Preventing Preterm Birth: Are We Making Any Progress?

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(Received June 20, 1997; accepted October 27, 1997)

Most industrialized countries have reported recent decreases in the size of infants born at term but no reduction, or even a rise in the incidence of preterm birth. This paper reviews recent secular trends in preterm birth and the evidence about possible reasons for those trends. The hypothesized reasons include ignorance about the causal determinants of preterm birth, failure to reduce exposure to recognized determinants, increases in multiple births, the use of early ultrasound (rather than menstrual dates) to estimate gestational age, early induction or cesarean section for pregnancy complications, and registration of extremely immature births of borderline viability.

INTRODUCTION

Preterm birth is arguably the most important public health problem facing infants and children in developed, industrialized countries [1-3]. It is the major cause of infant mortality and is associated with major long-term neurocognitive, respiratory, and ophthalmologic morbidity. Provision of intensive care for extremely preterm infants represents a major expenditure for the health care system [4], and giving birth to an infant requiring such care is a traumatic experience for parents, families, and society.

Although the last several decades have seen dramatic reductions in perinatal and infant mortality, virtually all of these reductions are attributable to improved access to and quality of high-risk obstetric and neonatal care [5, 6]. The major consequence has been a reduction in gestational age-specific mortality rather than prevention of preterm birth. In fact, recent trends in the United States suggest that preterm birth may even be on the rise [7]. In the remainder of this paper, I will examine recent secular trends in preterm birth in the U.S. and several other developed industrialized countries and propose several hypotheses to explain these trends. I will then summarize what is known about the causal determinants of preterm birth and review recent secular trends in those determinants to assess whether the trends in determinants can explain the trends in incidence of preterm birth. Next, I will review available evidence bearing on other hypotheses to explain the trends in preterm birth before reaching some tentative conclusions and making some recommendations about priorities for future research.

SECCULAR TRENDS IN PRETERM BIRTH

Most industrialized countries have reported an increase in mean birth weight over the last 20 years. Most of this trend appears due to an increase in the size of infants born at

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\[ b \] Abbreviations: IUGR, intrauterine growth retardation; LMP, last menstrual period.
term, rather than either a reduction in preterm birth or an increase in the size of preterm infants [8-10]. The increase in size of term infants appears to be primarily attributable to recent reductions in maternal smoking [11], increases in prepregnancy weight [12] and maternal weight gain [13-16], and perhaps to a smaller degree, a secular increase in maternal stature [17]. In the United States, preterm birth rates have not only failed to decrease, but recent figures even indicate a slight increase [7]. In Canada, a report based on a comparison of the Canadian birth database in 1986 vs 1972 showed no consistent change in the gestational age distribution, although there was a reduction in the trend toward rounding of gestational ages to months and half-months in 1972, and thus a general "smoothing" of the gestational age distribution in 1986 [10].

To my knowledge, the only industrialized country that has reported a clear decrease in the incidence of preterm birth is France, where both regional data from Hagenau [18] and national surveys [19] indicate as much as a halving of the preterm birth rate between the early 1970s and the late 1980s. Surprisingly, however, the same national surveys showed no trend toward an increase in mean birth weight [19]. French epidemiologists have attributed this unusual combination to a reduction in the birth weight of preterm infants, due to earlier induction of birth in pathologic pregnancies [19]. Most industrialized countries have experienced a similar increase in preterm inductions, however, and the unusual combination of a reduction in preterm birth and no increase in mean birth weight (a combination that has not, to my knowledge, been observed elsewhere) therefore suggests the possibility that the apparent reduction in preterm birth may be artefactual.

What are the possible explanations for this failure (outside of France, at least) to reduce the incidence of preterm birth, particularly in view of the striking increase in size of term infants and impressive reductions in perinatal and infant mortality? One possibility is that we have been unsuccessful in preventing preterm birth, either because we have not understood enough about its etiologic determinants or because we have been unsuccessful in modifying those determinants. But a second hypothesis is that the effect of favorable changes in determinants has been masked by other simultaneous changes. These other potential masking changes include: (1) an increase in the incidence of multiple births (twins, triplets, and higher-order multiples) owing to fertility-enhancing drugs and procedures; (2) the increasing use of early ultrasound, rather than last menstrual period, to estimate gestational age; (3) the above-mentioned tendency toward early (including preterm) induction or cesarean section for pathological pregnancies; and (4) an increase in registration of births near the borderline of viability. In the remaining sections of this paper, I will examine the evidence for each of these potential explanations.

ETIOLOGIC DETERMINANTS OF PRETERM BIRTH

A great deal is known about the etiologic determinants of fetal growth and intrauterine growth retardation (IUGR). Figure 1 shows a pie diagram containing "slices" corresponding to the etiologic fractions (population attributable risks) associated with widely accepted etiologic determinants of IUGR [5]. A determinant's etiologic fraction for IUGR is the proportion of IUGR occurring in a given population that can be attributed to exposure to the determinant within that population. It is calculated as follows, based on the relative risk (RR) of IUGR in exposed vs nonexposed women and P, the proportion of pregnant women in the population exposed to the determinant:

\[ EF = \frac{P(RR - 1)}{P(RR - 1) + 1} \]
As shown in Figure 1, maternal cigarette smoking during pregnancy is by far the most important determinant of IUGR; other important determinants include maternal stature, prepregnancy weight-for-height, gestational weight gain, parity, racial/ethnic factors, and fetal gender.

