AOGS Acta Obstetricia et Gynecologica Scandinavica
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ORIGINAL RESEARCH ARTICLE | Free Access

An audit of oral administration of Angusta® (misoprostol) 25 µg for induction of labor in 976 consecutive women with a singleton pregnancy in a university hospital in Denmark

Rikke B. Helmig, Lone E. Hvidman

First published: 20 April 2020 | **https://doi.org/10.1111/aogs.13876** | Citations: 7

Funding information

Both authors received a grant from Azanta A/S for supervision and for extracting data from patient files.

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Abstract

Introduction

Induction of labor (IOL) is used to improve the outcome of pregnancy for mother and child. Since 2013, oral misoprostol has been used for IOL at Aarhus University Hospital, Denmark. The purpose of the present paper is to describe our experience of the use of a new, 25-µg misoprostol tablet commercially manufactured for the purpose of IOL regarding efficacy and outcome for mother and neonate in both an inpatient and an outpatient regimen.

Material and methods

We performed an audit from 1 April 2016, including data on all IOL in women with singleton pregnancies until 1000 consecutive women were registered. Data from 976 consecutive women with gestational age $\geq 37^{+0}$ weeks induced in accordance with the "Aarhus protocol" were included in the present analyses. All inductions were by oral misoprostol. Outpatient induction is standard procedure in low-risk pregnancies, that is, pregnancies with a healthy mother and no signs of placental insufficiency. In the outpatient IOL, the first dose of misoprostol is administered after a normal cardiotocography registration at the hospital. Subsequent doses are taken at home according to a predefined regimen. Following delivery, data on baseline variables and outcome variables for the mother and neonate were retrieved from the medical records.

Results

In 71.9% of cases, the women were induced in an outpatient regimen. Delivery within 24 hours was achieved in 38.8% of women (nulliparous 32.3%, multiparous 50.9%) and within 48 hours in 70.1% (nulliparous 66.2%, multiparous 77.2%). Hyperstimulation during induction occurred in 0.6%. The mode of delivery was spontaneous vaginal in 75.5% of cases. The cesarean section rate was 14.9% (nulliparous 20.7%, multiparous 4.1%). Apgar <7 at 5 minutes and pH <7.0 in the umbilical artery was seen in 0.9% and 0.7%, respectively.

Conclusions

Induction of labor by a commercially produced low-dose (25 µg) misoprostol tablet for oral induction according to the "Aarhus protocol" is feasible in an outpatient as well as an inpatient regimen. Delivery was achieved within 48 hours for 70.1% of women. Few adverse events were seen; however, the audit was underpowered for safety.

Abbreviations

CS	cesarean section
Group 2a	nulliparous, single cephalic ≥37 weeks, induced
Group 4a	multiparous, single cephalic ≥37 weeks, induced (excluding previous cesarean section)
IOL	induction of labor
IQR	interquartile range
TGCS	ten group classification system

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Volume 99, Issue 10
October 2020
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Induction of labor by oral use of a low-dose (25 µg) misoprostol tablet led to delivery within 48 hours in 70.1% of women. In all, 72% of inductions were done with an outpatient regimen. The overall cesarean section rate was 14.9%.

1 INTRODUCTION

Induction of labor (IOL) is widely used to improve the outcome of pregnancy for mother and neonate. The induction rate varies in different parts of the world. In Denmark, the induction rate has increased from 12% in 2002 to 22% in 2016.[1] An ideal regimen for IOL should be safe for mother and neonate. Women with a low-risk pregnancy may opt for an outpatient regimen for IOL, but so far data are limited[2] and it is therefore not yet possible to determine whether IOL with an outpatient regimen is effective and safe.

Misoprostol can be administered vaginally or orally. In a recent meta-analysis[3] it was concluded that oral misoprostol was safer than vaginal misoprostol for IOL. Many women prefer oral to vaginal administration of the medicine.[4]

Until recently, however, no low-dose misoprostol tablet has been commercially available, resulting in an ongoing debate regarding whether off-label oral use is acceptable when labeled alternatives for vaginal administration are available.[5]

Most published studies on oral misoprostol for IOL have reported the use of a solution of misoprostol tablets 200 µg in water or misoprostol tablets 200 µg divided into four or more parts, potentially resulting in varying doses of the active substance.

