# Prognosis and risk factors for intrauterine growth retardation

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## ABSTRACT

**INTRODUCTION:** Intrauterine growth retardation (IUGR) is the term describing a foetus that has not reached its genetic growth potential. There is no international consensus on the definition of IUGR. The aim of this study was to describe a cohort of weight-restricted neonates and their mothers focusing on risk factors, catch up and neonatal outcome.

**MATERIAL AND METHODS:** This was a retrospective descriptive study of IUGR neonates with a birth weight below 70% of the expected whose mothers were admitted to the Neonatal Ward at Hvidovre Hospital during 2007-2009. Obstetrical and maternal risk factors and neonatal growth and outcome at six weeks, five months and 12 months of age were collected.

**RESULTS:** A total of 73 neonates and their mothers were included. Caesarean delivery was given in 78% of the cases. Maternal risk factors included gestational hypertension (33%), smoking (24%) and placental infarction (17%). Hypoglycaemic episodes developed in 31% of the neonates. At 12 months, 90% had caught up growth and 7% had a neurologically poor outcome. No infants died.

**CONCLUSION:** Maternal smoking and gestational hypertension are important risk factors for the development of IUGR. Special attention must be given to reducing the risk of hypoglycaemia. More studies are needed. Our purpose was to underline the need for a consensus on the definition of IUGR, catch-up and follow-up programmes in order to compare results in the future.

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Intrauterine growth retardation (IUGR) is the term describing a foetus that has not reached its genetic growth potential. Mortality and morbidity are increased in IUGR infants compared with infants who are appropriate for gestational age [1, 2]. IUGR infants have an increased risk of stillbirth, birth hypoxia, long-term consequences including short stature, impaired neurological development, diabetes and hypertension [2-5].

There is no international consensus on the definition of IUGR. Reduced foetal growth velocity determined by two prenatal ultrasound measurements has been proposed as a definition. But not all foetuses are scanned twice. Another definition used by The Danish Society of Obstetrics and Gynecology is a foetal ultrasound weight estimate below –2 standard deviations (SD) corresponding to –22% and equal to 78% of the expected weight [6]. Maternal risk factors associated with IUGR are high maternal age, overweight or low pre-pregnancy weight, substance abuse, smoking or assisted reproduction. Other established conditions include pre-eclampsia, pregnancy-induced hypertension, autoimmune diseases, diabetes and essential hypertension. Similarly, placental insufficiency is known to play an important role [7, 8].

The aim of this study was to describe a cohort of weight-retarded neonates and their mothers giving birth at Hvidovre Hospital during a three-year period. Obstetric and maternal risk factors, neonatal growth and outcome at six weeks, five and 12 months of age were the focus points of the study.

With this study we would like to stress the need for a consensus on the definition of IUGR for catch-up and follow-up programmes in order to compare results in the future.

## MATERIAL AND METHODS

This was a retrospective descriptive study of IUGR neonates with a birth weight below 70 percent of the expected whose mothers were admitted to the Neonatal Ward at Hvidovre Hospital in the period from January 2007 to December 2009.

A cut-off of 30% IUGR was chosen in the study because a local guideline prescribed that neonates smaller than this cut-off were to be admitted to the Neonatal Ward. The definition of IUGR was made from birth weight, gestational age and gender compared with the Scandinavian reference by Marsal et al [9]. Neonates with IUGR admitted to the Maternity Ward were not included in the study.

Obstetrical and maternal data were collected from the mother's medical records, looking at mode of delivery and risk factors, see **Table 1**. Gestational hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic ≥ 90 mmHg [10]. Pre (ultrasound) and postnatal measurements of IUGR by the Marsal formula were compared. Blood flow was measured in the umbilical artery with Doppler and represents a measure of the placental vascular resistance. Flow class II or higher is

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**TABLE 1**

Infant and obstetric/maternal characteristics.

