Preterm Birth 2

Primary, secondary, and tertiary interventions to reduce the morbidity and mortality of preterm birth

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Interventions to reduce the morbidity and mortality of preterm birth can be primary (directed to all women), secondary (aimed at eliminating or reducing existing risk), or tertiary (intended to improve outcomes for preterm infants). Most efforts so far have been tertiary interventions, such as regionalised care, and treatment with antenatal corticosteroids, tocolytic agents, and antibiotics. These measures have reduced perinatal morbidity and mortality, but the incidence of preterm birth is increasing. Advances in primary and secondary care, following strategies used for other complex health problems, such as cervical cancer, will be needed to prevent prematurity-related illness in infants and children.

Background

Interventions to reduce the morbidity and mortality related to preterm birth can be classified as primary (directed to all women before or during pregnancy to prevent and reduce risk), secondary (aimed at eliminating or reducing risk in women with known risk factors), or tertiary (initiated after the parturitional process has begun, with a goal of preventing delivery or improving outcomes for preterm infants).

Most obstetric interventions to reduce the morbidity and mortality of preterm birth are classified as tertiary—eg, regionalised perinatal care, treatment with tocolytic agents, antenatal corticosteroids, and antibiotics, and optimum timing of indicated preterm birth. These measures are intended to reduce the burden of prematurity-related illness more than to reduce the rate of preterm birth. Secondary prevention requires identification and reduction of risk, both of which have proved difficult. Primary prevention efforts adopted in Europe have not been embraced in the USA, owing perhaps to demographic and sociopolitical factors. After the successful implementation of interventions for other complex disorders, such as cervical cancer, primary prevention of prematurity-related illness is a desirable goal.

Preterm birth is generally classified as either indicated or spontaneous.[1,2] The most common diagnoses associated with indicated preterm births are hypertensive disorders, haemorrhage, and acute or chronic fetal compromise (fetal distress or intrauterine growth restriction). About two-thirds of preterm births are spontaneous; these births follow preterm labour and preterm premature ruptured membranes, or related diagnoses, such as cervical insufficiency. Efforts to address indicated preterm births are traditionally regarded separately from those for spontaneous preterm births. This distinction, however, is somewhat artificial and can even be misleading because intrauterine inflammation related to microbial infection, uterine vascular compromise, or decidual haemorrhage can exist for days, weeks, or longer before becoming clinically apparent as preterm cervical effacement, membrane rupture, labour, or vaginal bleeding.[3]

Until the many pathways that contribute to preterm parturition are more clearly understood, secondary and tertiary interventions to prevent preterm birth must take into consideration that prolongation of pregnancy intended to promote maturation might also allow continued exposure to a suboptimum or even hazardous intrauterine environment. Indeed, prevention of preterm birth is not a health outcome, but rather a surrogate endpoint for optimum fetal, infant, and lifelong health.[4,5]

Efforts focused on reducing or eliminating known risk factors assume that preterm birth would decline in proportion to the contribution of a specific risk factor. The failure of this approach has contributed to the understanding of preterm birth as a syndrome in which various pathological disorders contribute to the initiation and progression of preterm parturition.[3] A clear understanding of pathophysiology is lacking because interventional trials have been designed to answer clinical rather than mechanistic questions, such as whether an intervention can reduce the rate of preterm birth in women with risk factors in previous or present pregnancies. Thus, an unknown proportion of participants in any trial receive an intervention that has no opportunity to exert a beneficial effect, leaving the interpretation of the results open to debate. In this Review, we will try to use the results of clinical trials to formulate recommendations for care of women with risk factors for preterm birth.

Primary prevention of risk in women of reproductive age

Primary prevention of infant morbidity and mortality of preterm birth is an increasingly compelling strategy as the limitations of tertiary care become evident. Much remains to be learned about secondary prevention for women at risk, which is at best a strategy limited to removal rather than avoidance of risk. Primary prevention strategies for cancer and vascular disease have begun to show benefit only after decades of effort through education and public policy built on sound science. Even

greater perseverance is likely to be needed for preterm birth because the magnitude of the problem is underestimated by the public.[6]

Preconceptional primary prevention

Preconceptional interventions are attractive because many risk factors are difficult to address successfully during pregnancy.[7]

Public educational interventions

An inaccurate perception held by the public is that improved neonatal care has resolved the problems of preterm infants.[6] Increased awareness of preterm birth as the leading cause of infant mortality might offer an opportunity to inform the public about potentially avoidable risk factors.[8] For example, greater public and professional awareness of evidence that repeated uterine instrumentation—eg, uterine curettage or endometrial biopsy—is associated with an increased risk of subsequent preterm birth might, over time, influence decision-making about these procedures.[2,9–12] Similarly, choices made in fertility care might be affected by broader public knowledge of the increased risk of preterm birth in singleton gestations conceived with assisted reproductive technology.[13,14] Such educational efforts are not in place at the moment, but could be modelled on successful efforts to reduce the prevalence of smoking.

