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Quality Improvement in Perinatal Medicine and Translation of Preterm Birth Research Findings into Clinical Care

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Abstract

Billions of dollars are spent yearly in perinatal medicine on studies designed to improve outcomes for mothers and/or their neonates. However, implementing research findings is challenging and imperfect. Strategies for implementation must be multifaceted and comprehensive. These implementation challenges extend to, and are often greater in, translational and basic science research. The purpose of this review is to discuss current challenges in the provision of quality perinatal and neonatal medical care, particularly those related to preterm birth, and provide examples of prematurity-related perinatal quality collaborative initiatives. Finally, we will review considerations in implementing both clinical and translational/basic science prematurity research.

Keywords

spontaneous preterm birth; translational research implementation; perinatal quality collaboratives

Introduction

Billions of dollars of research money are spent each year within the fields of obstetrics and neonatology focusing on prevention or management strategies designed to improve outcomes for mothers and/or their neonates. However, the process of implementing research findings is challenging and imperfect. Appropriate and timely implementation may improve

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both maternal and neonatal morbidity and mortality. Conversely, premature adoption of studies without adequate scientific backing may produce inadvertent harm. For example, a trial demonstrating that intrapartum exposure to a medication reduces the risk of neonatal intraventricular hemorrhage is the first step necessary to change clinical practice. The actual real-world implementation of that medication is challenging and requires multiple steps, including necessary provider education, consideration of the logistics of making the medication available, and developing appropriate methods for ensuring appropriate use. Strategies for implementation must be multifaceted and consider the audience; for example, a comprehensive program would provide patient education, clinician guidelines, and national policy maker messages. These implementation challenges extend to, and are often greater in, ‘translational’ and basic science research. This review discusses current challenges related to the provision of quality care in perinatal and neonatal medicine, particularly as they relate to preterm birth. Further, we provide examples of perinatal quality collaborative initiatives within the field of prematurity. Finally, we review considerations in implementing both clinical and translational/basic science research within the field of prematurity.

Provision of Quality Medical Care

Over the past two decades, significant emphasis has been placed on not only the provision of medical care but the provision of “quality” medical care. This work was spurred by the Institute of Medicine’s influential report, published in 2001, entitled “Crossing the Quality Chasm.”¹ Initiatives in specific areas of healthcare, reaching across different fields of medicine, have caught the attention of policymakers, healthcare leaders, and payers. Increasingly, healthcare systems have realized the importance of integrated quality improvement approaches, in person learning solutions, and ongoing support following these initial improvement efforts. In order to appropriately discuss and evaluate the use of quality improvement initiatives and preterm birth research, it is essential to understand the critical components of quality improvement collaboratives. Quality improvement initiatives should identify a target for improvement, the study sample (which may involve a number of different organizations, hospitals, or providers within a hospital system), and measurable outcomes. Typically, these outcomes are patient, provider, and healthcare system specific. Initiatives may include “bundles,” which are often aimed at providing a specific set of algorithms or checklists for practicing providers, to ensure that national society guidelines and recommendations are followed. Theoretically, quality improvement collaboratives allow for change at multiple levels within the structure of an organization or across organizations.²

In February 2016, the Society for Maternal-Fetal Medicine, National Institute of Child Health and Human Development, and American College of Obstetricians and Gynecologists convened a “Quality Measures in High-Risk Pregnancies Workshop” to review topics specifically related to quality medical care in obstetrics.³ Preterm birth was identified as a major topic at the workshop, and several measures were proposed by the workshop participants as quality measures (Table 1).³

Preterm birth has been a focus of multiple local and state level quality collaborative initiatives across the United States. Preterm birth has modifiable risk factors, and the risk of

prematurity may be reduced with adequate inter-conception care, routine prenatal care, and specialty prenatal care as appropriate. Delivery gestational age is an objective measure that is easy to track and generally not subject to bias. Therefore, many studies and initiatives focusing on perinatal quality include preterm birth as a key outcome measure. For example, several maternal safety bundles that are the focus of the Council for Patient Safety in Women's Healthcare's Alliance for Innovation on Maternal Health have medically indicated preterm birth as key outcomes (<http://safehealthcareforeverywoman.org/aim-program/>). The following provide examples of long-standing population-based approaches to preterm birth provider education, consistent medical care, and risk reduction:

- A. The Ohio Perinatal Quality Collaborative** is an established statewide quality improvement project initially formed in response to a request from the Ohio Department of Medicaid in the Ohio Department of Health. It was designed broadly to improve perinatal health outcomes. Several key initiatives and studies have been produced from this collaborative. In 2011, Kaplan and colleagues used the Institute for Healthcare Improvement Breakthrough Series quality improvement model to modify the implementation procedures regarding indwelling catheters in the neonatal intensive care unit, and studied whether or not use of this initiative influenced the rate of late-onset sepsis among preterm infants.⁴ They reported excellent compliance with the education initiative, with greater than 90% compliance 7 months after the study began. Notably, though the majority of infections were related to indwelling catheters during the study period (69%), there was a 20% reduction in the incidence of late-onset infection after the intervention.⁴

