PREVENTING AND MANAGING PREMATURENESS

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Abstract
In the past decade the prevention and management of prematurity have begun to be addressed with more appropriate designs. A few strategies—very few—can now be recommended. A few, some widely implemented, can be abandoned. The risks and benefits of most interventions still require clarification.

It is commonly agreed among clinicians, researchers, and health policy makers in industrialized countries that the crucial perinatal problem is prematurity. One response to this recognition has been an emphasis on the need for a better understanding of the pathophysiology of prematurity as the key to prevention. Eastman's (19) classic comments—"only when the factors causing prematurity are clearly understood can any intelligent attempt at prevention be made"—is still quoted by those who hold this view, and it could still be regarded as largely true.

In contrast, several recent articles call for a greater sense of urgency, exhorting clinicians to stop worrying about causes and to implement preventive programs instead (32;33;36). It is tempting, in the face of stable prematurity rates and the insatiable demand for more neonatal intensive care facilities, to respond enthusiastically to the call. The only trouble with this advice is its lack of clarity about preventive programs: What is the scope of prevention and what components of which programs actually work?

First, the scope for prevention is limited by the fact that more than 60% of preterm deaths occur before labor or in infants with lethal malformations (86;87). Even when the infant is alive and not malformed at the onset of labor, some preterm deliveries are elective and others are complicated by factors that contraindicate delaying the delivery (e.g., bleeding). The remaining cases of preterm birth involving spontaneous uncomplicated preterm labor or preterm premature rupture of the membranes (PPROM) with a healthy fetus offer the widest scope for prevention; in some cases, however, delivery is already inevitable at the time of hospital admission. Potential preventive efforts in the uncomplicated group include true primary prevention, early identification of preterm labor or its premonitory signs, and inhibition of preterm labor.

Though it is often blurred in practice, the distinction between prevention and inhibition of preterm labor is an important one because the potential for net negative outcomes is even greater with prophylactic interventions. These interventions are used in women at risk, rather than in ones with an established problem, and are used for a greater proportion of the pregnancy.
Preventing and managing prematurity

Table 1. Preterm Births and Deaths by Week of Gestation, Victoria, Australia, 1988

<table>
<thead>
<tr>
<th>Gestation (weeks)</th>
<th>Births</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td>20</td>
<td>27</td>
<td>0.6</td>
</tr>
<tr>
<td>21</td>
<td>42</td>
<td>1.0</td>
</tr>
<tr>
<td>22</td>
<td>50</td>
<td>1.2</td>
</tr>
<tr>
<td>23</td>
<td>52</td>
<td>1.2</td>
</tr>
<tr>
<td>24</td>
<td>54</td>
<td>1.3</td>
</tr>
<tr>
<td>25</td>
<td>47</td>
<td>1.1</td>
</tr>
<tr>
<td>26</td>
<td>70</td>
<td>1.6</td>
</tr>
<tr>
<td>27</td>
<td>71</td>
<td>1.6</td>
</tr>
<tr>
<td>28</td>
<td>100</td>
<td>2.3</td>
</tr>
<tr>
<td>29</td>
<td>97</td>
<td>2.3</td>
</tr>
<tr>
<td>30</td>
<td>124</td>
<td>2.9</td>
</tr>
<tr>
<td>31</td>
<td>137</td>
<td>3.2</td>
</tr>
<tr>
<td>32</td>
<td>254</td>
<td>5.9</td>
</tr>
<tr>
<td>33</td>
<td>296</td>
<td>6.9</td>
</tr>
<tr>
<td>34</td>
<td>494</td>
<td>11.5</td>
</tr>
<tr>
<td>35</td>
<td>766</td>
<td>17.8</td>
</tr>
<tr>
<td>36</td>
<td>1,627</td>
<td>37.8</td>
</tr>
</tbody>
</table>

Note: PMR = perinatal mortality rate: stillbirths and neonatal deaths (to 28 days) per 1,000 total births. Total births in 1988 equaled 63,542.
Source: Perinatal Data Collection Unit, Health Department of Victoria.

WHAT IS PREMATURITY?

Prematurity will be taken to mean preterm delivery, that is, birth before 37 completed weeks of gestation. As some researchers and clinicians still use prematurity to mean low birth weight (<2,500 g) as well as preterm birth, we also refer to studies that quote outcomes in terms of birth weight only. Table 1 shows the distribution of preterm births at each week of gestation from weeks 20 to 36, together with the gestation-specific mortality. This table is a reminder that most preterm infants (80%) are born at 32-36 weeks, although only a quarter of the preterm deaths, and almost none of the intensive care admissions, occur after 31 weeks. The need to distinguish between these "mildly" preterm infants and the "extremely" preterm group born before 32 weeks will be raised in relation to the programs’ outcomes.

