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CLINICAL PRACTICE GUIDELINES

Management of Preterm Labour



NMRC
National Medical
Research Council



Chapter of Obstetricians
and Gynaecologists
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**Management of
Preterm Labour**

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Statement of Intent

These guidelines are not intended to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances and patterns of care evolve.

The contents of this publication are guidelines to clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care. Each physician is ultimately responsible for the management of his/her unique patient in the light of the clinical data presented by the patient and the diagnostic and treatment options available.

Foreword

Preterm birth is a major contributor to perinatal mortality and morbidity in developed countries. Approximately 6% of singleton births in Singapore occur at a gestation period of less than 37 weeks. Optimal management of preterm labour is crucial in reducing the perinatal morbidity and mortality associated with premature delivery. Doctors and other healthcare staff involved in the care of the pregnant patient must be aware of the risk factors and methods available to predict preterm labour.

In view of the compelling evidence for the use of intravenous tocolytic agents and maternal corticosteroid administration in improving perinatal outcome, all clinicians involved in the management of patients presenting with premature labour should be familiar with their use as recommended in these guidelines.

We are pleased to present these guidelines on the *Management of Preterm Labour* which were developed by the Chapter of Obstetricians and Gynaecologists, Academy of Medicine, Singapore for your reference.

PROFESSOR TAN CHORH CHUAN
DIRECTOR OF MEDICAL SERVICES

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1 Guideline development and objectives

1.1 Introduction

Preterm delivery is the major cause of perinatal mortality in the developed world and occurs in approximately 7% of all deliveries. Severe morbidity, especially respiratory distress syndrome, intraventricular haemorrhage, bronchopulmonary dysplasia and necrotising enterocolitis, are far more common in preterm infants than in term infants. Long-term impairments such as cerebral palsy, visual impairment and hearing loss are also more common in preterm infants.

1.2 Objectives

These guidelines aim to address the following issues:

- Prevention of preterm labour
- Prediction of pregnancies destined to end prematurely
- Prompt and effective management once preterm labour is diagnosed

1.3 Guideline development

These guidelines were developed by a workgroup consisting of specialists in the field of obstetrics and gynaecology appointed by the Chapter of Obstetricians and Gynaecologists, Academy of Medicine, Singapore. The workgroup conducted an exhaustive search of the obstetric literature with focus placed on data obtained from randomised controlled trials and robust observational studies. Clinical Practice Guidelines issued by the Royal College of Obstetricians and Gynaecologists (United Kingdom) and the American College of Obstetricians and Gynaecologists were also used as references during the formulation of these guidelines.

1.4 Target group

As preterm delivery is a major contributor to neonatal intensive care unit admissions, it is envisaged that these guidelines will improve the management of premature labour in Singapore and reduce perinatal morbidity and mortality associated with prematurity. All clinicians and healthcare staff involved in the care of the pregnant patient will benefit from the use of these guidelines.

2 Levels of evidence and grades of recommendation

Levels of evidence

Level	Type of Evidence
Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomisation.
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

Grades of recommendation

Grade	Recommendation
A (evidence levels Ia, Ib)	Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.
B (evidence levels IIa, IIb, III)	Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.
C (evidence level IV)	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates absence of directly applicable clinical studies of good quality.
GPP (good practice points)	Recommended best practice based on the clinical experience of the guideline development group.

3 Executive summary of recommendations

C Women at increased risk of preterm delivery may be identified by various risk factors in the obstetric history.

Grade C, Level IV

C Good antenatal care is important in the prevention of preterm delivery. Advice on bed rest and abstinence from sexual intercourse should be given to the high risk patient. In selected patients, prophylactic cervical cerclage and antibiotic treatment of women with bacterial vaginosis may be associated with a reduction in preterm delivery.

Grade C, Level IV

C Inhibition of preterm labour is contraindicated if delivery is in the best interest of the mother and/or the baby. Medical therapy used to inhibit labour should be discontinued if labour progresses.

Grade C, Level IV

A Intravenous beta-agonists administered between 20 and 36 weeks of gestation are useful in achieving uterine tocolysis in premature labour.

