Obstetric, neonatal and anesthetic considerations for preterm labor and delivery

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ABSTRACT

Preterm birth is a continuing obstetric problem that contributes significantly to the incidence of perinatal death and long-term handicap. In this context, various studies have shown preterm births account for between 69% and 83% of neonatal deaths. Despite this, the incidence of preterm birth has remained static for many years. One explanation for this is that the management of preterm labor has altered very little in the past 30 years. Strategies aimed at reducing the incidence of preterm birth include the identification of risk factors that increase the likelihood of preterm delivery. Treatment is then designed to target those risk factors and limit their effect. Although perinatal mortality has declined, mostly due to the improved management of very low birthweight babies rather than prevention of preterm labor, efforts to prevent preterm birth have been largely unsuccessful so far and preterm birth still represents a major health care problem to both developed and developing countries.

The parturient in preterm labor presents the obstetrician, the obstetric anesthetist and the neonatologist with a variety of problems. Despite improved antenatal and neonatal care over the last 3 decades, prematurity is still a leading cause of perinatal morbidity and mortality in developing and under-developed countries.[1] Alarmingly, the incidence of preterm birth has increased in North America from nearly 7-11% over the past 2 decades.[2] Similar trends have been observed in Bahrain since 1988.[3] This rising incidence of preterm delivery assumes even greater importance when it is realized how costly it is in terms of health care expenditures. In the United States of America (USA) for instance, it is estimated to cost $3 billion per annum.[4] In Bahrain, approximately 4% of the total national health budget is spent on preterm labor and preterm neonates.[3] This has led to increased research, endeavouring not only to determine the causes and pathophysiology of preterm labor, but even trying to provide early identification of women at risk for same. The sad result of preterm labor is that it all too often results in very low birth weight (VLBW) infants, weighing <1500 g at birth.

Definition and incidence. Preterm labor is defined as a regular uterine contraction producing cervical change (dilation or effacement) before 37 completed weeks of gestation. The terms preterm labor and preterm birth assume a lower gestational limit of 20 weeks.[5] Even so, many obstetricians will treat preterm labor in their patients somewhat earlier. Gestational age is often difficult to ascertain, and therefore many statistics refer to birth weights between 500 and 2499 g. However, this results in the exclusion of many term infants with growth retardation, and also the exclusion of preterm infants who are large for gestational age. The VLBW infant is defined as weighing <1500 g, which often

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corresponds to a gestational age of <32 weeks. The incidence of preterm birth is dependent on many factors, and since the mechanisms responsible for term labor remain undefined, it is not surprising that the cause of preterm labor is only partially understood.[6] Risk factors associated with prematurity can be grouped under 5 headings: maternal characteristics,[7,8] socio-economic factors, past reproductive history,[9-11] current pregnancy complications, and genital tract infections.[12-15] In more than one third of all cases no risk factor can be identified and the cause is unknown. Identification of the pregnancy at risk would heighten vigilance for signs of preterm labor. Prompt diagnosis allows for aggressive obstetric management, including pharmacologic therapy. Pharmacologic therapy as well as the timing and route of delivery are mainly obstetric decisions, but the implications for the anesthetist can be significant. Obstetric management will be discussed, along with the desirable and undesirable effects of many drugs commonly used by perinatologists. Anesthetic management of the parturient in preterm labor will depend on those decisions that might have been made as part of prior obstetric management. Anesthetic considerations include possible interactions of such drug therapy, as well as evaluation of current fetal well-being in order to select the best analgesia for labor and delivery, or anesthesia for cesarean section (CS). Early discussions between the perinatologist, neonatologist, and anesthetist will provide the opportunity for coordinated management, should delivery become inevitable.

Neonatal mortality. It is accepted that the survival rate increases as the birth weight or gestational age increases.[16] Over the last 10-20 years, there has been a significant improvement in the survival rate in VLBW subgroup, with the greatest improvement occurring in that subgroup with a birth weight of 750-1000 g. If they can be cared for in a neonatal intensive care unit, these newborns have a 70-80% chance of survival.[16] Infants with a birth weight of <750 g continue to have a high mortality rate. The introduction of exogenous surfactant therapy has markedly increased the survival chances for this patient population. Further improvement in the survival of this group may be expected with the increased use of surfactant therapy.

Neonatal morbidity. The issue of neonatal morbidity has become increasingly important as neonatal survival rates improve. Accordingly, obstetricians consider the risk of mortality and morbidity when making decisions for the timing and delivery of a preterm infant. When the incidence of neonatal morbidity in preterm singleton neonates without major congenital anomalies delivered in 5 tertiary centers between 1983 and 1986 was evaluated, the incidence of respiratory distress syndrome (RDS) was approximately 80-90% at 25-27 weeks, 55-65% at 28-30 weeks, 30-40% at 31-33 weeks, and <15% after 33 weeks of gestation.[17] However, the incidence of RDS remained clinically significant at 35 and 36 weeks of gestation

(6.4% and 3.3%).[17] Other findings included the facts that the incidence of grade III and IV enterocolitis declined after 31 weeks and was <1% after 34 weeks of gestation, and the incidence of neonatal sepsis similarly declined after 31 weeks and was <1% after 36 weeks of gestation. The economic costs for surviving preterm infants can be enormous, especially in the VLBW infants. In a review published in 1986, it was reported that the mean length of hospital confinement for infants who weighed 500-750 g at birth, and who survived, was 137 days; and the mean cost of care per infant was US $158,800.[18] Approximately one third of these infants had significant neuro-developmental handicaps. In a review of morbidity in such infants over a decade, major handicaps were found at one or 2 years of age in 26% of those surviving infants with a birth weight of <800 g; in 17% of survivors with a birth weight between 750 and 1000 g; and in 11% of survivors with a birth weight between 1000 - 1500 g,[16] (Major handicaps included severe mental retardation, significant degrees of cerebral palsy, major seizure disorders, blindness, and severe hearing defects). There was also a higher incidence of mild and moderate handicaps in those VLBW infants than in normal birth weight children.

