

This supplement is sponsored by Ferring Pharmaceuticals.

Modern Day Laboring

Induction of Labor for Low-Risk Women: Is 39 the New 41?

Rohan D'Souza, MD, MSc, MRCOG

Division of Maternal and Fetal Medicine
Department of Obstetrics & Gynaecology
Mount Sinai Hospital
University of Toronto
Toronto, Canada

Errol R. Norwitz, MD, PhD, MBA

Department of Obstetrics & Gynecology
Tufts Medical Centre and Tufts University School of Medicine
Boston, Massachusetts

Induction of labor (IOL) refers to the artificial initiation of labor undertaken when the benefits of delivery are deemed to outweigh the risk of awaiting spontaneous onset of labor.^{1,2} It is a common obstetric intervention that precedes 20% of all births.³ In high-risk pregnancies, the balance starts to shift in favor of delivery between 37 to 38 weeks of gestation, but the optimal timing of delivery in low-risk pregnancies is still not clear.

The 2004 American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin on the management of postterm pregnancy noted that well-dated pregnancies persisting beyond 294 days (42 weeks) were associated with oligohydramnios, birth injury, macrosomia, meconium aspiration syndrome, and stillbirth.⁴ It suggested that, while IOL at 41 weeks and continued expectant management were both acceptable management options, there appeared to be a small advantage to IOL at 41 weeks regardless of parity or method of induction. In 2012, authors of a systematic review on IOL for improving birth outcomes for women at or beyond term concluded that, compared with expectant management, IOL at or beyond 41 weeks was associated with a statistically significant reduction in all-cause perinatal death (relative

risk [RR], 0.31; 95% confidence interval [CI], 0.12–0.88) with a simultaneous decrease in cesarean delivery (CD) rates (RR 0.89, 95% CI 0.81 to 0.97).⁵ The number needed to treat with IOL to prevent 1 perinatal death was 410 (95% CI, 322–1492).⁵ IOL at 41 weeks is now the most common management strategy throughout North America. In this review, we summarize the most recent evidence to determine whether IOL in low-risk pregnancies at term should be deferred until 41 weeks or whether 39 is the new 41.

Fetal/neonatal implications of prolonging pregnancy beyond 39 weeks

Between 1:50 and 1:500 fetuses reach maturity *in utero* and then suffer a catastrophic event leading to permanent neurologic injury or death.⁶

Morbidity

Short-term morbidity from respiratory distress syndrome (RDS), sepsis, intraventricular hemorrhage (IVH), and necrotising enterocolitis (NEC) decrease with increasing gestational age and plateau after 37 to 38 weeks, while long-term morbidity as a result of retinopathy of prematurity (ROP) and bronchopulmonary dysplasia plateau much earlier at around 32 weeks; neonatal intensive care unit (NICU) admissions nadir at around 35 weeks.⁷ Long-term neurodevelopmental disorders, such as seizures, developmental delay/mental retardation, and cerebral palsy also reach their nadir between 38 and 39 weeks of gestation.⁸ Moreover, the odds of developing newborn encephalopathy rise sharply as gestational age is prolonged beyond 39 weeks, increasing to 13.2-fold at 42 weeks.⁹

A large retrospective cohort study conducted in California focused on neonatal complication rates at term and showed that the incidences of meconium and macrosomia increase with advancing gestation. In addition, the rates of severe neonatal complications (skull fractures, brachial plexus injuries, neonatal seizures, IVH, neonatal

DISCLOSURES

Dr. D'Souza has no conflicts of interest to report. Dr. Norwitz has no conflicts of interest to report.

TABLE 1 Neonatal complication rates by week of gestation at term¹⁰

Gestational age, wk	N	Meconium, %	Macrosomia, %	ICN admissions, %	Severe complications, % ^a
37	2053	11.0	0.58	8.5	3.56
38	4489	13.8 ^b	0.88 ^b	4.5 ^c	1.95 ^d
39	7626	18.3 ^c	1.15 ^b	3.1 ^b	1.84
40	9808	25.8 ^c	2.22 ^d	2.6	2.31 ^b
41	5717	31.9 ^c	3.58 ^c	3.4 ^d	3.14 ^d
42	2312	35.4 ^b	5.89 ^c	4.7 ^d	3.82 ^d
43	674	37.2	8.57 ^b	4.9	4.55 ^b

Abbreviation: ICN, intensive care nursery.

Statistical significance as compared with the rate of complication in the previous week of gestation.

^aIncluded birth trauma (including skull fracture and brachial plexus injuries), neonatal seizures, intracranial hemorrhage, neonatal sepsis, meconium aspiration syndrome, and respiratory distress syndrome.

^b $P < .05$, χ^2 test.

^c $P < .01$, χ^2 test.

^d $P < .001$, χ^2 test.

