks before birth to avoid recall bias. Exact definitions of the malformations, a standardized examination procedure (check list), qualified and specially trained investigators, as well as a population based prospective study design are mandatory (Table 2).

The described requirements and objectives of birth registries can be met by active rather than passive surveillance systems. In active systems, the newborn are examined by specially trained physicians, who diagnose, classify and encode the malformations. In passive registries, different individuals (e.g. physicians, midwives, nurses) and/or institutes report selected birth defects to a central registry. In most cases, the reporting persons have not examined the infants nor diagnosed the malformations themselves, having extracted information from records. In consideration of the described requirements, the Mainz registry was conceived as an active, population based birth registry.

During the study period, all livebirths, stillbirths, spontaneous abortions >15th week of gestation, and induced abortions were examined following standardized procedures. Stillbirths were defined as death after 20 weeks of gestation with a fetal weight of >500 g. The Mainz area has a population of about 400000 inhabitants. 94.9% of all newborn in the official German annual birth statistic (Statistisches Landesamt Rheinland-Pfalz, 2000) for this area were included in this study and subjected to a clinical examination and anamnestic data collection, respectively.

All neonates born in one of the three maternity hospitals in Mainz were examined within the first week of life by one of three pediatricians specially trained in neonatology, dysmorphology and clinical genetics. In addition to the clinical examination, ultrasound examination of the kidneys and the hips was performed. In cases with specific risk factors, anamnestic findings or clinical signs (e.g. microcephaly, sibling with congenital heart defect), an ultrasound examination of the brain and/or heart was performed, and additional investigations (e.g. chromosome analysis) were done. In stillbirths and abortions pathology findings were used. Chromosome analyses were carried out in all newborn with multiple anomalies as well as in all stillbirths, induced and spontaneous abortions. The morphologic screening focussed on major malformations and mild errors of morphogenesis (MEM).

Major malformations were defined as structural defects of the body and/or the organs, which affect viability and quality of life and which require medical intervention (e.g. spina bifida, heart defect, cleft lip and palate). MEM are minor malformations and/or informative morphogenetic variants that do not affect viability or quality of life and do not need therapeutic intervention (e.g. simian crease, preauricular tag). Major malformations were recorded according to EUROCAT (**Eu**ropean **R**egistration **o**f **c**ongenital **a**nomalies and **t**wins is a concerted action of the European Union) [6] and the International Clearinghouse for Birth Defects Monitoring System [10]. MEM were defined according to Méhes [18] and Aase [1]. Anamnestic and prenatal data were obtained from the prenatal records provided by gynecologists, from the histories recorded by the delivery hospital staff approximately six weeks prior to birth, as well as from the maternity files. The data included information on family history, social status, course of pregnancy, and environmental factors.

To determine significant associations between malformations and risk factors, we calculated prevalence odds ratios by comparing the anamnestic data of cases with those of controls. ‘‘Cases” were defined as neonates with major malformations (n=2144); ‘‘controls” were all newborns without major malformations (n=28796). Logistic regression models [2, 7] were used to calculate odds ratios (OR) as approximation of relative risks with 95% confidence intervals (CI). Associations of birth defects with causal or conjunctional risk factors were tested for statistical significance. ‘‘Causal” risk factors were defined as factors known to be involved in the causation of malformations (e.g. positive family history, toxic substances). ”Conjunctional” risk factors were defined as factors occurring in conjunction with malformations but not known to have causative significance (e.g. polyhydramnios).

Table 3 Study population Mainz congenital birth registry (1990–1998)

	Male		Female		Number	
	n	[%]	n	[%]	n	[%]
Livebirths	15534	51.0	14925	49.0	30459	98.4
Stillbirths	98	54.2	83	45.8	181	0.6
Spontaneous abortions	81	41.1	116	58.9	197	0.7
Induced abortions	47	45.6	56	54.4	103	0.3
Total	15760	50.9	15180	49.1	30940	100

