Chapter 6
Fetal thoracic and abdominal structural pathology and growth

6.1 Structural pathology in small-for-gestational age pregnancies

Fetal growth retardation is associated with an increased risk of congenital anomalies. The relation between intrauterine growth retardation (IUGR) and congenital fetal malformations has been addressed as early as the Sixties[33,41], i.e., long before routine ultrasound examinations during pregnancy were introduced. The technique itself had been introduced in 1958 by Donald et al.[10]. Schutt (1965)[33] and Polani (1974)[31] described the negative influences of chromosomal and genetic anomalies on birth weight.

Nowadays, ultrasound biometry allows identification of the small-for-gestational age (SGA) fetus and at the same time recognition of fetal anatomical abnormalities, which subsequently may lead to detection of abnormal karyotypes[35]. Most fetuses with major cytogenetic abnormalities display either external or internal structural defects[18], which may be recognized by detailed ultrasound examination. The presence of one structural defect may suggest the presence of other defects and/or a chromosomal abnormality[30]. SGA fetuses are generally considered to be at risk for a chromosome anomaly when: (i) additional sonographic structural anomalies are detected; (ii) there is a normal or increased amount of amniotic fluid (polyhydramnios); (iii) there is no evidence of impaired placental perfusion[35].

In 1974, Campbell described two patterns of intrauterine growth retardation which are of importance in the diagnosis and management of these fetuses[4]. Most prominent is the late or secondary or asymmetrical type of IUGR which is characterized by a lengthy period of normal growth with a sudden reduction in growth rate, usually in the third trimester of pregnancy. This "late flattening" type of growth retardation is frequently the consequence of conditions which cause reduced placental perfusion and is therefore associated with a redistribution of the fetal circulation in favour of the fetal brain (brainsparing effect) as has been demonstrated by Doppler ultrasound[44]. The early or primary or symmetrical type of IUGR is characterized by a persistent low growth rate, usually from the early second trimester, without any tendency to cessation of growth. Although this "low profile" growth pattern is often associated with a constitutionally normal small fetus, it can also be encountered in cases of genetic, chromosomal or structural fetal anomalies.

In clinical practice, however, the distinction between these two types of growth retardation can be difficult[11]. Also, a substantial overlap between the two growth patterns exists as was demonstrated by Kirkinen et al.(1983). In their subpopulation of SGA fetuses with congenital malformations, a "low profile" growth pattern was established in 45%. However, 21% displayed "late flattening" growth retardation[21]. Also in our own material (see subchapter 6.2) nearly half of the structurally and chromosomally normal SGA fetuses displayed proportionate or symmetrical growth retardation, whereas disproportionate or asymmetrical growth retardation was found in the majority of fetuses with an abnormal karyotype. The same had been reported by Nicolaides et al.(1991)[27]. These data illustrate that the distinction between symmetric and asymmetric fetal growth retardation is not as clear as previously thought and that management decisions should not be made based on patterns of growth alone. More recently, David and associates (1995) questioned the existence of two distinct categories of SGA fetuses[8]. The authors stress that both proportionate and disproportionate SGA fetuses are at risk of perinatal death and chromosomal aberrations and that although an elevated head-to-abdomen ratio is more frequently associated with adverse perinatal outcome, this finding is of no clinical value when umbilical artery Doppler velocimetry and biophysical surveillance are available[8].

Lubchenco et al.(1963) constructed fetal growth curves by comparing gestational age with birth weight[26]. In 1967, SGA infants were classified by Battaglia and Lubchenco as those whose weights were below the tenth percentile for their gestational age[2]. In The Netherlands, Kloosterman (1970) composed Dutch birth weight for gestation curves, corrected for fetal sex and maternal parity[22]. In our centre, SGA is defined as a fetal upper abdominal circumference below the tenth centile.

SGA fetuses may be either constitutionally small with no increased perinatal death or morbidity, or they may be growth-retarded. The distinction between SGA and IUGR is of great importance, though can be difficult in clinical practice[1]. Retardation connotes a delay in progress and in the context of IUGR, it implies a downward inflection of the normal growth rate. Inferences regarding growth rate require, by definition, serial observations. An observation of size at one time does not confirm that a change in the rate of growth has occurred. It may, however, be consistent with a decrease in growth velocity. Confusing fetal size with fetal growth is a methodologic criticism that can be made with respect to much of the current literature regarding IUGR[32]. Moreover, defining IUGR by certain thresholds of birth weight and/or fetal size or of birth weight centiles for gestational age only defines those fetuses who are SGA and automatically will include normal, genetically small fetuses[28].

