Published in final edited form as:

Am J Obstet Gynecol. 2009 March ; 200(3): 254.e1–254.e13. doi:10.1016/j.ajog.2008.08.052.

The Active Management of Risk in Nulliparous Pregnancy at Term: association between a higher preventive labor induction rate and improved birth outcomes

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Abstract

Objective—To determine if exposure of nulliparous women to a high rate of preventive labor induction was associated with improvement in birth health.

Study Design—A risk-scoring system was used to guide the frequent use of preventive labor induction in 100 nulliparous women. The birth outcomes of this group were compared to those of 352 nulliparous women who received usual care. Cesarean delivery was the primary study outcome. The Adverse Outcome Index and the rate of uncomplicated vaginal delivery were used to measure overall birth health.

Results—The exposed group experienced a higher labor induction rate (48% vs. 23.6%, $p = <0.001$), a lower cesarean rate (9% vs. 25.8%, $aOR\ 0.36\ p=0.02$), and better composite birth outcomes.

Conclusion—Exposure of nulliparous women to a high preventive induction rate was significantly associated with improvement in birth health. Prospective randomized trials are needed to further explore the utility of risk-guided preventive labor induction.

Keywords

Nulliparous; Birth outcomes; Cesarean delivery; Adverse outcome index; Preventive labor induction

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Reprints will not be available

This study was conducted in Philadelphia, Pa. the Hospital of the University of Pennsylvania, by members the Department of Family Medicine and Community Health.

This research was presented in poster format at the Annual Meeting of the Society of Maternal Fetal Medicine in Dallas Tx, February 1–4, 2006.

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INTRODUCTION

Between 1997 and 2006, the overall rate of cesarean delivery in the US steadily increased from 22.0% to 31.1% (1–2). Increases in cesarean delivery rates have occurred in all three major obstetric groups: nulliparous women, multiparous women without previous cesarean delivery, and women with history of cesarean delivery (3). Despite these increases, rates of other adverse birth outcomes – such as maternal mortality, NICU admission, and perinatal mortality – have not improved (1–3). Of concern, cesarean delivery, when compared to vaginal delivery, is associated with higher rates of a variety of adverse birth outcomes such as major post-partum infection, neonatal intensive care unit (NICU) admission, and maternal mortality (4–6).

The route of delivery for a nulliparous woman, as compared to a multiparous woman, is particularly important for two reasons. First, a nulliparous woman who experiences a cesarean delivery for her first delivery in 2008 is unlikely to undergo a trial of labor with subsequent pregnancy (1). Second, a nulliparous woman who experiences a cesarean delivery for her first delivery is more likely, in subsequent pregnancies, to experience obstetric complications including abnormal placentation (7), uterine rupture (8), and spontaneous stillbirth (4,9). While several recent reports have presented elective primary cesarean delivery as a way to prevent vaginal delivery-related pelvic floor damage and resultant uro-gynecological morbidity (10–12), others have suggested that such benefits may not be long lasting (13,14). There is no clear evidence that the benefits of elective primary cesarean delivery are equal to, or outweigh, the benefits of attempted vaginal delivery (15).

Within the context of increasing national cesarean delivery rates and uncertainty regarding the appropriate use of elective cesarean delivery, an alternative method of preventive obstetrics was recently introduced (16). This alternative method, called the Active Management of Risk in Pregnancy at Term (AMOR-IPAT), utilizes preventive labor induction to ensure that pregnant women enter labor at an optimal time for the mother-baby pair. AMOR-IPAT has been associated with low rates of cesarean delivery (4%–7%) in several studies involving patient cohorts of mixed parity (16,17). However, because of the particular importance of the mode of delivery for a woman's first pregnancy, we wanted to develop and perform a study to evaluate the association between AMOR-IPAT exposure and cesarean delivery in nulliparous pregnant women. In addition, we wanted to evaluate the association between AMOR-IPAT exposure and other aspects of birth health.

