

Management of Very Early-onset Fetal Growth Restriction: Results from 92 Consecutive Cases

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Abstract. *Aim: To evaluate management of early-onset intrauterine growth restriction (IUGR) and to define outcome according to obstetric setting. Patients and Methods: During an 11-year period (2000-2011), data of patients presenting with IUGR and preterm delivery of less than 30 weeks of gestation at a tertiary perinatal center were retrospectively reviewed. Results: A total of 92 pregnancies were investigated. Delivery was indicated for fetal reasons in 38 out of 92 patients. Sixteen children of our cohort died within one year post partum, out of which eight had suffered from severe early-onset IUGR causing iatrogenic preterm delivery. Concerning the fetal outcome, gestational age at delivery and antenatal exposure to corticosteroids were found to be crucial. Conclusion: In some cases, respiratory distress syndrome prophylaxis and a “wait and see” approach to management in favor of a prolongation of the pregnancy might be favorable. Randomized prospective trials in early-onset IUGR with threatened preterm deliveries are needed in order to define guidelines for an individually tailored management of early-onset preterm infants.*

Fetal growth restriction (FGR) has been defined as fetal smallness in correlation with placental insufficiency, *i.e.* pathological feto-placental perfusion (umbilical artery pulsatility index >95th centile), and poor perinatal outcome, as recently stated by the TRUFFLE and PORTO groups (1-3).

True intrauterine growth restriction (IUGR) must be differentiated meticulously from fetuses which are constitutionally small for their gestational age (SGA) who have normal perinatal outcome as the management of early-onset IUGR might implicate iatrogenic preterm delivery in order to prevent intrauterine death (4), whereas in constitutional SGA,

expectant management until term is appropriate. In IUGR with fetal deterioration, sonographic Doppler parameter curves reveal changes in terms of days or weeks. Firstly, end-diastolic umbilical flow is reduced until zero-flow or even reverse flow (5). Consequently, a brain-sparing response, characterized by a decrease of middle cerebral artery resistance index, might be observed. Pathological Doppler flow of the *ductus venosus* (*i.e.* zero flow or reverse flow) indicates that the fetus is at acute risk. However, in late-onset IUGR the chronology of these stages has recently been questioned (3).

Predictors for poor perinatal outcome in fetuses with IUGR are the cerebroplacental ratio (CPR) and pathological uterine artery Doppler sonography, with estimated fetal weight (EFW) below the third centile (4).

Differentiating early-onset from late-onset IUGR is mandatory in order to distinguish two clinical entities with differences in severity, association with pre-eclampsia, and sequence of fetal deterioration (4). Early-onset IUGR represents 20-30% of all cases of IUGR and is characterized by severe systemic cardiovascular adaption due to chronic hypoxia, and high mortality and morbidity. The gestational cut-off for differentiating early-onset from late-onset IUGR can be set at 32 weeks, however a clear cut-off has not yet been established (6).

The problems of iatrogenic extreme preterm delivery in active management must be weighed against the risk of intrauterine fetal demise. It was the aim of the present study to analyze the reality of pre- and perinatal management in a retrospective cohort from a single unit in extreme early-onset FGR between 22+5 and 29+6 gestational weeks. We investigated fetal and maternal parameters leading to indication for active extreme preterm delivery, obstetric management and one-year follow-up of the neonates.

Patients and Methods

Between 2000 and 2011, 92 early-onset IUGR preterm deliveries were recorded at the tertiary referral center at the University of Lübeck Hospital and enrolled in this retrospective study. Inclusion criteria were neonatal weight <10th percentile and gestational age at delivery between 22+5 and 30+0 weeks. For reasons of adequate

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percentile calculation, only Caucasians were included. Only singleton pregnancies were included; fetuses with anomalies, syndromes, congenital heart disease or aneuploidy were excluded from the final analysis. Patients in whom indications for preterm delivery were not IUGR alone were also excluded [e.g. those with premature rupture of membranes, premature contractions, vaginal bleeding, pre-eclampsia or hemolysis with elevated liver enzymes and low platelets (HELLP) *etc.*] (Figure 1).

Data were assessed by analysis of PIA Fetal Database software (GE-Viewpoint, Wessling, Germany) documentation. Percentiles were calculated according to Marsál *et al.* (7).

