DEFINITION

According to the World Health Organization (WHO) recommendation,[1] *preterm labor is* defined as labor starting earlier than 37 completed weeks (less than 259 days) from the first day of the last menstrual period and the term *premature* should no longer be used. The term *premature* was previously defined as a birth weight of less than 2500 gm. Therefore, this will include infants of low birth weight due to early delivery or due to growth retardation but exclude infants of preterm labor that have gestational weights of more than 2500 gm such as in diabetes mellitus. The problems of the preterm infant are closely associated with chronological maturity rather than birth weight per se and it is, therefore, more meaningful to adopt the WHO nomenclature of preterm labor. Nevertheless, adoption of the term *preterm labor is* not without practical problems in pregnancies where the date of the last menstrual period is in doubt or unknown. Infants weighing less than 2500 gm are, therefore, designated as *low birth weight* (LBW).

INCIDENCE

The true incidence of preterm births varies from country to country and from one geographic region to another within a country. In 1969, the incidence of preterm births in the United States was 9.8% of all pregnancies.[2] In Britain, 6.4% of all births were preterm in 1970, compared to 3.4% of all births in East Germany in 1974.[3] Nevertheless, preterm births account for 75-85% of early neonatal deaths which are not due to lethal congenital malformations.[4] Thus preterm births represent a sizeable proportion of potentially preventable causes of perinatal mortality and morbidity in
ETIOLOGY

**Epidemiologic Factors.** A number of epidemiologic factors have been implicated as being associated with an increased frequency of preterm labor but such associations do not necessarily indicate a direct cause and effect relationship. Further, in many of the studies, there was no cut distinction between preterm and term growth retarded infants, since the definition used was premature infants (based on birth weight) or low birth weight infants. Factors that have been associated with preterm labor, but where no cause and effect relationship can be clearly demonstrated, include race, socio-economic status, marital status, use of narcotics and previous pregnancy performance such as parity, previous abortion and preterm labor, previous fetal and neonatal deaths and previous bleeding and isoimmunization. Black women have a higher incidence of preterm birth (18.6%) than white women (8.3%). In the Obstetrical Statistical Cooperative study from 1970 through 1976, non-whites had 7% of preterm low birth weight babies compared with 3.4% in whites. Women of all racial groups under 15 years of age had the highest incidence of preterm low birth weight infants while women aged 25-29 years had the lowest incidences. Boldman and Reeds noted that the incidence of low birth weight infants was increased in urban living, low per capita income, low per capita energy consumption, low newspaper circulation, lack of radio and television and low density of physicians. The "ward" (pavilion) patients had a 67-84% increase in incidence of preterm births compared with the "private" patients. Baird found that the wives of laborers had the highest incidence of low birth weight babies, with the lowest incidence in wives of farmers and wives of craftsmen and professionals somewhere in between. Unmarried whites, but not non-whites, had a 90% higher incidence of preterm births than married whites. However, illegitimate pregnancies had a higher incidence of low birth weight babies (term and preterm) for all racial groups. Smoking increases the risks for both preterm births and lower gestational age. However, parity does not seem to have a significant effect on the incidence of preterm births per se. A history of previous abortion, preterm labor, fetal and neonatal deaths, antepartum bleeding (placenta praevia and abruptio placenta) and isoimmunization are all associated with an increased incidence of preterm births. The risks of preterm labor with some of these associated factors are summarized in Figure 1.

**Etiologic Factors.** The etiologic factors that have been frequently implicated in preterm labor can be classified into four major categories: maternal, fetoplacental, uterine and iatrogenic which are listed in Table 1. The majority of cases of preterm labor are without apparent or detectable cause and are often referred to as idiopathic preterm labor. A definitely avoidable iatrogenic cause of preterm labor is elective delivery prior to term because of an error in estimated gestational age. Greater reliance on fetal ultrasonographic cephalometry and tests of fetal pulmonary maturity have greatly improved accuracy of estimating gestational age but have not totally eliminated the iatrogenic cause of preterm births. Acute systemic illness in the mother with pyrexia, such as in pyelonephritis and febrile viral infections, can cause preterm labor and the increased uterine activity has been attributed to the prostaglandins released during pyrexia. Severe chronic systemic illnesses, such as chronic renal and cardiac diseases or chronic hypertension, are known to be associated with low birth weight infants but not necessarily preterm labor. Maternal endocrine causes giving rise to preterm labor include hyperthyroidism, hyperparathyroidism and hyperadrenocorticism. Trauma and injuries to the abdomen and gravid uterus can obviously induce preterm labor. Several studies have shown that women experiencing more orgasm with coitus in late pregnancy have increased uterine activity and an increased incidence of preterm labor. Coital activity appears to be significantly greater in women having preterm labor than in women with term labor, only when there is no obvious reason for the preterm labor. The incidence of preterm labor and delivery is increased in women who have previously had preterm births or delivery of low birth weight infants. Certain genital pathogens such as mycoplasmas are isolated more frequently from the cervixes of patients with a history of preterm labor. Nevertheless, the relationship between vaginal infections and preterm labor has not been unequivocally established.
Genetic abnormalities of the fetus are associated with preterm labor and fetal death in utero usually results in delivery of the fetus within two to three weeks. Antepartum hemorrhage, from placenta praevia or abruptio placenta, is associated with an increased incidence of preterm labor.[23,25]

Uterine factors such as overdistension of the uterus from polyhydramnios or multiple pregnancies often produce increased uterine activity and result in preterm labor. Preterm labor occurs in 30-47% of twin gestation and is twice as common in women with polyhydramnios compared to those with uncomplicated pregnancy.[26] Ten percent of all preterm deliveries are accounted for by multiple pregnancies.[5] The presence of an intrauterine contraceptive device increases the risk of preterm labor.[27] In women with congenital malformation of the uterus, the incidence of preterm labor may be as high as 20%, if the pregnancy continues beyond 20 weeks' gestation. More recently, 16% of patients who had spontaneous preterm labor, without any obvious complication of pregnancy, were found to have congenital fundal abnormalities of the uterus and an additional 8% had incompetent cervix.[28] These were ultrasonographically demonstrable in the puerperium compared to women delivering at term who had no such demonstrable anomalies. Premature rupture of the membranes precedes 15 to 34% of cases of preterm labor,[5,29,30] but the crux of the problem lies in the cause of the premature rupture of the membranes as the factor responsible for initiating the premature uterine activity rather than the rupture of the membrane itself. Indeed there is some preliminary support for the contention that intraamniotic infection may initiate preterm labor without premature rupture of the membranes.[31] Mechanical dilatation of the cervix to greater than 8 mm has been held responsible for the increased risk of preterm births seen in women who had previous induced abortions.[3,32-34] With the recent enthusiasm and recommendation for dilatation and evacuation for induced abortion up to 14 to 16 weeks' gestation, cervical trauma and incompetence may constitute a significant factor accounting for preterm labor in the future.

