

Psychosocial and Developmental Outcomes of Children Born following Intrauterine Growth Restriction: An Australian Pilot Study

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Abstract

Intrauterine growth restriction (IUGR) is associated with a negative effect on the growth and neurodevelopment of newborn babies, with substantial perinatal mortality and morbidity. Relatively less is known about the longer-term psychosocial sequelae following IUGR, especially in the years immediately preceding school entry, and this pilot study aimed to explore pregnancy and birth related factors related to this. Children born >32 weeks gestation with estimated foetal and birth weights <5th percentile for gestational age in 2007-2009 were identified. Parents completed several developmental assessment questionnaires including the Child Development Chart and Child Behaviour Checklist. Data were ultimately available for eight children with a mean age of 3.8 years. Abnormal Doppler features were found in six children. Two children had poor Apgar scores and three children had perinatal complications. With respect to behavioural and emotional outcomes, two children had Child Behaviour Checklist scores indicating externalising and internalising difficulties, and one child had a borderline fine motor skills score on the Child Development Chart. Amongst these three children (37.5%) with developmental concerns, older maternal age and lower birth weight were observed compared to children without apparent problems. These three children also had lower social skills scores than children without concerns. This pilot study supports the need for further prenatal and postnatal research that examines the psychosocial trajectory of children born following IUGR.

Keywords: Intrauterine growth restriction; Small for gestational age; Neurodevelopmental outcome

Introduction

Intrauterine growth restriction (IUGR) describes fetuses that have not reached their genetically determined potential size in-utero. When delivered, these babies tend to be small for gestational age and have low birth weight. IUGR is one of the most common intrauterine complications, with an estimated 3-10% of fetuses affected [1]. A commonly adopted definition of IUGR is an abdominal circumference or sonographic estimated foetal weight measurement <10th centile for a certain gestation [2,3] although there have been calls to use stricter cut-offs, particularly in research contexts [4]. Doppler velocity wave form analysis of fetal vessels is also often used in identifying and evaluating IUGR (Ott, 2006). The aetiology of IUGR relates to a complex and dynamic interplay between maternal factors, environmental factors, foetal factors and placental factors – although placental insufficiency is understood to be the leading cause [5].

IUGR may be broadly classified into two groups: symmetric and asymmetric. Symmetric IUGR has an early onset, where the foetus is proportionately small, and is associated with an increased risk of fetal disorders such as congenital abnormalities, chromosomal abnormalities and congenital infection [6-8]. In contrast, there is discordance in growth in the foetus in asymmetric IUGR, with growth of the head relatively preserved while the rest of bodily growth is retarded [9]. Asymmetric IUGR is usually a result of placental insufficiency and is thought to be relatively 'brain-sparing' as growth restriction successfully balances reduced oxygen delivery and consumption; meaning that fetal blood flow is redistributed to cardinal organs (brain, heart, and adrenal glands) [10-13]. About 20-30% of babies born following IUGR have symmetric IUGR [14].

Nonetheless, placental insufficiency leads to a reduction in nutrients to the foetus and chronic hypoxia ultimately has long-term impacts on brain growth, development and function as circulatory compromise deteriorates [15-19]. In this regard, IUGR is understood to be a risk

factor for poor neurodevelopmental outcome in children and increased cardio-vascular disease states in adulthood [20,21].

Research examining neurodevelopmental outcomes has typically focused of cognitive sequelae of IUGR [22]. Some of the cognitive deficits in children who were delivered following IUGR are reflected in their characteristically poor academic performance, as well as difficulties in the areas of visuo-motor and language skills, executive functioning, learning and memory, language development, and sustaining attention at follow-up into childhood [23-27]. Decreased motor co-ordination, poor muscle tone, and hyperactivity have also been noted [28]. Depending on the severity of the IUGR, these individuals may also have below average intelligence quotient scores [29,30]. It is important to note that the neurodevelopmental outcomes in children who had IUGR may be within the normal range, or they may only present with minimal problems although factors that mediate this are poorly understood [31].

