# Modern Management of Preterm Labour

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*Preterm birth is the leading cause of neonatal morbidity and mortality. Cervical insufficiency is not an all or nothing phenomenon but a continuous variable which can lead to preterm deliveries at different gestational ages. The relationship between shortened cervical length and spontaneous preterm birth is consistent in several studies. Shortened cervical length can be diagnosed by transvaginal ultrasonography and treated by transvaginal cervical cerclage (TCC). A nomenclature to the different stages of prevention, as primary, secondary and tertiary was suggested to facilitate comparison of studies. Apart from cervical cerclage, the most widely used tocolytics are betamimetics. Although they have been shown to delay delivery, betamimetics have not been shown to improve perinatal outcome, and they have a high frequency of unpleasant and even fatal and maternal side effects. There is growing interest in calcium channel blockers which appear to be more effective than beta-sympathomimetic drugs and have few side-effects.*

***Keywords:*** *Preterm labour, Management*

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## Introduction

Preterm birth is the leading cause of neonatal morbidity and mortality. Spontaneous preterm birth occurs before 37 weeks' gestation in 7-11% of pregnancies and before 34 weeks' gestation in 3-7% of pregnancies. Despite major improvements in medical care and socioeconomic status of the population in developed countries and extensive medical research, the incidence of preterm birth has not decreased over the years. Lowering the incidence of preterm birth and related neonatal morbidity and mortality remains a major goal in obstetrics. The etiology of preterm birth is multifactorial. One of the causes of preterm birth is cervical incompetence. The reported incidences of cervical incompetence vary between 0.05 and 1.8%[1]. This review will firstly focus on cervical incompetence as actually a very important continuous variable, and its management. Subsequently, this review will focus on current use of tocolytic drugs in the management of preterm labour.

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## Cervical incompetence, all or nothing?

Traditionally CI (CI= cervical incompetence) is defined as: *recurrent second trimester pregnancy loss caused by an inability of the uterine cervix to retain the pregnancy. The cervix effaces and dilates in absence of pain, contractions and vaginal blood loss. The membranes generally protrude into the vagina and their rupture is followed by a rapid and almost painless delivery of, in most cases, a living fetus*[2] . This traditional definition of CI implies that the incompetent cervix results in recurrent second trimester loss in subsequent pregnancies. Recent studies have shown that an incompetent cervix is not an all or nothing phenomenon causing repetitive preterm delivery in all subsequent pregnancies, but can express differently in subsequent pregnancies.[3] There seems to be various degrees of CI, leading to preterm deliveries at different gestational ages.

The traditional definition emphasizes that the cervix effaces and dilates in absence of pain and contractions, suggesting there is a distinct difference between preterm delivery due to CI and preterm delivery due to preterm labor. In the traditional hypothesis

of CI as a categoric variable, cervical length (CL) should be short for women with a history of incompetent cervix and normal for women with a history of spontaneous preterm delivery, regardless of gestational age.[4] In the alternative hypothesis of CI as a continuous variable, CL should correlate in a linear fashion with the gestational age at delivery in previous pregnancies.[5] CI and preterm labor are not distinct entities but rather part of a spectrum leading to preterm delivery. Furthermore, in case of a dilated cervix originated in the absence of uterine activity as in CI, the cervical change will eventually lead to some uterine activity, leading to the final expulsion of the conceptus[6]. Furthermore, when cervical ripening occurs the usual mechanical barrier between the vaginal flora and the chorioamnion-decidual interface is disrupted, which may further stimulate processes, like ascending infection culminating in spontaneous preterm birth[7]. The complex causative relationship between CI and preterm labor is still unsolved[8].

In summary, based on our current knowledge, the traditional definition of CI is obsolete. CI is a continuous variable, meaning that there are various degrees of CI and that CI and preterm labor are part of a spectrum leading to preterm delivery. Furthermore, the phenotypical expression of a certain degree of CI does not have to express consistently in subsequent pregnancies.

**Detection of short cervix**

Timely detection of the short cervix by digital examination in order to detect threatened preterm delivery due to CI has been used in prenatal care. For many years digital examination during pregnancy was used to detect imminent preterm delivery[9,10]. Dilatation of the cervical canal as an early sign of CI however, starts at the level of the internal os[11]. Therefore, diagnosis of CI by digital examination is always a diagnosis in a late stage of the process, at which point it is extremely difficult to postpone or prevent the imminent preterm delivery.

Initially, transabdominal ultrasonography was introduced to detect dilatation of the cervix[12] and imminent preterm delivery[13,14]. The supra vaginal part of the cervix can be visualized with full bladder. The pressure of a filled bladder on the cervix can close a dilated cervix, resulting in an overestimation of CL and an underestimation of cervical dilatation[15]. The overestimation of CL was overcome by the introduction of transvaginal ultrasonography of the cervix[16].

