Association of Preterm Birth With Brain Malformations

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ABSTRACT: This study investigates the rate of preterm birth in babies with congenital brain defects. Autopsy case reports of congenital brain anomalies were obtained from the literature. The control cases were from a large registry, a published report from the Metropolitan Atlanta Congenital Defects Program. From 428 publications, 1168 cases were abstracted that had autopsy studies of congenital brain defects and information on the gestational age (GA) at birth. The control data from Atlanta included 7738 infants with significant birth defects of any kind and 264,392 infants without birth defects. In the autopsy cases with brain defects, the mean GA was 36.6 wk, whereas the Atlanta data showed a mean GA of 39.3 wk for infants with no defects and a significantly shorter gestation of 38.1 wk ($p < 0.0001$) for infants with defects. In the Atlanta data, the rate of preterm birth was 9.3% for those with no defects compared with 21.5% ($p < 0.0001$) for those with defects. In the autopsy cases with brain defects, the rate of preterm birth was even greater (33.1%, $p < 0.0001$). In conclusion, these data show an association of brain defects with preterm births. (*Pediatr Res* 65: 642–646, 2009)

This study is the first to investigate the relative risk (RR) of being born preterm for infants who have a variety of congenital brain defects. Numerous studies have shown an association between congenital anomalies of any part of the body and preterm birth (1–18) or low birthweight (LBW) (19–24). For example, there were three large studies reported in 2001. Rasmussen *et al.* (14), in studies of 264,392 cases from the Metropolitan Atlanta Congenital Defects Program (MACDP), which is administered by the US Centers for Disease Control and Prevention, reported that preterm infants had a 2.43-fold increased risk of having a significant congenital defect compared with infants born at term. The risk for preterm birth in infants with defects was 21.5%, compared with 9.3% for infants without defects. Shaw *et al.* (15), in a study of 3,090,514 births from the California Birth Defects Monitoring Program, found a decreasing prevalence of birth defects with increasing gestational age (GA). Holmgren and Hogberg (16), in a study of 66,646 infants from the Swedish Medical Birth Registry, found that significant malformations were more common among infants born at 22–27 wk and 28–31 wk than at 32–36 wk. An earlier large study from the MACDP, by Mili *et al.* (12), showed an association between malformations and LBW.

An association with preterm birth or LBW has been found in several specific types of defects of the central nervous system (CNS). Creasy (25), in his textbook on maternal-fetal medicine, stated that multiple congenital anomalies and anomalies of the CNS are associated with a higher risk for preterm birth, but no references or statistics were offered. Rasmussen *et al.* (14) and Mili *et al.* (12) found an increase in preterm birth and LBW, respectively, in some defects affecting the head or CNS (anencephaly, hydrocephaly, microcephaly, encephalocele, spina bifida, microphthalmia, and cleft lip or palate), as well as syndromes that affect the brain (Down syndrome/trisomy 21, trisomy 13, and trisomy 18). Infants with anencephaly have long been known to have an abnormal profile of gestational length: there is a high incidence of both preterm and postterm birth (sometimes more than 50 wk gestation), with an overall reduction in mean gestational length (26). In infants with cleft lip or palate, there is also an increased incidence of preterm birth (27). There are similar reports for such associations with defects of other parts of the body, such as reduction limb defects (28); syndactyly (29); simian crease (30); gastroschisis and exophthalmos (31); intestinal atresia (32); congenital diaphragmatic hernia (33); esophageal atresia (34); hypospadias (35); renal agenesis (Potter's syndrome) (36); and congenital heart disease (37).

Investigating the association between congenital brain defects and preterm birth presents some challenges. Ascertainment of brain defects is difficult because they can be hidden within the cranium and may remain undetected until autopsy. Furthermore, the identification and classification of brain defects is not straightforward, as various names and descriptions are found for similar defects. Nevertheless, an extensive search of the neuropathology literature was undertaken to accumulate a large number of cases of congenital brain defects in which the GA was reported. This published autopsy data were compared with data from a large registry, the MACDP study by Rasmussen *et al.* (14), with permission. This may be the best approach at the present time.