Grade A, Level Ia

C To reduce the risk of pulmonary oedema, beta-agonists should be administered intravenously with the minimum volume of fluid. Beta-agonists should also be used with caution in a woman with multiple pregnancy.

Grade C, Level IV

C Beta-agonists should be administered via a controlled infusion device. The infusion rate should be increased at regular intervals until contractions have ceased or until the maternal pulse reaches 130-140 per minute.

Grade C, Level IV

A Oxytocin antagonists may also be useful in inhibiting preterm labour with potentially fewer maternal side-effects than beta-agonists.

Grade A Level Ib

A Maternal corticosteroid administration is beneficial in the preterm patient to reduce the incidence of Respiratory Distress Syndrome in the newborn.

Grade A, Level Ia

A Beta-agonists should be used to delay delivery for 24 to 48 hours in order to administer corticosteroids to promote foetal lung maturity.

Grade A, Level Ia

A Maternal corticosteroid administration should be given using two doses of 12 mg of betamethasone/dexamethasone intramuscularly 12 to 24 hours apart.

Grade A, Level Ia

C During intravenous administration of beta-agonists, maternal pulse and blood pressure should be monitored at regular intervals. A record of fluid balance should also be kept.

Grade C, Level IV

C Delivery of the preterm foetus should be in an obstetric unit with neonatal intensive care facilities. Foetal monitoring during labour is important to ensure foetal well-being.

Grade C, Level IV

4 Definition and prediction of preterm labour

4.1 Definition

A diagnosis of preterm labour is made if a patient presents at less than 37 weeks gestation with regular painful contractions occurring at least once every 10 minutes. This may be associated with cervical dilatation and/or effacement.

4.2 Prediction of Preterm Labour

C Women at increased risk of preterm delivery may be identified by various risk factors in the obstetric history.

Grade C, Level IV

The patients' obstetric history may provide clues as to whether she is at increased risk of premature delivery. The risk factors include the following:¹

- Young age of mother - less than 16 years of age
- Lower socioeconomic class
- Reduced body mass index (BMI) - BMI less than 19.0
- Cigarette smoking
- Previous preterm delivery
- Multiple pregnancy
- Cervical incompetence
- Uterine abnormalities
- Premature rupture of membranes
- Obstetric complications, including hypertension in pregnancy, antepartum haemorrhage, infection, polyhydramnios, foetal abnormalities.

More than 50% of women who deliver prematurely, however, have no known antecedent risk factors.²

Vaginal examinations to assess the cervical status^{3,4} and ultrasound visualisation of cervical length and dilatation^{5,6} have been suggested to be useful in the prediction of preterm labour.

The detection of foetal fibronectin in cervicovaginal secretions has been suggested to be useful in the prediction of preterm labour.^{7,8} However, in view of its poor specificity and a relatively high false positive rate,⁹ it is not recommended for routine screening of the general obstetric population.¹⁰

5 Prevention of preterm labour

C Good antenatal care is important in the prevention of preterm delivery. Advice on bed rest and abstinence from sexual intercourse should be given to the high risk patient. In selected patients, prophylactic cervical cerclage and antibiotic treatment of women with bacterial vaginosis may be associated with a reduction in preterm delivery.

Grade C, Level IV

5.1 Antenatal advice

Good antenatal care is important and can help to detect some of the maternal and foetal factors that could lead to preterm delivery. A patient with risk factors may be advised on the early warning symptoms and signs of preterm labour, the importance of bed rest and abstinence from sexual intercourse.

5.2 Cervical cerclage

The role of prophylactic cervical cerclage in women at high risk of premature labour is controversial.¹¹⁻¹⁴

5.3 Antibiotics

Patients with bacterial vaginosis may be at increased risk of preterm delivery. Antibiotic treatment (ampicillin, erythromycin, metronidazole) of women with bacterial vaginosis may be associated with a reduction in the incidence of preterm delivery.¹⁵

6 Inhibition of preterm labour

6.1 Aims of inhibition of preterm labour

The aims of inhibition of preterm labour are to:

- Achieve quiescence of uterine irritability, when arrangements are made for in utero transfer to an obstetric unit with tertiary perinatal facilities.
- Reduce the likelihood of preterm delivery occurring within 48 hours of beginning treatment so as to allow the concomitant use of corticosteroids to enhance foetal pulmonary maturity.