**Transvaginal ultrasonography**

Women are instructed to empty the bladder before the ultrasonographic examination and are examined in dorsal lithotomy position. A high-resolution endovaginal probe is inserted into the vagina and is placed into the anterior fornix. The appropriate sagittal plane to measure CL includes three essential landmarks, a small almost V-shaped notch that represents the internal cervical os, a triangular area of echodensity representing the external cervical os and a faint line of echodensity or echolucency between both cervical openings that represents the endocervical canal[17]. After an ultrasonographic image of the cervix that contains all three landmarks has been obtained, the transducer is withdrawn slightly to avoid an artificial increase of the endocervical canal as a result of pressure of the transducer against the uterine cervix and subsequently when the image starts to become blurry, the probe is reapplied only enough to restore the image[18]. Next, the image is frozen and electronic callipers are used to measure CL. CL is defined as the distance between the internal cervical os and the external cervical os. In case of funneling, defined as protrusion of the membranes into the endocervical canal, CL is measured as the distance between the apex of the funneling and the external cervical os. In some instances the endocervical canal is slightly curved and measurement in two steps along the curve results in a better representation of CL[19]. CL is measured several times and the shortest best image is used because the first measurement is usually a few mm longer than the second or third, due to transducer pressure on the cervical canal[18]. During an ultrasonographic examination, CL might change rapidly, resulting in funneling or increase of funneling and shorter CL[20]. An ultrasonographic session should take several minutes to observe possible rapid dynamic changes and the shorter CL is measured. These changes can be provoked by applying transfundal pressure[21]. When this manoeuvre provokes funneling and shortening of CL, the shorter CL is measured.

**Cervical length**

The relationship between CL and the risk of preterm delivery have been published[11,22,23]. Shortening of CL appears to be a continuous process, and funnelling is associated with the risk of preterm delivery[11,17,24]. However, not all short cervices show funneling, because of different processes of cervical shortening[25] and the funnel disappears when the cervix becomes shorter[26]. CL is much easier to measure than

funnelling[6,24]. Therefore, CL measurements by transvaginal ultrasonography are used to monitor and manage patients with an obstetric history consistent with CI, patients with a variety of risk factors for preterm delivery, patients presenting with preterm labor and as screening to identify those patients at risk in general populations. Abnormal ultrasonographic findings of the cervix do probably demonstrate a potential final common pathway of multiple pathophysiological processes, such as infection, immunologically mediated inflammatory stimuli, and subclinical abruptio placentae[27]. The relationship between CL and preterm delivery due to CI is based on studies among patients with risk factors for preterm delivery. However, risk factors for preterm delivery, does not necessarily mean risk factors for CI.

The relationship between CL and the risk of preterm delivery in asymptomatic women considered to be at high risk of preterm delivery have been reported[5,24,25,28,29]. A variety of risk factors is presented in these studies; one or more preterm deliveries, two or more voluntary terminations, previous cerclage, M llerian anomaly, DES exposure in utero, cone biopsy, and Ehlers-Danlos syndrome[29,30]. The essentials of the studies' designs and results, of these studies on the predictive value of CL, are as far as they are extractable from the publications presented in Table 1.

Many studies focused on the prediction of spontaneous preterm delivery in singleton pregnancies by transvaginal ultrasonography of the cervix in general obstetric populations. The studies on the predictive value of CL are presented in table 2. [17,31-38]

In general populations CL is normally distributed[17,36]. Both in high risk and low risk women, CL is an independent variable in the prediction of preterm delivery[24,25,34-36] and a short CL is related to an increased risk of preterm delivery[5,17,32,35,36]. In both populations CL is inversely correlated to the risk of preterm delivery[30,31,37,38]. CL measured between 11 and 14 weeks' gestation was not found to be associated with subsequent spontaneous preterm delivery[33]. A CL < 25 mm seems to be the optimal cut-off in discriminating those patients truly at high risk of preterm delivery among patients considered to be at high risk[24,25,30]. Transvaginal ultrasonographic follow-up of the cervix is advised to be performed in high risk women between 14 and 24 weeks' gestation [24,29,30]. The studies on screening of low risk populations used cut-offs between 15 and 39 mm. Obviously, the higher the cut-off the higher the sensitivity and the lower the specificity. There are currently no studies supporting the implementation of sonographic screening for short CL in a low risk group. Furthermore, effective treatment of low risk women with short CL has not yet been established.