Reprinted from *American Journal of Obstetrics and Gynecology*, 192, Caughey AB, Washington AE, Laros RK Jr. Neonatal complications of term pregnancy: rates by gestational age increase in a continuous, not threshold, fashion, 185-190, Copyright 2005, with permission from Elsevier.

sepsis, meconium aspiration syndrome, and RDS) reduced in frequency from 3.6% at 37 weeks to 1.8% at 39 weeks before rising again to 2.3% at 40 weeks and 4.6% at 43 weeks. Similarly, NICU admissions drop from 8.5% at 37 weeks to 2.6% at 40 weeks before rising again to 4.9% at 43 weeks (TABLE 1).¹⁰

Mortality

Stillbirths account for more perinatal deaths than complications of prematurity, congenital or chromosomal malformations, and sudden infant death syndrome combined.^{11,12} Most stillbirths are unexplained. Rates of unexplained stillbirth rise sharply from 0.49/1000 ongoing pregnancies at 39 weeks to 1.27/1000 at 41 weeks. Stated differently, the risk of stillbirth in the ensuing week is 1/2039 at 39 weeks, 1/1148 at 40 weeks, 1/786 at 41 weeks, and 1/486 at 43 weeks.^{13,14}

Perinatal Risk Index includes the cumulative probability of perinatal death (antepartum stillbirths, intrapartum stillbirths and neonatal deaths within four weeks of birth) at a given gestational week multiplied by 1000. A population-based study from Scotland showed that perinatal risk index was lowest in births occurring at 38 weeks (under 2/1000 births), rising sharply to approximately 6.0 and 4.5/1000 for births occurring at 42 weeks in nulliparous and multiparous women, respectively.¹⁵

Infant mortality, which refers to deaths in the first year after birth, increases with advancing gestational age from 1/1000 ongoing pregnancies at 39 weeks to 6/1000 at 43 weeks.^{16,17}

Can we predict and/or prevent perinatal mortality?

Despite a battery of available clinical, biochemical, and radiologic tests and predictive algorithms, we are still

unable to accurately predict stillbirth,¹⁸ and the rate of stillbirth in the United States has remained stubbornly unchanged.¹⁹ Interestingly, a policy of routine elective CD at 39 weeks could prevent 2 stillbirths per 1000 ongoing pregnancies or 6000 lives saved in the United States annually,²⁰ which far exceeds the efficacy of any other preventive strategy proposed to date. Routine IOL at 39 weeks has the potential to be equally beneficial.

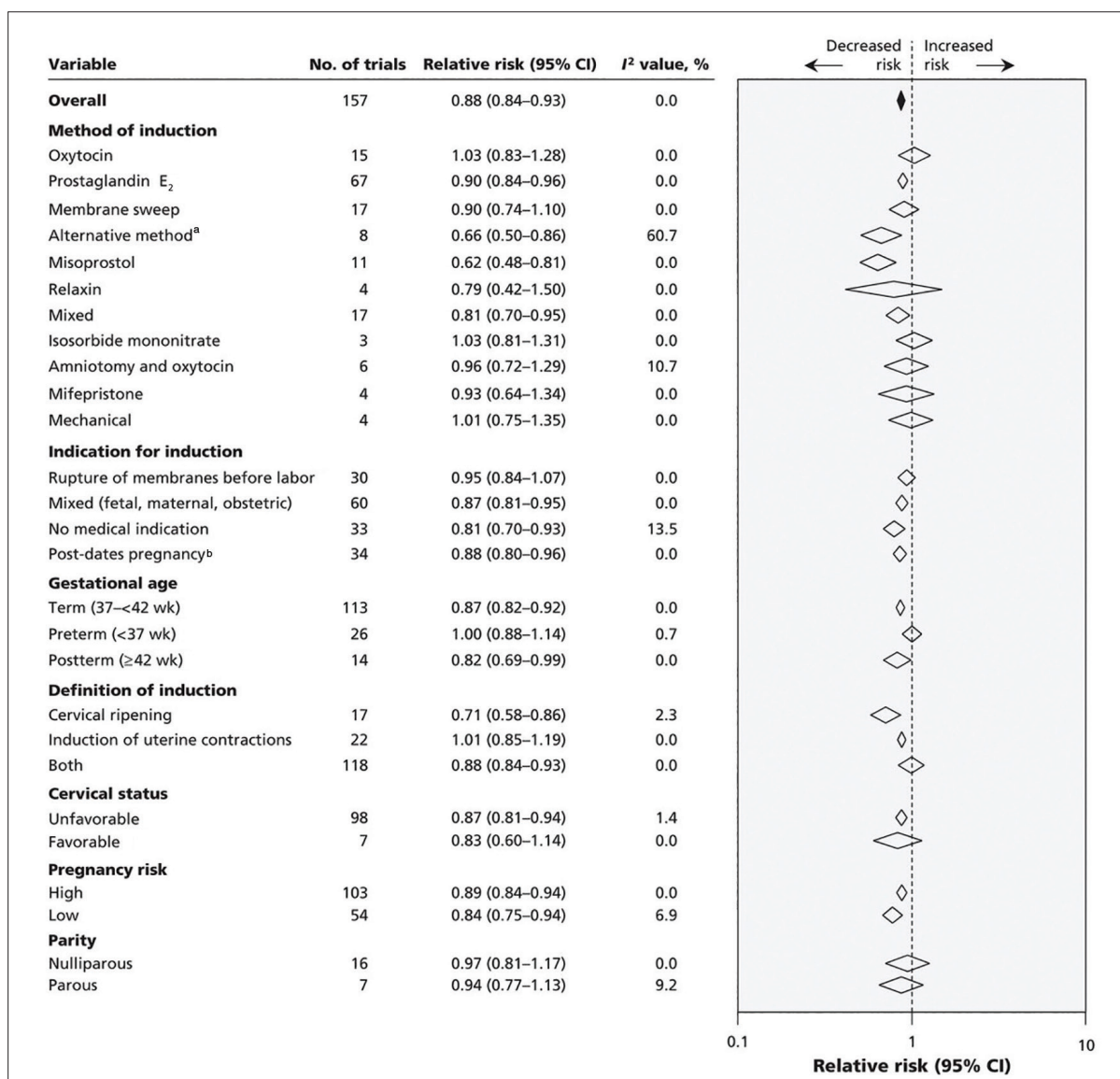
Optimal timing of birth for the fetus in low-risk singleton pregnancies

