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Published in:
Obstetrical and Gynecological Survey

DOI:
10.1097/01.ogx.0000650908.25143.57

Publication date:
2020

Neonatal Developmental and Behavioral Outcomes of Immediate Delivery Versus Expectant Monitoring in Mild Hypertensive Disorders of Pregnancy: 2-Year Outcomes of the HYPITAT-II Trial

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Am J Obstet Gynecol 2019;221:154.e1–154.e11

ABSTRACT

Hypertensive pregnancy disorders complicate up to 10% of pregnancies worldwide, resulting in significant maternal and neonatal morbidity. The only definitive treatment for hypertensive disorders is delivery. This issue was addressed in the Hypertension and Preeclampsia Intervention Trial at Near Term (HYPITAT-II). The study compared immediate delivery to expectant monitoring in women with pregestational hypertension or mild preeclampsia, with a result of 5.7% of the neonates diagnosed with respiratory distress syndrome, as compared with 1.7% in the expectant monitoring group. A follow-up study attempted to assess the developmental difference at the age of 2 between children from both the immediate delivery and expectant monitoring groups of this study.

Of 704 women from the original study, 504 were approached to participate in the follow-up, and 330 agreed. Participating parents were to fill out the "The Ages and Stages Questionnaire," which is a screening instrument to detect developmental delay in children. The questionnaire includes 5 developmental domains: communication, gross motor, fine motor, problem solving, and personal social behavior. Each of these domains includes 6 questions that can be rated at a level of 0, 5, or 10 points reflecting respectively whether the child is not yet able, sometimes is able, or is fully able to perform the behavior described. A maximum score of 60 can be achieved on each domain, and lower scores indicate less attainment of developmental milestones.

In the immediate delivery group, 28% of the infants had an abnormal ASQ score, compared with 18% in the expectant monitoring group ($P = 0.045$). In all of the developmental subdomains, a trend toward a higher percentage of abnormal outcomes was observed in the immediate delivery groups.

Overall, in this follow-up study of 342 children (49%) born from mothers included in the HYPITAT-II study, infants at 2 years of age had more often an abnormal ASQ score when in the immediate delivery group as compared with children in the expectant monitoring group. This finding remained consistent after an adjustment for birthweight and maternal education level, indicating that management policy remained a significant predictor of neurodevelopmental outcome of the child. The children in both management groups of the study, born preterm due to hypertensive disease, have an increased rate of abnormal neurodevelopmental scores. This finding is consistent with previous studies reporting hypertensive disorders and impaired development later in life. As reassessment of the HYPITAT-II study indicated that children born preterm had more often abnormal ASQ scores than children born at term, timing of delivery is significant and should be taken into consideration when contemplating whether to expectantly monitor or immediately deliver a child whose mother has a hypertensive pregnancy disorder. The study also found that birthweight was an independent predictor of abnormal neurodevelopment. All of these findings indicate that clinicians should consider that low birthweight, growth restriction, and early induction of labor can all have long-term negative effects on the development of a child.

The study concluded that despite relatively small gestational age differences between groups, neurodevelopmental problems at 2 years of age occur more often after immediate delivery compared with expectant monitoring in preterm hypertensive disorders of pregnancy, corrected for birth weight and maternal educational level. These findings did not include any indication of behavioral problems associated with immediate delivery. In conclusion, expectant monitoring remains the most appropriate management strategy for preterm hypertensive disorders.

EDITORIAL COMMENT

(The timing of delivery of pregnancies with a range of complications has received a lot attention over the past decade. Because of an increase in iatrogenic late preterm births and early term births, there was a push to delay deliveries to at least 39 weeks' gestation. This guideline from the American College of Obstetricians and Gynecologists (ACOG) became a quality metric supported by JCAHO and was widely adopted. The problem was that, in this push to avoid these births before 39 weeks' gestation, it appeared that such delay were also happening in some high-risk pregnancies as well. I recall giving a lecture on the topic at a local hospital, and a week later, one of the physicians there called me to relay a story of nurses questioning the delivery of a patient with severe preeclampsia at 36 weeks' gestation because of not wanting to cause a preterm birth. In response to these concerns and other issues related to timing of delivery, 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, and uncomplicated Di/Di twins were recommended to be delivered at 38 weeks' gestation.