Clinical observations suggest that children born following IUGR can also present with behavioural and emotional problems, particularly at later stages of development [32,33]. One study reported an increased risk of mental ill health in children aged 4-13 who had restricted inter-uterine growth [34] and data from other areas of enquiry have demonstrated that low birth weight and prematurity can confer an

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Received March 25, 2014; **Accepted** August 01, 2014; **Published** August 25, 2014

Citation: Lim LCD, Eapen V, Črnčec R, Smoleniec J (2014) Psychosocial and Developmental Outcomes of Children Born following Intrauterine Growth Restriction: An Australian Pilot Study. J Psychol Abnorm Child 3: 129. doi:10.4172/2329-9525.1000129

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increased risk for a range of mental disorders, including ADHD [35]. However, other groups have reported that notwithstanding certain academic difficulties, children attending school who had IUGR may show socio-emotional resilience [36]. Further examination of the possible psychosocial sequelae of IUGR is required better to understand the full extent of challenges faced by this cohort. Early detection of behavioural and emotional corollaries, as well as improved understanding of their genesis and course is critical for early intervention. There is, however, little research in this area at present specifically focused upon pre-school aged IUGR cohorts. This is notable in that the pre-school period represents a prime age for commencing effective psychosocial interventions where these are indicated. The present pilot study sought to examine psychosocial and developmental outcomes of pre-school aged children born following IUGR.

Methods

The study had ethical approval from the hospital where the research was conducted as well as from the governing University.

All children included in the study were born after 32 weeks gestation between 2007-2009 and had received prenatal care from the Feto-Maternal Unit (FMU) of a teaching hospital in South-Western Sydney, Australia. A 32 week cut-off was used to limit the confounding effects of prematurity upon the sample. Participants had an estimated fetal weight and birth weight below the 5th percentile for gestational age and gender according to the FMU internal database reference [37]. The 5th percentile criterion was used in line with calls for a stricter definition of IUGR [38] and is consistent with the cut-off used in other related research [36]. Gestational age was calculated based on the date of the mother's last menstrual period. Exclusion criteria were congenital infections, structural abnormalities, and genetic or chromosomal abnormalities, whether diagnosed pre- or post-natally. The research focused upon cases of asymmetric IUGR.

The mothers of these children were contacted by phone and invited to participate in the study. Those who were agreeable were then mailed a study pack containing the Child Behaviour Checklist [39], Child Development Chart [40] and a parent questionnaire.

The CBCL [37] has strong psychometric properties and was scored using the associated Achenbach System of Empirically Based Assessment scoring profile. This provided information on the child's behaviour in six specific behavioural domains; composite internalising and externalising domain scores; and an overall score relative to normative data.

The CDC [41] was scored by calculating the developmental quotient (that is, developmental age/chronological age) of the child in the domains of social, self-help, gross motor, fine motor, and language, as well as an overall developmental quotient, which was calculated as the average of the five domain scores. A developmental quotient ≥ 85 was considered to be within the average range, 71-84 reflecting low average development, and ≤ 70 reflecting significant delay.

The parent questionnaire was constructed for the purposes of the study to obtain specific information regarding demographics of the child and his/her family background. Parent questionnaire items are paraphrased in Table 1.

Other information about the pregnancy and birth details of the child were obtained from the FMU internal database and New South Wales Electronic Medical Records. These included gestational age at birth, birth weight and estimated foetal weight and their percentiles, mode of delivery, Apgar scores, and ultrasound Doppler studies.