METHODS

This is a literature review with a comparison of published cases to information in a registry, a very large population-based study by the MACDP. The cases were ascertained according to the presence of brain anomaly, and then GA was recorded.

Ascertainment of subjects. Eleven hundred sixty-eight subjects diagnosed with congenital brain defects and having information on GA at birth were ascertained from 428 publications (Supplemental table). Cases from pregnancies with multiple births were included. No subjects were included at less than

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Abbreviations: MACDP, Metropolitan Atlanta Congenital Defects Program; RR, relative risk

20 wk gestation, which is considered abortion rather than delivery. Where there were multiple brain anomalies in a subject, the most common defect was listed first. The defects were as follows (number of cases in brackets): porencephaly (209), polymicrogyria (192), multicystic encephalomalacia (117), pachygyria (112), lissencephaly (108), hydranencephaly (92), microcephaly (82), holoprosencephaly (65), anencephaly (52), hydrocephaly (27), gyral anomaly (25), corpus callosum agenesis (19), arhinencephaly (15), cerebellar anomaly (12), heterotopia (8), optic nerve hypoplasia (8), hemimegalencephaly (5), cerebellum agenesis (4), exencephaly (4), arachnoid cyst (2), encephalocele (2), megalencephaly (2), heterotopic brain (1), and massa intermedia absent (1).

The control group from the MACDP consisted of 256,654 infants reported as having no significant birth defects (14). A third group for comparison consisted of infants ascertained by the MACDP as having significant congenital defects of any kind. A detailed description of the methods for the MACDP data may be found in Rasmussen *et al.* (14). Briefly, the MACDP data included only major defects that could adversely affect the infant's health and development, and it was restricted to live-born singleton infants born in the Atlanta area from 1989 to 1995. MACDP cases were ascertained by review of hospital records of newborns and their mothers, vital records, discharge diagnoses, and cytogenetic studies. Pediatric hospital records were also reviewed to ascertain defects and to modify diagnoses after further studies. Defects had to be noted in the first year of life and diagnosed by the sixth birthday. Preterm was defined as 20 to 36 wk gestation, term as 37 to 41 wk, and postterm as 42 to 45 wk. The ascertainment of brain defects was as described earlier for defects in general. They selected 24 defects for individual analysis and these included the following defects that affect the CNS: anencephaly, spina bifida, Down syndrome, trisomy 13, and trisomy 18.

Statistical analysis. Statistical analyses were performed using the graphing and analysis program Prism (GraphPad Software, San Diego, CA). RR ratios, ORs, and 95% CIs were calculated by Prism, using Fisher's exact test in 2×2 contingency tables. The contingency tables were set up so that the two rows (representing the risk factors) were for defects and no defects and the two columns (representing outcomes) were for preterm and term plus postterm. This setup reflects the hypothesis that congenital defects are the risk factors and preterm birth is the outcome. This report focuses on RRs. ORs were always slightly higher. The main analysis included all 1168 autopsy cases. The rates of preterm birth were calculated for defects that occurred in isolation, defects that occurred multiply, and a total. In addition, analyses were performed for each of the 10 largest categories of defects.

RESULTS

The rate of preterm birth was 33.1% in the subjects with congenital brain defects. This is higher than the 9.3% rate of preterm births in infants without defects, and 21.5% in infants with serious defects in the MACDP data. Compared with infants without birth defects, the RR for preterm birth in those with brain defects was 3.565 (CI 3.283–3.872) ($p < 0.0001$) and the OR was 4.837 (CI 4.279–5.467) ($p < 0.0001$). Using the MACDP data, and preterm birth as the outcome, the RR for preterm birth in those with serious defects of any kind was 2.314 ($p < 0.0001$). In all of these analyses, there was a powerful ($p < 0.0001$) association between defects and preterm birth. Figure 1 shows the percent of subjects with brain defects, no defects, and defects of any kind, plotted against GA. The curve for brain defects is compared with those for no defects and defects of any kind from the MACDP data. The brain defects curve shows a greater shift toward preterm birth than occurs with the curve for defects of any kind.