Preterm labor. Risk factors. Numerous factors may be associated with preterm labor.[19] These associations however, do not necessarily indicate cause-and-effect relationships. In many cases, the cause of preterm labor is unclear.[20] The major maternal medical factors are being examined in order to understand the poor statistical morbidity results. There is a dose-related impact of smoking on the risk of preterm birth. The fact that the smoking-related risk of spontaneous preterm birth is more pronounced than that of induced preterm birth suggests that smoking is definitely associated with spontaneous preterm labor.[21-23] Sickle cell disease also remains a severe complicating factor in pregnancy, and perinatal mortality and maternal mortality rates are very often associated with preterm labor and delivery. A policy of exchange transfusion for all women with homozygous sickle cell disease (HbSS) after 28 weeks' gestation is recommended to reduce the risk of maternal complications in the third trimester and puerperium. There remains a role for earlier prophylactic blood transfusion programs in such women with poor obstetric and hematological histories.[24] As more young women of childbearing age with major organ failure are being treated by transplant surgeons, greater problems are seen for a pregnancy in these transplant recipients. Several concerns have arisen regarding the effects on the fetus of maternal immunosuppressive therapy, the risk factors faced by both the fetus and the mother secondary to the mother's organ disease, and the general outcome of the increasing number of pregnancies in this population.[25] Small studies published recently suggested that DDT (DDE 1,1-dichloro-2,2-bis [p-chlorophenyl] ethylene), which is highly effective against most malaria-transmitting mosquitoes and which is being used in malaria endemic areas, increases preterm birth.[26]

If this association is causal, it should be included in any assessment of the costs and benefits of vector control with DDT.[26] Certain infections are more consistently associated with preterm labor, such as bacterial vaginosis, *Trichomonas vaginalis Chlamydia trachomatis*, untreated syphilis[27] and *Neisseria gonorrhoeae*,[28] asymptomatic *group B streptococcal* colonization, and untreated acute pyelonephritis.[29] Other cervicovaginal microorganisms and infections have been implicated in preterm delivery, but published studies have noted inconsistent results.[29] Approximately 50% of preterm deliveries occur in women with no apparent risk factors. Subclinical infection could precipitate preterm labor in some of these cases.[30] Investigators have found positive amniotic fluid cultures[31] and products of infection such as elevated maternal serum C-reactive protein[32] in some patients with preterm labor. Studies of prostaglandins, their metabolites, and cytokines suggest a biochemical mechanism for preterm labor in the presence of infection. Empirical trials of antibiotic therapy have produced conflicting results.[32] The same pattern of biochemical changes involving prostaglandins and cytokines found in infection can also occur with aseptic inflammatory processes. Recent reports suggest that gum infection in pregnant women predisposes them to preterm labor in a separate process from the aforementioned but the evidence so far is not conclusive.[33] Prophylactic antibiotics are likely to be of benefit only in the subpopulation of patients with active infections.[34] It is estimated that as many as 20-25% of all preterm deliveries do not follow preterm labor. The obstetrician may perform elective delivery for maternal or fetal indications such as severe preeclampsia or fetal distress. Unfortunately, some cases of respiratory distress syndrome (RDS) too are iatrogenic.[35]

Prediction. Due to the large variety of risk factors that predispose to preterm birth, the earliest strategies, which were used in its prevention, were the identification of risk indicators for women who will deliver before term. Risk scoring was devised to assess a woman's potential for preterm birth based on the socioeconomic status, clinical history, lifestyle, and past obstetric and current perinatal complications. However, these strategies have proved to be of limited value. Unfortunately, there is insufficient evidence from randomized trials of preterm prevention programs to suggest that the use of prospective risk scoring can reduce the incidence of preterm delivery or can identify women who will benefit from such program.

Cervical assessment. Weekly cervical assessment as a predictor of preterm labor in women with uncomplicated pregnancies has had varying support.[36] The lack of efficacy of routine cervical examinations in reducing preterm deliveries suggests that such examinations do not identify women at risk of preterm delivery or that the interventions prompted by the test are ineffective.

Transvaginal ultrasound examination. Several published studies[37,38] have demonstrated an inverse relationship between cervix length and frequency of preterm delivery. The authors concluded that the length of the cervix was possibly an indirect indicator of cervical competence and that the cervical length should be seen as a continuous rather than a dichotomous variable. Traditionally, it has been taught that the cervix is either fully functional or incompetent. Currently, transvaginal ultrasonography is not indicated in the routine evaluation of the patient with a history of or current risk factor for preterm delivery. Further clinical trials are needed to determine the role of transvaginal ultrasonography in high risk populations and in the clinical trials to evaluate cerclage. Monitoring including fetal fibronectin detection,[39] salivary estriol[40] and home uterine activity[41] have all been attempted. No clear benefit has been found from routine assessment by any of the tests in the prediction or the prevention of preterm birth.[36]

Diagnosis. It is often difficult to determine whether a woman is in early preterm labor or false labor.[42,43] Criteria for the diagnosis of preterm labor include (1) gestational age between 20 and 37 weeks gestation, (2) documented uterine contractions of at least 4 in 20 minutes or 8 in 60 minutes, and (3) documented change in cervical dilation or effacement, cervical effacement of 80%, or cervical dilation of 2 cm.[43] Several investigators[44,45] have noted the predictive value of fetal breathing movements (as seen during real-time ultrasonography) in the diagnosis of preterm labor in parturients with intact membranes. It was observed that preterm women with contractions and fetal breathing movements were not likely to progress into active labor and that the pregnancy typically continued for at least another week.[44,45] Where fetal breathing movements were absent however, delivery was more likely to occur within 48 hours.

