

# Abnormal Retinal Vascular Morphology in Young Adults Following Intrauterine Growth Restriction

Ann Hellström, MD, PhD\*‡; Jovanna Dahlgren, MD, PhD‡; Karel Maršál, MD, PhD§; and David Ley, MD, PhD||

**ABSTRACT.** *Objective.* Intrauterine growth restriction (IUGR) resulting in low birth weight for gestational age may predispose one to development of cardiovascular disease later in life. Abnormal fetal blood flow in the presence of fetal growth restriction helps to distinguish infants with true fetal growth impairment from small but normal infants. Our goal was to investigate associations between IUGR with abnormal fetal blood flow and abnormal retinal vascular morphology at 18 years of age.

*Methods.* A prospective study was performed with 21 subjects with IUGR (abnormal fetal aortic blood flow velocity; birth weight small for gestational age; median birth weight deviation from the population mean of  $-31\%$  [range:  $-22\%$  to  $-42\%$ ]) and in 23 subjects with birth weight appropriate for gestational age [normal fetal aortic blood flow velocity; median birth weight deviation of  $-2\%$  (range:  $-10\%$  to  $22\%$ )]. The retinal vessel morphology was evaluated by digital image analysis.

*Result.* Subjects with IUGR ( $n = 21$ ) had significantly less retinal vascularization as evidenced by a lower number of vascular branching points (median: 26; range: 20–31) as compared with the subjects who were born appropriate for gestational age (median: 28; range: 26–32). Within the entire group ( $N = 44$ ), increasing negative birth weight deviation was associated with a reduced number of vascular branching points ( $r = 0.36$ ).

*Conclusion.* Our findings show that IUGR with abnormal fetal blood flow is associated with abnormal retinal vascular morphology in young adult life. *Pediatrics* 2004;113:e77–e80. URL: <http://www.pediatrics.org/cgi/content/full/113/2/e77>; *intrauterine growth restriction, small for gestational age, abnormal vessel morphology.*

ABBREVIATIONS. IUGR, intrauterine growth restriction; SGA, small for gestational age; BFC, blood flow class; AGA, appropriate for gestational age; GH, growth hormone; IGF-I, insulin like growth factor 1.

**I**ntrauterine growth restriction (IUGR) resulting in birth weight small for gestational age (SGA) is a recognized risk factor for development of neurologic deficits and cardiovascular disease later in

life.<sup>1,2</sup> In the 1970s, it was shown that nutritional deprivation during fetal development depressed mental ability in adults.<sup>3</sup> Since 1989, various studies have shown that children who are born with IUGR have an increased risk for hypertension<sup>4,5</sup> and coronary heart disease,<sup>6,7</sup> in both women<sup>8</sup> and men,<sup>9</sup> although the cause of this relationship is not well established. It has been hypothesized that the prenatal milieu, rather than the size at birth per se, leads to programming of neuroendocrine and vascular development.<sup>10</sup> The most frequent cause of IUGR is impaired placental function, which may be accompanied by characteristic changes in the umbilical artery and fetal aortic blood flow velocity waveform, suggesting an increase in placental resistance. We tested the hypothesis that IUGR with abnormal fetal blood flow is associated with long-term abnormal vascular morphology by analyzing retinal vasculature in young adults who were serially examined during fetal life with measurements of growth and blood flow velocity.

