4 DISCUSSION

4.1 Misoprostol and Dinoprostone

4.1.1 Use of Prostaglandins: Demographic Data

Regarding the demographic data of the main study the groups, did not differ in maternal age, gestational age, the Bishop score before starting induction or gravidity (cf. Table 3-1, page 41).

The initial Bishop score was slightly lower in the oral misoprostol group (3, Q1=2, Q3=4) and the control group (3, Q1=3, Q3=5) as compared with the vaginal misoprostol group (4, Q1=2, Q3=5).

On the other hand, there were more nulliparous patients randomised to the vaginal misoprostol and the control group with 43.3% and 42.1%, respectively, than to the oral misoprostol group with 36.7%.

The initial Bishop score and the portion of nulliparous patients in each group may have influenced the main outcome measures such as time to vaginal delivery and vaginal deliveries in the first 24 hours . This might be regarded as a positive presupposition leading to some kind of tendency. Though we find that the differences are not big enough to really expect noteworthy influences regarding the outcome parameters.

The main indication for induction of labour was pre-eclampsia (cf. Table 3-2, page 42). This can be explained by the Groote Schuur Hospital being a university teaching hospital and a tertiary referral centre for women with severe maternal disease. The Groote Schuur Hospital has a rate of approximately 4000 deliveries a year. Patients with severe pre-eclampsia are referred to this tertiary facility for further management from the Cape Peninsula Maternity and Neonatal Service which has approximately 25,000 deliveries per annum.

Mowbray Maternity Hospital is a secondary level centre with a birth-rate of 8000 per annum.

The women randomised for the pilot study were similar with respect to the median age, estimated gestational age at entry, and initial Bishop score. The median gestational age at entry was 38 in the combined vaginal and oral treated group and 39 in the oral group, the median pre-induction Bishop score was 4 in both groups. All patients were nulliparous because this was an inclusion requirement (cf. Table 3-32, page 67).

The indications for induction were similar for the groups. The main indication for induction of labour was pre-eclampsia (cf. Table 3-33, page 67). This again was due to the referral pattern of patients to Groote Schuur Hospital.

4.1.2 In the Course of Deliveries: Efficacy versus Safety

4.1.2.1 Vaginal Misoprostol versus Dinoprostone

The data discussed here are summarised in Table 4-1 on page 78.

Repeated vaginal application of misoprostol every 6 hours showed a comparable efficacy to the standard dinoprostone treatment in the main study.

The time from induction to delivery showed a significant advantage for patients with vaginal misoprostol with 12 h 19 min compared with dinoprostone with 14 h 49 min when all modes of delivery where included. When looking at the number of women delivering vaginally, the efficacy of both preparations was similar.

Referring to the success rate of vaginal deliveries in general, the success rate of vaginal deliveries within 24 hours of induction and the time from induction to vaginal delivery in this study of vaginal misoprostol resulted in a similar efficacy as dinoprostone did.

Regarding the deliveries within 24 hours in toto, vaginal misoprostol led to a significantly higher **success rate**. This did not hold true when looking at the success rate solely of vaginal deliveries within 24 hours. Since there were as many women delivering vaginally as by cesarean section in the groups (p=0.916), one could conclude that vaginal misoprostol leads to more cesarean sections within the first 24 hours. As the main indication for cesarean section in the vaginal misoprostol group was fetal distress, it seems obvious that the high delivery and cesarean section rate in the first 24 hours is caused by the action of vaginal misoprostol on the uterine tonus. This increased uterine tonus was partly expressed in tachysystole, not in a notable hyperstimulation syndrome, however. One hypothesis is that the application of vaginal misoprostol results in a general rise of uterine tonus not notable in fetal heart rate tracings, but causing fetal distress. To the physician, contraction anomalies or fetal heart rate abnormalities will always signal the need for special attention while a steady increase in tonus is not visible on the tocogram. Sudden additional uterine activity might stress the foeto-maternal unit to a point requiring immediate action.

The underlying mechanism for fetal distress in such a setting is not understood as yet, necessary data for contraction intensity are still lacking. Sometimes there is no obvious connection between fetal distress and visible abnormal uterine activity.

Kolderup et al. describe a rate of fetal bradycardia and late decelerations of 41% and a hyperstimulation syndrome of only 6% after application of 50 µg misoprostol vaginally. 20% of the cesarean sections in the misoprostol group and 5% in the dinoprostone control group were performed for fetal distress [209].

Rozenberg et al. conducted a study comparable to our dosage regimen. Vaginal misoprostol resulted in significantly more vaginal deliveries within 24 hours in the vaginal misoprostol group with 67.4% versus 56.8% after dinoprostone (RR 1.19, 95% CI 1.01-1.40) and a shorter induction to vaginal delivery interval, with a difference of 3.6 hours.
Though the efficacy of vaginal misoprostol was higher, the incidence of tachysystole and the cesarean section rate for fetal distress were about twice as high, but did not reach significance.
On the other hand, less cesarean sections for failed induction of labour were performed in the same group [210].

The indications for cesarean section in our study differed between the two groups, similar to Rozenberg's findings.
Dinoprostone caused less cesarean sections for fetal distress especially within the first 24 hours than vaginal misoprostol. The higher number of failed inductions after 24 hours in the dinoprostone group was noteworthy. This supports the provisional conclusion of vaginal misoprostol being more effective and dinoprostone offering more safety.

The subgroup analysis by indication for induction in Rozenberg's study showed a significant increase in meconium stained liquor, a pH of less than 7.20, and cesarean sections for fetal distress in cases where fetal compromise was the indication for induction of labour.
The fetal tolerance presenting in subjects where the indication for induction of labour was not related to the foetus was comparable for the groups [210].
Again, this indicates the strain for the foeto-maternal unit caused by induction of labour with vaginal misoprostol, especially when this unit already presents with complications beforehand.

The increased incidence of **tachysystole** after vaginal application of misoprostol in our study was also observed in other studies [189,211]. The aim of several studies published was to reduce the incidence of tachysystole and other adverse events by either reducing the dose of vaginal misoprostol or extending the dosage interval.

This goal was achieved in Los Angeles by Wing et al. by reducing the dose of vaginal misoprostol to 25 µg, applied every 4 hours into the posterior fornix. There was a significantly lower incidence of tachysystole with 7.1% in the misoprostol group than in the dinoprostone control group with 18.4% (p=0.02). Compared with dinoprostone, the induction to vaginal delivery interval was one hour shorter with misoprostol application. The success rate of vaginal deliveries within 24 hours showed no statistical differences [212].

A reduction in time from a 6-hour to a 3-hour interval leads to a slight increase in efficacy and in tachysystole as shown by Wing et al. in 1996 using 25 µg misoprostol intravaginally. The success rate of vaginal deliveries within 24 hours was 63.9% with the 3-hour regimen versus 55.4% in the 6-hour dosing group (p>0.05). Tachysystole occurred in 14.6% versus 11.2%, a hyperstimulation syndrome in 5.8% versus 2.7%, respectively, but these findings did not reach significance. There was no apparent measurable compromise of neonatal well-being or increased intervention for abnormal fetal heart rate tracings [191].

Farah et al. compared 25 µg with 50 µg doses of intravaginal misoprostol using a dosing interval of 3 hours. The time from start of induction to delivery was significantly shorter with 13 h 46 min after the higher dose of misoprostol versus 16 h 10 min (p=0.02). Although the incidence of hyperstimulation was similar between the groups, the incidence of tachysystole was nearly twice as high in the 50 µg group with 32.8% versus 15.6% (p=0.0001).
The authors concluded that the 25 µg vaginal dose is effective and associated with a lower incidence of tachysystole [213].

Several studies comparing 25 µg to 50 µg doses revealed that the 50 µg regimen had a higher efficacy. The incidence of tachysystole appeared to be increased, but no maternal or perinatal adverse events as a consequence of tachysystole were reported [213-215].
The optimum dosing regimen regarding efficacy and safety of the vaginal misoprostol administration turned out to be 25 µg every 3 to 4 hours [193,216].

