

GRIT trial: Delayed delivery for growth-restricted fetuses?

The GRIT study group. Infant wellbeing at 2 years of age in the Growth Restriction Intervention Trial (GRIT): multicentred randomised controlled trial. *Lancet*. 2004;364:513–520.

OBJECTIVE To compare 2 interventions for growth-restricted fetuses remote from term: early delivery to preempt intrauterine hypoxia, and delayed delivery for as long as possible to gain maturity.

RESULTS At 2 years, the overall rate of death or severe disability was 55 (19%) of 290 immediate births and 44 (16%) of 283 delayed births. After adjustment for gestational age and umbilical-artery Doppler category, the odds ratio was 1.1, indicating a trend toward more disability with immediate delivery, and the 95% credibility interval was 0.7 to 1.8.

EXPERT COMMENTARY Optimal timing of delivery in high-risk pregnancies continues to confound obstetricians and perinatologists. This randomized, controlled trial attempts to address the issue in the setting of fetal growth restriction. It involved 548 pregnant women in 13 European countries who had fetal compromise between 24 and 36 weeks of gestation. In all cases, it was uncertain whether immediate delivery was indicated. These women were randomized to immediate delivery (within 48 hours to permit steroid administration) or deferred delivery (until safe delivery could be delayed no longer because of worsening test results or the passage of time). The median interval between randomization and delivery was 0.9 days with immediate delivery and 4.9 days with delayed delivery. **Strengths** lie in the trial design, 2-year follow-up of infants, blinded outcomes assessment, and statistical analysis.

Weaknesses include the trial's multicenter

nature, lack of standardization for management interventions, and probable practitioner variability in disability assessment among the 69 hospitals involved.

Unanswered questions. We are not told the degree of growth restriction of the cases enrolled, or whether any misclassification errors occurred.

Decisions regarding route of delivery and intrapartum management were left to the provider's discretion and were not standardized; this is important because a number of intrapartum events can lead to perinatal morbidity and mortality. Unexplained antepartum fetal death occurred more frequently in the expectantly managed group; the only cases of intrapartum trauma or asphyxia occurred in that group as well.

That said, at 2 years the overall results are similar between the groups. Investigators concluded that, while obstetricians seem to be intervening at the appropriate time, early intervention may not translate into improved outcomes overall.

Absent from the dialogue is the medicolegal risk associated with what some would consider inordinate delay in delivery versus premature intervention. The former generally would have the less favorable medicolegal outcome.

BOTTOM LINE This study fails to definitively identify the optimal intervention in high-risk pregnancies remote from term. Antenatal testing remains imprecise, and fetal demise from delayed intervention must be weighed against the risk of long-term disabilities from intervening too early.

For now, the obstetrician must rely on close fetal surveillance and gestational age as the prime drivers of delivery decisions. It is also crucial that we adequately communicate

to patients the potential risks associated with the 2 strategies.

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Serum levels of 2 peptides help predict preeclampsia

Levine RJ, Maynard SE, Qian C, et al. Circulating angiogenic factors and the risk of preeclampsia. *N Engl J Med*. 2004;350:672–683.

OBJECTIVE To explore the role of angiogenic factors in preeclampsia—specifically, whether circulating soluble fms-like tyrosine kinase 1 (sFlt-1), which binds placental growth factor (PlGF) and vascular endothelial growth factor (VEGF), plays a pathogenic role.

RESULTS Increased levels of sFlt-1 and reduced levels of PlGF predicted the subsequent development of preeclampsia.

EXPERT COMMENTARY In this nested case-control study involving 120 pairs of women, researchers determined serum levels of 3 peptides known to be involved in modulating angiogenesis: sFlt-1, PlGF, and VEGF. They found that levels of sFLT-1 increased and PlGF decreased with advancing gestation in normotensive control pregnancies. These changes occurred earlier in gestation and to a more exaggerated extent among the cases that went on to develop preeclampsia. VEGF levels remained low throughout pregnancy, but did differ between cases and controls.

Levels of sFlt-1 increased 5 weeks prior to the development of clinical preeclampsia, while the decrease in PlGF could be noted in the middle trimester.

