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The neurocognitive outcome of IUGR children born to mothers with and without preeclampsia

Y. Leitner[2], S. Harel[2], R. Geva[2], R. Eshel[2], A. Yaffo[1] & A. Many[1]

[1]Department of Obstetrics and Gynecology and [2]Pediatric neurology, Lis Maternity Hospital, Tel Aviv Sourasky Medical Center, Tel Aviv University, Tel Aviv, Israel

Objective: **To examine long-term behavioral and neurodevelopmental outcome of children born growth restricted and exposed to hypertension in utero at 9 years of age.** ***Methods:*** **Somatic growth and neurocognitive outcomes were evaluated at age 9–10 years of age in 42 children born with intra uterine growth restriction (IUGR) after pregnancies complicated by hypertensive disorder (17 with maternal preeclampsia and 25 after gestational hypertension). This study group was compared to a control group of 78 IUGR children born after normotensive pregnancy.** ***Results:*** **Only weight was found to be significantly lower in the hypertensive-IUGR group, versus the normotensive IUGR children. No significant differences were found in any of the neurocognitive parameters including IQ, school achievements, and neurodevelopmental score at age 9–10 years.** ***Conclusion:*** **IUGR is a well known risk factor for later cognitive difficulties but maternal hypertensive disorder does not seem to add significantly to this risk.**

Keywords: IUGR, neurodevelopmental outcome, preeclampsia

Introduction

Intra uterine growth restriction (IUGR) the terminology for infants whose birth weight is below the 10th percentile for gestational age (GA) [1,2] occurs in 3–10% of all pregnancies. As previously described, it plays a significant role in short and long-term outcomes, reflected by neurodevelopmental and learning difficulties as well as in somatic growth failure and later risks for coronary heart disease, stroke and diabetes [3–8].

The incidence of preeclampsia is between 2 and 8%. Perinatal morbidity and mortality in newborns of mothers with preeclampsia is about five times more than the general population [9]. Preeclampsia and other hypertensive disorders during pregnancy are associated with IUGR in about one third of the cases. In our previous studies [10,11] at 3 years of age, a slight lower cognitive performance was noted in infants born to mothers with hypertensive disorder and especially in those with proteinuria, but at 6 years of age no significant differences in the neurological and cognitive outcome were found between two groups of IUGR children with and without maternal hypertension or preeclampsia. These findings suggested "catch-up" during childhood. Ounsted et al. [12], compared two large groups (100, 102, respectively) of children born to treated and untreated hypertensive mothers, and concluded that maternal hypertension is associated with a slight developmental delay in early childhood. Ehrenstein et al. [14], report of 17,457 young Danish adults who underwent intelligence testing at age 18 years, 891 (5.1%) were born after gestational hypertensive disorders. Compared with those born after normotensive pregnancies, the gestational hypertensive disorder was associated with a slightly reduced adult cognitive performance among male conscripts. The investigators, however, excluded from analysis those born small for GA to control for the potential effects of growth restriction on neurodevelopment.

There are, however, still very few published studies on the long-term outcome of children with both IUGR and preeclampsia, specifically studies differentiating the long-term cognitive outcome of growth restriction alone from those with concomitant maternal hypertensive disorder.

During the past 14 years our Child Development Center has been involved in a long-term prospective study following the neurodevelopmental outcome of children with IUGR [1]. We therefore, decided to take a specific look at the long-term neurodevelopment and cognitive performance of our IUGR study group at age 9–10 years, and compare those with both IUGR and maternal hypertensive disorder to their IUGR peers who were not exposed to maternal hypertension.

Subjects and methods

This study is part of a long-term prospective follow-up study on children born with IUGR, aimed at determining their neurodevelopmental and somatic outcomes at school age. Results of the study have been previously published [1].