Maternal and birth characteristics comprised age, size, smoking habit, body mass index [BMI=weight (kg)/size (m²) before pregnancy and at delivery, gravidity, parity, weeks of gestation at delivery and mode of delivery. Maternal data from ultrasound examination during pregnancy were registered (maternal Doppler sonography). Furthermore, data of previous pregnancies were included if available. Neonatal data were gender, weight, length and head circumference, neonatal pH levels, corticosteroid administration, fetal biometry and Doppler indices (*i.e.* resistance index and pulsatility index of the umbilical artery and median cerebral artery and *ductus venosus* flow pattern) and Apgar score at 1, 5 and 10 min. Antenatal Doppler ultrasound examinations were reviewed for the gestational age of occurrence of the first pathologies until delivery. Follow-up data of all children were obtained up to 1 year after birth. Neonatal death was classified early (day 0 to 6), up to one month (day 7 to 28) and later (day 29 to 365). Indications for delivery were analyzed.

Statistical analysis was performed with Microsoft Excel 2010 and GraphPad Prism 5 (GraphPad, La Jolla, USA). Fisher's exact test and Mann-Whitney *U*-test were applied.

Results

During the study period, a total of 15,403 children were born at the University Hospital of Schleswig-Holstein, 509 deliveries (3.3%) were before 30+0 gestational weeks, out of which 92 showed early-onset IUGR (Figure 2). The annual average of early-onset IUGR preterm deliveries was 0.8% (ranging from 0.3% to 3.0%). In 44 patients, maternal factors led to indication for iatrogenic preterm delivery (14 patients with HELLP, two with pre-eclampsia, 10 with preterm contractions, five with premature rupture of membranes, six with vaginal bleeding, five with preterm abruption of placenta, two with amnion infection syndrome) (Figure 2). In 38 patients, fetal parameters led to indication for preterm delivery: 18 had pathological Doppler parameters and 20 had pathological cardiotocography (in four cases, both cardiotocography and Doppler were abnormal; another three patients had an abnormal Doppler ultrasound with concomitant pre-eclampsia/HELLP).

Intrauterine fetal death occurred in 10 cases with known early-onset IUGR.

Maternal parameters and fetal outcome. Median maternal age was 31.1 years (range 18 to 46 years). Median maternal height and BMI were 167 cm (range 145 to 181) and

25.0 kg/m² before pregnancy and 28.1 kg/m² at delivery, respectively. Median weight gain throughout gestation was 8.2 kg (range 0-27 kg).

Twenty-two women of our cohort were smokers (24%) with a median daily consumption of 10.6 cigarettes (range=2-37), 11 of these were classified as heavy smokers (daily consumption >11 cigarettes) (50%). However, there was no significant difference in terms of neonatal weight (females: median weight in smokers 681 g, in non-smokers 661 g; *p*=0.6505, males: median weight in smokers 718 g, in non-smokers 699 g; *p*=0.8852), gestational weeks at delivery [189 days (SD±14.1) (*p*=0.7586)] or neonatal pH (*p*=0.7349) between heavy smokers and non-smokers in early-onset IUGR preterm deliveries.

Forty-four patients were primigravidae (40.5%), and 48 patients (59.9%) had been pregnant before. Four patients (8.3%) had already had a growth-restricted fetus in a prior pregnancy. Nine patients (18.75%) had a history of preterm delivery. Intrauterine fetal demise was found in two precedent pregnancies (4.2%); spontaneous abortion after 12 weeks in five patients (10.4%) and earlier than 12 weeks in 26 patients (54.1%). A history of induced abortion was found in 17 cases.

Median gestational age at delivery in early-onset IUGR preterm deliveries was 26+3 weeks (range=22+5 to 29+6 weeks). Cesarean section in live-born neonates was performed in 79 out of 92 cases (85.9%). Another 13 women (14.1%) had a vaginal delivery (among these, 10 were intrauterine fetal death, and two neonates died within 6 days).

Neonatal parameters and fetal outcome. Fifty percent of all 509 neonates in preterm deliveries <30 gestational weeks during the study period were males, 49.9% were females. In the early-onset IUGR preterm delivery group (*n*=92), 57 (62%) were females, 35 (38%) were males. In those fetuses in whom a fetal pathology led to preterm delivery, 60.5% were female, 39.5% male; in very preterm deliveries *i.e.* <24+6 weeks, 13 out of 19 (68.4%) were female.

The mean Apgar scores were lower for males, however, this was not significant. In cases of neonatal death, seven out of eight males died within the first week, whereas four out of eight girls died during the first week, another four during the first year.

