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ORIGINAL ARTICLE

Chaim Ismail · Awi Wiesel · Reinhard W. März
Annette Queisser-Luft

Surveillance study of Sinupret in comparison with data of the Mainz birth registry

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Abstract In about 80% of all pregnant women medical drugs are used during pregnancy. Phytomedicines play an important role in self- and prescribed medication. Since the thalidomide tragedy teratogenic effects of medicamentous treatment are well known. Only a few investigations and studies on the tolerability and safety of plant-based medicines in pregnancy have been published. From 1992–1997 a nationwide retrospective surveillance study of 762 pregnant women (786 newborns) was conducted to evaluate the safety of the herbal combination preparation Sinupret during pregnancy. Standardized questionnaires were used for retrospective and systematic examination of all pregnancies. All cases were treated with Sinupret for at least 24 hours. The data of the population-based Mainz birth registry were used for comparison, interpretation and evaluation of the Sinupret study. For infants with birth defects and/or clinically abnormal pregnancies single-case-analyses were performed. The study collective was representative for Germany. 13 single-case-analyses were performed. In three cases the pregnancy ended with an abortion and in one case with an intrauterine death of the fetus. Nine newborns (1.1%) were diagnosed with major malformations. The critical evaluation of the collective and the individual cases yielded no evidence of possible teratogenic and/or embryotoxic effects of the phytomedicine in 11 out of 13 cases. In the remaining two cases a causal relationship is theoretically possible but very unlikely. On the whole the study underlines the value of the pediatric epidemiologic research in malformations of the Mainz birth register for the monitoring, assessment and evaluation of pharmaceutical studies on drug safety during pregnancy.

Keywords Phytomedicine · Pregnancy · Drug safety · Surveillance study · Congenital anomalies

C. Ismail (✉) · R.W. März
Bionorica AG, Medical Science and Research II,
Kerschensteiner Str. 11–15, 92318 Neumarkt, Germany
e-mail: chaim.ismail@bionorica.de
Tel.: +49-9181-231162, Fax: +49-9181-231146

A. Wiesel · A. Queisser-Luft (✉)
Universitätskinderklinik Mainz,
Geburtenregister Mainzer Modell, Langenbeckstraße 1,
55101 Mainz, Germany
e-mail: queisser@kinder.klinik.uni-mainz.de
Tel.: +49-6131-172773, Fax: +49-6131-176693

Introduction

Major malformations (e.g. spina bifida, cleft lip and palate) are diagnosed in 5–8% of all newborns (Queißer-Luft and Spranger 1997), about one fifth of these birth defects are severe and life-threatening. Congenital malformations are structural defects of prenatal origin present at a child's birth (Warkany 1971). In at least 60% of the cases the etiology of congenital birth defects is not known. In about 20% the malformations are caused by monogeneous defects, in 5–10% by chromosome aberrations and in 2–10% by virus infections (Cornel 1993). The intrauterine development of infants may be influenced and very seriously damaged by external factors (e.g. chemical and physical noxae, use of medication during pregnancy, malnutrition, socio-ecological factors, occupational exposure). Such harmful influences may lead to malformations (Shepard 1995). Since no later than the thalidomide disaster we have been aware of the possibility of effects of medication during pregnancy (Lenz 1962; Lenz and Knapp 1962). As a result, marketing authorization for medicinal products is subject to very strict criteria. Epidemiological data from a systematic, qualitatively and quantitatively sufficient registration of congenital malformations, points for possible etiologic causes. The prevention of malformations can be determined and foundations for the investigation of scientific issues created.

