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Induction of labor in women with oligohydramnios: misoprostol compared with prostaglandin E2

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Abstract

Objective—To compare perinatal outcomes in women with oligohydramnios and an unfavorable cervix undergoing labor induction with misoprostol to prostaglandin E2.

Study design—We conducted a secondary analysis of women with oligohydramnios undergoing labor induction in the Consortium on Safe Labor study (2002–2008). Oligohydramnios was recorded in the medical chart. We evaluated perinatal outcomes. We limited the analysis to women with an unfavorable cervix defined by simplified Bishop score ≤ 4 . Misoprostol was compared with prostaglandin E2. Women could have received oxytocin, underwent mechanical dilation, or had artificial rupture of membranes, but women who underwent induction with both misoprostol and prostaglandin E2 were excluded. We calculated adjusted odds ratios (aOR) with 95% confidence intervals (CI), controlling for maternal age, maternal body mass index (kg/m^2), parity, and mechanical dilation.

Results—Among women with oligohydramnios and an unfavorable cervix who underwent induction of labor, 141 (39.4%) received misoprostol and 217 (60.6%) received prostaglandin E2. There were no significant differences in cesarean delivery, chorioamnionitis, postpartum

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Conflict of interest statement

The authors report no conflicts of interest.

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hemorrhage, transfusion, neonatal intensive care unit admission (NICU), NICU stay >72 hours, mechanical ventilation, and neonatal sepsis.

Conclusion—In women with oligohydramnios and an unfavorable cervix, induction of labor with misoprostol was comparable to prostaglandin E2.

Keywords

cesarean delivery; induction; misoprostol; oligohydramnios; prostaglandin E2

Introduction

Oligohydramnios is associated with an increased risk of perinatal morbidity and mortality.^{1, 2} To prevent antepartum stillbirth, the American College of Obstetricians and Gynecologists (ACOG) recommends induction of labor between 36 0/7 and 37 6/7 weeks in pregnancies complicated by oligohydramnios.³ Misoprostol (prostaglandin E1) is an effective induction agent when the cervix is not favorable.⁴ Although maternal and neonatal outcomes related to prostaglandin E2 use in women with oligohydramnios have been studied,^{8, 9} limited data are available regarding misoprostol for induction of labor in the setting of oligohydramnios. Misoprostol is associated with tachysystole with or without fetal heart rate changes compared with prostaglandin E2 and oxytocin.⁵ Because oligohydramnios is associated with fetal heart rate decelerations during labor^{1, 2, 6} and cesarean delivery^{6, 7}, we hypothesized that use of misoprostol compared with prostaglandin E2 was associated with increased risk of cesarean delivery in women with oligohydramnios and an unfavorable cervix. The aim of this study was to evaluate maternal and neonatal outcomes in women with oligohydramnios undergoing induction of labor with misoprostol compared with prostaglandin E2.

Methods

The Consortium on Safe Labor (CSL) was a retrospective cohort study of all women delivering at 23 weeks of gestation between 2002 and 2008 (87% of births occurred in 2005–2007) at 12 sites in 19 hospitals across 9 ACOG US districts.¹⁰ All participating institutions obtained Institutional Review Board (IRB) approval for the initial study.

Data were available for a total of 228,562 mothers with 233,736 newborns. Participating institutions extracted detailed data on maternal demographics, medical history, labor and delivery summary, and neonatal information. Data were abstracted and mapped to predefined categories at the data coordinating center where data cleaning and logic checks were performed. Sites validated four outcomes including cesarean delivery for non-reassuring fetal heart rate tracing, asphyxia, neonatal intensive care unit (NICU) admission due to a respiratory diagnosis, and shoulder dystocia. Data collected from electronic medical records were compared with information extracted from medical charts. High concordance was noted (greater than 95% for 16 out of 20 variables and greater than or equal to 91.9% for all 20 variables).¹⁰

