Doctoral Theses (Summaries)

Potential Hazards of Benzodiazepines for the Foetus

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The benzodiazepines (BZD) were introduced in the early 1960s and, having a plethora of pharmacologically advantageous effects (antianxiety, sedative, hypnotic, muscle relaxant, autonomic system depressant, and anticonvulsant) (Randall, 1973), they quickly became drugs of widespread use. Parallel with the more frequent use of BZD in the general population, there was also an increased use in pregnancy (Cree, 1973).

The teratogenic risks of BZD in humans are controversial. Some clinical investigations have found an association between maternal BZD use in early gestation and cleft lip and palate (Aarskog, 1975; Safra, 1975), while others have not (Shiono, 1984; Creizel, 1987).

Experimental studies that have examined the effects of prenatal exposure to BZD compounds have demonstrated marked interference in a variety of behavioural and neural functions as a consequence of the exposure (Kellog, 1992). To further elucidate this problem, studies on the adverse effects of BZD on the foetuses exposed to different levels of BZDs were initiated.

The first study included 8 children who had been excessively exposed to BZD in utero (Laegreid, 1989). Clinical features such as low Apgar scores, need for resuscitation, abstinence syndrome with hypotonia and convulsions, were common in the neonatal period. All the children had similar facial features and CNS dysfunction from birth. One child had an aplasia of one kidney and 2 had a cleft palate. One infant died and at autopsy, the child was found to have varying degrees of distortion of neuronal migration, with concomitant heterotopias. The 8 children were thoroughly investigated to exclude other factors of prenatal damage and found negative. The only common denominator of these cases was excessive BZD use by the mother during pregnancy. Gross motor disability was seen in all 8 children, 2 of whom had cerebral palsy. At follow-up, 2 children had become microcephalic, 2 were severely mentally retarded and 5 mildly so. Only one child was of normal intelligence.

The hypothesis of a teratogenic BZD syndrome was further tested in 2 retrospective case-control studies. In the first of these studies (Laegreid, 1990), 4 particular operational diagnoses of congenital malformation were chosen as the inclusion criteria. The diagnoses were: a) unspecified embryopathy and foetopa-

thy, b) unspecified congenital malformations of the urinary tract. Stored serum, taken from the mother at around gestational week 12, was screened for BZD. In all, 25 children with one or more of the particular diagnoses were identified. In the studied cases, 8 of 18 serum samples from early pregnancy were BZD-positive as compared with 2 of 60 control samples. The association between a BZD-positive serum test and these particular malformations was highly significant ($p \leq 0.0001$).

In the other retrospective case-control study (Laegreid, 1992), perinatal death was the inclusion criterion. Maternal drug use in pregnancies resulting in 73 perinatally dead infants was compared to a control group of mothers to 73 surviving infants. Information regarding medication in pregnancy and pre- and perinatal data was collected retrospectively. In addition, serum samples obtained in early pregnancy were screened for BZD. Eighteen case-mothers had used psychotropic drugs during pregnancy compared with 7 control-mothers. The association between psychotropic drug use, including BZD, and perinatal death was significant ($p \leq 0.05$).

Three prospective case-control studies comprised 17 children born to mothers who had used BZD in therapeutic doses throughout pregnancy. In the first of these studies the intrauterine growth and the neuro-behaviour of the BZD-exposed newborns were compared with 21 newborns foetally exposed to other psychotropic drugs (drug group) and 29 newborns with no known drug exposure (reference group) (Laegreid, 1992). Infants in the BZD group had an impaired intrauterine growth as compared with both the drug group and the reference group. Significant differences were found in the frequency of pre- and perinatal complications and in neuro-behaviour between the BZD group and the reference group as between the drug group and the reference group.

In the second and third prospective studies the 17 BZD exposed children were compared with the 29 children from the reference group regarding growth and neurodevelopment (Laegreid, 1992), and mental development (Laegreid, 1993). The growth and neurodevelopment, the latter according to the method developed by Touwen (Touwen, 1976), were studied at 6, 10 and 18 months of age. the BZD infants caught up their low mean birth weight, but head circumference remained at the same low level. A cluster of craniofacial anomalies was found in 5 infants. The gross motor development in BZD-exposed children was retarded at 6 and 10 months but was nearly normal at 18 months. Impaired fine motor function was found on all the follow-up occasions; at 18 months, a delay in the development of pincer grasp was the most prominent deviating finding. The mental development was assessed using the Griffiths' test (Griffiths, 1970) at 5, 10 and 18 months of age. The BZD-exposed children consistently demonstrated delayed developmental quotients at all ages. The most prominent deficits were found at 10 months within the subscales of personal-social behaviour, eye-hand co-ordination and performance. Hitherto unpublished results showed a delay also at 4 years of age most prominent in the subscales of locomotor and personal-social behaviour. Mothers in the BZD group did not differ from mothers in the reference group in the terms of educational level, employment or living area.