## METHODS

### Subjects

The subjects were part of a larger cohort ( $n = 178$ ) examined during fetal life in 2 prospective studies during a 3-year period, 1982–1985, at the Department of Obstetrics and Gynecology at Malmö University Hospital.<sup>11,12</sup> All subjects were examined serially with ultrasound and Doppler velocimetry with measurements of fetal growth and aortic blood flow velocity during the last trimester of pregnancy. At the age of 7 years, 149 subjects participated in a neurodevelopmental evaluation.<sup>13,14</sup> From the original cohort, subjects were selected with deviation in weight at birth and abnormal fetal blood flow ( $N = 21$ ) and a control group with normal fetal growth and normal fetal blood flow ( $N = 23$ ). Forty-four subjects thus were available for follow-up at a median age of 18.1 years (range: 17–19). Twenty-one of the subjects, 10 men and 11 women, were SGA at birth with a median deviation of weight at birth from the population mean of  $-31\%$  (range:  $-42\%$  to  $-22\%$ ), at a median gestational age of 38.7 completed weeks (range: 34–41). The blood flow velocity waveform of the fetal descending aorta was transformed into a semiquantitative variable, blood flow class (BFC), according to the degree of reduction of the diastolic component of the waveform and value of the pulsatility index.<sup>13</sup> The first fetal blood flow measurement was performed within 1 week after fetometry had showed suspected fetal weight deviation and then every second week. The last examination was performed at a median (range) time of 6 (0–41) days before delivery. In subjects in whom BFC changed during the course of study, the last measurement always represented the most severe abnormality. Fetal aortic BFC for the present study was defined according to the result of the last measurement performed before delivery. Nine subjects had BFC III (absence of positive flow throughout the diastole or reverse flow), 10 subjects had BFC II (nondetectable end-diastolic velocity), and 2 subjects had BFC I (positive diastolic flow and a pulsatility index of  $>2$

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**TABLE 1.** Retinal Vascular Branching Points, Visual Acuity, and BFCs According to Birth Weight for Gestational Age

	AGA* ( <i>n</i> = 23)	SGA* ( <i>n</i> = 21)	Significance of Difference ( <i>P</i> )
Retinal vascular branching points ( <i>n</i> )	26 (20–31)	28 (26–32)	<.03
Visual acuity BFC	1.20 (0.83–1.6) 0	1.29 (1–1.6) II (I–III)	NS -

NS indicates not significant.

\* Data represent median (range).

standard deviations above the mean reference value). The remaining 23 subjects, 13 women and 10 men, had a normal estimated fetal weight, normal aortic BFC, and a birth weight appropriate for gestational age (AGA; median weight deviation:  $-2\%$ ; range:  $-10\%$  to  $22\%$ ) at a median gestational age of 39.7 completed weeks (range: 36–42). Age at examination, height, weight, and head circumference did not differ significantly between the groups.

At follow-up, all subjects had an eye examination, including fundus photography after cycloplegia. Visual acuity ranged from 20/40 to 20/20 (median: 20/20; Table 1). Refraction ranged from  $-1.5$  to  $+2.0$  diopters. All fundus photographs were evaluated without knowledge of the subject's perinatal status by quantitative analysis of fundus morphology, using a computer-assisted digital mapping system.<sup>14</sup> All photographs were well focused with the optic disk well centered (within half a disk size off center). The original color transparency was projected simultaneously with the personal computer monitor image to facilitate definition of the different fundus structures of the scanned fundus photograph.

The retinal vascularization was analyzed with respect to number of branching points. Measurements of the retinal arterioles and venules (referred to as arteries and veins) were made by tracing each vessel (path length) from its origin on the optic disk to a reference circle with a radius of 3.0 mm from the geometric center of the optic disk. The number of vessel branching points within the reference circle was calculated automatically.

The fundus photographs from both eyes of an individual were evaluated, and the mean of the measurements was used for each individual in the analyses. The Committee for Research Ethics at Lund University approved the study, and informed consent was obtained from each subject.

### Statistical Methods

The median values of the number of branching points in subjects with IUGR were compared with those of the AGA individ-

