ARTICLE INFO

Definition of preterm birth :

Preterm birth (PTB), also known as premature birth, is the birth of a baby at fewer than 37 weeks' gestational age, as opposed to full-term delivery at approximately 40 weeks.[1] PTB is defined as birth before 37 weeks' gestation, very early PTB is before 32 weeks, early PTB occurs around 32–36 weeks, late PTB is between 34–36 weeks' gestation and early-term birth is delivered at 37–38 weeks' gestation.[8][9] Late PTB accounts for 75% of all PTB.[10]

These babies are known as premature babies or colloquially preemies (American English)[11] or premies (Australian English).[12] Symptoms of preterm labor include uterine contractions which occur more often than every ten minutes or the leaking of fluid from the vagina.[13] Premature infants are at greater risk for cerebral palsy, delays in development, hearing problems and sight problems.[1] The earlier a baby is born, the greater these risks will be.[1]

The cause of preterm birth is often not known.[2] Risk factors include diabetes, high blood pressure, multiple gestation (being pregnant with more than one baby), being either obese or underweight, a number of vaginal infections, air pollution including tobacco smoking, and psychological stress.[2][3][14] It is recommended that labor not be medically induced before 39 weeks unless required for other medical reasons.[2] The same recommendation applies to cesarean section.[2] Medical reasons for early delivery include preeclampsia.[15]
Preterm birth may be prevented in those at risk, if the hormone progesterone is taken during pregnancy.[5] Evidence does not support the usefulness of bed rest.[5][16] It is estimated that at least 75% of preterm infants would survive with appropriate treatment, and the survival rate is highest among the infants born the latest.[2] In women who might deliver between 24 and 37 weeks, corticosteroids improve outcomes.[6][17] A number of medications, including nifedipine, may delay delivery so that a mother can be moved to where more medical care is available and the corticosteroids have a greater chance to work.[18] Once the baby is born, care includes keeping the baby warm through skin-to-skin contact or incubation, supporting breastfeeding, treating infections and supporting breathing, sometimes through intubation.[2]

Preterm birth is the most common cause of death among infants worldwide.[1] About 15 million babies are preterm each year (5% to 18% of all deliveries).[2] In the United Kingdom they are about 7.9% and in the United States they are about 12.3% of all births.[19][20] Approximately 0.5% of births are extremely early perivable births, and these account for most of the deaths.[21] In many countries, rates of premature births have increased between the 1990s and 2010s.[2] Complications from preterm births resulted in 0.81 million deaths in 2015, down from 1.57 million in 1990.[7][22] The chance of survival at 22 weeks is about 6%, while at 23 weeks it is 26%, 24 weeks 55% and 25 weeks about 72%.[23] The chances of survival without any long-term difficulties are lower:[24]

**Symptoms & signs**

A preterm birth can be brought on by being induced, or can occur spontaneously. Preterm births can cause a range of problems.[25][26]

The main categories of causes of preterm birth are preterm labor induction and spontaneous preterm labor. Signs and symptoms of preterm labor include four or more uterine contractions in one hour. In contrast to false labor, true labor is accompanied by cervical dilatation and effacement. Also, vaginal bleeding in the third trimester, heavy pressure in the pelvis, or abdominal or back pain could be indicators that a preterm birth is about to occur. A watery discharge from the vagina may indicate premature rupture of the membranes that surround the baby. While the rupture of the membranes may not be followed by labor, usually delivery is indicated as infection (chorioamnionitis) is a serious threat to both fetus and mother. In some cases, the cervix dilates prematurely without pain or perceived contractions, so that the mother may not have warning signs until very late in the birthing process. A review into using uterine monitoring at home to detect contractions and possible preterm births in women at higher risk of having a preterm baby found that it did not reduce the number of preterm births.[27] The research included in the review was poor quality but it showed that home monitoring may increase the number of unplanned antenatal visits and may reduce the number of babies admitted to special care when compared with women receiving normal antenatal care.[27]

**Causes:**

While no one knows for sure what causes preterm labor, experts point to a number of factors that could play a role in triggering your uterus to begin contracting and your cervix dilating before your baby is ready to come out.

- Smoking, alcohol and drug use: Not only do these behaviors increase your risk of miscarriage, they also increase your baby's risk of being born early or at a low birth weight (toxins that cross the placenta can keep your baby from getting the necessary oxygen she needs to grow). If there’s ever a reason to quit, pregnancy is it.

- Short interval between pregnancies: Getting pregnant sooner than 18 months after giving birth to your last child increases your risk of preterm birth. And the longer you can wait, the less you’re at risk: A large recent study found that 20 percent of women who wait less than a year between pregnancies give birth before 37 weeks; the rate drops to 10 percent among women who wait a year to 18 months and is less than 8 percent in those who wait more than 18 months to conceive again.

- Uterine and vaginal infections: Infections — both those in the genital tract, such as bacterial vaginosis (BV) and sexually transmitted diseases (STDs) like trichomoniasis, along with infections in the uterus and amniotic fluid — are thought to be responsible for nearly half of all preterm births. Experts suspect they cause inflammation, which in turn leads to the release of prostaglandins — the same substance that initiates labor when you’re full-term. Untreated urinary-tract infections can have the same effect.

- Pregnancy complications: Complications (such as gestational diabetes, preeclampsia and excessive amniotic fluid) as well as problems with the placenta (such as placenta previa or placental abruption) can make an early delivery more likely.

- Structural anomalies of the uterus and/or cervix: A uterus that is malformed, extremely large or has other structural abnormalities can make it more difficult to carry a baby to term, as can problems with the cervix (such as having a short cervical length or an incompetent cervix — when the cervix doesn’t stay closed the way it’s supposed to during pregnancy).

- Gum infections: Pregnancy hormones make expectant moms more susceptible to periodontal disease, which in turn has been linked to preterm labor. Some experts suspect that the bacteria that cause inflammation in the gums can actually get into mom’s bloodstream, reach the fetus and initiate early delivery. Other research proposes another possibility: The bacteria that cause inflammation in the gums can also trigger the immune system to produce inflammation in the cervix and uterus, triggering early labor.