Figure 2 presents the analogous pie diagram for preterm birth [5]; its major message is that most cases of preterm birth occur without known cause. Besides the widely recognized determinants shown in Figure 2, recent research suggests that genital tract infection and stress, anxiety, depression, and other psychological factors may also play important etiologic roles, but further research is required to confirm and quantify those roles [21]. Prenatal care has often been touted (especially in the United States) as effective in reducing the risk of preterm birth. Yet support for this claim is based on two sources of evidence: (1) observational studies comparing outcomes in women with early and/or frequent care vs outcomes in women with delayed and/or infrequent care [20, 22]; and (2) nonrandomized comparisons of participants vs nonparticipants in special preterm prevention programs [23, 24]. Both types of studies are highly prone to confounding by self-selection. By contrast, virtually all randomized trials of prenatal care, including “intensive” prena-
tal care for women at high risk for preterm delivery, have yielded disappointing negative results [25-27].

The main determinant shown in Figure 2 that has shown a secular decrease over time is cigarette smoking [11]. Because cigarette smoking has a much smaller etiologic fraction for preterm birth than for IUGR (owing to its lower relative risk for preterm birth vs IUGR), recent decreases in maternal smoking might have been expected to lead to a small reduction in incidence of preterm birth. Of the other known or suspected determinants, only in utero DES exposure has shown such a secular trend, and thus no large reduction in preterm birth would be expected.

HAS A REDUCTION IN PRETERM BIRTH BEEN MASKED BY OTHER CHANGES?

Multiple births

Recent increases in the use of hormonal treatments, in vitro fertilization, and other new technologies for the treatment of infertility have resulted in a striking increase in the occurrence of multiple births, including higher-order multiple births. In the U.S., for example, the multiple birth rate between 1980 and 1992 increased from 1.8 to 2.4 percent in whites and from 2.4 to 2.8 percent in blacks [28]. Similar increases have been reported from Scandinavia [29, 30]. Because a large proportion of twins and the majority of higher-order multiple births are born preterm, such a trend would lead to a slight increase in overall incidence of preterm birth (in the absence of other changes).

Early ultrasound dating

Last menstrual period (LMP)-based gestational age dating has increasingly given way to dating by early ultrasound, usually performed early in the second trimester and based on the biparietal diameter or other anatomic ultrasonographic measurements. Available data are fairly consistent in showing that early ultrasound dating results in a shift to the left in the gestational age distribution. For example, in our study of 11,045 women with both LMP and early ultrasound estimates of gestational age, 799 (7.2 percent) delivered prior to 37 weeks based on the date of the last menstrual period vs 957 (8.7 percent) based on early ultrasound [31]. Similar results have been reported by investigators from both Alabama [32] and France [19], although one study from Detroit reported an opposite trend [33]. This shift in gestational age distribution by early ultrasound is probably caused by a number of falsely high LMP-based gestational ages due to late ovulation (and therefore late conception) [34]. Since late ovulation appears to be much more prevalent than early ovulation, and since the size of the fetus is obviously determined by the time since conception, early ultrasound-based dates would be expected to be slightly lower, on average, than LMP-based dates.

Preterm induction and cesarean section

With the improved viability of extremely preterm infants, recent obstetric practice has tended to become much more interventional when women develop pregnancy complications such as fetal distress, severe intrauterine growth retardation, or severe pre-eclampsia. Higher rates of preterm induction and cesarean section have been reported from both the United States [32] and France, [19] although in both reports, the trend toward higher intervention rates before term appears to explain only a small portion of the overall increase in preterm birth. The major reason for this small contribution is that many of the infants probably would have been born preterm in the absence of intervention, i.e., the effect of intervention is not so much to move would-be term births into the preterm range, but
rather to further reduce the gestational age of infants who would have been born preterm even in the absence of intervention.

**Increased registration of extremely immature births**

Another potentially important change in recent years has been the increasing tendency to report the birth of infants near the borderline of viability, i.e., those below 25 weeks gestational age and/or near or below 500 grams birth weight. This tendency may not only reflect a change in classification from stillbirth to livebirth but, more importantly, an increased tendency to register (as either stillbirths or livebirths) those fetuses or infants who may have previously been considered as miscarriages by their mothers and health care providers [34-36]. This tendency may also have been fuelled by legal, religious, cultural, and economic imperatives, which may differ substantially from one industrialized country to another. In fact, such a tendency could explain (at least in part) the United States’ poor international ranking in infant mortality. In one recent study, we demonstrated that an apparent increase in infant mortality in Canada in 1993 was eliminated merely by controlling for the proportion of births less than 500 grams [37].

**CONCLUSIONS**

With the possible exception of France, industrialized countries have seen no significant reduction in recent incidence of preterm birth. It may well be that some would-be improvement in preterm birth has been masked by simultaneous changes in the incidence of multiple births, the use of early ultrasound estimation of gestational age, earlier obstetric intervention in pathologic pregnancies, and increased registration of extremely immature infants. Further studies are required to quantify the contribution of each of these changes to the observed trends in preterm birth. Studies are currently underway in Montreal, nationwide in Canada, and other countries in an attempt to provide such a quantification.

**Acknowledgement:** *Dr. Kramer is a Distinguished Scientist of the Medical Research Council of Canada.*

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