Data were analysed using SPSS software. In light of the small

Parent/family variables
Parent age; Relationship to child; Marital status; Highest level of school education; Further/higher education; Employment status; Occupation
Number of children in the family; Family composition; Family cultural background; Primary language spoken at home; Family income bracket
Sibling medical, psychiatric or developmental difficulties
Parent medical, psychiatric or developmental difficulties
Child variables
Date of birth; Age; Sex
Perinatal complications
School/pre-school attendance and setting; Estimate of literacy and numeracy ability
Medical conditions and/or disabilities; Psychiatric problems; Developmental problems
Formal assessments previously completed
Current and previous therapies/interventions; Medication history

Table 1: Paraphrased items in the parent questionnaire developed for the study.

sample size recruited for this pilot study, a predominantly descriptive approach was taken to the data analysis, together with additional non-parametric analyses of some specific cases. Effect sizes of subgroup differences in continuous data were calculated as an alternative to non- or para-metric analyses. The Cohen's *d* metric was used and was calculated by dividing the mean difference between groups by the pooled standard deviation. This was of use as effect size is independent of sample size, and thus offers a view of the potential significance of the results. It is commonly reported that Cohen's *d* values of 0.2 – 0.49 reflect a small effect size, 0.5 – 0.79 reflect a medium effect size, and >0.8 reflect a large effect size.

Results

In total, there were 38 children who were born between 2007-2009, with estimated foetal weight and birth weight $<5^{\text{th}}$ percentile for gestational age and gender, who had received prenatal care from the FMU. One child was excluded due to chondroplasia diagnosed postnatally, five were excluded as their parents came from a non-English speaking background, and eight were uncontactable. The response rate was thus eight out of a potential 24 families (33%).

The demographics of the group showed some heterogeneity (Table 2). The children recruited to the study all lived with both parents, and had English as their main spoken language at home despite coming from different ethnic backgrounds. The majority of mothers were in professional occupations (87.5%), and most families (75%) were middle and upper income households within the local population. All of the parents who filled in the questionnaires had tertiary level education. None of the children were yet attending school due to their young age. Two children had started attending speech therapy earlier in the year (25%).

All of the children had estimated foetal weight and birth weight $<5^{\text{th}}$ percentile for gender and gestational age. Abnormal Doppler features were observed in six children. It was observed that 25% had abnormal umbilical artery end-diastolic flow, 37.5% had abnormal uterine artery Doppler, and 25% had redistribution in the middle cerebral artery (Table 3). Only two children had low Apgar scores and three children had perinatal complications (Table 3). Mothers of two of these children with perinatal complications had developed pre-eclampsia in their pregnancy.

While the majority of scores on the CBCL were within the normal range, borderline clinical range scores in the withdrawn and aggressive behaviour domains; as well as within the internalising, externalising and total scores (Table 4), occurred in two children.

Developmental quotient values on the CDC were all within the

Characteristic	Mean/Frequency	
Child's gender	Male	3 (37.5%)
	Female	5 (62.5%)
Child's age (years and SD)	3.78 (0.91)	
Mother's age (years and SD)	36.13 (6.62)	
Parents' marital status	De facto	3 (37.5%)
	Married	5 (62.5%)
Family make up	Lives with both parents 8 (100.0%)	
Number of children in family	1 child	4 (50.0%)
	2 children	2 (25.0%)
	3 children	2 (25.0%)
Child's birth order	First child	6 (75.0%)
	Second child	1 (12.5%)
	Third child	1 (12.5%)
Ethnicity	Australian	4 (50.0%)
	English	1 (12.5%)
	Filipino	1 (12.5%)
	Vietnamese	2 (25.0%)
Main language spoken at home	English 8 (100.0%)	
Mother's highest level of education	Technical college	3 (37.5%)
	University	5 (62.5%)
Maternal Occupation	Non-professional collar	1 (12.5%)
	Professional collar	7 (87.5%)
Paternal Occupation	Non-professional collar	5 (62.5%)
	Professional collar	3 (37.5%)
Family income (AUD)	<\$55,000	2 (25.0%)
	≥\$55,000	6 (75.0%)

Table 2: Demographics of the study population.