In 2013, a commercially produced low-dose (25 µg) misoprostol tablet for oral use became available in Denmark (Angusta®, Azanta A/S, Valby, Denmark). Since 2013, this low-dose (25 µg) misoprostol tablet has been used for IOL in our department whenever prostaglandin was indicated for IOL. A regimen with outpatient IOL in women with low-risk pregnancies was introduced in our department at the same time.

In spring 2017, the low-dose (25 µg) misoprostol tablet was approved for IOL in the Nordic countries (Denmark, Norway, Sweden, Finland and Iceland). Later, this low-dose (25 µg) misoprostol tablet was approved and put on the market in France and approved in several east-European countries, but it has not yet been used in clinical practice in these countries.

The purpose of this paper is to describe the "Aarhus protocol", an oral misoprostol regimen with use of Angusta® for IOL with regard to efficacy and outcome for IOL [6] for mother and neonate in both an inpatient and an outpatient setting.

2 MATERIAL AND METHODS

We conducted an audit of the use of low-dose (25 µg) misoprostol for the IOL at the Department of Obstetrics and Gynecology, Aarhus University Hospital—a tertiary referral delivery unit with 4500 to 5000 deliveries a year. From 1 April 2016, data on all consecutive IOL in women with singleton pregnancies were included until 1000 women induced by misoprostol according to the "Aarhus protocol" were registered. The inclusion period stopped on 4 October 2017. All inductions were by oral misoprostol.

In brief, the "Aarhus protocol" comprises up to six oral doses of 25 µg misoprostol on day 1, up to eight doses on day 2, and up to three doses on day 3. All doses are administered at 2-hourly intervals. The regimen is described in detail in Table S1.

The women are encouraged to contact the induction clinic by telephone if they have any doubts about further intake of misoprostol or experience contractions or bleeding. In case of contractions or bleeding, women are invited to an examination in the department.

At each visit, staff assess whether the outpatient regimen can continue or the woman should stay in the department.

Induction for inpatients follows the same regimen except that the fourth dose of misoprostol on days 1 and two is always preceded by a normal cardiotocography.

Twenty-four women with a gestational age less than 37 weeks (34^{+0}-36^{+6}) were excluded from the analyses. Thus, the analyses includes Group 2a: nulliparous, single cephalic ≥37 weeks, induced and Group 4a: multiparous, single cephalic ≥37 weeks, induced (excluding previous cesarean section [CS]) from the 10-group classification system (TGCS).[6, 7]

When IOL is indicated, the women are taken care of by a small group of experienced midwives. Clinical examination includes assessment of the uterus, the presentation of the fetus, vaginal examination noting length, consistency and dilation of the cervix. A cardiotocography registration is performed. If the cervix was effaced and the orificium dilated >1 cm, labor was induced by artificial rupture of membranes. If there is any uncertainty, an obstetrician is involved.

Outpatient induction is standard procedure in low-risk pregnancies, that is, pregnancies with a healthy mother and a healthy fetus with no signs of placental insufficiency. Included are women with mild preeclampsia, diet-controlled gestational diabetes and fetuses small for gestational age up to −20% with normal fetal Doppler flow. The first dose of misoprostol is administered after a normal cardiotocography registration at the hospital. Subsequent doses are taken at home every second hour. When the women are admitted in labor, the accumulated dose of misoprostol is recorded in the patient's journal.

Inpatient induction is necessary in the case of high-risk pregnancies, such as those involving moderate or severe preeclampsia, fetal growth restriction or diabetes, and also for logistical reasons if the women live a long way from the department or do not understand the written and oral information.

The following data were retrieved from the electronic patient files: parity, age, weight, body mass index, length of gestation, number of previous vaginal deliveries. The primary indication for IOL, and whether the induction was inpatient or outpatient, was noted. The outcome parameters in the present audit were misoprostol dose, the time that elapsed between the start of induction (first administration of low-dose [25 μg] misoprostol) and completed delivery and mode of delivery (spontaneous vaginal, instrumental vaginal or CS).