Tocolytic therapy. Initial assessment and therapy includes physical examination, intravenous hydration, bed rest, fetal heart rate (FHR) monitoring, and ultrasound evaluation. Maternal physical examination may include a vaginal examination with a sterile speculum to exclude preterm premature rupture of membranes (PROM). In many women, uterine contractions will cease with bed rest and hydration alone. Ultrasound evaluation is non-invasive and can be performed on admission to estimate gestational age and fetal weight. If necessary, amniocentesis can be performed to determine fetal pulmonary maturity, and to look for evidence of infection. Once the diagnosis of preterm labor has been established, the obstetrician must decide whether to begin tocolytic therapy. Criteria for the use of tocolytic therapy include: (1) gestational age between 20 and 34 weeks, (2) fetal weight of <2500 g, and (3) absence of fetal distress. The potential benefits of delaying delivery of the preterm infant (namely, decreased neonatal morbidity and mortality) must be weighed against the maternal and fetal risks (namely, maternal or fetal sepsis, or both; maternal side effects of tocolytic drugs; or further compromise of a distressed

fetus). There are many contraindications to the inhibition of labor, including fetal death, fetal anomalies incompatible with life, fetal distress that warrants immediate delivery, chorioamnionitis or fever of unknown origin, severe hemorrhage, and severe chronic or pregnancy induced hypertension, or both.

In some cases, there are benefits to a short course of tocolytic therapy. For example, tocolytic therapy could allow transport of the patient from a small community hospital to a tertiary care facility, which can provide optimal care for the preterm neonate. Also, a short course of tocolytic therapy could delay delivery for 24-48 hours, which allows administration of a glucocorticoid to accelerate fetal lung maturity. Finally, obstetricians could give a single bolus dose of a tocolytic agent to facilitate fetal resuscitation in utero in cases of fetal distress.[46-48] Controversy still remains regarding the use of tocolytic therapy in patients with preterm PROM. Preterm PROM nearly always leads to preterm labor and delivery. Preterm delivery accounted for most of the morbidity attributable to preterm PROM. Antibiotic and corticosteroid treatment could modify the outcome of pregnancy after preterm PROM. The extent of these morbidities attributable to preterm PROM also justifies consideration of the use of tocolysis, at least for a limited period of time (48 hours) after preterm amniorrhexis. When started after the onset of contractions following preterm PROM, tocolysis generally does not prolong the latency period, although some prolongation could occur before 28 weeks' gestational age. Prophylactic tocolysis started before the onset of labor increases the likelihood of delaying the onset of labor for 1-2 days, but not beyond, and aggressive long-term tocolysis could increase the maternal risk of chorioamnionitis and endometritis. None of the reviewed randomized studies demonstrated a significant neonatal risk, and none of these studies showed an improvement in neonatal outcome, although they did not test the combination of tocolysis and corticosteroid use with appropriate controls. The hypothesis that PROM remote from term should be managed within 1-2 days of prophylactic tocolysis and corticosteroids to enhance fetal pulmonary maturity is attractive, yet it remains inadequately evaluated.[49] However, it was suggested that tocolytic therapy could have some benefit in patients whose membranes ruptured before 28 weeks gestation.[50]

In an interesting outcome analysis that was carried out in Great Britain, it was again found that at 32 weeks, tocolysis yielded the lowest total number of adverse maternal and neonatal events.[51] At 34 weeks, both tocolysis and no tocolysis yielded similar overall outcomes. At 36 weeks, most clinical outcomes were good, regardless of strategy. Their analysis supports the empirical use of tocolysis at 32 weeks. At 34 weeks, either tocolysis or no tocolysis appeared to be reasonable alternatives. At 36 weeks, no tocolysis was probably preferred. Their analysis also suggested that amniocentesis should not be employed in the management of preterm labor at these gestational ages.[51]

Once the obstetrician has decided to start tocolytic therapy, an appropriate agent must be selected. Before 1980, some obstetricians used ethanol to treat preterm labor. Fortunately, the use of ethanol for tocolytic therapy has long been abandoned. Ritodrine was for a time the only drug approved by the Food Drug Association (FDA), USA for tocolytic therapy.[52] The efficacy of tocolytic therapy with this drug remains controversial. Prospective, randomized studies have provided conflicting results.[53-55] These studies have typically noted a high rate of success with a placebo, which probably suggests an incorrect diagnosis of preterm labor in some of the women. The first prospective, double-blind, placebo-controlled study of ritodrine was performed in a multicenter trial in Europe. Preterm delivery was delayed at least 7 days in 80% of the patients in the ritodrine group compared with 48% of patients in the placebo group. The first randomized, controlled, multicenter study of ritodrine in USA was conducted between 1972 and 1977. Another group studied 313 parturients with a singleton fetus, intact membranes, and a mean gestational age of 31 weeks at entry into their study.[56] When compared with the placebo group, ritodrine significantly prolonged pregnancy (33 versus 21 days). The infants of the ritodrine-treated mothers had a significantly decreased incidence of neonatal death and RDS. The ritodrine group included a greater number of women whose pregnancies extended beyond 36 weeks gestation and a greater number of infants with a birth weight of >2500 g. Several other investigators over the years however have raised questions regarding the efficacy of ritodrine in the treatment of preterm labor.[54-58] One team[55] performed a meta-analysis of 16 controlled studies in which tocolytic agents, primarily ritodrine, were evaluated. They concluded that beta-adrenergic agents delayed delivery for 24-48 hours but did not significantly decrease perinatal mortality or morbidity from respiratory distress. The Canadian Preterm Labour Investigators Group[57] studied 708 women with preterm labor in a randomized, controlled, multicenter study that compared the effects of ritodrine and a placebo for the treatment of preterm labor. There were no differences between the 2 groups in the following outcome measures: (1) incidence of delivery before 37 weeks gestation, (2) proportion of infants with a birth weight of <500 g, (3) incidence of perinatal mortality, and (4) neonatal morbidity. They did observe a significant decrease in the rate of delivery within 24 hours and within 48 hours in the ritodrine group. However, the authors stated that "this immediate effect has not led to clinically important reductions in the rates of preterm delivery or low birth weight."[57] In 1975, the first double-blind, placebo-controlled study of terbutaline reported 80% of the terbutaline-treated patients versus only 20% of patients who received a placebo reached 36 weeks' gestation. A similar placebo-controlled study failed to show any efficacy with terbutaline.[59] Likewise, others had found that terbutaline was not better than a