Public and professional policies

By contrast with public education strategies, policies adopted by government or medical bodies can exert a more immediate effect. For example, policies specifically intended to reduce the risk of higher-order multiple gestation have been successful in Europe, Australia, and the USA. Rates of triplet and higher-order multiple pregnancies had been rising rapidly in the USA until 1998, when the increase was arrested by voluntary adoption of limitations on the number of embryos transferred. The rate of higher-order multiple pregnancies fell by 50% between 1996 and 2003.[15,16]

A societal approach to improve pregnancy outcomes has been adopted in most European countries.[17] Examples of policies to protect pregnant women are minimum–paid-pregnancy leave of 14 weeks, time off for prenatal visits, exemption from night shifts, and protection from workplace hazards (even complete work leave, if necessary). Results of these policies have been presented in the EUROPOP (European programme of occupational risks and pregnancy outcome) study in which the risk of preterm birth was not related to employment, but was increased in women who worked more than 42 h per week (odds ratio [OR] 1·33, 95% CI 1·1–1·6) and who were required to stand for more than 6 h per day (1·26, 1·1–1·5).[18] Work in a standing position compared with that in a sitting position was associated with increased risk of preterm birth (1·56, 1·04–2·60) in a prospective observational study in Guatemala.[19] A similar study in North Carolina, USA, reported no association between standing or lifting and preterm birth, but the risk was 50% higher in women who worked nights than in those who worked days.[20] The ranges of locations, circumstances of work, and outcome definitions preclude straightforward comparisons of outcomes across geographic regions. Nevertheless, adoption of universal health-care coverage for women and children and optimum work policies for women are worthy goals.[21]

Nutritional supplements

Women planning to become pregnant are routinely advised to start taking prenatal vitamins before conception, chiefly to reduce risk of birth defects.[22] Multivitamin supplementation taken before, but not after conception, was associated with a reduced rate of preterm birth in an observational study; however, a randomised, placebo-controlled trial of vitamin supplementation that enrolled women before conception and continued through the first 2 months of pregnancy reported no effect of vitamins on the preterm birth rate.[23]

Smoking

In view of the association of maternal smoking with preterm and low-birthweight infants, a reduction in maternal smoking might be expected to reduce the rate of preterm birth.[24] The risk attributable to cigarette smoking is greater than 25% for preterm birth[25] and is about 5% for infant mortality.[26] In the USA, however, preterm-birth rates rose from 11·6% to 12·5% between 2000 and 2004 even though smoking in women aged 18–44 years declined from 25·5% to 21·7% during the same period.[27] Reduced prevalence of smoking would nevertheless have benefits for pregnant women and infants.

Primary prevention during pregnancy

Primary prevention strategies are directed at all pregnant women, and include treatment (eg, multivitamin supplements) and screening to select appropriate treatment (eg, urine culture).

Nutritional supplements during pregnancy

Although observational studies suggested lower rates of preterm birth in women taking dietary supplements,[28] protein and calorie supplementation during pregnancy was not beneficial when investigated in controlled trials.[29] Calcium supplementation did not reduce the rate of pre-eclampsia or preterm birth in a randomised trial of 4589 healthy nulliparous women.[30] The percentages of births before 37 weeks' and 34 weeks' gestation did not differ between supplemented and control groups, and nor did the rate of preterm premature rupture of membranes. A Cochrane review of ten trials that enrolled 14751 women did not find a significant effect of calcium supplementation on the risk of preterm birth (relative risk [RR] 0·81, 95% CI 0·64–1·03), despite a significant reduction in pre-eclampsia in calcium-treated women (12 trials, 15 206 women: 0·48, 0·33–0·69).[31]

Supplemental intake of vitamins C and E to prevent pre-eclampsia was studied in a randomised trial that enrolled 1877 healthy women.[32] Rates of births before weeks 37, 34, and 28 of gestation were not different. Treatment did not affect the incidence of preterm premature rupture of membranes, but respiratory morbidity was reduced in infants born to women taking supplemental vitamins. A trial of supplemental docosahexaenoic acid given to 291 women in the third trimester of pregnancy reported a 6-day increase in gestational age, but there was no effect on the rate of preterm birth.[33]