Iatrogenic causes of preterm labor are by far frequently due to induction of labor where the duration of pregnancy can be seriously questioned or where there is an urgent need for terminating the pregnancy due to maternal or fetal interests. Certainly the threefold increase of preterm labor associated with Rh isoimmunization is partially iatrogenic.[5]

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**Table 1**

Etiologic Factors in Preterm Labor

<table>
<thead>
<tr>
<th>A. Maternal</th>
<th>B. Uterine</th>
<th>C. Fetoplacental</th>
<th>D. Iatrogenic</th>
<th>E. Idiopathic</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Endocrine Disorders</td>
<td>2. Malformation</td>
<td>2. Fetal Death</td>
<td>2. Fetal or Maternal Indication</td>
<td></td>
</tr>
<tr>
<td>3. Trauma</td>
<td>3. Infection</td>
<td>3. Abruptio Placenta</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
MECHANISM OF ONSET OF LABOR

The exact hormonal mechanisms regulating the onset and maintenance of human labor at term are not understood and that of preterm labor is even less so. Many of the hormonal mechanisms applied to humans are extrapolated from animal studies[35] and it is now clear that such data are not applicable to the parturient woman. Many endocrine changes have been demonstrated in women near or at the time of labor but consistently similar changes have not yet been demonstrated in idiopathic preterm labor. Again, the sequence of such hormonal changes has not been conclusively demonstrated in human labor at term. The mechanism of action of hormones on the uterine muscle is dependent on the availability of their receptors in the myometrium. The final mediator of myometrial contraction is at the level of intracellular free ionic calcium (Ca++) (see below). Changes in hormone level will affect myometrial function through their own receptors or induction of other hormone receptors; and, through alteration of collagen or connective tissue turnover, to render the myometrium more distensible and elastic.

Steroid Hormones. The overall uterine effect of estrogen is to increase contractility and responsiveness to other uterotonic stimuli. Circulating estrogen levels increase throughout pregnancy. It is now generally agreed in most studies that maternal estrogen levels increase in the last few weeks prior to parturition. Estrogens increase production of uterine prostaglandins which are an important uterine stimulant. Additionally, in subprimate species, estrogens have also been demonstrated to induce and increase myometrial oxytocin receptors.[36,37] In rabbits, estrogens increase the number of alpha-adrenergic receptors which mediate contraction.[38] Thus estrogens can enhance uterine activity via one or more of all these three mechanisms. On the other hand, the overall effect of progesterone has been associated with uterine quiescence. Progesterone has been shown to decrease uterine oxytocin receptors[36] and increase beta-adrenergic receptors, which are associated with uterine relaxation in animals.[38] Progesterone has also been proposed to inhibit locally the progressive increases in the active portion of the uterine wall responding to uterotonic stimuli and is responsible for the poorer elasticity of the uterus.[39,40] Except for one study showing a significant fall in maternal circulating progesterone in the last few weeks prior to spontaneous term labor, the majority of reports have been unable to demonstrate the decline.[41] Likewise, changes in the estrogen/progesterone ratio which may indirectly reflect the opposing effects of these two hormones on uterine activity could not be demonstrated both in term and preterm labor.[42] Nevertheless, a local fall in uterine progesterone may still be operative but has not yet been demonstrated in women. However, there is an increase in progesterone-binding protein in the fetal membranes in the last few weeks of pregnancy, with a decrease in the metabolism of progesterone by these membranes, thus suggesting a local intracellular fall of progesterone.[43,44] This leads to a labilization of lysosomes and release of the enzyme phospholipase A2 which promotes the generation of arachidonic acid, an obligatory precursor and the rate limiting factor in the biosynthesis of prostaglandins. Changes in both maternal peripheral plasma estrogen and progesterone levels are, therefore, at best, inconclusive and contradictory. While elevated plasma estradiol and low progesterone levels have been found by some,[44,45] others have found no change in the estrogen/progesterone ratio in women with idiopathic preterm labor.[42,46] There are no published studies examining steroid hormone levels prior to the onset of preterm labor.

Although in many animal species, release of corticosteroids appears to be an important endocrine mechanism involved in the onset of parturition, there is insufficient evidence of such a role in human labor. Earlier suggestions of increased
maternal or fetal cortisol levels in women undergoing spontaneous term labor have not been subsequently supported.

**Prostaglandins.** Both prostaglandins E2 and F2a stimulate myometrium from pregnant human uterus. There is a substantial body of evidence to indicate that prostaglandins are present during spontaneous term labor and play an important role in uterine contractions during human labor. However, it is still unclear whether prostaglandin is responsible for initiating the labor or is merely an intermediate in the much more complex endocrine hierarchical changes that must occur in order to trigger labor. Increased levels of prostaglandins and their metabolites have been found in amniotic fluid and peripheral blood in spontaneous labor.\[47-50\] However, the evidence for prostaglandins triggering idiopathic preterm labor is much less persuasive. While several studies are able to demonstrate increased prostaglandins or their metabolite in the maternal blood or amniotic fluid when preterm labor is progressive, none has shown such changes prior to the onset of preterm labor or even in those that are preterm labor which ceased to progress.\[51\] Nonetheless, preliminary studies on the use of prostaglandin inhibitors in arresting human preterm labor indicate a measurable degree of success with some of these agents.

**Oxytocin.** Oxytocin has been well established as an agent for stimulating uterine contractions and induction of labor. Oxytocin receptors have been demonstrated in human myometrium and mammary tissue\[37,52\] and, in animals, estrogens increase while progesterone decreases the uterine oxytocin receptors. There is now incontrovertible evidence for the presence of oxytocin in both the maternal and the fetal circulation, with the fetal contribution being more evident in the first stage and the maternal contribution more obvious in the second stage of labor.\[53-56\] While it is not clear if oxytocin levels are altered in preterm labor, alcohol appears to suppress the episodic release of oxytocin in term labor.\[57\] The efficacy of ethanol in the treatment of preterm labor has been credited to this mechanism of action which is more readily demonstrable in the rabbit.\[58\] The role of oxytocin in human parturition does have a novel appeal. Because the action of oxytocin is limited to a few tissues (breast and uterus), oxytocin analogues which antagonize uterine oxytocin receptors, with little or no side effects, could be developed. Indeed, there is some preliminary hope for such an antagonist which is being evaluated in laboratory animals.\[59\]

It is increasingly obvious that clinical observations suggest that the mechanism of onset of term and preterm labor involves the removal of one or more of the complex multiple systems involved in maintaining uterine quiescence and preservation of the pregnancy. The type of mechanism involved may vary from situation to situation, even in spontaneous term labor, and may thus account for the failure to explain satisfactorily and conclusively any one mechanism in all instances. Indeed this wide latitude and ability to recruit more than one mechanism to initiate labor, depending on the circumstances, may confer an advantage in the economy of human reproduction and parturition. Nevertheless, that intracellular ionic alteration, namely free ionic calcium, is the final modulator of myometrial activity can be readily accepted. It is also the final mechanism by which all modalities of arresting preterm labor ultimately work directly or indirectly. Thus it is obvious that no single method of treating preterm labor is necessarily going to be of therapeutic benefit to all women with preterm labor.

**Intracellular Regulation of Myometrial Contraction.** Myosin is the principal protein of muscle contraction. It is an enzyme that converts the chemical energy of ATP to mechanical movement during the contraction process. The types of myosins found during pregnancy are different from those during nonpregnancy and such changes in the myometrial myosin appear to be specific to pregnancy and labor.\[60\]

Calcium appears to play a central role in the regulation of muscle contractility. Calcium is stored in the sarcoplasmic reticulum and accumulation of calcium in the sarcoplasmic reticulum is an ATP-dependent enzymatic process.