- Stress levels: Researchers theorize that severe emotional stress — not the kind caused by those raging hormones or a bad day, but the kind that’s related to a traumatic experience — can lead to the release of hormones that in turn trigger labor contractions.

- Occupational factors: Extreme physical stress on the job has also been linked to preterm labor. Researchers have found that women who stand for long periods of time (more than five hours a day) or who have jobs that are extremely physically exhausting are more likely to deliver early.

- Carrying multiples: Multiples are more likely than singletons to arrive early. (Note that infertility treatments make moms more likely to conceive multiples.)
Maternal age: Women younger than 17 and older than 35 are more likely than their younger counterparts to deliver prematurely. That’s one of the reasons doctors consider (even otherwise healthy) older expecting women to have a “high-risk” pregnancy.

A previous preterm birth: If you’ve given birth early previously, you’re at an increased risk of having a subsequent preterm birth.

If you were preterm yourself. A large 2015 study found that women who were born prematurely themselves are at a higher risk of giving birth prematurely (though those odds are still low, at 14.2 percent or less depending on how early you were born.

Most important to remember, however, is that having one of these risk factors doesn’t mean that you’ll necessarily go into preterm labor. Similarly, not having any of the risk factors doesn’t mean that you won’t (some women do for other reasons — or for no known reason at all).

Risk factors:

Maternal factors

A number of factors have been identified that are linked to a higher risk of a preterm birth such as being less than 18 years of age[47] and maternal BMI.[48]

Further, in the U.S. and the UK, Black women have preterm birth rates of 15–18%, more than double than that of the white population. Many Black women have higher preterm birth rates due to multiple factors but the most common is high amounts of chronic stress, which can eventually lead to premature birth.[49] Adult chronic disease isn’t always the case with premature birth in Black women, which makes the main factor of premature birth challenging to identify.[49] Filipinos are also at high risk of premature birth, and it is believed that nearly 11–15% of Filipinos born in the U.S. (compared to other Asians at 7.6% and whites at 7.8%) are premature.[50] Filipinos being a big risk factor is evidenced with the Philippines being the eighth-highest ranking in the world for preterm births, the only non-African country in the top 10.[51] This discrepancy is not seen in comparison to other Asian groups or Hispanic immigrants and remains unexplained.[47]

Pregnancy interval makes a difference as women with a six-month span or less between pregnancies have a two-fold increase in preterm birth.[52] Studies on type of work and physical activity have given conflicting results, but it is opined that stressful conditions, hard labor, and long hours are probably linked to preterm birth.[47]

A history of spontaneous (i.e., miscarriage) or surgical abortion has been associated with a small increase in the risk of preterm birth, with an increased risk with increased number of abortions, although it is unclear whether the increase is caused by the abortion or by confounding risk factors (e.g., socio-economic status).[53] Increased risk has not been shown in women who terminated their pregnancies medically.[54] Pregnancies that are unwanted or unintended are also a risk factor for preterm birth.[45]

Adequate maternal nutrition is important. Women with a low BMI are at increased risk for preterm birth.[55] Further, women with poor nutrition status may also be deficient in vitamins and minerals. Adequate nutrition is critical for fetal development and a diet low in saturated fat and cholesterol may help reduce the risk of a preterm delivery.[56] Obesity does not directly lead to preterm birth;[57] however, it is associated with diabetes and hypertension which are risk factors by themselves.[47] To some degree those individuals may have underlying conditions (i.e., uterine malformation, hypertension, diabetes) that persist. Women with celiac disease have an increased risk of the development of preterm birth.[43] The risk of preterm birth is more elevated when celiac disease remains undiagnosed and untreated.[4] Marital status is associated with risk for preterm birth. A study of 25,373 pregnancies in Finland revealed that unmarried mothers had more preterm deliveries than married mothers (P=0.001).[46] Pregnancy outside of marriage was associated overall with a 20% increase in total adverse outcomes, even at a time when Finland provided free maternity care. A study in Quebec of 720,586 births from 1990 to 1997 revealed less risk of preterm birth for infants with legally married mothers compared with those with common-law wed or unwed parents.[58] Needs update. Genetic make-up is a factor in the causality of preterm birth. Genetics has been a big factor into why Filipinos have a high risk of premature birth as the Filipinos have a large prevalence of mutations that help them be predisposed to premature births.[50] An intra- and transgenerational increase in the risk of preterm delivery has been demonstrated.[59] No single gene has been identified.

Subfertility is associated with preterm birth. Couples who have tried more than 1 year versus those who have tried less than 1 year before achieving a spontaneous conception have an adjusted odds ratio of 1.35 (95% confidence interval 1.22–1.50) of a preterm birth.[60] Pregnancies after IVF confers a greater risk of preterm birth than spontaneous conceptions after more than 1 year of trying, with an adjusted odds ratio of 1.55 (95% CI 1.30–1.85).[60] Exposure to heat also appear to increase the risk of preterm birth, with this occurring in about 25,000 pregnancies per year.[61]

Factors during pregnancy

Air pollution increases the risk of preterm birth.[14] One study attributed air pollution to 18% of premature births globally.[62] The countries with the highest air pollution associated preterm births are in South and East Asia, the Middle East, North Africa, and West sub-Saharan Africa. Living in an area with a high concentration of air pollution is a major risk factor, including living near major roadways or highways where vehicle emissions are high from traffic congestion or are a route for diesel trucks that tend to emit more pollution.[63][64]

The use of fertility medication that stimulates the ovary to release multiple eggs and of IVF with embryo transfer of multiple embryos has been implicated as an important factor in preterm birth. Maternal medical conditions increase the risk of preterm birth. Often labor has to be induced for medical reasons; such conditions include high blood pressure,[65] pre-eclampsia,[66] maternal diabetes,[67] asthma, thyroid disease, and heart disease.
In a number of women anatomical issues prevent the baby from being carried to term. Some women have a weak or short cervix [65] (the strongest predictor of premature birth) [68][69][70]. Women with vaginal bleeding during pregnancy are at higher risk for preterm birth. While bleeding in the third trimester may be a sign of placenta previa or placental abruption—conditions that occur frequently preterm—even earlier bleeding that is not caused by these conditions is linked to a higher preterm birth rate. [71] Women with abnormal amounts of amniotic fluid, whether too much (polyhydramnios) or too little (oligohydramnios), are also at risk. [47] The mental status of the woman is of significance. Anxiety [72] and depression have been linked to preterm birth. [47]