WHAT PROGRAMS CAN BE ABANDONED?

Failure to receive prenatal care early enough or often enough has been consistently associated with preterm delivery; consequently, ways of improving the uptake, as well as the type and quality of prenatal care, figure prominently in prevention programs despite the methodological problems involved in determining whether the association is causal. Lack of prenatal care may merely be a marker for causal factors, as it often reflects social disadvantages, poor coping skills, or a concealed or denied pregnancy. However, the Institute of Medicine’s review, Preventing Low Birth Weight (11), concluded that increased utilization of prenatal care is likely to be an effective strategy for preventing prematurity. In addition, a meta-analysis of assorted prenatal interventions has identified small but consistent beneficial effects on birth weight and concluded that their most likely causal mechanism was the incidental social support that accompanied the intervention (71).
Table 2. Multicomponent Prevention Programs

<table>
<thead>
<tr>
<th>Category</th>
<th>Interventions</th>
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</thead>
<tbody>
<tr>
<td><strong>Risk assessment</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
</tr>
<tr>
<td>Staff</td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td></td>
</tr>
<tr>
<td>Public</td>
<td></td>
</tr>
<tr>
<td><strong>Advice</strong></td>
<td></td>
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<tr>
<td>Reduce paid work</td>
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<tr>
<td>Reduce housework and child care</td>
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<tr>
<td>Reduce smoking</td>
<td></td>
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<tr>
<td>Reduce stress</td>
<td></td>
</tr>
<tr>
<td>Reduce travel, commuting, moving house</td>
<td></td>
</tr>
<tr>
<td>Reduce/stop sexual activity</td>
<td></td>
</tr>
<tr>
<td>Improve nutrition</td>
<td></td>
</tr>
<tr>
<td>Bed rest at home</td>
<td></td>
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<tr>
<td><strong>Self-monitoring of uterine activity</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Prenatal care</strong></td>
<td></td>
</tr>
<tr>
<td>Increased frequency of contact</td>
<td></td>
</tr>
<tr>
<td>Continuity of care (single caregiver)</td>
<td></td>
</tr>
<tr>
<td>Facilitated access to hospital</td>
<td></td>
</tr>
<tr>
<td><strong>Support systems</strong></td>
<td></td>
</tr>
<tr>
<td>Home visiting nurses/midwives</td>
<td></td>
</tr>
<tr>
<td>Home help</td>
<td></td>
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<tr>
<td>Family help</td>
<td></td>
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<tr>
<td>Social worker assignment</td>
<td></td>
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<tr>
<td>Stress management classes</td>
<td></td>
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<tr>
<td><strong>Specific obstetric interventions</strong></td>
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<tr>
<td>Regular cervical examination</td>
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<tr>
<td>Cervical suture</td>
<td></td>
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<tr>
<td>Bed rest in hospital</td>
<td></td>
</tr>
<tr>
<td>Progestogens</td>
<td></td>
</tr>
<tr>
<td>Betamimetics</td>
<td></td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td></td>
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</table>

The role of enhanced prenatal care and social support has been taken up in a variety of randomized trials with differing emphases.

**Multicomponent Prevention of Prematurity Programs**

Multicomponent prevention programs within traditional prenatal care have become widely established in the 1980s. Some programs include the reduction of term low birth weight as an objective. All use a mixture of interventions (Table 2) in a group of women defined, either by formal risk assessment or clinical judgment, to be at higher than average risk of preterm delivery.

Some strategies, such as staff and patient education concerning the early signs and symptoms of preterm labor and the need for an immediate response, are common to virtually all multicomponent programs. All include changes in prenatal care: more frequent visits, longer visits, and/or continuity of care from one or two professionals. Implicitly or explicitly, enhanced social support is an essential component. Most of the studies include serial cervical assessments, self-monitoring of uterine contractions, and advice on a variety of lifestyle modifications. Patient education, which is a core element of all of these programs, has received almost no evaluation in its own right,
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Table 3. Preterm Birth in Martinique