From the perspective of the fetus, the data overwhelmingly support delivery before 40 weeks of gestation; the only question is whether it should be 37 to 38 weeks or 39 weeks. While delivery at 37 to 38 weeks may be associated with the lowest perinatal mortality, it would increase the risk of RDS, NICU admission, mechanical ventilation, and hypoglycemia. Delivery at 39 weeks would increase perinatal mortality from 0.7/1000 (at 37 weeks) to 1.4/1000 (at 39 weeks), but would simultaneously reduce by 6-fold the risk of other adverse events.^{15,16,21-23}

Maternal implications of prolonging pregnancy beyond 39 weeks

A major concern regarding IOL is that it may increase the rate of CD and related complications. Early studies suggesting such an association were mostly observational and subject to inherent bias and serious methodologic errors (such as lack of power, inconsistent protocols, absence of preinduction cervical ripening, and a failure to control for parity, maternal comorbid conditions, or the passage of time). More recent evidence demonstrates that this is not true. In a 2012 systematic review comparing IOL versus expectant management for women at or beyond term that included 22 randomized controlled trials (RCTs) and 9383 women, perinatal mortality was 1/3730 for the IOL group and 13/3677 for the expectant management group

FIGURE Systematic review showing overall and subgroup analysis of the effect of induction of labor versus expectant management on the risk of cesarean delivery²⁴



Abbreviation: CI, confidence interval.

Values less than 1 indicate a decreased risk of cesarean delivery.

^aAcupuncture, breast stimulation, sexual intercourse, homeopathic preparations, castor oil, bath, or enema.

^bGestation >40 wk.

Reprinted with permission from *Canadian Medical Association Journal*.

(RR, 0.31; 95% CI, 0.12–0.88), clearly favoring IOL. Although operative vaginal delivery rates were higher following IOL (RR, 1.1; 95% CI, 1.00–1.21), CD rates were significantly lower (RR, 0.89; 95% CI, 0.81–0.97).¹⁸

A more recent systematic review that included 157 RCTs comparing IOL with expectant management suggested that IOL reduces CD rates by 12%, fetal death rates by 50%, and NICU admission rates by 14%, with no increase in maternal mortality (FIGURE).²⁴ This effect was significant both at term (RR, 0.87; 95% CI, 0.82–0.92 [113

RCTs]) and postterm (RR, 0.82; 95% CI, 0.69–0.99 [14 RCTs]) but not preterm (RR, 1.00; 95% CI, 0.88–1.14 [26 RCTs]). Surprisingly, CD rates were decreased even when the IOL was performed for no medical indication (RR, 0.81; 95% CI, 0.70–0.93 [33 RCTs]), when the cervix was unfavorable (RR, 0.87; 95% CI, 0.81–0.94 [98 RCTs]), and in both high-risk (RR, 0.89; 95% CI, 0.84–0.94 [103 RCTs]) and low-risk pregnancies (RR, 0.84; 95% CI, 0.75–0.94 [54 RCTs]).²⁴

These findings are consistent with the 2009 report from the Agency for Healthcare Research and Quality for

TABLE 2 Maternal complication rates by week of gestation at 39, 40, and 41 weeks

	39 weeks, %	40 weeks, %	41 weeks, %	Adjusted odds ratio ^a	P value
Primary cesarean delivery ²⁶	12.8	14.1	19.8	1.46 (1.44–1.48)	<.001
Operative vaginal delivery ²⁶	7.6	8.1	9.6	1.14 (1.11–1.16)	<.001
III/IV degree lacerations ²⁷	4.0	4.6	6.7	1.58 (1.44–1.73)	<.001
Postpartum hemorrhage ²⁷	2.5	3.1	4.1	1.21 (1.10–1.32)	<.01
Febrile morbidity ²⁶	1.6	2.0	2.7	1.49 (1.45–1.54)	<.001

^aAdjusted odds ratio (95% confidence intervals) represent 41 weeks vs 39 weeks in a multivariable model.

the US Department of Health and Human Services, which concluded that IOL was associated with shorter duration of labor and lower rates of CD, with no differences in rates of maternal infection, operative vaginal delivery, major perineal tears, postpartum hemorrhage (PPH), or need for blood transfusion.²⁵ In addition, large population-based studies on low-risk pregnancies suggest that, in addition to increased risk of CD, each successive week of gestation after 39 weeks is associated with an increase in other maternal complications, such as febrile morbidity, major perineal lacerations, and PPH (TABLE 2).^{26,27} Subanalyses of recent RCTs²⁸ and systematic reviews²⁴ show that nulliparous women and those with unfavorable cervixes are more likely to benefit from IOL than expectant management regardless of the indication for IOL.