The use of tobacco, cocaine, and excessive alcohol during pregnancy increases the chance of preterm delivery. Tobacco is the most commonly abused drug during pregnancy and contributes significantly to low birth weight delivery. [73] Babies with birth defects are at higher risk of being born preterm. [74]

Passive smoking and/or smoking before the pregnancy influences the probability of a preterm birth. The World Health Organization published an international study in March 2014. [75]

Presence of anti-thyroid antibodies is associated with an increased risk preterm birth with an odds ratio of 1.9 and 95% confidence interval of 1.1–3.5. [76]

A 2004 systematic review of 30 studies on the association between intimate partner violence and birth outcomes concluded that preterm birth and other adverse outcomes, including death, are higher among abused pregnant women than among non-abused women. [77]

The Nigerian cultural method of abdominal massage has been shown to result in 19% preterm birth among women in Nigeria, plus many other adverse outcomes for the mother and baby. [78] This ought not be confused with massage conducted by a fully trained and licensed massage therapist or by significant others trained to provide massage during pregnancy, which has been shown to have numerous positive results during pregnancy, including the reduction of preterm birth, less depression, lower cortisol, and reduced anxiety. [79]

Infection

The frequency of infection in preterm birth is inversely related to the gestational age. Mycoplasma genitalium infection is associated with increased risk of preterm birth, and spontaneous abortion. [80]

Infectious microorganisms can be ascending, hematogeneous, iatrogenic by a procedure, or retrograde through the Fallopian tubes. From the decidua they may reach the space between the amnion and chorion, the amniotic fluid, through the Fallopian tubes. From the decidua they may reach the amniotic fluid from being carried to term. Some women have a weak or short cervix [65] (the strongest predictor of premature birth) [68][69][70]. Women with vaginal bleeding during pregnancy are at higher risk for preterm birth. While bleeding in the third trimester may be a sign of placenta previa or placental abruption—conditions that occur frequently preterm—even earlier bleeding that is not caused by these conditions is linked to a higher preterm birth rate. [71] Women with abnormal amounts of amniotic fluid, whether too much (polyhydramnios) or too little (oligohydramnios), are also at risk. [47] The mental status of the woman is of significance. Anxiety [72] and depression have been linked to preterm birth. [47]

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Infectious microorganisms can be ascending, hematogeneous, iatrogenic by a procedure, or retrograde through the Fallopian tubes. From the decidua they may reach the space between the amnion and chorion, the amniotic fluid, and the fetus. A chorioamnionitis also may lead to sepsis of the mother. Fetal infection is linked to preterm birth and to significant long-term handicap including cerebral palsy. [81]

It has been reported that asymptomatic colonization of the decidua occurs in up to 70% of women at term using a DNA probe suggesting that the presence of micro-organism alone may be insufficient to initiate the infectious response.

As the condition is more prevalent in black women in the U.S. and the UK, it has been suggested to be an explanation for the higher rate of preterm birth in these populations. It is opined that bacterial vaginosis before or during pregnancy may affect the decidual inflammatory response that leads to preterm birth. The condition known as aerobic vaginosis can be a serious risk factor for preterm labor; several previous studies failed to acknowledge the difference between aerobic vaginosis and bacterial vaginosis, which may explain some of the contradiction in the results. [82]

Untreated yeast infections are associated with preterm birth. [83]

A review into prophylactic antibiotics (given to prevent infection) in the second and third trimester of pregnancy (13–42 weeks of pregnancy) found a reduction in the number of preterm births in women with bacterial vaginosis. These antibiotics also reduced the number of waters breaking before labor in full-term pregnancies, reduced the risk of infection of the lining of the womb after delivery (endometritis), and rates of gonoococcal infection. However, the women without bacterial vaginosis did not have any reduction in preterm births or pre-labor preterm waters breaking. Much of the research included in this review lost participants during follow-up so did not report the long-term effects of the antibiotics on mothers or babies. More research in this area is needed to find the full effects of giving antibiotics throughout the second and third trimesters of pregnancy. [84]

A number of maternal bacterial infections are associated with preterm birth including pyelonephritis, asymptomatic bacteriuria, pneumonia, and appendicitis. A review into giving antibiotics in pregnancy for asymptomatic bacteriuria (urine infection with no symptoms) found the research was of very low quality but that it did suggest that taking antibiotics reduced the numbers of preterm births and babies with low birth weight. [85] Another review found that one dose of antibiotics did not seem as effective as a course of antibiotics but fewer women reported side effects from one dose. [86] This review recommended that more research is needed to discover the best way of treating asymptomatic bacteriuria. [85] A different review found that preterm births happened less for pregnant women who had routine testing for low genital tract infections than for women who only had testing when they showed symptoms of low genital tract infections. [87] The women being routinely tested also gave birth to fewer babies with a low birth weight. Even though these results look promising, the review was only based on one study so more research is needed into routine screening for low genital tract infections. [87]

Also periodontal disease has been shown repeatedly to be linked to preterm birth. [88][89] In contrast, viral infections, unless accompanied by a significant febrile response, are considered not to be a major factor in relation to preterm birth. [47]

Genetics

There is believed to be a maternal genetic component in preterm birth.[90] Estimated heritability of timing-of-birth in women was 34%. However, the occurrence of preterm birth in
families does not follow a clear inheritance pattern, thus supporting the idea that preterm birth is a non-Mendelian trait with a polygenic nature.[91]

Prevention:
While medical advances have made it possible to successfully treat even the tiniest of premature babies, medical interventions to prevent preterm labor have been elusive, in large part because doctors still don’t understand it enough to be able to develop effective ways to treat it. But that doesn’t mean there’s nothing you as a concerned mom-to-be can do. Even if you’re not at risk for preterm labor (and especially if you are), there are plenty of ways to help keep your baby put until he or she is completely ready for a healthy and timely arrival.

