The Preparation of the Fetus for Preterm Delivery

A Clinical Practice Guideline for Professionals Involved in Maternity Care in Scotland

(PILOT EDITION)

Guideline produced in June 1997 and valid until June 1999
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1. INTRODUCTION

1.1 WHY A CLINICAL PRACTICE GUIDELINE ON PREPARATION FOR PRETERM DELIVERY?

Preterm delivery (defined as delivery before 37 completed weeks of gestation) occurs in around 7% of all pregnancies and is a major cause of infant mortality and morbidity. (The small percentage of births that occur preterm reportedly account for around 80% of neonatal deaths among normally formed infants). In Scotland in 1995, there were 3228 singleton livebirths at gestations of under 37 weeks and 111 of these (3.4%) died in the neonatal period. These deaths represented 61% of all neonatal deaths among singletons. Multiple pregnancy is, of course, associated with a higher risk of preterm delivery and of associated mortality.

There is now overwhelming evidence that appropriate management (principally administration of corticosteroids) prior to anticipated preterm delivery results in a large reduction in neonatal deaths and in morbidity due to respiratory distress syndrome (RDS), intraventricular haemorrhage (IVH) and necrotising enterocolitis (NEC). However, a recent Scottish audit showed that during the period 1990 - 1993 only 29% of infants delivered before 31 weeks in nine representative maternity units, received a full course of steroids prior to delivery. This audit evidenced deficiencies in clinical practice in Scotland prompted the SOGAP group to include 'Preparation of the fetus for preterm delivery' among its first topics for formal obstetric guideline development.

1.2 WHO HAS DEVELOPED THIS GUIDELINE?

The guideline has been developed by a multi-professional working group representing both teaching and district general hospitals throughout Scotland. Membership included obstetricians, neonatologists, a midwife, a pharmacist and a public health medicine consultant. The group was convened by the grant holders of the Scottish Obstetric Guidelines and Audit Project (SOGAP). The inclusion of other disciplines and of patient representatives was discussed by the group. It was agreed that all professional groups usually involved in clinical decision-making relating to preterm labour were adequately represented. SOGAP has a commitment to the involvement of both general practitioners and patients and these groups are represented in the development of guidelines on other topics.

The project was originally conceived, and the topics for guideline development chosen by, the Scottish Executive Committee of the RCOG with input from the funding body, the Clinical Resource and Audit Group (CRAG) of the SODoH.

1.3 FOR WHOM IS THIS GUIDELINE INTENDED?

The guideline has been produced under the auspices of the Scottish Executive Committee of the RCOG and is aimed at all healthcare professionals who share in maternity care. In particular, it is hoped that fellows and members of the RCOG and their trainees, midwives and neonatologists will find it helpful. The care of women judged to be at high risk of preterm delivery, and warranting the initiation of steroid therapy, should take place in a specialist maternity unit in order that there is ready access to a neonatal unit. The aspects of clinical care discussed in this guideline are, therefore, more applicable to hospital-based professionals than to those working in the community and the guideline has been written with this readership in mind.
1.4 WHAT METHODS HAVE BEEN USED IN THE DEVELOPMENT OF THIS GUIDELINE?

The development of the guideline has drawn on methodology outlined in the CRAG publication “Clinical Guidelines”, the SIGN publication “Clinical Guidelines: Criteria for Appraisal for National Use” and the NHS Executive’s “Clinical Guidelines”.

In preparing the Guideline, a systematic literature search was undertaken using CD plus Medline for the years 1986 - 1996 (principal search terms: premature labour, premature infant, tocolysis) and the Cochrane Pregnancy and Childbirth Database (CPCD) in order to identify evidence based on randomised controlled trials (RCTs), other forms of clinical study and expert opinion which is appropriate for translation into clinical practice in Scotland. Material identified from the searches was supplemented by references already known to group members and by scrutiny of the reference lists of identified publications for key references from earlier years.

The guideline development group particularly acknowledges the content of the National Institutes of Health (NIH) Consensus Development Conference Statement: “Effects of corticosteroids for fetal maturation on perinatal outcomes”, Patricia Crowley’s “Antenatal corticosteroid therapy: a meta-analysis of the randomised trials, 1972-1994”, the guideline prepared by Dr Crowley for the Scientific Advisory Committee of the RCOG: “Antenatal corticosteroids to prevent respiratory distress syndrome” and the ACOG technical bulletin on “Preterm labor” and has drawn on these documents in the preparation of this guideline.

The recommendations within this guideline have been graded according to the levels of evidence on which they are based, using the scheme adopted by SIGN which is based on the system proposed by the US Agency for Health Care Policy and Research. The scheme for grading of recommendations is reproduced here (Table I).

The guideline development group met on three occasions and developed successive drafts of the guideline. An advanced draft was then submitted for peer review to a panel of three Scottish obstetricians who had not been involved in the development process. The suggestions of the peer reviewers and views expressed by participants at the SOGAP National Meeting held in Glasgow in March 1997 were incorporated prior to submission to the SIGN editorial board and the Scottish Executive Committee of the RCOG. These bodies also subjected the guideline to peer review and suggestions from this review process have been incorporated in the final version.

Minutes of the guideline development process and copies of all publications quoted in the text are held at the SOGAP offices in Glasgow and Aberdeen.

