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Neonatal Developmental and Behavioral Outcomes of Immediate Delivery Versus Expectant Monitoring in Mild Hypertensive Disorders of Pregnancy: 5-Year Outcomes of the HYPITAT II Trial

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ABSTRACT

One in 10 pregnancies is affected by hypertensive disorders. These disorders, including hypertension, preeclampsia, worsening chronic hypertension, and superimposed preeclampsia, often require intervention in the form of delivery of the baby. Timing of delivery in hypertensive pregnancies—at term or preterm—comes with its associated risks. The current study aimed to analyze the impact of immediate versus expectant monitoring of hypertensive pregnancies on behavioral and neurodevelopmental outcomes at 5 years of age in affected offspring.

Study participants were pulled from the 2009–2013 HYPITAT II, consisting of women pregnant with hypertensive disorders and between the gestational ages of 34 and 36.6 weeks. Three hundred twenty-two of the 704 women from the HYPITAT II study were contacted about participation when their child reached 5 years old, and 148 consented to this 5-year follow-up study. Of these women, 76 and 72 were placed in the expectant monitoring group and immediate delivery group, respectively. Women were asked to complete surveys about their 5-year-old children. The Ages and Stages Questionnaire (ASQ) detected developmental delay, and the Child Behavior Checklist detected behavioral abnormalities in these children. Developmental outcomes of both 2- and 5-year-old children were also analyzed by the study team.

Study findings showed that 22% and 21% of the delivery group children and expectant monitoring group children had abnormal ASQ scores, respectively (absolute difference, 0.5%; confidence interval [CI], –13.7 and 14.7; $P = 0.94$). The varying ASQ scores between groups did not hold statistical significance. Additionally, findings showed 19% and 27% of the children in the delivery group versus expectant monitoring group had abnormal Child Behavior Checklist scores, respectively ($P = 0.3$). In analysis of the 2- and 5-year-olds, the study team found that fetal growth restriction was the most influential variable in development and behavioral outcomes at both time points (odds ratio [OR], 2.1; CI, 1.0–4.4, for abnormal development; OR, 2.2; CI, 1.1–5.5, for behavioral problems). Finally, the study team also observed that as maternal education increased, abnormal behavior and developmental outcomes decreased (OR, 0.6; CI, 0.3–1.1).

This study's findings did not prove that developmental and behavioral outcomes are significantly associated with gestational age at delivery. An increased risk in developmental delay was seen in 2-year-olds who had undergone immediate delivery. However, these findings were not observed 3 years later at age 5 years. Further research should be done to determine the best management of hypertensive pregnancies in regard to timing of delivery and preventing subsequent negative perinatal outcomes.

EDITORIAL COMMENT

(The timing of delivery of pregnancies with a range of complications has received enormous attention over the past decade. A consensus conference hosted by the National Institutes of Health, the

American College of Obstetricians and Gynecologists, and the Society for Maternal-Fetal Medicine led to the publication of a summary document that gave gestational ages to deliver a variety of pregnancy complications (*Obstet Gynecol* 2011;118:323–333). For example, placenta previa was recommended to be delivered at 36^{0/7} to 37^{6/7} weeks' gestation. Uncomplicated di-di twins were recommended to be delivered at 38 weeks' gestation. When considering these recommendations, in the case of placenta previa, immediate delivery increases the risk primarily to the neonate until 39 weeks' gestation is reached (*Am J Obstet Gynecol* 2008;199:370.e1–370.e7). However, expectant management of placenta previa increases the risk that the mother will experience a hemorrhage and potentially an emergent cesarean delivery; thus, the timing of delivery must balance the tradeoffs of the mother and baby (*J Reprod Med* 2010;55:373–381).

In the National Institutes of Health/American College of Obstetricians and Gynecologists/Society for Maternal-Fetal Medicine document, there was a recommendation for delivery of women with gestational hypertension to be at 37^{0/7} weeks' gestation to 38^{6/7} weeks' gestation and for those with mild preeclampsia to be delivered at 37^{0/7} weeks up to 37^{6/7} weeks. Interestingly, this is one of the complications for which there was a prospective trial to support this practice (*Lancet* 2009;374:979–988). The HYPITAT trial included 756 women with a singleton pregnancy at 36 to 41 weeks' gestation and complicated by gestational hypertension or mild preeclampsia; they were allocated to either labor induction or expectant management. In the induction group, labor was induced within 48 hours of randomization. Women in the expectant management group were monitored until the onset of spontaneous labor. The primary outcome was a composite of high-risk situations (ie, maternal mortality, maternal morbidity, progression to severe disease, and major postpartum hemorrhage). Secondary outcomes were cesarean delivery and a composite of adverse neonatal outcomes. The results from this trial found that there were no differences in neonatal outcomes, but that women had worse outcomes with more severe hypertension in the expectant management group.