The following adverse events were recorded: tachysystole (>5 contractions in 10 minutes without fetal heart rate changes in more than 20 minutes), uterine hyperstimulation (>5 contractions in 10 minutes with fetal heart rate changes in more than 20 minutes) and use of tocolysis. The outcome parameters for the neonates were Apgar score at 1, 5 and 10 minutes, and the pH of the umbilical cord blood (arterial and venous).

Selected post-labor outcome parameters were recorded for the mother (postpartum hemorrhage) and the neonate (neonatal intensive care unit admission, newborn encephalopathy and serious neonatal morbidity or perinatal death).

Results are presented as median values with interquartile ranges or percentages. A Chi-square test was performed to compare groups using GRAPHPAD PRISM version 8.2.1 for MacOS (GraphPad Software, La Jolla, CA, USA). The induction-to-delivery interval was examined using the Kaplan-Meier survival analysis. This statistical analysis was carried out using STATA 14 (Stata Corp, College Station, TX, USA).

2.1 Ethical approval

The study was approved by the Danish Data Protection Agency (j. number 1-16-02-361-15) and the Danish Medicines and Health Authority (j. number 3-3013-1089/1/Reference SMFS).

3 RESULTS

During the audit period, 7259 deliveries took place in the department. Vaginal delivery was planned for 6523 women and CS for 736 women (10.1%). Overall, there were 1115 IOLs in singleton cephalic nulliparous or multiparous women. The first method of induction was misoprostol in 976 women ≥37^{+0} and in 24 women in week 34^{+0}-36^{+6}, artificial rupture of membranes in 87 and intracervical balloon in 28 women. The overall induction rate among singletons with planned vaginal deliveries in the period was 17.1%.

Among women with planned vaginal delivery, the mode of delivery was spontaneous vaginal in 5596 (85.8%), instrumental vaginal in 400 (6.1%) and CS in 8.1%. Epidural analgesia was used in 1526 (23.4%) of singletons with planned vaginal delivery.

Table 1 shows the demographic characteristics according to in- or outpatient induction regimen and the primary indication for IOL.

Table 1. Characterization of the study population and primary indication for induction of labor (n = 976)

Weeks	(38^{+2} to 40^{+3})	(39^{+6} to 41^{+5})
Primary indication for induction of labor		
Gestational age 41^{+5} to 42^{+0}	13 (4.7%)	327 (46.6%)
Preeclampsia	69 (25.2%)	66 (9.4%)
Fetal growth restriction, oligohydramnios, reduced fetal movements	65 (23.7%)	40 (5.7%)
Maternal conditions [a]	13 (4.7%)	65 (9.3%)
Cholestasis in pregnancy	4 (1.5%)	46 (6.5%)
Gestational diabetes mellitus	24 (8.8%)	26 (3.7%)
Fetal conditions [b]	8 (2.9%)	3 (0.4%)
Discomfort of pregnancy	9 (3.3%)	43 (6.1%)
Psychosocial reason	7 (2.6%)	17 (2.4%)
Diabetes mellitus type 1 and 2	22 (8.0%)	2 (0.3%)
Suspected macrosomia >4000 g	2 (0.7%)	15 (2.1%)
Maternal medical disease	11 (4.0%)	21 (3.0%)
Other indications	27 (9.9%)	31 (4.4%)

Abbreviations: BMI, body mass index.

[a] Maternal conditions: maternal age, BMI, PROM.

[b] Fetal conditions: fetal malformations, polyhydramnios, immunization.

Most women (95.3%) were caucasian. Outpatient induction was used for 71.9%. The majority of outpatient inductions were due to a gestational age of 41^{+5} to 42^{+0} weeks, whereas indications for inpatient inductions were conditions posing a risk to the mother and/or the fetus.

The number of days with misoprostol intake for group 2a and group 4a and for inpatients and outpatients are shown in Table 2.