In comparison with the mentioned studies, our study shows a lower incidence of tachysystole even with a dose of 50 µg misoprostol given intravaginally. We conclude that this is the result of the longer dosage interval of 6 hours.
A similar rate of tachysystole was found by Srisomboon et al. with the same dose and dosage interval [217].

Vaginal misoprostol is a very potent induction agent, but it results in higher rates of tachysystole and fetal distress compared with dinoprostone. Considering safety, a low dose of 25 µg misoprostol vaginally every 3 to 6 hours is preferred for induction of labour in viable pregnancies.

Main study	**Oral misoprostol n=120**	**Vaginal misoprostol n=120**	**Dinoprostone control n=240**	**Oral misoprostol vs. control**	**Vaginal misoprostol vs. control**	**Oral vs. vaginal misoprostol**
	n (%)	**n (%)**	**n (%)**	**P Value**	**P Value**	**P Value**
Deliveries < 24 hours	67 (55.8)	109 (90.8)	181 (75.4)	*p*=0.000	*p*=0.000	*p*=0.000
NVD < 24 hours	47 (39.2)	69 (57.5)	131 (54.6)	*p*=0.007	*p*=0.653	*p*=0.007
IDT (t=hh:mm)	22:47 (11:13 / 31:21)	12:19 (08:25 / 16:46)	14:49 (09:52 / 23:56)	*p*=0.002	*p*=0.002	*p*=0.000
IVDT (t=hh:mm)	22:38 (12:33 / 31:07)	12:10 (08:31 / 16:34)	12:53 (09:02 / 18:38)	*p*=0.000	*p*=0.489	*p*=0.000
NVD	80 (66.7)	76 (63.3)	153 (63.8)			
C/S	39 (32.5)	42 (35)	82 (34.2)			
• **for fetal distress**	20 (16.7)	33 (27.5)	33 (13.8)	*p*=0.528	*p*=0.002	*p*=0.061
• **for FIOL > 24 hrs**	8 (6.7)	1 (0.8)	22 (9.2)	*p*=0.545	*p*=0.001	*p*=0.036
Tachysystole	1 (0.8)	7 (5.8)	2 (0.8)	*p*=1.00	*p*=0.008	*p*=0.066

IDT= induction to delivery time, IVDT= induction to vaginal delivery time t=time, h= hours, m= minutes,
NVD= natural vaginal delivery, C/S= cesarean section, FIOL= failed induction of labour,
P Value ~ Fisher's exact test or Mann-Whitney-test

Table 4-1 Summarised data – main study.

4.1.2.2 Oral Misoprostol

Oral misoprostol, which can be seen as an acceptable alternative to the vaginal route, resulted in a rate of tachysystole comparable to that in the dinoprostone group of the main study, though it showed a lower efficacy (cf. Table 4-1).

The **success rate** of deliveries irrespective of the route and vaginal deliveries within the first 24 hours was significantly lower compared with the other two groups. The time from first application to vaginal delivery was 22 h 38 min, about 10 hours longer than with vaginal misoprostol or dinoprostone.

Though the time from induction to delivery and the success rate within 24 hours were lower with oral misoprostol, the rate of natural vaginal deliveries without time limit were comparable to the other two groups. The indications for the cesarean sections after oral misoprostol show a lower rate of fetal distress. This indicates firstly that oral misoprostol is as effective as vaginal

misoprostol when no time pressure is present and secondly this procedure offers more safety than the vaginal application.

Tachysystole occurred in 0.8% of the patients in the oral misoprostol group and with dinoprostone. Compared with vaginal misoprostol, a trend towards less abnormal uterine activity was noted with oral misoprostol.

Kwon et al. also described a significantly shorter induction to delivery interval of 7 hours with vaginal misoprostol after 6-hourly application of 50 µg misoprostol either vaginally or orally (p=0.0013). Tachysystole was noted in 9% of the women in the oral group and 7.3% in the vaginal group. 16.7% of the women in the oral group had surgical delivery, but none of them had to have an emergency cesarean section. In the vaginal group, 6.1% out of 23.2% of surgical deliveries required an emergency cesarean section for non-reassuring fetal heart rate tracings. In these cases tachysystole or a hyperstimulation syndrome was not noted. The authors emphasize that none of the 6.1% of the patients presented with tachysystole or uterine hypertonia [218].

The efficacy of vaginal misoprostol is obviously superior to oral misoprostol when applied every 6 hours.

Contrary to our main study the oral misoprostol application in Kwon's study resulted in a higher rate of tachysystole than vaginal misoprostol did, but none of the cesarean sections in the oral group were performed for emergency reasons. The reason may be that oral misoprostol application does not induce an increase in the steady uterine tonus as the vaginal application. The study shows again that vaginal misoprostol leads to abnormal fetal heart rate tracings without the indication of an abnormal uterine activity.

The data mentioned here indicate that a 6-hour dosing interval brought no benefit with the oral misoprostol application. Considering Zieman et al.'s pharmacokinetic results of the oral misoprostol application with a quick rise of the active metabolite in serum and a decrease of nearly 100% after 4 hours [5], we conclude that a 4-hour interval may be more effective.

4.1.2.3 Pilot study

The pilot study evaluated the combined vaginal and oral regimen for induction of labour at term in viable pregnancies. Misoprostol was given every 4 hours.

In the main study and other literature mentioned here, it was noted that repeated doses of vaginal misoprostol cause an increase in tachysystole and fetal distress.

The combined vaginal and oral regimen has been suggested as being highly effective in mid-trimester termination of pregnancy [6].

The aim of the combined vaginal and oral regimen was to achieve a high degree of efficacy without having the undesirable consequence of tachysystole associated with repeated doses of vaginal misoprostol.

Although there were no statistical differences in the main outcome measures in this pilot study, some important trends were noteworthy (cf. Table 4-2, page 80).

Eighty percent of the women in the combined vaginal and oral group delivered within 24 hours irrespective of the route as compared with 55% in the oral group. The **success rate** of vaginal deliveries within 24 hours was 35% and 25%, respectively, this also did not reach statistical significance.

The median induction to delivery time, irrespective of the route, was three and a half hours shorter in the combined vaginal and oral group. There was a 9.7-hour time advantage from the start of induction to vaginal delivery with the combined vaginal and oral group.

A trend towards more women delivering within the first 24 hours and a shorter induction to delivery time with the combined vaginal and oral regimen as compared with the oral regimen was notable.

This was offset by a higher incidence of **tachysystole** in the combined vaginal and oral misoprostol group.

Pilot study	**Vaginal oral misoprostol**	**Oral misoprostol**	**Significance**
	n (%)	**n (%)**	**P Value**
Deliveries < 24 hours	16 (80)	11 (55)	*p*=0.176
NVD < 24 hours	7 (35)	5 (25)	*p*=0.731
IDT in general (t=hh:mm)	18:08 (09:08 / 23:56)	21:35 (13:39 / 27:15)	*p*=0.114
IVDT (t=hh:mm)	10:45 (07:17 / 18:30)	20:29 (10:29 / 22:49)	*p*=0.101
Tachysystole	3 (15)	1 (5)	*p*=0.605

IDT= induction to delivery time, IVDT= induction to vaginal delivery time t=time, h= hours, m= minutes, Quartiles in brackets correspond to Q1/Q3, P Value ~ Fisher's exact test or Man-Whitney-test

Table 4-2: Summarised data - pilot study.

In comparison with the main study, an advantage in efficacy by reducing the interval of the oral misoprostol application from a 6 hour dosing regimen to a 4 hour dosing regimen was not

observed. This may possibly be due to the very low number of randomised nulliparous patients in the pilot study, and the fact that it was exclusively conducted at Groote Schuur Hospital as a tertial referral centre with a high incidence of cesarean section due to the presence of many pathological cases.