More recently, the Ohio Perinatal Quality Collaborative instituted a program to enact system-level changes to increase the use of 17-alpha hydroxyprogesterone (17P) caproate among women with a prior singleton spontaneous preterm birth. The program tracked 2,562 women who were eligible for treatment with 17P between January 1, 2014 and November 30, 2015.⁵ Reductions in preterm birth were seen in all hospitals participating in the initiative, and in individuals at highest risk, including African-Americans and those receiving Medicaid. After adjusting for risk factors and birth clustering, institution of the progesterone program was associated with a reduction in the rate of preterm birth prior to 32 weeks' gestation of 13%.⁵ Importantly, this reduction was sustained over the study period. This finding is particularly notable because preterm birth less than 32 weeks is notoriously difficult to prevent, and recent nationwide improvements in the rate of preterm birth have been seen mainly among preterm deliveries 34–36 weeks, but not at earlier gestational ages.⁶

- B. The Vermont Oxford Network** is a nonprofit, voluntary collaboration of health care professionals focused on primarily post-natal prematurity care and neonatology with a long-standing attention to quality improvement collaboratives. The quality improvement collaboratives through the Vermont Oxford Network utilize the Network's existing data infrastructure in order to identify need, incorporate group training, and set benchmarks for improvement, and assess change.

One key study conducted in 10 self-selected studies in the Vermont Oxford Network evaluated whether the formation of multidisciplinary teams improved outcomes, focusing on either chronic lung disease (n=4 neonatal intensive care units) or infection (n=6 neonatal intensive care units). These teams met regularly over a 3-year period, analyzed care processes, reviewed performance data, and implemented 'better practices' based on the literature and the work of the team. Rates of these complications in the intervention neonatal intensive care units were compared to 66 other neonatal intensive care units who had not undergone this intervention. They found that the rate of oxygen use decreased from 43.5% to 31.5% at the neonatal intensive care units in the chronic lung disease multidisciplinary team group, and similarly, rates of coagulase-negative staphylococcus infection were reduced at the neonatal intensive care units in the infection team group from 22.0% to 16.6%.⁷ A companion study evaluating whether this intervention was cost-effective found that the average savings per hospital in patient care costs for very low birth weight infants in the infection group was \$2.3 million in the first year post-intervention (1996); this is equivalent to \$3.6 million in 2017.⁸

Recent work published by the Vermont Oxford Network in the area of perinatal quality has examined disparities in nursing care provided in the neonatal intensive care unit,⁹ influence of quality indicators vs. admission volumes on risk of neonatal mortality in preterm infants,¹⁰ and disparities in perinatal quality outcomes among very low birth weight infants receiving neonatal intensive care.¹¹

- C. **The Society for Maternal Fetal Medicine Prematurity Bundle:** In 2016, the Society for Maternal Fetal Medicine released a "Preterm Birth Toolkit," providing a comprehensive set of protocols and algorithms for clinical use when caring for women at risk for preterm birth, diagnosed with acute preterm labor, or those who have just had a preterm birth. The toolkit provides expert opinions in areas where evidence is less clear or literature is lacking, with the goal of striking 'a balance between standardization and clinical discretion.' Further, specific instruments designed to assess barriers and aid in the execution of the strategies outlined in the toolkit are included. The toolkit is available online (<https://www.smfm.org/publications/231-smfm-preterm-birth-toolkit>).

When is research ready for implementation?

Modern clinical practice frequently cites one pivotal study as rationale for practice management. However, though a single study may at times serve as a 'tipping point' by which national organizations base their decision to make specific changes in management recommendations, individual studies are rarely sufficient, in isolation, to effect large scale changes. When an apparent 'landmark' study is published, decisions regarding whether to proceed with changes to policies must also consider the strength of the preliminary data used as the justification for the study in addition to other evidence to support the particular test or intervention. In studies evaluating the evolution of healthcare evidence, the first published

study on a scientific question may find the most dramatic effect sizes; this is true for both clinical and basic science studies.¹² Subsequent validation studies following widespread implementation may fail to reproduce initial apparently dramatic effects, as the heterogeneity of the studied population increases and more evidence is accumulated.¹³

