Preterm birth: can we do better?

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Abstract

Preterm birth (PTB) remains the most serious complication in obstetrics and a substantial excess burden in US healthcare economics. The etiology of PTB is complex and likely has multiple physiological pathways. Unfortunately, current antenatal care screening methods have not been successful in predicting and, eventually, preventing PTB.

Although treatments such as progesterone, cerclage and pessary are available for patients with historical risk factors and shortened cervix, these treatments are not universally efficacious. Antenatal care is in great need of new prediction and prevention strategies.

The role of more global methods of screening and treatment is still undefined. Most women with clinical risk factors will not deliver early, and aggressive interventions in large segments of the population may not be warranted or cost effective. Furthermore, over half of women who experience PTB have no historical risk factors. Even second-trimester cervical length (CL) has only modest ability to predict which women will experience PTB.

There is thus a clear need to identify biomarkers that provide quantitative, individualized assessment of risk early in pregnancy that is specific for each individual woman. The ideal biomarkers would be indicative of the pathway leading to PTB, require no special testing equipment, have a low false positive and negative rate, and offer early identification, allowing adequate time to intervene. We need an aggressive and comprehensive approach to see a dramatic reduction in rates of preterm delivery in the U.S.

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Recent media reports have praised several states (Iowa, Virginia, Arkansas, Nevada and Oklahoma) for achieving

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reductions in the rate of preterm birth (PTB).[1] Though these reports represent progress, we must acknowledge that the current rate of 9.6% in the US, which is the highest among developed countries, is unacceptable, and that our current thinking about PTB requires revision.[2]

Preterm Birth as a Public Health Issue

PTB remains the most serious complication in obstetrics and a substantial excess burden in US healthcare economics. In addition, it accounts for 85% of neonatal morbidity and mortality worldwide,[3] is a leading cause of death in children <5 years of age, is responsible for nearly 1 million deaths per year, and a leading cause of chronic disability, straining the Medicaid budgets of most states.[4,5] Persistent and wide disparities in PTB also exist, especially for Africa-American women. [1]The rate of PTB increased in the United States until 2006, is now declining slightly.

Currently, the average cost of a stay in a neonatal intensive care unit (NICU) exceeds $10,000 for infants born at 34 weeks' gestation and is greater than $100,000 for those born at 28 weeks or earlier.[6] In the United States, over $26 billion per year is spent on PTB.[7] This estimate is likely low, as it does not include the costs of long-term care due to ongoing sequelae, which are significantly higher than the acute costs.7,8 Children affected by the consequences of PTB may face ongoing intellectual impairments, learning difficulties, motor deficits, other chronic medical issues, and reduced prospects for employment. Economic analyses alone do not fully capture the emotional and financial burdens to children and their families.

While some states and the March of Dimes are attempting to increase awareness of PTB, there is still insufficient media focus and public outcry about the emotional and financial costs and impact on society associated with PTB. Considering the serious consequences of PTB, public awareness of the problem is surprisingly low!

PTB may be spontaneous or iatrogenic, usually medically indicated. The recent downward trends of PTB rate has been weighted toward iatrogenic PTB and minimally impacted the early gestational age births, the children primarily born with short-term as well as long-term economic, physical, and emotional implications.

Challenges We Face

The etiology of spontaneous PTB is complex and likely has multiple physiological pathways. Unfortunately, current antenatal care screening methods have not been successful in predicting and, eventually, preventing PTB. In the majority of cases of PTB, our current approach is usually limited to waiting for symptoms of preterm labor (PTL) to occur, attempting to decrease the frequency and strength of contractions, administering steroids and, if appropriate, transferring patients to facilities with high-level neonatal care. However, this focus on preterm labor (PTL) has met with limited success. Contractions, rupture of membranes, and labor are late events in the physiologic cascade leading to PTB.[9] Uterine activity may not be evident until

weeks after modulation of progesterone receptors, activation of decidua, overexpression of proinflammatory cytokines, and cervical remodeling have begun.[9,10] When uterine contractions or cervical changes are present, the physiologic process of PTB may have been ongoing for several weeks.

Although treatments such as progesterone, cerclage and pessary are available for patients with historical risk factors and shortened cervix, these treatments are not universally efficacious. Antenatal care is in great need of new prediction and prevention strategies.

Addressing individual risk factors alone is unlikely to make a large impact. In a review across 39 countries, the only effective interventions noted were smoking cessation, decreased number of embryo transfers during assisted reproduction, cerclage, progesterone, and reducing nonmedically-indicated deliveries.[11] However, application of these interventions proved to be of limited value. The expected overall change in the rate of PTB from using these interventions was calculated to result in a 0.52% decrease in the overall rate of PTB.