Additional concerns

Other concerns that have been raised about routine IOL at an earlier gestational age are relatively minor. Iatrogenic prematurity (the inadvertent delivery of a premature infant), once a serious problem, has all but disappeared with the more liberal use of early dating ultrasound. Concerns about the “medicalization” of an otherwise normal physiologic process, although an ongoing debate in some communities, can be relatively easily addressed by reviewing the data on patient safety and improvements in both maternal and perinatal outcomes. Although precise data on the cost of routine IOL versus continued expectant management at 39 weeks is lacking, cost effective analyses of comparable situations (such as postterm pregnancy and term premature rupture of membranes) have shown significant cost savings with IOL.^{29,30} Similarly, patient satisfaction has been shown to be greater with IOL versus expectant management in comparable clinical situations.³¹

Conclusions

If a healthy pregnant woman asks you what the optimal gestational age is for her to deliver her baby, the answer is 39 weeks! Continuing the pregnancy beyond 39 weeks of gestation is associated with a small but consistent increase

in the risk of stillbirth as well as such other adverse events as RDS, NICU admission, mechanical ventilation, and hypoglycemia. Moreover, with the advent of newer cervical ripening agents, her risks are minimal. So why the reluctance to change practice? Is another large RCT needed to establish the benefit beyond a reasonable doubt? Do we really need more patient preference studies? Human reproduction is a wasteful process. There is little we as obstetric care providers can do about adverse events that occur in early pregnancy, such as failed implantation, recurrent miscarriage, cervical insufficiency, or preterm birth. But we can minimize injury and loss at the end of pregnancy. Thirty-nine weeks and out! Saved by birth!

References

1. ACOG Committee of Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 107: Induction of labor. *Obstet Gynecol.* 2009;114(2 pt 1):386-397.
2. Crane JM. Factors predicting labor induction success: a critical analysis. *Clin Obstet Gynecol.* 2006;49(3):573-584.
3. National Collaborating Centre for Women's and Children's Health. Induction of Labour. 2nd ed. London, UK: RCOG Press; 2008:104. <https://www.nice.org.uk/guidance/cg70/evidence/cg70-induction-of-labour-full-guideline2>. Accessed September 29, 2017.
4. ACOG Committee of Practice Bulletins—Obstetrics. ACOG Practice Bulletin. Clinical management guidelines for obstetricians-gynecologists. Number 55, September 2004 (replaces practice pattern number 6, October 1997). Management of postterm pregnancy. *Obstet Gynecol.* 2004;104(3):639-646.
5. Gülmezoglu AM, Crowther CA, Middleton P, Heatley E. Induction of labour for improving birth outcomes for women at or beyond term. *Cochrane Database Syst Rev.* 2012;(6):CD004945.
6. Feldman GB, Freiman JA. Prophylactic cesarean section at term? *N Engl J Med.* 1985;312(19):1264-1267.
7. Mercer BM. Preterm premature rupture of the membranes. *Obstet Gynecol.* 2003;101(1):178-193.
8. Petrini JR, Dias T, McCormick MC, Massolo ML, Green NS, Escobar GJ. Increased risk of adverse neurological development for late preterm infants. *J Pediatr.* 2009;154(2):169-176.
9. Badawi N, Kurinczuk JJ, Keogh JM, et al. Antepartum risk factors for newborn encephalopathy: the Western Australian case-control study. *BMJ.* 1998;317(7172):1549-1553.
10. Caughey AB, Washington AE, Laros RK Jr. Neonatal complications of term pregnancy: rates by gestational age increase in a continuous, not threshold, fashion. *Am J Obstet Gynecol.* 2005;192(1):185-190.
11. Cotzias CS, Paterson-Brown S, Fisk NM. Prospective risk of unexplained stillbirth in singleton pregnancies at term: population based analysis. *BMJ.* 1999;319(7205):287-288.
12. Fretts RC. The study of stillbirth. *Am J Obstet Gynecol.* 2009;201(5):429-430.