In the myometrial cell, the presence of calcium promotes actin-myosin interaction (Figure 2). Myosin must be phosphorylated before it can interact with actin.\[61\] Phosphorylation of myosin is catalyzed by the activity of myosin light-chain kinase, an enzyme that is activated by calcium. Phosphorylated actomyosin causes myometrial contraction.
Myometrial relaxation occurs when the myosin is dephosphorylated by the enzyme myosin light-chain phosphatase. Actin does not recognize dephosphorylated myosin and, therefore, no interaction occurs. Thus the contractile state of the smooth muscle is the result of the relative activity of the kinase and phosphatase enzymes.

Myosin light-chain kinase is, therefore, the key regulator of smooth muscle contractility. This enzyme is modulated by three cellular regulatory systems, namely:

1. Calcium (10^-6 - 10^-7 M) is necessary for myosin light-chain kinase activity,
2. Calmodulin (calcium dependent regulatory protein) must be associated with myosin light-chain kinase activity to activate the enzyme,\[62\] and
3. Phosphorylation of the myosin light-chain kinase by cAMP dependent protein kinase inhibits myosin light-chain kinase activity.\[63\]

These three regulatory mechanisms are affected by hormones and pharmacologic agents. Prostaglandin F2a, oxytocin and acetylcholine raise intracellular calcium and, therefore, promote uterine contractility. Progesterone, cAMP and isoproterenol promote calcium uptake and, therefore, depress uterine contractility.

PREDICTION OF POTENTIAL PRETERM LABOR

The high-risk factors that are associated with preterm birth have been used by several investigators to predict preterm labor and identify such patients for special management. Such attempts have so far met with poor accuracy.\[64-67\] Using high-risk factors such as age, weight, social class, smoking, threatened or previous abortion and previous poor history, Fedrick\[66\] correctly identified only 9% of primigravida and 25% of multigravida with preterm births. In another study, preterm births were predicted three times more than what eventually occurred,\[67\] although the correctly predicted preterm births accounted for two thirds of all preterm births. Unless such predictive attempts are used only for passive management (such as restricting physical activities), active treatment (such as with prophylactic oral tocolytic agents) may unnecessarily expose those who will not go into preterm labor to unneeded treatment that is not totally innocuous. Nevertheless, such identification will put those patients that are likely to go into preterm labor into a high risk category, thus warranting closer prenatal attention.

DIAGNOSIS

When preterm labor cannot be prevented, early diagnosis is the key to successful arrest of preterm labor. However, early diagnosis is often difficult until progressive cervical dilatation has occurred. Consequently, many patients receive treatment after preterm labor has become established or when such labor has progressed to an irreversible stage. On the other hand, many patients who may not be in preterm labor may unwittingly receive potent tocolytic agents and are, therefore, unnecessarily exposed to their side effects. Hence, it is crucial that the first step is to differentiate true from false labor, preterm from term gestation and complicated from uncomplicated pregnancies. If preterm labor is diagnosed, it becomes necessary to use sound judgment to assess the relative risk of preterm parturition compared to continued pregnancy. Optimum management, therefore, requires an accurate diagnosis.

Spontaneous uterine contractions occur and increase throughout gestation. Such spontaneous uterine contractions are of two types, the regular, high-frequency and low-intensity contractions which are usually imperceptible, and the irregular, low-frequency and high-intensity (10-15 mm Hg), Braxton-Hicks contractions. The uterine contractions of established or progressive labor are characterized by increase in frequency, intensity and regularity. False labor can be distinguished from true labor by the irregular, infrequent, painless and low-intensity features of the uterine contractions.
in the former. Nevertheless, it is sometimes difficult to distinguish false from true labor, since the contractions of false labor can be painful and the uterine contractions during active labor can be irregular.[68,69] Cervical dilatation is a better distinguishing feature since dilatation occurs with established progressive true labor in response to the high-intensity, high-frequency contraction. However, there is no conclusive evidence that any significant degree of early cervical effacement and dilatation accurately differentiates active preterm labor. In more than 50% of pregnant women, the internal cervical os is dilated one finger breadth or more by 31 to 36 weeks' gestation.[70,71] It should be emphasized that early cervical dilatation is more commonly found in multiparas, one third of whom may have a cervical dilatation of two to three centimeters by late midtrimester.[72,73] Based on the study of cervical dilatation during the last four weeks prior to term, a cervical dilatation of up to 2.1 centimeters is within two standard deviations of the mean, four weeks prior to term labor.[74] Nevertheless, a couple of studies have indicated that the demonstration of frequent regular contractions (three or more contractions over a 10 minute period), cervical effacement and early cervical dilatation, not exceeding 3 to 4 centimeters, were associated with preterm births.[75,76] Using such criteria, early prediction of labor would include only 20 to 29% of cases of false labor. Therefore, to make a diagnosis of preterm labor the following criteria should be made:

1. Regular painful contractions less than 10 minutes apart and lasting at least 30 seconds. These contractions should be present for at least 60 minutes.

2. Primigravid patients with intact membranes should have at least 3 centimeters of cervical dilatation in the presence of uneffaced cervix.

3. Multiparous patients with intact membranes in whom the cervix is uneffaced should have at least four centimeters of cervical dilatation.

4. Any patient with cervical effacement of 75% or more or with progressive cervical dilatation or effacement.

One difficulty in deciding whether labor is preterm or otherwise, is the inability of patients to remember their last menstrual period and, therefore, the correct gestational age. While a fetal size of 2000 gm. or more, in the absence of any other obstetric complication, is associated with the lower morbidity and mortality, the clinical assessment of fetal weight may differ from the true weight by a significant degree (200 gm. or more) when the fetal weight is in the lower range. Thus, in patients who have irregular cycles or have forgotten their last menstrual period, ultrasonographic cephalometry becomes necessary-and also when there is apparent disparity between the gestational age and the estimated fetal weight. The traditional method for evaluation of gestational age includes the date of onset of audible fetal heart tones, the date of onset of quickening, the date of the last menstrual period, regularity of the menstrual cycle and clinical assessment of uterine size and fundal height. Patients who are unregistered or who have questionable gestational age will require other methods to determine the true gestational age. Ultrasonographic cephalometry can be used to determine fetal biparietal diameter and gestational age, but the accuracy for gestational dating is better if performed during the midtrimester. Measurements of fetal abdominal circumference, ratio of head to trunk circumferences and total intruterine volume provide additional indices of fetal weight and fetal growth. In addition, amniocentesis may be indicated to assess fetal maturity by performing the lecithin-sphingomyelin ratio, the foam test, or examining the creatinine concentration and percentage of lipid positive cells in the amniotic fluid. Between 32 and 36 weeks, amniocentesis should be considered prior to inhibition of labor, since a lecithin-sphingomyelin ratio indicative of fetal pulmonary maturity is evident in 66% of pregnancies and may mitigate against the use of labor inhibiting drugs. While only 13% of such infants of this gestational age have developed respiratory distress syndrome,[77] pulmonary maturity in the fetus does not assure maturity of other organ systems, and other problems associated with prematurity may still occur. Thus, the decision not to treat a woman in preterm labor should not be made only on the basis of her mature lecithin-sphingomyelin ratio.
MANAGEMENT OF PRETERM LABOR

The management of preterm labor can be approached from three different but non-exclusive aspects, namely:

1. Prevention of Preterm Labor

2. Inhibition and arrest of Preterm Labor

3. Improved obstetric and neonatal management of preterm infant.

Prevention of Preterm Labor. Prevention of preterm labor is probably the most effective and least expensive way of reducing preterm labor and the associated perinatal morbidity and mortality. Prevention, therefore, focuses on high-risk factors that are associated with preterm labor. These high-risk factors have been described earlier (vide supra). Appropriate family planning and counseling should reduce unwanted pregnancies. Educational and social reforms and nutritional counseling are required for low socioeconomic factors. Elimination of smoking and excessive alcohol consumption is necessary when these factors contribute to preterm labor. Early diagnosis and appropriate treatment are required for hypertension, diabetes mellitus, anemia, hyperthyroidism and urinary tract infection. Early diagnosis and bedrest are indicated in multiple pregnancies and in patients with cardiac disease, cardiovascular disorders, placenta previa, and polyhydramnios. Maternal infections require early treatment with antibiotics. Those with repeated abortions or preterm labor due to congenital malformation of the uterus require surgical correction of the anomaly. Repetitive idiopathic preterm labor and those having high-risk factors for preterm labor should probably refrain from sexual intercourse in the third trimester or at least refrain from vigorous sexual intercourse that may give rise to excessive orgasm with risk of premature uterine activity.

Uterine tocolysis has been recommended in some centers whenever a procedure is performed that could provide premature uterine activity. For example, prophylactic ethanol therapy (vide infra) has been recommended whenever a cervical cerclage, appendectomy or other pelvic surgical procedure is performed during pregnancy. More recently 17α-hydroxyprogesterone caproate has been suggested for prophylaxis of preterm labor in women at high risk for preterm delivery (vide infra). While prevention of preterm labor may reduce a proportion of the patients at risk for preterm labor, it is unlikely to eliminate preterm labor. The scoring methods for identifying patients at high-risk for preterm labor have been found to lack the required sensitivity. Consequently, inhibition of preterm labor will continue to be necessary for treating those that present with premature uterine activity.

Inhibition of Uterine Activity. While continued intrauterine residence is in the best interest of the fetus for many patients with preterm labor, it is necessary to decide which pregnancies will benefit from such continuation and which ones will fare equally well with an extrauterine existence. With the progress and improvement made in the survival of low birth weight infants, it may not be necessary, in patients from 35 completed weeks of gestational age and with an estimated fetal weight of 2000 grams or more, to have arrest of their preterm labor. Additionally, inhibition of premature uterine activity should not be undertaken in the presence of certain prenatal complications such as premature rupture of the membranes, abruptio placentae, maternal genital or intrauterine infections, severe lethal congenital malformations and fetal death in utero.

Suppression of preterm labor may be for a short interval of up to 48 hours, to permit induction of fetal lung maturity by administering glucocorticoids to the mother or, for longer intervals, until the fetus is mature enough to warrant a safer extrauterine rather than continued intrauterine existence.

The efficacy of any modality of treatment for preterm labor can only be assessed in terms of subsequent clinical development, since the exact mechanism triggering the onset of term and preterm labor is incompletely understood.
Therefore, there is a wide margin of error in the accurate diagnosis of preterm labor sufficiently early enough for treatment to be effective (see discussion on diagnosis). There is considerable variation in the criteria adopted by individual physicians for diagnosing preterm labor, resulting in either overtreatment, early intervention or late intervention. Thus, success rates are greater among those providing treatment in unindicated cases, while those who intervene only after irreversible cervical effacement and dilatation have occurred will obtain less impressive results. Additionally, proper patient selection and suitable controls will influence the efficacy rates obtained by different investigators, while the therapeutic benefit, if any, of bed rest, hydration and mild sedation is undefined. Because these variables can influence the outcome of treatment, the efficacy of any modality for inhibiting preterm labor should be evaluated with these variables in mind. Therefore, randomized double blind controlled clinical trials, involving a sizeable number of patients with preterm labor, are essential in order to prove the efficacy of the various tocolytic agents used. This is not the case with many of the agents that are currently used. A critical analysis of 18 controlled clinical trials on the benefit of prevention and treatment of preterm labor with drugs, found only 13 of them methodologically adequate.[78] In spite of the postponement of delivery in some of these trials, only two of them favorably affected the outcome for the infant. Thus currently used indices and end-point for inhibition and arrest of preterm labor are not adequate enough to provide discrimination in the ultimate outcome of the infant, which is the final objective in the management of preterm labor.

**Beta Adrenergic Receptor Stimulants (beta mimetic agents).** In 1948, Ahlquist[79] demonstrated two kinds of adrenergic receptors, alpha and beta. Alpha receptor stimulation usually produces vasoconstriction while beta receptor stimulation produces vasodilatation and cardiac stimulation. Beta receptors can be further separated into two types, beta-1 receptors, the characteristic response of which is cardiac acceleration and lipolysis and beta-2 receptors, stimulation of which produces bronchial dilatation, vasodilatation and muscle glycogenolysis. Beta-2 receptors dominate the smooth muscle of the uterus, blood vessels, bronchioles, and diaphragm, while beta-1 are predominantly found in the heart, small intestine and adipose tissue. Any substance that is structurally similar to the naturally occurring catecholamines, epinephrine and norepinephrine will stimulate beta adrenergic receptors. The chemical structure of epinephrine and a variety of beta-mimetic agents are given in Figure 3. Basically these agents are structurally similar to epinephrine and differ only in 5.3 substitutions on the aromatic ring, the alpha and beta carbon and the amino group. Beta receptor activity is enhanced with increase in the size of the alkyl substitution at the amino group, while selectivity and specificity for beta-2 adrenergic receptors are improved with large amino group substitutions. Further selectivity and specificity for beta-2 receptors can be enhanced by hydroxyl groups at positions three and five of the aromatic ring and the presence of large amino substitutions. Substitution on the alpha carbon prolongs the duration of action of these compounds by oxidizing the monoamine oxidase inhibitor. The beta-mimetic agents such as isoxsuprine, orciprenaline, and isoprenaline are being overtaken by newer agents such as fenoterol, ritodrine, salbutamol and terbutaline, all of which are longer lasting, more specific for beta-2 receptors in the uterine muscle and carry less serious side effects.

At the cellular level, beta-2 receptor stimulant or agonist is coupled to adrenergic beta-2 receptor on the surface of the myometrial cell after which adenylyl cyclase is activated. Adenylyl cyclase catalyzes the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). Cyclic AMP then increases the activity of the enzyme protein kinase which is active in phosphorylation of proteins in the cell membrane. This increases the uptake and sequestration of intracellular calcium (Figure 2). The reduction of intracellular calcium is the final mediator in preventing activation of the contractile proteins of the muscle cell, thus resulting in muscle relaxation.

The ideal beta adrenergic agonist would be one that mainly influences the beta-2 receptors of the uterus with little or no influence on the beta receptors of the heart and blood vessels, so that minimum cardiovascular side effects will occur. However, all the currently available beta-mimetic agents do influence beta receptors of the heart and blood vessels to varying degrees but with clinically observable cardiovascular side effects of variable intensity. Even with agents that have predominantly beta-2 effects, hypotension secondary to relaxation of the vascular smooth muscle, which is predominantly served with the beta-2 adrenergic receptors, induces reflex cardioacceleration with a rise in cardiac output and blood pressure.
Ritodrine hydrochloride is a beta adrenergic stimulant with predominant effects upon beta-2 receptors and is a potent uterine relaxant with only minor cardiovascular and bronchial effects. The pharmacokinetics of ritodrine are summarized in Table 2. It was approved by the F.D.A. for use in treatment of preterm labor in the fall of 1979 and is currently the only agent approved by the F. D. A., among the variety of tocolytic agents that are being used for therapy of preterm labor.