MATERIALS AND METHODS

A retrospective cohort design was used to study the use of AMOR-IPAT in nulliparous women who delivered at the Hospital of the University of Pennsylvania (HUP). The first 100 nulliparous women who delivered at term following exposure to AMOR-IPAT ("exposed" women) did so between April 1998 and February 2004. The outcomes of these exposed women were compared to the outcomes of 352 randomly selected nulliparous women who received usual care ("non-exposed" women) and who delivered during the same time period. Physicians from the Department of Family Medicine and Community Health provided the prenatal care and labor management for all exposed study subjects, and physicians and nurse midwives from the Department of Obstetrics and Gynecology provided the prenatal care and labor management for all non-exposed study subjects. Study inclusion criteria included: 1) singleton pregnancy, 2) delivery on or after 37 weeks, 3 days gestation, and 3) no pre-38 week maternal or fetal contraindication for trial of labor (e.g., placenta previa, previous transverse uterine surgery, reactive HIV serology, fetal hydrocephalus, or major fetal anomaly). In both study groups, delivery could occur following spontaneous

labor, labor induction, or elective cesarean delivery. Data was collected from the medical records of each mother/baby pair and entered into an Access database.

The AMOR-IPAT method of care has been previously described (16–17). For each subject in the exposed group, specific risk factors for cesarean delivery were identified and placed in one of two risk categories: 1) a utero-placental insufficiency (UPI) category (i.e., factors that lead to UPI by interfering with placental growth or by accelerating placental aging) and/or 2) a cephalo-pelvic disproportion (CPD¹) category (i.e., factors that lead to CPD by either accelerating fetal growth or reflect a limited pelvic size). We converted the published odds ratio for cesarean delivery for each specific risk factor into a specific number of days using a previously published formula (16, appendix 1), and we subtracted the total number of risk-days that any given patient had in each of the two risk categories from 41 weeks 0 days gestation to estimate an upper limit of the optimal time of delivery (UL-OTD) for each risk category. The lower of the two category-specific UL-OTDs became each woman's final UL-OTD, but the final UL-OTD was never lower than 38 weeks 0 days gestation². If a patient did not develop spontaneous labor as she approached her UL-OTD, then she was offered preventive labor induction on or just before her UL-OTD. If a patient was scheduled for labor induction and had an unfavorable uterine cervix (modified Bishop's score < 6) (18), then she was offered cervical ripening with dinoprostone (PGE2 pledget), misoprostol (PGE1), or foley bulb. Occasionally, these ripening methods were combined. Ultrasound confirmation of pregnancy dating and adequate cervical ripening prior to the start of oxytocin were important components of the AMOR-IPAT method of care. Although preventive labor induction was the key intervention utilized in this study, it is important to point out that not all women in the AMOR-IPAT group underwent induction prior to delivery. In fact, 53% of the exposed group delivered following the spontaneous or non-induced augmented labor. However, induction of labor, with cervical ripening if needed, was regularly used in the exposed group if a woman did not develop labor by, or just before, her estimated UL-OTD.

We compared rates and proportions of prenatal and intra-partum covariates present in the exposed and non-exposed groups. We calculated means and medians of continuous variables. Normal distributions were compared using the student's T test and non-normal distributions were compared using the Wilcoxon rank-sum test. Thereafter we converted some continuous variables into clinically meaningful dichotomous variables, e.g., an "advanced maternal age" (AMA) variable was created by determining whether or not a woman was 35 years of age or older at the time of delivery. Dichotomous and categorical variables were compared using chi-squared techniques (Fisher's exact test). We used relative risk as the measure of association. We defined statistical significance for all tests as a p-value ≤ 0.05 , and a statistical trend as a p-value between 0.05 and 0.30.

We compared the pre-38 week of gestation risk of cesarean delivery in the two study groups using an indirect standardization procedure (19, 20*). Risk factors that could be identified before 38 weeks of gestation, that at least trended towards statistically different levels in the two groups ($p \leq 0.30$), and that also exhibited at least a trend towards an impact on cesarean delivery rates in the non-exposed group alone ($p \leq 0.30$) were used as variables in the indirect standardization. The expected cesarean delivery rate in the exposed group was divided by the actual cesarean delivery rate in the non-exposed group to give a Standardized Cesarean Ratio (SCR).

¹We prefer to use the term "cephalo-pelvic disproportion (CPD)" rather than "failure to progress (FTP)" because CPD implies a multi-factorial problem that can potentially be both predicted and prevented.

²Although the process of UL-OTD determination may appear complicated, its determination requires only a one-page scoring sheet and simple addition and subtraction.