The role of more global methods of screening and treatment is still undefined. Petrini, et al., estimated that using current treatment strategies such as progesterone treatment in all women with a history of PTB would only lower the overall rate of PTB by 0.3%.[12] Most women with clinical risk factors will not deliver early, and aggressive interventions in large segments of the population may not be warranted or cost effective.[13] Furthermore, over half of women who experience PTB have no historical risk factors. Even second-trimester cervical length (CL) has only modest ability to predict which women will experience PTB.[13,14,15]

There is thus a clear need to identify biomarkers that provide quantitative, individualized assessment of risk early in pregnancy that is specific for each individual woman. The ideal biomarkers would be indicative of the pathway leading to PTB, require no special testing equipment, have a low false positive and negative rate, and offer early identification, allowing adequate time to intervene.

In parallel, we must redouble our efforts to optimize current treatments, invest in development of new interventions and focus on incremental improvements in neonatal health and cost reduction. Although effective primary prevention has not yet been developed, secondary prevention (assessment of risk factors, screening for CL, and treatment of bacteriuria and other infections associated with PTB) and tertiary prevention (ensuring administration of corticosteroids and proximity to a NICU) are strategies still available. The ultimate measure of the benefit of an intervention is whether it: (1) improves the short-term and long-term health of the child, and (2) and lowers health care costs when applied to the general population.

Screening

Clinical Risk Assessment

The clinician's primary task is to ascertain the risk factors for PTB in the individual patient and address

preventable causes. Screening for risk factors from a woman's past medical, family and pregnancy history is inexpensive, requires no technology, and can begin at the preconception visit or the first prenatal visit.

The single most important risk factor for PTB and the one most likely to alter medical management is a history of a previous spontaneous PTB.[16] A woman with a single previous PTB has a 16% risk for PTB at <35 weeks' gestation.17 A woman with 2 previous PTBs has a 41% risk for PTB, and a woman with 3 previous PTBs has a 67% risk. Family history of PTB is an additional risk factor, as is multiple gestation, 60% of whom experience PTB.[18]

Many historical, social, behavioral, and medical risk factors for PTB have been reported in the literature (Table 1).[9,13,15,19-21] Simple questions as part of the screening form may uncover modifiable risk factors, such as smoking and substance abuse, and social risk factors that can be addressed by offering adequate support services, which are readily available in most communities but not adequately accessed by women who would benefit from these services to modify risk. Of note, the majority of patients surveyed by the Pregnancy Risk Assessment Monitoring System who reported a need for help with domestic violence or substance abuse did not receive assistance for modifying this risk.[22]

Unfortunately, many risk factors apply to large proportions of the population and are too imprecise to be useful for guiding direct individual interventions, as most women who have them will not have PTB.[23] At present, risk factors alone cannot effectively predict the risk for PTB among primigravidas. And even with more effective screening, it remains that all women are at risk for PTB, as evidenced by the fact that 50% of PTB occurs in women with no apparent risk factors for PTB.[24]

Table 1. Risk Factors for Spontaneous Preterm Birth

Historical
Personal history of preterm birth
Family history of preterm birth
Short inter birth interval
Cervical surgery
Recurrent first or second trimester loss
African descent
Maternal age
Medical
Maternal body mass index
Transfer of multiple embryos
Multiple gestation
Urinary tract infection
Cervicitis
Dental problems
Short cervical length
Vaginal bleeding
Social
Low socioeconomic status
Lack of social support
Domestic violence
Lack of food security
Poverty
High level of stress
Literacy
Behavioral
Smoking
Substance abuse
Recent change of domicile

Cervical Length

Regular monitoring of CL has been suggested for women with a history of PTB, with cerclage placement offered based on CL.[22,25,26,27,28]

Universal CL screening at 18 to 20 weeks' gestation for women without risk factors for PTB is hotly debated.[29-32] Some authors have demonstrated a cost benefit for universal screening based on decision analyses[30] with the belief that early detection of cervical shortening may allow time for intervention before PTL begins. Although universal screening for CL is not currently recommended, it may be a reasonable way to screen women who do not have a prior pregnancy history. Even so, it fails to detect 26% of PTB cases.[26]

Universal CL screening is warranted if it results in better outcomes and lower costs. CL screening could be a major step toward identifying women who deliver preterm but have no risk factors. However, screening has several limitations. Most important, a change in CL indicates that the process of cervical ripening has already begun. Many women with a short cervix will not deliver early and thus will receive serial monitoring and interventions unnecessarily. The ultrasonographer must be trained and demonstrate expertise in measurement of CL. In addition, there are significant costs related to equipment and errors in interpretation. Ideally, a test that predicts PTB before a significant change in CL occurs would allow the most time for intervention.