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>Total %</th>
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<tbody>
<tr>
<td>1980</td>
<td>6.7%</td>
<td>6.0%</td>
<td>10.0%</td>
<td>7.58%</td>
</tr>
<tr>
<td></td>
<td>1,276</td>
<td>2,250</td>
<td>1,984</td>
<td>(418/5,510)</td>
</tr>
<tr>
<td>1981</td>
<td>7.3%</td>
<td>5.3%</td>
<td>12.7%</td>
<td>8.40%</td>
</tr>
<tr>
<td></td>
<td>1,192</td>
<td>2,326</td>
<td>1,993</td>
<td>(463/5,511)</td>
</tr>
<tr>
<td>1982</td>
<td>7.5%</td>
<td>4.4%</td>
<td>12.1%</td>
<td>7.65%</td>
</tr>
<tr>
<td></td>
<td>1,068</td>
<td>2,526</td>
<td>1,872</td>
<td>(418/3,466)</td>
</tr>
</tbody>
</table>

Abbreviations: A = private specialist care; B = public free care, preterm-birth prevention program from 1980; and C = general practitioner care.

Source: McGregor (62) and further analyses.

Apart from a recent program in inner-city New York that uses a prenatal education videotape in English and Spanish (21). A comparison of women who viewed the videotape with those who did not reported a lower rate of preterm delivery in the former (9.5% compared with 11.5%). Unfortunately, this analysis did not adjust for the greater opportunities for viewing the tape that a longer gestation provided (2). No randomized trial of any educational intervention has been reported to date.

Problems in evaluating the early European and North American programs have been reviewed at length elsewhere (47). The most influential program was the subject of a preliminary report in 1982 showing a 65% reduction in preterm birth compared with historical and concurrent controls (26). Since that time, seven other U.S. programs have published similar accounts using historical (12;36;43;63;90) or concurrent (7;36) controls, although the reductions in preterm birth have never been as substantial as in the original paper of Herron, Katz, and Creasy (26). An eighth program, initially randomized, was reported in terms of secular trends when the intervention spread to all clients (70). All eight programs were associated with a significant reduction in preterm birth or low birth weight, although sometimes this benefit appeared only after excluding the first 1 or 2 years of a program (63;70), restricting the analysis to a subgroup of "preventable" preterm births defined retrospectively (99), or restricting it to women with spontaneous preterm labor (43).

Unfortunately, analyses of these kinds of trials can be very misleading. Published data from a preterm birth program in Martinique (Table 3) show similar findings to those described in the previous paragraph: a fall in the preterm birth rate within an institution when the program was established ("historical controls") and no fall in the other settings ("concurrent controls") (79). However, as the reanalyzed data for the combined population show, there was no reduction in preterm births in Martinique.

By contrast, none of the randomized trials was able to detect a reduction in preterm delivery (Table 4). In the first of these, the intervention, carried out by community health nurses, was rather different from programs based on the Creasy model since it emphasized prenatal class attendance and counseling on nutrition, exercise, food, finances, support, coping with stress, smoking, and alcohol (89). Randomization was by areas rather than by individuals. The trials in Philadelphia (54;57), Pittsburgh (70), and South Carolina (28), as well as the multicenter March of Dimes trial (13;23), succeeded in recruiting women at high risk of preterm delivery: the proportion of women delivering preterm in the control arms of these trials ranged from 12 to 24%. Only
in one site (San Diego) was the intervention associated with a significant reduction in preterm birth. Although this finding has been interpreted as meaning that the intervention worked for Hispanic women who made up the greater part of the high-risk population in San Diego, it is more likely to reflect the play of chance in a small study.

The pooled results of the March of Dimes trial together with the others in Table 4 suggest that the widespread implementation of multicomponent programs before the effectiveness of the individual components was established has been a costly and misleading episode.

Social Support: Home Visiting by Midwives

Four randomized trials of midwives who visited women at home have been reported. The first was carried out in women classified as being at high risk for preterm birth or who had other major complications such as twins, bleeding, or toxemia (92). In this French study the emphasis in the home visiting program was “supervision,” “attention,” or “follow-up,” of the women, who were visited weekly. The second trial, carried out with socially high-risk rather than medically high-risk women in the United States, stated the aims of the home visit to be parent education, the enhancement of existing informal support systems, and increased linking of the families with community services (74). The other two trials, carried out in England and Australia, aimed at providing social support to women at high risk by reason of their past reproductive history; education was a secondary component (6;72). The U.S. trial had insufficient power to detect even a virtual eradication of preterm birth, but the others were appropriately designed to detect a reduction of 25% (6), of 50% (92), or an increase in mean birth weight of 450 g (72).