In the U.S.A., a multicenter phase III clinical evaluation of ritodrine against ethanol and placebo for treatment of preterm labor was carried out on 366 patients.\cite{80} Of 313 singleton pregnancies with intact amniotic membranes, neonatal deaths and respiratory distress syndrome were significantly reduced with ritodrine treatment compared with control patients and pregnancy was significantly prolonged with ritodrine (41 days) compared with controls (24 days).\cite{80} More pregnancies reached greater than 36 weeks and more babies were delivered weighing more than 2500 grams with ritodrine treatment. Prior to the multicenter report, several of the participating investigators had reported their results based on small groups of patients. In a European multicenter double-blind study, ritodrine was found to be more effective in prolonging pregnancy in preterm labor than a placebo.\cite{81} In another study, ritodrine was more effective than chlordiazepoxide.\cite{82} Other uncontrolled studies have also suggested that ritodrine is effective in inhibiting preterm labor.\cite{83-86} An advantage of ritodrine is the reduction in respiratory distress syndrome seen in preterm infants whose mothers were treated with ritodrine, compared with controls.\cite{80,87}

### Table 2

**Pharmacokinetics of Ritodrine in Humans**

<table>
<thead>
<tr>
<th>A. Half-Lives</th>
<th>1. Oral Dose</th>
<th>First $t_{1/2}$</th>
<th>1.3 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Second $t_{1/2}$</td>
<td>12 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Intravenous Dose</td>
<td>First $t_{1/2}$</td>
<td>6-9 mins.</td>
</tr>
<tr>
<td></td>
<td>Second $t_{1/2}$</td>
<td>1.7-2.6 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Third $t_{1/2}$</td>
<td>3 hours</td>
<td></td>
</tr>
<tr>
<td>B. Excretion</td>
<td>Orally and intravenously -- 71-93% excreted in urine within 1 hour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. Transplacental Passage</td>
<td>Yes - Fetal blood levels 20% that of mother</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Ritodrine has been given intravenously, intramuscularly and orally for treatment of preterm labor. The dose regime for the two widely recommended routes are summarized in Table 3. The usual intravenous dose is 50-200 mcg per minute for 24 to 48 hours and can be titrated until uterine contractions are suppressed, after which the dose is maintained. Oral therapy can subsequently be commenced at 10-20 mg, 4-8 times daily starting 1/2-1 hour before stopping intravenous therapy and can be given until 36-38 weeks gestation.

The clinical side effects of ritodrine are more related to its action as a beta-mimetic compound. Elevation of maternal heart rate, increased pulse pressure, moderate decrease of serum potassium, transient elevation of blood glucose and plasma insulin have been documented. Thus the use of ritodrine in pregnant diabetics demands careful monitoring of their blood glucose levels to avoid ketoacidosis. Minor but frequent side effects include tremor (10-15%), palpitations (33%), nervousness (5-10%) and restlessness (5-10%). Side effects are generally rarely encountered during oral therapy. Only two maternal deaths, neither of which was related to the drug, have so far been reported in more than 480,000 patients treated.[80] Four patients have so far developed idiopathic pulmonary hypertension during treatment with ritodrine and corticosteroids. Contraindications to the use of ritodrine include overt cardiovascular disease and hyperthyroidism.

### Table 3

**Dose Regimen of Ritodine Hydrochloride for Treatment of Preterm Labor**

<table>
<thead>
<tr>
<th>A. Intravenous Infusion</th>
<th>1) Initial Dose: 50-100 mcg/min.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2) Increase by 50 mcg/min. every 10 min. until contractions stop or side effects occur.</td>
</tr>
<tr>
<td></td>
<td>3) Continue for 12 hours after contractions stop. 4) Maximum dose 350 mcg/min.</td>
</tr>
<tr>
<td>B. Oral Therapy:</td>
<td>1) Initial dose-10 mg, 1/2-1 hour before stopping IN. treatment.</td>
</tr>
<tr>
<td></td>
<td>2) 20 mg every 4 hours for 24 hours.</td>
</tr>
<tr>
<td></td>
<td>3) 10-20 mg every 4-6 hours thereafter if uterus quiescent.</td>
</tr>
<tr>
<td></td>
<td>4) Maximum dose-120 mg/day.</td>
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</tbody>
</table>

Isoxsuprine is probably among the earliest beta-receptor agonists which have been used for arresting preterm labor. Isoxsuprine inhibits spontaneous and oxytocin induced uterine activity both *in vitro* and *in vivo* during term labor.[89,90]
An efficacy rate of 72% of preterm labor being postponed by more than seven days was reported in two uncontrolled studies.[75,91] Uncontrolled studies have also demonstrated the efficacy of isoxsuprine in arresting preterm labor[92,93] but if the agent is infused only for one hour as opposed to 4 hours, then its efficacy is lost.[94] The usual dose of isoxsuprine for the treatment of preterm labor is 0.25 to 0.5 mg per minute intravenously and the rate and duration of infusion are adjusted according to suppression of uterine activity or development of maternal cardiovascular side effects. The patient should be placed in the lateral supine position to minimize the hypotensive side effects. After cessation of intravenous infusion the drug can be given intramuscularly, 5 to 20 mg every 3 to 6 hours and then orally after 24 hours. Side effects of isoxsuprine include maternal tachycardia, hypotension, nausea, sweating, drowsiness and headaches. An increase of fetal heart rate by 10 to 20 beats per minute has been observed.

Terbutaline has been shown to be effective in inhibiting myometrial contraction in vitro and in vivo during spontaneous and oxytocin augmented labor at term.[95,96] In two uncontrolled studies[97,98] and one small double-blind study,[76] terbutaline was found to be effective in treating preterm labor in women with intact membranes. In the double-blind study, terbutaline successfully maintained the pregnancies to the 37th week in 80% of patients while in the placebo group it was only 20%.[76] The dose of terbutaline used is 10 mcg per minute initially and is increased by 5 mcg per minute every 10 minutes up to a maximum of 25 mcg per minute or until uterine contractions cease -- whichever occurs first. This dose is maintained for 60 minutes once the contractions stop, after which the maintenance dose is decreased by 5 mcg every 30 minutes to the lowest effective dose. The lowered maintenance dose is continued for 8 hours if uterine contractions have completely stopped. After intravenous therapy, 250 mcg terbutaline is given intramuscularly four times a day for three days. The oral dose of 15 mg per day is given at the same time and maintained until 36 weeks' gestation.

Other Beta Adrenergic Agonists. Salbutamol[99] and fenoterol[100] were found to be useful in preterm labor but have not been rigorously evaluated in controlled trials. In a comparative study between buphenin, fenoterol and ritodrine, these three agents showed no difference in the prolongation of pregnancy.[101] Another study comparing fenoterol, hexoprenaline, ritodrine and salbutamol found that hexoprenaline produced the least effect on the maternal cardiovascular system but similar effects in prolongation of pregnancy.[102]

The long term effects of beta-mimetic agents on the infant, if any, have not been extensively looked into. In two studies, there appears to be no significant differences in body weights of the infants up to 18 months of age compared with controls.[103,104] However, both studies found some infants with central nervous system compromise such as cerebral palsy, intracranial hemorrhage and hemiparesis. Although the possible long term negative effects of the beta-mimetics should be closely monitored, it should be emphasized that preterm infants, even when the mothers are not treated to stop the preterm birth, have a much higher risk and incidence of such complications.