placebo in stopping preterm labor for more than 48 hours.[53] At least 2 controlled clinical studies have reported the efficacy of a 24-hour course of indomethacin therapy for tocolysis.[60,61] In both studies, patients were randomized to receive either indomethacin or a placebo. No study to date has randomized patients to receive either a calcium channel blocking agent or a placebo for tocolysis. It was observed that nifedipine was more effective than ritodrine or no treatment in a group of 60 women with a singleton pregnancy, intact membranes, and a gestational age between 20 and 35 weeks.[62] Unfortunately, the control group consisted of non-randomized patients who were added for comparison. But others observed that tocolysis with either nifedipine or intravenous ritodrine was equally effective in delaying delivery for 48 hours, 7 days, or until 36 weeks gestation.[63] All the above-mentioned treatments for preterm labor including the beta-agonists, which have been used for many years are currently being questioned. At the doses used, these agents have been shown to have a number of adverse effects, including serious cardiovascular complications.

Oxytocin antagonists. Ever since the discovery of oxytocin and elucidation of its role in the initiation of uterine muscle contraction, many researchers speculated on the potential role of oxytocin antagonists in the treatment of preterm labor.[64] The first antagonist which came into clinical use was Tractocile (Atosiban). It is used to delay imminent preterm birth in pregnant women. Its main advantage is that it is as effective as beta-agonists, calcium channel blockers, and prostaglandin inhibitors, but free of their side effects. The contraindications for its use are similar to those situations that make the use of other tocolytics unsuitable.

The preterm infant. Physiology. The healthy term fetus tolerates the stress of labor and delivery well. The preterm fetus (especially if it is <30 weeks gestation or has a weight of <1500 g) is physiologically less well adapted to this stress.[65] Some (but not all) studies suggest that the incidence of intrapartum acidosis and asphyxia is greater in the preterm fetus than in the mature fetus.[66] The preterm fetus has a decreased hemoglobin concentration and a decreased oxygen-carrying capacity.[65] It should be noted that these characteristics do not result in an increased risk of intrapartum fetal neurological injury.

There is a higher incidence of intraventricular hemorrhage (IVH) in the preterm infant, particularly in the fetus with a gestational age under 35 weeks.[65] Factors contributing to the development of IVH in preterm fetuses include (1) poor tissue support surrounding the germinal matrix blood vessels, (2) a disproportionately higher amount of total cerebral blood flow to the periventricular circulation, and (3) impaired autoregulation of cerebral blood flow, making blood flow to the periventricular area extremely sensitive to fluctuations in arterial blood pressure. Hypoxia-induced damage to the periventricular capillaries also increases

susceptibility to IVH.[68] In addition, the preterm fetus has a relative deficiency of clotting factors, which can be exacerbated by the presence of asphyxia.[667,68] These limitations increase the risk of hemorrhage if there is stretching and tearing of the subependymal vessels from the molding of the fetal head during labor and delivery.[69]

Method of delivery. The ideal method of delivery for the preterm infant (especially the VLBW infant) remains controversial, as has been for so many years. Although many investigators have tried to determine the preferred route of delivery for the low birth weight fetus, this issue remains debatable, as controversy persists on the merits of vaginal versus cesarean delivery, especially if the fetus is in a breech presentation. Controversy also persists as to whether forceps should be used to protect the more fragile preterm fetal head. Moreover, although it has long been thought that the use of a generous episiotomy could reduce resistance to the preterm fetal head and minimize the risk of injury, data to support this theory have not been forthcoming.[70] A policy of elective cesarean delivery increases the risks of maternal morbidity, but it remains unclear whether these are offset by benefits for the infant.[71] The incidence of CS in infants with a birth weight under 1500 g has steadily increased in USA and other countries.[72,73] Some reports have claimed decreased neonatal mortality with the liberal use of CS in preterm infants,[71] while others have found no advantage of CS over vaginal delivery.[72-75] However, most of these studies were retrospective and not well controlled. A large number of obstetricians perform CS for delivery of VLBW fetuses with a breech presentation. Similarly, cesarean delivery has been recommended for VLBW twins wherein twin A has a non-vertex presentation, although there are no prospective, controlled studies to support this practice.[76] Head entrapment behind an incompletely dilated cervix is more common in preterm fetuses with a breech presentation since the head is somewhat larger than the wedge formed by the buttocks and thighs. Several studies have noted that vaginal delivery of VLBW fetuses with breech presentation resulted in a higher rate of neonatal mortality.[74,75] No prospective, randomized studies have confirmed that CS results in a better outcome than vaginal delivery for the preterm fetus with a breech presentation. The survival rate remains low for infants with a birth weight of 500-750 g. In these cases, the obstetrician must decide whether to recommend cesarean delivery in cases of fetal distress or breech presentation. The obstetrician often asks a neonatologist to speak to the patient and her family concerning the infant's risk of morbidity and mortality so that they can make an informed decision regarding the method of delivery.