Levels of evidence in medical research studies were first used in 1979 in a report by the “Canadian Task Force on the Periodic Health Examination” to “grade the effectiveness of an intervention according to the quality of evidence obtained.” At that time, there were only 3 levels of evidence, which were simple – Level I included evidence from at least one randomized controlled trial; Level II-1 from at least one well designed cohort or case-control study and II-2 from comparisons of times and places with or without the intervention; and Level III was based on expert opinion or descriptive studies.¹⁴ The first guidelines specific to the United States were released in 1988 by the United States Preventive Task Force. The same three levels were used, but level II was further divided into II-3 which was evidence obtained from multiple time series designs with or without the intervention.¹⁵ In 2013, the Society for Maternal Fetal Medicine adopted the Grading of Recommendations Assessment, Development and Evaluation (‘GRADE’) system which provides further guidance as follows: A = high quality evidence – based on several high-quality studies with consistent results or one large, high-quality multicenter trial and further research is unlikely to change confidence in the estimate of effect; B = moderate quality evidence – based on one high-quality study or several studies with some limitations, and further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; C = low quality evidence – based on one or more studies with severe limitations, and further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; D = very low quality evidence – based on expert opinion, no direct research evidence, or one or more studies with very severe limitations, and any estimate of effect is very uncertain.¹⁶ The level of evidence can be used by individual clinicians as a guide to interpret the relative quality of the research. Further, it can be used to help judge the appropriateness for inclusion of a study in a meta-analysis or larger review such as a Cochrane Review.¹⁷

Specific considerations for implementing prematurity research

In all situations, the research population must be considered when determining the generalizability to practice and the real-world effects of a diagnostic test or therapeutic intervention. Particularly in obstetrics, significant racial and ethnic disparities are present. The rate of prematurity is nearly two-fold higher in black infants in the United States compared to white infants.^{18,19} The reasons for these disparities are poorly understood. Neither social nor genetic factors can entirely explain these differences in prematurity outcomes; it is likely that a combination of both social and genetic factors are responsible for the observed differences. Nevertheless, multiple measures of the quality of prenatal care, including the gestational age at the initiation of care and number of prenatal visits are known to differ by maternal race and ethnicity. These factors affect the *a priori* risk of preterm birth in the population and may, therefore, also impact the results of any study involving black women and infants. Likewise, a study demonstrating a positive effect in a primarily white or Hispanic population may not show similar effects in a primarily black population.

Multicenter studies enrolling broadly across the United States comprised of women who have socioeconomic status, race and ethnicity, and previous pregnancy history representative of a general obstetric population are the most generalizable.

Translational Research

The application of basic biomedical research into clinical practice is essential to move new bench knowledge beyond the lab and deliver it to patients. Particularly when genetic studies are considered, thousands of samples are needed to adequately estimate genetic associations and disease.²⁰ In all cases, an adequate sample size and power with a sufficient replication cohort is essential. Caution is needed when interpreting and implementing genetic study data in the setting of admixed populations is particularly prudent. Several large-scale, consortium-based sequencing projects have shown that admixed populations have significant genetic diversity compared to those with traditional African ancestry. For example, the 1000 genomes project demonstrated increased linkage disequilibrium (shared chromosomal segments inherited together), and a higher frequency of rare variants in those with African compared with European ancestry.²¹ Further, patterns of rare and common variants are specific to each ancestry group.²¹

It is imperative that there are clear, biologically plausible mechanisms linking translational and basic science research with clinical disease. For example, though the underlying mechanisms behind preterm birth are poorly elucidated, recent research supports that epigenetic modifications (such as DNA methylation at cytosine-guanine dinucleotide sites, or CpG sites) may influence gene expression and the risk for adverse outcomes. Evaluation of site-specific CpG methylation and/or gene expression in maternal blood in early pregnancy holds significant promise in efforts to find biomarkers that can be used to screen for preterm birth. Several small studies report CpG methylation differences are associated with delivery gestational age.²² Still other studies suggest a potential role for evaluation of CpG methylation differences in predicting neonatal infectious morbidity, as specific methylation changes in the calcitonin-related polypeptide alpha (*CALCA*) gene were implicated in the diagnosis of both early- and late- onset sepsis.²³ However, no CpG methylation tests currently have sufficient evidence to support commercial use by providers to predict preterm birth or outcomes related to prematurity.