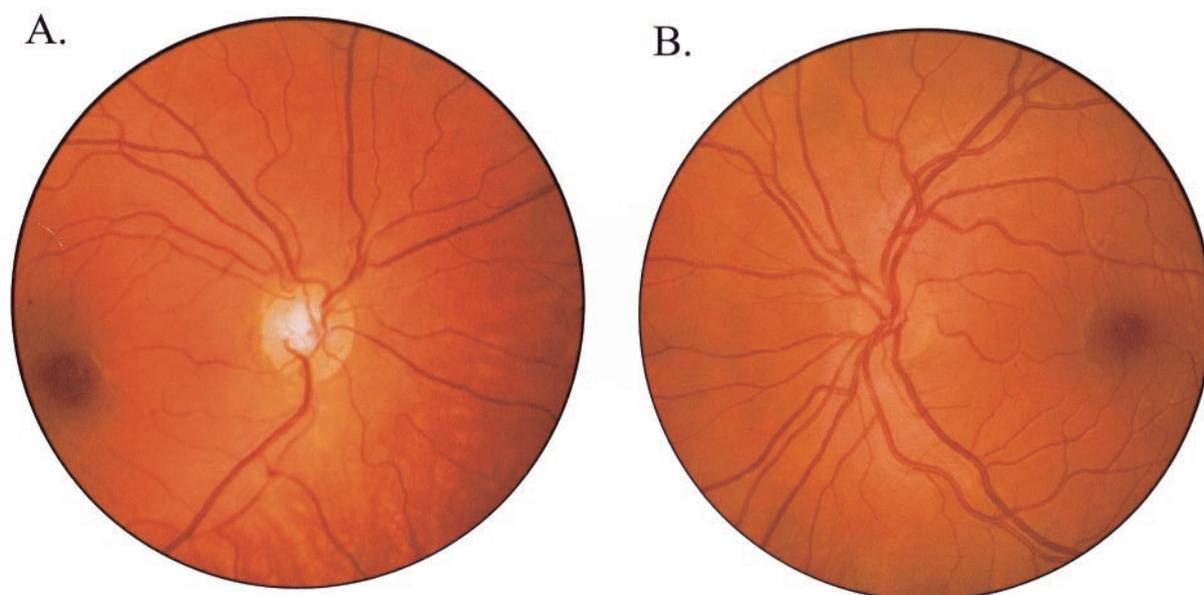
uals and control subjects by means of the Mann-Whitney test. Correlation between continuous variables was determined using linear regression analysis. Adjustment for the effect of multiple variables (gestational age, sex, and age at ophthalmologic examination) was performed using multiple regression analysis.  $P < .05$  was considered significant.

### RESULTS

Figure 1A demonstrates a reduced number of retinal vessel branching points of the optic nerve in a 18-year-old woman with an SGA birth weight and fetal aortic BFC III compared with that of an 18-year-old woman with normal fetal growth and normal fetal aortic BFC (Fig 1B).

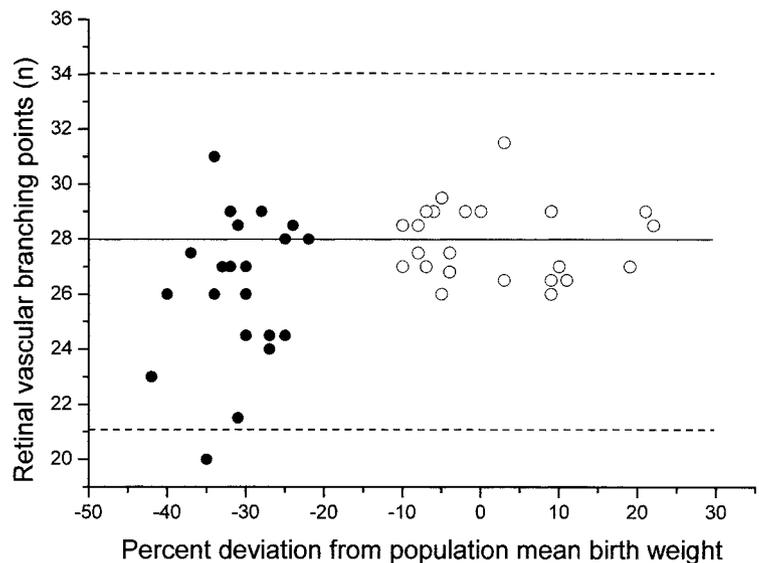
The relationship between birth weight deviation and number of retinal vascular branching points is shown in Fig 2. Within the entire group ( $N = 44$ ), increasing negative birth weight deviation was associated with a decrease in the number of retinal vascular branching points ( $r = 0.36$ ,  $P = .02$ ). Age at examination, sex, and the degree of abnormal fetal blood flow were not associated with number of retinal vessel branching points. Birth weight remained associated with number of vascular branching points when adjusted for gestational age at birth and sex using multiple regression analysis ( $r = 0.36$ ,  $P = .02$ ).