The mean birth weight of the 92 early-onset IUGR preterm neonates enrolled in our study was 680 g. The weight was below the third percentile in 49 cases (45.1%). The smallest live-born neonate weighed 390 g. Neonatal weights were <500 g in 21.8%, between 500 and 1,000 g in 71.1% and >1,000 g in 6.5%. The mean neonatal pH was 7.30 in the entire patient cohort. In the sub-group characterized by fetal indication for iatrogenic preterm delivery (*n*=38), the mean pH was 7.27.

The mean Apgar scores (still births were excluded from the analysis) were 5.9 at 1 min, 7.9 at 5 min and 8.7 at 10

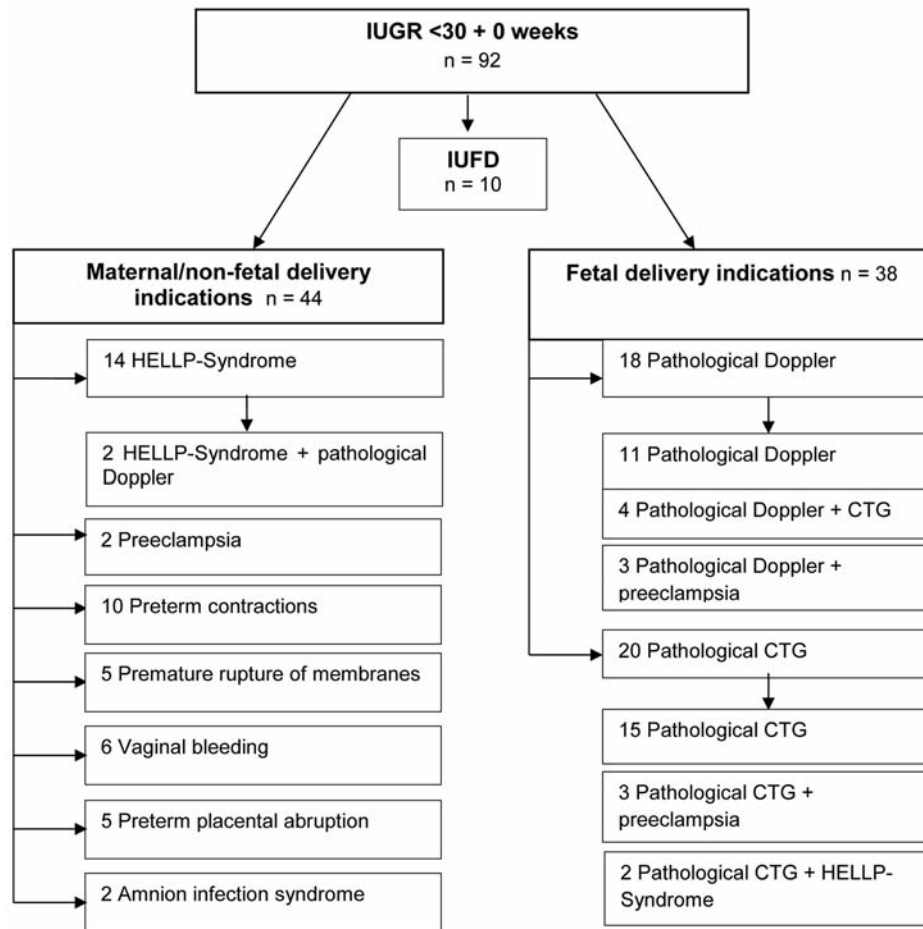


Figure 1. Different indications for delivery in early-onset intrauterine growth restriction (IUGR) preterm deliveries. CTG: Cardiotocogram, IUFD: intrauterine fetal death, hemolysis elevated liver enzymes low platelets (HELLP). CTG: Cardiotocogram; IUGR: intrauterine growth restriction; IUFD: intrauterine fetal death; HELLP: hemolysis elevated liver enzymes low platelets.

min. There was no significant difference in Apgar scores in terms of fetal or maternal indication for delivery. In preterm neonates with maternal delivery indication, a significant difference in 1-min ($p=0.0087$) and 5-min ($p=0.0032$) Apgar score was found between those of less than <28 gestational weeks and these of more than ≥ 28 weeks. In neonates with fetal indication, only 10-min Apgar score differed between <28 gestational weeks and ≥ 28 weeks. However, as neonates with a lower gestational age tend to have a reduced muscle tension, this result may rather be associated to gestational age than to other neonatal aspects.