Table 2. Number of days with intake of misoprostol, time from the first administration of low-dose (25 μg) misoprostol until delivery (hours), mode of delivery and outcome for the newborn by parity and regimen

	All (N = 976)		*P* value	All (N = 976)		*P* value
	Group 2a (N = 634) n (%)	Group 4a (N = 342) n (%)		Inpatient (N = 274) n (%)	Outpatient (N = 702) n (%)	
Number of days with intake of misoprostol						
Day 1 (≤6 tablets)	382 (60.3)	221 (64.6)	0.180	136 (49.6)	467 (66.5)	<0.001
Day 1 + 2 (7-14 tablets)	154 (24.3)	79 (23.1)	0.677	75 (27.4)	158 (22.5)	0.109
Day 1 + 2 + 3 (15-17 tablets)	98 (15.5)	42 (1.3)	0.177	63 (23.0)	77 (11.0)	<0.001
Time from the first administration of low-dose (25 μg) misoprostol until delivery (hours)						
<24 hr	205 (32.3)	174 (50.9)	<0.001	94 (34.3)	285 (40.6)	0.070
<48 hr	420 (66.2)	264 (77.2)	< 0.001	175 (63.9)	509 (72.5)	<0.001
Mode of delivery						
Spontaneous vaginal	416 (65.6)	321 (93.9)	<0.001	199 (72.6)	538 (76.6)	0.190

Women included in the audit are classified according to the ten-group classification system (TGCS).

Group 2a: nulliparous, with a singleton pregnancy, cephalic presentation with a gestational age ≥37 weeks, induced labor.

Group 4a: multiparous, with a singleton pregnancy (excluding previous cesarean section), cephalic presentation with a gestational age ≥37 weeks, induced labor.

Significantly more women following the outpatient regimen had medication only on day 1, and significantly fewer women following the outpatient regimen needed misoprostol on day 3. The median dose of misoprostol for inpatients (n = 274) was 150 μg (interquartile range 100-325 μg); for outpatients (n = 702) it was 150 μg (interquartile range 100-250 μg). Compared with group 2a, significantly more women in group 4a delivered within 24 hours and within 48 hours. Likewise, more outpatients than inpatients delivered within 24 hours and within 48 hours (Table 2). A Kaplan-Meier curve illustrating this is shown in Figure 1.

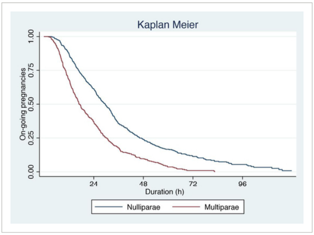

Figure 1

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Kaplan-Meier induction-to-delivery interval

In total, 128 inpatients (47.0%) and 463 outpatients (66.0%) received misoprostol only. As a supplementary method of induction, an intracervical balloon was inserted in 57 women (5.80%) (31 inpatients [11.3%], 26 outpatients [3.70%]) and oxytocin infusion was used in 167 women (17.1% [23.7% of inpatients and 14.5% of outpatients]).

The mode of delivery was spontaneous vaginal in 75.5% with an overall CS rate of 14.9% (Table 2). A significant difference was seen in the CS rate when comparing inpatients with outpatients. The indication for CS in outpatients was dystocia (53.3%), imminent fetal asphyxia (19.1%), failed induction (5.3%), maternal request (4.3%) and other (16%). The figures for inpatients were dystocia (23.5%), imminent fetal asphyxia (29.4%), failed induction (13.7%), maternal request (7.8%) and other (25.5%). Instrumental vaginal delivery by vacuum extraction occurred in 9.6% of cases. Among the neonates, 7.7% were admitted to the neonatal unit.

No significant difference was seen in important outcome parameters for neonates, such as Apgar score <7 at 5 minutes and pH values when comparing neonates of inpatient and outpatient regimens (Table 2).

Detailed data on neonates with an Apgar score <7 at 5 minutes can be found in Table S2 and neonates with pH <7 in A. umbilicalis can be found in Table S3.

Few adverse events for the mother were recorded (Table 3). Only half of the women with hyperstimulation, experienced it during induction, whereas the other half experienced it during labor related to oxytocin augmentation. Significantly more women in group 2a than in group 4a experienced adverse events, especially tachysystole during labor and puerperal pyrexia. No difference was found between women treated as inpatients and those treated as outpatients.