Table I Grading of recommendations

<table>
<thead>
<tr>
<th>Grade</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>A</td>
<td>Requires at least one randomised controlled trial as part of the body literature of overall good quality and consistency addressing the specific recommendation</td>
</tr>
<tr>
<td>B</td>
<td>Requires availability of well-conducted clinical studies but no randomised clinical trials on the topic of recommendation</td>
</tr>
<tr>
<td>C</td>
<td>Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.</td>
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</table>
Throughout the text of the guideline, it has been made explicit which individual recommendations are based on evidence from RCTs (Grade A recommendations), other designs of clinical studies (Grade B recommendations) or on the consensus view of the Guideline Development Group, indicating an absence of relevant studies, (Grade C recommendations).

Grade A recommendations (those based on evidence from RCTs) are highlighted by means of a shaded text throughout.

1.5 HOW WILL THIS GUIDELINE BE IMPLEMENTED AND REVIEWED?

This guideline was launched, along with three other guidelines being developed by SOGAP, at a National Meeting in March 1997 to which representatives of key disciplines from throughout Scotland were invited. Discussion of the Guideline in this forum allowed minor modifications to be made in the light of suggestions from a wider group. A lead clinician from each maternity unit in Scotland will be recruited to initiate the development of local protocols based on the four SOGAP guidelines. Local protocol development and implementation will be supported by site visits by the SOGAP team during the final year of the project timetable.

The impact of the SOGAP guidelines on the process and outcome of care will be monitored through the project's audit component. A profile of pre-guideline practice is currently being prepared based on the results of a questionnaire survey of relevant professional groups (to assess the process of care) and on analysis of relevant data collected by the Information and Statistics Division (ISD) of the NHS in Scotland (to assess the outcome of care). In due course, a similar profile of post-guideline practice will be compiled, using the same methods, in order that any changes can be identified.

In addition to the audit component described here, it is suggested that clinicians might include audit of compliance with recommendations relating to the use of antenatal steroids in local audit programmes. The Scottish Neonatal Consultants Collaborative Study Group have published a suggested minimum data set. This is reproduced in this document (Appendix I) and is commended to local audit groups.

This guideline is based on evidence and consensus views available at the time of final preparation (June 1997) and will be reviewed under the direction of the Scottish Executive Committee of the RCOG in June 1999 (or sooner if changing evidence requires it).

1.6 DECLARATION OF INTERESTS

Declarations of interests (personal, specific and non-specific; non-personal, specific and non-specific) as defined by SIGN have been obtained from all Guideline Development Group members. No conflicts of interest have been identified and copies of all declarations are held at the SOGAP offices in Glasgow and Aberdeen.
2. THE GUIDELINE

2.1 GESTATION RANGE TO WHICH RECOMMENDATIONS WITHIN THIS GUIDELINE APPLY

<table>
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<tr>
<th>Recommendations</th>
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| ✚ All women between 24 and 34 completed weeks of gestation considered to be at risk of delivery within 7 days should be viewed as candidates for antenatal corticosteroid administration. There are very few circumstances in which such treatment should be withheld\(^1\).  
(GRADE A) |
| ✚ The babies of women between 34 and 36 completed weeks of gestation considered to be at risk of delivery within 7 days may also benefit from antenatal steroid treatment. Individual circumstances should be taken into account when making a treatment decision for such cases. For example, delivery by planned Caesarean section might prompt the initiation of steroid therapy\(^1\).  
(GRADE C) |

The official WHO definition of preterm birth includes all births before 37 completed weeks of gestation. However, there is a clear need to subdivide preterm births as the outlook for a baby born after 36 weeks is quite unlike that for an infant born at 26 weeks. The appropriate gestation range during which perceived risk of delivery constitutes an indication for prophylactic management (principally steroid administration) has been a topic of debate and different sources of guidance on this subject have proposed different gestation ranges.

Evidence from recent meta-analysis\(^1\) indicates that the benefits of corticosteroids are not restricted to any particular gestation subgroup of preterm births, but that there is unambiguous benefit to babies born before 31 weeks, and probable benefit to those born after 34 weeks. (These findings are contrary to the conclusions of earlier reviewers\(^10\) who suggested that benefits were confined to infants of 30 - 34 weeks gestation).

The SOGAP working group endorse the gestation range of 24 - 34 weeks suggested by the NIH consensus group\(^6\), by the Scottish Neonatal Consultants' Collaborative Study Group in their proposals for audit\(^2\), and also by ACOG\(^8\). The proposed lower limit of 24 weeks is based on the accepted lower limit of viability, and the upper limit of 34 weeks is an arbitrary limit beyond which cost-effectiveness is questionable. However, the SOGAP group suggest that the upper limit of the gestation range within which steroid use is considered be extended to 36 completed weeks (as advocated in the RCOG Guideline\(^7\)), although it is acknowledged that the cost-effectiveness of steroid therapy is reduced at such gestations. (It has been estimated that 94 women at 34 - 37 weeks would need to be treated to prevent one case of RDS compared with only 5 women before 31 weeks\(^11\)). However, in some circumstances, and after consultation with paediatric colleagues, obstetricians may wish to use steroid therapy at gestations of up to 36 weeks.