We limited the analysis to women with a singleton gestation, delivery ≥ 36 weeks of gestation and no prior uterine scar. We excluded women without labor induction, multiple pregnancies, premature rupture of membranes, previous cesarean delivery, congenital or chromosomal abnormalities, and antepartum stillbirth. Induction of labor was determined according to documentation recorded in the medical chart along with the reason for admission. We limited the analysis to women with oligohydramnios, an unfavorable cervix, and known cervical exam. Oligohydramnios was recorded in the medical chart. In the CSL, ultrasound data such as an amniotic fluid index or maximal vertical pockets were not available. We calculated a simplified Bishop score using cervical dilation, effacement, and station (ranging 0–9) to determine the ripeness of cervix.¹¹ We defined an unfavorable cervix as a simplified Bishop score ≤ 4, which has similar sensitivity and specificity to the original Bishop score ≤ 6 defining an unfavorable cervix.¹¹ To avoid intraperson correlation, we selected the first delivery from each woman in the database. Women could have also received oxytocin, underwent mechanical dilation, or had artificial rupture of membranes during the course of induction, but women who were missing the method of induction, who received both misoprostol and prostaglandin E2, or neither were excluded. The final analysis was limited to 358 deliveries (Figure 1).

Information on maternal demographics, pregnancy outcomes, and induction agents was summarized. We investigated maternal outcomes including cesarean delivery, cesarean delivery indications (non-reassuring fetal heart tracing, failure to progress or cephalopelvic disproportion, failed induction), operative delivery, induction to delivery time, chorioamnionitis, endometritis, postpartum hemorrhage, and transfusion by induction method for misoprostol compared to prostaglandin E2. We also investigated neonatal outcomes including NICU admission, NICU stay more than 72 hours, need for mechanical ventilation, and neonatal sepsis.

Descriptive statistics were calculated for all study variables. Bivariate analyses were performed with Chi-square, Fisher's exact, or Wilcoxon rank-sum tests. Multivariable logistic regression models or log-linear models, when appropriate, were performed to evaluate the net effect of the use of misoprostol compared with the use of prostaglandins E2, controlling for maternal age, maternal body mass index (BMI, kg/m²), parity, and mechanical dilation. Gestational age at delivery and hypertension were not included in the models as our prior analysis showed no net effect of each on the outcomes of interest. The adjusted odds ratios (aORs) with corresponding 95% confidence intervals (CI) or the adjusted P-values were calculated. All statistical analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC).

Results

Maternal characteristics are presented in Table 1. Of 358 women with oligohydramnios and an unfavorable cervix undergoing induction with either misoprostol or prostaglandin E2, 141 (39.4%) received misoprostol and 217 (60.6%) received prostaglandin E2. Compared to those who received prostaglandin E2, women who received misoprostol were more likely to have public insurance or self pay ($P=.02$) and have mechanical dilation ($P<.01$).

Maternal and neonatal outcomes in women with oligohydramnios and an unfavorable cervix undergoing induction are presented in Table 2. There were no differences in cesarean delivery, cesarean indications, operative delivery, chorioamnionitis, postpartum hemorrhage, transfusion, NICU admission, NICU stay >72 hours, mechanical ventilation, and neonatal sepsis between the two groups. Endometritis occurred in 4.3% of women undergoing induction with misoprostol compared to no events for induction with prostaglandin E2 ($P < .05$). There was no difference in induction to delivery time.

Comment

Our study found that maternal and neonatal outcomes of induction of labor with misoprostol were comparable to those of prostaglandin E2 in women with oligohydramnios and an unfavorable cervix. The maternal and neonatal outcomes of misoprostol for cervical ripening in the general population have been studied.^{4, 5} Compared with prostaglandin E2 and oxytocin, misoprostol is associated with more vaginal deliveries within 24 hours and more uterine tachysystole with or without fetal heart rate changes.⁵ In a meta-analysis, misoprostol was not associated with an increased risk of cesarean delivery compared with prostaglandin E2.⁵ In our study of women with oligohydramnios who underwent induction of labor with an unfavorable cervix, misoprostol was not associated with an increased risk of cesarean delivery compared with prostaglandin E2. Further, there were no increased adverse neonatal outcomes associated with induction of labor with misoprostol compared with prostaglandin E2.