**Table 1.** Essentials of studies designs' and results of studies correlating measurements of cervical length with the risk of preterm delivery in high risk asymptomatic women

| Publications | No. of women | Blinded Yes/No | Endpoint PTD* (wks) | % PTD at endpoint | Gestational age cervical length (wks) | Cervical length cut-off (mm) | Sens* (%) | Spec* (%) | PPV* (%) | NPV* (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Andrews et al. 2000[28] | 69 | Yes | <35 | 26 | <20 | ?22 | 27 | 100 | 100 | 78 |
| | | | | | | ?25 | 33 | 100 | 100 | 79 |
| | | | | | 20-24 | ?22 | 31 | 93 | 57 | 82 |
| | | | | | | ?25 | 39 | 89 | 50 | 83 |
| | | | | | 25-29 | ?22 | 78 | 79 | 50 | 93 |
| | | | | | | ?25 | 89 | 73 | 47 | 96 |
| Berghella et al. 1997[30] | 96 | No | <35 | 16 | 14-30 | <16 | 29 | 94 | 50 | 88 |
| | | | | | | <25 | 59 | 85 | 45 | 91 |
| Berghella et al. 2003[29] | 183 | No | <35 | 20 | 10-14 | <25 | 14 | 97 | 50 | 82 |
| | | | | | 14-24 | <25 | 69 | 76 | 41 | 89 |
| Guzman et al. 2001[24] | 469 | No | <34 | 12 | 15-20 | ?25 | 56 | 80 | 23 | 95 |
| | | | | | 21-24 | ?25 | 64 | 76 | 16 | 97 |
| | | | | | 15-24 | ?15 | 81 | 72 | 29 | 96 |
| | | | | | | ?25 | 76 | 68 | 20 | 96 |
| Owen et al. 2001[25] | 183 | Yes | <35 | 26 | 16-19 | <15 | 10 | 100 | 100 | 76 |
| | | | | | | <20 | 10 | 99 | 83 | 76 |
| | | | | | | <25 | 19 | 98 | 75 | 77 |
| | | | | | | <30 | 38 | 87 | 50 | 80 |

* PTD = preterm delivery, Sens = sensitivity, Spec = specificity, PPV = positive predictive value, NPV = negative predictive value

**Table 2.** Essentials of studies designs' and results of studies correlating measurements of vervical length with the risk of preterm delivery in low risk women

| Publications | No. of women | Blinded Yes/No | Endpoint PTD* (wks) | % PTD at endpoint | Gestational age cervical length (wks) | Cervical length cut-off (mm) | Sens* (%) | Spec* (%) | PPV* (%) | NPV* (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Andersen et al. 1990[31] | 112 | Yes | <37 | 15.2 | <30 | <39 | 76 | 59 | 25 | 93 |
| Arinami et al. 1999[32] | 683 | Yes | ?34 | 1.0 | 26-28 | <25 | 57.1 | 93.2 | 8.2 | 99.5 |
| | | | | | | <30 | 85.7 | 76.0 | 3.6 | 99.8 |
| Carvalho et al. 2003[33] | 529 | Yes | <33 | NE* | 22-24 | ?20 | 40 | 97 | 23.5 | 98.8 |
| | | | <35 | NE | 22-24 | ?20 | 42.3 | 96.7 | 37.9 | 97.2 |
| Hassan et al. 2000[34] | 6877 | No | ?32 | 3.6 | 14-24 | ?15 | 8.2 | 99.7 | 47.6 | 96.7 |
| | | | | | | ?20 | 10.6 | 99.4 | 40.6 | 96.8 |
| | | | | | | ?25 | 14.7 | 98.8 | 31.6 | 96.9 |
| Heath et al. 1998[35] | 1252 | No | ?32 | 1.5 | 22-24 | ?15 | 58 | 99 | 52 | 99 |
| Hibbard et al. 2000[36] | 760 | No | <32 | 3.6 | 16-22 | ?22 | 18.5 | 97.9 | 27 | 9.8 |
| | | | | | | ?27 | 29.6 | 95.8 | 22.9 | 97.2 |
| | | | | | | ?30 | 44.4 | 89.9 | 14.8 | 97.6 |
| | | | <35 | 6.7 | 16-22 | ?22 | 21.6 | 97.7 | 47.0 | 94.0 |
| | | | | | | ?27 | 29.4 | 96.5 | 43.9 | 94.4 |
| | | | | | | ?30 | 41.2 | 90.7 | 27.0 | 95.0 |
| Iams et al. 1996[17] | 2915 | No | <35 | 4.3 | 24 | ?20 | 23.0 | 97 | 25.7 | 96.5 |
| | | | | | | ?25 | 37.3 | 92.2 | 17.8 | 97.0 |
| | | | | | | ?30 | 54.0 | 76.3 | 9.3 | 97.4 |
| | 2531 | No | <35 | 3.3 | 28 | ?20 | 31.3 | 94.7 | 16.7 | 97.6 |
| | | | | | | ?25 | 49.4 | 86.8 | 11.3 | 98.0 |
| | | | | | | ?30 | 69.9 | 68.5 | 7.0 | 98.5 |
| Taipale et al. 1998[37] | 3694 | Yes | <35 | 0.8 | 18-22 | ?29 | 19 | 97 | 6 | 99 |
| Tongsong et al. 1995[38] | 730 | NE | <37 | 12.5 | 28-30 | <35 | 66 | 62 | 20 | 93 |