The mean GA for subjects with brain defects was 36.6 wk compared with 38.1 wk for infants with birth defects of any kind and 39.3 wk for unaffected infants. Rasmussen *et al.* (14) reported a statistical significance of $p < 0.0001$ for the decreased GA of the infants with defects compared with those unaffected. In Figure 1, a pattern was seen of peaks occurring on even-numbered weeks in the data for infants with brain defects. The curve for the MACDP data on infants with

Figure 1. Percent of subjects with and without birth defects by GA. The solid line is for brain defects from the autopsy reports; the dashed line is for birth defects from the MACDP registry; and the dotted line is for infants without defects, from the MACDP registry.

Figure 2. The RR for birth at weekly GAs. The straight dotted line at 1.0 represents the reference data line for infants without defects (from the MACDP registry). To eliminate distortions that might arise from the saw-tooth pattern of peaks on even-numbered weeks, the data were calculated in bins of 2 wk at 1-wk intervals. The solid line is for brain defects from the autopsy reports, and the dashed line is for birth defects from the MACDP registry.

defects showed a more subtle stepwise pattern echoing the saw-tooth pattern in the brain defects curve. This pattern did not occur in the curve for infants without defects. This pattern reflects a bias for estimating the GA as an even number.

Figure 2 illustrates the pattern of the RR for birth at various GAs between 20 and 45 wk. Three curves were plotted: i) a straight line at 1.0 for the reference data for infants without defects; ii) the data on brain defects vs. data for infants without defects; and iii) the data for infants with defects of any kind. To eliminate distortions from the peaks on even-numbered weeks, the data were calculated in bins of 2 wk, *i.e.* an even week plus the adjacent odd week. This resulted in data at 1-wk intervals centered on half weeks. This graph shows a strong tendency for preterm birth in the two groups with congenital defects. The curve for defects of any kind showed an increased RR for preterm birth. The curve for brain defects also showed

an increase in RR throughout the preterm period, especially between 25 and 34 wk. The small numbers of cases before 25 wk make that data less reliable. Postterm births, as also shown in Figure 1, were fewer in the two groups with defects.

A further analysis was made of the rates of preterm birth for cases with just one brain anomaly listed, and for the 10 most numerous brain defects in this study. The number of cases with multiple brain defects was 158, 13.5% of the total. The rate of preterm birth for the 1010 cases with a single brain defect was 32.7%; the rate for total cases (1168, including multiple defects) was 33.1%; and the rate for multiple defects was 36.1%. It seems that having multiple brain defects is associated with a slightly increased rate of preterm birth. This could be interpreted as a dose effect, *i.e.* more defects leads to a higher rate of preterm birth.

The most common defect, porencephaly, had a preterm birth rate of 30.9% for the 175 cases with porencephaly only, which is slightly less than the 32.7% rate for all cases that had a single brain defect. The other brain defects, in order of highest rate of preterm birth (in cases with only a single defect), were hydrocephaly (65.2%, 23 cases); anencephaly (57.7%, 52 cases); multicystic encephalomalacia (50.5%, 107 cases); hydranencephaly (38.5%, 91 cases); holoprosencephaly (33.3%, 63 cases); microcephaly (26.9%, 78 cases); lissencephaly (24.3%, 103 cases); polymicrogyria (17.2%, 145 cases); and pachygyria (8.2%, 98 cases).

Cases with a live-born twin had a preterm birth rate of 52.1% (48 cases) and those with a dead twin had an even greater rate of 58.7% (63 cases).