Only a few studies on drug safety in pregnancy exist (Czeizel et al. 2000). With a few exceptions, the data available on the tolerability and safety of medicinal products during pregnancy come from in vitro and animal models (Schatz et al. 1997; Diav-Citrin et al. 1998;

Kulin et al. 1998; Robert et al. 1996). The results of these investigations are generally applied to humans (Neubert et al. 1987). The same also applies to bioavailability studies during pregnancy. Studies of this type exist only for a few, chemically defined substances. For plant-based preparations, which account for a large portion of medication and self-medication taken during pregnancy, such studies are almost non-existent. In Germany plant based medicines are evaluated by the responsible Federal Institute for Drugs and Medical Devices (BfArM) like chemically defined medical products according to the criteria of pharmaceutical quality, efficacy and tolerability. As long as there is no relevant documentation about safety or tolerability during pregnancy in humans, pharmaceutical companies are obligated to include a warning regarding the use of the medicinal product in the summary of product characteristics and the patient leaflet as well.

Inflammatory airway diseases are among the most frequent diseases found in general practice and also one of the most frequent diseases occurring during pregnancy. Plant-based preparations are often used for treatment of respiratory infections in pregnancy. Sinupret is one of the most frequently prescribed and used plant-based preparations for the treatment of respiratory ailments in the Federal Republic of Germany. Sinupret (Bionorica AG, Neumarkt, Germany) is a fixed herbal combination preparation which consists of the five different plants: gentian root, primrose flowers with calyx, common sorrel herb, elder flowers and vervain herb (Neubauer and März 1994; Richstein and Mann 1980; März et al. 1999).

As regards the question of the safety of taking Sinupret during pregnancy a retrospective surveillance study was carried out by the manufacturer in comparison with a non selected prospective birth cohort (Mainz Model). The objectives of the study were to examine the correlation of morphologic abnormalities in the newborn and the maternal use of Sinupret during pregnancy as well as the critical assessment of a possible teratogenic potential and/or an embryotoxic effect of Sinupret.

Patients and methods

The collective of the surveillance study (1992 to 1997) consisted of 762 pregnant women with 786 newborns or abortions treated with Sinupret during pregnancy. The treatment with Sinupret was carried out for at least 24 hours either with Sinupret sugar coated tablets or Sinupret drops, as desired.

For the Sinupret collective 150 physicians were ascertained from the database of the Bionorica AG (Neumarkt, Germany) and have been enrolled according the predefined inclusion criteria: Medical care and treatment of pregnant women, delivery of these pregnant women, and performance of the newborn screening examinations (U1 to U3) in the same center, as well as full consent of participation in the guidelines of the study. In this selected centers all pregnant women treated with Sinupret were chosen without any further selection.

The study involved 150 physicians (study centers) from all countries of the Federal Republic of Germany: Gynecologists (78 %), general practitioner (11%), ear-nose-throat [ENT] specialists (7%), internal specialists (2%), and other specialities (2%). The recording sites were evenly divided among rural areas, small-, medium-sized, and large towns or cities. A total of 117 practices were recruited in the following counties: North Rhine-Westphalia, Bavaria, Saxony, Baden-Württemberg, Hessen, and Schleswig-Holstein while the remaining regions were spread over the rest of Germany.

All pregnancies of the Sinupret collective were examined retrospectively, following a standardized procedure. A special standardized questionnaire was developed for data collection. Maternal risk factors, anamnestic data, data on the course of pregnancy and on medical treatment as well as possible adverse drug reactions were registered. In addition, the entries in the maternal pregnancy records (Hutzler 1996) were evaluated. The results of the neonatal examinations U1 to U3 (1st day of life to 6th week after birth) were also included in the data collection and analysis (Hakosalo 1973). The questionnaire for the neonatal data followed the guidelines of the Mainz Model. The definition of major malformations is adopted from the World Health Organization. The diagnostic classification of the deformities was based on ICD-10 (DIMDI 1994).

For the interpretation and evaluation of the results of the Sinupret study the data of the active prospective population-based Mainz congenital birth registry for congenital malformations (Mainz Model) was used for comparison. The Mainz Model represents a birth cohort, which includes 94.8% of all births in the region of Rheinhessen and therefore valid prevalence rates of malformations as well as anamnestic risk factors are calculated. For the cases with clinically abnormal pregnancies and/or newborns further special analyses of the individual cases were carried out. In the analyses of the individual cases the temporal relationships between maternal intake of Sinupret and the sensitive phase of pregnancy as well as the additional presence of anamnestic risk factors (e.g. malformations in the family, maternal age, pathological laboratory parameters) were examined.