When considering these recommendations, the tradeoffs are different for the 2 clinical situations. 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.e1–7). However, expectant management of placenta previa increases the risk that the mother will experience a hemorrhage, a transfusion, and potentially an emergent cesarean delivery. With the timing of delivery of twins, the tradeoffs are primarily between complications of prematurity versus the ongoing risk of stillbirth (*Am J Obstet Gynecol* 2015;212:630.e1–630.e7). These recommendations for timing of delivery were informed by existing data about the risks, occasionally decision analyses (*J Reprod Med* 2010;55:373–381), but very few prospective, randomized trials.

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.

Having answered the question about when to deliver mild preeclampsia in the early term period, the group of investigators in the Netherlands who seem to accomplish even more randomized trials than our own Maternal-Fetal Medicine Units Network sought to determine from 34 to 36 weeks whether it is better to deliver immediately or manage expectantly. In that study, HYPITAT-II, 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 (*Lancet* 2015;385:2492–2501). The primary 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 with slightly higher risk, did not reach statistical significance. In addition, there was no difference in the risk of cesarean delivery between the groups. This study, then, supported expectant management primarily for the neonatal outcomes.

In the article abstracted previously, the neonates from HYPITAT-II were followed up at 2 years of age to ascertain early neurodevelopment. They used the Ages and Stages Questionnaire and found that 28% of the children in the immediate delivery arm had an abnormal Ages and Stages Questionnaire as compared with 18% in the expectant delivery group ($P = 0.045$). As with all studies, there are limitations. In this study, of the original 704 neonates, only 330 agreed to do the follow-up, which may introduce selection bias. Another potential issue is that if there was a high mortality rate in these children and that mortality rate was even higher in the expectant management group, then these findings would inaccurately represent the impact of the study. However, although one might expect more stillbirths in the expectant management group, most evidence would support a higher infant mortality rate in the immediate delivery group. Ultimately, however, a study of this size would unlikely be powered to examine mortality differences.

Of note, this follow-up study supports the initial findings of the HYPITAT-II study, suggesting that before 37 weeks' gestation, the management of gestational hypertension or preeclampsia without severe features should be managed expectantly. However, to reduce the potential for maternal or fetal/neonatal morbidity, close follow-up with frequent maternal and fetal testing is necessary. Although such expectant management is increasingly being done out of the hospital, the frequency of testing and follow-up should not be reduced. Further, out-of-hospital management should really be reserved only for those individuals who are stable and can readily do the required follow-up to ensure that we do not see an increase in complications in these women.—ABC)

Maternal and Neonatal Outcomes Associated With Trophectoderm Biopsy

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Fertil Steril 2019;112:283–290.e2

ABSTRACT

The use of preimplantation genetic testing (PGT) is increasing rapidly, having gone from 4% of all cycles in 2005 to over 22% in 2015. Despite this increasing use, maternal and neonatal outcomes for pregnancies achieved via in vitro fertilization (IVF) with PGT have very little assessment. As trophectoderm biopsy removes cells that are destined to form the placenta, there is potential for an increased risk of adverse pregnancy outcomes associated with abnormal implantation. This cohort study assesses whether pregnancies achieved with trophectoderm biopsy for PGT have different risks of adverse obstetric and neonatal outcomes compared with pregnancies achieved with IVF without biopsy.

The primary aim of the study was to examine obstetric outcomes, specifically the incidence of preeclampsia or the presence of hypertension after 20 weeks of gestation in a previously normotensive woman and proteinuria. New-onset hypertension in