13. Yudkin PL, Wood L, Redman CW. Risk of unexplained stillbirth at different gestational ages. *Lancet*. 1987;1(8543):1192-1194.
14. Hilder L, Costeloe K, Thilaganathan B. Prospective risk of stillbirth. Study's results are flawed by reliance on cumulative prospective risk. *BMJ*. 2000;320(7232):444-445.
15. Smith GC. Life-table analysis of the risk of perinatal death at term and post term in singleton pregnancies. *Am J Obstet Gynecol*. 2001;184(3):489-496.
16. Hilder L, Costeloe K, Thilaganathan B. Prolonged pregnancy: evaluating gestation-specific risks of fetal and infant mortality. *Br J Obstet Gynaecol*. 1998;105(2):169-173.
17. Rand L, Robinson JN, Economy KE, Norwitz ER. Post-term induction of labor revisited. *Obstet Gynecol*. 2000;96(5 pt 1):779-783.
18. D'Souza R, Shah PS. Predicting stillbirths - still a distant reality. *BJOG*. 2015;122(1):56.
19. MacDorman MF, Reddy UM, Silver RM. Trends in stillbirth by gestational age in the United States, 2006-2012. *Obstet Gynecol*. 2015;126(6):1146-1150.
20. Hankins GD, Clark SM, Munn MB. Cesarean section on request at 39 weeks: impact on shoulder dystocia, fetal trauma, neonatal encephalopathy, and intrauterine fetal demise. *Semin Perinatol*. 2006;30(5):276-287.
21. Zanardo V, Simbi AK, Franzoi M, Soldà G, Salvadori A, Trevisanuto D. Neonatal respiratory morbidity risk and mode of delivery at term: influence of timing of elective caesarean delivery. *Acta Paediatr*. 2004;93(5):643-647.
22. Tita AT, Landon MB, Spong CY, et al; Eunice Kennedy Shriver NICHD Maternal-Fetal Medicine Units Network. Timing of elective repeat cesarean delivery at term and neonatal outcomes. *N Engl J Med*. 2009;360(2):111-120.
23. Clark SL, Miller DD, Belfort MA, Dildy GA, Frye DK, Meyers JA. Neonatal and maternal outcomes associated with elective term delivery. *Am J Obstet Gynecol*. 2009;200(2):156.e1-e4.
24. Mishanina E, Rogozinska E, Thatthi T, Uddin-Khan R, Khan KS, Meads C. Use of labour induction and risk of cesarean delivery: a systematic review and meta-analysis. *CMAJ*. 2014;186(9):665-673.
25. Caughey AB, Sundaram V, Kaimal AJ, et al. Maternal and neonatal outcomes of elective induction of labor. *Evid Rep Technol Assess (Full Rep)*. 2009;(176):1-257.
26. Cheng YW, Nicholson JM, Nakagawa S, Bruckner TA, Washington AE, Caughey AB. Perinatal outcomes in low-risk term pregnancies: do they differ by week of gestation? *Am J Obstet Gynecol*. 2008;199(4):370.e1-e7.
27. Caughey AB, Stotland NE, Washington AE, Escobar GJ. Maternal and obstetric complications of pregnancy are associated with increasing gestational age at term. *Am J Obstet Gynecol*. 2007;196(2):155.e1-e6.
28. Koopmans CM, Bijlenga D, Groen H, et al; HYPITAT study group. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. *Lancet*. 2009;374(9694):979-988.
29. Goeree R, Hannah M, Hewson S. Cost-effectiveness of induction of labour versus serial antenatal monitoring in the Canadian Multicentre Postterm Pregnancy Trial. *CMAJ*. 1995;152(9):1445-1450.
30. Gafni A, Goeree R, Myhr TL, et al. Induction of labour versus expectant management for prelabour rupture of the membranes at term: an economic evaluation. TERMPROM Study Group. Term Prelabour Rupture of the Membranes. *CMAJ*. 1997;157(11):1519-1525.
31. Hannah ME, Ohlsson A, Farine D, et al. Induction of labor compared with expectant management for prelabor rupture of the membranes at term. TERMPROM Study Group. *N Engl J Med*. 1996;334(16):1005-1010.

Cervical Ripening in Alternative Settings: Balancing Logistics and Patient Care

Julian N. Robinson, MD

Department of Obstetrics and Gynecology
Brigham and Women's Hospital
Boston, Massachusetts

Sarah E. Little, MD

Department of Obstetrics and Gynecology
Brigham and Women's Hospital
Boston, Massachusetts

In the United States, 23.8% of all pregnant patients underwent induction of labor in 2015.¹ A recent survey suggested that 18% of obstetric units in the United Kingdom (UK) were, or were planning to start, carrying out induction of labor in the outpatient setting.² Outpatient cervical ripening has been traditionally carried out on the hospital campus. In some of these cases should we be moving cervical ripening to the office setting—potentially a substantial distance from the hospital and labor and delivery unit? If an obstetrician has the right office setup and systems in place and selects the appropriate patient population, the returns in patient and provider convenience and satisfaction could be considerable. A downstream return would be improved efficiency for the obstetrician on the labor and delivery suite and for all other providers and patients using that facility. In this article we explore the safety and overall value of a shift to induction of labor in the office setting in the United States.