One-year overall survival of all investigated fetuses, including those with intrauterine fetal death, was 71.7% (66 newborns), whereas 16 died within one year (Figure 3). The different sub-groups according to age at death are shown in Table I.

In eight of the 16 neonates who died within one year (50%), fetal aspects of early-onset IUGR had been the indication for iatrogenic preterm delivery.

In 58 out of 82 pregnancies (70.7%) with live-born neonates, corticosteroid administration for respiratory distress syndrome (RDS) prophylaxis was completed properly. Neonates with fetal indication for iatrogenic preterm delivery and adequate RDS prophylaxis had significantly higher 5-min ($p=0.0287$) and 10-min ($p=0.0033$) Apgar scores, as given by the attending neonatologist, this difference was not found in the sub-group with maternal indication for preterm delivery (Table II).

In both sub-groups (maternal and fetal indication for iatrogenic preterm delivery), a significant difference (maternal $p=0.0375$, fetal $p=0.0211$) was found in long-term survival according to adequate RDS prophylaxis.

In seven out of 10 cases of intrauterine fetal death, fetal weight was below the third percentile (70%), and five (50%) had pathological Doppler findings of the umbilical artery in precedent Doppler sonography before intrauterine fetal demise.

Retrospective data of prenatal Doppler ultrasound was available for 75 out of 92 cases with IUGR (81.5%); in the