Ethanol. The use of ethanol for inhibiting human preterm labor stems partially from studies in pregnant rabbits at term, demonstrating that the release of bioassayable endogenous oxytocin at parturition could be effectively inhibited by ethanol in this species.[58] These observations have been confirmed both during parturition and lactation using more sensitive and specific radioimmunoassays of oxytocin.[105] The observation that intravenous ethanol could successfully postpone delivery in pregnant rabbits at term[106] was then applied to the treatment of human preterm labor.[107,108]

While the mechanisms of action of ethanol in the rabbit could be clearly shown to be the suppression of oxytocin, the mode of action of ethanol inhibiting human preterm uterine contractions is less well defined. It has been proposed that the mechanism of action of ethanol in suppressing human preterm labor is through inhibition of oxytocin release by the neurohypophysis. Such a proposed mode of action of ethanol has only been indirectly supported by the reduction in the frequency of episodic release of oxytocin, when ethanol is given to pregnant women in spontaneous labor at term.[57] This observation is for term labor and thus the thesis that ethanol suppresses neurohypophysial release of oxytocin in human preterm labor is, at best, unproven. Ethanol may have some direct action on the myometrial activity probably via
a reversible interaction with the calcium ions in the myometrial cells.\textsuperscript{[109]}

The efficacy of ethanol in treating preterm labor has been explored by several investigators.\textsuperscript{[94,107,108,110,113]} In two uncontrolled studies of 52 and 50 human preterm labors with intact membranes, success rates of 67-68\% respectively have been reported\textsuperscript{[107,110]} but in a similar uncontrolled study of 15 patients, Graff\textsuperscript{[111]} obtained only 7\% success in postponing delivery by 3 or more days. Similarly, in controlled studies, it has not been the uniform experience that ethanol was more successful than either glucose or barbiturates in postponing delivery in preterm labor (Table 4). Indeed, except for one study showing a significantly higher success rate with ethanol in postponing preterm birth,\textsuperscript{[108]} three subsequent studies showed no difference between the control group and the ethanol treated group (Table 4).\textsuperscript{[94,112,113]}

Such differences in success rate stem in part from differences in the criteria for the diagnosis of preterm labor and the ethanol dosage regime but essentially underscores the difficulty in diagnosing early preterm labor from false labor. Although the published data provide conflicting conclusions on the ability of ethanol to postpone preterm births for more than 3 days, it is generally accepted that ethanol is effective in suppressing preterm labor for at least 24-48 hours, when the membranes are intact and the cervix is less than 4 centimeters dilated. With preterm rupture of the membranes, published experiences indicate successful postponement of delivery for 24-48 hours.\textsuperscript{[107,111]}

Ethanol can be given both orally and intravenously in the treatment of preterm birth. Generally, the intravenous route is preferable for the treatment of preterm labor, since a more steady and constant blood level of ethanol can be readily achieved. Nevertheless, oral administration has been and can be used at home, if required. The protocol for the dosage of ethanol recommended in preterm labor is given in Table 5. It is noteworthy that the maximum length of time for administration of intravenous ethanol for preterm labor is 12 hours and can be repeated again. Generally, it is best to continue the ethanol infusion for several hours after cessation of uterine contractions. It is important to emphasize that if ethanol is administered again within 10 hours of the last ethanol treatment, the loading or initial dose of ethanol should be adjusted approximately as shown in Table 5. The dose of ethanol recommended has been calculated to produce a blood level of 120-180 mg/dl.

\textbf{Table 4}

\textbf{Controlled Studies of Ethanol in Treatment of Preterm Labor with Intact Membranes}

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of Patients</th>
<th>Agent Used</th>
<th>Success (%)</th>
<th>No. of Patients</th>
<th>Success (%)</th>
</tr>
</thead>
</table>

Historical Review and Recent Advances - Chapter 10

Table 5

Dose Regimen of Intravenous Ethanol for Treatment of Preterm Labor

<table>
<thead>
<tr>
<th>Initial Treatment</th>
<th>Loading Dose: 7.5 ml of 10% ethanol solution per kg body weight x 2 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance Dose</td>
<td>Maintenance Dose: 1.5 ml of 10% ethanol solution per kg body weight x 10 hours</td>
</tr>
<tr>
<td>Repeat Treatment</td>
<td>Loading Dose: 10% original dose x n (n = number of hours since discontinuation of ethanol)</td>
</tr>
<tr>
<td>Maintenance Dose</td>
<td>Maintenance Dose: As in initial treatment</td>
</tr>
</tbody>
</table>

Treatment with intravenous ethanol necessitates constant supervision of these patients. Maternal side effects include intoxication with blood concentrations of 100 to 150 mg/dl, anesthesia with blood levels of 250-300 mg/dl, and coma with levels of more than 350 mg/dl. With the dose regime of ethanol for treatment of premature labor, most women are overtly intoxicated and usually experience nausea, vomiting, crying and restlessness and some degree of respiratory depression. Such side effects carry the hazards of aspiration pneumonitis. Ethanol affects metabolism in a variety of ways. Suppression of gluconeogenesis and significant hypoglycemia can occur, if there is depletion of hepatic glycogen from a fasting state. Maternal lactic acidosis has been reported- and dehydration with electrolyte disturbance may occur. Hypotension and urinary incontinence, although uncommon, can occur.
Since ethanol readily crosses the placenta to reach the fetal circulation within a minute, it is, therefore, present in the newborn if the maternal blood ethanol levels are high. Preterm infants are at a higher risk of developing respiratory distress syndrome[117] and may be intoxicated at birth or have marked suppression of the central nervous system if depressant medications are given. Therefore, it is prudent that treatment with ethanol be stopped if preterm labor is imminent in spite of treatment. However, maternal treatment with ethanol appears to reduce the risk of respiratory distress syndrome in the newborn, if the ethanol has been eliminated by the mother and the fetus." Two premature infants with abnormal bone marrow morphology associated with maternal alcohol infusion have been reported.[119] Metabolic acidosis, muscular hypotonia, lethargy and apnea have also been noted.[120,121]

Contraindications to the use of ethanol for preterm labor include patients with decompensated liver disease, maternal or fetal acidosis and reformed alcoholics. General anesthesia and narcotic medications should preferably be avoided when ethanol is given to stop labor. Ethanol will shorten the half-lives of diphenylhydantoin and warfarin and should be used cautiously in diabetic patients because of ethanol induced hypoglycemia due to suppression of gluconeogenesis.

**Prostaglandin Synthetase Inhibitor.** Prostaglandins have been shown to be synthesized and released from the decidua and fetal membranes in spontaneous human term labor[122] and are able to induce uterine contractions throughout pregnancy. Thus attention has been focused on inhibiting the synthesis of prostaglandins by the use of prostaglandin synthetase inhibitors (PGSI) to arrest preterm labor. The mode of action of many of the PGSI is to suppress the activity of the prostaglandin synthetase enzymes which are necessary for the conversion of the essential precursor fatty acid, arachidonic acid, to cyclic endoperoxides and then to prostaglandins F and E (Figure 4). Specifically most of the PGSI inhibit the enzyme cyclo-oxygenase which is required for the bioconversion of arachidonic acid to cyclic endoperoxides.

