The risk of cerebral palsy in survivors of multiple pregnancies with co-fetal loss or death.

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Condensation

This population based study showed that both co-fetal loss and co-fetal death were risks for cerebral palsy in survivors of twin and triplet pregnancies.

The risk of cerebral palsy in survivors of multiple pregnancies with co-fetal loss or death.

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Abstract

Objectives: This study investigated the risks for cerebral palsy in survivors of multiple pregnancies with co-fetal loss (<20 weeks gestation) or co-fetal death.

Study Design: Total Western Australian population based case control study including 741 cases of cerebral palsy.

Results: Antenatal co-fetal loss or death occurred in 3% of all cases of cerebral palsy, a small but significant contribution. The odds ratio for cerebral palsy in survivors of co-fetal loss, including iatrogenic pregnancy reduction, was 2.65 [95% CI 0.78, 8.98], giving population attributable proportion of 7.28% [95% CI 0, 27.5%], compared to 4.25 [95% CI 1.12, 16.10] and 10.6% [95% CI 1.0, 35.6%] for survivors of co-fetal death.

Conclusions: This study quantifies the contribution of co-fetal death to cerebral palsy and suggests that co-fetal loss makes a similar though somewhat smaller contribution. This has implications concerning the wisdom of iatrogenic pregnancy reduction and the recording of early co-fetal losses.

Key words

Case Control Studies

Cerebral Palsy

Epidemiology

Multiple pregnancy

Risk facto

Introduction

Cerebral palsy (CP) is the most common severe physical disability in childhood[1, 2]. Multiple birth children are at especially high risk for CP acquired in the antepartum or intrapartum period, relative to single-born children[3]. In the latest report from the Western Australian Cerebral Palsy Register (WACPR), the CP rate was 9.05 [95% CI 6.0, 12.1] per 1000 neonatal survivors of multiple births compared to 2.19 [95% CI 1.9, 2.5] per 1000 neonatal survivors of singleton births, 1995-99[4]. The etiologies of CP acquired in the antepartum and intrapartum period are not well understood in singletons or multiple birth children. Maternal and fetal complications such as pre-eclampsia and preterm birth are more common in multiple pregnancies relative to singleton pregnancies and are associated with CP. However, these factors do not fully account for the increased prevalence of CP in survivors of multiple pregnancies[1].

One of the unique antenatal risks associated with multiple pregnancies is co-fetal death in the antepartum period[5, 6]. In the largest population-based study of CP to date, the crude rate of CP in live-born twins whose co-twin died in the antepartum period was 5.4% compared to 0.48% in live-born twin pairs[7]. Co-fetal loss before 20 weeks gestation has also been identified as a possible risk for CP[8-10], although the evidence is scant and inconclusive. The identification of co-fetal losses is a challenge as there is no statutory requirement to record them, therefore most are unreported[11] and doubtless many are undetected.

The case control study of perinatal death and cerebral palsy (CCCP) (de Groot, Blair, Watson, & Stanley, personal communication, 2008) provided a rare opportunity to investigate and compare the risk for CP associated with co-fetal loss

and co-fetal death in a population-based register of CP cases and population-based sample of live controls matched for year of birth, plurality and gestation of delivery.

Materials and Methods

The study sample comprised the 741 CP cases and 738 live controls in the CCCP. The CP cases were ascertained from the WACPR and included all cases born in WA in 1980-95, excluding cases with CP acquired in the post neonatal period or with minimal motor impairment. The live controls were ascertained from the Maternal and Child Health Research Data Base (MCHRDB), a total population database of birth notifications in Western Australia[12]. Matching for birth date within twelve months, for gestational age at delivery within a week and for plurality of delivery was attempted. These criteria were expanded when perfectly matched controls were not available. Where more than one match existed for a case, the control was selected at random from all possible matches. Unaffected co-multiples of selected CP cases and live controls were excluded from selection as live controls for CP cases.