The Mainz Model was launched in 1990. All children born (approx. 3,800 per year) in the maternity hospitals of Mainz are examined clinically and sonographically during the first week of life according to a standardized procedure by pediatricians specially trained in neonatology and clinical genetics. Major malformations and mild errors of morphogenesis are registered with special care. Parallel to the clinical examination, data on the family medical history, history of the pregnancy, social anamnesis as well as general exposure data (e.g. medicines, nicotine, alcohol, drugs) is taken from the maternal pregnancy records and the gynecological patient files. These anamnestic data are collected about six weeks before birth. Stillbirths, spontaneous abortions as well as induced abortions are included in the survey by findings from the pathology department[1]. The anamnestic data are coded, documented and evaluated together with the examination findings in a strictly anonymous form – with complete observance of data protection laws and professional secrecy[2].

The statistical analyses of the data were performed by the SAS statistical software package. The odds ratios (OR) with 95%-confidence intervals (95% CI) were calculated in univariate analyses to illustrate the differences and similarities between the study collective and the Mainz birth cohort.

Results

The surveillance study documented a total of 762 pregnancies with Sinupret intake from 1992 to 1997. 59.4% (454) of these pregnant women were treated with Sinupret exclusively for sinusitis, 20.2% (154) exclusively for bronchitis and 20.2% (154) for both ailments (sinubron-

[1] Pediatric pathology Johannes Gutenberg-Universität Mainz (Director: Prof. H. Müntefering)

[2] Department of Epidemiology of the German Cancer Research Center, Heidelberg (Director: Prof. J. Wahrendorf)

Table 1 Anamnestic risk factors: comparison between the study collective and the Mainz birth cohort (*OR* odds ratio, *CI* 95% confidence interval)

Risk factors	Study collective (%)	Mainz model (%)	Comparison	
			OR	CI
Family-related risks	14.6	12.7	1.2	(0.96–1.44)
Severe disease of mother	8.9	9.4	1.0	(0.73–1.22)
Age of mother >35	8.0	14.7	0.5	(0.39–0.66)
Age of mother <18	0.7	0.6	1.1	(0.45–2.70)
Obesity (BMI >30)	9.8	3.5	2.9	(2.23–3.71)
Treatment for infertility	4.2	3.3	1.3	(0.90–1.85)
Multiple pregnancy	2.9	1.5	1.9	(1.26–3.03)
Placental insufficiency	1.6	1.6	0.9	(0.55–2.19)
Premature labor	14.2	8.5	1.8	(1.44–2.19)
Arterial hypertension	2.6	2.8	1.0	(0.60–1.47)
Proteinuria	0.8	1.2	1.0	(0.50–1.92)
Nicotine abuse	11.8	8.6	1.4	(1.14–1.78)
Alcohol abuse	0.1	0.1	1.2	(0.16–8.97)

Table 2 Analyses of the individual cases of the study collective: causal relationship of the documented disorders of the pregnancy and maternal use of Sinupret

Patient	Defect	Category	Week of gestation Sinupret intake	Causal
1	Abortion, 8th week	Abortion	6–7	Improbable
2	Abortion twin, 8th week	Abortion	19–20	Excluded
3	Abortion triplet, 8th week	Abortion	35–36	Excluded
4	Stillbirth twin, 39th week	Stillbirth	19–20, +30	Excluded
5	Talipes calcaneus	Deformation	16–16	Excluded
6	Talipes calcaneus	Deformation	25–26	Excluded
7	Talipes adductus	Deformation	20	Excluded
8	Talipes equinovarus	Malformation, deformation	32–35	Excluded
9	Renal duplication	Malformation	12–14	Excluded
10	Cleft lip	Malformation	14–16	Excluded
11	SUA	Malformation	21	Improbable
12	Aplasia of corpus-callosum laryngo-tracheomalacia	Malformation (syndrome)	22–23	Excluded
13	Trisomy 21	Chromosomal aberration	25–26	Excluded