There were no clinically significant improvements in gestation at delivery in these four trials. The first two suggested that the programs were successful by reporting beneficial effects in selected subgroups (47). However, other small subgroups showed equivalent adverse effects of home visiting. Such findings have the status of hypotheses until tested formally in trials of an adequate size. There were more perinatal deaths among the group who had been visited at home in three of the four trials (6;72;92); this result was both clinically and statistically significant in the French trial.
Social Support: Resource Mothers or Family Workers

Ways of providing social support with nonprofessional workers have been tried in South Carolina (22), Alabama (45), Colorado (18), and England (91). The first three studies involved older, experienced mothers of similar social background as a resource for pregnant women. The first two used concurrent matched controls rather than randomized allocation. In the English study, women at high risk of preterm delivery or low birth weight, on social grounds or because of their prior reproductive history, were offered a “family worker” who would give practical help and support in any way that the pregnant woman wished (91). No reduction in preterm birth rates could be detected in any of the four studies, although there was an association with lower rates of low birth weight in South Carolina.

Despite the results of these social support interventions, interpretations based on subgroup analyses continue to promote the view that home visiting programs are likely to be effective in reducing preterm birth (9;75).

The attractions of the social support hypothesis are the way in which it links the evidence on stress and pregnancy outcome, the differential social class exposure to stressful life events, and differential vulnerability to stressful life events. Problems with the hypothesis include its use as a global, undefined term for a wide variety of approaches to improved care; the conflation of tangible, informational, and emotional supports into a single factor; and the implicit suggestion that “social support” is likely to be effective in the face of major life disruptions such as marital breakdown, domestic violence, or unemployment. The strength of the evidence for the benefits of social support on health lies in the observational data on naturally occurring social support systems (5). The trials described earlier did detect beneficial effects of increased social support on some other personal and family outcomes (9;72;75;91), but their overall effects suggest either that we have not yet found a way to supplement, enhance, or replace existing family and community networks effectively or that the importance of the stress hypothesis has been overrated in relation to preterm birth.

Risk Assessment

All of the prenatal programs used some form of risk assessment as the first step. One factor contributing to their lack of success was the poor predictive power of risk assessment (30;69). The rate of preterm delivery in Philadelphia was 22% in the high-risk group and 12% in the low-risk group, so that almost 40% of preterm births were among the latter (53;56). Low birth weight rates in the English family worker support trial differed very slightly in the high-risk group from those in the whole population (91). Discrimination is even poorer for nulliparous women, who were excluded from most of the trials discussed earlier. Two critical reviews of formal risk scoring confirm these problems and describe their potential harmful effects as “unnecessary intervention in women’s private lives, from superfluous intervention and treatments, from creating unnecessary stress and anxiety, and from allocating scarce resources” (1;76).

Bed Rest

Bed rest as a form of prophylaxis is associated primarily with twin pregnancies, which are known to be at high risk for both mildly and extremely preterm delivery. The need for bed rest to be timed in relation to the maximum risk period, the potential hazards, and the economic costs and benefits have been discussed for over 25 years (37;82). Three controlled trials have been published, one in Finland and two in Zimbabwe (15). One of the latter trials successfully identified women at very high risk and randomized them to routine or selective bed rest (17). Meta-analysis of these three trials confirms...
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that bed rest increases rather than decreases the rate of preterm birth (15). A recently completed Australian randomized trial where bed rest was provided earlier in pregnancy (20–30 weeks) could detect no change in mean gestation at delivery (52), nor could a trial of bed rest from 24 weeks for triplet pregnancy, although this sample was too small to give a conclusive answer (16).

WHAT NEEDS FURTHER DEVELOPMENT?

Assessing the Role of Infection

The new initiatives related to infection are usually, although not exclusively, associated with the problem of PPROM. In the past, several things militated against the acceptance of infection as an important factor. First was a continuing debate on whether infection preceded or followed membrane rupture and preterm labor. Another was the fact that a number of different micro-organisms were claimed to be responsible. The third was that many of the micro-organisms were not recognized pathogens but were accepted as part of the normal flora of the genitourinary tract. Recent reviews have emphasized the variety of substances produced by host cells and micro-organisms (8;62). These substances can facilitate the spread of organisms into the lower uterine segment, impair the physical and functional integrity of the fetal membrane, and promote the production of biologically active peptides by uterine tissues (8;62;85;88), possibly setting off the cascade of events leading to established labor and parturition. Spontaneous labor and PPROM are both possible outcomes of infection. If infection does play an important role in preterm birth, it might help to explain the relatively strong association with prior infertility and the high rate of preterm birth among infants conceived by such new reproductive technologies as in vitro fertilization. The low pathogenicity of the suspect micro-organisms has drawn attention to the important and largely unstudied role of host factors in resistance.