Smoking cessation in pregnancy

Pregnancy is an optimum time to encourage smoking cessation.[34] A review of smoking cessation programmes reported that a 5–15 min counselling session delivered by a trained provider who offered pregnancy-specific counselling significantly reduced smoking rates. The reduction in smoking was modest, but clinically significant (RR 1·7, 95% CI 1·3–2·2). Persistent attention to smoking reduction and cessation in prenatal visits was emphasised in most programmes. Smoking cessation in pregnancy can be further improved by specific funding for such services.[35] One programme reported results in 3569 poor women who received care coordination, nutritional counselling, or psychosocial counselling to address specific risks such as smoking and inadequate weight gain.[36] The proportion of low-birthweight infants was lower for women who stopped smoking than for women who continued to smoke (8·5% *vs* 13·7%). The rate of low birthweight was lower in women who achieved adequate weight gain than in those who did not (6·7% *vs* 17·2%); however, these results were measured in birthweight, not gestational age. A Cochrane review reported that smoking cessation programmes in pregnancy successfully reduce the incidence of preterm birth (0·84, 0·72–0·98).[37]

Prenatal care

Improved access to prenatal care has been regarded as a way to reduce prematurity because of the association between early registration for care and low rates of preterm birth. This association, however, seems to derive more from the high rate of preterm birth in women who receive no prenatal care than from the content of care for those who receive it. Early access to prenatal care did not influence the rate of preterm birth in women enrolled in a study of prenatal diagnosis techniques in the first trimester.[38] Rates of preterm birth remained high in African-American women despite early entry into prenatal care.

The content of prenatal care for women at increased risk of preterm birth has been studied, but prematurity prevention within routine prenatal care has received little attention in North America.[39] By contrast, European prenatal care has emphasised primary prevention of risk during pregnancy with social and financial support for low-risk pregnant women.[17] This approach has been associated with reduced rates of preterm birth over time in France,[40] but has not been tested in controlled trials. Attempts to adopt parts of the European care model in the USA have emphasised identification of at-risk women rather than avoiding risk for the larger group of low-risk women who deliver as many as half of preterm infants.[41]

Periodontal care

The risk of preterm birth is associated with the severity of periodontal disease and increases when periodontal disease progresses during pregnancy,[42] but the basis for this association is uncertain. The increased risk of preterm birth might result from haematogenous transmission of oral microbial pathogens to the genital tract, or, more likely, from shared variations in the inflammatory response to microorganisms in the oral and genital tracts.[43,44] Periodontal care has been advocated as an intervention to reduce rates of preterm birth, but randomised trials have not reported reduced rates of preterm birth in women treated for periodontal disease.[45–47] The effects of preconceptional periodontal care on preterm birth have not been reported.

Screening of low-risk women

Screening for and treatment of asymptomatic bacteriuria prevent pyelonephritis,[48] and have been reported to reduce the rate of preterm birth.[49,50] Optimum screening and treatment protocols to prevent preterm birth are not well defined.

Systems to assess risk of preterm birth are largely based on a history of preterm birth and present pregnancy risk factors, such as multiple gestation and bleeding, but more than 50% of preterm births arise in pregnancies without obvious risk factors.[51] Most historical risk factors, including previous preterm birth, have low sensitivity.[52] In an effort to identify new risk factors in apparently healthy women that might be amenable to intervention, Goldenberg and colleagues[52] reported that the number and gestational age of previous preterm births were the strongest clinical risk factors, and that the presence of fetal fibronectin in cervicovaginal fluid, cervical length, and bacterial vaginosis were the factors most strongly linked to risk of spontaneous preterm birth in singleton pregnancies.[52]

Although genital-tract infection and colonisation are consistently associated with increased risk of preterm birth, antibiotic treatment does not reliably reduce this risk. Screening for and treatment of *Ureaplasma urealyticum*,[53] group B streptococcus,[54] and *Trichomonas vaginalis* does not reduce the rate of preterm birth, and, in the case of trichomonas, can actually increase risk of preterm birth.[55,56] Routine screening for and treatment of bacterial vaginosis to reduce preterm birth have been extensively studied.[57–66] Although bacterial vaginosis can be eradicated by antimicrobial therapy, meta-analyses

and reviews have shown that treatment does not reduce the occurrence of preterm birth in low-risk women and it is not recommended.[67–70]

Routine second-trimester digital or ultrasonographic assessment of cervical length in uncomplicated pregnancies can identify women who are at increased risk of preterm birth,[52,71–76] but the sensitivity is low (25–30% for digital examination and 35–40% for endovaginal sonography). Cerclage for short cervix in women without a previous early birth is apparently ineffective,[77,78] but a randomised trial in this population reported a significant reduction in preterm birth in women with cervical length of 15 mm or less given vaginal progesterone compared with those given placebo.[79] A trial (NICHD MFMU SCAN trial) of 17α-hydroxyprogesterone caproate in nulliparous women with short cervices is underway.