Aim for 18 months between pregnancies. Your rate of preterm labor drops significantly if you wait at least a year — and optimally 18 months — between when you last gave birth and when you conceive again.

See your doctor. Getting early and regular prenatal care can help your doctor pinpoint and help you treat any risk factors for preterm labor and ensure you have the healthiest pregnancy possible.

Control what you can. Smoking, drinking, using drugs not prescribed by your doctor or having untreated diabetes can all lead to preterm labor. Eliminate any that apply to you.

Watch your weight. Gaining too much weight during pregnancy can up your odds of developing gestational diabetes and preeclampsia, both of which increase preterm labor risk. Gaining too little weight also puts you at risk. So aim for the right gain (25 to 35 pounds for most women) and you’ll greatly improve your chances of delivering at full term.

Take your prenatal vitamins. A daily prenatal supplement enhances your overall health, improving the odds that you’ll carry to term. In fact, research suggests that folic acid (which already does so much good for your baby) may also lower the risk of placental abruption (the placenta separating from the uterine wall) and preeclampsia, two conditions that are responsible for a good percentage of early deliveries.

Eat well. Getting all the nutrients your body needs from a healthy, balanced pregnancy diet not only results in a healthier baby but also one that arrives at the right time. Adequate intake of certain omega-3 fatty acids (found in salmon, DHA eggs, walnuts and flax seed) has been shown to reduce preterm labor (and boosts your baby’s brain development). Other studies have shown that vitamin C (citrus, berries, bell peppers) and calcium (milk and other dairy products or fortified juices) can also be helpful in preventing preterm labor.

Eat often. Research suggests that it’s not enough to ship your baby all the right nutrients — you should also make those shipments as regular as possible. Pregnant women who eat at least five times a day (three meals and two snacks, or five smaller meals, for instance) are less likely to deliver prematurely.

Drink up. Drinking enough water (more if you’re exercising or it’s very hot) will keep you hydrated. And staying hydrated increases your odds of keeping baby put, since dehydration can lead to premature contractions.

Be good to your gums. Preventative dental care is one of your first (and best, and easiest) lines of defense in preventing preterm labor, since it can be triggered by gum disease. So brush, floss and visit your dentist at least once during your pregnancy — not just for your regular cleaning, but also to take care of any little problems before they become big ones.

Go when you gotta go. Holding in your urine, besides being uncomfortable, can inflame your bladder — which in turn could irritate your uterus and set off contractions. Not going when you gotta go could also lead to a urinary tract infection, another cause of preterm contractions. So make a habit of peeing when you’ve got the urge to go.

Treat it. If you’re considered high-risk because you have BV, ask your practitioner if an oral antibiotic is right for you. Some studies show that symptomatic women with BV who are treated with antibiotics have a reduced risk of preterm delivery. Other studies, though, have disputed those findings, saying that there is no reduction in the rate of premature delivery even if the infection (both BV and other STDs) is treated. Your practitioner will be able to guide you.

Explore your options. If you’ve already had one preterm labor, recent research has found that the hormone progesterone (given as a shot or a gel during weeks 16 through 36) reduces the risk for preterm birth in women with a prior history — so ask your practitioner if it might help you.

Screenings for preterm labor risk
Two screening tests may be useful in predicting whether you’re at risk for preterm birth. However both are only recommended for high-risk women, since positive test results aren’t an accurate predictor of early delivery (though negative results can help avoid unnecessary interventions — and needless anxiety).

Fetal fibronectin (fFN): This test detects a protein that’s in amniotic fluid; while it’s normally found in cervical and vaginal secretions before 20 weeks of pregnancy, after 20 weeks a presence above a certain level may reflect inflammatory damage of the placenta and is an early indicator of labor. Some research has shown that this test is better at predicting women who won’t go into labor than those who will — so if you have a negative fFN test, it’s unlikely you’ll go into preterm labor within the next few weeks. If it’s positive, the good news is that your practitioner will likely be able to take steps to prevent a preterm birth and prepare your baby’s lungs for an early delivery if necessary.

Cervical length measurement: Via ultrasound, a practitioner measures the length of your cervix. If there are any signs that your cervix is shortening or opening, your practitioner may take some steps to prevent early labor — such as putting you on bed rest or perhaps stitching your cervix closed, called cerclage. However some studies that have found cerclage isn’t as effective in preventing preterm labor as was once believed, so talk to your doctor before he performs the procedure on you.

Diagnosis
Placental alpha microglobulin-1
Placental alpha microglobulin-1 (PAMG-1) has been the subject of several investigations evaluating its ability to predict
imminent spontaneous preterm birth in women with signs, symptoms, or complaints suggestive of preterm labor.[92][93][94][95][96][97] In one investigation comparing this test to fetal fibronectin testing and cervical length measurement via transvaginal ultrasound, the test for PAMG-1 (commercially known as the PartoSure test) has been reported to be the single best predictor of imminent spontaneous delivery within 7 days of a patient presenting with signs, symptoms, or complaints of preterm labor. Specifically, the PPV, or positive predictive value, of the tests were 76%, 29%, and 30% for PAMG-1, fFN and CL, respectively (P < 0.01).[98]

Fetal fibronectin

Fetal fibronectin (fFN) has become an important biomarker—the presence of this glycoprotein in the cervical or vaginal secretions indicates that the border between the chorion and decidua has been disrupted. A positive test indicates an increased risk of preterm birth, and a negative test has a high predictive value.[47] It has been shown that only 1% of women in questionable cases of preterm labor delivered within the next week when the test was negative.[99]

Ultrasound

Further information: Cervical incompetence

Obstetric ultrasound has become useful in the assessment of the cervix in women at risk for premature delivery. A short cervix preterm is undesirable: A cervical length of less than 25 mm at or before 24 weeks of gestational age is the most common definition of cervical incompetence.[100]