DISCUSSION

Limitations of the study. A standard ascertainment process whereby cases are ascertained by review of hospital records, vital records, and discharge diagnoses is quite inadequate because brain defects can be hidden within the cranium. The ascertainment of brain defects from autopsy studies is also difficult. That is the major reason why extensive studies of the association between congenital brain defects and preterm birth have not already been done. Another weakness is that the control data on babies without defects comes from a specific population, whereas the data on babies with brain defects does not. However, the large data sets and the strong statistical correlations ($p < 0.0001$) suggest that the results are meaningful, despite the problems. Standard ascertainment is simply not possible, and this approach may be the best we can do at this time.

Brain defects and preterm birth. This study shows a high risk for preterm birth in babies with brain defects. This suggests that babies with brain defects are predisposed to be born preterm. The reverse, that preterm birth predisposes to congenital brain defects, is not plausible. Although the brains of preterm infants are particularly vulnerable to injury, the brain malformations in this study developed *in utero*, not at birth. This data on brain defects should not be surprising, in light of the previous studies showing an association between preterm birth and congenital defects of many types.

Can brain defects induce preterm birth? A dead embryo or fetus seems to trigger its own abortion, and possibly a defective conceptus can trigger preterm delivery. There is a high incidence of anomalies in aborted embryos and fetuses (38), often affecting the CNS (39,40). Freud (41) concluded that some unknown factor was causing both preterm birth and cerebral palsy (CP). This is in harmony with the hypothesis of a continuum of reproductive casualty (42–44) whereby pathologic factors of pregnancy produce damage from abortion through stillbirth and neonatal death, to survival with brain dysfunctions, such as CP, epilepsy, mental deficiency, and learning disorders. Other supporting opinions include “. . . early damage to the cerebral motor cortex leads to preterm delivery; that is, the affected fetus triggers its own early delivery (45).” “. . . birth defects may contribute significantly to the proportion of infants who are delivered before 37-wk gestation (15).” “The fetus itself may be one of the causes of preterm delivery. If growth retarded or malformed, the fetus is prone to be born prematurely . . . (10).”

Congenital brain defects may have some direct interaction with the mother that leads to preterm birth, *e.g.* through soluble factors or distention of the uterus. Alternatively, some types of brain defects might be emblematic of an underlying condition that affects the mother and leads to preterm birth. The current data show that certain types of defects are most strongly associated with preterm birth, *e.g.* hydrocephaly (65.2%), anencephaly (57.7%), multicystic encephalomalacia (50.5%), and hydranencephaly (38.5%). Further studies of such defects might lead to clues as to the causes of the preterm birth. Among the causes of preterm birth, some defects might be associated with a greater tendency for medical decisions for early delivery, and some might be associated with greater distention of the uterus; for example, from polyhydramnios (excessive amniotic fluid). However, perhaps more interesting and more useful would be any findings of associations with soluble factors that might influence preterm labor.

Polyhydramnios and preterm birth. Polyhydramnios, which causes distention of the uterus, is associated with preterm birth (46–48); with CP (11); with malformations (12,17); and, particularly, with proximal gut obstruction with failure of fetal swallowing (46–48). It has been thought that distention of the uterus may predispose to preterm birth. The distention may be a contributing factor, but it is not that simple. It has been shown that the preterm birth rate does not increase with the severity of the polyhydramnios (49,50). Instead, some additional factor in the cases with polyhydramnios plus malformations seems to be responsible for an increased rate of preterm birth. In cases with polyhydramnios, malformations were associated with preterm births regardless of the amount of amniotic fluid (49,50).