Fetal heart rate monitoring. Today, most obstetricians use continuous electronic fetal heart rate monitoring (FHR) monitoring once preterm labor has been diagnosed. Preterm gestation often complicates the interpretation of FHR patterns. Preterm fetuses could

exhibit decreased variability, with the baseline FHR higher in preterm fetuses than in term fetuses.[77] The presence of chorioamnionitis or the use of beta-adrenergic agonists can similarly make the interpretation of the FHR tracings difficult. There is ongoing controversy regarding the value of continuous electronic FHR monitoring as opposed to intermittent auscultation of the FHR. A randomized trial was reported that compared continuous electronic FHR monitoring (with selective fetal blood gas sampling) with periodic auscultation of the FHR during preterm labor in women with a fetus weighing between 700 and 1750 g.[78] There was no significant difference between the groups in the incidence of CS, low 5-minute Apgar scores, intrapartum acidosis, intracranial hemorrhage, and perinatal death. But at 18 months of age, the incidence of cerebral palsy was significantly higher in the electronic FHR group than in the intermittent auscultation group.[79]

Anesthetic considerations. The high incidence of operative vaginal and cesarean deliveries of the preterm fetus necessitates efficient anesthetic management.[43] Provision of effective obstetric analgesia can in itself be an integral part of intrauterine resuscitation of a distressed fetus. The choice of appropriate anesthetic techniques and agents can actually decrease anticipated intrapartum maternal and fetal complications. Thus, appropriate selection of anesthetic techniques and agents could potentially benefit the preterm or even a distressed fetus. Anesthetic management must include consideration of associated medical, obstetric, and social conditions as well as possible drug interactions between anesthetics and prior maternal drug therapy. Once the diagnosis of preterm labor has been made, the anesthetist must be prepared for obstetric intervention. Inhibition of labor for preterm pregnancy is far from an exact science, and as stated previously, the anesthetist is often presented with a patient requiring emergency induction of anesthesia who could already be receiving a variety of potent systemic medications in an attempt to inhibit the preterm labor.

Labor and vaginal delivery. It is accepted that the preterm fetus has less protein-binding capacity than a term fetus. This leads to increase circulating free drug concentrations. In addition, the preterm fetus cannot metabolize and excrete drugs as efficiently as a term fetus. The preterm fetal blood-brain barrier is also thought to be more permeable to circulating drugs. Circulating maternal stress-related catecholamines decrease uteroplacental perfusion. The preterm fetus is extremely sensitive to decreases in uteroplacental perfusion and could rapidly develop fetal asphyxia.[65] The fetal response to possible asphyxia increases cerebral blood flow and therefore exposure to maternally administered drugs. Induction of epidural analgesia which will decrease maternal stress enhances uteroplacental perfusion, as long as maternal arterial pressure is maintained.[80] It is for these reasons that epidural analgesia or combined spinal-epidural for labor

and delivery is believed superior compared with the use of sedatives or narcotics, or both. Preliminary data have indicated that epidural analgesia is at least as safe for the fetus as administering no anesthesia in labor, or using local infiltration or pudendal block at delivery.[81] Vaginal delivery of the preterm fetus could necessitate a generous episiotomy, whether or not forceps are used, to decrease extracranial pressure and to better control the delivery. Epidural analgesia or low spinal anesthesia ("saddle block") provides excellent perineal anesthesia at delivery and can facilitate an atraumatic delivery. Choice of local anesthetic for epidural anesthesia could be of some importance to the fetal outcome. Bupivacaine is an amide local anesthetic with a low fetal-to-maternal plasma concentration ratio secondary to its relatively high (90%) protein binding.[82] Lidocaine, with a lower protein binding (60%),[82] will give a relatively larger anesthetic load to the fetus. Gestational age does not seem to alter the fetal pharmacokinetics or pharmacodynamics of lidocaine.[83] However, the asphyxiated preterm fetus is more sensitive than the asphyxiated term fetus to the depressant effects of lidocaine.[84,85] Ion trapping of local anesthetic by an acidotic fetus will greatly increase the fetal-to-maternal plasma concentration ratio. 2-Chloroprocaine is an ester anesthetic, rapidly hydrolyzed in both maternal and fetal plasma, and thus exposes the acidotic fetus to a smaller level of local anesthetic. Often 2-chloroprocaine is the preferred local anesthetic to intensify or extend epidural anesthesia to facilitate an operative vaginal or abdominal delivery of the distressed preterm fetus. "Single-shot" spinal anesthesia with lidocaine produces fetal drug levels that are 15-30% of those measured following epidural anesthesia.[86] The small amount of local anesthetic needed for "single shot" spinal anesthesia for vaginal delivery (for example 35 mg of hyperbaric 5% lidocaine) permits the choice of local anesthetic to be made independently of fetal considerations. Cesarean delivery of a non-distressed fetus can be carried out under regional anesthesia if time permits. The choice of local anesthetic for epidural anesthesia in the non-distressed fetus is not an issue. Approximately 18-22 mL of 2% lidocaine with epinephrine or 0.5% Bupivacaine with epinephrine will provide surgical anesthesia in 20-30 minutes. Spinal anesthesia for cesarean delivery, (for example 10-12 mg of hyperbaric 0.75% Bupivacaine) is an alternative to epidural anesthesia. A significant percentage of parturients given spinal anesthesia will have hypotensive episodes after induction.[87,88] Prompt treatment of maternal hypotension has been shown to make such episodes inconsequential to fetal outcome in the term fetus.[89,90] This may not be the case during abdominal delivery of a distressed preterm fetus. Therefore, meticulous attention to hydration and pharmacologic support of maternal blood pressure must be maintained. Vast documentation of successful outcomes of spinal anesthesia for abdominal delivery of the preterm fetus confirms it to be an excellent method of surgical anesthesia in these cases.