The preferred mode of cervical ripening for women with oligohydramnios has not been determined. Previous studies comparing women with oligohydramnios and women with a normal amniotic fluid level showed that cervical ripening with misoprostol¹² and prostaglandin E2^{13, 14, 15} was not associated with an increased risk of cesarean delivery or adverse neonatal outcomes. In addition, no differences in cesarean delivery rates have been reported in studies comparing prostaglandin E2 and mechanical dilation in women with oligohydramnios.^{8, 9} A previous meta-analysis found that misoprostol was associated with an increased risk of tachysystole compared with prostaglandin E2.⁵ Because oligohydramnios is associated with increased risk of fetal heart rate decelerations during labor^{1, 2, 6}, a hypothetical concern is an increased risk of cesarean delivery in women undergoing induction of labor with misoprostol. However, it was reassuring that our study did not demonstrate an increased risk of cesarean delivery associated with misoprostol compared with prostaglandin E2 when used in women with oligohydramnios with an unfavorable cervix.

Our study found an increased rate for endometritis in women with an unfavorable cervix undergoing induction of labor with misoprostol compared with prostaglandin E2. The reason for the increased risk of endometritis is unclear and this increased rate might be chance. Previous small studies comparing misoprostol and oxytocin did not find increased risks for endometritis with misoprostol.^{16, 17} However, our study was not large enough to perform a multivariable logistic regression study to evaluate for confounders such as number of cervical examination. Larger prospective studies are needed to evaluate the risks for

endometritis in women with oligohydramnios undergoing induction of labor with misoprostol.

Limitations of our study include the retrospective nature of the analysis and variability of definitions for oligohydramnios across clinical sites. Ultrasound data such as an amniotic fluid index or maximal vertical pockets were not available in this study. Due to the lack of ultrasound data, there is a risk of misclassification. Another limitation is that induction protocols varied across the study sites. Providers were aware of the diagnosis of oligohydramnios. Due to the lack of data regarding maternal and neonatal outcomes associated with misoprostol in women with oligohydramnios, some providers may have chosen not to use misoprostol. Also, we did not have information on the dose of misoprostol or the route of administration. Because 50 micrograms of misoprostol compared with 25 micrograms causes more tachysystole¹⁸ and ACOG recommends the use of 25 micrograms,⁴ we suspect that 25 micrograms of misoprostol was used in the majority of inductions in the CSL. Similarly, we assume that vaginal administration was the most likely route used since ACOG has not endorsed buccal or oral routes for misoprostol until further studies support their safety.⁴ It is also possible that our findings may be explained by selection of women for a particular induction agent that was based on unmeasured factors rather than the induction agent itself. However, we only included women with an unfavorable cervix to limit the selection bias. Lastly, due to the small sample size, there is a chance of type II error. Given the clinical data from a diverse U.S. population, our findings are more widely applicable. Further, our data on misoprostol in women with oligohydramnios are novel.

In conclusion, misoprostol use for labor induction in women with an unfavorable cervix was not associated with an increased risk of cesarean delivery in the setting of oligohydramnios compared with prostaglandin E2. Prospective randomized studies are needed to better evaluate the maternal and neonatal outcomes of misoprostol compared with prostaglandin E2 in women with oligohydramnios and an unfavorable cervix.