Data on the antepartum, intrapartum, delivery, and neonatal period, up to the time of first discharge home, were obtained from medical records at hospitals where the babies were born, as well as any transfer hospitals. Additional antenatal information was sought from obstetricians and general practitioners involved in the pregnancy, delivery and neonatal care of the babies. In multiple pregnancies, data were collected on all co-multiples, including co-multiples who were lost or died in the antepartum period. The data were collected by registered nurses with training in midwifery and neonatal care who were blind to case control status.

CP cases were classified using the system adopted by the WACPR[4]. CP type was coded by type of movement disorder and bodily distribution (e.g., spastic

hemiplegia). CP severity was coded as mild, moderate or severe, based on functional impairment of the affected body part. CP disability score was a summed score that took into account CP type, CP severity, level of intellectual disability and presence of co-morbid epilepsy, deafness, and/or blindness[13]. The CP disability score is an ordinal scale from 1–12 and equates approximately to the following levels of motor impairment on the Gross Motor Function Classification system (GMFCS) [14]. A score in the range 1–4 equates to GMFCS I and II, 5–8 to GMFCS level III and 9–12 to GMFCS IV and V.

Data were analyzed using SPSS 15.0. Odds ratios and population attributable risk were calculated using standard conventions for case control studies[15].

Approval to conduct the CCCP study was obtained from the King Edward Memorial Hospital and Princess Margaret Hospital Ethics Committee, the Government of Western Australia Department of Health Confidentiality of Health Information Committee and all participating hospitals and clinicians.

Results

Plurality of pregnancy and birth

Of the 741 cases and 738 live controls, 77 CP cases and 84 live controls were survivors of 161 multiple pregnancies. On account of matching, tthese CP cases and live controls did not differ by year of birth, or gestational age at delivery. Seventy percent of the cases and live controls were conceived naturally and there was no significant difference in the number of cases and live controls conceived by Assisted Reproductive Technology (ART).

Co-fetal loss and co-fetal death in cases and live controls from multiple pregnancies.

Co-fetal demise occurred in 26 (16%) of the 161 pregnancies that began as multiple gestations. Half were co-fetal losses before 20 weeks gestation and half were co-fetal deaths from 20 weeks gestation. There were no pregnancies where both a co-fetal loss and a co-fetal death were detected (see Table 1).

Co-fetal loss (< 20 weeks gestation)

Co-fetal losses were detected in seven twin and six triplet pregnancies (see Table 2). Five CP cases and two live controls were single-born survivors from twin pregnancies. Four cases and two live controls were twin survivors from triplet pregnancies. Seven losses were spontaneous abortions, of which six were detected through serial ultrasound and one from a hospital record that documented the miscarriage. Three losses were fetocides, two were twin to singleton pregnancy reductions and one was a triplet to twin pregnancy reduction. Both survivors from the twin to singleton pregnancy reductions were CP cases. The survivor from the triplet to twin pregnancy reduction was a CP case and the other co-multiple was a neonatal death. Three losses were identified from placental examination that revealed fetal papyracea. The gestational week of loss was known for 10 of the 13 pregnancies. Eight losses, including the three fetocides, occurred in the first trimester. Three losses occurred in the first three weeks of the second trimester. In three multiple pregnancies with co-fetal loss, the gestational week of loss was unknown. However, these losses were confirmed to have occurred before 20 weeks, through examination of fetal papyracea in two pregnancies and serial ultrasonography in the third pregnancy (see Table 3).

Co-fetal death (=> 20 weeks gestation)

Antenatal stillbirths occurred in ten twin pregnancies and three triplet pregnancies. Eight CP cases and two live controls were survivors from twin

pregnancies and two CP cases and one live control were survivors from triplet pregnancies. Three CP cases and one live control from twin pregnancies were delivered in the same gestational week as the death of the co-fetus. Five CP cases and one live control from twin pregnancies were delivered at a later gestational week than the death of the co-fetus. One CP case from a triplet pregnancy was delivered in the same gestational week as the death of the co-fetus. One CP case and one live control from triplet pregnancies were delivered at a later gestational week than the death of the co-fetus (see Table 4).