Table 3. Adverse events in mother by regimen and parity

	All women (N = 976)		*P* value	All women (N = 976)		*P* value
	Group 2a (N = 634) n (%)	Group 4a (N = 342) n (%)		Inpatient (N = 274) n (%)	Outpatient (N = 702) n (%)	
Women with at least one adverse event	149 (23.5)	42 (12.4)	<.001	50 (18.2)	141 (20.1)	.516
Tachysystole	20 (3.2)	1 (0.3)	.003	3 (1.1)	18 (2.6)	.155
Uterine hyperstimulation	8 (1.3)	4 (1.2)	.901	4 (1.5)	8 (1.1)	.683
Postpartum hemorrhage ≥1000 ml	73 (11.5)	29 (8.5)	.139	30 (10.9)	72 (10.3)	.751
Retained placenta or membranes	27 (4.3)	9 (2.6)	.198	10 (3.6)	26 (3.7)	.968
Puerperal pyrexia	46 (7.3)	3 (0.9)	<.001	14 (5.1)	35 (5.0)	.937
Infection	6 (0.9)	1 (0.3)	.248	2 (0.8)	6 (0.9)	.846
No cases of cardiorespiratory arrest, damage to internal organs, hysterectomy, intensive care admission, maternal death, pulmonary embolus or stroke were recorded.						

Women included in the audit are classified according to the ten-group classification system (TGCS).

Group 2a: nulliparous, with a singleton pregnancy, cephalic presentation with a gestational age ≥37 weeks, induced labor.

Group 4a: multiparous, with a singleton pregnancy (excluding previous cesarean section), cephalic presentation with a gestational age ≥37 weeks, induced labor.

4 DISCUSSION

This audit adds to the knowledge on the outcome of IOL by Angusta®, a new low-dose (25 μg) oral misoprostol tablet manufactured for IOL, as well as knowledge on induction with an outpatient regimen. We found that the use of low-dose (25 μg) misoprostol tablet for both outpatient and inpatient IOL resulted in delivery within 48 hours for 70.1% of women with few adverse events. We are aware, though, that this audit of 976 women and neonates is underpowered for safety.

The main limitation of this audit is the retrospective single-center design, so it relies on the validity of procedure coding. We are, however, confident that the data presented are representative of our population induced with misoprostol as only a small group of midwives are responsible for management of labor induction, and as our electronic patient file includes a schedule which is completed for all labor inductions.

The "Aarhus-protocol" for IOL was implemented in the department before our audit period.

It is based on experience from all women—676 in total—induced by oral misoprostol in our department in 2014 either as inpatients or in a semi-outpatient setting with administration of the medication in the department. Outpatient treatment was carried out for 77%. The protocol includes detailed instructions for the woman as well as the staff regarding intake of medication and when the woman should contact the hospital.

Before starting to collect data, we defined all variables regarding mother and child, to be extracted from the electronic patient files. In a recent publication it is recommended that trials on IOL should report on a set of core outcome, to standardize reporting.[6] We have data on 22 of the 28 suggested outcomes.

It is a strength of this audit that all inductions were handled according to a predefined regimen and that a misoprostol tablet manufactured for IOL with a known content of the active agent was used for IOL. With the exception of a recent Danish study,[8] previous published studies on oral misoprostol for IOL have used 200-μg misoprostol tablets in solution or have divided the tablets into four or more parts, potentially resulting in varying doses of the active substance.

Half of the women in the inpatient regimen and two-thirds of the women induced in the outpatient regimen needed misoprostol only on day 1, because they were subsequently in labor or artificial rupture of membranes was possible. In a prospective study of induction with 50 μg of misoprostol every 4 hours up to three times a day,[9] induction was defined as successful if the active phase was reached or delivery had occurred within 24 hours of the initial dose of misoprostol. The authors found that induction was successful for 46% of the parturient. Vaginal delivery was achieved in 87% of cases. The authors emphasize the need for a uniform definition of successful induction that would enable comparison of different regimens. We found that delivery within 24 hours of the first dose of misoprostol occurred in 32% of women in group 2a and 50% of women in group 4a. In other studies of low-dose regimens, delivery within 24 hours was achieved in 65%-80% of cases.[4, 10] Most of these studies initially used 25 μg every 2 hours, but increased the dose during the first day if contractions had not yet started. The total dose on day 1 was therefore higher than the dose used in our protocol; which may explain the difference in the proportion delivering within 24 hours. However, the question is whether delivery within 24 hours is an important goal. Our main concern is a safe delivery with unaffected neonates as assessed by the Apgar score and pH values in the umbilical artery, and we set a high priority on enabling women to stay at home as much as possible during induction. Among the neonates, 0.7% had a pH of <7.0 in the umbilical artery and 0.9% had an Apgar score <7 after 5 minutes. These figures are comparable to those found in other studies of inpatient low-dose regimens, in which an Apgar score of <7 at 5 minutes was recorded in 0.5% and 0.7% of cases.[11, 12] In 2018, 0.6% of neonates in Denmark had an Apgar score of <7 at 5 minutes and 0.5% had a pH <7.0 in the umbilical artery.[13] As induced pregnancies include more high-risk cases, the slightly higher incidence rate is not surprising. At 7.7%, the rate of admittance to the neonatal unit after IOL does not differ from the rate for our whole population of neonates.