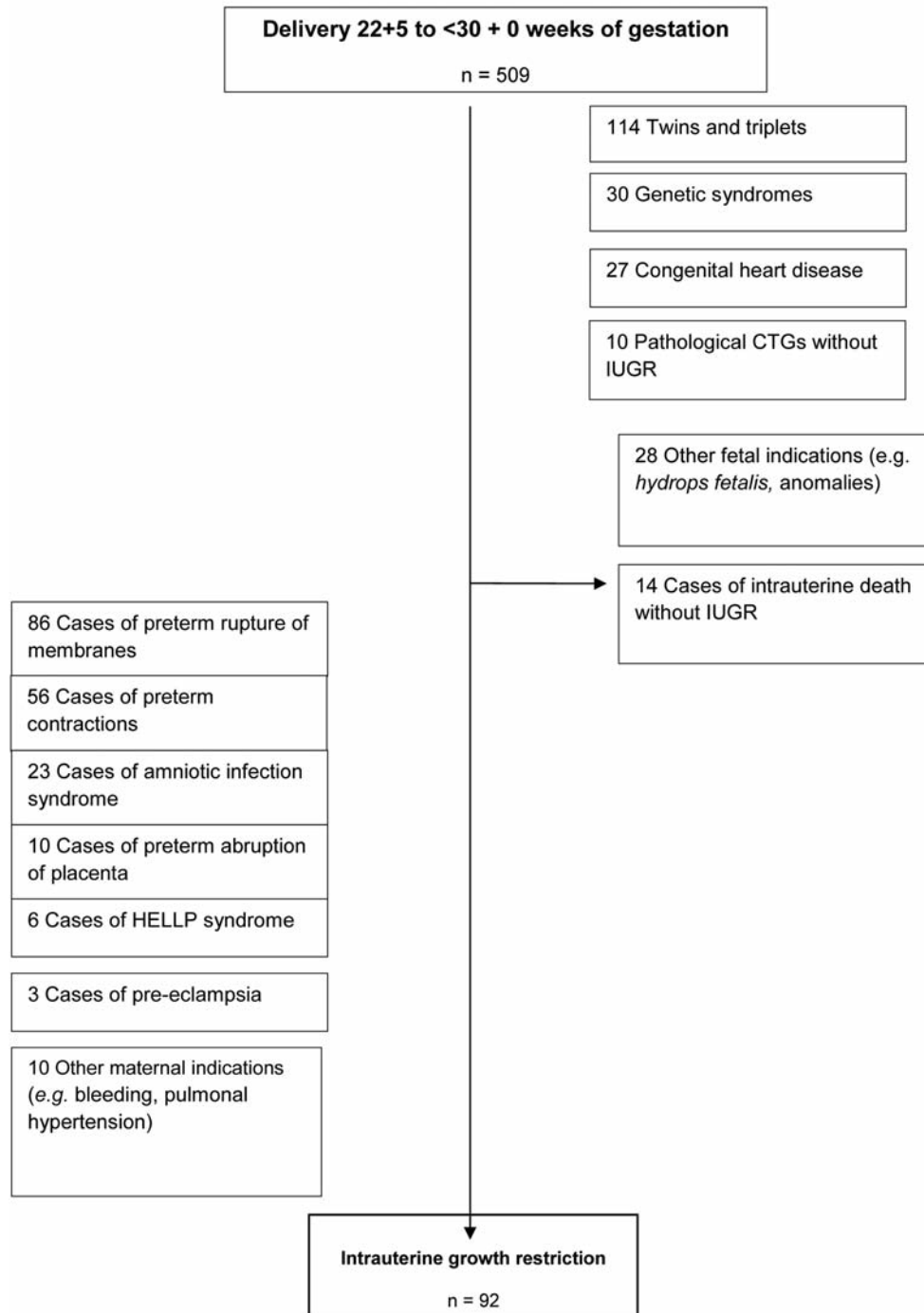


Figure 2. Study population with exclusion criteria in preterm deliveries. CTG, Cardiotokogram; IUGR, intrauterine growth restriction; HELLP, hemolysis elevated liver enzymes low platelets.

sub-group with IUGR as main indication for iatrogenic preterm delivery, for 37 out of 38 cases (97.4%). Average time interval between first and last Doppler ultrasound was 5.4 days, and between first Doppler and delivery it was 6.0 days (ranging from 0 to 24 days).

During the first antenatal Doppler examination, umbilical artery resistance index showed pathological values in 24 cases and brain sparing was registered in 10 cases; abnormal *ductus venosus* flow pattern was seen in one case (only the most striking pathologies were counted). At the last Doppler

Table I. *Peripartal death according to indication for delivery.*

	Survivors (%)	Peripartal death (%)	Death Day 0-6	Death Day 7-27	Death Day 28-365
Maternal indication for delivery, n=44	36 (81.8%)	8 (18.2%)	7	-	1
Fetal indication for delivery, n=38	30 (78.9%)	8 (21.1%)	4	1	3
Total (IUFD included), n=92	66 (71.7%)	26 (28.3%), 10 IUFD	11	1	4

IUFD: Intrauterine fetal death.

Table II. *APGAR scores according to respiratory distress syndrome (RDS) prophylaxis in maternal and fetal indications for delivery.*

	1-Min APGAR	Range (Min-max)	SD± p-Value	5-Min APGAR	Range (Min-max)	SD p-Value	10-Min APGAR	Range (Min-max)	SD p-Value
Maternal indication n=41									
Adequate RDS Prophylaxis	6.2	2-9	±1.93 0.494	8.1	4-10	±1.18 0.512	8.8	7-10	±0.92 0.7595
Insufficient RDS prophylaxis	5.8	1-8	±2.10	8.1	4-9	±1.52	9.0	7-10	±0.81
Fetal indication n=38									
Sufficient RDS Prophylaxis	6.3	4-9	±1.29 0.078	8.1	6-10	±0.78 0.0297	8.7	7-10	±0.66 0.0033
Insufficient RDS prophylaxis	4.7	1-9	±2.67	6.8	4-10	±1.93	8.0	7-10	±1.05

Table III. *Outcome depending on respiratory distress syndrome (RDS) prophylaxis in maternal and fetal indications in early-onset intrauterine growth restriction.*

	Survivors, n (%)	Peripartal death, n (%)	Death Day 0-6, n	Death Day 7-27, n	Death Day 28-365, n
Maternal indication					
Sufficient RDS prophylaxis	28 (90.3%)	3 (9.7%)	2	-	1
Insufficient RDS prophylaxis	8 (61.5%)	5 (38.5%)	5	-	-
Fetal indication					
Sufficient RDS prophylaxis	24 (88.9%)	3 (11.1%)	1	-	2
Insufficient RDS prophylaxis	5 (50.0%)	5 (50.0%)	3	1	1

sonography close to delivery, absent or reversed end-diastolic flow in the umbilical artery was found in 24 cases, brain sparing in four cases and abnormal flow in the *ductus venosus* in another two fetuses (Figure 4).

In 18 out of 38 IUGR fetuses with fetal indication for preterm delivery, pathological Doppler was the main indication for delivery (two cases with isolated brain sparing, pathological umbilical artery resistance indices in 16 cases, out of which three had concomitant abnormal *ductus venosus* flow pattern).

Discussion

In our study population, the frequency of early-onset IUGR preterm deliveries was 0.8% (range 0.3% to 3.0%) per year.

Forty-four out of the 82 iatrogenic preterm early-onset IUGR deliveries (54%) resulted from maternal pathologies. This observation emphasizes the crucial impact of early-onset IUGR-associated pathologies (pre-eclampsia and HELLP, as well as preterm contractions) (8).