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References

1. Divon MY, Marks AD, Henderson CE. Longitudinal measurement of amniotic fluid index in postterm pregnancies and its association with fetal outcome. *Am J Obstet Gynecol.* 1995; 172:142–146. [PubMed: 7847525]
2. Casey BM, McIntire DD, Bloom SL, et al. Pregnancy outcomes after antepartum diagnosis of oligohydramnios at or beyond 34 weeks' gestation. *Am J Obstet Gynecol.* 2000; 182:909–912. [PubMed: 10764472]
3. American College of Obstetricians and Gynecologists. Medically indicated late-preterm and early-term deliveries. Committee Opinion No. 560. *Obstet Gynecol.* 2013; 121:908–10. [PubMed: 23635709]
4. American College of Obstetricians and Gynecologists. Induction of labor. ACOG Practice Bulletin No. 107. *Obstet Gynecol.* 2009; 114:386–97. [PubMed: 19623003]
5. Hofmeyr GJ, Gulmezoglu AM. Vaginal misoprostol for cervical ripening and induction of labour. *Cochrane Database Syst Rev.* 2010 Oct 6.(10):CD000941. [PubMed: 20927722]
6. Manzanares S, Carrillo MP, González-Perán E, et al. Isolated oligohydramnios in term pregnancy as an indication for induction of labor. *J Matern Fetal Neonatal Med.* 2007; 20(3):221–224. [PubMed: 17437223]
7. Melamed N, Pardo J, Milstein R, et al. Perinatal outcome in pregnancies complicated by isolated oligohydramnios diagnosed before 37 weeks of gestation. *Am J Obstet Gynecol.* 2011; 205:241, e1–6. [PubMed: 22071052]
8. Wang W, Zheng J, Fu J, Zhang X, et al. Which is the safer method of labor induction for oligohydramnios women? Transcervical double balloon catheter or dinoprostone vaginal insert. *J Matern Fetal Neonatal Med.* 2014; 27(17):1805–8. [PubMed: 24397441]
9. Shechter-Maor G, Haran G, Sadeh-Mestechkin D, Ganor-Paz Y, Fejgin MD, Biron-Shental T. Intra-vaginal prostaglandin E2 versus double-balloon catheter for labor induction in term oligohydramnios. *J Perinatol.* 2015; 35(2):95–8. [PubMed: 25275693]
10. Zhang J, Troendle J, Reddy UM, et al. Contemporary cesarean delivery practice in the United States. *Am J Obstet Gynecol.* 2010; 203:323. [PubMed: 20643390]
11. Laughon SK, Zhang J, Troendle J, et al. Using a simplified bishop score to predict vaginal delivery. *Obstet Gynecol.* 2011; 117:805–811. [PubMed: 21383643]
12. Dede FS, Haberal A, Dede H, et al. Misoprostol for cervical ripening and labor induction in pregnancies with oligohydramnios. *Gynecol Obstet Invest.* 2004; 57:139–143. [PubMed: 14707473]
13. Larson JD, Rayburn WF, Turnbull GL, et al. Effects of intracervical prostaglandin E2 on fetal heart rate and uterine activity patterns in the presence of oligohydramnios. *Am J Obstet Gynecol.* 1995; 173:1166–1170. [PubMed: 7485313]
14. Cirik DA, Ta kin EA, Karcaaltincaba D, et al. Study of uterine and fetal hemodynamics in response to labor induction with dinoprostone in prolonged pregnancies with normal amniotic fluid and oligohydramnios. *J Matern Fetal Neonatal Med.* 2014; 27(7):691–5. [PubMed: 24003884]
15. Venturini P, Contu G, Mazza V, et al. Induction of labor in women with oligohydramnios. *J Matern Fetal Neonatal Med.* 2005; 17(2):129–32. [PubMed: 16076620]
16. Ferguson JE, Head BH, Frank FH, et al. Misoprostol versus low-dose oxytocin for cervical ripening: a prospective, randomized, double-masked trial. *Am J Obstet Gynecol.* 2002; 187(2): 273–9. [PubMed: 12193911]
17. Mozurkewich E, Horrocks J, Daley S, et al. The MisoPROM study: a multicenter randomized comparison of oral misoprostol and oxytocin for premature rupture of membranes at term. *Am J Obstet Gynecol.* 2003; 189(4):1026–30. [PubMed: 14586349]
18. Sanchez-Ramos L, Kaunitz AM, Delke I. Labor induction with 25 microg versus 50 microg intravaginal misoprostol: a systematic review. *Obstet Gynecol.* 2002; 99(1):145–51. [PubMed: 11777525]

Figure 1.
Cohort flow diagram.

Table 1

Maternal, obstetrical and neonatal characteristics.