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|---|---|
| *Infant characteristics (N = 73)* | |
| Birth weight, g, mean (range) | 1,659 (745-2,631) |
| Birth lenght, cm, mean (range) | 42.7 (36-48) |
| Birth head circumference, cm, mean (range) | 30.2 (21.7-34.0) |
| Gestational age, weeks, mean (range) | 35.1 (28.0-41.6) |
| Premature < 32 weeks, n (%) | 12 (16) |
| Gemelli, % | 27 (37) |
| Asphyxia Apgar < 7/5, n | 1 |
| Hypoglycaemia, n (%) | 22 (31) |
| CPAP, n (%) | 29 (39) |
| Syndromes: trisomy 21, 22Q11, Silver Russell, n (%) | 3 (4) |
| *6-week follow-up (N = 38)* | |
| Ultrasound of cerebrum, n (%) | 35 (48) |
| Eye examination, n (%) | 25 (34) |
| *5-month follow-up (N = 49)* | |
| Weight, g, mean (range) | 6,268 (3,850-8,270) |
| Height, cm, mean (range) | 63.2 (54-72) |
| Head circumference, cm, mean (range) | 41.8 (38.5-44.5) |
| *12-month follow-up (N = 39)* | |
| Weight, g, mean (range) | 8,782 (6,890-12,650) |
| Height, cm, mean (range) | 74.1 (65-83) |
| Head circumference, cm, mean (range) | 45.6 (41.7-48.0) |
| Cerebral palsy, n | 1 |
| Delayed development, n (%) | 6 (8) |
| Followed by a neuropaediatrician, n (%) | 5 (7) |
| *Obstetric/maternal characteristics (N = 73)* | |
| Caesarean delivery, n (%) | 57 (78) |
| Induction of labour, n (%) | 38 (52) |
| Gestational hypertension, n (%) | 24 (33) |
| Placental infarction, n (%) | 12 (17) |
| Flow class II or higher, n (%) | 13 (18) |
| Brain sparing, n (%) | 12 (16) |
| Maternal smoking during pregnancy, n (%) | 17 (24) |
| Maternal age, years, (range) | 30.8 (20-40) |
| Alcohol intake during pregnancy, n (%) | 5 (7) |
| Assisted reproduction, n (%) | 10 (14) |

CPAP = continuous positive airway pressure

defined as a pulsatility index greater than –3 SD and is an indicator of increased mortality and asphyxia [6]. Self-reported smoking in the second and/or third trimester of one cigarette or more per day was listed as maternal smoking. Alcohol intake during pregnancy was defined as two or more drinks per week and was self-reported.

Neonatal data were collected from the neonates' medical records. The following data were registered: anthropometric data, gestational age, respiratory distress syndrome with continuous positive airway pressure/respiratory treatment, signs of infection, antibiotic treatment and seizures.

Neonatal hypoglycaemia was defined as a blood glucose level of less than 2.5 mmol/l [11].

In accordance with local guidelines for the follow-up programme for neonates with more than 30% IUGR born at Hvidovre Hospital, the following was provided:

At 6 weeks of age, a nurse examination, cerebral ultra sonography and eye examination. Furthermore, cerebral ultrasonography was performed to find malformations and micro calcifications as a sign of congenital infection. Eye examination was made to reveal chorioretinitis.

At five months of age, a clinical examination by a neonatologist.

At 12 months of age, a clinical examination by a neonatologist and/or a neuropaediatrician.

At all follow-up visits, anthropometric data were collected. The age was corrected to term and a Z-score was calculated based on the World Health Organization anthropometrics [12]. Catch-up was defined as a Z-score for height or weight above –2 at 12 months corrected age [5]. At follow-up, an overall assessment was made for mental outcome, verbal development, judgment of gross and fine motor skills and anthropometric data. No standardized test was used.

### Statistical methods

Data were stated as medians and ranges. Fisher's exact test was used to compare groups. The registry of data was approved by the Danish Data Protection Agency.

*Trial registration:* not relevant

## RESULTS

A total of 79 neonates and their mothers fulfilled our IUGR criteria. Six neonates were excluded due to birth at other hospitals or incorrect coding. Thus, a total of 73 neonates and mothers were included. Six patients were referred to other hospitals postnatally and therefore not seen for follow-up. No children died.

From 2007 to 2009, 17,085 births were recorded at Hvidovre Hospital. The 73 neonates with IUGR represent 0.4% of all neonates born at Hvidovre Hospital in the period.

Obstetric data showed that 78% of the neonates were delivered by caesarean section (Table 1). There was no significant difference between the grade of IUGR determined pre- and postnatally (p = 0.109), although eleven cases (15%) were not found intrauterinely but only postnatally.

Maternal data showed a high frequency of the following risk factors: gestational hypertension (33%), smoking (24%) and placental infarction (17%), Table 1.

The neonatal data showed that the mean gestational age was 35.1 weeks and the mean birth weight 1,659g. 16% of the neonates had a gestational age below 32 weeks and 63% were singletons. There was no

significant difference between gestational age and the degree of growth retardation (p = 0.50). There was no significant difference in the degree of growth retardation between singletons and twins (p = 0.314).

In four cases, we found underlying diseases such as trisomy 21, 22q11 deletion syndrome, Silver Russell syndrome and congenital heart disease.

As a standard treatment, all IUGR neonates were given early feeding, which included either breastfeeding or formula milk within the first two hours after delivery. Eleven neonates (15%) were given intravenous prophylactic glucose.

Neonates with hypoglycaemia were given intravenous glucose (15%), while some were treated with oral feeding (12%) resulting in increased blood glucose levels.