Management

Awareness

Many of our patients are unaware of the risk factors for or causes of PTB. Women can be highly motivated to avoid PTB but they do not always have adequate information. We can teach all patients, especially high-risk women, about the causes of PTB and the need for self-monitoring. Most women are not aware of their own level of risk for PTB, and risky behaviors may continue as a result of inadequate knowledge.[33] Based on screening assessments, we should provide each patient with her own personal risk for PTB and engage her as a proactive partner in preventing PTB.[9]

With better awareness of risk, physicians and patients are in a better position to target optimal weight management, and to tackle smoking cessation and avoidance of drugs and alcohol. As an example, aggressive programs for smoking cessation can include education and behavioral counseling, as well as pharmacological intervention.[9,34,35]

Progestins

Current recommendations of the American Congress of Obstetricians and Gynecologists (ACOG) include offering treatment with weekly injectable 17 alpha-hydroxyprogesterone-caproate (17-OHP) starting at 16 to 20 weeks' gestation for women with a history of PTB.[36,37] For women with a short cervix (< 15 mm), providing daily vaginal progesterone well before contractions or other symptoms of parturition begin may delay the onset of PTB.[17]

Progestins are currently our best intervention, but we still have much to learn about them. Even the basic mechanism of action is not well understood. Manuck, Lai et al. are evaluating methods for identifying women who are likely to respond to progesterone.[38] Remaining questions include the optimal dose, best vaginal preparation of progesterone (gel vs micronized), and effect of BMI on administration and effectiveness.[39]

Cerclage

It has been recommended to offer prophylactic cerclage to women with a history of cervical insufficiency,[40] and offer ultrasonographically-indicated cerclage to women with a short cervix (<15mm) and a history of PTB.[25,41]

An alternative for patients who wish to avoid surgery or who are poor surgical candidates is a vaginal pessary. In a recent randomized trial, pessaries demonstrated similar effectiveness to cerclage and vaginal progesterone strategies in women with singleton pregnancy, previous spontaneous PTB and short cervix.[42] Unfortunately we do not have direct comparison trials between progesterone, cerclage and pessary for patients at risk.

Care Management

Prematurity prevention programs have been investigated by several centers.[24,43,44,45,46,47] Increased contact with physicians and nurses in a specialized PTB clinic decreases the rate of PTB.[48,49] Compared with the current standard of care, a preterm prevention clinic resulted in prolongation of pregnancy by 1 week and reduction in a measure of composite morbidity from 16.3% to 5.7%, illustrating that an aggressive, comprehensive approach in a collaborative model including the primary physician and maternal-fetal-medicine specialist can prolong pregnancy.[50]

Specialty prematurity prevention clinics are staffed by or offer access to social workers, case managers, nutritionists, genetic counselors, telemedicine providers, and other skilled individuals who can address issues related to adequate transportation, safe and affordable housing, domestic violence counseling, and obtaining prescription medications. This type of care management can ensure that patients are compliant with regular treatment and evidence-based interventions such as 17-OHP.[51] Among women on progestins, a simple check-in by telephone decreased the rate of PTB (<35 weeks) by 50%.[49] Case management based on Medicaid status reduced the rate of PTB at 24-28 weeks and reduced NICU days, saving millions of dollars.[48]

Other Interventions

Screening for asymptomatic bacteriuria is required during pregnancy. Screening and eliminating cervicitis has also been shown to reduce PTB.[52]

For women in whom PTB appears imminent, effective interventions include corticosteroids for acceleration of fetal pulmonary maturation and MgSO4 for neuroprotection for women between 24 and 32 weeks' gestation.[53,54,55] Tocolysis may be given for up to 48 hours to facilitate these treatments.[56]

Checking fetal fibronectin every 2 weeks from 24 to 32 weeks, in the highest risk patients, is not currently the standard of care, but may facilitate appropriate administration of corticosteroids when necessary.

The Future

Paradigm Shifts

Prenatal care has been traditionally focused on identifying and managing preeclampsia, which is less common than PTB. Introducing the same level of surveillance and care for prevention of PTB would entail asking patients at each visit about signs and symptoms such as back pain and cramping, and would entail increased visits in the mid-portion of pregnancy, rather than the end.