chitis). The mean duration of treatment was 10.4 days for sinusitis, 11.8 days for bronchitis and 11.9 days for the combination of the two ailments. The choice of the dosage form of Sinupret (sugar coated tablets or drops) corresponded to the market situation in Germany and the treatment duration and/or dosage of the medicinal product largely to the manufacturer's recommendation.

The documentation of the medication during pregnancy yielded that 30.6% of the patients had been prescribed other medicinal products in addition to Sinupret for the treatment of the sinusitis and/or bronchitis. The additional medication illustrates the medicamentous options for the treatment of sinusitis or bronchitis: Other plant-based products were used in 11.9%, antibiotics in 4.1%, decongestant nasal drops in 3.9%, non-steroidal analgesics in 3.4%, homeopathic drugs in 3.5%, and chemically defined secretolytic agents were prescribed in 2.4% of the cases.

Compared to the Mainz birth registry the distribution of the study collective was found to be nearly equal. The average maternal age of the Sinupret collective was 28.8 years and that of the Mainz cohort 28,7. First pregnancies accounted for 41.2%, second for 31.4% and third for 12.1% of all gravidities. The statistical mean for the duration of pregnancy was 39.6 weeks in the Sinupret collective and 39.2 weeks of gestation in the Mainz collective. At first sight the proportion of complicated pregnancies appeared relatively high (22.3%), but it was dominated by the risk factor "premature labor" which was documented in 14.2% of all pregnancies of the study collective. The comparison of the documented anamnestic risk factors was summarized in Table 1.

The following parameters demonstrated higher percentages in the study group and showed statistically significant deviations from the collective of the Mainz Model: Pregnant women with obesity (body mass index >30 at the begin of pregnancy), multiple pregnancies (22 twin pregnancies and one triplet pregnancy; a total of 2.9%), premature labor, and nicotine abuse. A significantly lower percentage was identified for mothers >35 years. All other tested pregnancy risks showed no significant differences (table 1).

From 762 included pregnancies 786 newborns (782 livebirths, three abortions, and one stillbirth) were documented. The distribution of gender reflects the well known androtropy (51.7% male and 48.3% female infants). The somatic parameters birth weight, body length and head circumference differed not from that of the

Mainz birth cohort and were located within the standard curves and standard references for West-European infants (Brandt 1986).

Congenital malformations and/or chromosome aberrations were diagnosed in six and deformities in three newborns of the Sinupret collective. The proportion of newborns with birth defects is 1.1%. Three pregnancies ended prematurely by spontaneous abortions and one with intrauterine death of the fetus. These specific 13 individual cases were examined in separate analyses. In one of the four pregnancies which ended in abortion or stillbirth, a temporal correlation between the maternal treatment with Sinupret and fetal outcome should be discussed. In 8 out of the 9 newborns with deformations, malformations and/or with chromosome aberrations a causal relationship could be completely ruled out. In one infant with single umbilical artery (SUA) the association between Sinupret intake and the present malformation was theoretically possible but not likely. The results of the individual case analyses are summarized in Table 2.

Discussion

Inflammatory diseases of the airways are among the most frequent ailments. The number of respiratory diseases differs between the various age groups and is about 2,500 cases per year per 1,000 inhabitants. According to Bhandari (1984), the incidence in women of the 21–30 age group is 2.12 "colds" per year and in the 31–40 age group 1.99 colds per year. The same author gives an incidence of 8.3% for women for the complications of acute airways diseases (sinusitis, bronchitis, sinubronchitis). In Germany, plant-based preparations (e.g. Sinupret) are often prescribed for these group of ailments. The present study was performed to enable a statement concerning the safety and teratogenic potential of the plant-based drug Sinupret in pregnancy.