6.2 Contraindications to inhibition of preterm labour

In the following situations where delivery is imminent or when other obstetric factors dictate that delivery should not be delayed, inhibition of preterm labour may be withheld:

- Fulminating pre-eclampsia
- Severe abruptio placenta
- Foetal distress
- Severe chorioamnionitis in the presence of rupture of membranes
- Foetal demise or lethal foetal anomaly
- Development of serious side-effects during the use of beta-agonists (see section 7.1.3)

Therapy should be discontinued if labour progresses despite treatment.

C Inhibition of preterm labour is contraindicated if delivery is in the best interest of the mother and/or the baby. Medical therapy should be discontinued if labour progresses.

Grade C, Level IV

7 Modalities of treatment

When a patient with suspected preterm labour is examined, a full history must be obtained and a clinical examination must be performed. The clinical examination should include a speculum examination of the cervix to exclude rupture of membranes, digital examination to assess the cervical status, assessment of foetal presentation and estimated foetal weight. Vaginal and cervical microbiological cultures and a midstream specimen of urine culture may be considered to exclude an infective aetiology.

The aims of treatment are to:

- Achieve uterine quiescence, and
- Reduce adverse perinatal morbidity to the foetus.

The aims of treatment and the potential side effects of such treatment should be explained to the patient. Discussion with a neonatologist at this stage will also be helpful in the co-management of the patient.

7.1 Beta-agonists

Beta-agonists (salbutamol, ritodrine and terbutaline) are the most widely used tocolytic agents for the suppression of uterine contractions.

A Intravenous beta-agonists administered between 20 and 36 weeks of gestation are useful in achieving uterine tocolysis in premature labour.

Grade A, Level Ia

7.1.1 Patient selection

Meta-analyses of randomised trials have concluded that the use of intravenous beta-agonists significantly reduces the proportion of women delivering within the first 48 hours after beginning treatment.^{16,17}

7.1.2 Administration

C To reduce the risk of pulmonary oedema, beta-agonists should be administered intravenously with the minimum volume of fluid. Beta-agonists should also be used with caution in a woman with multiple pregnancy.

Grade C, Level IV

C Beta-agonists should be administered via a controlled infusion device. The infusion rate should be increased at regular intervals until contractions have ceased or until the maternal pulse reaches 130-140 per minute.

Grade C, Level IV

The dose should be increased at regular intervals until uterine contractions are inhibited, or maternal pulse reaches 130-140 per minute, or other side effects become excessive (see section 7.1.3). The maximum recommended dose is 350 micrograms per minute for ritodrine infusion and 45 micrograms per minute for salbutamol infusion. The dose may be reduced slowly if uterine contractions have ceased.

Many studies include the use of oral maintenance treatment after the contractions have stopped. However, the use of oral maintenance therapy remains controversial.¹⁸

7.1.3 Side effects and risks

Palpitations, tremors, nausea, vomiting and headaches are commonly reported symptoms. Serious side effects and risks which have been reported are as follows:

- **Maternal Tachycardia**

A frequent dose-related effect is maternal tachycardia. Heart rate should not be allowed to exceed 130-140 beats per minute due to the associated risk of pulmonary congestion.

- **Pulmonary Oedema**

Pulmonary oedema is commonly associated with aggressive intravenous hydration. Fluid balance should be carefully monitored. If pulmonary oedema occurs, the treatment should be discontinued and diuretic treatment be considered.¹⁹

- **Myocardial Ischaemia**

Myocardial ischaemia is an uncommon but serious side effect due to increased maternal cardiac output with beta-agonist administration.

- **Hyperglycaemia**

Diabetic patients will need additional monitoring and adjustment of glucose levels as beta-agonists influence carbohydrate metabolism, especially when combined with maternal corticosteroid administration.