Preterm birth and thromboemboli. Infants with malformations have a higher frequency of IUGR regardless of GA (4,21,51). Furthermore, preterm babies have a significant propensity for IUGR (52). This fact may direct our attention to problems with the placenta. A major feature of the placenta is vascular supply, and many types of malformations of the brain (53,54) and other organs (55–58) have been attributed to disruptions of vascular supply. Studies of the placenta, in

cases of CP in very LBW infants have shown a significant association with thrombi of chorionic plate vessels (59,60). Thromboemboli can circulate right through the foramen oval of the fetal heart to the brain and other organs and may cause infarctions that kill areas of tissue and disrupt normal development. A genetic predisposition to coagulopathy could exacerbate this problem and there is an increased frequency of genetic thrombophilia in women with complications of pregnancy (61). Coagulopathy is also associated with an increased risk for stroke, neural tube defects, spontaneous abortion, IUGR, placental abruption, and limb defects (62). Coagulopathy due to the factor V Leiden mutation is associated with placental thrombosis and CP (63). Lynch *et al.* (64) have suggested that the factor V Leiden mutation is associated with CP through fetal or neonatal cerebral vascular events, with embolization from the fetal side of the placenta.

Preeclampsia, IUGR, porencephaly, perinatal stroke, and CP. Further to the idea that there may be connections between thromboemboli, brain malformations, and preterm birth: Perinatal stroke, an important cause of CP, is a type of brain injury caused by thromboembolism or hemorrhage, and it is strongly associated with preeclampsia and IUGR (65). Preeclampsia is thought to result from a vascular defect in the placenta, resulting in reduced uteroplacental blood flow (66), and preeclampsia is associated with thromboembolism (61). CP is strongly associated with preterm birth (67) and CNS malformations (24). Perinatal stroke may also be associated with preterm birth; 18 of the 40 cases in one study were born preterm (68). Porencephaly, the most common cerebral malformation in this study, is associated with the factor V Leiden mutation (64,69), CP (70), and preterm birth (this study). Hydranencephaly, like porencephaly is a fluid-filled defect in the brain, and it is also thought to be caused by vascular disruption (71). In this study, 38.5% of the hydranencephaly cases were born preterm. These numerous strong cross-associations are unlikely to be due to chance, especially because there is a plausible chain of connection.

In conclusion, babies with brain defects have a strong propensity to be born preterm. Either the brain defects themselves or the underlying cause of the defects may be inducing preterm birth. A search for the mechanisms involved in this induction might be facilitated by identifying and focusing on those types of brain defects that are most strongly associated with preterm birth. Because coagulopathy is associated with congenital brain defects, it may also be somehow involved in the induction. Unfortunately, this study offers no stronger clues for solving the intractable and growing problem of preterm birth. It should also be considered that there might be a number of preterm births that are caused by brain or other defects that are not easily identified.