Asymptomatic women with a positive test for fetal fibronectin have an increased risk of preterm birth before 35 weeks' gestation, especially within 2 weeks of a positive test. The basis for this association is believed to be disruption of the maternal-fetal decidual interface, which is generally related to inflammation.[52] Although the sensitivity of the test for preterm birth before 35 weeks' gestation is only about 25%, the sensitivity for birth before 28 weeks' gestation was as high as 65% in one study.[52] On this basis, a placebo-controlled trial of metronidazole and erythromycin was undertaken in women with a positive test for fetal fibronectin at 21–26 weeks' gestation.[80] Preterm birth rates before weeks 37, 35, and 32 were unaffected by antibiotic treatment (OR 1·17 [95% CI 0·80–1·70], 0·92 [0·54–1·56], and 1·94 [0·83–4·52], respectively). Thus, screening for fetal fibronectin is not recommended in pregnancies that are not at risk.

The combination of digital examination, fetal fibronectin test, and cervical sonography in nulliparous and low-risk multiparous women was investigated in a secondary analysis of data from the preterm prediction study.[81] The sensitivity of cervical sonography was 39% for birth before 35 weeks' gestation in low-risk women. Sensitivities for the more widely available and less costly tests—digital examination and fetal fibronectin—were below 25%. The combination of serum markers for preterm birth, cervicovaginal fetal fibronectin, and ultrasonographic measurement of cervical length showed greater sensitivity and positive predictive value.[82]

Secondary prevention: treatment for women at risk of preterm birth

Secondary prevention efforts are directed at women with evident risk of preterm birth on the basis of either obstetric history (eg, a previous preterm birth or known uterine anomaly) or present pregnancy risk factors (eg, multiple gestation or bleeding).

Preconceptional interventions

With rare exception, preconceptional interventions to reduce the risk of preterm birth are based on an obstetric history of preterm birth; therefore, the definition of previous preterm birth is crucial.[83] The upper boundary is commonly agreed to be 37 weeks' gestation, although the risk of recurrence declines as the gestational age of the index preterm birth approaches 37 weeks.[84] Assignment of a lower limit to demarcate preterm birth from spontaneous abortion is controversial, ranging from 13 weeks' to 24 weeks' gestation.[83] The lowest gestational age for which an increased risk of preterm birth is seen in subsequent pregnancies is optimum for clinical use, and was defined as 18 weeks' gestation for spontaneous preterm births in an analysis of data from the preterm prediction study.[85] Previous births before 17 weeks' gestation did not confer an increased risk of recurrent preterm delivery.[85]

The risk of recurrence is increased for both spontaneous and indicated preterm births.[86–89] Risk increases as the gestational age of the previous preterm birth declines and as the number of preterm births increases.[84] Careful review of records from previous pregnancies is needed to estimate the risk and identify opportunities to eliminate or reduce risks, including some that might need preconceptional intervention (eg, correction of Müllerian anomalies),[90] and others that would influence prenatal care (eg, prophylactic progesterone or cerclage). Prepregnancy medical risk factors can be identified in as many as 40% of preterm births,[91] which suggests that women with these risks might benefit from preconceptional interventions such as control of diabetes, seizures, asthma, or hypertension. There is no evidence that recommendations for care between pregnancies for women with previous preterm birth can actually influence the preterm birth rate.[92] A randomised trial of interconceptional home visits and counselling by midwives aimed at reducing low birthweight and preterm birth reported no evidence of benefit in 1579 women.[93]

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A randomised, placebo-controlled trial tested interconceptional antimicrobial treatment in women with a previous early preterm birth.[94] Women were randomly assigned to receive metronidazole and azithromycin or placebo every 3 months between pregnancies, but there was no effect on the rate of recurrent preterm birth. The proportion of women enrolled whose qualifying preterm birth was related to infection is unknown.[95]

Postconceptional interventions

Secondary prevention of indicated preterm birth

Studies aimed at secondary prevention of indicated preterm births have typically enrolled women with risk factors for pre-eclampsia—eg, nulliparity, twin pregnancy, diabetes, chronic hypertension, or a previous pregnancy complicated by pre-eclampsia or intrauterine growth restriction. Trials of various agents (low-dose aspirin,[96,97] vitamins C and E,[98] and fish oil[99,100]) have been done to assess the effect on the rate of pre-eclampsia. Cochrane reviews have shown small reductions in preterm-birth rates (8% reduction in risk [29 trials, 31151 women, RR 0·92, 95% CI 0·88–0·97]), small-for-gestational-age babies (10% reduction in risk [36 trials, 23638 women, 0·90, 0·83–0·98]), and fetal or neonatal death (14% reduction in risk [40 trials, 33098 women, 0·86, 0·76–0·98]) in trials of antiplatelet drugs, chiefly low-dose aspirin.[101] Although a Cochrane review showed a significant reduction in pre-eclampsia in women given supplemental calcium, there was no corresponding effect on the rate of preterm birth (ten trials, 14751 women: 0·81, 0·64–1·03) or perinatal death (ten trials, 15141 babies; 0·89, 0·73–1·09).[31] A similar review of antioxidants to prevent pre-eclampsia showed a reduction in the disorder, but there was evidence of a possible increased risk of preterm birth.[102]