Fetal gender – no significant difference in neonatal outcome. While gender was equally distributed considering all 502 preterm deliveries, based on our results, early-onset IUGR occurred more often in females than in males (62% vs. 38%). According to the literature, female preterm neonates are proven to have a better outcome than males (9). However, we did not observe any gender-based differences in terms of outcome in our patient population. Our findings reflect inconsistencies in current literature (10).

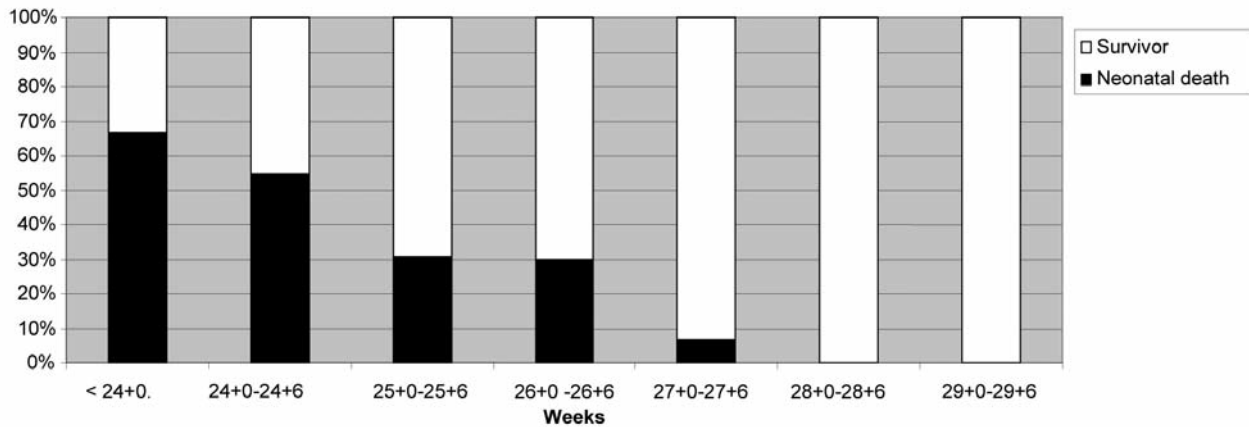


Figure 3. Postpartal death according to gestational week at delivery.

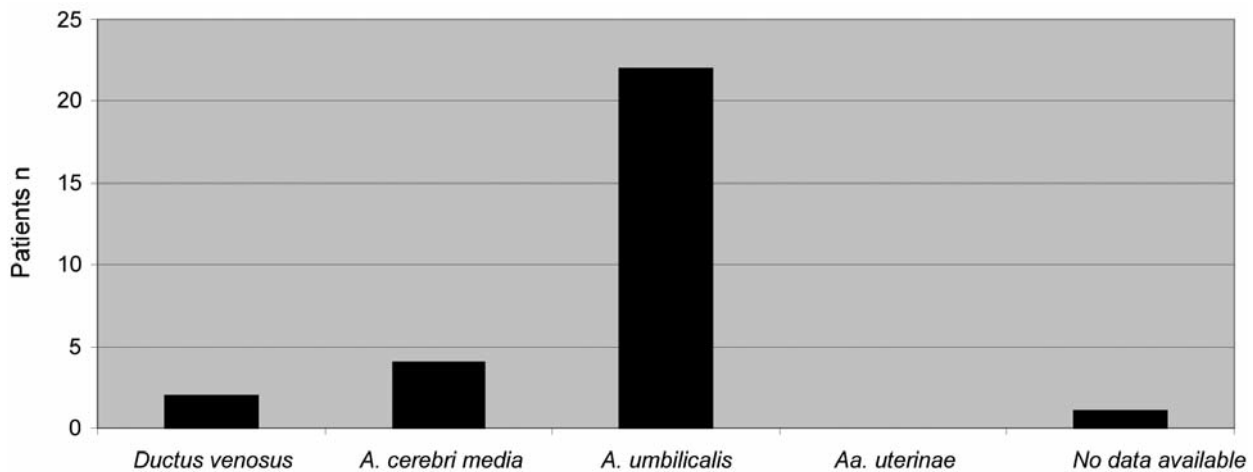


Figure 4. Pathological Doppler findings before delivery.