Results

Descriptive results

During the study period of nine years (1990–1998) we examined 30940 newborn infants and fetuses following the described procedure. The descriptive data are summarized in Table 3. 29855 (96.5%) of all newborns were singleton. There were 518 twins, 15 triplets and 1 quadruplet. The mean maternal age in this birth cohort was 28.7 years; 237 (0.8%) of women were younger than 18 years and 2672 (8.4%) older than 35 years. Ultrasound examinations of the kidneys were performed in 27700 (1.1% with pathologic findings), of the hips in 17983 (1.4% with pathologic findings), and of the brain

Table 4 Prevalence rates of major malformations according organ categories comparison of Mainz and EUROCAT – diagnosis-based distribution

Organ categories (/10000 infants)	Mainz 1990–1998	EUROCAT 1980–1994
Musculoskeletal system	239	74
Internal urogenital system	162	33
Cardiovascular system	113	59
Digestive system	71	27
Central nervous system	68	22
External urogenital system	58	15
Facial clefts	44	15
Chromosome aberrations	42	29
Ear	13	5
Eye	12	6

Study population: 30940 infants, Mainz, 1990–1998; 2144 (6.9%) infants with major malformations

Table 5 Prevalence rates of mild errors of morphogenesis (MEM) comparison of Mainz data and study by Méhes – diagnosis-based distribution

MEM (/100 infants)	Mainz 1990–1998	Méhes 1988
Sydney line	7.3	1.1
Auricular pit(s)	7.2	0.2
Short hallux	5.5	0.5
Diastasis recti	4.0	1.0
Simian crease	2.7	4.0
Haemangioma	2.5	1.0
Sacral sinus	1.3	1.0
Naevi	0.9	0.5
Preauricular tag(s)	0.9	0.6
Syndactyly (2/3 of toes)	0.8	0.5
Preauricular sinus	0.7	0.2

Study population: 30940 infants, Mainz, 1990–1998; 11104 (35.8%) infants with MEM

Fig. 6 Univariate odds ratios (OR) with 95 per cent confidence intervals (CI) for causal risk factors and major malformations

Causal risk factor	OR	CI
Parent with malformation	*6.8*	*3.3–13.8*
Sibling with malformation	*2.1*	*1.5–2.9*
Consanguinity	*3.1*	*2.0–4.6*
Maternal age >35 years	*1.2*	*1.0–1.3*
Paternal age >50 years	1.1	0.6–1.9
Diabetes mellitus	*3.0*	*2.1–4.2*
Severe maternal disease	1.1	0.9–1.2
Maternal obesity	1.1	0.9–1.3
Maternal medication (1st trimester)	1.1	0.9–1.3
Antiallergics (1st trimester)	*2.3*	*1.1–4.9*
Alcohol abuse	2.6	0.9–7.5
Nicotine abuse	1.0	0.9–1.2
Drug abuse	0.2	0.1–1.4
>3 MEM	*3.8*	*2.9–5.0*

Study population: 30940 infants, Mainz, 1990–1998; 2144 cases and 28796 controls

Table 7 Univariate odds ratios (OR) with 95 per cent confidence intervals (CI) for conjunctional risk factors and major malformations

Conjunctional risk factor	OR	CI
Polyhydramnios	*6.0*	*4.1–8.6*
Oligohydramnios	*3.4*	*2.5–4.7*
Placental insufficiency	*1.6*	*1.2–2.2*
Gestational diabetes	*1.6*	*1.0–2.6*
Premature labour	*1.5*	*1.1–2.3*
Vaginal bleeding	*1.2*	*1.0–1.4*
Hypertonia	1.0	0.8–1.3
Pre-eclampsia	1.4	0.9–2.3
Urinary tract infection	1.0	0.8–1.3
Anemia	0.9	0.7–1.2
Gestational age <28th week	*8.1*	*6.7–9.9*
Gestational age <32nd week	*3.9*	*3.0–4.9*
Monocygotic twins	1.1	0.9–1.5
Multiple pregnancy	0.9	0.8–1.3

Study population: 30940 infants, Mainz, 1990–1998; 2144 cases and 28796 controls

Table 8 Statistical significant increased multivariate odds ratios (OR) with 95 per cent confidence intervals (CI) for risk factors and major malformations