Intrauterine growth is a complex process, for which the basis is formed by the intrinsic (genetic) fetal growth potential. Growth is further regulated by extrinsic factors. Generally speaking, intrauterine growth retardation can be considered as a failure of a fetus to reach its expected growth potential and can be the result of diverse etiologies including congenital malformations. A classification for causes of fetal growth retardation is given in Table 1[14,34].

Table 1 Causes of intrauterine growth retardation

Fetal conditions	. genetic anomalies (chromosomal, syndromal) . structural anomalies . infection
Placental factors	. incomplete trophoblast invasion . abnormal villous function . infection . chromosomal anomalies . multiple gestation
Maternal conditions	. compromised uteroplacental perfusion (vascular disease, pre-eclampsia) . congenital uterine anomalies . systemic disease . malnutrition . smoking, alcohol or drugs . altitude
Idiopathic	

Winick (1971) has described three consecutive phases of fetal growth: (i) the phase of cellular hyperplasia during the first 16 weeks of gestation, characterized by a rapid increase in cell number, (ii) the second phase of concomitant hyperplasia and hypertrophy, occurring between the 16th and 32nd weeks and involving increases in cell number and size and (iii) the phase of cellular hypertrophy taking place between 32 weeks' gestation and term, which is characterized by a rapid increase in cell size and during which most fetal fat deposition is thought to occur[43]. Although the exact pathogenetic mechanism underlying the association between congenital malformations and IUGR remains to be determined, Johnson and Evans (1987) postulated that the presence of a structural anomaly may be associated with reduced cell division and therefore reduced organ growth, thus resulting in IUGR and subsequently in a lower birth weight[17]. This was illustrated in our study on twin pregnancies with one structurally affected fetus compared to twin pregnancies with proven absence of structural fetal anomalies. Within the affected sets of twins, a significantly lower birth weight of the affected twin compared

with the normal co-twin was noted[15]. Other possible mechanisms include IUGR predisposing to the development of congenital anomalies and an until now unknown mechanism resulting in both the congenital anomaly and IUGR[32].

In a literature study (Medline 1966-1996) on SGA or intrauterine growth retardation related to fetal (thoracic and abdominal) structural pathology only few reports focus on this relation, whereas most studies either exclude structural and/or chromosomal anomalies or only report the rate of chromosomal anomalies. The latter can partly be explained by the fact that ultrasound-detected anatomic anomalies often lead to invasive prenatal diagnosis through which an abnormal fetal karyotype is detected.

Swaab and co-workers (1978) found that the mean birth weight in term anencephalic fetuses was about 1000 g less than the mean birth weight in normal fetuses minus the weight of the brain[37]. Vorherr (1982) however stated, that anencephalic fetuses show "no or only minor reduction in weight" in his study[40]. Of the congenital deformities without chromosomal anomalies, those which affect the central nervous system and/or the skeletal system have the most marked effect on fetal growth[19]. IUGR is also common in fetuses with congenital gastrointestinal abnormalities such as duodenal atresia[13], omphalocele[7], and pancreatic agenesis[16], but these are also frequently associated with other malformations[3,23]. Apart from infants with multiple deformities, the most important malformations with low weight for gestation are anencephaly, Potter's syndrome and renal agenesis[19].

More recently, Khoury et al. (1988) published data from the Metropolitan Atlanta Congenital Defects Program[20]. In their study of 13.074 infants with major structural malformations, growth retardation was diagnosed in 22 per cent. IUGR was defined as a birth weight below the race-, sex- and gestational age-specific tenth percentile. It was suggested that the risk of major congenital anomalies occurring in a fetus with IUGR was approximately 8 per cent[20]. In the same year Wennergren and co-workers (1988) reported severe congenital malformations in 11 per cent of their SGA infants, in whom IUGR had been detected antenatally. The majority consisted of cardiac and chromosomal anomalies (trisomy 21, 18 and 13); no details were given on (intra)thoracic and/or (intra)abdominal structural pathology[42]. In their one year review of 790 admissions to their neonatal intensive care unit (NICU), Ling et al.(1991) report that infants with congenital anomalies account for 35% of all NICU infants with IUGR and for 26% of the total NICU mortality[24]. In 10 per cent (78/790) of their admissions one (35/78) or more (43/78) congenital anomalies were diagnosed. Within their subgroup of single congenital anomalies, pulmonary and gastrointestinal anomalies (not further specified) were present

in 11 out of 35 neonates[24]. Van Vugt et al.(1991) found structural anomalies in 15.7% of their population of 261 so-called non-uteroplacental IUGR fetuses (defined as symmetric growth retardation below the 5th percentile, with normal uteroplacental Doppler indices). The majority of structural anomalies consisted of renal anomalies (17/261) and neural tube defects (11/261). No (intra)thoracic anomalies were diagnosed, whilst with respect to (intra)abdominal anomalies, in four fetuses an abdominal wall defect was established. A bowel obstruction and a diaphragmatic hernia were both found once[38].