For ethical reasons, owing to the large numbers of cases and the methodical impossibility of proving the absolute safety of a medicinal product during pregnancy, the retrospective analysis of systematically collected, structured individual case data was given preference over a prospective study design. A controlled study (active control, placebo or without treatment) in the form of an equivalence study would require tens or hundreds of thousands of cases. A controlled study with only "a few" thousand cases would only have been able to reveal or exclude a drastically raised risk of malformation which after the decades of positive clinical experience with the medicinal product would not to be expected anyway. A real control group (pregnant women with sinusitis or bronchitis, untreated or treated with a specific medication) would not be definable and therefore not possible.

The study approach of a retrospective, systematic surveillance study without a control group yields possible method-related biases such as a lack of relation to the population, selection by the reporting physicians. Heterogeneity of the investigators and documenting physicians, absence of a standardized study plan for the newborns and absence of uniform definitions of the malformations limits the study. The number of cases of 762 documented pregnancies is to be considered small for an epidemiological study, but sufficient as a collection of case observations.

It is to be assumed that there is a selection bias in the study collective. Pregnant women were selected only on the basis of whether or not they were taking Sinupret while pregnant. Since no other inclusion or exclusion criteria were applied, the risk of deliberate patient selection was minimized.

In comparison to the collective of the Mainz model and the information given in the literature, the study collective corresponds with the average conditions in Germany (Bayerische Landesärztekammer 1994; Queißer-Luft et al. 1996).

The documented medication in pregnancy due to other ailments than sinusitis/ bronchitis corresponded to the expectations for the respective indications and agrees with study results in the Federal Republic of Germany (Queisser-Luft and Spranger 1997).

For a few risk factors (Table 1) significantly higher figures were identified in the study group. Epidemiological associations between congenital anomalies and anamnestic risk factors have been previously reported (Chowchock et al. 1980; D'Alton and DeCherney 1993; Nora 1993; Queisser-Luft et al. 1996; Shepard 1995; Stoll et al. 1989; Stoltenberg et al. 1999). They are used to describe high risk populations for birth defects. Anamnestic risk factors are of two different types: Cause related (anamnestic risks reflecting causal factors of malformations) and conjunctional (anamnestic risks indicating a pathological process) risk factors. Multiple pregnancies and premature labor reflect sequential risk factors without any causal influence on the development of malformations. In the case of the newborns, an increased proportion of multiple births children is remarkable. The relatively high incidence of premature labor in the Sinupret study is comparable with the data obtained from mothers in another pregnancy collective (Jahn and Berle 1996).

Nicotine abuse and maternal obesity belong to causal risk factors. In the literature associations between fetal malformations and maternal nicotine abuse during pregnancy are often discussed (Kallen 2000; Wyszynski et al. 1997). Although the data of this study were taken from the maternal pregnancy records (Jahn) the nicotine consumption in the study collective was distinctly higher than in the compared surveys (Pineda-del Villar et al. 1994; Queißer-Luft et al. 1994), Maternal obesity is in discussion as a causal risk factor for major malformations e.g. neural tube defects (Queißer-Luft et al. 1998; Shaw et al. 1996). The same applies to the age distribution of the pregnant women, particularly the under 18 and the over 35 age groups which have been identified as a high-risk group for congenital malformations (Pineda-del Villar et al. 1994; Queißer-Luft et al. 1994). The lower percentage of mothers >35 years the Sinupret

group corresponds with the low prevalence of chromosomal aberrations.

With a systematic examination of newborns, stillborn babies and abortions one would expect a prevalence of malformations of about 2–3% in passive (EUROCAT 1997) and about 6–7% in active (Lynberg and Edmonds 1992) registries. The number of nine newborns with malformations per 783 newborns corresponds to 1.1% and is below the expected value. A comparison to systematic surveys of malformations is only possible to a restricted extent.

