Infants with intrauterine growth restriction (IUGR) have been reported to feature 5- to 10-fold higher rates of morbidity and mortality during the neonatal period and have a higher risk for neurological deficiencies including cerebral palsy. Between 7% and 9% of newborns are affected by growth restriction and about 50% of unexplained stillbirths born are affected by growth restriction.

IUGR infants are subject to an increased risk for adverse short- and long-term outcome compared with SGA children. Key words: Doppler ultrasound, intrauterine growth restriction, neurodevelopmental impairment, small for gestational age.

were included in the study. Cases with severe structural, genetic, or functional fetal anomalies were retrospectively excluded from further analysis. Group assignment to IUGR and SGA was based on the presence or absence of distinct signs of placental insufficiency such as pathological Doppler waveforms in the umbilical (elevated pulsatility index, absent or reversed end-diastolic flow) or middle cerebral artery (decreased pulsatility index) as well as a cerebroplacental Doppler ratio (middle cerebral artery pulsatility index/umbilical artery pulsatility index) below 1. In cases of ambiguous or incomplete prenatal data, postnatal placental morphology was used for discrimination.

### Perinatal and long-term outcome

Perinatal adverse outcome parameters included the presence of periventricular leukomalacia (PVL), intraventricular hemorrhage (IVH), convulsions, asphyxia, and meconium obstruction. Asphyxia was defined by an umbilical artery pH of less than 7.0 or an Apgar score of 3 or less after 1 minute or less than 3 after 5 minutes, respectively. Postnatal follow-up included daily cerebral ultrasound during the first week of life and subsequently once a week until discharge. Cerebral magnetic resonance imaging was performed in cases with severe PVL and IVH during the first year of life.

Evaluation of the long-term neurodevelopmental outcome was performed at the Department of Pediatrics and Adolescence Medicine at the Medical Uni-
versity of Graz. Examiners were not aware of the respective group assignment of the individual infants. The overall degree of disability was classified into mild, moderate, severe, or without impairment, according to Marlow et al. Major and minor neurological dysfunctions was assessed according to Touwen. Bayleys Developmental II Test was used to evaluate the infants’ cognitive and psychomotor development, whereas cerebral palsy was differentiated into diplegia, hemiplegia, and tetraplegia. Referring to motor skills and impairment, infants with cerebral palsy were classified into levels 1-5 by the use of the Gross Motor Function Classification System. In addition to the neurodevelopmental status, infant growth was evaluated at 2 years of corrected age. Growth delay was defined as body weight below the respective 10th centile.

Statistical analysis
Statistical analyses were performed by using the Fisher exact test for categorical variables and the Mann-Whitney test for continuous variables applying a significance level of $\alpha = 0.05$ (PRISM 5; GraphPad Software Inc, La Jolla, CA). Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs) and $P$ values.

RESULTS
During the time period from June 2003 to July 2009, a total of 14,470 singleton pregnancies were delivered at our institution. From this population 565 infants (3.90%) had a birthweight of 2500 g or less and less than the 10th percentile for the respective gestational age. Forty-seven cases (8.32%) were retrospectively excluded from the study because of major congenital malformations or incomplete data, leaving 219 IUGR and 299 SGA infants for the perinatal outcome analysis. These 3.57% (1.5% IUGR and 2.07% SGA) of all singleton deliveries in the observed period. Pre- and perinatal data are presented in Table 1.

Demographic data of mothers were comparable: mean maternal age was somewhat higher in the IUGR group (30 [16-43] vs 29 [15-43] years, $P = .015$). There were 142 (64.84%) and 176 (58.86%) nulliparous women, and 49 (22.37%) and 59 (19.73%) women were smoking, respectively.

Infants with IUGR were delivered significantly earlier than those with SGA (mean gestational age 35 [24-42] weeks vs 38 [25-42] weeks, $P < .0001$) and had an overall lower birthweight (1690 [176-2500] g vs 2293 [500-2500] g, $P < .0001$, Figure). The overall mortality was significantly higher for fetuses with IUGR (17 of 219, 7.76% vs 3 of 299; 1.0%; OR, 8.3; 95% CI, 2.4–28.7) and most of these deaths occurred prenatally (14 of 17; 82.35%; and 2 of 3, 66.67%, respectively).

In the IUGR group, maternal comorbidities, including HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, preeclampsia, diabetes mellitus, and hypertension, were significantly more frequent (Table 1). Furthermore, nonreassuring fetal heart rate patterns (82 of 219; 37.44% of IUGR vs 52 of 299, 17.39% of SGA; OR, 2.8, 95% CI, 1.9–4.3), oligohydramnios (70 of 219; 31.96% of IUGR vs 29 of 299, 9.70% of SGA; OR, 4.37; 95% CI, 2.72–7.05), and cesarean section (161 of 219; 73.52% of IUGR vs 105 of 299, 35.12% of SGA; OR, 5.1; 95% CI, 3.5–7.5) were more common in the IUGR group. The majority of cesarean sections in the IUGR group (n = 117; 72.67%) were electively performed before the onset of labor. In the SGA group, 45 infants (42.86%) were delivered by elective cesarean section.

The overall rate of neonatal complications was significantly higher in IUGR infants (50 of 205; 24.4%) compared with SGA fetuses (3 of 297; 1%; OR, 31.6; 95% CI, 9.7–103.0). These included PVL, meconium obstruction, and convulsions, whereas IVH, asphyxia, and postnatal mortality were comparable.