In subchapter 6.2 our own experience regarding the association between small-for-gestational age fetuses and structural anomalies is discussed on the basis of a retrospective analysis of 461 singleton pregnancies in which fetal anomalies were mainly of intrathoracic or intraabdominal origin.

6.2 Tertiary centre referral of small-for-gestational age pregnancies: a 10-year retrospective analysis

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Summary

Between 1981 and 1991, 461 pregnant women between 15 and 40 weeks of gestation (mean 30 weeks) with completed follow-up were referred to our centre for prenatal diagnosis because of a small-for-gestational age (SGA) fetus or combined SGA and structural abnormality. The referral diagnosis was based either on biparietal diameter measurements or on measurement of the upper-abdominal circumference. SGA in our centre was defined as a fetal upper-abdominal circumference below the tenth centile. SGA was confirmed by ultrasound in 75 per cent of the fetuses, whilst combined SGA and fetal structural abnormality was substantiated in only 16 per cent of the fetuses. However, in our centre structural abnormality was detected in 34 fetuses, who were referred because of SGA alone. Nearly half of the structurally normal SGA fetuses displayed a normal head-to-abdomen (H/A) ratio, whereas an increased H/A ratio was found in 13/15 fetuses with an abnormal karyotype. An abnormal karyotype was present in 20 fetuses, which is 7 per cent of the total SGA population. Nearly 50 per cent represented triploidy associated with oligohydramnios. SGA was confirmed by a birth weight below the tenth centile in 89 per cent, below the fifth centile in 77 per cent, and below the 2.3rd centile in 55 per cent of infants. Structural abnormality was confirmed in 65

per cent of infants, whereas in 19 per cent of infants the abnormality was missed or a misclassification was made. Perinatal mortality was 31 per cent for all SGA fetuses, 27 per cent for SGA fetuses without anomalies, and 62 per cent for SGA fetuses with structural abnormality.

Introduction

An association between small-for-gestational age (SGA) fetuses and structural abnormality has been suggested in a number of reports, with incidences ranging between 5 and 22 per cent depending on the cut-off level for SGA (5 or 10 per cent) and the pregnant population studied[36,38,39].

Our Division of Prenatal Diagnosis serves as a tertiary referral centre for anomaly scanning, which includes referrals of pregnancies suspected of a SGA fetus. We wish to present data on 461 pregnancies with completed follow-up which were referred to our centre between 1981 and 1991 because of SGA or combined SGA and fetal structural abnormality. In this retrospective study the following questions were addressed: (i) How did the referral diagnosis relate to the findings at our centre? (ii) How did the latter findings relate to the postnatal findings? (iii) What was the association between SGA and structural abnormality? (iv) What was the fetal outcome?

Materials and Methods

Data were available from 461 singleton fetuses with completed follow-up; twins were excluded from this study. Maternal age ranged between 21 and 38 years (mean 27 years) and gestational age at presentation varied between 15 and 40 weeks (mean 30 weeks). In 442 pregnancies, the referral diagnosis was a SGA fetus, which was based on either a biparietal diameter measurement or measurement of the upper-abdominal circumference. In the remaining 19 pregnancies, a combination of SGA and structural fetal abnormality was suspected.

At the Division of Prenatal Diagnosis, fetal biometry measurements and a fetal anomaly scan were performed in each instance, using a Diasonics CV 100 (1981-1989; carrier frequency 3.5 and 5.0 MHz) or a Toshiba SSA 270 (1990-1991; frequency 3.75 MHz). Fetal biometry measurements included the biparietal diameter, head circumference, upper-abdominal circumference, femur length, and calculation of the head-to-upper abdominal (H/A) ratio for establishing proportionate or symmetrical (H/A ratio 10-90 per cent) and disproportionate or asymmetrical (H/A ratio $>$ 90 per cent) SGA[6]. SGA was defined as a fetal upper-abdominal circumference below the tenth centile[5]. SGA

was confirmed postnatally when fetal birth weight was below the tenth centile according to the Kloosterman tables corrected for maternal parity and fetal sex[22]. Oligohydramnios was considered present when the diameter of the largest amniotic fluid pool measured 1 cm or less. If indicated, karyotyping was carried out via amniocentesis, late chorionic villus sampling or cordocentesis, or after delivery.