Initial observations in rats showed that PGSI inhibit the synthesis and release of prostaglandins from uterine muscle in vitro and spontaneous uterine contractions in the rat. PGSI delayed the onset of labor in rats, subhuman primates,[123] and in humans.[124]

Several studies, most of which were uncontrolled, have used indomethacin (daily oral doses of 100 mg or daily rectal doses of 200 mg), aspirin, flufenamic acid and naproxen and found that they prolonged pregnancy in human preterm labor (Table 6).[125-133] In a small controlled study, indomethacin given for 24 hours was shown to be significantly better than a placebo for arresting preterm labor.[130] In another controlled study, oral or rectal indomethacin, given over a prolonged period of time, successfully postponed delivery by a mean interval of 43 days in 51 patients with preterm labor, including premature rupture of the membranes, twin gestation and quadruplet pregnancy. In spite of the promising results in preterm labor, there is considerable reservation about the effect of the PGSI on the fetus. Van Kets, et al.[132] had 3 out of 8 perinatal deaths which were possibly related to the drug among 51 preterm labor patients treated with indomethacin. One fetus was macerated, one had *Escherichia coli* sepsis and the third had an intraventricular hemorrhage with an atrial septal defect.

**Table 6**

**Clinical Trials of Prostaglandin Synthetase Inhibitors for Treatment of Preterm Labor**
Indomethacin crosses the placenta freely and fetal circulatory levels equilibrate with those of the maternal blood levels by 5 hours after oral administration. The half-life of indomethacin in the newborn (14.7 hours) is 7 times longer than in the nonpregnant adult (2.2 hours).[^134] Thus indomethacin may inhibit biosynthesis of prostaglandins in fetal tissues with serious developmental and functional sequelae. Perinatal hemorrhage due to impaired platelet aggregation[^135] and constriction of feto-maternal vessels via contraction of the smooth muscle are potential risks when a PGSI is used for postponing preterm births. Other potential risks include premature closure of the ductus arteriosus with resulting pulmonary hypertension and cardiac failure.[^136] Nevertheless, only 3 cases of drug-related premature closure of the ductus have been reported.[^126] An infant with tricuspid insufficiency and severe heart failure was reported after 10 days of maternal treatment with salicylates prior to delivery.[^137] Administration of indomethacin to the mother, up to 15 times the dose used in humans, produced intrauterine narrowing of the fetal ductus arteriosus in rats.[^138] It appears that the gestational age when PGSI is given to the mother is an important variable influencing its effect on closure of the ductus arteriosus. Therefore, at present, routine clinical use of PGSI for arresting preterm labor and prolonging pregnancy cannot be advocated until carefully designed double blind clinical studies, involving a substantial number of patients, are undertaken to demonstrate both the efficacy and safety of these agents in the treatment of labor.

**Magnesium Sulfate.** Magnesium sulfate decreases uterine activity and in one study this compound was successful in arresting preterm labor in 77% of patients compared with 45% with alcohol treatment and 44% with dextrose solution.[^113] A potential but real side effect of magnesium sulfate is central nervous system depression. Thus, the patients

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[^135]: Perinatal hemorrhage due to impaired platelet aggregation and constriction of feto-maternal vessels via contraction of the smooth muscle are potential risks when a PGSI is used for postponing preterm births.

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[^138]: It appears that the gestational age when PGSI is given to the mother is an important variable influencing its effect on closure of the ductus arteriosus.
should be monitored for loss of deep tendon reflexes and respiratory depression. It is preferable that the magnesium sulfate is not infused for more than 24 hours, because the newborn infant may exhibit signs of hypermagnesemia which includes loss of muscle tone and drowsiness when such prolonged administration is given.\[139\] The excretion of magnesium by the newborn infant is considerably slower than that of adults. The dose of magnesium sulfate as used by Steer and Petrie[113] is 4 grams of 10% solution of magnesium sulfate given intravenously as an initial loading dose. The injection is given slowly to avoid flushing and vomiting. A maintenance intravenous infusion dose of 2 grams per hour is then given until uterine contractions stop or until labor becomes irreversible. The maintenance infusion can be Restarted if contractions reappear after stopping. The ability of magnesium sulfate to inhibit pregnant human myometrium is related to the dose given. Magnesium sulfate concentration of 9.6 to 12.0 mg/dl will effectively arrest uterine contractions.\[140-142\] It should be emphasized that magnesium sulfate is a relatively safe agent and its efficacy in inhibiting uterine contractions during pregnancy makes it a suitable agent for treatment of preterm labor. However, more adequate controlled studies in patients with preterm labor are necessary to determine the usefulness of magnesium sulfate in the treatment of preterm labor.

**Diazoxide.** Diazoxide, a powerful antihypertensive agent was found to inhibit uterine contractions during pregnancy.\[143\] Diazoxide is a benzothiadiazine which is structurally similar to the thiazide diuretic but does not possess its diuretic properties. It inhibits spontaneous uterine muscle contraction in pregnant women both in vitro and in vivo. Although diazoxide is similar to the beta-mimetic agent in its cardiovascular effects and metabolic effects, it is not considered a beta-adrenergic agonist because its betamimetic effects are not blocked by beta-adrenergic blockade. Preliminary data suggest that diazoxide can inhibit preterm labor effectively.\[144,145\] However, extensive evaluation in controlled studies has not been reported on the use of diazoxide in preterm labor. In rats and baboons, diazoxide is able to prolong their pregnancies.

In general, it is recommended that diazoxide be infused slowly in low doses so as to reduce the cardiovascular effects. A dose of 300 mg intravenously over 15 minutes appears to produce only mild cardiovascular effects. Side effects of diazoxide include lowering of blood pressure and an increase of heart rate, cardiac output, stroke volume, and blood flow through the coronary, femoral and renal vessels. Urinary excretion of sodium, water, potassium chloride, bicarbonate and uric acid are reduced but secretion of renin is increased. Diazoxide probably inhibits insulin release and, therefore, blood sugar is increased. Hypoglycemia may occur in the neonate. Alopecia and hypertrichosis lanuginosa have been noted in some infants whose mothers were given diazoxide. Diazoxide is contraindicated in patients with compensated hypertension (coarctation of aorta), women with coronary insufficiency, myocardial infarction, congestive heart failure or cardiac arrhythmias.