Clinical Illustration

- Mrs AB is a 25 year old primigravida with insulin-dependent diabetes and a twin pregnancy. She presents with regular, painful contractions at 28 weeks gestation.
- Mrs AB should be viewed as being at risk of preterm delivery within 7 days and steroid therapy initiated.
## 2.2 CONTRA-INDICATIONS AND CAUTIONS FOR STEROID THERAPY

<table>
<thead>
<tr>
<th>Recommendations</th>
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<tbody>
<tr>
<td>- The decision to use antenatal corticosteroids should not be altered by fetal race or gender. (Grade A)</td>
</tr>
<tr>
<td>- Pre-labour preterm rupture of the membranes (PPROM) need not be regarded as a contra-indication to steroids. (Grade A)</td>
</tr>
<tr>
<td>- Maternal diabetes, pre-eclampsia, treated suspected chorio-amnionitis and treated tuberculosis need not be regarded as contra-indications to steroids. (Grade C)</td>
</tr>
<tr>
<td>- Clinically suspected, but untreated infections (intrauterine or tuberculous) may be regarded as contra-indications to initiating steroid therapy. (GRADE C)</td>
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Crowley's recent meta-analysis indicates that neither race nor gender affect the likelihood of a fetus benefiting from antenatal steroids. This meta-analysis includes a sub-analysis relating to the use of steroids in association with PPROM. The incidence of RDS is substantially reduced by steroid administration in this group. However, there is a theoretical risk that steroid-use in women with PPROM may increase risks of infection. Because of these concerns, the NIH consensus group recommended that the upper gestation limit for steroid therapy be reduced from 34 weeks to 30 - 32 weeks in patients with PPROM. However, after full consideration, (and in line with the RCOG guideline), the SOGAP working group feel that this reduced gestation range is unnecessary but that steroids may be inappropriate for most women with PPROM at 34 - 36 weeks gestation.

Maternal diabetes predisposes the preterm infant to RDS, especially when diabetic control has been poor. Glucocorticoid therapy in diabetic women is likely to result in a deterioration in diabetic control with subsequent adverse effects on fetal lung maturation. Randomised trials of antenatal steroids have included only 35 diabetic women and there are, therefore, insufficient data on which to assess the net effects of steroids in this group. However, after full consideration, the view of the SOGAP group is that the benefits of steroids probably outweigh these theoretical disadvantages in diabetic women and that, with appropriate monitoring, diabetic control can be achieved despite steroid administration. Again, in the 34 - 36 week gestation range, steroids can usually be omitted in diabetic women.

Conflicting evidence exists about the effects of steroid administration in women with severe proteinuric hypertension. The first randomised trial of antenatal steroid therapy demonstrated an excess of fetal deaths among the treated group. Only two subsequent trials have permitted similar analysis and failed to confirm the excess of intrauterine deaths reported by Howie and Liggins. Observational data similarly suggest no excess risk of fetal death among patients with proteinuric hypertension treated with glucocorticoids. On balance, the SOGAP group feel that the results of the meta-analysis giving a typical odds ratio for fetal death of 3.75 among steroid-treated women with hypertension need not influence clinical practice, and that it is appropriate to manage women with hypertension in the same way as other women. The meta-analysis was very heavily weighted by the results of only one trial, is based on a secondary analysis of data obtained in that trial (rather than being obtained from a trial designed with the specific aim of investigating the effects of steroids in women with hypertensive disease) and its results are at variance with clinical experience.
Tuberculosis in pregnancy is uncommon in Scottish obstetric practice but has been cited as a contra-indication to antenatal steroid therapy. However, the considered view of the SOGAP group is that treated tuberculosis need not represent a contra-indication.

An important caution, highlighted in the most recent Report on Confidential Enquiries into Maternal Deaths in the UK (1991-'93), is that delay in delivery in efforts to gain fetal maturity must not overide maternal considerations. Such delays were felt to contibute to three maternal deaths from hypertensive disease in this triennium.

Readers are cautioned against over-liberal use of steroids as preliminary work in experimental animals has suggested that antenatal steroid exposure may be associated with hypertension in adult life.

Clinical Illustrations

◊ Mrs CD is a 30 year old primigravida with no medical or obstetric history of note. She presents at 35 completed weeks gestation with preterm pre-labour rupture of the membranes (PPROM).

♦ Mrs CD should be viewed as being at risk of preterm delivery within 7 days but, in view of her relatively advanced gestation and the presence of ruptured membranes (where there may be a theoretical concern that giving steroids might exacerbate infection) the treatment decision might reasonably be to omit steroid therapy.

◊ Mrs EF is a 30 year old para 1+0 patient with insulin-dependent diabetes and a singleton pregnancy. She presents at 32 completed weeks gestation with ruptured membranes but no evidence of uterine contractions.

♦ Mrs EF should be regarded as at risk of preterm delivery within 7 days and steroid therapy initiated. Neither her diabetes nor the presence of ruptured membranes need be regarded as contra-indications.
2.3 IDENTIFICATION OF WOMEN AT RISK OF PRETERM DELIVERY