- **Multiple Pregnancy**

Beta-agonists should be used with caution in a woman with multiple pregnancy as there is a higher risk of cardiac failure and pulmonary oedema from the intravenous therapy as compared with its use in a singleton pregnancy.²⁰

7.2 Other tocolytic agents

Other pharmacological agents which have been used for uterine tocolysis, albeit less frequently than beta-agonists, include nitric oxide donors, magnesium sulphate,²¹ indomethacin, nifedipine and oxytocin antagonists.

Particular caution should be exercised when using indomethacin as it causes vasoconstriction of the ductus arteriosus²² and altered cerebral blood flow.²²⁻²⁴

Magnesium sulphate is used infrequently as it is associated with significant maternal and foetal side effects.²³⁻²⁴

A Oxytocin antagonists may also be useful in inhibiting, preterm labour with potentially fewer maternal side effects than beta-agonists.

Grade A, Level Ib

Recent data from randomised controlled trials suggest that atosiban, an oxytocin antagonist, may be just as effective as beta-agonists in the inhibition of preterm labour, with potentially fewer maternal side effects.²⁵

7.3 Antibiotics

The contribution of subclinical genital tract infection to the aetiology of preterm birth is gaining increasing recognition. The usefulness of commencing antibiotics in women in established preterm labour (with intact membranes) is controversial. Some studies report a significant prolongation in the gestational age when antibiotics are used²⁶ while others do not show a similar effect.²⁷

7.4 Role of bed rest, reduced physical activity and abstinence from sexual intercourse

In a patient at increased risk of recurrent preterm contractions, the role of bed rest, reduced physical activity, avoidance of nipple stimulation and abstinence from sexual intercourse may be explained to the patient, especially if the preterm labour is related to antepartum haemorrhage.

8 Role of maternal corticosteroid administration

Respiratory Distress Syndrome (RDS) affects 40 to 50% of babies born before 32 weeks gestation. Antenatal corticosteroids have been used for more than 2 decades to reduce the morbidity associated with RDS in preterm births.

A Maternal corticosteroid administration is beneficial in the preterm patient to reduce the incidence of RDS in the newborn.

Grade A, Level Ia

A meta-analysis of 15 randomised controlled trials indicates that antenatal corticosteroid therapy reduces the incidence of RDS.²⁸ There is an associated reduction in the risk of neonatal death and intraventricular haemorrhage.²⁸ The efficacy of neonatal surfactant therapy is enhanced by antenatal exposure to corticosteroids.²⁹

A Beta-agonists should be used to delay delivery for 24 to 48 hours in order to administer corticosteroids to promote foetal lung maturity.

Grade A, Level Ia

8.1 Corticosteroid therapy

The following points should be considered when using maternal corticosteroid therapy:^{19,30}

- All women between 24 and 36 weeks of pregnancy at risk for preterm delivery may benefit from antenatal corticosteroid therapy.
- Patients eligible for therapy with tocolytic agents are also eligible for treatment with antenatal corticosteroids.

- **A** Maternal corticosteroid administration should be given using two doses of 12 mg of betamethasone/dexamethasone intramuscularly 12 to 24 hours apart.

Grade A, Level Ia

The effect of treatment is optimal if the baby is delivered more than 24 hours and less than 7 days after the start of treatment.¹⁹

- As treatment for less than 24 hours is still associated with significant reduction in neonatal mortality, antenatal corticosteroids may still be given unless immediate delivery is anticipated.
- When the risk of preterm delivery persists or recurs following initial treatment, decisions to repeat treatment should be made on an individual basis.

8.2 Precautions when administering corticosteroids

Corticosteroid therapy does not appear to increase the risk of maternal or foetal infection regardless of whether the membranes are ruptured or not at the time of treatment. The following points must also be considered when administering corticosteroids:

- Corticosteroids may be used with caution in patients with severe pre-eclampsia/hypertension.
- Impaired glucose tolerance may occur if repeated doses of corticosteroids are given, especially in conjunction with beta-agonist therapy.
- The extremely rare complication of adrenal insufficiency should be considered if there is an unexplained collapse of either the mother or baby who are exposed to repeated courses of neonatal corticosteroids.

9 Monitoring and Delivery

9.1 Monitoring during beta-agonist administration

C During intravenous administration of beta-agonists, maternal pulse and blood pressure should be monitored at regular intervals. A record of fluid balance should also be kept.