Insurance coverage and reimbursement strategies that favor improved neonatal outcomes could support changes in practice that emphasize early identification and treatment for women at risk for PTB. These might include 'Pay-for-Performance' initiatives aimed at improving quality, efficiency and value of care. They also include greater support for case management, pregnancy centering or other evidence-based care models. Value-based payment is accelerating with hospitals and health plans; it is likely a matter of time for similar models emphasizing value and outcomes to impact physician payments.

The ability to predict PTB early in the course of pregnancy could markedly improve neonatal outcomes. Time-intensive programs focusing on patient education and modification of risk factors could be targeted to the correct population. Even if we cannot substantially decrease the rate of PTB, simply increasing the gestational age at which it occurs is likely to achieve the desired outcomes of reducing disability, improving neonatal outcomes, and decreasing costs associated with PTB.[6,8, 55, 56] Identifying patients who are at risk for PTB early will allow us to improve the availability of care by assuring proximity to a tertiary care center and giving antenatal corticosteroids and MgSO4 for neuroprotection as needed.[56]

Identifying High-Risk Women Early using Newly Developed Methods

At present, for the majority of patients, we have no opportunity to intervene because risk factors for PTB are absent. Screening for demographic and clinical factors alone is not adequate. The appearance of symptoms of PTL is too late for most evidence-based interventions to be effective at stopping or delaying PTB, and tocolysis does not extend gestational age.[9] There are many opportunities for basic science investigations, including unanswered questions about chorioamnionitis, premature cervical ripening, genetic predisposition and other possible triggers for PTB. We must focus on early prediction and improved diagnostic techniques. An inexpensive and accurate way to detect women at risk remains a high priority.

Multi-marker serum proteomics is being developed to predict PTB during the second trimester.[58] Such a test could be combined with a treatment algorithm to classify women who require more intensive surveillance or interventions

(Figure 1).

Attempts to create prognostic models are ongoing but are only modestly successful.[3,59] Early studies are exploring genomics as a predictor of PTB.[60,61,62]