Using the shorter dosage interval of 4 hours Bennett noted a higher efficacy of the oral regimen. 50 µg misoprostol was applied either orally or vaginally every 4 hours. The median time from induction to vaginal birth was 18 h 45 min compared with 16 hours in the vaginal misoprostol group (p=0.38). No significant differences in birth route between the two groups were noted, though it was described that a non-reassuring fetal heart rate tracing was the indication for two cesarean sections in the oral group and six in the vaginal group (RR 2.47, 95% CI 0.49-12.49). Tachysystole and hyperstimulation were noted more frequent in the vaginal misoprostol group. It was concluded that the fetal heart rate tracing abnormalities in the vaginal group might be attributed to excessive uterine activity. The authors concluded, considering fetal safety, that the oral administration is an appropriate alternative for labour induction [134].

Looking at the efficacy of the combined vaginal and oral application in nulliparous patients, one could draw the conclusion that it is positioned between the oral only regimen and the vaginal only regimen.

Safety though can not be guaranteed even if only the first dose of misoprostol is applied vaginally.

4.1.2.4 Mode of Delivery

The **mode of delivery in the main study** did not differ between the groups because circa 2/3 of the patients in each group delivered vaginally. The number of operative vaginal deliveries was very small. 1/3 of the patients in each group had a cesarean section (cf. Table 4-1, page 78).

Looking at the indications for these cesarean sections, the efficacy and safety of the different modes of application of the two prostaglandins is obvious.

The main indication for a cesarean section in the vaginal misoprostol group was fetal distress. 27.5% of the women in the vaginal misoprostol group had a cesarean section for fetal distress versus 13.8% (p=0.002) in the dinoprostone and 16.7% (p=0.061) in the oral misoprostol group.

Therefore, the rate of failed induction after 24 hours was significantly lower in the vaginal misoprostol group with 0.8% than in the dinoprostone group with 9.2% (p=0.001) or the oral misoprostol group with 6.7% (p=0.036).

As compared with the other groups, the efficacy of vaginal misoprostol seems to be higher, as there is only a small number of operative deliveries for failed induction of labour.
However, the high rate of fetal heart rate abnormalities are clinically relevant.

The **route of delivery in the pilot study** was similar in the two groups. The cesarean section rate was 65% in the vaginal oral group, and 70% in the oral one (p=1.000).
The high cesarean section rate in this study was not a result of inducing the patients with misoprostol, because average incidence of cesarean sections in nulliparous patients induced with dinoprostone is similar at Groote Schuur Hospital. The main reason for the high operative delivery rate is the fact that there is a fairly high rate of patients in this tertiary referral centre induced for severe pre-eclampsia with underlying placental insufficiency. This increases the number of operative deliveries for fetal distress. In addition, the severe maternal disease also means that clinicians are often unwilling to continue the induction beyond 24 hours. The value of randomisation was therefore, that although the cesarean section rates were high in both groups studied, the differences in the indications for cesarean section were highlighted.

The main indication for cesarean section in the combined vaginal and oral group was fetal distress with 62% of the women as compared with 21% in the oral group (p=0.054). In contrast thereto, only 23% of the women in the combined vaginal and oral group had a cesarean section for failed induction of labour after 24 hours versus 43% in the oral group (cf. Table 4-3).

Indication for C/S	**Vaginal oral misoprostol**	**Oral misoprostol**	**Significance**
	n=13 (%)	**n=14 (%)**	**P Value**
Fetal distress	8 (62)	3 (21)	p=0.054
FIOL after 24 hours	3 (23)	6 (43)	p=0.420

C/S= cesarean section, FIOL= failed induction of labour, P Value ~ Fisher exact test
Table 4-3: Indications for cesarean sections - pilot study.

The relatively large number of cesarean sections for fetal distress in the combined vaginal and oral group, and for failed induction in the oral group suggests that misoprostol has a more powerful uterotonic effect when given by the combined vaginal and oral regimen.

The trend towards the higher efficacy of the combined vaginal and oral regimen was offset by an increase in tachysystole and cesarean section for fetal distress.

The pilot study demonstrated that the combined vaginal and oral regimen had no advantages over the oral regimen.

The findings of the larger study comparing repeated doses of oral or vaginal misoprostol were the same. In essence, it appears that the administration of even one vaginal dose of misoprostol increases uterine contractility to a clinically significant level, which may result in an adverse fetal outcome.
The indication for induction of labour should also have a fundamental influence on the choice of the mode of induction.

Patients with possible underlying placental insufficiency should rather be induced with oral misoprostol or dinoprostone to prevent fetal distress and placental abruption.

4.1.2.5 Safety, Contraindication and Setting

There seems to be no simple connection between hyperstimulation of the uterus and fetal outcome measures in most studies, though there is a definite trend towards more cesarean sections for fetal distress after vaginal misoprostol [134,218].
The cumulative intrauterine pressure seems to be elevated mainly in the vaginal misoprostol group leading to a higher incidence of abnormal fetal heart rate tracings indicating a cesarean section (cf. Table 4-1 page 78).

A study by Danielsson et al. showed that the uterine tonus after vaginal misoprostol application increased more slowly in comparison with the oral application and remained at a higher level over a longer period. In Montevideo units, uterine activity over time was rose steadily after 200 µg and 400 µg doses of vaginal misoprostol, whereas the activity after oral misoprostol rose slightly within the first hour and then stayed at a continuous level. This indicates the high efficacy of vaginal misoprostol, which may result in uterine hyperactivity (cf. Figure 1-7, page 20 and Figure 1-8, page 20).
Abdominal pain was more pronounced after vaginal treatment as a result of the higher uterine tonus [129].

These findings match the pharmacokinetic course of the active metabolite of misoprostol shown in Zieman et al.'s study with a much greater area under the curve after vaginal than oral application [5].

Baring in mind the indications for cesarean sections in these two studies and comparing them with the existing literature, we conclude, considering fetal safety, that oral misoprostol is the alternative for induction of labour in viable pregnancies.

After studying uterine hyperstimulation after administration of misoprostol and testing the drug on patients with previous cesarean section, we can definitely say that for patients with a history of uterine surgery such as cesarean section and transmural myom-enucleation, its use is contra-indicated [136,146,219-223].

Other contraindications are twin pregnancies, severe pre-eclampsia, HELLP-syndrome, where placental insufficiency could be caused by a sudden and intense stress on the foeto-maternal unit. Relative contraindications should be pathological findings on utero- and foetoplacental Doppler sonography, foetus small for gestational age and CTG anomalies with placental insufficiency as the possible underlying reason.

Hofmeyr et al. tried to find a solution to the problem of uterine hypertonia by small titrated oral doses of 20 µg 2-hourly to "fine-tune" the uterine response and minimise the risk of hyper-stimulation. The short half-life of the oral preparation was seen as a possible advantage, given the varying response of women to prostaglandins. The control group received 2 mg vaginal dinoprostone six hours apart. 38% of the women in the misoprostol group did not deliver vaginally within 24 hours as compared with 36% in the control group (RR 1.08; 95% CI 0.89-1.31). There were fewer cesarean sections with 16% versus 20%, a longer induction to delivery time with 17 h 10 min versus 14 h 15 min and an increased incidence of uterine tachysystole with 7% versus 5% in the misoprostol group, these differences did not reach significance. There were no differences in clinically important uterine hyperstimulation, maternal complications or neonatal outcomes [224].

Regarding safety, the titrated oral application of misoprostol might be a possible way inducting labour. Further investigation could be useful.

The efficacy of vaginal misoprostol could be intensified by buccal application.
Comparing the buccal route of 200-300 µg with the vaginal route of 50-100 µg every 6 hours, Carlan et al. found that the time to delivery was similar, and 63% versus 67% delivered vaginally within 24 hours, respectively. The incidence of tachysystole was significantly higher after buccal application with 38% versus 19% (p=0.01). The authors found a comparable efficacy and think it may be an ideal method of cervical ripening in women with unripe cervices and premature rupture of membrane. It shows a rapid onset and could be used especially in patients who are unable to eat. The frequent uterine contraction abnormalities were explained by the chosen dose of buccal misoprostol [225].

The buccal route seems highly effective in spite of the remaining safety concern regarding the high rate of tachysystole. The rapid absorption and the patient's inability to swallow make it the better choice for cases of postpartum haemorrhage, where the fetal outcome can no longer be influenced.