The median number of retinal branching points (median: 26; range: 20–30) in young adults with IUGR ( $n = 21$ ) was significantly lower than the me-



**Fig 1.** A, Reduced retinal vascularization in an 18-year-old woman with a birth weight SGA and fetal aortic BFC III. B, Normal vascularization in an 18-year-old woman with normal birth weight and normal fetal aortic BFC.

**Fig 2.** Number of retinal branching points in subjects with IUGR ( $n = 21$ ; ●) and in subjects who were born AGA ( $n = 23$ ; ○) in relation to a healthy reference group of control subjects.<sup>29</sup> The upper dotted line depicts the 5th centile and the lower dotted line depicts the 95th centile range, and the solid centerline indicates the median in relation to percentage of birth weight deviation from the mean of the normal population.



dian number of branching points of individuals who were born AGA ( $n = 23$ ) with normal fetal blood flow (median: 28; range: 26–32;  $P < .03$ ; Table 1). Among the individuals who were born with IUGR, not all had retinal vascular branching points below the median: 7 of 21 had branching points at or above the median. However, 7 of 21 had a number of branching points below the 25th centile of the reference group, whereas none among the AGA individuals had a number of branching points below the 25th centile.

## DISCUSSION

Our findings indicate that IUGR with abnormal fetal aortic blood flow is, in some cases, followed by a reduced number of retinal vascular branching points at young adult age. It is unclear whether this finding is restricted to the retina or represents a more global effect of vascular growth within the body.

A reduced number of retinal vascular branching points have been found in children with congenital growth hormone (GH) deficiency<sup>15</sup> and in subjects with Laron syndrome.<sup>16</sup> As both of these groups of patients have low levels of GH during a period when vascularization is not yet completed, GH or some factor in the GH axis, eg, insulin-like growth factor I (IGF-I), may be of importance for normal vascularization. In addition, experimental studies have shown that IGF-I regulates the action of vascular endothelial growth factor on both proliferation and survival of endothelial cells.<sup>17</sup> Several studies on SGA children have shown that these children have lower IGF-I levels, both in intrauterine life<sup>18–20</sup> and postpartum,<sup>21</sup> than do AGA children. However, IGF-I was not measured on the present study group, as these analyses could not be performed at time of birth of these individuals.

An important feature of the background study on intrauterine blood flow<sup>12</sup> is that the clinicians who treated the patients were blinded to the Doppler velocimetry results. Thus, the findings on fetal aortic flow did not influence the timing of delivery and outcome of pregnancy. It can be speculated whether

a more active obstetric approach based on the examination of fetal blood flow in IUGR fetuses might have a beneficial effect on their cardiovascular health later in life. This calls for more prospective interventional studies in pregnancies suspected of IUGR with follow-up.

During the past decade, several studies have reported that low birth weight is associated with raised blood pressure, increased mortality as a result of coronary heart disease,<sup>2,22</sup> and metabolic changes.<sup>23</sup> It has been hypothesized that “undernutrition before birth programs persisting changes in a range of metabolic and physiologic variables.”<sup>24</sup> In addition, it has been shown that vascular function may be affected in children with a history of low birth weight. Martin et al<sup>25,26</sup> showed that schoolchildren who were born SGA had impaired endothelial function in small and large arteries as well as carotid stiffness. These findings of functional deficits contributed to a better understanding of the link between low birth weight and cardiovascular disease.

Our observation lends support to these findings and suggests that both organ function and morphology may be affected in individuals after IUGR. It may be speculated that the retinal vascular pattern noted in young adults who were born SGA may reflect similar changes in other vascular systems with similar architecture and autoregulation, ie, cerebral, coronary, and renal vessels.

Abnormal fetal blood flow velocity in IUGR, which was present in the IUGR subjects in the present study, is an expression of placental dysfunction with resulting fetal hypoxemia and altered nutrition.<sup>12,27,28</sup> Whether it is the abnormal fetal blood flow or the resulting IUGR that is responsible for the abnormal retinal vascular morphology cannot be clarified from the present study.

It may be speculated that a reduction in oxygen delivery as well as nutritional deprivation during fetal life may be mechanisms for our finding of a reduced number of vascular branching points in the ocular fundus at young adult age. The implications

of these findings in other organ tissues need additional investigation.

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