The logistics of cervical ripening

There are 2 essential elements to the practice of clinical obstetrics: the management of the patient's care and the administration of the logistics of the labor ward. In contemporary practice, a never-ending drive for more efficient health care delivery leads to constraints on space and patient flow within the hospital, raising the need for awareness of logistics in our practice paradigm. In a system with many providers looking after a small number of patients, the importance of the logistical management of the labor ward may not be optimized. Areas of obstetric practice where this is increasingly seen are cervical ripening and induction of labor. If there are many patients admitted for cervical ripening and induction of labor, a hospital's obstetric triage and labor facilities can become congested with nonactive patients, presenting challenges to the efficient processing of acutely presenting patients, spontaneously laboring parturients, and other elective scheduled obstetric cases.

There has been a plethora of obstetric research recently as to the optimal method for cervical ripening and

induction of labor. Should we be using prostaglandin E₂ (PG E₂), misoprostol (PG E₁), cervical balloons, oxytocin, or various combinations of these therapeutic options? The findings from this body of research are introducing us to a combination approach to therapy, with balloons being used alongside a pharmaceutical agent.^{3,4} Embracing new therapeutic options may lead to an overenthusiastic approach, with more inductions occurring at a cost of more space and resource utilization on the labor ward for the modest benefit of a small reduction in time of intervention and marginal cost savings. It can be questioned as to whether this research is carried out due to the intrinsic potential value of the possible findings or due to the simple result of an infatuation with the randomized controlled trial (RCT). Induction is a research topic with relatively easy subject recruitment, and a number of simple and relatively safe interventions are available. It is hard to see the biological plausibility of a method of induction affecting meaningful obstetric variables (such as the size of the fetus, the position and station of the presenting part, or the dimensions of the maternal pelvis once active labor is established). Perhaps it is time to step back and focus our attention not on the methodology but on the logistics of cervical ripening and induction of labor.

A first step in analyzing the logistics of cervical ripening and induction of labor is to avoid blending the 2 together as a continuous process and to clearly separate them into their individual elements. A loss of clarity of thinking in obstetric practice is often seen with cervical ripening and induction, as well as with induction and augmentation of labor. Many patients are often considered to be in the induction phase of labor when they are actually really still undergoing cervical ripening, and many patients are considered to be being augmented when they are in reality being induced. This confused practice is costly in terms of space, monitoring, and provider and nursing time, and can lead to an inefficiently run labor and delivery suite. Some units, in the quest for more efficient systems, already have separated cervical ripening from induction of labor and moved cervical ripening to the outpatient department only to find that they have shifted a potential barrier to efficiency from the labor ward to triage or the clinic. Part of the rationale of the movement from inpatient to outpatient cervical ripening was an intent to reduce cost, but fiscal research in this area is conflicting.^{5,6} Based on the principles of dilution of patient numbers and dissolution of hospital clinical time, the logical location for the most efficient and economical practice of cervical ripening may be the individual providers' offices. The immediate barrier to such a management style is the concern over whether this practice is safe.

DISCLOSURES

Dr. Robinson has no conflicts of interest to report. Dr. Little has no conflicts of interest to report.

Safety of outpatient cervical ripening

The practice of outpatient cervical ripening already has undergone research scrutiny, including well conducted RCTs for PG E₂,⁷⁻⁹ misoprostol,¹⁰ and cervical balloons,¹¹ as well as multiple cohort studies.¹²⁻¹⁸ Although there is little biological plausibility that a different space or room is going to affect the outcome of cervical ripening, it is possible that the uterine or fetal response to the intervention may make a particular setting less appropriate or safe. This is less likely for a mechanical method and more likely for pharmacologic interventions, particularly with stronger agents or with increasing dose.

Outpatient use of the cervical balloon appears, not surprisingly, to be no different in efficacy from the inpatient setting and it appears to be very safe in both settings.^{11,18} Research on outpatient PG E₂ has shown both a shorter time period to delivery⁸ and no difference in outcome,^{7,9,16} with no studies demonstrating it to be unsafe in the outpatient setting.^{7-9,12,13} However, some studies suggested a need for early removal of vaginal insert¹³ or a more frequent occurrence of a nonreassuring fetal-heart rate (although these studies did not report adverse maternal or fetal outcomes).⁷ Studies into the outpatient use of misoprostol have shown it to have a shorter period of time for cervical change compared with placebo,^{15,17} to be more efficacious at a higher dose,¹⁶ and to be more efficient than PG E₂.¹⁰ Although both uterine tachysystole and nonreassuring fetal-heart tracing are well recognized potential complications of misoprostol use,¹⁹ and such events did occur in this research, none of the studies demonstrated a difference in maternal or fetal outcomes between the outpatient and inpatient settings.^{10,14-17} In summary, study to date has shown no difference in maternal or fetal outcome for cervical ripening comparing the outpatient to the inpatient setting; it has demonstrated, however, that uterine tachysystole or nonreassuring fetal heart tracing may lead to outpatient cervical ripening being abandoned or continued in the inpatient setting.