The small number of cases in the study collective and the biases mentioned above, as well as all the absence of a standardized examination procedure for the newborns, and the difference in the level of training of the investigators, must be regarded as causes for the differences in the prevalence of malformations. These requirements are met by active data collection systems where complete data can be obtained. Therefore the assessment of the individual cases in comparison to historical controls from the literature is performed.

In three out of four pregnancies, which ended in abortion or intrauterine death of the fetus, there were no temporal and/or causal relationship between the intake of Sinupret and the outcome. In one case the abortion took place shortly after the treatment with Sinupret so that a temporal correlation might be possible theoretically. A causal relationship cannot be ruled out totally, although other risk factors (e.g. a existing infection of the mother, an imminent abortion) are more probable.

In the case of the newborn with clubfoot an etiological connection with the consumption of Sinupret is highly unlikely, but can be constructed theoretically. The Sinupret intake was late in pregnancy, the time of gestation at which clubfeet occur as result of exogenous influences (e.g. oligohydramnios). A possible enteroviral infection of the mother during early weeks of pregnancy or nicotine abuse should be discussed as known risk factors (Pryor et al. 1991; Van den Eden et al. 1990). A causal relationship In the infant with single umbilical artery with the Sinupret intake (21st week of gestation) cannot be excluded. Mostly, a single umbilical artery occurs early in pregnancy but in rare cases secondary obliterations late in pregnancy have been described (Heifetz 1996; Saller et al. 1990). An etiological connection with possible causal factors such as nicotine abuse, virus infection and treatment of paternal infertility must be discussed (Blackburn and Cooley 1993; Horta et al. 1997). In the children with deformations the pathogenesis of the birth defect excludes a causal relationship (Spranger et al. 1982) In all other cases with malformations and/or with the chromosome aberrations the phytomedicine was taken after completion of organogenesis and exclude an etiological connection.

The analyses of the individual cases indicate that other risk factors like viral or bacterial infections during pregnancy may be causes of congenital malformations (MacKenzie and Houghton 1974; Koskomies et al. 1978). The evaluation of the reports on individual basis did not display any certain, concentrated pattern of malformations or disorders. Only in one case was a temporal connection between the time when Sinupret was taken and the possible consequence, but it was not possible to conclude a causal relationship. In summary it may be stated that the analysis of the data from the present surveillance study reveals no evidence of a possible teratogenic and/or embryotoxic effect of the phytomedicine.

Conclusions

The study underlines the value of pediatric epidemiological research on malformations for monitoring and assessment of pharmaceutical studies on drug safety during pregnancy. Only a few studies on drug safety of herbal preparations in pregnancy exist. Possible etiological causes of congenital malformations can be determined by epidemiological studies and thus prevented. On the other hand safety and tolerability of medication during pregnancy can be assured. The cooperation between Bionorica and the birth registry focused on the critical evaluation of the recruited study collective and the analyses of the single cases with abnormal course of pregnancy or birth defects. A reasonable correlation between the intake of Sinupret and teratogenic or embryotoxic effects was not proven. Other possible anamnestic risk factors having no causal relationship to the studied medication appear more evident.

References

Bayerische Landesärztekammer, Kassenärztliche Vereinigung Bayerns (1994) Kommission für Perinatologie und Neonatologie: BPE Jahresbericht 1993. Munich

Bhandari M (1984) Epidemiologische Studie über die Verbreitung von Erkältungskrankheiten in Allgemeinpraxen des Raumes Marburg-Biedenkopf. Haag und Herrchen, Frankfurt, pp 27–28

Blackburn W, Cooley NR (1993) The umbilical cord. In: Stevenson RE, Hall JG, Goodman RM (eds) Human malformations and related anomalies. Oxford Monographs on Medical Genetics 27, pp 1081–1141

Brandt I (1986) Human growth. Developmental biology, prenatal growth. Plenum Press, New York