Epidemiological studies have been inconsistent and inconclusive, but a recent meta-analysis of papers on asymptomatic bacteriuria resolved the discrepancies in this specific problem and found a strong association between untreated asymptomatic bacteriuria and preterm delivery/low birth weight. Antibiotic treatment reduced the occurrence of the latter (84). The question of treatment is far from straightforward since substances produced by disrupted micro-organisms may stimulate some of the same immunoenocrinological processes described earlier (62).

The major development need, with respect to infection, is strengthened links with descriptive and analytic epidemiology and well-designed trials that will address extremely preterm as well as mildly preterm deliveries.

Assessing the Role of Physical Activity

The relationship of physical effort to the outcome of pregnancy is controversial; however, several important articles provide enough evidence to show the need to take things further. The first is a descriptive and analytic study of women who continued endurance exercise through pregnancy; their mean gestational length was significantly shortened. More than 20% (6;29) of these very low-risk women gave birth preterm. There was also evidence of a dose-response effect. Exercise before pregnancy or restricted to the first 20 weeks had no such effects (9).

Attention to the extent, timing, duration, and type of exercise is essential in future studies, as there is evidence, in at least some countries, of women’s increasing participation in regular strenuous exercise.

Inconsistent findings on the relationship of maternal work and pregnancy out-
come is in part explicable by changing patterns of employment and social class, in part by difficulty in defining the relevant aspects of domestic and paid employment, and in part by simple comparisons that take no account of other methodological pitfalls.

The work of Mamelle et al. (60) that identified sources of occupational fatigue with a high explanatory power for preterm birth has been confirmed by similar results in a large Canadian retrospective survey (61); however, a small population-based, prospective study in London could detect no association of workload with shortened gestation (83). A large prospective study in Guatemala found associations of manual work with the birth of infants who were both preterm and growth retarded and some evidence of a “dose”-related effect as well (44).

The best attempt so far to separate the effects of physically demanding work from the adverse social circumstances that often accompany it was a large survey of female resident physicians in the United States that compared such residents with the spouses of their male counterparts (40). No significant effect of workload on preterm birth was detected, except a marked increase where the mother worked more than 100 hours a week. This latter finding is in agreement with the French and Canadian work discussed above.

A possible preventable role for physical work would have important social policy implications (22;59).

Cervical Cerclage
An earlier review drew attention to the poor quality of early evaluations of cervical cerclage, both with the “matched” studies and with the comparisons of obstetric practices within single institutions (47). At the time of the review, three randomized trials had been reported. None of them could detect a beneficial effect of cervical cerclage on gestation at delivery. One used cerclage electively in twin pregnancies diagnosed by ultrasonography in the first trimester after induced ovulation. Preterm labor and neonatal deaths were equally common in both treated and untreated groups. The second trial, which was much larger, evaluated the use of the procedure in women at moderate risk of preterm labor as indicated by their past obstetric history. There were no differences in preterm birth rates. The third trial, which was the most powerful, recruited women at high risk, predicting the incidence of preterm labor in the untreated group to be 30%. It was, as it turned out, 33% in both groups.

The largest study found no benefits of treatment and also found the cerclage group to have experienced more interventions of all sorts (hospital admission, tocolytic drugs, induction of labor, and cesarean delivery) and to have reported more self-monitored uterine contractions. Since then a large multicenter randomized trial, in women whose obstetricians were “uncertain” about the benefits of cervical cerclage, had demonstrated a “marginally statistically significant benefit in terms of delivery before 33 weeks gestation; birth of an infant <1500 g; miscarriage, stillbirth or neonatal death.” These results suggest that the operation had an important beneficial effect on 1 in 20–25 women. The working party regarded these results as inconclusive and recruitment for the study continues (68).

More attention to the natural history, onset, and sequence of preterm labor in individual women might help to clarify who benefits from cervical cerclage.

