Bioethics of Translating Limited Evidence into Clinical Practice: Case Study of the Cerebroplacental Ratio


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Abstract

Bioethics can help address the challenges of translating research into clinical practice in the twenty-first century. The cerebroplacental ratio in obstetrical ultrasound provides a case study of how bioethical principles can help advance practical approaches when evidence is limited. This can help clinicians use cerebroplacental ratio when additional risk factors are present in critical cases that warrant increased surveillance; disclose limited information appropriately; allocate resources; and weigh benefits against risks. Balancing the key ethical principles of respect for autonomy, beneficence, non-maleficence, and justice within this context illuminates how bioethics can assist health care providers as well as help set a research agenda. Such analyses are essential to improving clinical care, given the rapid pace at which medicine is evolving.

Résumé

La bioéthique peut aider à relever les défis que représente la transposition de la recherche dans la pratique clinique au XXI[e] siècle. Le rapport cérébro-placentaire à l'échographie obstétricale fournit une étude de cas sur la façon dont les principes bioéthiques peuvent contribuer à faire progresser les approches cliniques lorsque les données probantes sont limitées. La bioéthique pourrait aider les cliniciens à utiliser le rapport cérébro-placentaire pour les cas critiques qui justifient une surveillance accrue lorsque d'autres facteurs de risque sont présents, mais aussi à communiquer des renseignements limités de manière appropriée, à affecter les bonnes ressources et à soupeser les risques et les avantages. Dans ce contexte, l'équilibre des principes éthiques importants que sont le respect de l'autonomie, la bienfaisance, la non-malfaisance et la justice illustre comment la bioéthique peut aider les fournisseurs de soins de santé et contribuer à la mise au point d'un programme de recherche. Étant donné le rythme rapide auquel la médecine évolue, de telles analyses sont essentielles à l'amélioration des soins cliniques.

Key Words: bioethics; obstetrics; ultrasonography; translational medical research

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INTRODUCTION

Broader application of bioethical principles, including respect for autonomy, beneficence, nonmaleficence, and justice, may address challenges in research and knowledge translation. Obstetricians must make difficult decisions when empirical evidence is limited. Not all aspects of medicine are suited to randomized controlled trials (RCTs), although pressures to better understand effective interventions have fostered a perceived need for more RCTs. Meta-analyses and systematic reviews also have limitations. RCTs require funding, approval, participant enrolment, and delay of results. The lag from "bench to bedside" can be 17 years.[1]

The cerebroplacental ratio (CPR) in obstetrical ultrasound provides a valuable case study of how bioethics can help resolve dilemmas in applying limited and observational data to improve clinical care, while keeping pace with evolving

knowledge. Specifically, the extent to which the evidence links this tool to other risk factors might guide how the CPR is used to mitigate adverse outcomes, rather than using it to intervene more dramatically to directly affect outcomes.

CEREBROPLACENTAL RATIO: EVIDENCE TO DATE

In obstetrical ultrasound, the CPR is a surveillance metric that represents the degree of fetal brain-sparing due to hypoxia when complications compromise fetal health. The CPR is a ratio of the middle cerebral artery pulsatility index to the umbilical artery (UA) pulsatility index. This ratio has the advantage of being more sensitive in detecting fetal brain-sparing when its individual components are borderline normal or when one component is normal and the other is abnormal.[2]

Low CPR has been associated with several adverse obstetrical outcomes, mostly in retrospective studies. These include risk factors such as intrauterine growth restriction (IUGR),[3,4] reduced fetal growth velocity,[5] and decreased fetal movements[6] that are associated with downstream complications. Low CPR has also been directly associated with downstream adverse outcomes, such as perinatal death[7] and composite neonatal morbidity,[8,9] independently of other risk factors and in fetuses that are appropriately grown for gestational age (AGA).[2] In twins, sparse evidence has shown low CPR to be associated with perinatal loss[10] and fetal growth disorders.[11,12] Early-term delivery in SGA fetuses with low CPR and increased surveillance in term AGA fetuses with low CPR have been suggested.[13] Clinicians and researchers are often hesitant to apply the results of observational studies owing to concerns about implicit bias.

In this article, we present ways that bioethical principles can help translate CPR evidence into clinical practice and inform research. Specifically, applying CPR when other risk factors for downstream adverse perinatal complications are also present might improve clinical care and optimize benefits while minimizing risk and potential bias, respecting autonomy, and avoiding undue health care system burdens.

BIOETHICAL FRAMEWORK: FIVE MAJOR QUESTIONS REGARDING CLINICAL USE OF THE CPR

What Should Obstetricians Do in Cases of IUGR with Low CPR but Otherwise Normal Doppler Findings?

Should these patients have increased surveillance?

There would be little risk and some possible benefit from increasing ultrasound frequency or doing additional nonstress tests, particularly because IUGR cases already undergo increased surveillance. In terms of resource allocation and concerns of justice in a public health care system, additional resource use would be marginal, and clinical benefits might be optimized.

Is earlier delivery indicated? How much earlier?

Delivering too early may increase complications related to prematurity, but earlier delivery may avoid potential adverse outcomes associated with low CPR. In terms of how much earlier to consider delivery for low CPR, more data are needed for such a major intervention. Should delivery occur as early as in cases of umbilical artery absent end-diastolic flow (early-term, 36–37 weeks) or umbilical artery reversed end-diastolic flow (preterm, 34 weeks or sooner), or somewhere in between?