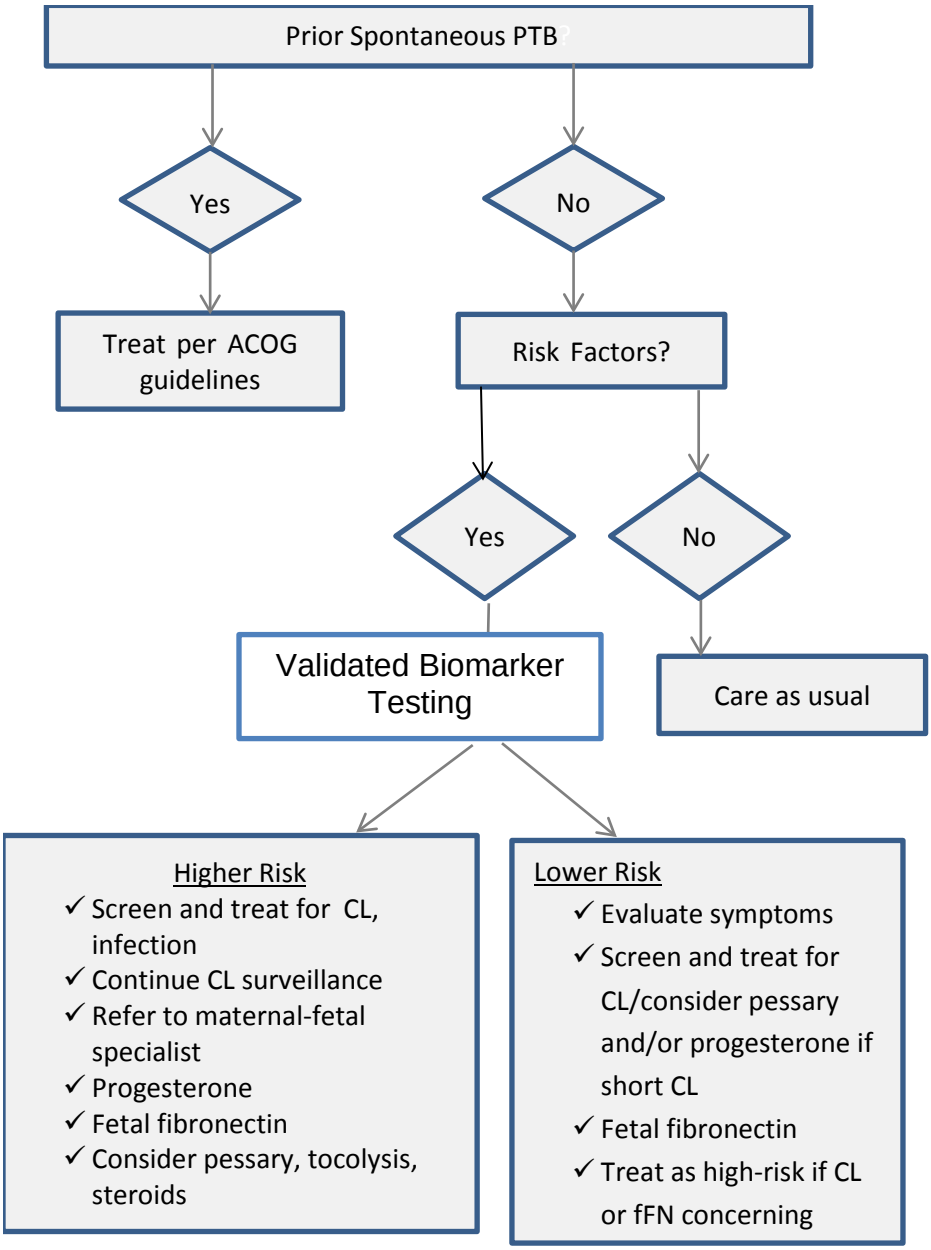

Figure 1. Treatment Algorithm for Focused Risk Management

Developing accurate biomarkers would not only be clinically useful, but could speed the progress of research by limiting low-risk patients from clinical trials. In the past, these studies have been diluted by inclusion of women unlikely to benefit from the interventions studied. If proteomic risk stratification is

successful, trials of treatments to prevent PTB and its consequences can enroll fewer subjects and be completed more economically and quickly. Studies of pharmacogenomics would also be possible.

In addition, several new clinical interventions are being studied. Atosiban is in use in Europe and is being explored as a tocolytic.[63] Early treatment of vaginal infections with antibiotics and the use of probiotics are likewise under investigation. Comparisons between pessary, cerclage and vaginal progestins are also underway.

Conclusions

Celebration may be premature for the recent decrease in the rate of PTB. The results of our current treatments are inadequate. The recent small decrease in the rate of PTB is primarily related to changes in physician behavior and elective inductions.[64]

Can we do better? We can't keep doing what we are doing and expect success. We have to change behavior. With passionate advocacy and out-of-the-box strategy, we can do better. This was proven in France through implementation of an aggressive and comprehensive health policy for the prevention of preterm delivery directed at all pregnant women—not just women considered to be at high risk. With this aggressive and comprehensive approach, the proportion of deliveries before 37 weeks decreased from 8.2% in 1972 to 4.9% in 1988—a 41% reduction—and the proportion of deliveries before 34 weeks decreased from 2.4% in 1972 to .09% in 1988—a 96% reduction.[65, 66]

We need an aggressive and comprehensive approach to see a dramatic reduction in rates of preterm delivery in the U.S. The road to a primary prevention strategy is long. Until primary prevention is possible, we must treat PTB as a complex, multifactorial condition that demands multifaceted solutions:

- Identify at-risk patients early so that treatment can begin before late signs of parturition are observed. Aggressively screen every patient as early as possible, and provide her with an individualized assessment of risk.

- Study neonatal outcomes and costs rather than focusing on the overall rate of PTB. With the right interventions, we may find that simply prolonging pregnancy is sufficient to impact neonatal outcomes, lifelong sequelae, and costs of care.[6,49]

- Actively educate patients and engage them in their care.

- Use validated biomarker approaches to move toward early, patient-specific, risk-specific interventions.

- Individualize the frequency and content of prenatal visits to emphasize risk assessment and prevention of PTB.

- Reduce outcome disparities for minorities and disadvantaged communities

- Do the low-cost, low-technology, non-glamorous work of addressing modifiable risk factors: social support, smoking cessation, education, intensive case management, etc.

- Maximize use of current evidence-based interventions such as progesterone, cerclage, liberal use of CL, and continue to study which populations should receive screening and treatment.

- Build and retain local and regional community networks of obstetric providers and maternal-fetal-medicine specialists. Streamline referrals, create a suite of interventions and programs for coordinated, collaborative prevention of PTB, and provide resources for community physicians.

- Encourage funding agencies to allocate more resources to the study of prevention of PTB.

- Encourage patients and ACOG to lobby members of Congress for additional funding to study prevention of PTB.

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