The term ‘pharmacogenetics’ was first coined in 1957, and used to describe the variability in the response to a standard dose of drugs attributable to a single nucleotide polymorphism(s). In modern times, the term pharmacogenomics is more commonly used, as this encompasses the effect of the entire genome (rather than an individual gene or genes) on drug response. Robust pharmacogenetics data from other medical fields demonstrates variable drug response in individuals by racial and ethnic subgroups, which is attributed to the underlying minor allele frequency of a particular single nucleotide polymorphism. For example, beta-blocker drugs may be less effective in individuals with specific functional variants in the G protein-coupled pathway of the beta-1 adrenergic receptor (*ADRB1*) and G protein receptor kinase 5 (*GRK5*) genes; these variants are more common in individuals with African ancestry.²⁴ It is not unreasonable to hypothesize that these variants may also influence response to beta-blockers for the treatment of chronic hypertension during pregnancy,

though this has not been studied. The best example of pharmacogenomics research applied to obstetric and neonatal medicine is related to use of codeine in breastfeeding mothers. Maternal carriage of the cytochrome CYP2D6*N allele results in ultra-rapid metabolism of codeine to morphine which may produce codeine-related sedation, respiratory depression, and neonatal death. In this instance, since testing for CYP2D6 genotype is not widely available and there are suitable alternatives for post-delivery pain control, simple practice recommendations have been made to use other narcotic medications when indicated. Further, placement of a ‘black box’ warning regarding CYP2D6 use in nursing mothers resulted in significant press attention, aiding in quickly disseminating the information to prescribers and caregivers.

The future of implementation science and the provision of quality care

Comprehensive computer science models are being developed to improve the synthesis and interpretation of evidence and then measure the uptake of this information. Global implementation science is a priority of the National Institutes of Health; several initiatives are underway in other fields including online discussions, cyber seminars, and webinars. This includes the ‘Research to Reality’ online community of practice, designed to link cancer control practitioners and researchers to move evidence-based programs into practice. In obstetrics, initiatives to translate research ‘from bench to bedside’ are the focus of several national conferences. For example, the planned meeting theme for the 2019 Annual Scientific Meeting for the Society for Reproductive Investigation is “From Innovation to Impact.”

Conclusions

It is estimated that it takes a minimum of 17 years or more to translate research into clinical practice.²⁵ While rapid translation could bring new effective life-saving interventions into clinical practice, the inappropriate translation of research into clinical practice ultimately results in suboptimal care at the level of the individual patient, whether it be from failure to incorporate knowledge of diagnostics or therapeutics with adequate knowledge, or exposure to unnecessary iatrogenic harms. Every effort should be made by researchers and stakeholders to facilitate dissemination of research knowledge to expedite implementation, while monitoring ‘real-world’ outcomes.

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Key Points

- Implementation of clinical and translational research studies into clinical practice is challenging and imperfect
- The process of implementation occurs over years to decades but may be facilitated by multicenter networks and perinatal quality collaboratives
- Strategies for implementation of prematurity research must be multifaceted and comprehensive

Table 1
Quality measures in preterm birth

Adapted from Iriye BK, Gregory KD, Saade GR, Grobman WA, Brown HL. Quality measures in high-risk pregnancies: Executive Summary of a Cooperative Workshop of the Society for Maternal-Fetal Medicine, National Institute of Child Health and Human Development, and the American College of Obstetricians and Gynecologists. *Am J Obstet Gynecol* 2017;217:B2–B25; with permission.

Quality Measure	Role in Prevention	Role in Treatment
Transvaginal ultrasound cervical length screening	Identification of women with short cervix provides opportunity for treatment	Presence of long cervix is helpful in determining who is not at risk for preterm birth among women with symptoms of preterm labor
Vaginal progesterone for cervical shortening	Studies suggest treatment is associated with reduction in preterm birth and is supported by ACOG and SMFM	No current evidence to support vaginal progesterone use for treatment of acute preterm labor.
Intramuscular 17-alpha hydroxyprogesterone caproate (17P) for women with a history of spontaneous preterm birth	History of spontaneous preterm birth is a significant risk factor for recurrence; prophylaxis with 17P is associated with reduced risk of recurrence and is supported by ACOG and SMFM	No current evidence to support treatment with 17P for treatment of acute spontaneous preterm labor.
Cerclage for women with a prior spontaneous preterm birth and cervical shortening	Ultrasound-indicated cerclage in women with a prior spontaneous preterm birth reduces risk of recurrent preterm birth	Cerclage is not indicated as a treatment for acute preterm labor
Antenatal corticosteroids	Use of antenatal corticosteroids is associated with reduced neonatal morbidity and mortality. Use is recommended by ACOG and SMFM.	Not applicable.
Magnesium sulfate for neuroprotection	Meta-analyses demonstrate decreased moderate-severe cerebral palsy or death; current use for women at risk of imminent preterm birth between 24–32 weeks gestation is standard of care per ACOG and SMFM	Not applicable.
Antenatal use of low-dose aspirin	Evidence suggests reduction in adverse outcomes and reduction in risk of pre-eclampsia in high risk women	Not applicable.

Abbreviations:

17P = 17-alpha hydroxyprogesterone caproate

ACOG = American College of Obstetricians and Gynecologists

SMFM = Society for Maternal-Fetal Medicine