Smoking – no significant difference in neonatal outcome in early-onset IUGR. Smoking has a strong impact on fetal weight, and smoking more than 20 cigarettes daily is significantly associated with SGA (11). Approximately one third of all German women aged 20-45 years are smokers. In young women under 25 years, 50% are smokers; of those with lower socioeconomic status, 40% smoke. Recent data suggest that in Germany, 20-35% of all pregnant women are smokers (12, 13).

In our study, 24% of all mothers (22/92) with early-onset IUGR were smokers. This high percentage highlights smoking as one of the main risk factors for IUGR. In a comparable German IUGR study, 17% were smokers (14).

However, our data did not support the assumption of significant differences in terms of fetal weight and neonatal outcome between smokers and non-smoking mothers.

Apgar score – significant difference between <28 weeks and ≥28 weeks. From a neonatal perspective, 1- and 5-min Apgar scores were significantly lower in the early-onset IUGR group <28 gestational weeks at delivery in comparison to those fetuses who were born >28 weeks ($p=0.0087$ and $p=0.0032$ for 1 and 5 min). In the sub-group with fetal indication for delivery <28 weeks vs. ≥28 weeks, only the 10-min Apgar score was statistically significantly higher in ≥28 weeks neonates ($p=0.00502$). However, these observations were not surprising due to the physiological cardio-respiratory distress in extreme preterm neonates and the fact, that 5- and 10-min Apgar scores have a stronger impact on long-term outcome than the Apgar score after 1 min (15).

RDS prophylaxis – significant difference in Apgar and one-year-survival. Corticosteroid administration was considered

sufficient if intramuscular betamethasone was applied twice before delivery (48 and 24 h before delivery). According to current data, adequate RDS prophylaxis reduces perinatal mortality and cognitive impairment in very preterm neonates between 23 and 25 gestational weeks during a 18- to 22-month post partum period by about 40%. Furthermore, the rate of cerebral sequelae (hemorrhage, periventricular leukomalacia) and respiratory distress syndrome in preterm neonates is significantly reduced (16).

In our study encompassing 92 fetuses with early-onset IUGR, 79 were born alive before 30+0 gestational weeks; of the remainder, 10 died in utero, and three neonates died within one week after birth. In 58 cases (70.7%), adequate RDS prophylaxis was applied antenatally.

The main reason for not having completed RDS prophylaxis was emergency delivery, when cesarean section could not be postponed for 2 days due to acute fetal distress. However, in the present study, we demonstrate that omission of RDS prophylaxis was directly associated with worse one-year survival ($p=0.0375$ for maternal indication for delivery and $p=0.0211$ for fetal indication for delivery).

In 38 patients with fetal indication for preterm delivery, 5- ($p=0.03$) and 10-min ($p=0.0033$) Apgar scores were significantly higher after adequate corticosteroid administration (Table III).

Our observations emphasize the importance of RDS prophylaxis, not only in imminent preterm delivery, but also in early-onset IUGR fetuses, when iatrogenic preterm delivery before 34 weeks is likely. With regard to minor side-effects, RDS prophylaxis should be applied generously.

Intrauterine fetal death and Doppler sonography. In developed countries the prevalence rate for late stillbirth ranges between 2 and 5 per 1,000 births and has decreased very little during the past decades. According to the literature, IUGR associated with placental insufficiency is assumed to be the cause of 25-60% of stillbirths and highlights the key role of placental pathology in stillbirths (17, 18).

During the study period, a total of 100 cases of intrauterine death were registered (0.6%). This percentage is in line with current literature. In our patient collective, 10% of intrauterine fetal deaths ($n=10$) were associated with IUGR.

In a recent meta-analysis, uterine artery pulsatility index >90th centile during the second trimester had a moderate to high predictive accuracy for stillbirth related to placental abruption, SGA or pre-eclampsia (19).

In our study population, the mean gestational age at diagnosis of intrauterine death was 26+2 (range=22+5 to 29+5) weeks. Fetal weights under the third percentile were found for seven fetuses (70%) (range=255 g to 950 g). Abnormal Doppler values of the umbilical artery had been diagnosed in five out of the 10 fetuses in precedent Doppler sonography before intrauterine fetal demise (50%). The time

interval between finding an abnormal umbilical artery resistance index and stillbirth was between 3 and 45 days (24 days on average). Three pregnancies presented with normal Doppler sonography, in two cases there had not been any previous Doppler examination. Thus, in these pregnancies, intrauterine fetal death was difficult to anticipate.