<table>
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<tr>
<th>Recommendations</th>
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<tbody>
<tr>
<td>PPROM at 24 - 34 completed weeks gestation should be viewed as an indication to initiate steroid therapy. (GRADE A)</td>
</tr>
<tr>
<td>Women presenting with clinical features suggestive of labour (persistent contractions ± evidence of cervical dilatation) at 24 - 36 completed weeks gestation should be considered as candidates for steroid therapy. (GRADE A)</td>
</tr>
<tr>
<td>Women presenting with obstetric complications likely to lead to early delivery, or for whom early delivery has been scheduled, (eg hypertensive disease, intrauterine growth retardation, placenta praevia) at 24 - 36 weeks gestation should be considered for steroid therapy which should, ideally, be commenced at least 24 hours prior to delivery. (GRADE A)</td>
</tr>
<tr>
<td>None of the described predictors of preterm delivery (eg Creasy score, fetal fibronectin estimation) are sufficiently sensitive and specific to be used in routine clinical practice and assessment of risk of preterm delivery must be based on clinical features. (GRADE B)</td>
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Women delivering within the "gestation window" suggested as appropriate for antenatal steroid therapy constitute a heterogeneous group. Around 10% undergo elective preterm delivery due to maternal or fetal medical problems. This group is readily identifiable and the decision to begin steroid administration some 24 hours prior to planned delivery, unambiguous. A further 20-50% of preterm deliveries are preceded by pre-labour rupture of the membranes (PROM). Again, this group can be identified and (in the absence of overt chorio-amnionitis) steroids commenced.

A greater problem exists in identifying the largest group of women who will deliver within the "gestation window": those with idiopathic preterm labour. Numerous predictors of spontaneous preterm birth have been evaluated: from the ‘Creasy’ score to cervico-vaginal fetal fibronectin. Fetal fibronectin is felt to be the most specific marker currently available for identifying potential preterm labour. Nevertheless, as a screening test at 24-36 weeks it has a positive predictive value of only 25-30% and its value requires to be assessed through further clinical trials before it is incorporated into routine practice.

Currently therefore, risk of preterm delivery within 7 days must be assessed clinically on the basis of contractions, while recognising that clinical assessment remains inaccurate. Clinical assessment of risk of impending delivery may include digital examination of the cervix, in which case cervical change or a cervical dilatation of ≥2cm (primigravidae) or ≥3cm (multigravidae) and/or ≥50% effacement would be regarded as indications to begin steroids.

Clinical Illustrations
◊ Miss GH an 18 year old primigravida, presents at the antenatal clinic with severe proteinuric pre-eclampsia at 33 completed weeks gestation. Ultrasound assessment suggests fetal growth retardation and induction is planned.
♦ Steroid therapy should be initiated and induction delayed for at least 24 hours from the start of treatment if possible. Evidence of deterioration in maternal or fetal well-being may, of course, require that delivery be achieved within 24 hours.

◊ Miss IJ is a 17 year old primigravida who presents at the antenatal clinic at 30 weeks gestation with a blood pressure of 140/100mmHg and ++ proteinuria on dipstix testing. She is admitted for assessment.
♦ Although there are no immediate plans to deliver Miss IJ, she must, nevertheless, be regarded as at risk of preterm delivery within 7 days and steroid therapy instituted.
## 2.4 THE STEROID REGIMEN

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<th>Recommendations</th>
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<tr>
<td>- An extensively studied steroid regimen, which has proved effective in placebo-controlled RCTs comprises two doses of betamethasone, 12mg, intramuscularly, 24 hours apart(^1,^6). (GRADE A)</td>
</tr>
<tr>
<td>- Any regimen which delivers a total dose of 24 mg of betamethasone or dexamethasone within a period of 24 - 48 hours is also acceptable(^1,^6). (GRADE A)</td>
</tr>
<tr>
<td>- Steroid therapy should be initiated even when delivery within a few hours is anticipated (GRADE C)</td>
</tr>
<tr>
<td>- The steroid regimen should not be repeated within 7 days (and after 7 days only after full consideration of the need for repeat administration)(^1). (GRADE A)</td>
</tr>
<tr>
<td>- Steroid metabolism is potentiated by enzyme-inducing anticonvulsants (phenytoin, phenobarbitone, primidone, carbamazepine). Women with epilepsy taking any of these drugs and requiring antenatal steroids should receive a steroid regimen providing a total of 48mg (rather than 24mg) of steroid, as two doses of 24mg, 12 hours apart. (GRADE C)</td>
</tr>
<tr>
<td>- Women with multiple pregnancy should receive the same dose of antenatal steroid as women with singleton pregnancies. (GRADE C)</td>
</tr>
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</table>

The most extensively studied regimens of steroid treatment for the prevention of RDS are betamethasone, 12mg, IM, twice, 24 hours apart and dexamethasone, 6mg IM, four times, 12 hours apart. These regimens are reported to be equally effective and to deliver equivalent concentrations of steroid to the fetus\(^6\). Thus, there is no evidence that one of these regimens is any more effective than the other. The SOGAP working group have opted for the betamethasone regimen as two injections are more convenient than four and the standard NHS cost is slightly less\(^21\).

Some obstetric units in Scotland have adopted a steroid regimen comprising two doses of 12mg of steroid given 12, rather than 24, hours apart. Ballard and Ballard\(^22\) provided a review on the *Scientific basis and therapeutic regimens for use of antenatal glucocorticoids* for the NIH Consensus Conference. They have reviewed the pharmacokinetics of various steroid regimens. betamethasone 12mg is reported to bind to glucocorticoid receptors with an affinity more than five times higher than cortisol and to provide > 75% receptor occupancy "which should provide a near maximal induction of glucocorticoid-regulated genes in fetal target tissues". The half life in the fetal circulation is reportedly around 12 hours. These authors conclude that "the corticosteroid preparation and administration regimen chosen by Liggins in his initial clinical study appears to be optimal with regard to efficacy" and report that, in a follow-up to their original trial, Howie and Liggins\(^23\) found no increased benefit from administering twice the dose of betamethasone (24mg every 24 hours). The SOGAP group thus endorse the recommendation of the NIH consensus statement\(^6\) that two doses of betamethasone given 24 hours apart is an appropriate regimen and that "higher or more frequent doses do not increase the benefits of antenatal corticosteroid therapy and may increase the likelihood of adverse effects". However, the SOGAP group are unaware of any data specifically indicating that alternative dosage schedules delivering a total of 24mg of steroid over a shorter period have disadvantages, and do not advocate alteration of established local practices.