	Misoprostol n=141	Prostaglandin E2 n =217	P-value ^b
N (%)			
Maternal age (y), mean (SD)	26.9 (7.1)	27.8 (6.3)	.22 ^c
BMI at delivery (kg/m ²), mean (SD)	31.4 (5.8)	31.0 (6.5)	.57 ^c
Race or ethnicity, n (%)			.09
Non-Hispanic white	75 (53.2)	136 (62.7)	
Non-Hispanic black	16 (11.4)	24 (11.1)	
Hispanic	37 (26.2)	38 (17.5)	
Asian or pacific islander	1 (0.7)	7 (3.2)	
Other or unknown	12 (8.5)	12 (5.5)	
Insurance, n (%)			.02
Private	64 (45.4)	130 (59.9)	
Public or self-pay	48 (34.0)	57 (26.3)	
Other	29 (20.6)	30 (13.8)	
Parity, n (%)			.15
0	113 (80.1)	157 (72.4)	
1	14 (9.9)	37 (17.1)	
2 or greater	14 (9.9)	23 (10.6)	
Pregnancy complications, n (%)			
Gestational diabetes/Pre-existing diabetes	6 (4.3)	19 (8.8)	.10
Hypertensive disorder	19 (13.5)	20 (9.2)	.21
Dilation on admission (cm) - median (10th, 90th percentile)	1 (0,1.5)	1 (0,2)	.09 ^d
Effacement on admission - median (10th, 90th percentile)	50 (30,70)	50 (10,70)	.27 ^d
Station on admission - median (10th, 90th percentile)	-2 (-3,-1.8)	-2 (-3,-1.8)	.14 ^d
Simplified Bishop score ^a , n (%)			.97
0	10 (7.1)	17 (7.8)	
1-2	52 (36.9)	80 (36.9)	
3-4	79 (56.0)	120 (55.3)	
Gestational age at delivery (wk), mean (SD)	39.3 (1.3)	39.1 (1.4)	.19 ^c
Neonatal birth weight (g), mean (SD)	3,147 (485)	3,183 (463)	.48 ^c
Induction methods: total of n (%) can be >100%			
Oxytocin	70 (49.7)	122 (56.2)	.22
Artificial rupture of membrane	53 (37.6)	103 (47.5)	.07
Mechanical dilation	47 (33.3)	19 (8.8)	<.01

Abbreviations: y (year), SD (standard deviation), BMI (body mass index)

Two groups are mutually exclusive.

^aSimplified Bishop score: cervical dilation, effacement, and station (range 0-9)^bChi-square test was used unless indicated otherwise.

^cStudent's t test^dWilcoxon–Mann–Whitney test

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Table 2

Maternal and neonatal outcome.

	Misoprostol n=141	Prostaglandin E2 n =217	aOR (95%CI) ^a
Maternal outcome			
Cesarean delivery	55 (39.0)	71 (32.7)	1.22 (0.73–2.03)
Cesarean indications ^b			
NRFHT	24 (43.6)	26 (36.6)	1.37 (0.60–3.13)
FTP/CPD	27 (49.1)	44 (62.0)	0.49 (0.21–1.17)
Failed induction	3 (5.5)	0 (0)	NA
Operative vaginal delivery	13 (9.2)	20 (9.2)	1.26 (0.56–2.82)
Chorioamnionitis	6 (4.3)	6 (2.8)	1.02 (0.30–3.49)
Endometritis	6 (4.3)	0 (0)	NA
Postpartum hemorrhage	7 (5.0)	6 (2.8)	1.10 (0.25–4.77)
Transfusion (n=112; 191) ^c	11 (9.8)	6 (3.1)	3.11 (1.00–9.69)
Neonatal outcome			
NICU admission	9 (6.4)	15 (6.9)	1.03 (0.43–2.50)
NICU stay >72 hours (n=141; 216) ^c	7 (5.0)	11 (5.1)	1.08 (0.40–2.96)
Mechanical ventilation	2 (1.4)	9 (4.2)	0.29 (0.05–1.58)
Neonatal sepsis	3 (2.1)	4 (1.8)	0.96 (0.21–4.45)
Induction to delivery time (minute), - median (10th, 90th percentile)	752 (311.5, 1957)	772 (270, 2468.5)	p=.76^d

Number shown as n (%) unless specified.

Abbreviations: NRFHT (Non-reassuring fetal heart tracing), FTP/CPD (Failure to progress or cephalopelvic disproportion), NA (not available), SD (standard deviation), NICU (neonatal intensive care unit)

Prostaglandin E2 (referent)

^aAdjusted odds ratios (aORs) were controlled for maternal age, BMI at delivery, parity, and gestational age.^bWomen could have indications other than NRFHT, FTP/CPD, or failed induction; thus totals are not 100%.^cDue to missing data.^dThe adjusted P-value was estimated based on multivariable log-linear model.