In our study, the overall rate of CS after IOL was 14.9%, which is comparable to the frequency of 16% among women with a similar low-dosage regimen.[8] More than half of the CS with the outpatient regimen were due to dystocia and only few were because of failed induction. With the inpatient regimen, the indication for CS was imminent fetal asphyxia in nearly 30% of cases, as inpatients are at a higher risk than outpatients; the rate of CS among women in group 2a was 20.7%, whereas for women in group 4a it was 4.1%. In a large study with World Health Organization data, the TGCS system was used to depict trends in delivery mode over time in 21 countries. In the countries with a high human development index, the cesarean rate was 29.8% in group 2a and >12% in group 4a.[14] Especially for group 4a, this is higher than reported in other studies.[15]

Postpartum hemorrhage ≥1000 ml occurred in 10.5% of women in the audit, which is slightly higher than the general rate in the department of 9.3% but similar to the result in the low-dosage regimen mentioned above.[8] It is well known, however, that induced labors are associated with an increased risk of postpartum hemorrhage.[16]

Knowledge of safety and women's preferences regarding outpatient induction with oral misoprostol is limited, as only a few studies on this issue exist.[2] Outpatient induction has been found to be feasible with rare important adverse events and is favored by women, but more data are needed.[17, 18]

An unpublished qualitative study on IOL from our department compared the semi-outpatient regimen for IOL with the “Aarhus protocol” for IOL. Women were asked how they had experienced the time from induction to labor. Most reported being satisfied with the outpatient regimen and did not find the time from induction to delivery to be a problem. They emphasized the importance of thorough information and the possibility of contact with the department 24/7.

Most women in our population (71.9%) were treated with an outpatient regimen. A possible concern is that women may experience tachysystole or uterine hyperstimulation at home, leading to fetal asphyxia. We found hyperstimulation during induction in only 0.6% of the women and all were effectively treated with terbutaline. Three of these women delivered quickly, whereas the remaining three had normal labor afterwards. In all these cases, the Apgar score after 5 minutes was ≥7. In earlier studies of low-dose misoprostol included in a Cochrane review,[2] the rates of hyperstimulation were highly heterogeneous, varying between 0.9% and 9%. A low-dose oral solution regimen had the lowest risk of hyperstimulation.[10]

We found no difference in the frequency of adverse events among neonates and mothers between in- and outpatients. Moreover, the risks of CS and instrumental vaginal delivery were not increased among outpatients.

The current audit indicates that with thorough assessment and a well-defined regimen, outpatient IOL with oral low-dose misoprostol is feasible and can be offered to low-risk pregnant women without apparent higher risk than inpatient inductions.

5 CONCLUSION

IOL by a commercially produced low-dose (25 μg) misoprostol tablet for oral induction according to the “Aarhus protocol” is feasible in an outpatient as well as an inpatient regimen. Delivery was achieved within 48 hours for 70.1% of women. Few adverse events were seen; however, the audit was underpowered for safety.

ACKNOWLEDGMENT

The authors thank Lars Henning Pedersen, MD, Department of Obstetrics and Gynecology, Aarhus University Hospital, Skejby, Denmark for statistical analysis of data.

CONFLICT OF INTEREST

Both authors report grants from Azanta A/S during the conduct of the audit, and personal fees from Azanta A/S outside the submitted work.

Supporting Information

REFERENCES

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