Crowley's meta-analysis\(^1\) indicates that babies delivered between 24 hours and 7 days after commencing corticosteroid treatment show the most marked benefit (typical odds ratio for RDS, 0.35; 95% C.I, 0.26-0.46). However, the odds ratios for RDS in infants delivered less than 24 hours (0.80; 95% C.I, 0.56-1.15) or more than 7 days (0.63; 95% C.I, 0.38-1.07) after commencing steroids suggest a (statistically non-significant) trend towards treatment benefit. In view of this evidence, the SOGAP
working group endorses the recommendation of the NIH Consensus Statement\(^6\) that steroid therapy should be initiated even when delivery is anticipated within a few hours. Available data indicate that for optimal benefit steroid therapy should be **commenced** at least 24 hours prior to delivery. Data are unavailable to provide more detailed guidance as to the optimal timing of steroid administration prior to elective preterm delivery.

The NIH consensus Statement\(^6\) states that the potential risks and benefits of repeated administration of corticosteroids after 7 days are unknown. The RCOG also emphasis this point in their Guideline\(^7\): “It is important to emphasise that all evidence concerning safety and immediate and long-term side-effects is derived from randomised trials where a **single course of treatment was administered**. There are no randomised trials of repeated doses of antenatal corticosteroid therapy”.

Theoretical risks of repeated courses of treatment include long-term effects on cognitive or neurological development, impaired glucose tolerance, osteoporosis and depression of fetal/maternal adrenals. The SOGAP working group therefore advocate a clinical philosophy of a low threshold for initiating a first course of antenatal steroid but a higher threshold, and full clinical consideration, for initiating subsequent courses. Multiple courses of steroids, for example in women under observation with a diagnosis of placenta praevia, are discouraged.

Enzyme inducing anticonvulsants are known to potentiate steroid metabolism and will therefore reduce the efficacy of antenatal steroids (in the same way as they reduce the efficacy of contraceptive steroids). It is suggested therefore (on theoretical grounds) that women on such anticonvulsants receive an increased dose of antenatal steroid, with a reduced time interval between doses in order to compensate for the effects of induced enzymes.

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**Clinical Illustrations**

◊ **Miss KL** is a 17 year old primigravida patient who presented at 30 completed weeks gestation with a history of regular, painful contractions over a period of four hours. Clinical assessment suggested that regular contractions were occurring and the cervix was found to be soft and partially effaced, although undilated. Miss KL was felt to be at risk of preterm delivery within 7 days and a full course of steroid administered. Over a period of 48 hours, contractions settled and Miss KL was discharged home.

Miss KL presented again, 10 days later with a similar history and clinical findings.

♦ This guideline advocates a **low** threshold for a first course of antenatal steroids (therefore first use of steroid in this patient was appropriate) but advocates a **higher** threshold for subsequent courses of steroid. Therefore steroid therapy should not be initiated during Miss KL’s second admission at least until repeat cervical assessment has confirmed change in cervical state and until consultant advice has been sought.

◊ **Mrs MN**, a 35 year old para 4 + 2 patient is admitted at 31 completed weeks gestation with clinical features suggestive of placental abruption. On auscultation the fetal heart rate is 120 beats per minute.

♦ A first dose of steroid should be given at this point while the patient is being assessed as to mode of delivery. Steroid therapy should be initiated even when delivery within a few hours is anticipated.
2.5 ASSOCIATED THERAPIES

2.5.1 TOCOLYTICS

<table>
<thead>
<tr>
<th>Recommendations</th>
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<tr>
<td>p Tocolysis (pharmacological inhibition of uterine contractions) should be used only rarely and for periods not exceeding 48 hours. It may be indicated for women presenting with preterm labour at 24-34 weeks gestation to permit transfer to a tertiary centre with appropriate neonatal care facilities or to permit a full course of steroids to be administered. (GRADE A)</td>
</tr>
<tr>
<td>p The β-mimetic agent, ritodrine, administered via a syringe pump or controlled low fluid volume infusion device has proven efficacy for short-term tocolysis. As its efficacy diminishes and hazards increase with time, its use should be limited to 48 hours. It is the first line tocolytic of choice except in women with cardiac disease, hyperthyroidism, diabetes or hypertension. (GRADE A)</td>
</tr>
<tr>
<td>p The prostaglandin synthetase inhibitor, indomethacin, is the tocolytic of choice for women with cardiac disease, hyperthyroidism, diabetes or hypertension. The perinatal effects of this drug are not yet established and it cannot currently be advocated as first line agent for general use. (GRADE B)</td>
</tr>
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</table>

Ritodrine was introduced in the UK in 1974 and is the principal β-mimetic which has been used for the inhibition of preterm labour. The risk/benefit equation relating to β-mimetic therapy has been extensively debated over the past 20 years and the role of ritodrine became particularly contentious following the publication of the largest RCT of ritodrine-use from the Canadian Preterm Labor Investigators Group. Keirse has incorporated the results of the Canadian study into his meta-analysis for the Cochrane Pregnancy and Childbirth Database, which is now based on some 1600 cases. The meta-analysis confirms that β-mimetics significantly delay delivery for more than 24 hours, but that this delay is not associated with a significant reduction in RDS or perinatal death. These conclusions are shared by the authors of another systematic review of 328 published studies.