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REFERENCES

- Marden PM, Smith DW, McDonald MJ 1964 Congenital anomalies in the newborn infant, including minor variations. *J Pediatr* 64:357-371
- Yerushalmy J, van den Berg BJ, Erhardt CL, Jacobziner H 1965 Birth weight and gestation as indices of "immaturity." *Am J Dis Child* 109:43-57
- Stewart AL, Keay AJ, Smith PG 1969 Congenital malformations; a detailed study of 2500 liveborn infants. *Ann Hum Genet* 32:353-360
- Mehes K, Mestyan J, Knoch V, Vinceller M 1973 Minor malformations in the neonate. *Helv Paediatr Acta* 28:477-483
- Lubchenco LO 1976 The High Risk Infant. WB Saunders, Philadelphia, p 217
- Kaltreider DF, Kohl S 1980 Epidemiology of preterm delivery. *Clin Obstet Gynecol* 23:17-31
- Christianson RE, van den Berg BJ, Milkovich L, Oechsli FW 1981 Incidence of congenital anomalies among white and black live births with long-term follow-up. *Am J Public Health* 71:1333-1341
- Berkowitz GS 1981 An epidemiologic study of preterm delivery. *Am J Epidemiol* 113:81-92
- Lieberman E, Ryan KJ, Monson RR, Schoenbaum SC 1988 Association of maternal hematocrit with premature labor. *Am J Obstet Gynecol* 159:107-114
- Hartikainen-Sorri A-L, Sorri M 1989 Occupational and socio-medical factors in preterm birth. *Obstet Gynecol* 74:13-16
- Torfs CP, van den Berg BJ, Oechsli FW, Cummins S 1990 Prenatal and prenatal factors in the etiology of cerebral palsy. *J Pediatr* 116:615-619
- Mili F, Edmonds LD, Khoury MJ, McClearn AB 1991 Prevalence of birth defects among low-birth-weight infants. A population study. *Am J Dis Child* 145:1313-1318
- Bhat BV, Babu L 1998 Congenital malformations at birth—a prospective study from south India. *Indian J Pediatr* 65:873-881
- Rasmussen SA, Moore CA, Paulozzi LJ, Rhodeniser EP 2001 Risk for birth defects among premature infants: a population-based study. *J Pediatr* 138:668-673
- Shaw GM, Savitz DA, Nelson V, Thorp JM 2001 Role of structural birth defects in preterm delivery. *Paediatr Perinat Epidemiol* 15:106-109
- Holmgren PA, Hogberg U 2001 The very preterm infant—a population-based study. *Acta Obstet Gynecol Scand* 80:525-531
- Queisser-Luft A, Stolz G, Wiesel A, Schlaefter K 2002 Malformations in newborn: results based on 30940 infants and fetuses from Mainz congenital birth defect monitoring system (1990-1998). *Arch Gynecol Obstet* 266:163-167
- Thong MK, Ho JJ, Khatijah NN 2005 A population-based study of birth defects in Malaysia. *Ann Hum Biol* 32:180-187
- van den Berg BJ, Yerushalmy J 1966 The relationship of the rate of intrauterine growth of infants of low birth weight to mortality, morbidity, and congenital anomalies. *J Pediatr* 69:531-545
- Drillien CM 1970 The small-for-date infant: etiology and prognosis. *Pediatr Clin North Am* 17:9-24