Secondary prevention of spontaneous preterm birth

Studies of secondary interventions to reduce spontaneous preterm birth have typically enrolled women selected from three populations: those with a previous spontaneous preterm birth;[103] those with a major risk factor in the present pregnancy, such as multiple gestation;[104] and those with a previous preterm birth and a present pregnancy risk factor (eg, bacterial vaginosis or short cervix).[105–107] The results have been largely unsatisfactory in all three populations, but useful information can be derived. First, both hypothesis-testing and hypothesis-generating analyses have been reported, a point generally lost in brief summaries of complex trials. Also, because the causes of preterm birth are so diverse, studies based on risk factors inevitably enrol women in whom the intervention tested is not applicable.[95] Furthermore, although an effective intervention can interrupt a causal pathway (eg, an antibiotic can eliminate a genital microorganism), the ultimate clinical effect can be measured more by host and environmental factors than by the treatment tested.[108] Finally, the timing of an intervention can affect its clinical efficacy, as might be the case for antibiotic trials.[109]

Modification of maternal activity

Despite the absence of evidence of any benefit, bed rest, limited work, and reduced sexual activity are frequently recommended to reduce the likelihood of preterm birth in pregnancies at risk of both indicated (pre-eclampsia or intrauterine growth restriction) and spontaneous preterm births.[110,111] Yost and colleagues[112] reported no relation between coitus and risk of recurrent preterm birth. Research on these factors essentially stopped before information from recent studies became available. Neither bed rest nor coital abstinence has, for example, been studied in women with short cervices.

Nutritional supplements

Trials of supplemental omega-3 polyunsaturated fatty acids have been done on the basis of low rates of preterm birth in populations with a high dietary intake. The postulated mechanism is that omega-3 polyunsaturated fatty acids reduce concentrations of proinflammatory cytokines. Dietary supplementation with omega-3 polyunsaturated fatty acids has been associated with reduced production of inflammatory mediators, and a randomised trial of omega-3 supplements undertaken in women at risk of preterm birth showed a 50% reduction in preterm–birth rate.[99] A subsequent randomised trial of supplemental fish oil noted a reduction in recurrent preterm birth (RR 0·54, 95% CI 0·30–0·98).[100] Another trial (NICHD MFMU omega trial) of supplemental omega-3 polyunsaturated fatty acids in women with a previous preterm birth will report results in 2008.

Improved care for women at risk

Although perhaps helpful in adolescents,[113,114] more intensive prenatal care, including social support, home visits, and education, has not reduced rates of preterm birth in other women.[115–119] Early reports suggesting that frequent provider-initiated contact for women with previous preterm births might reduce recurrence risk were overturned by a large, controlled trial that showed no reduction in rates of preterm birth, but showed an excess of care without benefit.[120] A Cochrane systematic analysis reported no benefit of more intensive prenatal care in women at increased risk.[121]

Antibiotic treatment

There is controversy over antibiotic treatment in women with a previous preterm birth who are reported to have bacterial vaginosis. Support for antibiotic treatment originated from secondary analyses of a trial in women at risk of preterm birth,[105] in which benefit was limited to women with bacterial vaginosis, and another trial that enrolled women with bacterial vaginosis,[58] in which benefit was limited to those with previous preterm birth. Other trials of antibiotic treatment in women with bacterial vaginosis have reported conflicting results because of variation in timing, dose, and choice of

antibiotic.[122–124] Arguments in favour of antibiotic screening and treatment of at-risk women, as summarised by Lamont,[109] emphasise the need for clindamycin treatment in women with evident bacterial vaginosis before 20 weeks' gestation. Arguments against antibiotic treatment note the increased rate of preterm birth in women given metronidazole,[55,80,124] and the generally negative results of a Cochrane review of 15 trials involving 5888 women.[68] The reviewers concluded that although antimicrobial treatment can eradicate bacterial vaginosis in pregnancy, it does not reduce the risk of preterm birth or preterm premature membrane rupture before 37 weeks' gestation in all women or in those with a previous preterm birth.[68] However, there is evidence that treatment before 20 weeks of gestation might reduce the risk of preterm birth.