The Canadian evidence of lack of clinical benefit of β-mimetics in terms of improved perinatal outcome coincided with increased awareness of the potential risks of such therapy as a result of publicity surrounding coroners’ enquiries into two maternal deaths following ritodrine administration for preterm labour (“The Independent”, 11.1.93, p.5). Recent reviewers have concluded that, although there is doubt about the benefits of ritodrine therapy in terms of fetal outcome, risks to the mother may be reduced by appropriate administration and fluid restriction. The SOGAP working group advise, therefore, that the use of ritodrine be restricted to the limited circumstances outlined above and endorse the infusion regimens included in the RCOG ritodrine Guideline of 1994 (and updated in January’97). These are reproduced in Table II.

The Cochrane Pregnancy and Childbirth Database (CPCD) has concluded that inhibitors of prostaglandin synthesis are the only other category of drug meriting consideration for the inhibition of preterm labour; all others being either obsolete (eg ethanol, progesterone) or experimental (eg oxytocin analogues, calcium channel blockers such as nifedipine). The most widely used of these agents has been indomethacin which has been shown to be a more potent inhibitor of uterine contractions than any β-mimetic, but the CPCD concludes that “there are too few data from controlled comparisons, either with no treatment or with other drug treatments to recommend them (PG-synthetase inhibitors) as a first-line approach in the inhibition of preterm labour”.

Current concerns about the safety of indomethacin tocolysis include premature closure of the fetal ductus arteriosus, increased risk of neonatal bronchopulmonary dysplasia, necrotising enterocolitis and renal dysfunction, and also concerns about maternal renal impairment.

It may be that future updates of this guideline will be able to draw on a greater body of evidence relating to tocolysis with indomethacin and other agents such as nifedipine (for which initial reports are favourable) and that the recommendation that ritodrine usually represents the tocolytic of choice may be altered.
Table II  Guidance on Ritodrine Infusion Rates

<table>
<thead>
<tr>
<th>I. SYRINGE PUMP</th>
<th>II. CONTROLLED INFUSION DEVICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Add 3x5 ml ampoules of ritodrine to 35 ml of 5% w/v dextrose</td>
<td>Add 3x5 ml ampoules of ritodrine to 500 ml of 5% w/v dextrose</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DOSE</th>
<th>RATE</th>
<th>DOSE</th>
<th>RATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 micrograms/min</td>
<td>1 ml/hour</td>
<td>50 micrograms/min</td>
<td>10 ml/hour</td>
</tr>
<tr>
<td>100 micrograms/min</td>
<td>2 ml/hour</td>
<td>100 micrograms/min</td>
<td>20 ml/hour</td>
</tr>
<tr>
<td>150 micrograms/min</td>
<td>3 ml/hour</td>
<td>150 micrograms/min</td>
<td>30 ml/hour</td>
</tr>
<tr>
<td>200 micrograms/min</td>
<td>4 ml/hour</td>
<td>200 micrograms/min</td>
<td>40 ml/hour</td>
</tr>
<tr>
<td>250 micrograms/min</td>
<td>5 ml/hour</td>
<td>250 micrograms/min</td>
<td>50 ml/hour</td>
</tr>
<tr>
<td>300 micrograms/min</td>
<td>6 ml/hour</td>
<td>300 micrograms/min</td>
<td>60 ml/hour</td>
</tr>
<tr>
<td>350 micrograms/min</td>
<td>7 ml/hour</td>
<td>350 micrograms/min</td>
<td>70 ml/hour</td>
</tr>
</tbody>
</table>

2.5.2  THYROTROPIN-RELEASING HORMONE (TRH)

Recommendation
- Insufficient data are available to provide convincing evidence that the addition of TRH to steroid regimens results in increased benefits. Currently, TRH should be used only in the context of clinical trials\(^{37}\).
  (GRADE A)

Thyroid hormones and glucocorticoids act synergistically to enhance biochemical, structural and functional lung maturity. Crowther's meta-analysis for the Cochrane Pregnancy and Childbirth Database\(^{37}\) included 7 trials including a recent, large-scale, Australian RCT (ACTOBAT) and showed that adding TRH to glucocorticoids did not significantly reduce mortality or the risk of RDS. Currently, therefore the SOGAP working group endorse the conclusions of the NIH consensus panel\(^{6}\) and of the RCOG guideline\(^{7}\) that the use of TRH remains experimental and cannot be confidently recommended except in the context of further RCTs.
2.5.3 ANTIBIOTICS

**Recommendations**

- Routine antibiotic treatment is not currently recommended in the management of idiopathic preterm labour with intact membranes (GRADE A).