- Crichton JU, Dunn HG, McBurney AK, Robertson A-M, Tredger E 1972 Minor congenital defects in children of low birth weight. *J Pediatr* 80:830-832
- Fortune DW, Kitchen WH 1977 Malformations in infants of very low birth weight. *Med J Aust* 1:239-242
- Riley MM, Halliday JL, Lumley JM 1998 Congenital malformations in Victoria, Australia 1983-95: an overview of infant characteristics. *J Paediatr Child Health* 34:233-240
- Croen LA, Grether JK, Curry CJ, Nelson KB 2001 Congenital abnormalities among children with cerebral palsy: more evidence for prenatal antecedents. *J Pediatr* 138:804-810
- Creasy RK 1984 Preterm labor and delivery. In: Creasy RK, Resnik R (eds) *Maternal-Fetal Medicine: Principle and Practice*. WB Saunders, Philadelphia, pp 415-443
- Honnebier WJ, Swaab DF 1973 The influence of anencephaly upon intrauterine growth of fetus and placenta and upon gestation length. *J Obstet Gynaecol Br Commonw* 80:577-588
- Saxen I 1974 Cleft lip and palate in Finland: parental histories, course of pregnancy and selected environmental factors. *Int J Epidemiol* 3:263-270
- Calzolari E, Manservigi D, Garani GP, Cocchi G, Magnani C, Milan M 1990 Limb reduction defects in Emilia Romagna, Italy: epidemiological and genetic study in 173,109 consecutive births. *J Med Genet* 27:353-357
- Rogala EJ, Wynne-Davies R, Littlejohn A, Gormley J 1974 Congenital limb anomalies: frequency and aetiological factors. *J Med Genet* 11:221-233
- Dar H, Carney FE, Winter ST 1971 Dermatoglyphics and the simian crease in infants of low birth weight. *Acta Paediatr Scand* 60:479-481
- Byron-Scott R, Haan E, Chan A, Bower C, Scott H, Clark K 1998 A population-based study of abdominal wall defects in South Australia and Western Australia. *Paediatr Perinat Epidemiol* 12:136-151
- Cragan JD, Martin ML, Moore CA, Khoury MJ 1993 Descriptive epidemiology of small intestine atresia, Atlanta, Georgia. *Teratology* 48:441-450
- Dott MM, Wong LY, Rasmussen SA 2003 Population-based study of congenital diaphragmatic hernia: risk factors and survival in metropolitan Atlanta 1968-1999. *Birth Defects Res A Clin Mol Teratol* 67:261-267
- Depaepe A, Dolk H, Lechat MF 1993 The epidemiology of tracheo-oesophageal fistula and oesophageal atresia in Europe. EUROCAT Working Group. *Arch Dis Child* 68:743-748
- Carmichael SL, Shaw GM, Nelson V, Selvin S, Torfs C, Curry CJ 2003 Hypospadias in California. Trends and descriptive epidemiology. *Epidemiology* 14:701-706
- Ratten GJ, Beischer NA, Fortune DW 1973 Obstetric complications when the fetus has Potter's syndrome. *Am J Obstet Gynecol* 115:890-896
- Tanner K, Sabrine N, Wren C 2005 Cardiovascular malformations among preterm infants. *Pediatrics* 116:e833-e838
- Colvin ED, Bartholomew RA, Grimes WH, Fish JS 1950 Salvage possibilities in threatened abortion. *Am J Obstet Gynecol* 59:1208-1222