Chowchock S, Ainbender E, Presscott G (1980) The recurrence risk for neural tube defects in the United States: a collaborative study. Am J Med Genet 5: 309–314

Cornel MC (1993) Registration and prevention of congenital anomalies. Thesis, Rijksuniversiteit, Groningen

Czeizel AE, Rockenbauer M, Olsen J, Sørensen HAT (2000) Oral phenoxymethylpenicillin treatment during pregnancy. Arch Gynecol Obstet 263: 178–181

D'Alton ME, DeCherney AH (1993) Prenatal diagnosis. N Engl J Med 328: 114–120

DIMDI [Department of Epidemiology of the German Cancer Research Center Heidelberg/Deutsches Institut für Medizinische Dokumentation und Information] (1994) ICD 10. Internationale statistische Klassifikation der Krankheiten und verwandter Gesundheitsprobleme, 10th revised edn, Vol 1. Systematisches Verzeichnis. Urban & Schwarzenberg, Munich, pp 779–835

Diav-Citrin O, Park YH, Veerasuntharam G, Polachek H, Bologa M, Pastuszak A, Koren G (1998) The safety of mesalamine in human pregnancy: a prospective controlled cohort study. Gastroenterology 114: 23–28

EUROCAT (1997) Report 7. Surveillance of congenital anomalies (1980–1994). Scientific Institute of Public Health – Louis Pasteur, Brussels

Hakosalo JK (1973) Cumulative detection rates of congenital malformations in a ten year follow-up study. Acta Pathol Microbiol Scand Suppl 242: 1–59

Heifetz SA (1996) The umbilical cord: obstetrically important lesions. Clin Obstet Gynecol 39: 571–587

Horta BL, Vitora CG, Menezes AM, Halpern R, Barros FC (1997) Low birthweight, preterm birth and intrauterine growth retardation in relation to maternal smoking. Paediatr Perinat Epidemiol 11: 140–151

Hutzler D (1996) Überarbeitete Neuauflage des Mutterpasses 1996. Dtsch Ärzteblatt 93: 1980–1987

Jahn A, Berle P (1996) Zur Qualität antepartaler Daten in der Hessischen Perinatalerhebung. Ein Vergleich mit Angaben im Mutterpaß und Ergebnissen einer Schwangerenbefragung. Geburtshilfe Frauenheilkd 56: 132–138

Kallen K (2000) Multiple malformations and maternal smoking. Paediatr Perinatal Epidemiol 14: 227–233

Koskomies O, Lapinleimu K, Saxèn L (1978) Infections and other maternal factors as risk indicators for congenital malformations: a case-control study with paired serum samples. Pediatrics 61: 832–837

Kulin NA, Pastuszak A, Sage SR, Schick-Boschetto B, Spivey G, Feldkamp M, Ormond K, Matsui D, Stein-Schechman AK, Cook L, Brochu J, Rieder M, Koren G(1998) Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors: a prospective controlled multicenter study. JAMA 279: 609–610

Lenz W (1962) Thalidomide and congenital abnormalities. Lancet I: 271–272

Lenz W, Knapp K (1962) Thalidomide embryopathy. Arch Environ Health 5: 100–105

Lynberg MC, Edmonds LD (1992) Surveillance of birth defects. In: Halperin W, Baker EL, Monson RR (eds) Public health surveillance. Van Norstrand Reinhold, New York, pp 157–177

MacKenzie JS, Houghton M (1974) Influenza infections during pregnancy: association with congenital malformations and with subsequent neoplasms in children, and potential hazards of live virus vaccines. Bacteriol Rev 38: 356–370

März RW, Ismail C, Popp MA (1999) Wirkprofil und Wirksamkeit eines pflanzlichen Kombinationspräparates zur Behandlung der Sinusitis. Wien Med Wochenschr 149: 202–208