One possible reason for the failure of antibiotics to reduce rates of preterm birth is that they might not effectively prevent or treat chorioamnionitis. Two antibiotic trials looking at placental histology reported no difference in histological chorioamnionitis between women randomly assigned antibiotics versus placebo.[125,126] Another possible reason for antibiotic failure is that host factors, such as diet, smoking, and genetic variations in inflammatory response, might influence the risk of infection-related preterm birth, irrespective of antibiotic treatment. The association between preterm birth and microorganisms colonising and infecting the genital tract must be further elucidated before antimicrobial agents can be used effectively and safely to prevent preterm birth. The appropriate role for antimicrobial therapy to reduce risk of preterm birth will be established when questions about the selection and timing of treatment, the role of concurrent exposures (eg, smoking), and host factors (such as genetic polymorphisms) are answered.[95,108]

Progesterone

Progesterone supplementation for women at risk of preterm birth has been investigated on the basis of several plausible mechanisms of action, including reduced gap-junction formation, oxytocin antagonism (leading to relaxation of smooth muscle), maintenance of cervical integrity, and anti-inflammatory effects. Small studies done before 1990 in women with recurrent miscarriages and preterm births were reviewed by Keirse,[127] who reported "no support for the view that 17α-hydroxyprogesterone caproate protects against miscarriage, but suggests that it does reduce the occurrence of preterm birth." Additional studies showed a reduced risk of preterm birth in women with previous preterm delivery who were given progesterone.[103,128] The risk of preterm birth was reduced by about a third in two trials of progesterone supplementation, given as intramuscular injections of 250 mg per week of 17α-hydroxprogesterone caproate[103] and as daily vaginal progesterone.[128] Meta-analyses have shown that the risk of recurrent preterm birth was reduced by 40–55% (RR 0·58, 95% CI 0·48–0·70 and 0·45, 0·25–0·80).[129,130] Two systematic reviews[130,131] noted that studies of progesterone have not been sufficiently powered to detect an effect on neonatal or infant outcomes. Progesterone has not been uniformly beneficial in all populations at risk. A placebo-controlled trial done in 250 women with short cervices reported a reduced rate of preterm birth in women who received vaginal progesterone,[79] and a randomised, placebo-controlled trial reported that 17α-hydroxy-progesterone caproate had no effect on the rate of preterm birth in 600 women with twin pregnancies.[104]

The effect of supplemental progesterone compounds is not universally seen in women with previous preterm births, indicating that some pathways to recurrent preterm birth are not influenced by this therapy. Trials in women with other risk factors—eg, a positive fetal fibronectin test, bleeding, or preterm labour in the current pregnancy, have not been reported. The absence of effect in twin pregnancy[79] coupled with reductions in preterm birth in women with historical risk[103,128] and short cervix,[79] and the published work on cerclage, suggest that the effect of progesterone might be related to modulation of inflammation or cervical ripening more than to an effect on uterine contractility. The potential benefit of clinical use of progesterone supplementation awaits further study. Although the rate of preterm birth might not decline appreciably if treatment is limited to women with previous preterm births,[132] the savings of treating only these women have been estimated at more than $2 billion per year in the USA alone.[133,134]

Cervical cerclage

Studies using cervical sonography to observe the process of cervical effacement in normal and complicated pregnancies have shown that a short cervix in mid-pregnancy is associated with an increased risk of early delivery, and is linked especially to recurrent preterm birth. Cervical length is inversely related to risk of preterm birth, so that a length that is less than the tenth percentile might imply reduced or insufficient cervical function.[73,135] Reduced cervical length or effacement also arises in response to biochemical influences of paracrine, endocrine, or inflammatory origin, or in response to biophysical effects of uterine stretch or contractions. One or more congenital, biochemical, or biophysical factors might arise in any individual, so that selection of appropriate interventions to arrest preterm cervical effacement is not straightforward. Cerclage seems to be appropriate only in the setting of a structural defect or deficiency that needs to be repaired, but identification of appropriate candidates is difficult. The clinical value of cervical cerclage has been studied in observational[136–141] and randomised trials,[77,106,107,142–148] from which the following conclusions emerge. Cervical cerclage in women with short cervices (<15 mm) and without previous preterm births does not reduce the rate of spontaneous preterm births.[77,78] Although cerclage might benefit women with short cervices who have a previous preterm birth, the evidence is not conclusive, and selection

of the appropriate candidates for cerclage is uncertain.[78,106,107,137–139,142–144,149] Prophylactic cerclage for women with a history of preterm birth without sonographic demonstration of short cervix in the present pregnancy is not justified by the evidence. There is evidence that these women can be monitored by serial sonographic examination of the cervix, followed by cerclage if the cervix shortens.[136,138,139,150,151]

In a meta-analysis of data from four trials,[78] the risk of birth before 35 weeks' gestation was reduced with cerclage in women with previous preterm birth and a short cervix (defined as <2·5 cm) in the present pregnancy (RR 0·63, 95% CI 0·48–0·85). Cerclage in women with short cervices who did not have previous preterm births showed no advantage (0·84, 0·60–1·17). In women with twin gestations, cerclage for short cervix was associated with an increased risk of preterm birth (2·15, 1·15–4·01).