* PTD = preterm delivery, Sens = sensitivity, PPV = positive predictive value, NE = not extractable, Spec = specificity, NPV = negative, predictive value

According to the American College of Obstetricians and Gynecologists, ultrasonography lacks discriminatory power to recommend its routine use for screening[39]. Basedon these facts, the authors would like to state that screening of women at low risk by transvaginal ultrasonography is not a useful diagnostic tool in the prevention of preterm delivery.

**Transvaginal cervical cerclage (TCC)**

A TCC may be inserted prophylactically before pregnancy or during the first trimester or it may be placed therapeutically during later pregnancy after detection of cervical changes[40]. During a therapeutic cerclage procedure, if the membranes are exposed to the vagina, the procedure is also called an emergency cerclage procedure. Another used differentiation of therapeutic cerclages is urgent versus emergent. The emergency cerclage is by some called a salvage cerclage. The type of cerclage procedure used, prophylactic or therapeutic, is frequently not clearly stated in the existing literature. This makes proper interpretation of the results extremely difficult.

A less confusing nomenclature for TCC would ease studying and interpretation of the literature. Classification of TCC according to the different stages of prevention, as primary, secondary and tertiary TCC may be more appropriate. Primary prevention means averting the occurrence of a disease. Secondary prevention implies breaking off the disease process before the emergence of clinically recognizable disease. Tertiary prevention means prevention of complications caused by the disease process, and is thus more or less synonymous to treating a disease.

**Primary transvaginal cervical cerclage**

The primary TCC is a prophylactic cerclage

performed based on history. In general a primary TCC is performed at a gestational age of 10 tot 12 weeks. Recently, several studies compared primary transvaginal cerclage with transvaginal follow-up of the cervical length and secondary intervention, if necessary[3,41-43]. Management with transvaginal follow-up of CL with secondary intervention as indicated appears to be a safe alternative to the traditional primary TCC and prevents the majority of women from undergoing an unnecessary intervention. The estimated serious complication leading to pregnancy loss occurs in about 1 in 50 prophylactic cerclage procedures[44]. Frequently reported complications include chorioamnionitis, preterm rupture of membranes, preterm labor, dislocation of the cerclage, cervical laceration and cervical dystocia. Reported cases of more rare complications are uterine rupture, endotoxic shock and maternal death.

**Secondary transvaginal cervical cerclage**

The secondary TCC is a therapeutic cerclage performed after the detection of cervical changes. These cervical changes are preferably detected by transvaginal ultrasound. The cervical changes should not be so severe that the membranes are exposed to the vagina. So far only three observational studies and two randomized trials have been published comparing treatment with and without secondary TCC after detection of cervical changes on transvaginal ultrasonography [27,45-49]. (Table 3) After reviewing the literature, a secondary cerclage with bed rest seems to be the preferred management for women at high risk of preterm delivery due to CI based on history and measurement of short CL.

**Tertiary transvaginal cervical cerclage**

The tertiary TCC is a therapeutic cerclage performed after the detection of cervical changes of such a severity that the membranes are exposed to the vagina. Only two trials have been published that compared management with a tertiary cerclage and man-

**Table 3.** Essentials of designs' and results of studies comparing treatment with and without secondary transvaginal cervical cerclage after detection of cervical changes on transvaginal ultrasonography