We calculated and compared rates of various birth outcomes in the two groups. An intention to treat approach was taken based on exposure to AMOR-IPAT. If a woman was in the AMOR-IPAT exposed group developed either spontaneous labor, or a standard indication of labor induction prior to meeting criteria for a preventive labor induction, then for data analysis purposes she remained in the AMOR-IPAT exposed group. Likewise, if a woman in the non-exposed group underwent induction of labor for any reason, then for data analysis purposes she remained in the non-exposed group. The primary outcome of the study was mode of delivery, and four secondary outcomes were identified a priori: [1] major perineal injury (3rd or 4th degree tear), [2] neonatal intensive care unit admission, [3] one-minute APGAR score less than four, and [4] five-minute APGAR scores less than seven. We also assessed the association between AMOR-IPAT exposure and a variety of other birth outcomes using chi-squared methods (Fisher's exact test).

We used multivariable logistic regression to adjust for potential confounding in the association between AMOR-IPAT exposure and the primary and secondary outcomes. Most covariates that could be defined only after 38 weeks 0 days gestation were not used in the final logistic model due to possibility that these variables could be in the causal chain between expectant management and the development of adverse outcomes. Specific covariates that were not included in our final regression model included several preadmission issues (e.g., development of pre-eclampsia, oligohydramnios or failed antenatal testing prior to labor onset); several admission-related issues (e.g., gestational age, cervical Bishop's score, amniotic membrane status, and blood pressure); and several intra-partum issues (e.g., temperature elevation, need for augmentation of labor, and birth weight). However, we developed exploratory models that contained these variables in order to investigate the data more completely.

In order to evaluate overall birth health, we used two composite outcomes to compare the two study groups. The Adverse Outcomes Index (AOI) is a previously published score (21) that uses ten specific weighted outcomes to "assess not only the occurrence of deliveries with poor outcomes but also the number and relative severity of the outcomes" in any given group (Appendix 1). The AOI was calculated for each individual in each group and the outcomes of the two groups were then compared using Wilcoxon rank-sum analysis. In addition, we created a composite outcome called "uncomplicated vaginal delivery" that identified a vaginal delivery not associated with the need for mechanical assistance (vacuum or forceps), major perineal injury (3rd or 4th degree tear), post partum hemorrhage (> 500 cc's) or NICU admission. The rate of this outcome was determined for each group, and the rates were then compared using chi-squared techniques (Fisher's exact method).

Finally, we determined various labor-related time intervals for each group and made comparisons using Wilcoxon rank-sum methods. We collapsed data related to gestational age at delivery, timing of induction and mode of delivery into half-week sub-strata and then encoded the data so as to enable graphic representation. We also performed a survival analysis to compare the patterns of delivery as a function of gestational age in the study groups, and calculated an adjusted Cox proportional hazard ratio. Data were analyzed using the STATA Statistical Program (version 8, College Station, TX). The IRB of the University of Pennsylvania approved the study protocol.

RESULTS

When comparing the demographic, past medical, past obstetric and prenatal variables present in the exposed and non-exposed study groups, 10 of 23 variables were present at statistically different levels (Table 1). For example, exposed subjects were more likely to have Medicaid insurance, asthma, cigarette use, and a low hemoglobin level, while non-

exposed women were more likely to be older, have chronic hypertension, and have an elevated 1-hour 50 gram glucose tolerance test. Using indirect standardization, we estimated that the AMOR-IPAT exposed group should have had a 25.3% cesarean delivery as compared to the 25.8% rate that actually occurred in the non-exposed group (data not shown). The standardized cesarean delivery ratio was therefore 0.98, suggesting that the two study groups had very similar pre-38 week risk of cesarean delivery.

When examining intrapartum characteristics, women in the exposed group were characterized by four important qualities: 1) they were more likely to deliver earlier in the term period of pregnancy (median gestational age of delivery 39.1 weeks vs. 40.0 weeks, $p < 0.001$), 2) they were more likely to have their labor induced (47% vs. 24.2%, RR 1.95, 95% CI [1.47–2.57]), 3), they had a lower median modified cervical Bishop's score on admission (3.8 vs. 4.6, $p = 0.01$), and 4) they were more likely to receive prostaglandins medication (PGE2 or PGE1) for cervical ripening (45 % vs. 23.9 %, RR 1.89, 95 % CI [1.42–2.51]) (Table 2). Graphic displays of gestational age at delivery (Figure 1a) and the timing and frequency of labor induction (Figure 1b) demonstrate very different distributions of these activities in the two study groups. Survival analysis of time-to-delivery during the term period demonstrates the continuous nature of earlier delivery in the exposed group as compared to the non-exposed group (Figure 2). The Cox Proportional Hazard Ratio was 1.74 (95% CI 1.39–21.8, $p < 0.001$).