Results

Table I relates the referral diagnosis to findings at the prenatal centre. SGA was confirmed by ultrasound in 344/461 (75 per cent) fetuses, whilst combined SGA and fetal structural abnormality was substantiated in only 3/19 (16 per cent) fetuses. However, in our centre structural abnormality was detected in 34 fetuses who were referred because of SGA alone. The nature of the malformations is presented in Table II.

In the 344 fetuses with confirmed SGA, the following results were determined. H/A ratio data were available from 265 fetuses. The H/A ratio was normal (10-90th centile) in 102/265 (39 per cent) cases, but raised (> 90th centile) in 163/265 (61 per cent) fetuses. In the presence of a raised H/A ratio, fetal birth weight was below the tenth centile in 93 per cent against 83 per cent in the presence of a normal H/A ratio ($x^2=6.90$; $P< 0.001$). For fetal birth weight below the 2.3rd centile, the percentage was 64 per cent against 44 per cent ($x^2=10.05$; $P< 0.005$), and for the Caesarian section rate because of fetal distress, 58 per cent against 40 per cent ($x^2=7.69$; $P< 0.01$).

Table I. Diagnosis at our centre relative to referral diagnosis (n=461 fetuses)

	Diagnosis at Prenatal Centre				
Referral diagnosis	SGA+ SA-	SGA+ SA+	SGA- SA+	SGA- SA-	Total
SGA+,SA-	293	34	2	113	442
SGA+,SA+	14	3	-	2	19
Total	307	37	2	115	461

SGA=small for gestational age; SA=structural abnormality

Table II. Nature of the structural abnormality associated with SGA (n=37)

	True positive	False positive	False negative/ Misclassification
Congenital heart defects	2		2
Congestive heart failure	5		1
Renal and urinary tract defects			
Bilateral agenesis	9	1	
Cystic kidneys	3		
Obstructive uropathy (pelvic diameter > 10 mm)		1	
Neural tube defects	2	1	1
Omphalocele		1	
Two-vessel umbilical cord	1		
Multiple congenital anomalies	2	2	2
Facial cleft			1

Postnatally, SGA was confirmed by a birth weight below the tenth centile in 295/332 (89 per cent) infants. Birth weight was below the fifth centile in 257/332 (77 per cent) infants and below the 2.3rd centile in 184/332 (55 per cent) infants. Structural abnormality was confirmed postnatally in 24/37 (65 per cent) SGA infants, whereas in 7/37 (19 per cent) of infants structural abnormality was misclassified or missed (Table II). In this subset, birth weight was below the tenth centile in 28/31 (90 per cent), below the fifth centile in 23/31 (74 per cent) infants, and below the 2.3rd centile in 15/31 (48 per cent) infants.

Karyotyping was performed in 68 cases, 49 prenatally and 19 postnatally. Gestational age at prenatal karyotyping ranged between 26 and 35 weeks (mean 28 weeks). Prenatal karyotyping was carried out because of structural fetal anomalies (n=14), associated oligohydramnios (n=17), or severe symmetrical intrauterine growth retardation alone (< 2.3 centile; n=18), and was performed through amniocentesis (n=32), cordocentesis (n=11), or late chorionic villus sampling (n=6). In 19 infants, a postnatal karyotype was obtained because of congenital anomalies (n=17) or severe unexplained SGA (birth weight <2.3 centile; n=2).

An abnormal karyotype was established in 20 cases, which is 7 per cent of the total SGA population. In eight of these 20 cases, the abnormal karyotype was determined after delivery. There were 16 numerically abnormal karyotypes, of which seven were triploidies and four were structurally abnormal karyotypes (Table III). In 16 (80 per cent) fetuses, an abnormal karyotype was established, whilst ultrasound did not reveal any

Table III. Abnormal karyotypes (n = 20)

Triploidy	7
Trisomy 13	1
Trisomy 18	4
Trisomy 21	3
45,XO	1
46,XY,t(1,6)(q11;q21.3)	1
46,XY,q+	1
13q syndrome	1
46,XY,del 7 q34	1

structural pathology. There was no relationship between fetal structural pathology, abnormal karyotype, and gestational age at presentation. H/A ratios were available in 15 fetuses and raised in 13 fetuses (87 per cent). Amniotic fluid volume was assessed in 17 cases, of which 14 were characterized as oligohydramnios and three as normal. Gestational age at delivery for all SGA fetuses varied between 18 and 40 weeks (mean 32 weeks).