| Publications | Population | CL*(mm) F* (%) | GA* (wks) ultrasound | Cerclage N | No cerclage N | Endpoint PTD*(wks) | PTD cerclage endpoint (%) | PTD no cerclage endpoint (%) | P |
|---|---|---|---|---|---|---|---|---|---|
| Althuisius et al. 2001[45] | History<br>• PTD <34 wks due to cervical incompetence<br>• Uterine anomaly<br>• Exposure to DES<br>• Cervical conization<br>Current pregnancy<br>• Symptoms of cervical incompetence | CL<25 | <27 | 19 | 16 | <34 | 9 | 44 | 0.002 |
| Berghella et al. 1999[46] | History<br>• ? 1 PTD 14-34 wks<br>• ?2 D&C*<br>• uterus anomaly<br>• cervical conization<br>• DES exposure | CL<25 and/or F>25% | 14-24 | 39 | 24 | <35 | 46.2 | 20.8 | NS* |
| Heath et al.1998 [47] | General obstetric | CL<16 | 23 | 22 | 21 | <32 | 5 | 52 | 0.001 |
| Rust et al. 2000 [27] | History<br>• PTD<br>• cervical conization<br>• cervical LEEP / Laser<br>• Uterine anomaly<br>Current pregnancy<br>• Multiple gestation<br>• Abnormal LUS* | CL<25 and/or F>25% | 16-24 | 31 | 30 | <34 | 38.7 | 30 | NS |
| Rust et al. 2001 [49] | History<br>• PTD<br>• cervical conization<br>• cervical LEEP / Laser<br>• Uterine anomaly<br>Current pregnancy<br>• Multiple gestation<br>• Abnormal LUS | CL<25 and/or F>25% | 16-24 | 55 | 58 | <34 | 34.9 | 36.2 | NS |

CL = cervical length, F = funnelling, LUS = lower uterine segment, PTD = preterm delivery, D&C = dilatation and curettage,
GA = gestational age, NS = not significant

agement with bed rest[50,51]. Based on previous studies, in case of imminent preterm delivery due to CI with exposure of the membranes to the vagina through a dilated external cervical os, management with tertiary cerclage and bed rest results in a better prognosis compared to just bed rest.

However, the results of systematic reviews on the management of CI are conflicting. The future research should be structured similarly, in order to be able to make sufficient comparisons and draw definite conclusions.

**Tocolytic Drugs**

As mentioned previously, preterm birth is a major contributor to perinatal mortality and morbidity, and no progress has been made over the last two decades in reducing the incidence of preterm birth in developed countries but some benefits have been identified from prolongation of pregnancy by enabling corticosteroids to be administered to hasten fetal lung maturation and to effect transfer to a centre with neonatal intensive care facilities. A range of tocolytic agents has been used to inhibit preterm labour in order to allow time for such co-interventions to occur. The tocolytics which have been most widely tested are the betamimetics (ritodrine, salbutamol and terbutaline), and they have been shown to be effective in delaying delivery by up to seven days and longer, but not with an improved perinatal outcome.

Betamimetics have a high frequency of unpleasant, sometimes severe maternal side effects including tachycardia, hypotension, tremulousness and a range of biochemical disturbances. Furthermore, betamimetics have been associated with at least 25 maternal deaths mainly from pulmonary edema. Therefore, an effective tocolytic agent with less side effects than the betamimetics is an urgent need.

**Calcium Channel blockers (CCBs)**

Calcium channel blockers (CCBs) are nonspecific smooth muscle relaxants, predominantly used for the treatment of hypertension in adults. They exert their tocolytic effect by preventing the influx of extracellular calcium ions into the myometrial cell. They have been demonstrated in vitro to have potent relaxant effect on human myometrium[114] .The most widely used and studied CCB is nifedipine which (like nicardipine) belongs to the dihydropiridine group. Currently nifedipine is gradually replacing betamimetics as the most commonly used tocolytic agent in clinical practice.

CCBs are a heterogeneous group and do not have a single class effect. The aim of this section of this part of this review is to present a summary of the use, safety and side effects of CCBs, especially nifedipine in the management of preterm labour.

**Pharmacology of Calcium Channel Blockers**

In cardiac, skeletal and smooth muscle, contraction is triggered by a rise in cytosolic calcium. The level of intracellular calcium depends on entry through calcium channels and intracellular release from mitochondria or the sarcoplasmatic reticulum. CCBs are able to block the flow of extracellular calcium into cardiac and smooth muscle cells and to influence contraction. There are different calcium channels. Activation can occur by an action potential (voltage-dependent channels), or by binding of a calcium receptor in the cell membrane which allows entry of extracellular calcium or activates a second messenger (receptor-operated channels). CCBs influence the voltage dependent channels. Three different types of calcium channels receptors are the nifedipine-like, the verapamil-like and the diltiazem-like[52]. The density of the channels is not influenced by long-term treatment with CCBs, therefore no tachyphylaxis or withdrawal symptoms will occur when therapy is stopped. It should be noted that the absence of tachyphylaxis is in marked contrast with clinical experience with betamimetics [53]. Although calcium blockers have very different chemical and pharmacodynamic characteristics, they exhibit rather similar pharmacokinetic properties. In spite of a high oral absorption rate bioavailability is low because of a considerable first pass effect. CCBs are mainly metabolised in the liver. The biologically inactive metabolites are excreted by the kidneys for 70-80%. The remainder is excreted in the faeces. Half-life is short and most metabolites are inactive [54].