39. Padgett DH 1970 Neuroschisis and human embryonic maldevelopment. New evidence on anencephaly, spina bifida and diverse mammalian defects. *J Neuropathol Exp Neurol* 29:192–216
40. Creasy MR, Alberman ED 1976 Congenital malformations of the central nervous system in spontaneous abortions. *J Med Genet* 13:9–16
41. Freud S 1897 *Die Infantile Cerebrallähmung*. Alfred Holder, Wein
42. Lilienfeld AM, Parkhurst E 1951 A study of the association of factors of pregnancy and parturition with the development of cerebral palsy; a preliminary report. *Am J Hyg* 53:262–282
43. Lilienfeld AM, Pasamanick B 1955 The association of maternal and fetal factors with the development of cerebral palsy and epilepsy. *Am J Obstet Gynecol* 70:93–101
44. Nelson KB 1968 The 'continuum of reproductive casualty.' *Clin Dev Med* 27:100–109
45. Stanley F, Blair E, Alberman E 2000 *Cerebral Palsies: Epidemiology and Causal Pathways* (Clinics in Developmental Medicine). Cambridge University Press, Cambridge, p 151
46. Scott JS, Wilson JH 1957 Hydramnios as an early sign of oesophageal atresia. *Lancet* 273:569–572
47. Pierro A, Cozzi F, Colarossi G, Irving IM, Pierce AM, Lister J 1987 Does fetal gut obstruction cause hydramnios and growth retardation? *J Pediatr Surg* 22:454–457
48. Cheng W, Mya GH, Saing H 1996 Does the amniotic fluid protein absorption contribute significantly to the fetal weight? *J Paediatr Child Health* 32:39–41
49. Many A, Hill LM, Lazebnik N, Martin JG 1995 The association between polyhydramnios and preterm delivery. *Obstet Gynecol* 86:389–391
50. Lazebnik N, Many A 1999 The severity of polyhydramnios, estimated fetal weight and preterm delivery are independent risk factors for the presence of congenital malformations. *Gynecol Obstet Invest* 48:28–32
51. Khoury MJ, Erickson JD, Cordero JF, McCarthy BJ 1988 Congenital malformations and intrauterine growth retardation: a population study. *Pediatrics* 82:83–90
52. Secher NJ, Hansen PK, Thomsen BL, Keiding N 1987 Growth retardation in preterm infants. *Br J Obstet Gynaecol* 94:115–120
53. Friede RL 1989 *Developmental Neuropathology*. Springer-Verlag, Berlin
54. Norman MG, McGillivray BC, Kalousek DK, Hill A, Poskitt KJ 1995 *Congenital Malformations of the Brain: Pathological, Embryological, Clinical, Radiological and Genetic Aspects*. Oxford University Press, New York
55. Poswillo D 1973 The pathogenesis of the first and second branchial arch syndrome. *Oral Surg Oral Med Oral Pathol* 35:302–328
56. Hoyne HE, Higginbottom MC, Jones KL 1981 The vascular pathogenesis of gastroschisis: intrauterine interruption of the omphalomesenteric artery. *J Pediatr* 98:228–231
57. Robinow M, Schatzman ER, Oberheu K 1982 Peromelia, ipsilateral subclavian atresia, coarctation, and aneurysms of the aorta resulting from intrauterine vascular occlusion. *J Pediatr* 101:84–87
58. Soltan HC, Holmes LB 1986 Familial occurrence of malformations possibly attributable to vascular abnormalities. *J Pediatr* 108:112–114
59. Kraus FT 1997 Cerebral palsy and thrombi in placental vessels of the fetus: insights from litigation. *Hum Pathol* 28:246–248
60. Redline RW, Wilson-Costello D, Borawski E, Faranoff AA, Hack M 1998 Placental lesions associated with neurologic impairment and cerebral palsy in very low-birth-weight infants. *Arch Pathol Lab Med* 122:1091–1098
61. Kupfermanc MJ, Eldor A, Steinman N, Many A, Bar-Am A, Jaffa A, Fait G, Lessing JB 1999 Increased frequency of genetic thrombophilia in women with complications of pregnancy. *N Engl J Med* 340:9–13
62. Shashi V, Rickheim A, Pettenati MJ 2001 Maternal homozygosity for the common MTHFR mutation as a potential risk factor for offspring with limb defects. *Am J Med Genet* 100:25–29
63. Thorarensen O, Ryan S, Hunter J, Younkin DP 1997 Factor V Leiden mutation: an unrecognized cause of hemiplegic cerebral palsy, neonatal stroke, and placental thrombosis. *Ann Neurol* 42:372–375
64. Lynch JK, Nelson KB, Curry CJ, Grether JK 2001 Cerebrovascular disorders in children with factor V Leiden mutation. *J Child Neurol* 16:735–744
65. Wu YW, March WM, Croen LA, Grether JK, Escobar GJ, Newman TB 2004 Perinatal stroke in children with motor impairment: a population-based study. *Pediatrics* 114:612–619
66. Roberts JM, Cooper DW 2001 Pathogenesis and genetics of pre-eclampsia. *Lancet* 357:53–56
67. Nelson KB, Ellenberg JH 1986 Antecedents of cerebral palsy. Multivariate analysis of risk. *N Engl J Med* 315:81–86
68. Govaert P, Mattys E, Zecic A, Roelens F, Oostra A, Vanzielegheem B 2000 Perinatal cortical infarction within middle cerebral artery trunks. *Arch Dis Child Fetal Neonatal* Ed 82:F59–F63
69. Debus O, Koch HG, Kurlmann G, Strater R, Vielhaber H, Weber P, Nowak-Gottl U 1998 Factor V Leiden and genetic defects of thrombophilia in childhood porencephaly. *Arch Dis Child Fetal Neonatal* Ed 78:F121–F124
70. Ho SS, Kuzniecky RI, Gilliam F, Faught E, Bebin M, Morawetz R 1998 Congenital porencephaly: MR features and relationship to hippocampal sclerosis. *AJNR Am J Neuroradiol* 19:135–141
71. Jung JH, Graham JM, Schultz N, Smith DW 1984 Congenital hydranencephaly/porencephaly due to vascular disruption in monozygotic twins. *Pediatrics* 73:467–469