

Overview: new perspectives on the stubborn challenge of preterm birth

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Introduction

The rates of preterm birth and low birthweight have risen in the United States, despite unprecedented growth in the understanding of almost every dimension of human biology at a cellular and genetic level.¹ No health problem affects more of our children more profoundly than this one, threatening all racial and ethnic groups, but particularly minority populations and the poor.^{1,2} Improved medical knowledge and technical capacity allow many more premature babies to survive, but the costs to the baby, the baby's family and society can be tremendous.³⁻⁶ The sequelae are particularly severe in the most premature babies with very low birthweight, who are more likely than full-term infants to die in their first year and to suffer significant health problems, hospitalisations, slow growth, and behavioural, attentional and learning disorders.^{4,6} Thus, the challenge of this major problem derives not so much from an inability to save small babies once born but, rather, an inability to protect them from lifelong damage, and most importantly, to preserve their growth *in utero* until closer to term. We simply do not know how to prevent the problem in any effective way.^{2,7}

Researchers have been seeking effective prevention strategies for more than a quarter of a century. In 1985, Dr Emile Papiernik convened leading researchers in the field to examine progress to date, with particular emphasis on social causes and public health-based, randomised trials aimed at providing social and other supports to pregnant women.⁸ Much of the research discussed was in progress at the time. Final results were presented at a subsequent conference, held in Chatham, Massachusetts, USA, convened in 1988 by

Drs H. Berendes, S. Kessel and S. Yaffe.⁸ The conference addressed risk-assessment activities that might identify those subgroups of pregnant women likely to benefit from educational materials aimed at increasing awareness of the signs and symptoms of preterm labour. This approach was motivated in large part by promising results from early clinical trials suggesting the efficacy of tocolytic agents, such as ritodrine, in treating spontaneous preterm labour.⁹ Various risk prediction scoring systems had been developed^{10,11} and tested in a wide variety of clinical obstetric situations. However, risk-scoring schemes tested both in large unselected and in high-risk obstetric populations¹² did not provide accurate and efficient means for classifying pregnant women according to their preterm delivery risk.

During the decade following these conferences, major risk identification and reduction trials were completed. A third conference was convened in 1997 in Charleston, South Carolina, USA, to examine progress and propose future directions for research and interventions.³ The news was generally disappointing. The previously reported significant impact of tocolytic therapy on halting preterm labour had not been confirmed in larger clinical trials.¹³ Programmes aimed at preventing or ameliorating the impact of preterm labour through the monitoring of uterine activity and the provision of immediate access to health care had provided mixed results.¹⁴ Preterm prevention programmes designed to provide nursing care with or without monitoring of uterine activity had failed to demonstrate meaningful improvements in pregnancy outcomes. These observations were particularly disappointing as considerable increases in clinical resources such as unscheduled visits or administration of prophylactic tocolytic agents were not associated with a reduction in preterm delivery rates.¹⁵

Other programmes had placed considerable emphasis on providing social support to those women determined to be at high risk of preterm delivery

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because of their socio-economic and psychosocial characteristics.^{16,17} Evidence from such programmes was mixed. Still other programmes had focused on addressing perceived or documented maternal nutritional deficiency with provision of maternal multivitamin, iron, zinc, folate, or calcium supplementation.^{18–21} On balance, evidence from these nutritional intervention trials did not clearly support the efficacy of nutritional interventions as a means for preventing preterm delivery.

Since the Charleston conference, there have been no major breakthroughs reported. For example, results from prevention programmes that focused on providing antimicrobial interventions failed to confirm earlier reports of substantial preterm birth reductions with treatment.⁷ Preterm prevention efforts had been thwarted by the relatively insensitive and non-specific risk-screening protocols developed and implemented to date. The systems have been augmented over the years with additional biochemical, microbiological and physiological risk markers such as change in cervical length or uterine activity.^{14,22} However, interventions have not been proved to prevent preterm delivery once risk markers can be detected.

Lack of progress in reducing the frequency of preterm delivery has been due, in part, to our limited understanding of the aetiology of preterm labour, preterm premature rupture of membranes, and maternal and fetal medical conditions necessitating early delivery. Failure of recent intervention programmes to reduce the preterm births in large unselected obstetric populations, coupled with the available literature concerning the risk factors of preterm delivery,²³ underline the complex multifactorial aetiology of preterm labour.

However, the Charleston conference did produce a promising research agenda. Building on the risk assessment literature, participants called for better, prospective databases to identify key factors. These factors could be studied within the context of various aetiological pathways to preterm labour, such as infection and vasculopathy.²⁴ These include stress-induced susceptibility to infection and vascular change.³ Building on recent advances in the understanding of the mechanisms of normal and preterm labour and delivery, the conference participants called for new, multidisciplinary research incorporating basic biological, clinical, and epidemiological strategies.

The March of Dimes Birth Defects Foundation accepted the challenge from the Charleston conference

to promote 'multidisciplinary research on all aspects of preterm birth and [to create] more opportunities for the multidisciplinary exchange of research developments'.³ Preventing preterm birth, along with preventing birth defects, has been central to the mission of the Foundation for almost four decades. Substantial proportions of the Foundation's budget have been applied to investigation of the biochemical events governing normal labour and the pathogenesis of preterm labour. However, progress has been slow, and in 1997 the Foundation convened outside advisors to guide its consideration of a new research programme. The questions posed to the group began with whether epidemiological techniques might form the basis for the programme, recognising that the science of epidemiology had sharpened its investigative precision in recent years and that epidemiological research can sometimes circumvent ignorance of biochemical mechanisms to gain major insight, e.g. that folic acid can prevent spina bifida and that placing the baby to sleep on its back can reduce the risk of sudden death. The advisors also addressed whether there was enough new scientific information to justify a new programme, what investigative approaches were currently most promising, and whether there was a research niche that might be filled meaningfully by the March of Dimes. The decision was made to fund a major new programme using epidemiological techniques to probe at least one relevant biological/biochemical/genetic endpoint in a defined population or populations.

The rationale, aims, and methodological approaches of the six proposals that received funding are described in this supplement by their principal investigators.^{25–30} Their publication here, after only a few months into the study, addresses two of the secondary but important goals of the March of Dimes Foundation's *Perinatal Epidemiologic Research Initiative*, namely that the six research groups interact and support each other as much as possible, and that the fresh perspective and innovations offered by these projects be used to educate, stimulate, and perhaps provoke to action others from the broader scientific community. This publication is also responsive to the Charleston conference recommendation to develop and improve 'mechanisms to increase the speed by which research findings can be disseminated and transferred into practice, programs and policies'.³

Although considerably different in approach and populations studied, these investigations also reveal

overlapping themes. To various degrees, they are exploring the roles of infection, genetics and stress. These themes are further developed in this issue with updated reviews of infection as a risk factor,³¹ individual susceptibility associated with genetic polymorphisms,³² and biophysical and epidemiological perspectives on the contribution of stress to preterm delivery.^{33,34} These themes may not prove to be those that lead directly to the final answer, but they reflect the most compelling hypotheses that can be framed from current data.

From observing the differences in prematurity rates among the populations of different countries and among different populations in the US, we know that some things work. When the research described here is completed, we will most surely understand better what those things might be.

Acknowledgement

The authors would like to acknowledge the efforts of Ms Keegan Sprinkle, who so ably assisted Ms Ellen Fiore in managing the project.

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