Serial Cervical Assessment
An alternative approach to prediction of preterm birth that does not involve risk assessment is serial evaluation of the shortness, effacement, and state of dilation of the cervix. Problems in recommending this approach to all pregnant women, or indeed
to a subset of them, have been reviewed in detail elsewhere (47), but the difficulties include the very variable proportion of women reported to have high cervical changes (8–38%); the range of associated predictive values (14–28%); the risk of releasing prostaglandins from the cervix; and the finding that pelvic examinations at term are associated with PPROM. A controlled trial that allocated women by birth date to serial cervical assessment was unable to reduce the preterm birth rate using this strategy, but the allocation resulted in very uneven groups and there may have been some bias (67). A randomized trial is currently under way in France.

**Monitoring of Uterine Activity**

The poor performance of risk assessment has led to attempts to measure parameters more clearly associated with the process of labor within the end-organ. One of these—serial cervical assessment—was discussed earlier; however, a second method—monitoring of prenatal uterine activity—shows more promise. The rationale for such monitoring and a review of activities before 1980 has been published by Bell (3), who went on to report longitudinal studies, diurnal variation, and the predictive value of this technique in a small group of women at extremely high risk of preterm birth. The predictive value has been confirmed in a randomized (blind) trial among socially high-risk pregnant black women (55).

An improved tocodynamometer was subsequently adapted to store several hours of data and transmit them by telephone to permit ambulatory monitoring from home. Studies with concurrent controls (47) and one small trial using alternate allocation to tocodynamometer or self-palpation (66) confirmed a dramatic reduction in preterm birth rate (12% vs. 41%; 15% vs. 45%). This result was due in part to an extraordinarily high rate of preterm births in the controls. However, a series of randomized trials in which the control group received frequent, provider-initiated contact with a knowledgeable nurse found this method to be as effective as the monitor (35;36;80). The frequency of contact was about five times a week, substantially greater than any of the social support interventions discussed earlier.

Recent awareness of the lack of success of multicomponent preterm birth prevention programs has markedly increased interest in monitoring of uterine activity at home. A complete supplement was devoted to this topic by the journal *Obstetrics and Gynecology* in July 1990. The main problem in interpreting the randomized trials reported in this supplement is their exclusion of relatively large proportions (18–22%) of the groups allocated to home monitoring for what is described as noncompliance (41;42;97). Another problem is the tendency to report outcomes only for those women who present with preterm labor, which leads a fourth article to claim a dramatic difference in preterm birth between monitored and standard care groups (42% and 65%; p = 0.022). This difference is in fact 23/127 compared with 28/118, and thus is not significant (29). The effectiveness of home monitoring of uterine activity remains unclear.

Apart from the unresolved question of the possible cointervention effects of frequent contact, there are two other important issues. First, what is the proportion of preterm births in which a potentially preventable problem might have been identified by monitoring of uterine activity? In one unpublished study, only 20% of preterm births and only 2% of births were identified (Orleans, Leff, and Haverkamp, personal communication). Elsewhere, Main et al. (57) reported that only 1% of high-risk women delivered before 34 weeks gestation solely because of preterm labor. Second, the effectiveness of monitoring uterine activity cannot be separated from the effectiveness of tocolysis. Therefore the place of monitoring of uterine activity remains uncertain.
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Tocolytic Agents
The poor quality of research on preventing or inhibiting preterm uterine activity has been documented in reviews for more than a decade (65). Despite the major role given to tocolytics in prematurity prevention programs where the aim of early identification of the symptoms and signs of preterm labor is to facilitate early and aggressive tocolytic therapy, the effectiveness of even the most widely used agents is unclear in some important respects. A detailed review is available (39).

Meta-analysis of 16 randomized trials comparing betamimetic agents with placebo-treated controls or those receiving no active treatment shows a significant reduction in the proportion of infants delivered within 24 hours, 48 hours, or 1 week after the initiation of the treatment, with a corresponding reduction in preterm birth rates. In the same group of studies, however, the reduction in low birth weight was of borderline significance, and no reduction in perinatal mortality or respiratory distress syndrome could be detected. Thus tocolytic therapy, even with the widely used betamimetic agents, can only be recommended at present for its short-term benefits of delaying delivery for 48 hours or so, giving time for the administration of corticosteroids and transfer to a hospital with perinatal intensive care facilities (Level III) for birth (39).

The maternal hazards of tocolytic therapy with betamimetic drugs are substantial: 1 in 20 respondents to a survey among the Society of Perinatal Obstetricians had encountered a maternal death; 69% had seen pulmonary edema, 49% myocardial ischemia, 41% severe hypotension, and 23% diabetic ketoacidosis (94). Given these reports, even the limited benefits of tocolytic therapy must be weighed carefully against the risks.