The cesarean delivery rate of the exposed group was 9% which was significantly lower than the 25.8% cesarean delivery rate found in the non-exposed group (RR 0.35, 95% CI [0.18–0.67], $p < 0.001$). Importantly, AMOR-IPAT exposure was associated with a significantly lower rate of cesarean delivery rate for both utero-placental insufficiency (UPI) and cephalo-pelvic disproportion (CPD) (Table 3). When controlling for potential confounders using logistic regression, the association between AMOR-IPAT exposure and a lower cesarean delivery rate remained highly significant. The final logistic model included five variables: AMOR-IPAT exposure (aOR 0.36, 95% CI 0.15–0.87, $p = 0.02$), male sex of fetus (aOR 1.93, 95% CI 1.06–3.52), advanced maternal age (aOR 3.20, 95% CI 1.16–8.84), weight gain ≥ 30 lbs (aOR 2.77, 95% CI 1.33–5.79); and epidural analgesia (aOR 11.88, 95% CI 1.58–89.59). The cesarean delivery rates were lower in the exposed group, as compared to the non-exposed group, for deliveries that occurred following both spontaneous labor (0% vs. 18.5%) and for deliveries that occurred following induction of labor (12.8% vs. 43.5%). Finally, the frequency of cesarean delivery as a function of gestational age in the two study groups had different distributions (Figure 1c).

In addition to an association with a lower cesarean delivery rate, exposure to AMOR-IPAT was associated with a significantly lower overall NICU admission rate (5% vs. 11.9%, OR 0.42, 95% CI 0.17–1.03, $p = 0.045$), and a lower major perineal trauma rate in women experiencing vaginal delivery (7.7% vs. 16.9%, aOR 0.41, $p = 0.037$). Adjustment for confounding variables lowered the strength of association between AMOR-IPAT exposure and a lower NICU admission rate to that of a statistical trend (aOR 0.58, 95% CI 0.25–1.36). Multivariate logistic modeling did not change the weak associations noted between exposure and improved APGAR scores (data not shown). Exposure to AMOR-IPAT was not associated with higher rates of any major adverse maternal or neonatal outcome.

Importantly, AMOR-IPAT exposure was associated with improved rates of the two composite outcomes. The mean AOI score in the exposed group was 3.1, as compared to 6.3 in the non-exposed group ($p = 0.026$). As noted in appendix 1, the difference in mean score was primarily driven by two maternal ICU admissions in the non-exposed group, but most of the ten adverse outcome occurred more frequently in the non-exposed group. In addition,

the exposed group had a higher uncomplicated vaginal delivery rate (59% vs. 47.4%, RR 1.24, 95% CI [1.02–1.51], $p=0.041$).

Rates of several lesser outcomes differed between the two groups (Table 4). AMOR-IPAT exposure promoted labor when fetuses tended to be smaller (median birth weight 3134 grams vs. 3380 grams ($p < 0.001$)). Exposure was linked to a lower rate of macrosomia (infants with birth weight ≥ 4000 grams [4% vs. 9.7%, RR 0.41, 95% CI 0.13–1.14]) and a higher rate of low birth weight infants (≤ 2500 grams [8% vs. 1.1%, RR 7.04, 95% CI 2.16–22.9]). Importantly, none of the AMOR-IPAT exposed neonates who delivered following induction of labor and who weighed less than 2500 grams at birth required NICU admission. In addition, no infant born to an exposed induced woman required NICU admission for respiratory insufficiency. Women in the exposed group who delivered vaginally were significantly less likely to have a 3rd or 4th degree perineal injury (aOR 0.41, 95% CI [0.18–0.95], $p=0.04$). Median estimated blood loss was significantly lower in the exposed group (300 ccs vs. 500 cc's, $p < 0.001$). Although the difference in blood loss was impacted by differences in cesarean delivery rates, the difference persisted when the analysis was limited only to vaginal deliveries (median 300cc's vs. 400 ccs, $p < 0.001$). The exposed group experienced repetitive late decelerations in only 8% of cases as compared to 21.3% in the non-exposed group (RR 0.38, 95% CI [0.25–0.81], $p=0.002$) and the exposed group had thick meconium at rupture of membranes only 3% of the time, as compared to 15.6% in the non-exposed group (OR 0.19, 95% CI [0.06–0.60], $p < 0.001$). Rates of assisted vaginal delivery, maternal fever, neonatal hyperbilirubinemia and low umbilical cord pH were similar in the two study groups.