Management

Preterm birth at 32 weeks and 4 days with a weight of 2,000 g attached to medical equipment about 75% of nearly a million deaths due to preterm deliver would survive if provided warmth, breastfeeding, treatments for infection, and breathing support.[131] If a baby has cardiac arrest at birth and is before 23 weeks or less than 400 g attempts at resuscitation are not indicated.[132]

Tertiary interventions are aimed at women who are about to go into preterm labor, or rupture the membranes or bleed preterm. The use of the fibronectin test and ultrasonography improves the diagnostic accuracy and reduces false-positive diagnosis. While treatments to arrest early labor where there is progressive cervical dilatation and effacement will not be effective to gain sufficient time to allow the fetus to grow and mature further, it may defer delivery sufficiently to allow the mother to be brought to a specialized center that is equipped and staffed to handle preterm deliveries.[133] In a hospital setting women are hydrated via intravenous infusion (as dehydration can lead to premature uterine contractions).[134]

Steroids

 Severely premature infants may have underdeveloped lungs because they are not yet producing their own surfactant. This can lead directly to respiratory distress syndrome, also called hyaline membrane disease, in the neonate. To try to reduce the risk of this outcome, pregnant mothers with threatened premature delivery prior to 34 weeks are often administered at least one course of glucocorticoids, a steroid that crosses the placental barrier and stimulates the production of surfactant in the lungs of the baby.[17] Steroid use up to 37 weeks is also recommended by the American Congress of Obstetricians and Gynecologists.[17] Typical glucocorticoids that would be administered in this context are betamethasone or dexamethasone, often when the pregnancy has reached viability at 23 weeks.

In cases where premature birth is imminent, a second “rescue” course of steroids may be administered 12 to 24 hours before the anticipated birth. There are still some concerns about the efficacy and side effects of a second course of steroids, but the consequences of RDS are so severe that a second course is often viewed as worth the risk. A 2015 Cochrane review supports the use of repeat dose(s) of prenatal corticosteroids for women still at risk of preterm birth seven days or more after an initial course.[135]

A Cochrane review from 2020 recommends the use of a single course of antenatal corticosteroids to accelerate fetal lung maturation in women at risk of preterm birth. Treatment with antenatal corticosteroids reduces the risk of perinatal death, neonatal death and respiratory distress syndrome and probably reduces the risk of IVH.[136]

Concerns about adverse effects of prenatal corticosteroids include increased risk for maternal infection, difficulty with diabetic control, and possible long-term effects on neurodevelopmental outcomes for the infants. There is ongoing discussion about when steroids should be given (i.e. only antenatally or postnatally too) and for how long (i.e. single course or repeated administration). Despite these unknowns, there is a consensus that the benefits of a single course of prenatal glucocorticosteroids vastly outweigh the potential risks.[137][138][139]

Antibiotics

The routine administration of antibiotics to all women with threatened preterm labor reduces the risk of the baby to get infected with group B streptococcus and has been shown to reduce related mortality rates.[140]

When membranes rupture prematurely, obstetrical management looks for development of labor and signs of infection. Prophylactic antibiotic administration has been shown to prolong pregnancy and reduced neonatal morbidity with rupture of membranes at less than 34 weeks.[141] Because of concern about necrotizing enterocolitis, amoxicillin or erythromycin has been recommended, but not amoxicillin + clavulanic acid (co-amoxiclav).[141]

Tocolysis

A number of medications may be useful to delay delivery including: nonsteroidal anti-inflammatory drugs, calcium channel blockers, beta mimetics, and atosiban.[142] Tocolysis rarely delays delivery beyond 24–48 hours.[143] This delay, however, may be sufficient to allow the pregnant woman to be transferred to a center specialized for management of preterm deliveries and give administered corticosteroids to reduce neonatal organ immaturity. Meta-analyses indicate that calcium-channel blockers and an oxytocin antagonist can delay delivery by 2–7 days, and [8]-agonist drugs delay by 48 hours but carry more side effects.[102][144] Magnesium sulfate does not appear to be useful to prevent preterm birth.[145] Its use before delivery, however, does appear to decrease the risk of cerebral palsy.[146]
Mode of delivery

The routine use of caesarean section for early delivery of infants expected to have very low birth weight is controversial,[147] and a decision concerning the route and time of delivery probably needs to be made on a case-by-case basis.

Neonatal care

Incubator for preterm baby

After delivery, plastic wraps or warm mattresses are useful to keep the infant warm on their way to the neonatal intensive care unit (NICU).[148] In developed countries premature infants are usually cared for in an NICU. The physicians who specialize in the care of very sick or premature babies are known as neonatologists. In the NICU, premature babies are kept under radiant warmers or in incubators (also called isolettes), which are bassinets enclosed in plastic with climate control equipment designed to keep them warm and limit their exposure to germs. Modern neonatal intensive care involves sophisticated measurement of temperature, respiration, cardiac function, oxygenation, and brain activity. Treatments may include fluids and nutrition through in travenous catheters, oxygen supplementation, mechanical ventilation support,[149] and medications. In developing countries where advanced equipment and even electricity may not be available or reliable, simple measures such as kangaroo care (skin to skin warming), encouraging breastfeeding, and basic infection control measures can significantly reduce preterm morbidity and mortality. Billilights may also be used to treat newborn jaundice (hyperbilirubinemia). Water can be carefully provided to prevent dehydration but no so much to increase risks of side effects.[150]

In terms of respiratory support, there may be little or no difference in the risk of death or chronic lung disease between high flow nasal cannulae (HFNC) and continuous positive airway pressure (CPAP) or nasal intermittent positive pressure ventilation (NPPV).[151] For extremely preterm babies (born before 28 weeks’ gestation), targeting a higher versus a lower oxygen saturation range makes little or no difference overall to the risk of death or major disability.[152] Babies born before 32 weeks probably have a lower risk of death from bronchopulmonary dysplasia if they have CPAP immediately after being born, compared to receiving either supportive care or assisted ventilation.[153]

One review found that when premature infants are given osteopathic manipulations, they are less likely to require as lengthy of a hospital stay than if they are not manipulated.[154]

There is insufficient evidence for or against placing preterm stable twins in the same cot or incubator (co-bedding).[155]