**Side effects and Safety**

Most side effects of CCBs are due to vasodilata-tion of peripheral vessels. Compared to other drugs side effects of CCBs are mild and no tachyphylaxis is induced [55]. The most common side effects are tachycardia, palpitations, peripheral edema, headaches and facial flushing. Other less common side effects are constipation, dizziness, nausea, bradycardia, fatigue and increased liver enzymes. Contra-indications are conducting defects, hypotension and left-ventricular heart failure. Hepatic and renal failure are not absolute contra-indications for the use of CCBs. In several randomised trials the administration of nifedipine is

**Table 4.** Maternal and fetal side effects associated with tocolytic therapy

| | Side effects | | Nifedipine | Ritodrine |
|---|---|---|---|---|
| Maternal | cardiovascular: | Hypotension | + | ++ |
| | | Tachycardia | + | ++ |
| | | Flushes | ++ | - |
| | | Headache | ++ | + |
| | | pulmonary oedema | - | + |
| | | Palpitations | - | + |
| | metabolic: | Hypokaliemia | - | ++ |
| | | increased liver enzymes | + | + |
| | | Hypoglycaemia | - | ++ |
| | | Hyperglycemia | - | ++ |
| | subjective: | Nausea | + | ++ |
| | | Dizziness | + | - |
| | | Tremor | - | + |
| | | Anxiety | - | + |
| Fetal | cardiovascular: | Tachycardia | - | ++ |
| | | decreased blood flow | - | - |
| | metabolic: | Hypoglycaemia | - | + |
| | | Hyperglycemia | - | + |
| | | Hyperbilirubinemia | - | + |
| | other: | Teratogenicity | - | + |

: absent; + : occasionally; ++ : frequent

associated with less maternal side effects compared with ritodrine [56-58]. Table 4 shows a summary of maternal and fetal side effects of nifedipine and ritodrine.

Studies in human pregnancy did not show any significant alterations in uterine blood flow [59]. Incidence of major malformations was not increased[60]. Nifedipine and nicardipine are excreted in breast milk. In breast milk the concentration of nifedipine equals the serum concentration. When therapy is stopped nifedipine can still be found in breast milk for three days. The American Academy of Pediatrics considers nifedipine compatible with breast-feeding [61].

In conclusion nifedipine appears to have few serious side effects. The influence on mater-nal cardiac output and heart rate is mild in contrast to ritodrine, a drug known to increase cardiac output and to cause tachycardia. Furthermore, nifedipine does not cause fetal tachycardia. The absence of drug-induced fetal tachycardia may help the obstetrician to diagnose intra-uterine infection at an early stage. Although evidence of serious adverse effects of dihydropyridines in pregnancy is absent, nifedipine, nicardipine and nimodipine are still classified in "safety-group" C. This means that animal studies have revealed adverse effects on fetuses but there are no controlled studies in women and animals available. The drug should be given only if the potential benefit justi-fies the potential risk to the fetus [61]. It should be noted that the doses used in these animal studies exceeded the maximum recommended human dose considerably.

**CCBs for tocolyis**

Systematic review of the randomised controlled trials in which CCBs were compared to placebo, no treatment, or an alternative tocolytic treatment was conducted [62]. This review included 12 randomised trials of appropriate quality testing the effects of CCBs for tocolysis in preterm labour [58,63-74].

This systematic review showed that the use of CCB's resulted in a statistically significant decrease in the number of women giving birth within seven days of initiation of treatment comparing with any other tocolytic agent (relative risk (RR) 0.76; 95% confidence interval (CI) 0.60, 0.97) (Table 5) and prior to 34 weeks gestation (RR 0.83; 95%CI 0.69, 0.99) (Table 6). The number needed to treat (NNT) for the outcome of birth within 7 days is 11 (95% CI 6, 100). This means that, on average, for every 11 women treated with CCBs instead of any other tocolytic drugs, one less birth occurs within this time period. However, the confidence intervals indicate that as few as six or as many 100 women would need to be treated with a CCB to achieve this result. Maternal adverse drug reaction was reduced with CCBs (RR 0.32; 95% CI 0.24, 0.41) and cessation of treatment for maternal drug reaction was markedly reduced (RR 0.14; 95% CI 0.05, 0.44) (Table 7). The NNT for maternal adverse drug reaction was three (95% CI 3, 4) and for drug reaction requiring cessation of treatment was 14 (95% CI 10, 25). A trend toward superior tocolytic benefit was apparent in the outcomes of birth prior to 37 weeks gestation (RR 0.95; 95% CI 0.83, 1.09), within 48 hours of initiation of treatment (RR 0.80; 95%CI 0.61, 1.05) and for pregnancy prolongation (interval from treatment to delivery), (weighted mean difference (WMD) 3.83 days; 95% CI -3.04, 10.70).