Characteristics	Mean/Frequency	
Estimated Foetal Weight percentile <5 th	8 (100%)	
Birth weight percentile <5 th	8 (100%)	
Gestational age at birth (weeks and SD)	35.13 (1.96)	
Birth weight (grams and SD)	1732.63 (409.23)	
Apgar score <7	At 1 minute	2 (25.0%)
	At 5 minutes	1 (12.5%)
Delivery method	Vaginal	3 (37.5%)
	Caesarean	5 (62.5%)
Birth induction	1 (12.5%)	
Complications before/after birth	3 (37.5%)	
Abnormal umbilical artery end-diastolic flow	2 (25.0%)	
Abnormal uterine artery Doppler	3 (37.5%)	
Middle cerebral artery redistribution	2 (25.0%)	

Table 3: Key antenatal and perinatal factors.

normal range except for one child who scored within the lower bounds of the low average range within the fine motor domain (73.91) (Table 5).

Therefore, out of the eight children studied, three were identified to have developmental problems (37.5%). We will refer to these three participants individually below as Participants 1, 2, and 4. We note that Participants 2 and 4 started attending speech therapy several months before the commencement of the study and had low scores on the CBCL, and Participant 1 had a low developmental quotient in the CDC fine motor domain. Further details regarding these three children are provided in Table 6 below.

It is difficult clearly to draw associations between antenatal and other variables for these three children given the heterogeneity of their presentations. For example, Participant 4 was born at an earlier gestational age than Participant 1 but with a higher birth weight.

However, Participant 4 had poorer Doppler features and lower Apgar scores (Table 6). One noticeable feature in both Participants 2 and 4 was the borderline clinical range scores in their CBCL scores (particularly in the internalising score) and that both were attending speech therapy.

Data pertaining to the three children identified as having possible developmental concerns (PDC) were compared with those of the five children without such problems (no concerns). It is of interest to note that three of the five children in the no concerns group had a history of perinatal complications (60%) while none in the PDC group had any complications. Generally, the no concerns group had a higher proportion of abnormal Doppler features than the PDC group. Two children in the no concerns group had abnormal uterine artery Doppler features (40%) compared to one in the PDC group (33%). Two children in the no concerns group had redistribution in the middle cerebral arteries (40%) while none of the PDC had any redistribution. In both groups there was one child with abnormal umbilical artery end diastolic flow.

Table 7 compares the two groups using the Cohen's *d* effect size. The no concerns group had a slightly later mean gestational age at birth than the PDC group, with an associated higher mean birth weight, but both had a small effect size ($d = 0.29$ and 0.44 , respectively). The effect size for maternal age between the two groups was of medium size ($d = 0.74$). The difference between the two groups was prominent in the CDC mean scores, as demonstrated by the large effect sizes in all but one domain, and in particular that relating to social development ($d = 2.71$).

Discussion

Population studies in Western societies suggest that approximately 20% of children have developmental concerns [42,43]. The rate of possible developmental concerns in our pilot study population was 37.5%, which is approximately double that rate. Within this study,

CBCL domain	Descriptive category and frequency	
Anxious/Depressed	Normal	8 (100.0%)
	Withdrawn	7 (87.5%)
Sleep problems	Normal	8 (100.0%)
	Somatic problems	8 (100.0%)
Aggressive behaviour	Normal	7 (87.5%)
	Borderline	1 (12.5%)
Destructive behaviour	Normal	8 (100.0%)
	Internalising score (T score category)	6 (75.0%)
Externalising score (T score category)	Borderline	2 (25.0%)
	Normal	7 (87.5%)
Total score (T score category)	Borderline	1 (12.5%)
	Normal	7 (87.5%)
	Borderline	1 (12.5%)

Table 4: KOutcomes on the Child Behaviour Checklist.

CDC domain	Minimum DQ ¹	Maximum DQ ¹	Mean DQ (SD)
Social	84.85	107.41	96.65 (7.80) note
Self help	90.91	107.41	98.75 (4.96)
Gross motor	90.91	128.89	103.84 (12.18)
Fine motor	73.91	107.41	95.76 (9.98)
Language	86.44	128.89	101.41 (13.07)
Global	90.30	109.78	99.28 (7.35)

DQ=developmental quotient

Table 5: Child Development Checklist outcomes based on developmental quotient values.

these appeared to be more common within behavioural and emotional domains, including in areas such as aggressive and internalising behaviours and poor social skills, consistent with studies examining older children [44]. We would nonetheless state at the outset that given the pilot nature of this study and the small sample size, the results of the study do need interpretation with appropriate caution.