Nutrition

In a 2012 policy statement, the American Academy of Pediatrics recommended feeding preterm infants human milk, finding "significant short- and long-term beneficial effects," including lower rates of necrotizing enterocolitis (NEC).[156] In the absence of evidence from randomised controlled trials about the effects of feeding preterm infants with formula compared with mother’s own breast milk, data collected from other types of studies suggest that mother’s own breast milk is likely to have advantages over formula in terms of the baby’s growth and development.[157] It is unclear if fortification of breast milk improves outcomes in preterm babies, though it may speed growth.[158] Supplementing human milk with extra protein may increase short-term growth but the longer-term effects on body composition, growth and brain development are uncertain.[159][160] The evidence from clinical trials is uncertain regarding the effects on preterm babies’ growth of supplementing human milk with carbohydrate[161] and fat.[162] When a mother’s breast milk is not available, formula is probably better than donor breast milk for preterm babies in terms of weight gain, linear growth and head growth but there may be little or no difference in terms of neurodevelopmental disability, death or necrotising enterocolitis.[163] There is some indication that preterm babies who cannot breastfeed may do better if they are fed only with diluted formula compared to full strength formula but the clinical trial evidence remains uncertain.[164] Higher protein formula (between 3 and 4 grams of protein per kilo of body weight) may be more effective than low protein formula (less than 3 grams per kilo per day) for weight gain in formula-fed low-birth-weight infants.[165] There is limited evidence to support prescribing a preterm formula for the preterm babies after hospital discharge.[166]

Hearing assessment

The Joint Committee on Infant Hearing (JCIH) state that for preterm infants who are in the neonatal intensive care unit (NICU) for a prolonged time should have a diagnostic audiologic evaluation before they are discharged from the hospital.[167] Well babies follow a 1-2-3-month benchmark timeline where they are screened, diagnosed, and receiving intervention for a hearing loss. However, very premature babies it might not be possible to complete a hearing screen at one month of age due to several factors. Once the baby is stable an audiologic evaluation should be performed. For premature babies in the NICU, auditory brainstem response (ABR) testing is recommended. If the infant doesn’t pass the screen, they should be referred for an audiologic evaluation by an audiologist.[167] If the infant is on aminoglycosides such as gentamicin for less than five days they should be monitored and have a follow up 6–7 months of being discharged from the hospital to ensure there is no late onset hearing loss due to the medication.[167]

Premature baby’s health

A baby born before 34 weeks will almost always need to stay in the neonatal intensive care unit (NICU) for the first few days, weeks or, in some cases, months of his or her life. Babies born between 34 and 37 weeks of gestation who have no other health problems generally do fine — and often only need a short stay in the NICU before they head home.

While prematurity has been linked to cerebral palsy, slow growth, learning difficulties and developmental delays, thanks to modern medical care your chances of bringing home a normal, healthy baby are very high. Learn more about premature babies here and join the Moms of Preemies group to meet other members who have experienced preterm labor.
Role of neuroprotection in premature birth

Chorioamnionitis and preterm premature rupture of membranes (PPROM)

Chorioamnionitis is a primary risk factor for preterm labour and delivery, with higher incidence with decreasing gestational ages (1,11). One systematic review concluded that chorioamnionitis increases risk for both cerebral palsy (CP) and cPVL (12). However, subsequent systematic reviews and large-scale retrospective studies have found no or only weak associations between chorioamnionitis and IVH, PVL, or CP (13–15). Conflicting findings may relate to whether PPROM has occurred (16) and whether prompt treatment with antibiotics was initiated. The Society of Obstetricians and Gynaecologists of Canada (SOGC) recommends administering penicillin and a macrolide (or a macrolide alone if a patient is allergic to penicillin) to any mother presenting with PPROM and expected to deliver at ≤32+6 weeks GA (17). This empirical regimen also offers coverage against Group B streptococcus and may help prolong pregnancy and reduce morbidity for both mother and newborn (17) (level of evidence 1a).

Neonates born at ≤32+6 weeks GA to mothers with suspected or confirmed chorioamnionitis, PPROM, preterm labour, or an unexplained onset of nonreassuring fetal status, should be carefully evaluated, have a blood culture drawn, and be started on empiric antibiotics. All such infants are at higher risk for early onset sepsis and may be asymptomatic initially (18,19). Duration of rupture of membranes for longer than 72 hours is also an independent risk factor for IVH or intraparenchymal hemorrhage (odds ratio [OR] 2.33, 95% confidence interval [CI] 1.420 to 3.827) (20). Antibiotics should be discontinued after 36 to 48 hours if blood cultures are negative.

Antenatal corticosteroids

Corticosteroids accelerate organ system maturity in animal models (21). Vasoconstriction is apparent in the fetal brain when antenatal corticosteroids are used, which may protect against injury. One Cochrane meta-analysis (22) has demonstrated that treatment with antenatal corticosteroids is associated with reducing neonatal morbidities and mortality, including IVH (average relative risk [RR] 0.55, 95% CI 0.38 to 0.91). The timing of the last dose of corticosteroid before delivery also influences risk for brain injury, with significantly reduced risk observed when the interval since the last dose is greater than 48 hours, compared with less than 24 hours (23). Routinely administering antenatal corticosteroids within 7 days to all mothers expected to deliver a premature infant at ≤34+6 weeks GA (and between 35+0 and 36+6 weeks GA in select clinical situations) is recommended, with the optimal interval being greater than 48 hours between the last dose administered and birth (24) (level of evidence 1a).

Magnesium sulphate

Magnesium has several intracellular actions, including anti-inflammatory effects and inhibiting the influx of calcium into cells (25,26). One Cochrane review (27) and a meta-analysis of five randomized control trials (RCTs) (28) demonstrated that magnesium sulphate effectively decreases risk for CP (RR 0.69, 95% CI 0.55 to 0.88) and for the composite outcomes of death or cerebral palsy (RR 0.86, 95% CI 0.75 to 0.99). There is insufficient evidence that a repeated course of antenatal magnesium sulphate should be administered for fetal neuroprotection (25). The current recommendation is to consider magnesium sulphate for all women experiencing imminent preterm delivery (≤33+6 weeks GA), which is consistent with SOGC guidelines (level of evidence: 1a).