When compared with any other tocolytic agent, the use of CCBs resulted in a statistically significant increase in gestation at birth (WMD 0.70 wks; 95% CI 0.19, 1.20), and a reduction in neonatal respiratory distress syndrome (RDS) (RR 0.63; 95% CI 0.46, 0.88) (Table 8), necrotising enterocolitis (RR 0.21; 95% CI 0.05, 0.96) and intraventricular haemorrhage (RR 0.59; 95% CI 0.36, 0.98). The risk reduction for the outcome of respiratory distress syndrome (RDS) gives

**Table 5.** Birth within 7 days of treatment 62

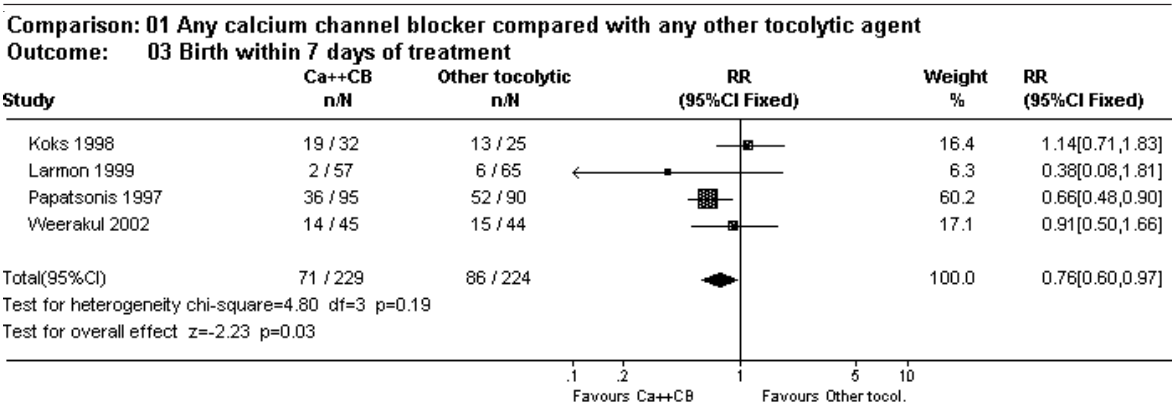
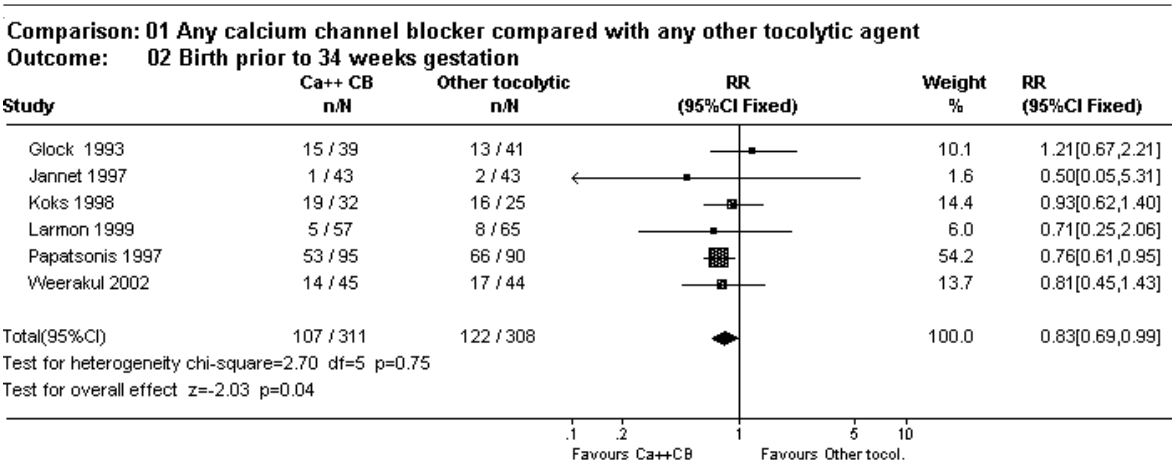



**Table 6.** Maternal adverse drug reaction requiring cessation of treatment [62]



a NNT of 14 (95% CI 8, 50) and for intraventricular haemorrhage 13 (95%CI 7, 100). Less neonatal jaundice was also shown for infants of women receiving CCB's (RR 0.73; 95% CI 0.57, 0.93). No statistically significant differences were shown for the outcomes of birthweight, admissions to neonatal intensive care unit, Apgar score < 7 at five minutes, neonatal sepsis, or perinatal mortality.