Drugs used for the induction and maintenance of general anesthesia can potentially anesthetize the preterm infant; thus, both the induction to delivery time and the uterine incision to delivery time must be minimized. A retrospective study of almost 4000 babies born by cesarean delivery under general or regional (mainly epidural) anesthesia analyzed neonatal outcome according to l- and 5-minute Apgar scores, the need for oxygen by mask, the need for tracheal intubation, and neonatal death.[89] Cord blood analysis was not reported. It was concluded that preterm neonates (all types of maternal anesthesia) had a 2-5 times higher incidence of a one minute Apgar score of 0-4 than did term neonates. The estimated relative risk of a one minute Apgar score of 0-4 for neonates born under general anesthesia was 3 times greater compared with regional anesthesia, regardless of the gestational age. There was significant improvement in the 5-minute Apgar scores, and there was no difference in neonatal mortality.[90] Newborn sensitivity to general anesthetics could be manifested as low Apgar scores. It is postulated that immediate neonatal ventilation, oxygenation, and therefore rapid elimination of the anaesthetic agents would lead to a significant improvement in the 5-minute Apgar scores. This practice must be emphasized in resuscitation of the "depressed" preterm neonate, although the same would be true for any newborn. Following administration of a non-particulate antacid, providing left uterine displacement and appropriate denitrogenation, rapid sequence induction of anesthesia is begun with intravenous thiopental (4 mg/kg). Intravenous ketamine (1 mg/kg) is an acceptable alternative induction agent except in the preeclamptic parturient, or perhaps those women with certain coexisting neurologic or cardiac diseases.[91] Intubation is facilitated with one to 1.5 mg/kg of intravenous succinylcholine. "Light" anesthesia must be avoided as increased maternal catecholamine production could decrease uteroplacental perfusion. Two-thirds MAC of any of the volatile inhalational agents is then administered. Maternal inspired oxygen concentration should be at least 50%. In term gestations undergoing elective cesarean delivery, fetal PO_2 will not rise above 50 mm Hg after the maternal PO_2 has reached 300 mm Hg.[92] Some anesthetists will deliver up to 100% oxygen to the mother during abdominal delivery of a premature or distressed fetus. After delivery, the volatile agent can be discontinued, the nitrous oxide concentration increased, and a supplemental intravenous narcotic drug given. Additional neuromuscular relaxation using either succinylcholine or a non-depolarizing agent is given intravenously as required, but the peripheral neuromuscular blockade must be monitored.

Hyperventilation should be avoided. There is well documented evidence that shows a rapid shift of the oxyhemoglobin curve to the left. Respiratory alkalosis increases maternal oxygen-hemoglobin affinity, and hyperventilation via intermittent positive pressure ventilation decreases uteroplacental blood flow. The result is decreased maternal oxygen presentation to the fetoplacental unit, resulting in the creation of further problems such as fetal acidosis and hypoxia for the fetus.

Management implications. Beta-adrenergic agents (ritodrine or terbutaline). The mechanism of action of these beta-adrenergic agents is by direct stimulation of the beta-receptors located in the uterine muscle cells. This leads to an increase of cyclic AMP, increased uptake of calcium by the sarcoplasmic reticulum, and a subsequent decrease in intracellular calcium. When these beta-adrenergic drugs were first introduced, it was thought that their pharmacologic actions would be limited to beta-adrenergic receptors, namely causing uterine relaxation, bronchodilation, vasodilatation, increased renin-aldosterone secretion which causes fluid and sodium retention, augmentation of glycolysis and increased insulin secondary to hyperglycemia due to direct stimulation of the Islets of Langerhans. It has since been determined that when these agents are administered, especially by the intravenous route, they exert significant beta1-adrenergic stimulation which can lead to tachycardia, palpitations, increased stroke volume, increased cardiac output, arrhythmias, chest pain, tremors, increased irritability, decreased bowel movement, increased lipolysis and ketosis. The administration of beta-adrenergic agents is therefore associated with significant biochemical and metabolic changes. Serum glucose levels increase, while serum potassium levels decrease. This hypokalemia is due to increased insulin secretion with a shift of potassium to the intracellular compartment. Thus total potassium in the body does not change and usually there is no need for an infusion of it. However, some authorities recommend an infusion of potassium should the level fall below 3 mEq/L for fear of cardiac dysrhythmias. As a result of the lipolysis, there is increased circulation of fatty acids. Hyperglycemia and ketosis create a problem only for the diabetic patient, which is why beta-adrenergic agents are probably contraindicated in severe diabetics. The maternal hyperglycemia can result in fetal and neonatal hyperglycemia followed by reactive neonatal hypoglycemia. Blood glucose levels in the neonate must therefore be closely monitored. Also there is a decrease in maternal colloid osmotic pressure caused by fluid retention and fluid administration. The oxygen requirements for these patients are also increased because of their increased metabolic rate. Acute pulmonary edema is a particular problem after administration of these drugs.[93-95] Characteristics include: 1) the development of pulmonary edema without cardiac enlargement, 2) persistent low cardiac output despite normal ventricular preload, 3) a high body temperature, and 4) long-term ritodrine therapy. The lack of cardiac enlargement, normal pulmonary capillary wedge pressure, and negative fluid balance before the onset of respiratory failure indicate that pulmonary edema may be caused by an increased pulmonary vascular permeability rather than fluid

overload. If a higher than normal pulmonary arterial pressure is verified, a ventilation-perfusion lung scan should be utilized to rule out pulmonary embolism.[96] Bacteremia can also play a role in the development of pulmonary edema by increasing the pulmonary vascular permeability.[97] Previous studies have reported that ritodrine might cause vascular endothelial injury through the activation of the complement system. Postoperative increases in hemoglobin concentration without blood transfusion and the reduced concentration of total plasma protein could support the presence of increased pulmonary vascular permeability.[98]