Risk factor	OR	95% CI
Parent with malformation	5.8	2.8–12.2
Sibling with malformation	5.8	2.7–12.2
>3 MEM	3.2	2.5–4.2
Diabetes mellitus	3.0	2.1–4.3
Antiallergics (1st trimenon)	2.7	1.4–5.3
Consanguinity	2.6	1.7–4.0
Polyhydramnios	4.1	2.8–6.0
Oligohydramnios	2.4	1.7–3.3
Gestational age <32nd week	3.4	3.0–3.8

Study population: 30940 infants, Mainz, 1990–1998; 2144 cases and 28796 controls

in 1595 (5.1% with pathologic findings) of all live-births.

2144 (6.9%) children had major malformations. The prevalence rates of major malformations (per 10000 births; diagnosis-based distribution) according organ categories are shown in Table 4, together with the (passively collected) data of EUROCAT. Malformations of the musculoskeletal, the internal urogenital, and the cardiovascular system accounted for more than 60% of all major malformations. In 11104 (35.8%) of all infants mild errors of morphogenesis (MEM) were diagnosed. Prevalence figures for vaious MEM (per 100 births) are listed in Table 5.

Associations between major malformations and risk factors

Results of the univariate analyses for causal risk factors are shown in Table 6, those for conjunctional risk factors in Table 7.

Multivariate logistic regression models (Table 8) showed significant associations between major malfor-

mations, six causal and three conjunctional risk factors, respectively.

Discussion

The composition of this population-based birth cohort from Mainz is in accordance with the expected figures for Europe [6] as regards the number of stillbirths, induced abortions, multiple pregnancies, distribution of gender, and mean maternal age. The overall prevalence of 6.9% for major malformations in Mainz is within the range reported by active birth registries [15]. It is much higher than prevalence of 2.4% provided by the EUROCAT registration which is in the lower range of other passive registries [10]. Passive monitoring services collect only approximately 50% of the true number of congenital malformations [15, 22, 24]. Reasons to explain the lower prevalence data reported by passive registries have been mentioned above. In addition, our prevalence is higher due to the inclusion of abnormalities noted by ultrasound and special studies. Thus, malformations of the internal urogenital system were diagnosed in 1.6% of all infants by ultrasound within the first week of life compared with 0.33% of infants in the EUROCAT registry in which ultrasound examinations were done less regularly. The prevalence of renal defects in Mainz corresponds to figures reported in the literature [13, 26, 27]. The inclusion of stillbirths and abortions in the monitoring system, as well as the careful, continuous registration and systematic coding increased the prevalence figures. However, the frequency of chromosome aberrations is the same in Mainz and EUROCAT demonstrating that the higher overall frequency of malformations reflects a higher clinical ascertainment rate rather than a higher local morbidity.

The prevalence of mild errors of morphogenesis (MEM) was 36.8% and outside the range of 14.7% to 21.0% reported by others [14, 16, 18, 20]. However, figures similar to ours were reported by Holmes et al. [8], who published 39.9%. The difference between the higher and lower figures is explained by the higher ascertainment rate in active registries by specially trained personal; as well as the types and numbers of MEM included in the surveillance protocols. It should be stressed that most MEM can be regarded as variants of morphogenesis without pathogenic significance. Only if they occur in clusters or in association with major malformations and/or mental deficiency can they be regarded as indicators of a pathological development [17, 19, 30].

Epidemiological associations between congenital anomalies and anamnestic risk factors have been previously reported [4, 5, 21, 23, 29, 31, 32]. They identify predictive factors and thus define populations at risk for birth defects.

The calculated prevalence odds ratios confirm well known associations between anamnestic data (e.g. consanguinity, hydramnios) and major malformations, in addition to indirectly validating the recording system. They generate new hypotheses to be tested in future studies, such as the relationship between maternal intake of antiallergic substances within the first trimester of pregnancy and birth defects. The minimal difference between the results of the uni- and multivariate analysis reflects the validity of the Mainz data based on a birth cohort of more than 30000 infants. The increased odds ratios identify populations at risk for major malformations and contradict the hypothesis that the majority of fetal birth defects occur in pregnancies without specific risks [3].

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