Gestational age and birth weight are two of the possible pregnancy predictors for compromised developmental outcomes identified in the literature [45,46] and our findings suggest a similar trend with an IUGR cohort. The small sample size in the present investigation does not unfortunately permit the specification of potential cut-offs for lower versus higher risk. While existing literature points to an association between perinatal complications and poor neurodevelopmental outcome [47], none of the children with perinatal complications in our study were observed to have clinically significant scores on any of the measures used.

Older maternal age appeared to be related to developmental outcomes, based on the medium effect size observed between children observed to have possible developmental concerns following IUGR compared with those who did not. Maternal age is often studied

with regard to placental insufficiency and the rate of IUGR, however the link between the two seems to be relatively weak [48]. Maternal hypertensive disease has also been reported to be associated with IUGR [7, 10,30]. But while two mothers of the children in our study had pre-eclampsia, their children did not appear to have obvious developmental or behavioural/emotional difficulties.

Abnormal ultrasound Doppler studies were present in most children in the present study, although at varying degrees and in different blood vessels. While redistribution of blood flow in the middle cerebral arteries, and reversed or absent end-diastolic flow in the umbilical arteries have been shown to be vessels of concern in the study of IUGR and subsequent neurodevelopmental outcomes, our study had results that were inconclusive on this point, and tended to suggest the contrary.

We would also observe that many of the observed neuro developmental outcomes in this study, such as decreased fine motor co-ordination, are consistent with earlier reports in the literature.

There are several limitations to the pilot study. Firstly, the final sample population that was included in the study was smaller than expected; with a number of participants lost at the follow-up stage leading to a final response rate of 33%. Related to this, it appears that the final sample were of higher socio-economic standing than the community from which they were drawn, and perhaps relative to non-responders. Nonetheless, given socio-economic factors are generally understood to be protective with respect to neurodevelopment, this may suggest our overall findings are conservative. Secondly, the study was limited to parent self-report, with this undertaken in-part to maximise uptake. It is conceivable that this methodology led to reduced sensitivity and specificity with respect to identification of difficulties. Thirdly, the inclusion criteria were also affected by the small sample size. This meant that the study population could have been more homogeneous were a larger sample available and stricter inclusion criteria implemented. This in part highlights the lack of a fixed definition for IUGR, particularly for research purposes, which the reader should be aware of. Finally, the absence of a control group limits the interpretation of the results.

Nonetheless, when considered alongside available evidence from the literature, higher birth weight and corresponding later gestational age seems to be associated with improved developmental outcomes, which has implications for the management of the timing of delivery. This continues to be a significant challenge in the field as there is a need to minimise the risks of prematurity and yet have the IUGR foetus be in the best possible condition at delivery before it starts to deteriorate due to hypoxia with the associated risk in morbidity and mortality which this brings. Some studies have concluded that altering timing of delivery provides little benefit in reducing the deterioration that may already have mostly taken place by the time of IUGR diagnosis. However, one of the more prominent studies in this area, the Growth Restriction

	Participant 1	Participant 2	Participant 4
GA at birth (weeks)	34.86	37.57	33.14
Birth weight (grams)	1146	2200	1470
Apgar scores (at 1 min, at 5 mins)	9, 9	9, 9	6, 8
Perinatal complications	None	None	None
Doppler studies	Bilateral notching in uterine arteries	Normal	Increased resistance in the uterine arteries and absent end-diastolic flow in the umbilical arteries, without redistribution in the middle cerebral arteries
CBCL scores	Normal	Borderline clinical range scores in the aggressive behaviour, and internalising and externalising domains; clinical range score for the CBCL total score	Borderline clinical range scores in the withdrawn behaviour and internalising domains
CDC scores	Mild delay score on the fine motor domain and in global score	Normal	Normal
Current interventions	None	Speech therapy	Speech therapy

Table 6: Summary of characteristics of children identified as having possible developmental concerns.