Ritodrine induced pulmonary edema could occur due to excessive intravenous fluid administration to counteract hypotension due to the increased intravascular capacity or due to decreased urine excretion due to the antidiuretic effect of ritodrine.[69] Previous reports have suggested that long-term administration of beta-adrenergic drugs could desensitize beta-adrenergic receptors, resulting in a poor response of myocardial contractility to exogenous inotropic support. This depression of the beta-adrenergic receptors could contribute to the pulmonary edema. During pregnancy, the cardiac output and blood volume increases by 25-50% above prepregnancy levels. Therefore, further stimulation of the heart by beta-adrenergic agents may precipitate acute heart failure. Multifetal gestations have a higher risk of pulmonary edema due to further rise in cardiac output and blood volume above those in singleton gestations.[96] Fluid overload can be further attributed to 2 factors: first, the administration of fluid concomitant with the intravenous infusion of these drugs, and secondly, the antidiuretic effect of these drugs. If time allows, corticosteroids are administered in conjunction with the beta-adrenergic to accelerate fetal lung maturity. Some of these corticoids may then cause fluid retention, and they mask infection such as chorioamnionitis. The role of corticosteroids in predisposing to pulmonary edema has recently diminished with the use of drugs that have minimal sodium and water retention. Toxins increase the permeability of the pulmonary vascular bed, thus contributing to pulmonary edema.[97] Chorioamnionitis is important because not only does it lead to premature labor, but also it adds to the risk of intrauterine fetal infection, and thus to the hazards of acute pulmonary edema.[30] Pulmonary edema with a beta-adrenergic agent usually follows the intravenous administration and rarely the oral route.[58] The treatment of pulmonary edema is to stop the tocolytic drug, administer a diuretic and give oxygen by face-mask or by endotracheal tube with or without positive end-expiratory pressure (PEEP), depending on the oxygen saturation as determined using a pulse oximeter. In a small percentage of patients, invasive monitoring is required; for example, a pulmonary artery catheter to regulate fluid intake, and an arterial line for repeated studies of blood gases and blood chemistry. Beta-adrenergic agonists cross the blood-placental barrier, causing fetal tachycardia,

increased beat-to-beat variability and fetal hyperglycemia. Fetal acidosis could also occur subsequently to maternal acidosis. After delivery, the neonate could develop a reactive hypoglycemia. However, no lasting harmful effects on the neonate are attributed to these drugs provided the problems are recognized and treated accordingly.[58]

Magnesium sulfate. Magnesium sulfate, as a tocolytic agent, acts by decreasing the actin-myosin interaction in the uterine muscle.[99] Such an action is produced by decreasing the influx of calcium into the uterine muscle cell. Magnesium sulfate acts also on striated muscle fibres by decreasing acetylcholine release at the myoneural junction, increasing the threshold of depolarization of the motor end-plate to acetylcholine, and blocking the post-junctional membrane. Magnesium sulfate is usually administered intravenously by injecting a loading dose of 4-6 g in 20 minutes, followed by a maintenance dose of 1.5-3 g/hour.

Prolonged infusion of magnesium sulfate has been used for the treatment of refractory preterm labor. Magnesium sulfate therapy is indicated when the use of beta-adrenergic drugs is not advisable, for example, in cardiac, diabetic or thyrotoxic patients. It can also be used alone or in combination with other tocolytic drugs.[99] Following stabilization of the patient, other oral tocolytic drugs may replace intravenous magnesium sulfate. Long-term magnesium sulfate tocolytic therapy either alone or in combination with other tocolytic agents has been reported to be safe and effective with minimal maternal side effects. In a recent article, a case was reported where stress fractures secondary to osteoporosis may have been associated with prolonged magnesium sulphate therapy and concomitant bed rest in a higher order multiple pregnancy.[100] There has been only one previous report of a disturbance in maternal calcium homeostasis, which showed decreased bone density as a result of prolonged magnesium infusion.[101] Other possible contributing factors to osteoporosis include heparin thromboprophylaxis and suboptimal calcium supplementation. Therefore, in circumstances of prolonged bed rest and magnesium sulphate tocolysis, additional daily calcium supplementation might be well advised.[100,101] The therapeutic plasma level of magnesium sulphate is 4-8 mg/dL. Above 10 mg/dL the deep tendon reflexes are lost; above 15 mg/dL respiration is depressed, mainly due to a peripheral action; and above 20 mg/dL, clinical myocardial depression is manifested by varying degrees of electrocardiogram blockage such as prolonged P-R interval and widening of the QRS complex, plus a decrease in cardiac output. Magnesium sulphate is eliminated by the kidneys; thus, repeated evaluation of magnesium blood levels is essential in patients with impaired renal function. The deep tendon reflexes are useful clinically in determining the degree of magnesemia: if they are normal, this indicates a reasonable therapeutic level, while their absence

indicates an overdosage. Magnesium sulphate potentiates the action of depolarizing and especially nondepolarizing muscle relaxants.[102] Thus, the dose of nondepolarizing muscle relaxants should be reduced by one-third, a nerve stimulator should be used to regulate the dosage, and recurarization following reversal should always be considered. With succinylcholine, the full dose (1.5 mg/kg) should be administered before intubation to ensure complete relaxation, since the extent of magnesium sulphate potentiation is variable. Estimating the volume of prophylactic intravenous hydration needed before induction of regional anesthesia with its resultant vasodilatation is complicated in the parturient receiving magnesium therapy. With epidural anesthesia, biceps and triceps reflexes should replace the commonly used patellar reflex, since the epidural block could affect reflexes in the lower limbs. Magnesium sulphate crosses the blood-placental barrier, causing loss of beat-to-beat variability. The neonatal effects of hypermagnesemia include lethargy, abdominal distension, skin vasodilatation, hypotension and hypotonia. That is one of the reasons a neonatologist should be present at the delivery of a preterm baby, particularly when tocolytic therapy has been utilized. With adequate renal function, the neonatal effects will usually disappear within 48-hours.