Mode of delivery

Expectant management can provide more time for antenatal corticosteroids to take effect and for the fetus to mature. One Cochrane review (29) comparing women randomized to deliver immediately versus expectant management care showed the latter group gave birth an average 4 days later, with no differences in neonatal brain injury.

There is no evidence that routine caesarean section confers protective benefit over vaginal delivery for preterm infants at risk for mortality or IVH, including intraparenchymal lesions (30), except when they are in breech position (31,32). It is possible that urgency of delivery entails higher risk for brain injury than mode of delivery (33).

There is insufficient evidence of the benefits or harms of immediate versus deferred delivery to recommend optimal delivery timing. However, there appears to be no benefit to immediate delivery without other, dear indications. There is also insufficient evidence to recommend routine caesarean section for women in preterm labour, unless the fetus is malpresenting. Although the ultimate decision on mode of delivery lies with the labouring mother and her obstetrical team, the discussion should be multidisciplinary (level of evidence: 2b).

Timing of umbilical cord clamping

Cord clamping at delivery terminates placental transfusion and decreases perfusion to a newborn’s organs. In Canada, 42% of preterm infant deliveries documented delayed cord clamping in 2017 (1). One systematic review (34) found that delaying cord clamping for up to 180 seconds was associated with less acute brain injury overall (RR 0.59, 95% CI 0.41 to 0.85), but not with reducing intraparenchymal lesions or severe IVH specifically. Delayed cord clamping also appears to protect against motor disabilities later in life (35,36).

Other systematic reviews have found that delayed cord clamping or cord milking, when compared with immediate cord clamping, reduces overall risk for acute brain injury (RR 0.62, 95% CI 0.43 to 0.91) (37). Umbilical cord milking allows faster infant resuscitation while potentially providing the same benefits as delayed cord clamping. Meta-analyses comparing immediate cord clamping with cord milking found that infants whose cords were milked had a lower incidence of acute brain injury overall (37). No adverse effects were observed in any of the reviewed studies. One recent, large RCT showed no difference between immediate and delayed cord clamping. However, the study combined death with an array of morbidities for its primary outcome, rather than focusing on death and severe brain injury, and 21% of neonates in the 'delayed' group were clamped at ≤30 seconds (38).

All infants who do not need immediate resuscitation should receive delayed cord clamping of 30 to 120 seconds (level of evidence: 1a). Delayed cord clamping is preferred over...
umbilical cord milking because the studies assessing impacts of cord milking are few, techniques vary, and there have been no follow-up studies. Cord milking may be considered when delayed cord clamping cannot occur (level of evidence: 2).

**Hypothermia**

Preterm infants are at high risk for rapid heat loss (39). Cold stress can accelerate oxygen consumption and impair resuscitation (40). Hypothermia has been associated with increased risk for acute brain injury and death (40,41). One systematic review (42) demonstrated that preterm infants experienced less hypothermia upon admission to the NICU when resuscitation or stabilization included using polyethylene wrapping or a bag to keep them warm. Other recommended measures to prevent hypothermia include regulating the temperature in the delivery room at 25°C to 26°C, using a preheated servo-controlled radiant warmer with a temperature sensor (43), providing a thermal mattress, putting a hat on the infant, and providing a preheated transport incubator (level of evidence: 1a).

**Inotropes and hypotension**

No consistent definition of hypotension or standardized approach to managing this condition in preterm infants presently exists (44). Common definitions of hypotension include a mean arterial blood pressure less than the infant’s GA or <30 mmHg for two consecutive measurements. However, multiple studies have associated the use of vasopressors to treat hypotension in preterm infants with developing IVH and other brain injuries (45–47). The use of inotropes has been clearly associated with mortality and brain injury in this at-risk group (45,48), with potential lasting effects on motor development (49). A mean arterial pressure less than the infant’s GA or PCO2 levels <72 mmHg is a risk factor for acute brain injury in ELBW infants (50). The apparent blood pressure and perfusion to organs, Lightburn et al. (51) found no difference in cerebral blood flow velocities among extremely low birth weight (ELBW) infants with and without documented hypotension.

A Cochrane review found no evidence for the routine use of volume expansion in preterm infants without cardiovascular compromise and insufficient evidence that infants with cardiovascular compromise benefit from volume expansion when outcomes such as severe disability, cerebral palsy or mortality were reviewed (52).

Because the use of inotropes is a significant risk factor for acute brain injury, the care provider should be cautious when treating hypotension in premature infants. Indications to consider inotropes should include, along with low blood pressure, a combination of prolonged capillary refill, decreased urine output, elevated lactate or echocardiography findings. Potential iatrogenic reasons for hypotension, such as hyperinflation or dehydration, should also be ruled out. Therefore, a chest x-ray and a slowly infused fluid bolus before initiating inotropes should be considered.

**Prophylactic indomethacin and ibuprofen**

In Canada, in 2017, 28% of preterm infants <32 weeks GA were documented as having a patent ductus arteriosus (PDA), and just under one-half of these infants underwent treatment (1). When left untreated, an estimated 58% of infants dose their PDA spontaneously by day 3 (53). Preterm infants with a hemodynamically significant PDA have an increased risk for acute brain injury (54), but treatment with a cyclo-oxygenase inhibitor can have significant side effects, particularly on the renal system. One Cochrane review assessing the effects of prophylactic indomethacin in preterm infants found a significant reduction in IVH (RR 0.88, 95% CI 0.80 to 0.98), including severe IVH with ventriculomegaly, and in intraparenchymal lesions (RR 0.66, 95% CI 0.53 to 0.82) (55). However, there were no long-term neurodevelopment benefits observed at 18 months of age (56), and follow-up study results did not support use of indomethacin as a treatment that improved long-term infant outcomes (57). One 2011 Cochrane review assessed the prophylactic use of ibuprofen, which is thought to have a better side effect profile than indomethacin, but this study found no difference in IVH or mortality (53). Because many PDAs often close spontaneously and the potential for side effects from cyclo-oxygenase inhibitors are significant, the prophylactic use of indomethacin or ibuprofen should be targeted based on combined risk factors including GA, exposure to antenatal steroids, and birth site (58) (level of evidence: 1a).