Grade C, Level IV

During intravenous administration of beta-agonists, the following maternal parameters should be monitored at regular intervals:

- Maternal pulse
- Blood pressure
- Record of fluid balance (input/output chart)
- Auscultation of lung fields
- Urea and electrolytes, if intravenous administration exceeds 24 hours.

Foetal monitoring is important to ascertain whether the contributory cause of preterm labour (eg. abruptio placenta) is causing foetal distress. Monitoring by cardiotocography is useful. When preterm labour is successfully inhibited, an ultrasound scan may be ordered to exclude intrauterine growth retardation.

9.2 Delivery of the preterm foetus

C Delivery of the preterm foetus should be in an obstetric unit with neonatal intensive care facilities. Foetal monitoring during labour is important to ensure foetal well-being.

Grade C, Level IV

When delivery of the preterm foetus is imminent, either as a result of failure of tocolysis or the presence of contraindications to commence tocolysis, the safe delivery of the foetus in an obstetric unit with neonatal intensive care facilities is prudent. Foetal monitoring during labour is important to ensure foetal well-being.

In the absence of obstetric risk factors or complications that would otherwise preclude a vaginal delivery, a preterm foetus with a vertex presentation may be delivered vaginally. However, if the presentation is not vertex, delivery by Caesarean section may be considered.

10 Recommendations for evaluation

In view of the data from randomised controlled trials that intravenous agents for tocolysis confer a significant benefit in delaying delivery by 24 to 48 hours to allow concomitant corticosteroid administration to accelerate foetal pulmonary maturity, key criteria for monitoring and audit may include:

- Incidence of preterm delivery in each obstetric unit
- Frequency of use of intravenous tocolytic agents and corticosteroids prior to preterm delivery i.e. the proportion of preterm deliveries given both tocolytic agents and corticosteroids

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12 Workgroup members

The members of the workgroup are:

Chairperson: Dr Chang Tou Choong

Members: Dr Selina Chua
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Management of Preterm Labour



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and Gynaecologists
Academy of Medicine

Prediction of Preterm Labour

Women at increased risk of preterm delivery may be identified by various risk factors in the obstetric history.

Prevention of Preterm Labour

Good antenatal care is important in the prevention of preterm delivery. Advice on bed rest and abstinence from sexual intercourse should be given to the high risk patient. In selected patients, prophylactic cervical cerclage and antibiotic treatment of women with bacterial vaginosis may be associated with a reduction in preterm delivery.

Contraindications to Inhibition of Preterm Labour

Inhibition of preterm labour is contraindicated if delivery is in the best interest of the mother and/or the baby. Medical therapy used to inhibit labour should be discontinued if labour progresses.

Modalities of Treatment

Intravenous beta-agonists administered between 20 and 36 weeks of gestation are useful in achieving uterine tocolysis in premature labour.

To reduce the risk of pulmonary oedema, beta-agonists should be administered intravenously with the minimum volume of fluid. Beta-agonists should also be used with caution in a woman with multiple pregnancy.

Beta-agonists should be administered via a controlled infusion device. The infusion rate should be increased at regular intervals until contractions have ceased or until the maternal pulse reaches 130-140 per minute.

Oxytocin antagonists may also be useful in inhibiting preterm labour with potentially fewer maternal side-effects than beta-agonists.

Role of Maternal Corticosteroid Administration

Maternal corticosteroid administration is beneficial in the preterm patient to reduce the incidence of Respiratory Distress Syndrome in the newborn.

Beta-agonists should be used to delay delivery for 24 to 48 hours in order to administer corticosteroids to promote foetal lung maturity.

Maternal corticosteroid administration should be given using two doses of 12 mg of betamethasone/dexamethasone intramuscularly 12 to 24 hours apart.

Monitoring During Beta-agonist Administration

During intravenous administration of beta-agonists, maternal pulse and blood pressure should be monitored at regular intervals. A record of fluid balance should also be kept.

Delivery of the Preterm Foetus

Delivery of the preterm foetus should be in an obstetric unit with neonatal intensive care facilities. Foetal monitoring during labour is important to ensure foetal well-being.