Implicit concerns emerge about maternal autonomy regarding disclosure that evidence is limited and about the patient's role in balancing benefits against risks (informed consent). If the primary concern is adverse outcomes associated with low CPR, patients may prefer earlier delivery (e.g., 36–37 weeks). If concerns about late prematurity take precedence, delivery around 38 weeks might be preferred (e.g., IUGR with otherwise normal Doppler findings) with additional surveillance.

Should All Singletons Get a Third-Trimester Screening Ultrasound in Which Growth and Doppler Results (Including the CPR) Are Documented?

Benefits, risks, and resource allocation are the main considerations. Universal third-trimester ultrasound screening in low-risk pregnancies is neither cost-effective nor clinically beneficial.[14] Even with increased detection of late-onset IUGR, there are more false positives for SGA fetuses closer to term, exacerbating maternal anxiety and short-term neonatal morbidity with unnecessary early-term delivery.[15] For CPR, a large prospective observational study determined that low CPR <10th percentile on routine ultrasound at 36–38 weeks was a poor predictor of adverse perinatal outcomes.[16] CPR varies with gestational age, rising until 34 weeks gestation, then slowly decreasing until term[17]; therefore centile cutoffs are preferred to absolute values. This study's cutoff for low CPR was higher than usual (<2.5–5th percentile). This is bioethically relevant because lower cutoffs increase specificity while reducing sensitivity, whereas higher cutoffs have the opposite effect, blunting associations with adverse perinatal outcomes. Nevertheless, the study's findings corroborate the evidence for reduced reliability of adverse outcome prediction with *universal* late-term ultrasound, so this would not be recommended.

In Singletons Demonstrating Appropriate Growth with a Third-Trimester Ultrasound for Other Indications, is CPR Recommended, and What Should Be Done if it is Low?

Third-trimester ultrasounds involve fetal assessment to rule out IUGR and ensure appropriate interval growth because reduced growth velocity, especially by more than 30 centiles between 28 and 36 weeks, is associated with increased risk of stillbirth.[5] In AGA fetuses, given the current evidence, clinical response to low CPR might depend on other factors such as two or more episodes of decreased fetal movement,[6] decreased growth velocity,[5] or low-normal estimated fetal weight. In those cases, we may recommend follow-up ultrasound or potentially consider early-term induction, in rare instances. Since low CPR has been associated with intrapartum fetal compromise and adverse perinatal outcomes in AGA fetuses, in retrospective studies, obstetricians might have a lower threshold to expedite delivery in labour (e.g., reduced tolerance for atypical fetal heart tracings) when low CPR has been previously documented, pending availability of more prospective data.

In Monochorionic Twin Pregnancies, is Enough Evidence Available to Have a Thorough Disclosure Discussion with Pregnant Women?

With monochorionic twins, resource allocation is less problematic because these pregnancies already involve frequent ultrasound surveillance for complications specific to multiple gestations. If low CPR is detected, how should this information be disclosed, out of respect for patient autonomy, while balancing the potential harms of disclosure with significantly limited evidence in multiples?

The risk–benefit balance of patients knowing versus not knowing information is not a new dilemma. Knowing may cause unnecessary anxiety, but ignorance may lead to unintended consequences such as missed follow-ups. In the face of serious complications, patient perception that information was withheld may damage the physician–patient relationship. Conversely, knowledge might positively alter patient behaviours (e.g., increased vigilance about reduced fetal movement, with earlier triage presentation). If obstetricians increase surveillance based on low CPR, the reason should be communicated appropriately, minimizing patient distress.

In Monochorionic Twins or AGA Fetuses with Low CPR, Should Obstetricians Prepare for Possible Preterm Birth? Should a Low CPR Prompt Decisions to Deliver and, if so, When?

Further evidence is required before significant alterations to clinical management are made, particularly when interventions might have major consequences (preterm birth) compared with increased surveillance in the face of compounding risk factors. One might apply a bioethical approach by optimizing benefits and minimizing harms incrementally, first with minor interventions such as increased surveillance, neonatal intensive care unit consultation, and consideration of antenatal steroid administration (as appropriate), before moving towards major interventions such as earlier delivery or cesarean delivery.

Evidence from minimal intervention may indicate, for example, that only persistently low CPR over sequential scans is associated with adverse outcomes, which might inform the approach to timing of delivery. This incremental research agenda would promote greater data collection, including neonatal outcomes, before exposing these pregnancies to the risks associated with the complications of prematurity. The clinical impact of these interventions should be taken into account, such as masking of abnormal Doppler results after antenatal corticosteroid administration. Throughout an incremental research process, the maintenance of equipoise is essential to trial design, with perhaps a rebalancing and adjustment of thresholds for intervention in higher risk patients, based on observational data, compared with lower risk patients.

CONCLUSIONS

Bioethical approaches can aid clinicians in applying limited evidence in practice. As we seek to translate evolving knowledge from research more effectively into clinical practice, our ability to successfully use observational data to ethically inform patient care is critical. The CPR's role in obstetrical ultrasound provides a case-based example of how to convert bioethical principles into usable clinical tools. Increasing surveillance when low CPR is observed along with other risk factors for downstream obstetrical complications can optimize benefits, minimize risk, and efficiently use resources while respecting patient autonomy. This approach can also help set an incremental research agenda, gradually escalating or reducing the degree of intervention as more evidence comes to light regarding the benefit of intervention. Bioethical perspectives can thus improve the ways in which we build knowledge and expertise, leading to improved clinical care at a pace that strives to keep up with the rapid production and dissemination of new information.

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