**Hypercapnia/ hypocapnia and ventilation mode**

Hypercapnia, defined as PCO2 blood levels >60 mmHg, is a risk factor for acute brain injury in ELBW infants that may impair cerebral autoregulation and cause vasodilatation (59). Rising PCO2 levels also appear to be a dose-dependent predictor for IVH risk (60). However, permissive hypercapnia (defined as allowing PCO2 levels of 45 mmHg to 55 mmHg) is a common strategy to minimize risk for lung injury and bronchopulmonary dysplasia in preterm infants. Various RCTs have evaluated infants managed with permissive hypercapnia PCO2 or with PCO2 levels above the typical hypercapnia range (PCO2 55 mmHg to 65 mmHg), compared with normocapnia (PCO2 35 mmHg to 45 mmHg). Authors found no difference in the incidence of severe IVH with ventriculomegaly, intraparenchymal lesions or long-term neurodevelopmental outcomes (61,62). However, median PCO2 levels higher than 72 mmHg or lower than 32 mmHg were both independently associated with acute brain injury (63). Both extreme hypercapnia (PCO2>60 mmHg) and hypocapnia (PCO2 <35 mmHg) appear to cause brain injury and should be avoided (64,65). Monitoring PCO2 via blood gases or transcutaneous or end-tidal CO2 is recommended for infants born at ≤32+6 weeks GA, with a goal of achieving PCO2 levels of 45 mmHg to 55 mmHg in the first 72 hours postdelivery (level of evidence: 1b).

Volume-targeted ventilation has been associated with lower odds of severe IVH (OR 0.53, 95% CI 0.37 to 0.77) compared with pressure-limited ventilation (66). Early use of rescue high-frequency oscillatory ventilation may increase the risk of IVH (RR 1.77, 95% CI 1.06 to 2.96) (67). Whenever possible, volume-targeted ventilation should be used in premature infants in the first 72 hours postdelivery (level of evidence: 1a).

**Head positioning**

Routine care of the preterm infant in the first 72 hours postdelivery can affect cerebral blood flow (68). Maintaining a neutral head position may avoid jugular venous obstruction, reduce ipsilateral venous congestion, and potentially lower risk for IVH (68). Few clinical trials have been conducted to address this issue and most relevant studies have used a nonrandomized, convenience sample design (69). In general, these studies documented changes in cerebral blood flow based on infant head positioning, noting either an increase in cerebral...
blood volume (69) or a decrease in jugular blood flow (70) when an infant’s head was turned 90 degrees. A few studies have also found decreased intracranial pressure when the head was midline and elevated (71–73), although one Cochrane review found no significant difference in IVH rates for head position at 0 versus 90 degrees (74). Based on infant physiology and the relative ease of implementing this practice, and because fluctuations in intracranial pressure may increase risk for acute brain injury, consideration should be given to keeping the infant’s head midline or neutral with the torso and the head of the bed elevated at 30 degrees (level of evidence: 5).

Transport

Transporting a preterm infant (≤ 32 + 6 weeks GA) between facilities is believed to be an independent risk factor for acute brain in jury. Possible causes for this include noise, vibration and acceleration during travel (75). Several studies, however, found no worse outcomes for infants transferred between neonatal centres (76,77), and at least one suggested the act of transport was not an independent risk factor for acute brain injury (78). The increased risk of acute brain injury in preterm infants born outside tertiary centres may relate to the decreased likelihood of receiving antenatal corticosteroids (79) and resuscitation (78) by teams who may lack specific training and expertise for preterm infant care. Transport to a tertiary care centre should occur when appropriate. When it is deemed unsafe to move a mother before delivery, antenatal corticosteroids should be administered and neuroprotective measures taken throughout stabilization and transport, in consultation with a tertiary care team (level of evidence: 5).

Nurturing environment

Neurodevelopmental delay is common among infants born extremely preterm, even when their MRIs appear relatively normal (80,81). Fostering a care environment that encourages skin-to-skin contact, maternal voice exposure and interaction, light cycling, and a low general noise level, is crucial for optimal brain growth (82,83). Developmental care strategies can mitigate painful procedures (84) and decrease opioid use (85), which are both associated with adverse neurodevelopmental outcomes (86–88). Finally, because substandard growth has been associated with brain injury and neurodevelopmental delay (89), early parenteral nutrition to optimize growth is also essential (90).

Conclusion

Infants born at ≤ 32 + 6 weeks gestation are at higher risk for intracranial ischemic and hemorrhagic injuries, which often occur in the first 72 hours postbirth. Antenatal strategies to reduce the incidence of acute brain injuries include administering maternal corticosteroids and prompt antibiotic treatment for chorioamnionitis. Perinatal strategies include delivery within a tertiary centre, delayed cord clamping, and preventing hypothermia. Postnatal strategies include empiric treatment with antibiotics when chorioamnionitis is suspected, the cautious use of inotropes, the avoidance of blood PCO2 fluctuation, and neutral head positioning. Clinicians should be aware of the policies and procedures that, especially when combined, can provide neuroprotection for preterm infants. Acute brain injury, which can occur in the form of infarction caused by ischemia and/or hemorrhage caused by reperfusion within the cerebral ventricles or parenchyma, is a common and serious morbidity associated with prematurity. The pathophysiology of injury involves the premature infant’s fragile cerebral vasculature and immature autoregulatory system, with rapid changes in perfusion causing ischemia or intraventricular hemorrhage (IVH) into the brain. In Canada, approximately 21% of preterm infants born at ≤ 32 + 6 weeks gestational age (GA) show an abnormal brain image (IVH or parenchymal lesions) on cranial ultrasound. While another variant of white matter brain injury, cystic periventricular leukomalacia (cPVL), is in decline, the noncystic form of PVL is becoming increasingly recognized due to magnetic resonance imaging (MRI). Abnormal brain images in the neonatal period are strongly associated with neurodevelopmental impairment in the long term.

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