Perinatal mortality was defined as intrauterine or neonatal death and was 31 per cent (106/344) for all SGA fetuses studied, 27 per cent (83/306) for SGA fetuses without associated anomalies, and 62 per cent (23/37) for SGA fetuses with structural abnormality. When only taking into account pregnancies below 30 weeks of gestation, the percentages were 70 (74/106), 64 (53/83), and 91 per cent (21/23), respectively.

In the remaining 117 fetuses, in which SGA could not be confirmed by ultrasound, gestational age at birth varied between 20 and 42 weeks (mean 37 weeks). There were no abnormal karyotypes and the perinatal mortality was 8 per cent (10/117). Mortality was determined by neonatal complications (brain haemorrhage, respiratory insufficiency) following premature delivery in eight cases, unexplained intrauterine death in one case, and umbilical cord entanglement in the remaining case.

Discussion

Despite the retrospective nature of this study, a number of observations can be made. Our data demonstrate that even at a cut-off level of 10 per cent for the upper-abdominal circumference, an incorrect diagnosis of SGA was made in nearly 25 per cent of the cases referred. In some cases only the fetal biparietal diameter had been measured, whereas in others the upper-abdominal circumference measurement was at variance with that obtained in our centre. The pick-up rate of combined SGA and fetal structural abnormality was even worse. It amounted to only 8 per cent, which was mainly due to structural abnormality being missed during the ultrasound examination. This highlights the need for a proper anomaly scan when biometric findings indicate the presence of a SGA fetus.

Approximately 90 per cent of the SGA fetuses established by ultrasound in our centre displayed a reduced birth weight. Less accurate was the diagnosis of fetal structural abnormality. Whereas 65 per cent was diagnosed correctly, there were six false positives and seven misclassifications or false negatives. No particular organ could be incriminated for the misclassifications, false negatives, or false positives.

A raised H/A ratio corresponded to a significantly higher percentage of very small fetuses when compared with a normal H/A ratio. A raised H/A ratio was also associated with a significantly higher Caesarian section rate because of fetal distress. The H/A ratio has been used to differentiate between proportionate or symmetrical and disproportionate or asymmetrical SGA fetuses, the latter particularly being associated with impaired placental perfusion[9,12,25,29]. Our data are less conclusive in that nearly half of the structurally and chromosomally normal SGA fetuses displayed a normal H/A ratio, whereas a raised H/A ratio was established in the majority (13/15) of fetuses with an abnormal karyotype. This is in agreement with Soothill et al.(1992), who emphasized the limited significance of H/A ratio in the discrimination between placental insufficiency and abnormal karyotype in the SGA fetus[36].

Approximately 7 per cent of the SGA fetuses displayed an abnormal karyotype, which is not essentially different from observations elsewhere[36,38,39]. Of interest is that 25 per cent of the karyotyping was performed in SGA cases alone. Particularly the combination of unexplained SGA and severe oligohydramnios should be followed by karyotyping to exclude triploidy. This was confirmed in the present study, in which triploidy represented nearly half of the numerically affected chromosome patterns and oligohydramnios was the predominant finding. However, it should be emphasized that

even when high resolution ultrasound equipment is used, minor markers for a particular abnormal karyotype may be overlooked, especially in the presence of oligohydramnios.

The perinatal mortality rate for SGA alone (27 per cent) was approximately 30 times that for unselected obstetric populations in industrialized nations and highlights the risks attached to the SGA fetus. Structurally affected SGA fetuses fared even worse, with a perinatal mortality rate as high as 62 per cent. This was determined by the severity of both SGA (47 per cent below the 2.3rd centile) and structural abnormality.

It can be concluded that the diagnosis of SGA should always be followed by a fetal anomaly scan. Prenatal recognition of structural abnormality and additional karyotyping are essential to avoid obstetric interventions in those pregnancies which are destined to end in perinatal death. Triploidy should be excluded in the presence of SGA and severe oligohydramnios. The H/A ratio seems to be of limited importance in the differentiation between placental insufficiency and abnormal karyotype in the SGA fetus.

6.3 References

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