**Hormone Therapy.** Progesterone and progestins suppress myometrial contractions by elevating the excitation threshold and, therefore, could prolong pregnancy.\[146,147\] On the other hand, estrogens decrease the excitation threshold of contraction in the myometrium. In women, there have been suggestions that there is a fall in circulating progesterone and a rise in estrogen at the approach or onset of labor. However, a majority of publications in this area indicate that there is no convincing fall in circulating estrogen levels at the approach of labor but a rise in estrogen level is much more readily agreed upon. This hypothesis has been extended to premature labor and several investigators have attempted to show either elevated circulating estrogen levels or a fall in progesterone levels in patients with preterm labor.\[146,148,149\] None of these studies have convincingly and conclusively demonstrated that either is the case with preterm labor in the human. Neither has the arrest of preterm labor with any of the modalities of treatment used so far demonstrated a reversal of the alteration in either circulating estrogen or progesterone occurring pari passu with the inhibition of the uterine contractions. It is thought that restoration of progesterone dominance will result in uterine quiescence,\[146\] but several double-blind control studies using progesterone or medroxyprogesterone acetate have uniformly failed to demonstrate any labor-suppressing effect of progesterone in human preterm labor.\[148-149\] More recently, based on a very small number of patients who were at risk...
for preterm labor, it was found that 17α-hydroxyprogesterone caproate (Delalutin) was significantly more effective than a placebo in preventing preterm delivery. If the true incidence of preterm labor is taken into consideration, as well as the accuracy of several risk scoring systems that have been applied for predicting preterm labor, then it is quite obvious that any efficacy of prophylactic treatment in preventing preterm birth in this group of patients has to be demonstrated in a large number of patients, so as to obviate inappropriate results from inadequate sample size. No adverse neonatal effects were seen in the offspring of 17α-hydroxyprogesterone caproate treated patients and the drug was given from the 16th week of pregnancy in doses of 250 mg once a week, until the 36th week of pregnancy or until delivery. The long term effects of such treatment on the genital tract and pituitary gonadal axis of the offspring remain to be determined. The experience of diethylstilbestrol on the reproductive tract of the offspring of mothers treated with this compound should caution us against use of hormonal agents before their efficacy and safety for a particular purpose are well established. Finally, the dose of progesterone or 17α-hydroxyprogesterone caproate is small compared to the daily production rate of progesterone during either early or late pregnancy. Therefore, at present, hormonal therapy to arrest preterm labor cannot be advocated as the first line of treatment, until incontrovertible data on its efficacy and safety are produced.

Calcium Antagonists. In preliminary studies from Europe, calcium antagonists have been found to be effective in postponing preterm births. In one study, ten patients with preterm labor treated with the calcium antagonist, nifedipine, had their preterm labor arrested and delivery was postponed by a mean interval of 14 days, after 3 days of treatment with nifedipine. In another study the calcium antagonist was used together with a betaadrenergic agonist. The calcium antagonist was claimed to have reduced cardiovascular effects and may have potentiated the uterine tocolytic effect of the beta-agonist. Thus far, there are no control studies of calcium antagonists in the treatment of human preterm labor. No serious side effects, either on the mother or fetus, were observed with the calcium antagonists. Maternal heart rate may increase transiently by 10 to 25 beats per minute.

IMMINENT PRETERM BIRTH

The mode of delivery for the preterm fetus remains controversial, since incontrovertible data supporting either vaginal or abdominal delivery are not readily available. The mode of delivery for the preterm fetus is determined to some extent by the presentation (breech versus cephalic), the fetal weight and gestational age.

Preterm Cephalic Presentation. There is even less consensus for the optimal route of delivery in the preterm vertex presentation compared with the preterm breech. Cesarean section significantly improved the neonatal survival of the very low birth weight infants, but vaginal delivery also has advantages, such as the fetal chest compression facilitating lung expansion and the more complete placental transfusion to the fetus. Thus it is evident that cesarean section should be more liberally used in the delivery of the preterm vertex. Nevertheless, cesarean section is probably more indicated in those below 30 weeks gestation, while those infants greater than 32 weeks’ gestation who carry a lower risk of immaturity may be delivered vaginally. If vaginal delivery is permitted, a generous episiotomy should be done and outlet forceps liberally used to protect the less rigid fetal skull.

During labor, the preterm fetus should be monitored with continuous fetal heart recording. It is noteworthy that the heart rate is slightly higher with lower gestational age. Cesarean section should be performed if there is any evidence of impending fetal asphyxia which contributes to the development of respiratory distress syndrome. Prophylactic use of barbiturates, analgesics and sedatives which have been shown to have brain-protective effects against hypoxia, by lowering cerebral metabolism, have been recommended but others have pointed to the adverse effect of these agents on infant behavior. At present, routine use of these agents in preterm births cannot be recommended until more conclusive data are available.

Preterm Breech. Breech presentation is more frequent in preterm labor with an incidence of 25% at 28 weeks' gestation
compared with 2-3% at term. The preterm breech has a poorer perinatal outcome, which is related to the route of delivery resulting in birth trauma and asphyxia and also to the higher incidence of congenital malformations. The corrected perinatal mortality of preterm breeches is three times higher and the Apgar scores significantly lower with vaginal delivery than with cesarean section.\cite{156,157} Because of this increased neonatal morbidity and mortality, cesarean section should be recommended for preterm births, except when major congenital malformations that are incompatible with survival or excessively small size infants (below 750 grams) are found.\cite{158} The lower limit of fetal weight to be selected for cesarean will have to be determined according to the neonatal mortality and survival statistics of each intensive care nursery. Nevertheless, some workers have pointed out that cesarean section is not invariably required for the preterm frank or complete breech fetus.\cite{150}

**INDUCTION OF FETAL LUNG MATURATION**

Many studies on human pregnancy have indicated that the administration of glucocorticoid to the mother resulted in a reduction of the incidence of respiratory distress syndrome.\cite{159-172} These studies provide compelling evidence for the efficacy of glucocorticoid in inducing fetal lung maturation and, therefore, reducing the risks of respiratory distress syndrome. The effectiveness of glucocorticoid in inducing fetal lung maturation is more obvious for pregnancies of less than 32 weeks' gestational age, but less evident when the pregnancy is more than 32 weeks. Besides gestational age, Apgar score at birth and a traumatic delivery of the small preterm fetus are important determinants in the risk of developing respiratory distress syndrome. Glucocorticoid receptors are found in most fetal tissues but are in greater concentration in the fetal lung. Some glucocorticoids cross the placenta much more readily than others and some of them have a greater affinity for binding to fetal lung glucocorticoid receptors. In this respect, dexamethasone and betamethasone cross the placenta readily to produce adequate circulating levels in the fetus. Both dexamethasone and betamethasone have a higher affinity for binding to glucocorticoid receptors in the fetal lung and have longer plasma and biological half-lives compared with hydrocortisone, triamcinolone and methyl prednisolone. Based on currently available data, the administration of glucocorticoid to induced fetal maturation is probably indicated in preterm labors occurring before the 32nd week of gestation, if preterm birth is imminent. Because the risk of such glucocorticoid therapy, if any, has not been clearly defined, the use of such therapy to accelerate fetal lung maturation in preterm labor after 32 weeks' gestation remains debatable. The transplacental passage of betamethasone and dexamethasone and the presence of glucocorticoid receptors in many fetal tissues are factors that would dissuade this author from the routine use of glucocorticoid after the 32nd week of gestation in preterm labor, until conclusive data on its efficacy and safety are established. If betamethasone is given, the usual dose used in most studies has been 12 mg twice a day for 48 hours, while the dose for dexamethasone is between 8 and 12 mg daily for up to three days.
Figure 1. High risk factors associated with preterm delivery (Drawn from data of obstetrical statistical cooperative study.)

Figure 2. Interaction of calcium with actin and myosin in the myometrial cell to cause myometrial contraction.
Figure 3. Chemical structure of epinephrine and beta-mimetic agents that can inhibit uterine contractions.

Figure 4. Scheme for the biosynthesis of prostaglandins (E and F) and the site of action of prostaglandin synthetase inhibitors.

1. Site of action of Type I prostaglandin synthetase inhibitors such as indomethacin, fenamates, and ibuprofen.

2. Site of action of Type II prostaglandin synthetase inhibitors such as phenylbutazone.

REFERENCES