Although the use of misoprostol results in a fairly high tachysystole and hyperstimulation rate, cervical ripening [226] and induction of labour have been tested in an **outpatient setting**. The aim was to discover their safety and efficacy in outpatient management.
Incerpi and colleagues conducted an outpatient study of patients with diabetes at a gestational age of more than 38 ½ weeks who received 25 µg misoprostol or placebo vaginally on days 1, 4, 7. Deliveries within 7 days of the first dose were similar with 54% and 57% , respectively. The mean induction to delivery interval was even shorter in women who received placebo with 111 h 52 min versus 142 h 10 min with misoprostol. There was no difference in numbers of vaginal and cesarean deliveries. In this special setting, the vaginal misoprostol was well tolerated.
By narrowing the interval for re-dosing, the induction to delivery interval could possibly be reduced [227].
Stitely et al. administered 25 µg vaginal misoprostol or placebo in 60 patients at postdate on two consecutive days. Using the mentioned regimen, the induction to delivery interval was shorter in patients who received misoprostol. The number of inpatient labour inductions was reduced with misoprostol [228].

Other authors report that for reasons of fetal and maternal safety, the treatment with misoprostol in an outpatient setting is not recommended as there is the need for close surveillance of uterine activity all along [4,229].

4.1.2.6 Secondary Outcome Parameters

Oxytocin augmentation in the main study was used in 16.6% of the patients in the oral misoprostol group, as compared with 16.2% in the dinoprostone group. Women induced with vaginal misoprostol had statistically less augmentation (cf. Table 4-4).

Oxytocin AROM	Oral misoprostol n=120	Vaginal misoprostol n=120	Dinoprostone control group n=240	Oral misoprostol vs. control	Vaginal misoprostol vs. control	Oral vs. vaginal misoprostol
	n (%)	n (%)	n (%)	P Value	P Value	P Value
Oxytocin	20 (16.6)	8 (6.6)	39 (16.2)	*p*=1.00	*p*=0.012	*p*=0.039
AROM	40 (33.3)	28 (23.3)	97 (40.4)	*p*=0.207	*p*=0.001	*p*=0.115
No. of doses	3 (2/4)	2 (1/3)	2 (1/2)			

AROM= Artificial rupture of membranes, Quartiles in brackets correspond to Q1/Q3, P Value ~ Fisher's exact test

Table 4-4: Use of oxytocin and artificial rupture of membranes – main study.

The same trend was seen in the pilot study, where women in the combined vaginal and oral group needed less augmentation than women in the oral group (cf. Table 4-5).

Oxytocin and AROM	Vaginal oral misoprostol n=20	Oral misoprostol n=20	Significance
	n (%)	n (%)	P Value
Oxytocin	7 (35)	12 (60)	*p*=0.205
AROM	7 (35)	11 (55)	*p*=0.341
No. of doses	3 (2/3)	3 (3/3)	

AROM= Artificial rupture of membranes, P Value ~ Fisher exact test

Table 4-5: Oxytocin and artificial rupture of membranes - pilot study.

Most other studies, irrespective of the dosing regimen, showed the same trend towards less use of oxytocin augmentation with vaginal misoprostol induction as compared with oral misoprostol or dinoprostone.

Wing et al. noted a significant difference between the 25 µg dose of vaginal misoprostol application every 3 hours with 45.7% to 72.6% with the dinoprostone induction ($p<0.0001$) [192].

Another study by Wing et al. showed the use of oxytocin in 75.4% of the women induced with 50 µg oral misoprostol and in 59.1% after 25 µg vaginal misoprostol, applied 4-hourly ($p=0.01$) [196].

This again shows a trend towards a higher efficacy of vaginal misoprostol, the strong uterotonic effect does require less additional uterotonic support with oxytocin.

The reduced need for **artificial rupture of membranes** with the vaginal misoprostol regimen in 23% of the women in the main study is important in hospital settings with a high human immunodeficiency virus carrier rate, because this lowers the transmission rates. The oral misoprostol route with 33% of artificial rupture of membranes would also be beneficial because fewer vaginal examinations would have to be performed, which would probably result in a lower rate of sub- and postpartum infectious morbidity in immunocompromised women.
This is also true of the pilot study as there where less artificial rupture of membranes performed in the combined vaginal and oral group, although this did not reach a significant difference.

The efficacy of vaginal misoprostol can also be seen in the number of necessary **doses** as seen in Table 4-4 on page 86. Most patients in the vaginal misoprostol and control group only needed two doses to have regular contractions, patients in the oral treatment group had to take a median of three tablets.

A meta-analysis of studies comparing the vaginal to the oral route of misoprostol administration conducted by Sanchez-Ramos in 2000 concluded that there are no differences in fetal outcome measures between the vaginal and the oral misoprostol route. Effectiveness is similar regarding induction to delivery interval and success rate within 12 and 24 hours.
The proportion of patients experiencing tachysystole and hyperstimulation was similar in both groups.
Interestingly, the rate of cesarean section was significantly lower among the women induced with oral misoprostol [137].

4.1.3 Maternal and Fetal Outcome: Complications

There were no differences noted in common gastrointestinal side-effects like nausea, vomiting or diarrhoea in both studies (cf. Table 4-6 and Table 4-7 on page 88).

Gastrointestinal side-effects rarely arise after oral application up to 1600 µg [230]. Higher doses may cause shivering and pyrexia. Looking at the main study, these effects were also rare, a significant difference was seen only in low pyrexia, appearing twice in the vaginal misoprostol group.

Maternal side effects	Oral misoprostol n=120	Vaginal misoprostol n=120	Dinoprostone control n=240	Significance
	n (%)	n (%)	n (%)	P Value
Low pyrexia ≤ 38°C	0	2 (1.7)	0	*p*=0.49
High pyrexia > 38°C	1 (0.8)	0	0	*p*=0.222
Shivering	1 (0.8)	1 (0.8)	0	*p*=0.366
Vomiting	1 (0.8)	4 (3.3)	3 (1.3)	*p*=0.247
Nausea	0	2 (1.7)	2 (0.8)	*p*=0.365
Diarrhoea	0	0	0	NS
Abruption	1 (0.8)	4 (3.3)	6 (2.5)	*p*=0.413

P Value ~ Pearson χ^2 , NS= not significant

Table 4-6: Maternal side effects – main study.

Pyrexia was also noted in three patients of the pilot study, which would again point to the possibility of a short-term temperature rise after application of misoprostol no matter which route of application is used. Especially for prophylaxis and treatment of postpartum haemorrhage, the possible side effects of pyrexia and shivering should be kept in mind.

Maternal side effects	Vaginal oral misoprostol n=20	Oral misoprostol n=20	Significance
	n (%)	n (%)	P Value
Nausea	5 (25)	4 (20)	*p*=1.00
Vomiting	2 (10)	3 (15)	*p*=1.00
Shivering	4 (20)	2 (10)	*p*=0.661
Diarrhoea	0	0	
Pyrexia ≤ 38°C	1 (5)	0	*p*=1.00
Pyrexia > 38°C	0	2 (10)	*p*=0.487

P Value ~ Fisher exact test

Table 4-7: Maternal side effects – pilot study.

The fairly high number of abruptions in all three groups of the main study may be attributed to the fact that Groote Schuur Hospital is a tertial referral centre with a high rate of patients being induced for pre-eclampsia and gestational proteinuria. Therefore, we emphasize again - as mentioned above - that severe pre-eclampsia or HELLP-syndrome should be taken as an absolute contraindication for induction of labour with misoprostol. In these patients, inductions with dinoprostone should also be commenced carefully and labour ward staff should be attentive to possible signs of abruption.

Fetal outcome did not indicate a higher risk in any of the routes in the main study (cf. Table 3-19, page 57 and Table 3-20, page 57) or the pilot study (cf. Table 3-39, page 73). The absence of any serious adverse events was noteworthy because this study was carried out with a group of women including high-risk patients. Underlying placental insufficiency characterised many of the women studied, which highlighted differences in drug effects if any.