- Patients with idiopathic preterm labour and intact membranes might appropriately be included in an RCT to evaluate the role of antibiotics in these circumstances (the ORACLE trial). (GRADE C)

- For women at risk of preterm delivery because of PPROM, prophylactic antibiotics delay delivery and reduce maternal and neonatal infective morbidity. (Whether they influence perinatal mortality and childhood disability remains unknown.) It is suggested that the use of prophylactic antibiotics in these circumstances is appropriate, but for patients and clinicians who remain uncertain about the overall benefits, inclusion in an RCT to clarify this issue (the ORACLE trial) is an option. (GRADE A)

- The most appropriate prophylactic antibiotic regimen for women with PPROM is unknown. Clinicians who choose to use prophylaxis (rather than participate in an RCT) might use: erythromycin 500mg qds plus co-amoxyclav (Augmentin) 375mg tds for 7 days or clindamycin 150mg qds for 7 days. (GRADE C)

There is increasing recognition that subclinical intra-amniotic infection may be an important aetiological factor among those cases of preterm labour previously thought of as idiopathic. The hypothesis that antibiotic therapy might be of benefit in the care of women in preterm labour is thus attractive. Crowley has undertaken a meta-analysis of 8 trials (judged as being generally of poor quality) relating to antibiotics in preterm labour with intact membranes. The conclusion of her meta-analysis was that there is no evidence that antibiotics are of benefit in this clinical situation. The ORACLE study (MRC Preterm Antibiotic Uncertainty Study) aims to provide further evidence on this point, and the SOGAP working group consider that antibiotics should not routinely be used in idiopathic preterm labour with intact membranes at present, but that this recommendation be reviewed once the findings of the ORACLE trial are available.

Crowley has also conducted a meta-analysis relating to antibiotics in preterm pre-labour rupture of the membranes (PPROM) which included data from 13 trials. Again, the trials were regarded as being of variable methodological quality, but the conclusion was that the use of antibiotics in these clinical circumstances does delay delivery and reduce maternal and neonatal infection. However, this benefit has not been reflected in a demonstrable effect on perinatal mortality.

An independent systematic review by Mercer and Arheart employed a rigorous search strategy and similarly concluded that antibiotic therapy in the presence of PPROM results in pregnancy prolongation and in reduction of maternal and neonatal infectious morbidity. These authors highlight the wide range of antibiotic regimens employed in studies to date and acknowledge that the optimal regimen remains unknown.

At the present time, the SOGAP group suggests that clinicians might employ the same combination of antibiotics (erythromycin plus Augmentin) as were chosen for the combination therapy arm of the ORACLE trial. The dosage schedule chosen for ORACLE (erythromycin 250mg qds plus Augmentin 375mg qds for 10 days) differs from conventional clinical prescribing. The SOGAP group suggests that clinicians choosing to use this combination of antibiotics might prefer to use more conventional doses of erythromycin 500mg qds plus co-amoxyclav (Augmentin) 375mg tds for 7 days.
The ORACLE combination was selected as providing coverage against gram-positive and -negative anaerobes, gram-positive aerobes and also chlamydia and ureaplasma. However, it has been suggested that up to 10% of postpartum pyrexias are attributable to mycoplasma hominis. The SOGAP group acknowledges that the ORACLE combination does not provide cover against this organism and suggest clindamycin (150mg qds for 7 days) as an alternative prophylactic regimen which would provide such cover. The group are aware that some obstetricians have a reluctance to prescribe clindamycin in the context of prophylaxis because of a fear of serious intestinal side-effects. However, there is a precedent for recommending clindamycin for prophylaxis in that it is one of the agents recommended for prophylaxis against infective endocarditis by the British Society for Antimicrobial Chemotherapy\textsuperscript{42,43}. In their first report of 1990\textsuperscript{42}, this group had specifically requested reports of side-effects related to clindamycin prophylaxis. In their update of 1992\textsuperscript{43}, they indicate that no reports of side-effects had been received.

### 2.5.4 VITAMIN K, PHENOBARBITONE

<table>
<thead>
<tr>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>✗ Currently available evidence does not suggest that antenatal administration of either Vitamin K or phenobarbitone is of value for most women at risk of preterm delivery \textsuperscript{44,45}. (GRADE A)</td>
</tr>
<tr>
<td>✗ The babies of women treated with enzyme-inducing anticonvulsants (carbamazepine, phenytoin, primidone, phenobarbitone) are at increased risk of haemorrhagic disease of the newborn caused by deficiency of Vitamin K-dependent clotting factors. All women on these drugs should receive prophylactic Vitamin K (Konakion) 20mg orally daily from 36 weeks gestation until delivery. If such a woman is perceived to be at risk of delivery prior to 36 weeks gestation and steroid therapy is initiated, then Vitamin K therapy should be initiated simultaneously. (GRADE B)</td>
</tr>
</tbody>
</table>

Crowther has contributed a meta-analysis to the CPCD on the role of Vitamin K prior to preterm delivery\textsuperscript{44}. This included three small trials of good methodological quality. The meta-analysis suggested a decrease in incidence of severe IVH associated with Vit. K administration, but this was not reflected in a decrease in neonatal deaths or in RDS. The conclusion was that there are too few data to recommend routine use of antenatal Vitamin K. The companion SOGAP guideline on *The Management of Pregnancy in Women with Epilepsy* has addressed the issue of antenatal Vitamin K therapy for women on enzyme-inducing anticonvulsants. The SOGAP *Epilepsy* group concluded that all women on enzyme-inducing anticonvulsants should receive oral Vitamin K (Konakion 20mg daily) from 36 weeks until delivery, and that those perceived to be at risk of delivering earlier than this should commence Vitamin K prophylaxis simultaneously with the commencement of steroid prophylaxis.