Six CP cases and two live controls were survivors from same-sex twin pairs and two CP cases were survivors from opposite-sex twin pairs. One of the CP cases from a triplet set was the same sex as the co-multiple who died in the antepartum period and the other CP case was the opposite sex to the co-multiple who died in the antepartum period. In the third triplet set, the live control was the opposite sex to the co-multiple who died in the antepartum period. In these 3 triplet sets, the additional co-multiple (i.e., not selected as CP case or live control) was a survivor without CP.

Risk of cerebral palsy in survivors of multiple pregnancies with co-fetal loss or death.

The odds ratio for CP in survivors of multiple conceptions with co-fetal loss was 2.65 [95% CI 0.78, 8.98] and the PAR was 7.28 [95% CI 0, 27.5%]. For survivors of co-fetal death, the odds ratio for CP was 4.25 [95% CI 1.12, 16.10] and the PAR was 10.6% [95% CI 1.0, 35.6%].

Characteristics of CP cases from multiple pregnancies with and without co-fetal loss or death.

Spasticity was the predominant type of CP in survivors of multiple pregnancies with or without co-fetal demise, consistent with all CP[1] (see Table 5). Only two cases from twin pregnancies and singleton births had non-spastic types of

CP and both these cases were born at term. In common with multiple births generally, gestational age at delivery tended to be suppressed, except for singletons from twin pregnancies (see Table 6). There was little difference in the distribution or severity of motor impairment between cases from pregnancies with co-fetal loss or death. Though the numbers are small, cases from multiple pregnancies with co-fetal demise tended to have more severe motor impairment than cases from multiple pregnancies with no co-fetal demise (see Table 5).

Comment

This population-based study confirmed a high rate (16%) of co-fetal demise in multiple pregnancies; that co-fetal death is associated with CP in survivors; and suggests that co-fetal loss is also associated with CP in survivors. Antenatal co-fetal loss or death occurred in 19/77 (25%) of the multiple pregnancies that delivered CP cases and in 19/741 (3%) of all cases of CP, a small but significant contribution.

We believe this is the first study to measure the association between co-fetal loss and CP. While losses prior to 20 weeks will have been under ascertained, given that the medical records from which they were ascertained were made prior to the identification of CP and that the data abstractors were blind to case control status, there is no reason to believe that the degree of under ascertainment would have differed between cases and controls. The absence of zygosity and chorionicity data disallows speculation on causal mechanisms.

While numbers are small, all the co-fetal losses with a known gestational week of loss occurred in the first fifteen weeks of pregnancy. If it is important to identify co-fetal losses, this suggests that routine ultrasound examination should be initiated earlier than 12 weeks gestation. A further justification for early ultrasound examination is that the optimal time for determining chorionicity and amnionicity is 9–10 weeks gestation[16].

Although the risk of CP associated with co-fetal loss did not reach statistical significance, this may well be due to lack of power resulting from the small sample size. While the estimated central tendency of risk for co-fetal loss is about half that of co-fetal death, the difference was not statistically significant, suggesting that the timing of co-fetal demise may not be very important in the etiology of CP in survivors of multiple pregnancies. If supported by larger studies, this will have ramifications for

the practice of multiple pregnancy reduction in the interests of optimizing outcome, since all the three pregnancy reductions reported in this study were followed by CP in the survivors. In monochorionic pregnancies, the loss or death of a co-twin is a biologically plausible mechanism for cerebral impairment in survivors. The mechanisms for cerebral impairment in survivors of co-fetal loss or death in dichorionic or polychorionic pregnancies are unknown. Larger samples with confirmed chorionicity, amnionicity and zygosity are needed to answer this question.

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