Several studies comparing different regimens of misoprostol application with dinoprostone showed that there were no noteworthy fetal adverse events registered, even when higher rates of tachysystole and hyperstimulation were noted [134,187,189,191,192,194,212,231-235].
Carlan et al. compared a misoprostol oral dose of 200-300 µg with a vaginal dose of 50-100 µg and noted no adverse neonatal outcomes even with doses that high [231].

El-Sherbiny et al. described a trend towards more neonatal complications after intravaginal treatment with 50 µg misoprostol compared with the lower intravaginal dose of 25 µg misoprostol, which did not reach statistical significance, although the authors said that an intravaginal dose of 25 µg every 4 hours would induce labour safely and effectively [216].

Regarding the fetal parameter, Kwon et al. anticipated that there would be discussion about the use of especially vaginally administered misoprostol. Comparing the oral with the vaginal route of misoprostol, Kwon et al. noted that significantly more infants in the vaginal group presented with one-minute Apgar scores of less than 7 (p=0.03) and required positive pressure ventilation (p=0.01). The other fetal parameter did not differ [218].

4.2 Subgroup Analysis

4.2.1 Parity - Multiparae versus Nulliparae

In general, as summarised in Table 4-8 and Table 4-9, there was an advantage of efficacy and safety for multiparous women induced for labour over women expecting the first child.

This seems obvious as multiparous patients often present with favourable cervical scores before term. The tissue of the cervix is better prepared for giving birth.

This was noteworthy in the **dinoprostone** group. Multiparous patients seemed to show an advantageous rate of delivery within 24 hours irrespective of the route. This held true when looking at the vaginal deliveries within 24 hours only, in fact significantly more multiparous than nulliparous patients delivered. This success rate of vaginal deliveries within 24 hours was comparable to the vaginal misoprostol group.

Success rate	**Oral misoprostol**	**Vaginal misoprostol**	**Dinoprostone control group**	**Oral misoprostol vs. control**	**Vaginal misoprostol vs. control**	**Oral vs. vaginal misoprostol**
Deliveries 24 hrs	**n (%)**	**n (%)**	**n (%)**	**P Value**	**P Value**	**P Value**
Multiparous	44/76 (57.9)	62/68 (91.2)	112/139 (80.6)	*p*=0.001	*p*=0.068	*p*=0.000
Nulliparous	22/44 (50)	47/52 (90.4)	69/101 (68.3)	*p*=0.041	*p*=0.003	*p*=0.000
P Value	*p*=0.449	*p*=1.00	*p*=0.034			

NVD 24 hrs	**n (%)**	**n (%)**	**n (%)**	**P Value**	**P Value**	**P Value**
Multiparous	33/76 (43.4)	46/68 (67.6)	93/139 (66.9)	*p*=0.001	*p*=1.00	*p*=0.004
Nulliparous	14/44 (31.8)	23/52 (44.2)	38/101 (37.6)	*p*=0.574	*p*=0.487	*p*=0.293
P Value	*p*=0.247	*p*=0.015	*p*=0.000			

NVD=natural vaginal deliveries, P Value ~ Fisher's exact test

Table 4-8: Success rate of deliveries within 24 hours after start of induction in nulliparous and multiparous women.

Moreover, the time from induction to delivery in multiparous patients was only two hours longer with dinoprostone than with vaginal misoprostol (cf. Table 4-9).

Looking at delivery time and safety, dinoprostone seems to be the agent with the highest efficacy in multiparous patients.

IDT (t=hh:mm)	Oral misoprostol	Vaginal misoprostol	Dinoprostone control group	Oral misoprostol vs. control	Vaginal misoprostol vs. control	Oral vs. vaginal misoprostol
	median (quartiles)	median (quartiles)	median (quartiles)	P Value	P Value	P Value
Multiparous	20:57 (10:11 / 30:24)	11:42 (08:20 / 17:00)	13:50 (09:03 / 20:45)	*p*=0.005	*p*=0.102	*p*=0.000
Nulliparous	23:52 (13:45 / 34:43)	13:30 (08:45 / 16:38)	16:15 (12:03 / 31:53)	*p*=0.122	*p*=0.002	*p*=0.000
P Value	*p*=0.204	*p*=0.462	*p*=0.004			

IVDT (t=hh:mm)	median (quartiles)	median (quartiles)	median (quartiles)	P Value	P Value	P Value
Multiparous	20:00 (11:05 / 30:18)	11:32 (08:24 / 16:43)	12:15 (08:51 / 17:00)	*p*=0.001	*p*=0.544	*p*=0.000
Nulliparous	23:34 (17:40 / 31:58)	14:08 (09:56 / 16:26)	14:24 (10:27 / 19:24)	*p*=0.000	*p*=0.656	*p*=0.001
P Value	*p*=0.091	*p*=0.222	*p*=0.140			

IDT=induction to delivery time, IVDT= induction to vaginal delivery time, t= time, h= hours, m= minutes,
Quartiles in brackets correspond to Q1/Q3, P Value ~ Mann-Whitney-test

Table 4-9: Induction to delivery interval in multiparous and nulliparous women in hours.

The 24 hour success rate, regardless of the mode of delivery, was highest after **vaginal misoprostol**, irrespective of parity, compared with the other groups. But looking at the vaginal deliveries within 24 hours the success rate in the vaginal misoprostol group decreased remarkably as compared with the other two groups, especially in women expecting the first child. This means that there were more cesarean sections within 24 hours in the vaginal misoprostol group than in the oral misoprostol group and the dinoprostone group. These cesarean sections were mainly necessitated by fetal distress. There were no cesarean sections for failed induction of labour after 24 hours in these nulliparous patients (cf. Table 4-10, page 92).

Vaginal misoprostol is effective, but not safe in nulliparous women. In multiparous patients it is effective, but not as safe as dinoprostone.
Oral misoprostol is not as effective as vaginal misoprostol regarding speed and the success rate within 24 hours.

Kwon et al. compared the time from induction to delivery in nulliparous and multiparous patients after application of either oral or vaginal misoprostol. Vaginal misoprostol was more effective than oral misoprostol irrespective of the parity.
In the vaginal group, no advantage for women of different parity was found. Oral misoprostol led to a shorter induction time in multiparous women (11 h 42 min vs. 21 h 36 min) [236].

C/S	Oral misoprostol	Vaginal misoprostol	Dinoprostone control group	Oral misoprostol vs. control	Vaginal misoprostol vs. control	Oral vs. vaginal misoprostol
C/S rate	**n (%)**	**n (%)**	**n (%)**	**P Value**	**P Value**	**P Value**
Multiparous	23/76 (30)	18/68 (27)	31/139 (22)	*p*=0.131	*p*=0.310	*p*=0.376
Nulliparous	16/44 (36)	24/52 (46)	51/101 (51)	*p*=0.082	*p*=0.368	*p*=0.223
P Value	*p*=0.312	*p*=0.020	*p*=0.000			

C/S for FD	n (%)	n (%)	n (%)	P Value	P Value	P Value
Multiparous	11/76 (15)	15/68 (22)	13/139 (9)	*p*=0.018	*p*=0.012	*p*=0.167
Nulliparous	9/44 (21)	18/52 (35)	20/101 (20)	*p*=0.547	*p*=0.036	*p*=0.095
P Value	*p*=0.274	*p*=0.094	*p*=0.017			

C/S for FIOL	n (%)	n (%)	n (%)	P Value	P Value	P Value
Multiparous	5/76 (6.6)	1/68 (1.5)	6/139 (4.3)	*p*=0.524	*p*=0.430	*p*=0.213
Nulliparous	3/44 (6.8)	0/52 (0)	16/101 (15.8)	*p*=0.184	*p*=0.001	*p*=0.093
P Value	*p*=1.00	*p*=1.00	*p*=0.003			

C/S= cesarean section, FD= fetal distress, FIOL= failed induction of labour, P Value ~ Fisher's exact test

Table 4-10: Rate of cesarean sections and cesarean sections for fetal distress and failed induction of labour in multiparous and nulliparous patients.

Though in the main study of this thesis the efficacy of the **oral misoprostol** route was also lower than the vaginal route the rate of natural vaginal deliveries without time limit in nulliparous patients with 61.4% was higher compared with patients of the same parity in the vaginal misoprostol group and the dinoprostone group with 50% and 45.5%, respectively (Table 3-15 page 54).