Strengths and weaknesses. The analytic, statistical, and methodological aspects of this study are sound. However, because of the nested, case-control design, it is impossible to calculate sensitivity, specificity, and positive and negative predictive values for any of these analytes. As an accompanying editorial notes,

not all women with abnormal changes in sFlt-1 and PlGF went on to develop preeclampsia.¹ A larger, prospective trial is needed to establish the clinical utility of these markers in predicting preeclampsia.

Endothelial dysfunction has long been a hallmark of preeclampsia, and various associations or explanations have been proposed (Savvidou²). Levine et al provide a framework that fits the symptoms of edema, hypertension, proteinuria, and resultant end-organ dysfunction into a paradigm that is useful in its organization, ability to generate testable hypotheses, and suggestion of potential therapy other than delivery.

Unanswered questions. This research adds to our understanding of how the pathology of preeclampsia propagates and becomes clinically recognizable. It offers less insight into the equally interesting question of what causes the initial perturbation that goes on to cause preeclampsia. Another important question is whether we should be developing a screening test for a condition that can as yet be cured only by delivery.

One might argue that knowing who is at increased risk would allow closer fetal testing, maternal observation, and an opportunity for earlier intervention in the form of antenatal steroid administration or delivery. However, these may be relatively small advantages over conventional prenatal screening, given the risks of increased maternal anxiety and the additional burden on a system of care that is already financially stressed and legally embattled.

BOTTOM LINE This study is the latest of several publications³⁻⁵ that suggest we may finally be moving toward a more complete understanding of preeclampsia. It should be of interest to all obstetricians because it adds to general, specialty-specific background knowledge and holds promise as a source of therapy. These observations also raise the possibility of a predictive test for preeclampsia that might be applied before clinical symptomatology appears.

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Topical lidocaine eases pain of vulvar vestibulitis

Zolnoun DA, Hartmann KE, Steege JF. Overnight 5% lidocaine ointment for treatment of vulvar vestibulitis. *Obstet Gynecol*. 2003;102:84–87.

OBJECTIVE To assess the efficacy of nightly 5% lidocaine ointment for vulvar vestibulitis.

RESULTS After 7 weeks of treatment, 76% of 61 women were able to have intercourse, compared with 36% before therapy ($P = .002$). The intercourse-related pain score—based on a 100-mm visual analog scale—was 39.11 points lower after treatment (95% confidence interval [CI] 30.39–47.83; $P < .001$), with a decrease of 10.37 points in the daily pain score (95% CI 3.53–17.21; $P = .004$). Although few patient characteristics predicted treatment response, women with interstitial cystitis and other vulvar conditions were least likely to benefit.

EXPERT COMMENTARY Vulvar vestibulitis, a perplexing syndrome of chronic burning/pain with few overt physical findings, has responded poorly to medical therapies. When these fail, the only treatment demonstrated to give any improvement is surgical excision of the vestibule, a rather extreme treatment with side effects that can be severe.

Recently, less invasive vestibulitis treatments have been described, with rates of improvement that approach those of surgical excision. For example, Murina and colleagues¹ showed that repeated submucous

vestibular injection of lidocaine and methylprednisolone yields substantial improvement in 68% of subjects, a rate similar to that of vestibulectomy—without the side effects.

Now Zolnoun et al report that a topical lidocaine application, even less invasive than submucosal injections, leads to a similar rate of improvement. Patients applied lidocaine 5% ointment to the vestibule via a saturated cotton ball every night and removed it about 8 hours later. Side effects were limited to transient burning at the application site in some patients.

Findings confirm anecdotal evidence. Local lidocaine application is one of several vestibulitis therapies that heretofore was supported only by anecdotal evidence. Zolnoun and colleagues are to be complimented for summarizing patient outcomes, which make it possible for us to quote benefits and risks for topical lidocaine ointment to our patients.

Weaknesses. Investigators failed to include a control group, but many reports of vestibulitis therapies suffer from this shortcoming. However, the history of severe, persistent vestibular pain in the patients in this study makes it unlikely that their pain abated from the emollient effects of the petrolatum base. It will be interesting to see how this treatment fares in a randomized controlled trial.

BOTTOM LINE In light of the safety, simplicity, and low expense of topical lidocaine, it seems reasonable to consider its use in patients with pain isolated to the vestibule who have achieved a normal pattern of vaginal flora free of fungal organisms.

A 2-month trial certainly should be considered before resorting to more drastic treatments such as vestibulectomy. ■

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