Progestogens
Reanalysis with pooling of the published trials of 17-hydroxyprogesterone caproate has detected a reduction in preterm labor and preterm birth with this treatment, although there was no reduction in perinatal mortality (38). All the trials were small, but the findings are promising enough to warrant a major study as soon as possible.

Managing Preterm Premature Rupture of the Membranes
PPROM is associated with about a third of preterm births in most populations. A recent critical review of treatment concluded that no interventions (tocolytics, prophylactic antibiotics, prompt delivery, amnioinfusion) were of proven benefit and therefore that they should be used only within trials (73).

Route of Delivery
Randomized trials to determine whether elective cesarean delivery confers any benefits on the extremely preterm fetus (26–31 weeks) have proven very difficult to implement (51). Both funding and recruitment have been problematic. Meanwhile, the practice of cesarean delivery when delivery occurs at these gestations is becoming increasingly entrenched. In Missouri, the use of cesarean section for very low birth weight (VLBW) infants (500–1,499 g) increased from 24% to 44% in the years 1980–84 (58). In Victoria, Australia, the rate increased from 15% to 30% for infants 500–999 g and from 39% to 52% for infants 1,000–1,499 g in the years 1982–85 (50). Malloy et al. (58) concluded that there was little evidence of benefit in Missouri other than a possible postponement of deaths, from the first day to some other time during the first week. In Victoria, birth weight specific neonatal mortality of VLBW infants was unchanged from 1982 to 1985 (50). Because long-term follow-up is underway for the latter infants, it will be possible to determine whether cesarean delivery is associated with lower rates.
of impairment in surviving VLBW infants even though it was not associated with improved survival.

Surveys of obstetric practice show an increased willingness to carry out an abdominal delivery prior to 30 weeks among physicians who have graduated more recently (95). However, cesarean section at very early gestations carries well-defined risks to the mother (and to any future infants). The unresolved question of fetal benefits is in urgent need of resolution with appropriate trials before the practice becomes established as normative.

WHAT CAN BE PROMOTED?

Smoking Cessation

Cigarette smoking increases the risk of extreme prematurity, most probably by its association with prepartum hemorrhage (including placenta previa) and PPROM (64). Because cigarette smoking is still very prevalent among pregnant women, with publications showing smoking rates of 25–30% (4;48;90), the implementation of effective antismoking programs should have a high priority during pregnancy. Ten randomized trials, nine reviewed in detail elsewhere (48) and one published since (20), have been reported; in addition, there are two studies that involved concurrent nonrandomized controls (48). The weakest part of most trials has been the intervention itself, which is poorly specified, often restricted to written information on the hazards of smoking to the fetus with, in some cases, poor implementation by the staff as well (46;98).

The most effective smoking cessation programs have involved self-help and behavioral strategies for quitting smoking and preventing relapse, using a self-help manual, a series of self-help booklets, and written material supplemented by a home visit with intermittent contact by telephone and mail (20;50).

No trial completed so far has been large enough to assess the prevention of extremely preterm delivery and only a handful of trials have been able to assess the effects of smoking on birth weight. With one exception, probably explained by problems with self-reporting, all trials that are large enough have been able to demonstrate an increase in birth weight commensurate with the achieved reduction in smoking.

In light of these findings and in the knowledge that no trial has shown an increase in cigarette use among the intervention group or any subset of it compared with controls, interventions that focus on self-help and behavioral strategies for quitting and include pregnancy-specific material can be recommended. Such programs are less likely to be perceived as “victim-blaming” than are programs that only advise on the fetal hazards.

At the same time, all those responsible for the care of pregnant women should support strategies that aim at a progressive reduction in cigarette smoking in society as a whole. The goals here are to increase cigarette excise taxes; to ban all forms of tobacco advertising; to challenge legally whether tobacco manufacturers are responsible for health outcomes; to enforce the laws that prohibit sales to children and adolescents; to make public areas nonsmoking; and to develop smoking policies for institutions and workplaces.