The efficacy of cerclage can vary according to the cause of the short cervix: preterm birth was decreased by cerclage when the concentration of interleukin 8 in cervical secretions was low, but increased when the treatment was used in women with raised cervical interleukin-8 concentrations.[152] The view emerging from existing studies is that cerclage will ultimately be deemed beneficial only in instances in which preterm cervical effacement or shortening happened in the absence of inflammation. Until such a diagnosis can be made, cerclage should be reserved for patients believed to have anatomical insufficiency rather than either early delivery history or sonographic findings alone.

Tertiary interventions for women with immediate risk of preterm birth

Detection of conditions proximate to preterm birth offers another opportunity to improve outcome. The most common presenting complaints of preterm labour are uterine contractions, ruptured membranes, and vaginal spotting or bleeding. The last two are typically recognised, but detection of early preterm labour is a challenge because the symptoms and signs of preterm labour arise commonly in normal pregnancy. Diagnosis of preterm labour might be improved by use of transvaginal sonographic measurement of cervical length or testing for the presence of fetal fibronectin in cervicovaginal fluid.[153–155] Both tests improve diagnostic accuracy primarily by reducing false-positive diagnosis.

Early diagnosis of preterm labour

Programmes to identify women at risk of preterm birth and to educate them to recognise the earliest signs and symptoms of labour did not affect the rate of preterm birth in randomised trials.[117,156,157] Educational programmes that also used sensitive electronic monitors to detect uterine contractions daily did not reduce the preterm birth rate in studies of at-risk women.[120,158] In the largest trial, 2422 women at increased risk of preterm birth were randomly assigned to three groups: the first was educated and had weekly nursing contact; the second was educated and had daily nursing contact; and the third was educated and had daily nursing contact plus daily uterine-contraction monitoring.[121] Women contacted daily received more treatment for preterm labour, but eligibility for tocolysis and the rate of preterm birth were the same in all three study groups.

Treatment of women with acute risk of preterm birth

Treatment to arrest preterm labour established by progressive cervical dilation and effacement or membrane rupture does not prolong pregnancy sufficiently to allow further intrauterine growth and maturation. Treatment can, however, defer preterm birth long enough to allow for interventions that reduce neonatal morbidity and mortality: antenatal transfer of the mother and fetus (especially those expected to be born before 32 weeks' gestation) to a hospital equipped to care for preterm infants in a regionalised system allowing training, and development and maintenance of the necessary skilled personnel and facilities. This approach is associated with improved outcomes for preterm infants.[159–162]

Antibiotic treatment of all women with threatened preterm labour to prevent neonatal infection with group B streptococcus is recommended because preterm infants have an increased risk of this infection.[163] Rates of neonatal group B streptococcus infection and corresponding mortality rates have declined since this strategy was adopted in the USA.[163]

Antenatal administration of corticosteroids to the mother reduces neonatal morbidity and mortality from respiratory distress, intraventricular haemorrhage, necrotising enterocolitis, and patent ductus arteriosus.[164,165] Glucocorticoids act generally in the developing fetus to promote maturation over growth. In the lung, corticosteroids promote surfactant synthesis, increase lung compliance, reduce vascular permeability, and generate a greater response to postnatal surfactant treatment. Randomised, placebo-controlled trials and meta-analyses confirm the beneficial effects of antenatal corticosteroids, including reduced occurrence of respiratory distress syndrome, intraventricular haemorrhage, neonatal death, necrotising enterocolitis, patent ductus arteriosus, and bronchopulmonary dysplasia.[164] A single course consists either of two doses of 12 mg betamethasone given intramuscularly, 24 h apart, or four doses of 6 mg dexamethasone given intramuscularly every 12 h. The duration of fetal benefit after a course of glucocorticoids is uncertain. Data suggest that a repeat course might confer modest additional neonatal benefit, whereas multiple courses can reduce fetal growth.[165] The present practice is to limit antenatal steroids to a single course given when risk of preterm birth is first recognised after 24 weeks of gestation.