No study to date has suggested that outpatient or office cervical ripening is unsafe, but none has been adequately powered to state that it is safe as a definitive conclusion. It is exceedingly unlikely that an RCT, adequately powered to determine safety data, will ever be carried out. We know from the already published literature that a conservative estimate of a significant adverse safety event would be 1:1000. Therefore, to determine a 20% reduction (with 80% power using a 2-tailed chi-square test with an alpha of 0.05 and assuming equal numbers in each arm) would require 352,000 in each arm (a total of 705,760 patients), and to determine a 50% reduction would require 94,114 in each arm for a total of 188,228 patients. It is exceedingly unlikely that such an RCT will be carried out.

Ripening agent and patient safety

In the absence of the existence of a definitive outpatient safety trial, is the concept of office-based cervical ripening something we should consider? Choice of method

and patient selection can optimize safety. Balloon cervical ripening methods are the safest, but they may not be the most attractive option for the patient as an office intervention, until a more compact device with a very short tail is developed. Hygroscopic cervical dilators may be a more acceptable option for women due to their smaller length.

An efficacious agent, such as a balloon or prostaglandin with a modest dose, a conservative protocol with a judicious amount of fetal monitoring, used in a low-risk population of nulliparous patients at an earlier gestational age (39 to 40+ weeks) may be a good proposition.

A good proposition is one that fills a clinical need, is acceptable to the parturient, is practical, and improves workflow in the inpatient obstetric setting. It should also be safe. How safe? One cannot abrogate risk, but one can approach it rationally. Office cervical ripening may be considered safe when compared with other commonly performed routine obstetric practices, such as trial of labor after cesarean delivery, external breech version, expectant management of postdates pregnancy, laboring with a large baby, laboring with a history of prior shoulder dystocia, and performing a cesarean delivery for maternal request alone. We have probably reached the point where offering outpatient cervical ripening in the United States is rational if we use careful patient selection and one of the mechanical dilatation methods or a modest prostaglandin protocol for office use.

Liberal use of office cervical ripening could change radically how we manage induction of labor. Currently, we need a good indication or a favorable cervix, often ignoring those who have an unfavorable cervix until they are very postdates with placental dysmaturity and a higher chance of fetal intolerance of labor and cesarean delivery. Currently, a long course of frequent cervical ripening is not practical or attractive, but conducting the practice in an office setting could change this. Office cervical ripening may be acceptable for the patient at earlier gestational age (39 to 40 weeks) with an unfavorable cervix. Many episodes of ripening may be more palatable when convenience is prioritized, avoiding a busy hospital campus, admission procedures, waiting rooms, and hospital delays. A recent small RCT of misoprostol 25 µg versus placebo at cervical sweep in women at gestational age of 38.5 weeks and greater with a Bishop score of less than 4 showed an average decrease in the interval from intervention to delivery of approximately 2 days (3.35 days in the misoprostol group [95% confidence interval (CI), 1.12–9.46] vs 5.42 days in the placebo group [95% CI, 2.39–10.11]).²⁰

When might cervical ripening be appropriate in your office?

As with all medical interventions, if this is a treatment that you are going to practice, you should compose and follow a well-thought-out protocol. A practical approach starts with thorough counseling of the patient. Does the indication, if any, warrant the intervention? Does

the woman know what she is signing up for in terms of nature and duration of the possible interventions, chance of failure, and options if failure does occur?

If, after thorough counseling, the parturient is interested in office cervical ripening, the next step is assessing the appropriateness of the intervention. It is certainly an option for the nulliparous woman or the multiparous patient with an unfavorable cervix. The hospital setting would be a better choice with increasing parity and favorability of cervical assessment. The fetus should be normally grown with normal amniotic fluid volume and no history of abnormal fetal testing. Occurrence of rupture of the membranes or any incident of antepartum bleeding would be a sensible contraindication, as would significant uterine contractions, abdominal pain, prior cesarean delivery, or any other uterine surgery. Multiple pregnancy would be a sensible contraindication and more challenging fetal monitoring needs make these pregnancies a poor practical choice in any case. For similar reasons significant obesity makes a mother a poor practical choice. Indeed, any factor that impedes accurate fetal monitoring should disqualify a patient for outpatient cervical ripening.

Fetal monitoring should immediately precede the cervical ripening. Fetal surveillance is best performed with a cardiotocogram/nonstress test (as opposed to an ultrasound biophysical profile, as the absence of significant uterine activity should be confirmed). Such preintervention monitoring should be for a reasonable amount of time. For the intervention, a balloon or hygroscopic dilator or a modest dose of prostaglandin seem the best choices. With the balloon or dilator, the device can be placed in the usual fashion and the patient can have repeat monitoring and then go home with instructions to return to the hospital if the device falls out. With a prostaglandin, the patient should be monitored for a sensible period of time after placement of the drug before leaving the office. In both cases the mother should have instructions to present promptly to the hospital if abdominal pain, significant uterine contractions, or vaginal bleeding occurs. There should be a method of communication available that rapidly accesses the patient to prompt advice and instruction if anything out of the ordinary occurs.

We have been using outpatient cervical ripening in our institution for more than 15 years and we are unaware of a significant safety event. We are now in the process of starting cervical ripening in the office, off the hospital campus, in a select group of patients.