Administration of Corticosteroids

Despite continuing controversy and lack of consensus among obstetricians (94;95) about the net benefit of giving corticosteroids to women in preterm labor, meta-analysis of the 12 randomized trials confirm that the administration of corticosteroids 24–48 hours before birth significantly reduces the risk that the infant will develop respiratory dis-
tress syndrome. The pooled odds ratio is 0.48, 95% confidence interval 0.40–0.58. This result can be achieved without increasing the risk of maternal or fetal infection. Even when there is PPROM the findings are similar. These benefits are associated with a significant reduction in early neonatal deaths, periventricular hemorrhage, necrotizing enterocolitis, and duration of hospital stay (14). Limited follow-up has shown no deleterious effects of the treatment on growth and development.

There seems to be some reluctance among clinicians to act in accordance with the trials’ results, although the widespread dissemination and discussion of the meta-analytic findings may go some way towards changing the relevant clinical practices.

**Birth at a Perinatal Center**

In that there have been no randomized trials to assess the benefits of transferring infants, before or after birth, to hospitals with perinatal intensive care facilities, the judgment that delivery at a Level III hospital helps the fetus is less securely grounded than the other strategies discussed in this section.

Population-based studies of mortality patterns by place of birth have been reported from countries with very different patterns of care: the United States (25;77;78), England (81), the Netherlands (96), Canada (31), and Australia (49). The earlier papers showed a lower mortality rate for infants of 1,000–1,499 g delivered in hospitals with intensive care facilities and staff. Almost all infants in this weight range are very preterm, born after 27 weeks gestation. Data from more recent years in the Netherlands and Australia demonstrate reduced mortality for even more preterm infants as well (49;96). However, benefits for the mildly preterm infant have been less consistently found.

The English study attempted to determine whether the increased survival rate was attributable to “better care” or “better babies” by comparing subgroups defined by the mother’s place of residence. U.S. and Dutch studies adjusted for 8–22 confounding factors and still found the benefits of Level III delivery to be substantial. In England, higher survival rates were achieved at the price of a marginally significant increase in prevalence of major impairments.

**Reporting Results**

Although preterm delivery is often treated as if it were a clear-cut binary variable, in reality it is nothing of the kind. At the lower boundary, despite underregistration of infants perceived to be nonviable, the least mature 5% of infants incur over a third of preterm deaths (Table 1). Prolongation of pregnancy by 1 week at this stage (20–24 weeks) would have no effect on the preterm birth rate. Such prolongation might even increase preterm births and deaths if pregnancies below 20 weeks were also prolonged and some previously excluded fetuses became registered. The pressure on neonatal intensive care would be even greater. At the upper boundary more than a third of all preterm infants are born after 36 completed weeks of gestation and more than half after 35 weeks. Even a minor change would make a substantial difference to the rate of preterm birth. Yet the probable change in preterm deaths or utilization of neonatal resources would be very small.

Goldenberg et al. (24) recently demonstrated how the shift from menstrual and clinical pregnancy testing to reliance on sonographic evidence, together with exact calculation of gestation instead of rounding off the weeks, was associated with an apparent major change in the preterm birth rate (12–17%), despite an unchanged birth weight distribution. This exemplifies the possible contribution of definitional issues to preterm birth rates.
Given that so-called prematurity prevention programs mostly aim at reducing the rate of preterm delivery, it would be more appropriate for them to report outcomes in terms of gestation rather than by birth weight. To take account of the very different significance of preterm birth at 25 weeks of gestation compared with preterm birth at 35 weeks, results should be analyzed as survival curves.

Endpoints
The problem of endpoints in relation to preterm delivery goes beyond the usual problem that there are several important reasonable endpoints: gestation at delivery, birth weight, major neonatal complications, and survival. The additional issue is that there may be conflict between endpoints: better survival but more major impairments; worse survival but fewer days of neonatal care; or a better fetal outcome at the expense of significant maternal risk (classical cesarean section, pulmonary edema from tocolytics). Reports of trials should do justice to the complexities.

Into the 1990s
Population strategies, made popular with reference to changes in preterm birth in France, need even more careful evaluation than high-risk strategies since they are applied to all women, most of whom will give birth at term without any intervention at all.

The recent history of prematurity prevention illustrates the expected lack of randomized trials and continuing use of inappropriate study designs. More than that, it demonstrates both the reluctance of concerned clinicians to take up practices shown to have substantial benefits (e.g., corticosteroids for promoting pulmonary maturity) and the tenacious hold of other ideas despite lack of evidence (e.g., bed rest, cesarean delivery of very premature infants). Thus the first need of the 1990s is effective ways of transferring the results of research into everyday clinical decision making. The other need, at institutional and regional planning levels, is an explicit and rational method of assessing innovations before and during implementation, including criteria for withdrawal of the program (93).

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