All infants born consecutively after September 1992 at our medical center, with a birth weight <10th percentile for GA according to local birth weight curves [15] were included in the study and were prospectively followed up until age 9–10 years. The study group included both term and preterm newborns. Children with genetic syndromes, major malformations, congenital infections or significant birth asphyxia were excluded from the study. The children included in the study group all had a late (mid-second-third trimester) onset of IUGR, verified clinically and/or by prenatal ultrasound. We therefore, assumed that the majority of children in this study had suffered a vascular-placental induced growth restriction. This assumption was supported by pathologic studies of the placentae revealing vascular pathology in over 85%.

The medical records of both mothers and newborns were reviewed by a pediatric neurologist, and an interview was

Correspondence: Ariel Many, MD MHA, Lis Maternity Hospital Tel Aviv Sourasky Medical Center, 6 Weizman st, Tel Aviv, Israel. E-mail: many@post.tau.ac.il

conducted covering parental, medical, demographic and obstetric histories. Items describing maternal hypertension, proteinuria or edema during pregnancy were included in the obstetric risk questionnaire, as part of the study.

Preeclampsia was defined according to the criteria set by the American College of Obstetrics and Gynecology (ACOG). This included a systolic blood pressure of 140 mm Hg or higher or a diastolic blood pressure of 90 mm Hg or higher occurring after 20 weeks of gestation in a woman whose blood pressure has previously been normal and proteinuria, with excretion of 0.3 g or more of protein in a 24-h urine specimen or +2 in deepstick urine test. Maternal gestational hypertension was defined when no proteinuria was found. All parents provided their informed consent, and the study was approved by the local Ethics committee.

The children were followed up annually from birth by a team of pediatric neurologists and psychologists at the Tel Aviv Child Development Center. At the 9–10 years follow-up participants underwent a comprehensive neurodevelopmental evaluation. The full protocol was previously described [1]. IQ was constructed based on the performance in the general information subsets and the block design subsets of the WISC-R95 two-test short form [16]. Academic achievements were evaluated using the Kauffman Assessment Battery for Children (K-ABC) [17]. Biometric parameters (height, weight, head circumference) were taken by a qualified nurse.

The study group comprised 120 children whose medical records were complete for both maternal gestational blood pressure, presence of proteinuria or edema, and for the outcome parameters of somatic growth and neurocognitive parameters at age 9–10 years. Of these, 42 children were exposed to maternal hypertension during pregnancy (17 fulfilled the full ACOG criteria for preeclampsia, and 25 showed gestational hypertension only), and 78 served as the "IUGR control group", whose mothers were registered as normotensive during pregnancy.

Statistical analysis

The size of each of the study groups and the control group enabled us to detect a five points difference in the IQ, with a power of 80% and α error of 0.05. In order to compare the groups-means of the biometric measures and the neurodevelopmental and intellectual outcome parameters of 9–10 year-old children, Unpaired t test and Pearson χ^2 analyses were performed. Mann-Whitney U analyses were performed for comparing the parent's educational parameters.

Results

No significant differences were found at birth between the three IUGR groups for maternal or other demographic characteristics. This was also true when we compared hypertensive+preeclamptic group to the normotensive group except for birth weight, that was significantly lower for the hypertensive+preeclamptic group (1591 g ± 540 vs 1781 g ± 392, $p < 0.047$) Smoking was very uncommon in the study and control groups.

At age 9–10 years weight was significantly lower only for the hypertension group ($p < 0.024$) but not the preeclamptic group while other biometric parameters were not statistically different. While weight remained lower – it remained above the 10th percentile for age.

No statistically significant differences were found between the groups in IQ, school achievements, and neurodevelopmental score at age 9–10 years (Table I). Outcome was the same for IUGR hypertensive children with birth weights <5 percentile (extreme IUGR) and those born <10 percentile (not shown).