Conclusions: The significant association between BZD use and minor and major anomalies supports the hypothesis of the teratogenicity of BZD, especially when taken in excessive doses. The deviating neuro-behaviour in the newborn period may be due to abstinence and/or intoxication symptoms of the drug per se. The study suggests that the use of BZD in therapeutic doses throughout pregnancy can have negative effects on the development of children up to 4 years of age. No conclusion about the long-term course can be drawn. The follow-up of the children in school age is vital.

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First published in Acta Obstet Gynecol Scand 1992; 71:655–656

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Detection and Delivery of Severely Small for Gestational Age Fetuses

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Small for gestational age (SGA) fetuses are considered a risk group in perinatology. Antenatal detection SGA fetuses may be difficult for the obstetrician. In this study, the detection of severely SGA fetuses was investigated retrospectively using symphysis-fundus (SF) measurements, and prospectively using ultrasonic fetal weight estimation and fetal femur length (FL) to abdominal circumference (AC) ratio. A fetus or newborn infant was considered severely SGA when the birth weight (BW) falls below the 2.5th percentile or below –2 standard deviations (SD).

The significance of antenatal detection in the choice of the delivery place was investigated in a case-control study. In addition, the assessment of intrapartal fetal well-being, using cardiotocography (CTG) scores in vaginal, term, severely SGA deliveries was investigated retrospectively in a case-control study. Finally, the risk factors and deliveries associated with premature, severely SGA newborn infants with BW below –2SD, compared with next-born preterm appropriate for gestational age (AGA) newborn infants were studied retrospectively in a case-control study.

Using SF measurements, the old Finnish standard chart was of little value in detecting SGA fetuses. In 81 cases, the sensitivity was only 30 %. It improved to 62 %, when the new Finnish chart or the Turku chart were used. The specificities for these charts were as follows: 91 %, 70 %, and 70 %.

Using ultrasonic weight estimation, the detection rate of severely SGA fetuses was 82 %; the specificity was 92 %; and the positive predictive value was 84 %, in 186 cases. In 78 cases involving FL to AC ratios, these values were: 56 %, 78 %, and 52 %, respectively. Thus, in selected screening groups it is possible to antenatally detect most SGA fetuses with ultrasound examinations.

Severely SGA fetuses were delivered by cesarean section in 33 % of 72 cases. In 144 control cases, the cesarean section rate was 21 %. Of every five preterm SGA fetuses, four were delivered abdominally, due to suspected fetal distress. The incidence of acidotic umbilical pH values (pH value below 7.20 in the umbilical artery) was higher in the SGA group than that observed in the control group.

Of 72 severely SGA infants, 26 (36 %) required care in the neonatal intensive care unit (NICU). The most common indications for treatment were breathing difficulties other than respiratory distress syndrome, hypothermia and hypoglycemia. All premature SGA newborn infants needed such care. None of SGA newborn infants were taken to the NICU for the sole reason of small size. Two of the three intrauterine SGA deaths occurred in twin pregnancies in this study.

Intrapartal CTG scoring during the second stage of labor seemed to provide no advantage in the prediction of well-being of 103 severely SGA term fetuses over that of 103 AGA term fetuses. In both study groups, the sensitivity of low CTG scores to predict neonatal acidosis was poor. Even so, the visual CTG

scores had rather good sensitivity (75 %) in the detecting acidotic newborn infants in the SGA group. Apgar scores gave varying correlations with umbilical pH-values.

Important maternal risk factors associated with premature delivery (below 37 weeks of gestation) of 153 severely SGA newborn infants (from 1979 to 1988) included primiparity, previous SGA delivery, pre-eclampsia and hypertension. These factors were involved in 67 % of the SGA group versus 9 % of the AGA contral group. Congenital malformation (18 %) was the dominant fetal factor for preterm, severely SGA delivery. Oligohydramnion was also associated with preterm, severely SGA pregnancies.

Of 140 preterm, severely SGA fetuses (13 stillborn infants excluded), 83 % were born by cesarean section. Of 149 preterm AGA cases (4 stillborn infants excluded), 30 % involved abdominal delivery. Neonatal depression, as judged by Apgar scores, occurred significantly more often in preterm SGA newborn infants than in preterm AGA newborn infants. Every preterm, severely SGA newborn infant required care in NICU, compared to 61 % of preterm AGA newborn infants. The rate of perinatal deaths in preterm, severely SGA cases was 12 % compared to 5 % in preterm AGA cases. The neonatal mortality was significantly higher in the preterm SGA than in the preterm AGA group.

It is concluded that severely SGA fetuses, and especially those of premature status, quite often need special observation during pregnancy, labor and/or after delivery. Therefore, it seems to be important to antenatally determine with ultrasound examinations the fetal size and exclude congenital malformations and chromosomal abnormalities which may affect fetal development and treatment. Further, severely SGA fetuses should be delivered in hospitals where neonatal intensive care facilities are available.

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First published in Acta Obstet Gynecol Scand 1992; 71: 321–322

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