References

1. Martin JA, Hamilton BE, Osterman M, Driscoll AK, Mathews TJ. Births: Final data for 2015. *Natl Vital Stat Rep.* 2017;66(1):1.
2. Sharp AN, Stock SJ, Alfirevic Z. Outpatient induction of labour in the UK: a survey of practice. *Eur J Obstet Gynecol Reprod Biol.* 2016;204:21-23.
3. Levine LD, Downes KL, Elovitz MA, Parry S, Sammel MD, Srinivas SK. Mechanical and pharmacological methods of labor induction: a randomized controlled trial. *Obstet Gynecol.* 2016;128(6):1357-1364.
4. Carbone JF, Tuuli MG, Fogertey PJ, Roehl KA, Macones GA. Combination of Foley bulb and vaginal misoprostol compared with vaginal misoprostol alone for cervical ripening and labor induction: a randomized controlled trial. *Obstet Gynecol.* 2013;121(2 pt 1):247-252.
5. Austin K, Chambers GM, de Abreu Lourenco R, Madan A, Susic D, Henry A. Cost-effectiveness of term induction of labour using inpatient prostaglandin gel versus outpatient Foley catheter. *Aust N Z J Obstet Gynaecol.* 2015;55(5):440-445.
6. Ten Eikelder M, van Baaren GJ, Oude Rengerink K, et al. Comparing induction of labour with oral misoprostol or Foley catheter at term: cost-effectiveness analysis of a randomised controlled multi-centre non-inferiority trial [published online ahead of print April 25, 2017]. *BJOG.* 2017;doi:10.1111/1471-0528.14706.
7. Wilkinson C, Bryce R, Adelson P, Turnbull D. A randomised controlled trial of outpatient compared with inpatient cervical ripening with prostaglandin E₂ (OPRA study). *BJOG.* 2015;122(1):94-104.
8. O'Brien JM, Mercer BM, Cleary NT, Sibai BM. Efficacy of outpatient induction with low-dose prostaglandin E₂: a randomized, double blind, placebo-controlled trial. *Am J Obstet Gynecol.* 1995;173(6):1855-1859.
9. Biem SR, Turnell RW, Olatunbosun O, Tauh M, Biem HJ. A randomized controlled trial of outpatient versus inpatient labour induction with vaginal controlled-release prostaglandin-E₂: effectiveness and satisfaction. *J Obstet Gynaecol Can.* 2003;25(1):23-31.
10. Meyer M, Pflum J, Howard D. Outpatient misoprostol compared with dinoprostone gel for preinduction cervical ripening: a randomized controlled trial. *Obstet Gynecol.* 2005;105(3):466-472.
11. Sciscione AC, Muench M, Pollock M, Jenkins TM, Tildon-Burton J, Colmorgen GH. Transcervical Foley catheter for preinduction cervical ripening in an outpatient versus inpatient setting. *Obstet Gynecol.* 2001;98(5 pt 1):751-756.
12. Salvador SC, Simpson ML, Cundiff GW. Dinoprostone vaginal insert for labour induction: a comparison of outpatient and inpatient settings. *J Obstet Gynaecol Can.* 2009;31(11):1028-1034.
13. Tassone SA, Pearman CR, Rayburn WF. Outpatient cervical ripening using a sustained-release prostaglandin E₂ vaginal insert. *J Reprod Med.* 2001;46(6):599-600.
14. Chang DW, Velazquez MD, Colyer M, Klaus P, Mallipeddi SK, Rayburn WF. Vaginal misoprostol for cervical ripening at term: comparison of outpatient vs. inpatient administration. *J Reprod Med.* 2005;50(10):735-739.
15. Stitely ML, Browning J, Fowler M, Gendron RT, Gherman RB. Outpatient cervical ripening with intravaginal misoprostol. *Obstet Gynecol.* 2000;96(5 pt 1):684-688.
16. Kipikasa JH, Adair CD, Williamson J, Breen JM, Medford LK, Sanchos-Ramos L. Use of misoprostol on an outpatient basis for postdate pregnancy. *Int J Gynaecol Obstet.* 2005;88(2):108-111.
17. Gaffaney CA, Saul LL, Rumney PJ, et al. Outpatient oral misoprostol for prolonged pregnancies: a pilot investigation. *Am J Perinatol.* 2009;26(9):673-677.
18. McKenna DS, Duke JM. Effectiveness and infectious morbidity of outpatient cervical ripening with a Foley catheter. *J Reprod Med.* 2004;49(1):28-32.
19. Hofmeyr GL, Gülmezoglu AM, Pileggi C. Vaginal misoprostol for cervical ripening and induction of labour. *Cochrane Database Syst Rev.* 2010;(10):CD000941.
20. PonMalar J, Benjamin SJ, Abraham A, Rathore S, Jeyaseelan V, Mathews JE. Randomized double blind placebo controlled study of preinduction cervical ripening with 25 µg of misoprostol in the outpatient setting to prevent formal induction of labour. *Arch Gynecol Obstet.* 2017;295(1):33-38.