Discussion

We found no significant differences in the neurodevelopment, cognitive outcome and school achievements between the preeclampsia, maternal hypertension and normotensive IUGR groups. While more children in the hypertensive groups were performing in the low-normal range of IQ and academic achievement, these differences did not reach statistical significance. This is in contrast with our previous study of the same children at age 3 years [10,11], where we found lower IQ ($p < 0.03$) in the preeclampsia group, however, it does concur with the outcome we described at age 6 years for the more severe IUGR (<5 percentile BW) hypertensive pregnancies. This trend of "normalization" with age, in both neurodevelopment and cognition is in accordance with other outcome parameters in the IUGR children. The earlier influences of biological factors as reflected by lower cognitive achievements as well as small stature and weight at a young age are later compensated for by environmental factors, as maternal education [12]. Studies on the outcome of IUGR children have found positive correlations between somatic catch-up and cognitive outcome [13]. In the present group of hypertensive IUGR children, somatic growth at age 9–10 years differed from normotensive IUGR only in weight, but was not different for head circumference or height. Despite this difference- the weight of the hypertensive group remained above the 10th percentile for age indicating some "catch-up" growth (Table I), in correlation with the positive neurocognitive outcome. It remains to be verified over time if hypertensive pregnancy affects more specifically the catch-up in weight than it effects head circumference or height.

While our sample is small, affecting its statistical power, the prospective, longitudinal nature of the study, and the fact the

Table I. Comparison between normotensive IUGR children and hypertension/preeclampsia IUGR children at birth and at 9–10 years.

Parameter	Maternal normotension Iugr (78)	Maternal hypertension Iugr (25)	Maternal preeclampsia Iugr (17)	p^*	p^{**}
GA	36.47 ± 2.37	35.85 ± 2.65	34.92 ± 3.41	0.092	0.279
Birth weight (g)	1781 ± 392	1668 ± 430	1546 ± 532	0.100	0.226
Maternal education (years)	13.36 ± 2.54	13.08 ± 1.71	13.50 ± 2.40	0.839	0.621
Height (cm) 9 years	132.01 ± 6.02	129.96 ± 6.32	132.25 ± 5.13	0.879	0.146
Weight (kg) 9 years	29.32 ± 7.70	25.58 ± 4.68	27.38 ± 6.43	0.337	0.024
Head circumference (cm) 9 years	51.36 ± 1.78	50.66 ± 1.17	51.58 ± 1.74	0.636	0.072
IQ 9 years	101.67 ± 13.40	99.62 ± 9.69	101.2 ± 18.43	0.904	0.481
Neurodevelopment 9 years	87.47± 8.24	85.48 ±9.12	84.29 ±12.30	0.194	0.309
Kaufmann 9 years	602.90 ± 80.38	598.16 ± 79.05	612.94 ± 98.89	0.656	0.798

p^* preeclamptic versus normotensive
p^{**} hypertensive versus normotensive

same group of children is described over the years makes the findings important, in light of the very few studies available. The large study described by Ehrenstein et al. [13], reporting only a slightly reduced adult cognitive performance among male conscripts exposed to gestational hypertension, supports our own observation in the specific group of both hypertension and IUGR.

We did not evaluate the data based on indication for delivery. The GRIT follow up study examined pregnancies complicated by IUGR and compared children outcome between those immediately delivered and those with deferred delivery [18]. This study failed to demonstrate any difference at age 6–13 between the groups.

Our study has few limitations. We do not report arterial/venous fetal doppler flow studies in the groups. Our study includes mainly late onset IUGR, (mean GA 35 weeks). The importance of flow studies are well established in the literature in evaluating short outcome of neonates, but its significance in long-term follow-up is to be investigated [19]. Another reservation that should be kept in mind is that most of the children in the study group were born after a relatively mild hypertensive disorder, were usually under continuous medical surveillance, very few women were treated with anti hypertensive agents and the neonates did not suffer from extreme prematurity (mean GA = 35 weeks) or devastating perinatal events. The outcome of severe preeclampsia remote from term could be different and remains to be investigated.

Like other investigators, we previously found IUGR children were significantly delayed in growth parameters and neurocognitive performance at age 9–10 years [1] when compared to AGA matched controls. Gestational hypertension in general and preeclampsia specifically, as opposed to other perinatal risk factors, did not add a significant risk beyond the placental induced growth restriction itself. This prognostic message should be presented to both physicians and parents.

Declaration of Interest: The authors report no conflict of interests.

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