Tocolysis

Tocolytic drugs are used to prolong pregnancy in women with acute risk of preterm birth caused mainly by active

preterm labour and, less commonly, by ruptured membranes. The main rationale for use of these drugs is a 48 h delayed delivery that allows transfer to a specialist unit and corticosteroids to reduce neonatal morbidity and mortality. No studies have shown that any tocolytic drug can reduce the rate of preterm birth. Most studies of tocolytic agents lack power and use delay in delivery as a surrogate endpoint for implied improvements in neonatal outcome related to administration of steroids. Reviews and meta-analyses have been used to study efficacy and safety. A placebo-controlled trial of preterm labour reported that treatment with transdermal glyceryl trinitrate before 28 weeks' gestation was associated with a significant decrease in composite neonatal morbidity.[166] The Cochrane collaboration regularly produces meta-analyses of obstetric interventions including tocolytic drugs. These meta-analyses suggest that calcium-channel blockers and an oxytocin antagonist (atosiban) can delay delivery by 2–7 days with an optimum risk-benefit ratio.[167,168] The Cochrane analysts concluded that β_2-agonist drugs, such as ritodrine and terbutaline, can delay delivery by 48 h, but carry greater side-effects than other agents,[169] and that magnesium sulphate is ineffective.[170] Reports of possible adverse neonatal effects of magnesium derive from secondary analyses that are confounded by inclusion of infants with morbidity related to congenital anomalies, twin-twin transfusion syndrome, and sudden infant death syndrome at age 1 month, 3 months, 4 months, and 8 months.[171] Although the cyclo-oxygenase inhibitor indometacin reduced the occurrence of preterm birth when compared with placebo and other tocolytic agents in some controlled trials, the Cochrane analysts reported that the volume of evidence did not allow firm conclusions about efficacy.[172]

Care after preterm premature rupture of the fetal membranes

Preterm premature rupture of the fetal membranes precedes 30% of preterm births in developed countries. Management consists of maternal and fetal surveillance for labour, infection, and abruption, and administration of corticosteroids[164,165] or antibiotics. The benefit of antibiotic treatment was established mainly by two clinical trials in which prophylaxis with ampicillin plus erythromycin[173] and erythromycin or amoxicillin/clavulanic acid[174] was associated with prolongation of pregnancy, a reduced rate of maternal chorioamnionitis, and a reduced frequency of neonatal morbidity, measured as composite neonatal outcome. Kenyon and colleagues[174] reported higher rates of necrotising enterocolitis in neonates whose mothers were given amoxicillin/clavulanic acid and thus they recommended use of erythromycin.

Care after acute treatment for preterm labour

Continued suppression of contractions after acute tocolysis does not reduce the rate of preterm birth.[175,176] Posthospitalisation surveillance with outpatient monitoring of uterine contraction also has no effect on the rate of preterm birth or low birthweight, or gestational age at delivery.[177–179]

Delivery of preterm infants

Routine caesarean delivery of all preterm or very-low-birthweight infants is controversial, but most evidence does not support the practice.[180–182] Neonatal intracranial haemorrhage seems to arise as commonly before and after labour as it does during labour and delivery. For infants in breech presentation, caesarean delivery might avoid trapping of the aftercoming head and other manipulations that could lead to trauma or hypoxia, but evidence supporting the use of caesarean section is absent. Optimum delivery of very-low-birthweight babies might nevertheless appropriately lead to a caesarean section without labour because of complications associated with growth restriction, ruptured membranes, cord prolapse, bleeding, or expected difficulty with vaginal breech delivery.

Conclusions

Most interventions intended to reduce preterm birth do not show consistent benefit when tested rigorously in randomised trials, which, in turn, are limited by the data available at the time of their design. Although the preterm birth rate has not declined, survival has increased for infants born preterm. Even though some obstetric interventions, such as screening for asymptomatic bacteriuria, antenatal corticosteroid treatment, and prophylaxis for group B streptococcal disease, have contributed to the decline in mortality, most of the improvement in survival can be attributed to better neonatal care and its increased use. The reduction in recurrent preterm birth in women given prophylactic progestagen compounds holds promise because of the putative mechanism of action and potential effect of progestagen compounds on the morbidity and cost of preterm birth.

Organised systems of perinatal care—commonly termed regional perinatal networks, in which mothers who are likely to deliver preterm are looked after in an institution with obstetric and neonatal specialists and appropriate equipment during labour, delivery, resuscitation, and newborn care—have consistently been associated with the greatest survival rates. An investigation of the specific components of neonatal care is beyond the scope of this review, but the use of surfactant, advances in newborn resuscitation techniques, better understanding of respirator use and fluid management, progress in surgical techniques and anaesthesia, and appropriate use of antibiotics have all played important parts in the increased preterm survival. However, continued impressive improvements in survival of very-low-birthweight infants as a result of these interventions is unlikely. Instead, if developed countries are to achieve substantial advances in neonatal mortality and reduce

the preterm birth-related disability, the mechanisms of preterm parturition must be unravelled to allow preterm birth to happen only when serving the health of both infant and mother.

Conflict of interest statement

We declare that we have no conflict of interest.

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