Neubauer N, März RW (1994) Placebo-controlled, randomized double-blind clinical trial with Sinupret sugar-coated tablets on the basis of a therapy with antibiotics and decongestant nasal drops in acute sinusitis. Phytomedicine I 3: 177–181

Neubert D, Chahoud I, Platzek T, Meister R (1987) Principles and problems in assessing prenatal toxicity. Arch Toxicol 60: 238–245

Nora JJ (1993) Causes of congenital heart diseases: old and new modes, mechanisms, and models. Am Heart J 125: 1409–1419

Pineda-Del Villar L, Martinez-Basalo MC, Delgado W, Prieto-Carrasquero M, Villasmil Y (1994) Epidemiology of congenital malformations at the Hospital Pedro Garcia Clara, Ciudad Ojeda, Venezuela. Invest Clin 35: 19–34

Pryor GA, Villar RN, Ronen A, Scott PM (1991) Seasonal variation in the incidence of congenital talipes equinovarus. J Bone Joint Surg Br 73: 632–634

Queißer-Luft A, Spranger J (1997) Fehlbildungen bei Neugeborenen: Mainzer Modell. Kinderarzt 28: 1–6

Queißer-Luft A, Schläfer K, Schicketanz K-H, Spranger J (1994) Erfassung angeborener Fehlbildungen bei Neugeborenen: das Mainzer Modell. Dtsch Arztebl 11: 747–750

Queisser-Luft A, Eggers I, Stolz G, Kieninger-Baum D, Schlaefer K (1996) Serial examination of 20,248 newborn fetuses and infants: correlation between drug exposure and major malformations. Am J Med Gen 63: 268–276

Queißer-Luft A, Kieninger-Baum D, Menger H, Stolz G, Schlaefer K, Merz E (1998) Erhöht mütterliche Adipositas das Risiko für kindliche Fehlbildungen? Ultraschall Med 19: 40–44

Richstein A, Mann W (1980) Treatment of chronic rhino-sinusitis with Sinupret, a double blind prospective clinical trial. Therapie der Gegenwart 119: 1055–1060

Robert E, Musatti L, Piscitelli G, Ferrari CI (1996) Pregnancy outcome after treatment with the ergot derivate, cabergoline. Reprod Toxicol 10: 333–337

Saller DN, Keene CL, Sun C-Cj, Schwartz S (1990) The association of single umbilical artery with cytogenetic abnormal pregnancies. Am J Obstet Gynecol 163: 922–925

Schatz M, Zeiger RS, Harden K, Hoffman CC, Chilingar L, Petitti D (1997) The safety of asthma and allergy medications during pregnancy. J Allergy Clin Immunol 100: 301–306

Shaw GM, Velie EM, Schaffer D (1996) Risk of neural tube defects – affected pregnancies among obese women. J Am Med Assoc 275: 1093–1096

Shepard TH (1995) Catalog of teratogenic agents, 8th edn. The John Hopkins University Press, Baltimore

Spranger J, Benirschke K, Hall JG, Lenz W, Lowry RB, Opitz JM, Pinsky L, Schwarzacher HG, Schmith DW (1982) Errors of morphogenesis: concepts and terms. J Pediatr 100: 160–165

Stoll C, Alembik Y, Roth MP, Dott B, De Greeter B (1989) Risk factors in congenital heart disease. Eur J Epidemiol 5: 382–391

Stoltenberg C, Magnus P, Skondal A, Lie RT (1999) Consanguinity and recurrence risk of birth defects: a population based study. Am J Med Genet 82: 423–428

Van den Eden SK, Karagas MR, Daling JR, Vaughan TL (1990) A case-control study of maternal smoking and congenital malformations. Paediatr Perninat Epidemiol 4: 147–155

Warkany J (1971) Congenital malformations. Notes and comments. Year Book Medical Publisher, Chicago

Wyszynski DF, Duffy DL, Beaty TH (1997) Maternal cigarette smoking and oral clefts: a meta-analysis. Cleft Palate Craniofacial J 34: 206–210