Oral misoprostol leads to less cesarean sections for fetal distress than vaginal misoprostol in both parity groups, though this does not reach significance, it just shows a trend (cf. Table 4-10 page 92).

The conclusion is that oral misoprostol has advantages in nulliparous patients regarding safety as compared with the other regimen when there is no time limit. An induction period of two to three days, however, should be expected in some of those patients.

4.2.2 Bishop Score (< 4 versus ≥ 4)

It is obvious that the success rate of deliveries within 24 hours after the start of induction of labour and the induction to delivery time is advantageous for women presenting with a favourable cervix as shown in Table 4-11 and Table 4-12.

Success rate	Oral misoprostol	Vaginal misoprostol	Dinoprostone control group	Oral misoprostol vs. control	Vaginal misoprostol vs. control	Oral vs. vaginal misoprostol
Deliveries < 24 hrs	**n (%)**	**n (%)**	**n (%)**	**P Value**	**P Value**	**P Value**
BS < 4	30/61 (49.2)	50/59 (84.7)	84/121 (69.4)	*p*=0.010	*p*=0.030	*p*=0.000
BS ≥ 4	36/59 (61)	59/61 (96.7)	97/119 (81.5)	*p*=0.006	*p*=0.005	*p*=0.000
P Value	*p*=0.205	*p*=0.028	*p*=0.036			

NVD < 24 hrs	**n (%)**	**n (%)**	**n (%)**	**P Value**	**P Value**	**P Value**
BS < 4	19/61 (31.1)	31/59 (52.5)	62/121 (51.2)	*p*=0.012	*p*=0.875	*p*=0.026
BS ≥ 4	28/59 (47.5)	38/61 (62.3)	69/119 (58)	*p*=0.203	*p*=0.632	*p*=0.142
P Value	*p*=0.092	*p*=0.356	*p*=0.303			

BS= Bishop score, NVD= natural vaginal deliveries, P Value ~ Fisher's exact test

Table 4-11: Deliveries within 24 hours in women with initially favourable und unfavourable cervical scores, irrespective of the route.

The rate of vaginal delivery and cesarean section is dependent on the uterotonic potency and the cervical ripening effect of the agent. An excessive uterotonic potency though might lead to adverse events with the result of a surgical delivery.

IDT	Oral misoprostol	Vaginal misoprostol	Dinoprostone control group	Oral misoprostol vs. control	Vaginal misoprostol vs. control	Oral vs. vaginal misoprostol
IDT (t=hh:mm)	**median (quartiles)**	**median (quartiles)**	**median (quartiles)**	**P Value**	**P Value**	**P Value**
BS < 4	24:10 (11:20 / 33:15)	12:55 (08:25 / 17:15)	15:50 (10:42 / 28:20)	*p*=0.054	*p*=0.023	*p*=0.000
BS ≥ 4	19:30 (11:10 / 29:50)	11:25 (07:54 / 16:00)	14:10 (09:03 / 20:00)	*p*=0.020	*p*=0.029	*p*=0.000
P Value	*p*=0.214	*p*=0.153	*p*=0.056			

IVDT (t=hh:mm)	**median (quartiles)**	**median (quartiles)**	**median (quartiles)**	**P Value**	**P Value**	**P Value**
BS < 4	23:13 (15:15 / 30:17)	12:55 (08:57 / 17:27)	13:33 (09:42 / 19:20)	*p*=0.000	*p*=0.939	*p*=0.001
BS ≥ 4	19:40 (11:20 / 31:58)	11:35 (08:25 / 16:00)	12:33 (08:16 / 16:24)	*p*=0.002	*p*=0.389	*p*=0.000
P Value	*p*=0.470	*p*=0.255	*p*=0.510			

IDT=induction to delivery time, IVDT= induction to vaginal delivery time, t= time, h= hours, m= minutes,
Quartiles in brackets correspond to Q1/Q3, P Value ~ Mann-Whitney-test

Table 4-12: Induction to delivery interval in women with initially favourable und unfavourable cervical scores.

Vaginal misoprostol seems to be more potent than oral misoprostol and dinoprostone when comparing the number of deliveries within 24 hours, irrespective of the route, in both groups of Bishop scores. Regarding vaginal deliveries within 24 hours of induction vaginal misoprostol shows similar effects as dinoprostone in patients with low and high cervical scores.
Oral misoprostol is less effective, especially in women presenting with low cervical scores. This is again pronouncedly apparent in the induction to delivery time in women with an unfavourable cervix.

The number of vaginal deliveries in the vaginal misoprostol and dinoprostone group are similar, there are no advantages for women with ripe compared with unripe cervices within the treatment groups (cf. Table 4-13).
The highest success rate of vaginal deliveries was noted in the oral misoprostol group in patients with high Bishop scores.

Rate of NVD	Oral misoprostol	Vaginal misoprostol	Dinoprostone control group	Oral misoprostol vs. control	Vaginal misoprostol vs. control	Oral vs. vaginal misoprostol
	n (%)	n (%)	n (%)	P Value	P Value	P Value
BS < 4	33/61 (54)	37/59 (63)	73/121 (60)	*p*=0.259	*p*=0.444	*p*=0.220
BS ≥ 4	47/59 (80)	39/61 (64)	80/119 (67)	*p*=0.059	*p*=0.390	*p*=0.043
P Value	*p*=0.003	*p*=0.520	*p*=0.164			

NVD=natural vaginal deliveries, P Value ~ Fisher's exact test
Table 4-13: Rate of vaginal deliveries with initial low and high Bishop scores.

This leads to the presumption that oral misoprostol applied every 6 hours has a better effect in women with a favourable cervix, but needs a longer time to ripen the cervix and cause efficacious contractions than the other regimen. In the end, oral misoprostol leads to a higher success rate of vaginal deliveries including patients delivering after 24 hours.

C/S rate	Oral misoprostol	Vaginal misoprostol	Dinoprostone control group	Oral misoprostol vs. control	Vaginal misoprostol vs. control	Oral vs. vaginal misoprostol
	n (%)	n (%)	n (%)	P Value	P Value	P Value
BS < 4	28/61 (45.9)	21/59 (35.6)	46/121 (38)	*p*=0.339	*p*=0.870	*p*=0.271
BS ≥ 4	11/59 (18.6)	21/61 (34.4)	36/119 (30.3)	*p*=0.107	*p*=0.613	*p*=0.064
P Value	*p*=0.002	*p*=1.00	*p*=0.222			

C/S= cesarean section, P Value ~, Fisher's exact test
Table 4-14: Cesarean section rate in women with low and high Bishop scores.

This observation is supported by the low rate of cesarean section in women with favourable cervices of the oral misoprostol group as seen in Table 4-14.

Women with ripe cervical scores have the highest chance to deliver vaginally with the 6-hourly oral misoprostol treatment when there is no time limit.

A narrowing of the application interval to 4 hours in these patients might shorten the induction to vaginal delivery interval.

When considering the indication for cesarean section, the vaginal and oral misoprostol treatment of women with unfavourable cervical scores results in a high rate of fetal distress and should therefore be used with caution in these patients (cf. Table 4-15). An initial lower dose of 25 µg would be preferable.

C/S for FD	Oral misoprostol	Vaginal misoprostol	Dinoprostone control group	Oral misoprostol vs. control	Vaginal misoprostol vs. control	Oral vs. vaginal misoprostol
	n (%)	n (%)	n (%)	P Value	P Value	P Value
BS < 4	16/61 (26.2)	17/59 (28.8)	16/121 (13.2)	*p*=0.039	*p*=0.014	*p*=0.839
BS ≥ 4	4/59 (6.8)	16/61 (26.2)	17/119 (14.3)	*p*=0.216	*p*=0.066	*p*=0.006
P Value	*p*=0.006	*p*=0.839	*p*=0.853			

C/S=cesarean section, FD= fetal distress, P Value ~ Fisher's exact test

Table 4-15: Cesarean sections for fetal distress in women with initially favourable and unfavourable cervical scores.