Prior to 36 weeks, however, it is less clear what the optimal management is. Severe preeclampsia

is managed expectantly until 34 weeks' gestation, and so is mild preeclampsia. Traditionally, mild preeclampsia is also managed expectantly from 34 to 36 weeks' gestation as well, but there are similar tradeoffs between mother and fetus/neonate between immediate delivery and expectant management. The current study abstracted above attempted to examine these tradeoffs. This study was a 5-year follow-up to the randomized trial, HYPITAT II, in which women with a diagnosis of gestational hypertension or preeclampsia without severe features at 34^{0/7} weeks until 36^{6/7} weeks' gestation were randomized to delivery versus expectant management up to 37^{0/7} weeks' gestation. The primary short-term neonatal outcome was worse in the immediate delivery group with more suspected sepsis, transient tachypnea of the newborn, and admissions to the neonatal intensive care unit. The maternal outcomes, although were slightly higher risk, did not reach statistical significance. Additionally, there was no difference in the risk of cesarean delivery between the groups.

Recently, there was a study of the 2-year outcomes of HYPITAT II that demonstrated a small but significant difference with worse developmental outcomes among those neonates delivered immediately versus those managed expectantly (*Am J Obstet Gynecol* 2019;221:154.e1–154.e11). The current article reports on the 5-year developmental outcomes from the trial. Fundamentally, it demonstrates no difference in developmental outcomes at 5 years of age. Interestingly, it also showed that children who had fetal growth restriction at birth were at increased risk of lower developmental scores. It also showed that children born to more highly educated mothers had better developmental scores.

Thus, while the prior HYPITAT studies suggested that expectant management of preeclampsia without severe features should be recommended until 37 weeks' gestation, the current study suggests that, in the setting of fetal growth restriction, one might consider delivering even sooner. I do think the issue of fetal growth restriction is an important one. We know that one reason to identify fetal growth restriction is to increase surveillance and deliver prior to stillbirth. But, given that fetal programming responses to the intrauterine environment that lead to fetal growth restriction, we really need a tool to

identify impending growth restriction. An approach of delivering such patients when fetuses are at the 15th or 20th centile is interesting, but would, of course, increase intervention without clear benefit.

Meanwhile, we have another study with longer-term outcomes that does not support earlier findings. While I would not be inclined to start routinely delivering patients with hypertensive disorders of pregnancy prior to 37 weeks, I do think that thoughtful and more

aggressive fetal assessment may be indicated. A fetus that has decreased growth, even without having achieved the 10th centile, might benefit from delivery prior to 37 weeks' gestation in this setting. However, elucidating which ones may benefit will be the continuing clinical and scientific challenge in the management of both hypertensive disorders of pregnancy and fetal growth restriction.—ABC)

Investigating the Association Between Post-Term Birth and Long Term Cognitive, Developmental and Educational Impacts: A Systematic Review and Meta-analysis

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ABSTRACT

The impact of preterm birth on infant risk has been well established. However, the majority of the research on postterm birth, defined as 42 weeks and 0 days' gestational age and greater, has been focused on its association with immediate, short-term outcomes such as infection, stillbirth, and complications surrounding delivery. The authors of this study aimed to evaluate the cognitive and educational outcomes of postterm birth through systematic review and meta-analysis of the literature.

This was a systematic review of the literature within MEDLINE database. Titles were screened by key exposure terms and utilized to filter for relevant literature. Further, articles were deemed relevant if the exposure was linked to postterm delivery. Applying outcome terms to the search produced 2 groups: poor cognition or educational achievement. Abstract review was performed and screened for inclusion criteria, including neurodevelopmental, cognitive, or educational outcome scores reported at or greater than 1 year of life; summary outcomes for postterm infants; comparison group of non-postterm infants; and cohort, case-control, or randomized trials.

The literature review resulted in a total of 1318 publications, and further screening allowed for 13 articles to be eligible for review, published between 1969 and 2017. The 2 studies with binary cognitive outcomes reported an association between postterm infants and a higher risk of low cognitive scores in comparison to the term infants observed (odds ratio, 1.06 [1.04–1.08]). Four of the articles reported an association between postterm infants and a reduced mean cognition (–1.90 [–3.50 to –0.31]). Postterm birth's association with negative outcomes decreased minimally when other developmental measures were factored in (odds ratio, 1.06 [1.00–1.13]), which was also observed in mean scores (–1.44 [–3.00 to 0.11]). Notably, none of the 13 studies analyzed found variation within mean education outcomes.

Through the meta-analysis and the review of these 13 studies, the authors found a small association between postterm birth and negative cognitive outcomes in comparison to term deliveries. These findings proved consistent across all studies reported by the 13 publications. These findings can be utilized to improve pregnancy outcomes and timing of delivery. Findings surrounding educational outcomes had less evidence and should be further studied.