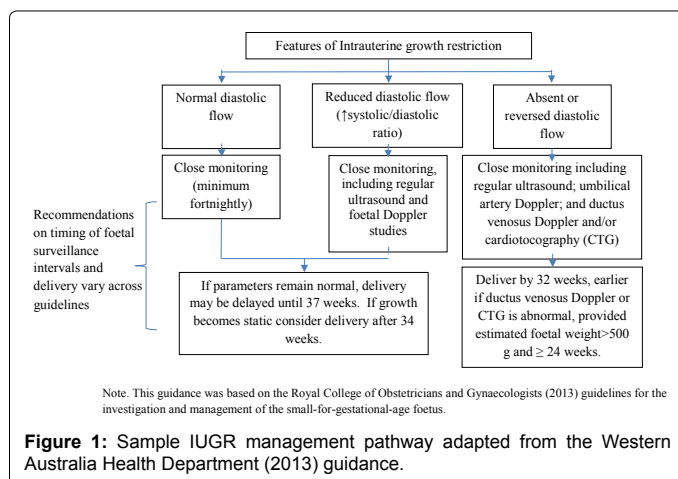
		Gestational age (weeks)	Birth weight (grams)	Maternal age (years)	CDC Social DQ ¹	CDC Self-help DQ ¹	CDC Gross motor DQ ¹	CDC Fine motor DQ ¹	CDC Language DQ ¹	CDC Global DQ ¹
With psychosocial difficulties (n=3)	Mean	35.19	1605.33	39.00	88.82	96.40	94.23	87.71	90.56	91.55
	SD	1.95	539.88	6.08	4.36	4.83	3.75	12.51	3.80	2.04
No psychosocial difficulties (n=5)	Mean	35.80	1809.00	36.00	101.34	100.15	109.61	100.59	107.91	103.92
	SD	2.01	357.62	6.57	4.85	4.98	11.89	4.27	12.28	4.53
Cohen's <i>d</i> effect size		0.29	0.44	0.74	2.71	0.76	1.74	1.38	1.91	3.52

Table 7: Group differences between children identified as having possible developmental concerns and children not so identified.

Intervention Trial (GRIT), compared the effect of delivering early and delaying birth in IUGR fetuses and concluded that while IUGR fetuses were being delivered at the right time to minimise mortality, they were perhaps being delivered too early to minimise brain damage. A more recent, on-going study is the Trial of Umbilical and Foetal Flow in Europe (TRUFFLE) which similarly aims to determine the method which best optimises timing of delivery of preterm IUGR fetuses based on their neurodevelopmental outcome.

Conclusions and Practice Guidelines

The methodology of the present study did not allow any specific comment or recommendation on antenatal surveillance and optimising the timing of delivery in IUGR. We would alert the reader to several recently published clinical practice guidelines for screening and management of IUGR that address this question. Recommendations on timing of foetal surveillance intervals and delivery vary somewhat in these and other guidelines, and in general terms, delivery is indicated when risk of foetal death or morbidity is greater than the risk of prematurity. Part of the Western Australian Health Department (2013) guidance on managing IUGR, which was adapted from the Royal College of Obstetricians and Gynaecologists (2013) guidelines, is included in Figure 1.



IUGR continues to be a condition that requires early identification and follow-up and timely intervention to minimise morbidity and mortality. Currently, birth weight and gestational age at birth are two of the most important predictors, and maternal age is also of relevance. While this study is limited due to the small sample size, the findings were consistent with the purported association between IUGR and poor psychosocial outcomes. Emotional and behavioural problems may well be over-represented in children from this cohort, even by pre-school age – in addition to the presence of cognitive and academic difficulties that have already been established within the literature. Future research building upon this methodology is indicated, particularly given the known benefits of early interventions for emotional and behavioural difficulties commencing at this age.

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