The high uterotonic effect of vaginal misoprostol is seen in the high rate of fetal distress and low rate of failed induction of labour irrespective of the initial cervical status (cf. Table 3-29, page 64).

The vaginal route is highly effective but does not guarantee safety.

Oral misoprostol can be used as an alternative to dinoprostone in patients with low and high Bishop scores.

Hofmeyr et al. induced women at a gestational age of 34 and more with either a titrated oral misoprostol solution every 2 hours or dinoprostone. The misoprostol doses of 20 µg were increased to 40 µg after two or three doses.

The success rates of natural vaginal deliveries within 24 hours in women with intact membranes, both unfavourable and favourable cervical scores were much higher compared with our subgroup

analysis, but comparable to the findings of vaginal deliveries in toto. In the misoprostol group, 47% of the patients with unfavourable scores and 24% with favourable scores did not achieve vaginal delivery within 24 hours of induction. The cesarean section rate was lower with 17% and 10%, respectively [224].

The higher success rate within 24 hours might be due to the increased cumulative dose of the titrated solution over time.

The differences are most likely attributed to the definition of low and high Bishop scores in Hofmeyr's study. A favourable cervix was defined by a Bishop score of over 6. In our study the high Bishop score was defied as ≥ 4 and < 7.

Comparing oxytocin and oral misoprostol for induction of labour in women with a Bishop score ≥ 6, oxytocin is superior. It results in a shorter induction to delivery time, and is associated with a lower hyperstimulation rate [197].

To increase the efficacy of oral misoprostol, the dose should be increased or the dosage interval decreased to 4 hours. An increase in the dose might lead to more adverse events, especially in women with low cervical scores.

Therefore, a decreased dosage interval of 4 hours and a lower initial oral misoprostol dose of 25 µg followed by an increase in the dose would be beneficial especially to women with low cervical scores.

4.3 Comparison of Nulliparous Patients of the Main Study and the Pilot Study

As there were only nulliparous patients eligible for the pilot study, a comparison of this study to the nulliparous patients induced with oral misoprostol of the main study was carried out; the results are shown in Table 4-16.

In the main study, the success rate of deliveries within 24 hours, irrespective of the route, of 50% in nulliparous patients after oral misoprostol was slightly lower than that of the oral group in the pilot study with 55%. The rate of vaginal deliveries within 24 hours, though, was slightly lower in the pilot study.

Main study vs. pilot study	**Oral misoprostol 4-hourly Pilot study**	**Oral misoprostol 6-hourly Main study**
	n=20 (% or quartiles)	**n=44 (% or quartiles)**
Deliveries < 24 hours	11 (55)	22 (50)
NVD < 24 hours	5 (25)	14 (31.8)
IDT in general (t=hh:mm)	21:35 (13:39 / 27:15)	23:52 (13:45 / 34:43)
IVDT (t=hh:mm)	20:29 (10:29 / 22:49)	23:34 (17:40 / 31:58)
Rate of NVD	6 (30)	27 (61.4)
C/S rate	14 (70)	16 (36.4)

NVD= natural vaginal deliveries, IDT= induction to delivery time, IVDT= induction to vaginal delivery time, t= time, h= hours, m= minutes, C/S= cesarean section rate, Quartiles in brackets correspond to Q1/Q3

Table 4-16: Comparison of the pilot study and nulliparous patients in the main study.

This is noteworthy as there were twice as many cesarean sections performed in the pilot study which was conducted at Groote Schuur Hospital only. These results are due to the shorter application interval, but especially to the fact that there is a high incidence of pathological cases treated at Groote Schuur Hospital. The induction to delivery interval was reduced with a shorter induction interval of 4 hours, especially regarding natural vaginal deliveries.

5 A GENERAL DISCUSSION OF THE USE OF MISOPROSTOL IN OBSTETRICS AND GYNAECOLOGY

The oral administration of misoprostol has much potential in obstetrics and gynaecology. The efficacy of misoprostol has already been demonstrated in numerous studies and the oral route of administration is associated with less complications than the vaginal route in induction of labour.

Misoprostol has been shown to be equally efficacious when compared with prostaglandin E_2 (dinoprostone) and gemeprost in early and late pregnancy. Misoprostol can be administered orally, buccally, vaginally and rectally and has the advantages of chemical stability in light and at room temperature. It has no constricting effect on the bronchi and blood vessels. The only side effects are shivering and diarrhea, both of which are dose dependent and self limiting.

Misoprostol is an attractive alternative in third trimester induction because it is considerably cheaper than other agents. Cost effectiveness of misoprostol was evaluated in Lübeck, Germany; it showed that induction of labour with misoprostol in 70 women was effective, safe and cost 58.80 €. The authors calculated that if dinoprostone had been used, the treatment would have cost 4368.00 €. Patients readily accepted the off-label use [237].

It should not be used for induction of labour where a risk of uterine rupture exists. We do not recommend its use in patients who have had previous uterine surgery, including cesarean section, who have twin pregnancies or who are grandmultiparous. The trend to use lower doses of misoprostol for induction of labour will no doubt further reduce the risk of uterine rupture and fetal distress in labour.

Prior to transcervical intervention, misoprostol can be used to soften the cervix, minimising the risk of cervical dilatation. The use of misoprostol prior to suction termination of pregnancy has become routine in many countries.

Medical termination of pregnancy is best performed using a combination of an anti-progestin such as mifepristone followed by misoprostol. This results in a complete abortion rate of more than 95% in the first trimester. Medical termination of pregnancy with misoprostol is also very effective in the second trimester although more patients require evacuation of the uterus to

remove the placenta. The risk of bleeding after second trimester termination of pregnancy means that it is safer to perform on an in-patient basis.

Finally, misoprostol can be a life saving uterotonic agent in controlling post-partum haemorrhage [238]. According to World Health Organisation (WHO) estimates, there were 529,000 maternal deaths in 2000 [239] and 14 million cases with obstetric haemorrhages a year [240]. The most important cause of maternal death in the world is postpartum haemorrhage; it is estimated to claim 150,000 maternal lives annually. Most of them occur in developing countries [240-242]. Almost 99% of maternal deaths occur in developing countries [243] in areas with inadequate transport systems and limited access to skilled caregivers and emergency obstetric care services [244]. In September 2003, the International Federation of Obstetrics and Gynaecology (FIGO) made postpartum haemorrhage its top priority to "ensure that misoprostol is available to all pregnant women whose lives could be saved using it" [245]

Misoprostol can be administered orally for the active management of the third stage or as an adjunctive therapy in treating a post-partum haemorrhage. It can be easily administered rectally to an unconscious patient.

In spite of these facts, misoprostol has not yet found an acceptable place in the advanced scientific world of gynaecology and obstetrics. Why so?

Here are some facts about the discussion taking place in the USA about misoprostol:

- August 23, 2000, announcement of Searle Pharmaceuticals, now incorporated in Pfizer:
  Searle issues an urgent drug warning concerning unapproved use of intravaginal or oral misoprostol in pregnant women for induction of labour or abortion.
  It states that Searle became aware of the drug's use in obstetrics and gynaecology and noted serious adverse events, including uterine hyperstimulation and uterine rupture, which resulted in fetal and maternal death. In addition the company cautions *"…the effect of Cytotec on the later growth, development, and functional maturation of the child when it has been used for induction of labour or cervical ripening has not been established."* [246].
- September 28, 2000, Food and Drug Administration (FDA) approves mifepristone (RU486) in combination with misoprostol for first trimester induction of abortion [247].

- October 26, 2000, the American College of Obstetricians and Gynecologists (ACOG) representing 40´000 medical doctors in the USA writes to the FDA on safety of misoprostol [248].