Based on the data included in this review, CCB's are shown to be a more effective tocolytic agent than betamimetics (less births within 7 days of imitation of treatment and before 34 weeks gestation) with improvement in some clinically important neonatal outcomes (less respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis and jaundice) and a marked reduction in adverse maternal side effects.[62] This supports the conclusion that CCBs should be preferred over betamimetics for those women who are considered likely to benefit from tocolytic treatment.

**Table 7.** Maternal adverse drug reaction requiring cessation of treatment 62

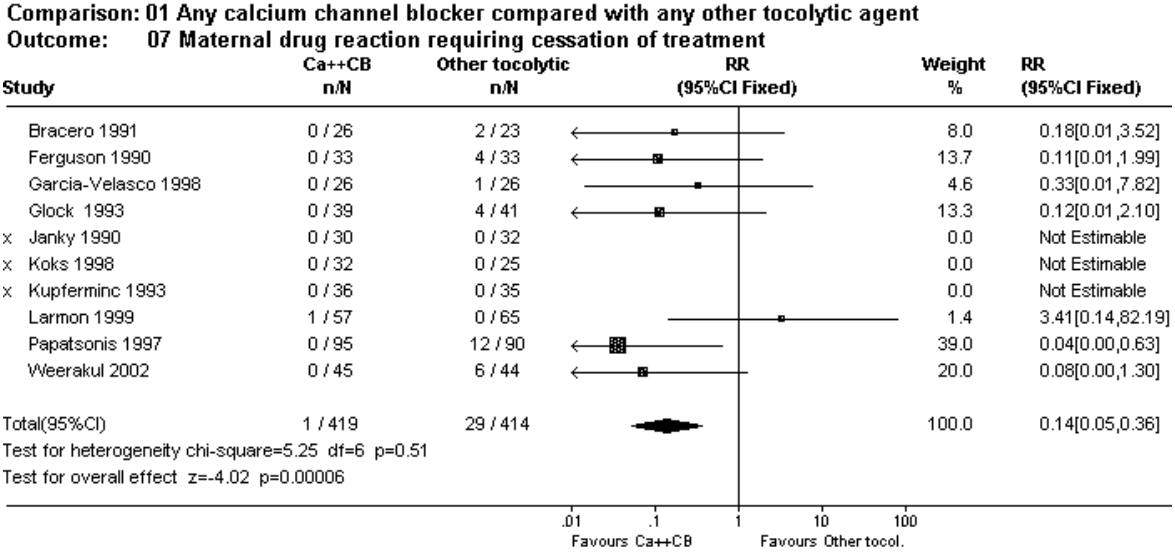
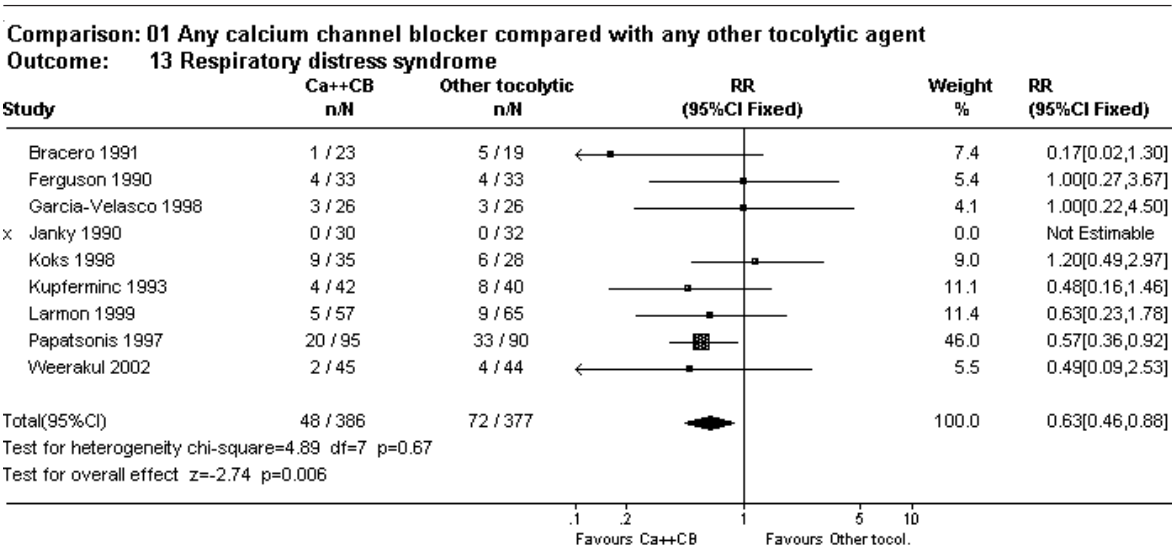



**Table 8.** Respiratory distress syndrome(Cochrane review, King et al[183])



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