Long-term outcome
A total of 157 infants did not follow the 2 year evaluation, leaving 146 (72.27% of the 202 survivors) infants in the IUGR group and 215 (72.64% of the 296 survivors) in the SGA group for long-term outcome analysis. Results are presented in Table 2.

There were significant differences in the long-term outcomes of the 2 groups: neurodevelopmental impairment at 2 years of age was significantly more frequent in the IUGR group (36 of 146; 24.66%) compared with SGA infants (12 of 215; 5.58%; OR, 5.5, 95% CI, 2.8–11.1). Infants with IUGR had significantly more severe (6 of 146; 4.11% of IUGR vs 0 of 215; 0% of SGA, OR, 19.9; 95% CI, 1.1–357.0) and mild (22 of 146; 15.07% of IUGR vs 7 of 215; 3.26% of IUGR).
SGA, OR, 5.3; 95% CI, 2.2–12.7) deficiencies, whereas the difference in moderate impairment did not reach significance (8 of 146; 5.48% vs IUGR, 5 of 215; 2.33% of SGA; OR, 2.4; 95% CI, 0.78–7.60). Severe impairment included 3 cases of cerebral palsy in the IUGR group, whereas there were none in the SGA group. There was further a significant higher rate in growth delay in the IUGR-group (31 of 146; 21.23% vs 16 of 215; 7.44% SGA group; OR, 3.3; 95% CI, 1.8–6.4).

COMMENT

The findings of our study confirm previous observations that IUGR infants are at increased risk for adverse outcome compared with SGA infants.3,17 During their fetal life, IUGR infants in our population had a higher risk to die and to be born preterm, predominantly by cesarean section. In the neonatal period, these infants had more complications including PVL, convulsions, and meconium obstruction, whereas their long-term development was complicated by higher rates of neurological impairment and growth delay. Intrauterine growth restriction did occur more often in women with comorbidities including hypertension, preeclampsia, HELLP syndrome, or gestational diabetes.

In our retrospective study, we identified our SGA population (ie, all infants with low birthweight, which is commonly defined by a weight of less than 2500 g and subsequently included all infants with birthweight below the 10th percentile for the respective gestational age).18 This approach resulted in a clearly defined population of small infants; however, it inevitably led to the exclusion of infants that weighed more than 2500 g but nonetheless were beneath the 10th percentile.

We then classified our study population according to distinct signs of placental dysfunction including prenatal Doppler parameters, as well as postnatal placental morphology in selected cases, and analyzed the short- and long-term outcome of IUGR infants compared with children being small for gestational age without such signs of placental insufficiency. This design seems to be advantageous compared with the majority of pediatric studies on long-term outcome using a mixed population of babies just being small or light at birth.10–16 The latter might lead to a bias by underestimating the real impact of intrauterine growth restriction on neurological outcome.

Moreover, we report on a relatively large study population with long-term data of 72% of the surviving infants of both groups, respectively. However, a limitation of our study is its retrospec-
tive design that genuinely increases the likelihood of biased results and fails to determine several prospective parameters including the exact gestational age when growth restriction developed. We took care to guarantee correct group assignment; however, even in the most careful manner, this remains to be a subjective discrimination that is ultimately a simplification of the underlying pathophysiology.30

In addition, long-term results must be interpreted with caution because not all surviving infants were available for neurodevelopmental evaluation, hence leaving the possibility that the increased rates of adverse outcome observed in IUGR infants were altered by selection bias.

As Baschat and colleagues17,24 recently reviewed, there are 4 independent risk factors influencing neurodevelopmental outcome. These are gestational age at delivery, fetal body and head size, and abnormal Doppler flow in the umbilical and middle cerebral artery. The latter 2 are easily detectable in fetal life and are used for surveillance and guidance to direct obstetrical management.8,31,32 However, the optimal criteria for delivery of affected fetuses are still under debate and may be answered by the results of the Trial of Umbilical and Fetal Flow in Europe (TRUFFLE) study.13

We observed that IUGR infants were significantly more often born preterm in contrast to SGA babies, and this was frequently caused by maternal reasons. More than 50% of children with IUGR who were born before 33 weeks of gestation died, and children who were born before 32 weeks of gestation had a considerably poorer neurodevelopment. As stated in previous text, preterm birth is an obvious additional factor having an impact on neurological outcome. One may argue that preterm delivery and not IUGR itself may influence outcome. However, according to our data, IUGR frequently leads to preterm delivery, and that is in contrast to the SGA population, which was mostly delivered near term.

The main purpose of our study was to confirm the importance of discrimination of small babies into high and low risk for neurodevelopmental delay. From a prospective point of view, in counseling parents with IUGR fetuses, it is important to communicate that the affected infant will very likely be delivered preterm and will be at risk for perinatal complications and neurodevelopmental impairment. Women with an IUGR fetus should be informed about the long-term effects because mere survival might not be the only outcome relevant to parents.

We believe that reported numbers are of significance for physicians dealing with affected pregnancies and may help in the management of this condition. Because IUGR infants seem to be at increased risk for long-term sequelae, parents should be advised to follow up with regular checks in units in which infant development can be evaluated in a standardized manner and deficits can be detected early to allow specialized care. Prospective studies are needed to confirm our results.

REFERENCES