A further meta-analysis, also by Crowther in the CPCD has examined the role of antenatal phenobarbitone\textsuperscript{45}. Similarly, available results suggest that the administration of phenobarbitone prior to imminent, very preterm delivery may reduce IVH and neonatal mortality. However the conclusion is that there is insufficient evidence to warrant introduction of this treatment into clinical practice.
2.6 MODE OF DELIVERY

Recommendation

- Prematurity, per se should not be regarded as an indication for Caesarean section. Vaginal delivery should be planned unless there are other indications for operative delivery.
  (GRADE C)

Grant has contributed a meta-analysis to the CPCD\textsuperscript{46} assessing the value of a policy of elective Caesarean section versus selective Caesarean section for women in preterm labour at risk of delivering immature babies. The meta-analysis included 5 trials which, unfortunately, only included a total of 104 women. The conclusion was that currently available data are insufficient to justify a policy of elective Caesarean delivery for the small baby (regardless of whether presenting by the vertex or the breech).

It has been suggested that delaying the clamping of the umbilical cord following delivery of a preterm infant may have benefits. A meta-analysis by Elbourne in the CPCD covered six trials addressing this issue. The conclusion reached was that there are currently insufficient data to support a policy of either immediate or delayed cord clamping and that decisions about when to clamp the cord should be based on the urgency of the need for resuscitation.

2.7 PREPARATION FOR THE CARE OF THE PRETERM INFANT

Recommendations

- The most appropriate nutrient for a preterm baby is milk from his own mother\textsuperscript{47,48}. Mothers at risk of preterm delivery should receive appropriate support to establish breast feeding.
  (GRADE B)

- Staff should acknowledge the psychological impact on parents of delivering a preterm infant. Efforts should be made to make parents aware of the likely size of their forthcoming infant and of the special elements of care which will be required.
  (GRADE C)

Wilson\textsuperscript{47} and Lawrence\textsuperscript{48} have reviewed the nutrition of the preterm baby and emphasise that “over the past few years there is growing advocacy for providing the preterm infant with his own mother's milk whenever possible”. Although preterm formula can provide adequate nutrients, there is evidence that it takes longer to establish full enteral feeding in preterm infants fed formula rather than breast milk, and that breast feeding protects against necrotising enterocolitis, even if supplemented. The Canadian Paediatric Association\textsuperscript{49} and other authors\textsuperscript{50,51} advocate that preterm infants receive folate and vitamin B-12 supplements in addition to maternal milk.

The final two recommendations in this section reflect the growing recognition of the psychological impact on parents of delivery of a small, preterm infant\textsuperscript{52}. Medical and midwifery staff caring for mothers identified as being at risk of preterm delivery should be aware of those forms of support available locally, should prepare parents for the potential small size of their forthcoming infant (perhaps by means of a visit to the neonatal unit to see an infant of similar gestational age) and should pave the way for supportive care in the hospital, transitional and home settings.
3. REFERENCES QUOTED IN TEXT


7. Scientific advisory committee of RCOG. RCOG Guidelines No.7 Antenatal corticosteroids to prevent respiratory distress syndrome.


REFERENCES


28. Scientific Advisory Committee of RCOG. RCOG Guidelines No.1 For the use of ritodrine.


4. ADDITIONAL REFERENCES

The following references were selected from those retrieved in the Medline search undertaken in the development of this guideline as being of relevance to the subject and were studied in the course of writing the guideline. These references are not cited in the final text but are provided here for the information of guideline users.

4.1 REFERENCES RELATING TO USE OF STEROIDS


4.2 REFERENCES RELATING TO IDENTIFICATION OF WOMEN AT RISK OF PRETERM DELIVERY


4.3 REFERENCES RELATING TO TOCOLYSIS


4.4 REFERENCES RELATING TO THE ROLE OF INFECTION AND THE USE OF ANTIBIOTICS IN PRETERM LABOUR


4.5 REFERENCES RELATING TO OTHER ASSOCIATED THERAPIES


4.6 REFERENCES RELATING TO MODE OF DELIVERY


4.7 REFERENCES RELATING TO PREPARATION FOR THE CARE OF A PRETERM INFANT


### APPENDIX I *

**Suggested Minimum Data Set For Audit Of Compliance With Recommendations On Antenatal Steroids**

<table>
<thead>
<tr>
<th>Name of woman</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital Number</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was she delivered in this hospital?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Were antenatal corticosteroids given in a previous admission this pregnancy?</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>

1. Working estimate of gestation at birth    
2. Time of admission to this hospital    
3. Date of admission to this hospital    
4. Time of delivery    
5. Date of delivery    
6. Period from admission to birth    
7. Was this more than 48 hours?    
8. Were antenatal corticosteroids given in this admission?    
9. If NO, what reasons were given?    
10. Time started antenatal corticosteroids    
11. Date started antenatal corticosteroids    
12. Period from starting antenatal corticosteroids to delivery

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* From the Scottish Neonatal Consultants’ Collaborative Group - Trends and variations in use of antenatal corticosteroids to prevent neonatal respiratory distress syndrome: recommendations for national and international comparative audit - BJOG 1996;103,534-540