The PORTO study (Prospective Observational Trial to Optimize Pediatric Health in Intrauterine Growth Restriction) showed that abnormal umbilical artery Doppler and EFW below the third centile were strongly and most consistently associated with adverse perinatal outcomes (20).

The question why intrauterine death occurred in five cases despite suspicious prenatal Doppler findings and IUGR, and why cesarean section had not been performed in order to prevent stillbirth must be further elucidated: Three out of the five fetuses were early-onset stillbirth <24+6 gestational weeks. With regard to the extreme preterm pregnancy in combination with severe IUGR and extremely poor prognosis, the patients actively opted for expectant management. In the two remaining cases (27+0 and 29+3 weeks with prior abnormal Doppler findings of the umbilical artery), the women were non-compliant and declined to consult the specialized department again before the intrauterine fetal death occurred.

The prognosis of very preterm neonates in relation to birth weight centiles has been calculated in so-called Prematurity Risk Evaluation Measure scores. Survival decreases with decreasing weight centiles. Survival of neonates with a birth weight at the third centile is the same as that of neonates with a birth weight at the 50th centile but with a 2-week shorter gestational age at delivery. According to the authors, active management of intrauterine growth restriction at the limits of viability should not be commenced before 26 weeks of gestation (1).

However the Growth Restriction Intervention Trial (GRIT) study stated that mortality did not differ between the “instant delivery group” after 48 h and the “wait and see group” with later delivery. The lack of difference in mortality suggests that in general, sick preterm babies are delivered at the correct moment to minimize mortality. According to the study, obstetricians might indeed deliver too early in terms of brain damage (21).

Death in early-onset IUGR. In the PORTO study, the percentage of fetal or neonatal deaths was much lower compared to our study: out of 1,116 non-anomalous singleton infants with EFW below the 10th centile, six resulted in perinatal deaths, including three stillbirths and three early neonatal deaths. However, in the PORTO study, perinatal deaths occurred between 24+6 and 35+0 weeks gestation, corresponding to birth weights ranging from 460 to 2,260 g. Perinatal deaths occurred more commonly in pregnancies with severe growth restriction (EFW below the third centile) and associated with abnormal Doppler findings.

The TRUFFLE trial (Trial of randomized umbilical and fetal flow in Europe) aimed at defining monitoring criteria for instant delivery in early-onset IUGR. In patients with very preterm fetal growth restriction and a high umbilical artery Doppler pulsatility index, no significant difference was reported when monitoring was performed by cardiotocography, early *ductus venosus* changes or late *ductus venosus* changes, but a tendency towards the latter was recently stated (22).

According to the PORTO study, despite antenatal detection of IUGR and associated maternal risk factors, not all perinatal deaths can be prevented. However, the question of whether to prolong pregnancy in order to prevent stillbirth or to perform instant delivery with the imminent risk of extreme preterm delivery remains unsolved (20).

This aspect is reflected by our observations: In eight of the 16 neonates who died within one year (50%), fetal indication in early-onset IUGR had been the reason for iatrogenic preterm delivery. It remains unclear whether intrauterine death had been prevented, but perinatal death occurred instead due to extreme preterm delivery in these cases. To answer this question, randomized prospective trials in early-onset IUGR preterm deliveries are urgently needed. Explicit recommendations for the management of early-onset IUGR are still lacking. Some prospective studies analyzed the question of whether active extreme early preterm delivery is beneficial for neonates. The GRIT study group conducted a randomized prospective study on 588 IUGR fetuses between 24 and 36 gestational weeks. Patients were randomized into two groups: either the “instant delivery group” after 48 h or the “wait and see group” with later delivery, when delivery was inevitable. In the subgroup of very early-onset IUGR with a gestational age below 31 weeks, perinatal mortality and 2-year follow-up showed less impairment (according to defined criteria) in the “wait and see group” (5% vs. 13%), indicating that obstetricians’ tendency towards active management should be questioned (21).

Conclusion

Our data support the observation that fetal deterioration is often accompanied by maternal complications, rendering the obstetrical situation even more challenging. The strong impact of the time at delivery in very preterm IUGR deliveries, as well as the strong impact of accomplished prophylaxis for RDS on neonatal outcome suggest that even in cases of severe IUGR at risk for intrauterine demise, the “wait and see” management in favor of prolonged gestation and RDS prophylaxis accomplishment might be favorable. In these cases, informed consent of the patient and close monitoring are mandatory. Ongoing prospective studies will probably shed more light on this matter.

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