Prostaglandin synthetase inhibitors. Prostaglandins are important for initiating uterine contractions and maintaining them by increasing intracellular calcium. By inhibiting prostaglandin synthesis this group of drugs can stop preterm labor.[60] An example is indomethacin,[103] which has the advantage of maternal cardiovascular stability. However, certain potential dangers are associated with its use, and these concerns regarding its effects on the fetus have thus limited its use. Indomethacin can cause premature closure of the ductus arteriosus in the fetus, leading to pulmonary hypertension and acute heart failure. Since the sensitivity of the ductus arteriosus to contract in response to indomethacin is increased with gestational age, it is recommended that it be used only in the early part of pregnancy, for example, below 34 weeks' gestation. It can also cause bleeding in the mother and fetus by decreasing platelet aggregation and reducing factor XII activity. Before use of major regional anesthesia, a platelet count should be obtained. Indomethacin should not be used in patients with a known bleeding disorder, renal or hepatic disease, bronchial asthma or peptic ulcer. These agents have also been associated with transient renal dysfunction and oligohydramnios.

Calcium channel blocking agents. The release of calcium is important for uterine contractions. Thus calcium channel blocking agents have been used in the treatment of preterm labor.[104] The most commonly used drugs are verapamil and nifedipine. Their use with beta-adrenergic drugs reduces the stimulating effect, but their prolonged use could cause intrauterine growth retardation of the fetus. Calcium channel blockers have a wide variety of anesthetic interactions. The dose of calcium channel blocker necessary to inhibit preterm labor is rarely associated with impairment of atrioventricular conduction and hypotension. Nifedipine has the fewest side effects on cardiac conduction, more specific effects on myometrial contractility, and less effect on serum electrolytes than other calcium channel blockers. However, it does have the potential for creating vasodilatation and hypotension.[105] A moderate reflex tachycardia is sometimes seen after the therapy has been started. An exaggerated hypotensive response might also be anticipated in a parturient that has been recently tocolysed with a calcium channel blocker should she receive a volatile inhalational anaesthetic. Two clinical studies have suggested that short-term administration of nifedipine does not adversely affect either uteroplacental or fetal circulation, whereas some animal studies had shown adverse fetal effects. Postpartum maternal hemorrhage could result from uterine atony, and it is advisable to have readily available compatible blood components along with large-bore intravenous access.

Antibiotics. Many centers will institute antibiotic therapy, especially in a parturient with premature rupture of membranes who is delivered abdominally.[106] Most antibiotic regimens use ampicillin or a cephalosporin, both of which are devoid of neuromuscular blocking potential. Use of other antibiotics with possible potentiation of neuromuscular relaxants,[107] especially in the parturient receiving magnesium sulphate, demands the use of a neuromuscular blockade monitor for efficient administration of neuromuscular blocking drugs during general anesthesia.

The results of antibiotic trials for the treatment of preterm labor have been inconsistent. In the absence of reasonable evidence, the prophylactic antibacterial therapy leads to a significant prolongation of pregnancy in the setting of preterm labor.[108] Antibiotics should be used only for protecting the neonate from group B streptococci sepsis.[109] They should not be used for the purpose of prolonging pregnancy. Meta-analyses do not support their use as prophylactic therapy.[110,111]

Oxytocin antagonists. Partial uterotonic antagonism was first demonstrated in 1960 by modifying the oxytocin molecule at position 2.[112] Further changes to the parent molecule produced a series of analogues displaying full oxytocin antagonism. One of these analogues (a deaminated O-ethyl substitution at position 2) proved to be a full antagonist in vitro; however it showed only a partial effect when tested in women.[113] This led to further development until finally a new antagonist with high receptor affinity for the oxytocin receptor in vitro and in vivo was found. Atosiban soon became the most potent analogue developed for inhibiting uterine contractions initiated by oxytocin in the human uterus.[114] Atosiban acts by competing with oxytocin for receptors in the myometrium and potentially in the decidual and fetal membranes as well. This results in inhibition of contractions and a reduction

in oxytocin-mediated prostaglandin release. Atosiban also showed a dose-related inhibition of oxytocin-stimulated inositol phosphate production and abolishment of oxytocin-stimulated increases in intracellular calcium.[114] Clinical efficacy of atosiban is comparable to beta-agonists, if not better, and has many less side-effects compared to other tocolytic drugs. This factor contributed to the tenfold higher treatment discontinuation rate in those women receiving beta-agonists compared with atosiban.[115] Furthermore, women receiving beta-agonists are far more likely to transfer to alternative tocolytic drugs. This is due to their non-specific pharmacological activity, which affect beta-receptors throughout a wide range of body systems, including the cardiovascular and metabolic systems. Indications and contraindications for the use of atosiban are almost similar to other tocolytic drugs. No toxic effects of atosiban have been reported in embryo-toxicity studies. Small amounts of metabolites of atosiban have been shown to pass in the breast milk of lactating women. The undesirable maternal side-effects were of mild severity and included nausea and vomiting, headache, flushing, tachycardia and hypertension, and hyperglycemia.[115]

The duration of treatment should not exceed 48 hours, and the total dose administered should preferably not exceed 330mg of atosiban during the full course of therapy. Atosiban is given in three stages: an initial bolus injection of 6.75 mg followed by an infusion of 0.9% NaCl with atosiban (300 μg per minutes for 3 hours); then followed by a lower dose infusion of 100 μg per minute for a maximum of 45 hours. The treatment can be repeated up to 3 times.

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