At the six-week follow-up, 38 infants were seen, and sonography of the cerebrum was performed in 35 (48%) of the cases. In four cases, positive findings were made including: dilatation of the ventricles, bleeding, subependymal cyst and haemangioma. Three of the four would have been found following guidelines for premature infants, the fourth had clinical symptoms that would have necessitated further examination. Eye examination was performed in 25 cases (34%) of which ten were premature infants. No chorioretinitis was found.

At the five-month follow-up, 23% of the infants had not caught up for weight.

At the 12-month follow-up, 90% of the infants had caught up, see **Figure 1**. Syndromes and prematurity were related to the remaining 10% of the cases. A total of 39 (53%) of the infants were seen in the outpatient clinic, see Table 1. Five infants were followed by a neuropaediatrician and a physiotherapist due to syndromes and cerebral palsy.

## DISCUSSION

In this retrospective study, we described risk factors for severe IUGR and one-year follow-up. The prevalence of neonates with more than 30% growth retardation was in line with typical literature findings as listed in the Danish Society of Obstetrics and Gynaecology guideline [6]. The frequency of 0.4% IUGR neonates in this study is between the 1% of neonates with a 28% growth retardation and the 0.13% (–3 SD) with a 33% retardation cited in the guideline [6].

Obstetric and maternal risk factors for IUGR are well described in many studies and the present cohort is comparable to cohorts described in other studies except for the higher rate of gestational hypertension.

Not surprisingly, 78% of the neonates were delivered by caesarean section. In the background population, 23% of all pregnant women in Denmark deliver by caesarean section [13]. The fact that pre- and postnatal measurements of the degree of IUGR were the same shows that IUGR estimation made by foetal ultrasound is reliable.

Maternal aspects, such as gestational hypertension, were high-risk factors in this study compared with the international literature [14] and the background population in Denmark [13]. 0.9% of all pregnant women in Denmark develop gestational hypertension during pregnancy [13].

Smoking was seen in 24% of the cases in our study; in comparison, 9.4% in the background population of pregnant women in Denmark smoke [13]. Smoking is an established risk factor for IUGR as shown by Doctor et al [15]. Neonatal data showed a high incidence of hypoglycaemia, which was also found in a Canadian study of small for gestational age infants under the 5th percentile, where 28% developed hypoglycaemia [16]. The critical value for hypoglycaemia causing brain damage is not known, but our attention must be intensified to avoid hypoglycaemic episodes in these high-risk infants.

At six weeks of age, cerebral ultrasound and eye examination had no aetiologic or prognostic importance in IUGR neonates, except from premature neonates with a gestational age below 32 weeks who followed the prematurity guidelines.

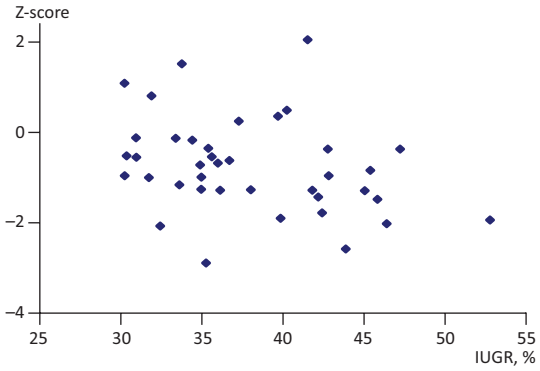
At 12 months of age, the rate of catch up for both height and weight was about 90%, which is comparable to the international literature [5]. Quick weight gain early in the childhood has been associated with a high risk of developing metabolic problems later in life [4, 17].

One can question whether weight catch up at 12 months is beneficial or not.

It is difficult to conclude anything about neurological outcome at the age of 12 months due to the

**FIGURE 1**

Weight at corrected age of 12 months (Z-score) in relation to the degree of intrauterine growth retardation at birth (IUGR, %). Z-score above –2 standard deviation shows catch-up.



Boy born at gestational age 31 + 1, weight 1,275 g, 30% intrauterine growth retardation.

small sample size, insufficient follow-up data because of the retrospective design and the lack of a standardised test measuring neurological development. The mode of follow-up of neurological outcome is still being explored. Padilla et al examined preterm IUGR infants and preterm appropriate for gestational age infants with the Hammersmith Infant Neurological Examination and the Bayley scale for Infant Development version II at one year, but found no difference between the two groups [18].

Magnetic resonance imaging (MRI) has been used to show a mild delay in myelination in IUGR infants with brain sparing in utero [19]. MRI may be the expedient mode of examination combined with a standardised clinical test to identify children at risk of developing neurological problems.

The lack of international consensus on the definition of IUGR makes comparison between studies difficult. We want to underline the need for a consensus on the definition of IUGR, catch up growth – and for follow-up programmes in order to compare results in the future.

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