  The ACOG Committee on Obstetric Practice would like to emphasize that the following clinical practices appear to minimise the risk of uterine hyperstimulation and uterine rupture in patients undergoing cervical ripening or induction in the third trimester:

  1. *If misoprostol is to be used for cervical ripening or labour induction in the third trimester, one quarter of a 100 µg tablet (i.e., approximately 25 µg) should be considered for the initial dose.*
  2. *Doses should not be administered more frequently than every 3-6 hours.*
  3. *Oxytocin should not be administered less than 4 hours after the last misoprostol dose.*
  4. *Misoprostol should not be used in patients with a previous cesarean delivery or prior major uterine surgery.*

  The ACOG's conclusion is that: *"…misoprostol is a safe and effective agent for cervical ripening and labour induction when used appropriately. Moreover, misoprostol contributes to the obstetrician-gynaecologist's resources as an effective treatment for serious postpartum haemorrhage in the presence of uterine atony."* [248]

This announcement is based on extensive clinical experience with the agent and a large body of published reports. Metaanalysis of the Cochrane Pregnancy and Childbirth group trials identified 62 clinical trials of vaginal misoprostol only for cervical ripening or induction of labour [249].
These studies indicate, that misoprostol is more effective than other prostaglandins, that intrapartum exposure to misoprostol has no adverse health consequences on the foetus in the absence of fetal distress and that there is no plausible biological basis for such a concern.

On April 17, 2003, the Food and Drug Administration (FDA) approved a new label for the use of Cytotec® during pregnancy, so that it is no longer "contraindicated in pregnancy" but rather that it should not be taken by pregnant women to reduce the risk of ulcers induced by non-steroidal anti-inflammatory drugs. Furthermore, the labelling does not contain claims

regarding the efficacy and safety of Cytotec®. Therefore the Committee on Obstetric Practice reminds fellows that this agent should be used as previously recommended with one additional point:

5. *Patients undergoing cervical ripening or labour induction with misoprostol should undergo fetal heart rate and uterine activity monitoring in a hospital setting* [250].

The evidence of misoprostol's efficacy and safety has been proven by the recommandation for the use of induction of labour by the WHO. Furthermore it has recently been placed on the list of "essential drugs" in the WHO manual of "Managing Complications in Pregnancy and Childbirth" [251].

On the 18th and 19th of September 2005, the Fédération Internationale de Gynécologie et d´ Obstétrique (FIGO) implemented the delegation of acts that will reduce maternal mortality due to PPH: *"…misoprostol in the active management of the third stage of labour be delegated to nurses, midwives and general practitioners throughout their countries. Obstetricians and gynaecologists take the lead to train all professionals in the proper use of these medications* [252].

Pfizer, who now owns the drug, is not supporting its use in obstetrics and gynaecology, although more than 200 publications have been published in peer-reviewed journals discussing its effectiveness and safety [253].
Generic misoprostol is now manufactured in China, Egypt, Colombia and Brazil.

7 CONCLUSIONS

The induction of labour at term still poses an unsolved problem in more than 20% of all pregnancies. Today, mostly pharmacological methods are used to induce labour in obstetrics. In recent years, prostaglandins became the favoured labour-induction agents, with prostaglandins of the E_2-group prevailing worldwide since 1978.

Prostaglandin of the E_1-group, misoprostol, which plays an outstanding role in literature today, was not used until 1993 to induce labour at term in a vital pregnancy.
But misoprostol can also be used with other indications, for example in cases of postpartal atony. Due to its efficiency and few side effects, its easy application and good availability, its stability in light and at room temperature as well as the low costs, misoprostol prevents a significant number of maternal deaths all over the world today. By now it belongs to the essential medicines of the WHO.
In most countries there has been no application for approval of misoprostol (Cytotec®) in gynaecology and obstetrics by its current licensee Pfizer and it is not easily available there. This prevents easy accessibility of a lifesaving drug in "low recourse settings" in which bleeding in the postpartum period, septic abortion and pre-eclampsia are the most common causes of maternal deaths.

It was this study's intent to find out whether replacing the established prostaglandin E_2 with the E_1-group misoprostol (Cytotec®) brings clinical advantages in the induction of labour at term.
It became clear that misoprostol is very efficient for the named indication.
The mode of application has different effects on the uterus due to the varying pharmacological bioavailability of misoprostol after being applied orally or vaginally.
Misoprostol is very effective when applied vaginally. Oral application results in a longer period of time until birth, but shows lower incidence of foetal stress as an indication for caesarean section and tachysystole. The mode of delivery as well as foetal and maternal parameters were the same in all groups, thus proving Cytotec®'s safety in both ways of application. Regarding efficiency and safety, the listed studies show almost similar results for misoprostol and the commonly used dinoprostone E_2 (Prepidil® or Prandin®).

These findings complement the conclusions of a large number of published articles that misoprostol, regarding contraindications, is a very useful agent for inducing labour. With its advantages, it is an alternative to the established Prostaglandins of the E_2-group and will play a major role in obstetrics in the near future.

9 SCHLUSSFOLGERUNG

Die Geburtseinleitung bei über 20% der Schwangeren am Termin stellt ein nicht gelöstes Problem in der Geburtsmedizin dar. Heute stehen die medikamentösen Methoden zur Geburtseinleitung im Vordergrund. In den letzten Jahren haben sich die Prostaglandine den obersten Rang in diesem Bereich erobert. Dabei haben sich seit 1978 Prostaglandine der E_2-Gruppe weltweit durchgesetzt.

Erst 1993 wurde ein Prostaglandin der E_1-Gruppe, Misoprostol (Cytotec®), das mittlerweile in der Literatur eine herausragende Rolle spielt, erstmalig für die Geburtseinleitung am Termin bei vitaler Schwangerschaft eingesetzt.
Cytotec® ist aber auch für andere Indikationen geeignet.
So ist Cytotec® bei Auftreten von postpartaler Atonie Dank seiner guten Verfügbarkeit, Effektivität, leichten Applikationsweise, Stabilität bei Licht und Raumtemperatur, der geringen Nebenwirkungsrate sowie der günstigen Kosten, das Medikament, das heute weltweit einen nicht unerheblichen Teil maternaler Todesfälle zu verhindern vermag.
Die bisher in den meisten Ländern unterlassene Beantragung der Lizensierung von Misoprostol durch den bisherigen Lizenzhalter Pfizer für die Anwendung in der Gynäkologie und Geburtsmedizin führt unter anderem auch zur Verhinderung eines einfachen Zugangs zu einem lebensrettenden Medikament in „low recource settings“, wo die drei wichtigsten Ursachen maternaler Todesfälle Blutungen in der Postpartalperiode, septischer Abort und Präeklampsie sind. Es gehört mittlerweile zu den unverzichtbaren Medikamenten der WHO.

Es war das Anliegen der vorliegenden Studien zu eruieren, ob ein Wechsel vom bewährten Prostaglandin E_2 auf das in den meisten Ländern nicht zugelassene E_1-Präparat, Cytotec®, klinische Vorteile im Bereich der Geburtseinleitung am Termin mit sich bringt.
Es konnte festgestellt werden, dass Cytotec® sehr wirkungsvoll für die genannte Indikation ist. Der Applikationsmodus hat, auf Grund der pharmakologischen Verfügbarkeit von oral und vaginal verabreichtem Misoprostol, einen unterschiedlich starken Effekt auf den Uterus.
Misoprostol vaginal verabreicht ist sehr effektiv. Die orale Gabe führt dagegen zu einer längeren Zeit von Applikation bis Geburt, zeigte jedoch eine geringere Inzidenz an Polysystolie und fetalem Stress als Sectioindikation. Die Entbindungsmodi und kindlichen sowie maternalen Parameter waren in allen Gruppen gleich, so dass letztendlich die Sicherheit von Cytotec®, oral

wie auch vaginal appliziert, belegt ist. Die aufgeführten Studien lassen den Schluss auf nahezu gleiche Effektivität und Sicherheit wie das herkömmliche Dinoproston E_2 (Prepidil® oder Prandin®) zu.

Diese Ergebnisse ergänzen die Aussagen einer Vielzahl veröffentlichter Literatur, dass Cytotec® bei Berücksichtigung der Kontraindikationen ein geeignetes Medikament zur Geburtseinleitung am Termin darstellt.
Es ist ein Medikament, welches mit seinen Vorteilen, eine Alternative zu den herkömmlichen Prostaglandin E_2-Präparaten ist und damit in Zukunft einen hochrangigen Platz in der Geburtsmedizin einnehmen wird.