Regarding time intervals throughout maternal and neonatal admissions, the exposed group had a longer median time between admission and onset of labor (360 min vs. 144 min, $p < 0.001$), but the length of the first stage of labor was not statistically different (8.0 hours vs. 7.1 hours, $p=0.19$). Furthermore, the exposed group had a significantly shorter median second stage of labor (42 min vs. 53min, $p = 0.05$) and significantly fewer exposed women had a second stage longer than two hours (10% vs. 18.8%, $p = 0.02$). The findings related to the duration of first and second stages were present despite considerable right censoring in the non-exposed group related to its higher cesarean delivery rate. In keeping with differences in group cesarean delivery rates, the median time from delivery to maternal discharge was significantly shorter in the exposed group (48 vs. 53 hours, $p < 0.001$). The overall median hospital admission time was shorter for both exposed mothers (64 hours vs. 67 hours, $p = 0.02$) and exposed neonates (48 hours vs. 53.5 hours, $p < 0.001$).

COMMENT

In this study we found a significant association between exposure of nulliparous women to a high rate of *preventive* labor induction and a lower rate of primary cesarean delivery. In addition, the exposed group had a significantly lower Adverse Outcome Index and a significantly higher rate of uncomplicated vaginal delivery. Hence, the lower cesarean delivery rate that was associated with AMOR-IPAT exposure was paralleled by a better pattern of other undesirable birth outcomes and a higher rate of uncomplicated vaginal delivery.

Multiple prospective studies have found that routine induction of labor at 41 weeks gestation, as compared to expectant management beyond 41 weeks gestation, leads to lower cesarean delivery risk and decreased neonatal mortality (22–24). AMOR-IPAT pushes gestational age of delivery in the exposed group to below 41 weeks (median age of delivery 39 weeks and one day). A recently published randomized clinical trial involving women of mixed parity found that nulliparous women treated with AMOR-IPAT ($n=65$), as compared

to compared to women treated with usual care (n=63), had cesarean delivery rates of 18.5% and 25.8%, respectively (p=0.23) (34). There is only one previous randomized controlled trial that compared routine nulliparous labor induction at 39 weeks gestation to expectant management until 42 weeks (25). This study showed lower rates meconium stained amniotic fluid and lower rates of fetal resuscitation in the early induction group, but no change in NICU admission or cesarean delivery rates. However, in this study, women randomized to the expectant management group who required post-dates induction (a group of women who were at increased risk for adverse outcomes) were excluded from the analysis. Two prospective randomized trials from the 1970's involving groups of mixed parity (26,27) showed modest improvements in neonatal birth outcomes in the induced groups, but no significant change in cesarean delivery rate. However, these studies were relatively small (n=111 [25], n=264 [26]) and occurred prior to the availability of cervical ripening agents. In contrast, the clinical activity described in the two previously published retrospective studies involving AMOR-IPAT (16–17) included women who received cervical ripening and had greater power. These two studies reported numerically lower nulliparous cesarean delivery rates in the exposed group. The first (16) showed a 6.9% nulliparous cesarean delivery rate in the exposed group as compared to a rate of 20.1% in the nonexposed group (p=0.11). The second (17) showed an 8.1% nulliparous cesarean delivery rate in the exposed group as compared to a rate of 14.2% in the nonexposed group (p=0.008).

The goal of reduction of cesarean delivery in nulliparous women is probably not attainable simply by raising the threshold for performing this procedure, e.g., tolerating longer periods of dystocia, or greater amounts of fetal intolerance of labor. Raising these thresholds would probably increase the incidence of birth-related morbidity for both the mother and the neonate (28,29). Rather, the goal is attainable only if other changes occur within the management of term pregnancy that prevent the common causes of cesarean delivery.

AMOR-IPAT contains several significant changes in the management of term maternity care. First, it encourages labor to occur at earlier gestational ages. Previous studies have suggested that adverse birth outcomes become more frequent with increasing gestational age during the term period (30–33). The survival analysis captured in Figure 2 demonstrates that AMOR-IPAT exposure was associated with the systematic delivery of exposed women earlier within the term period of pregnancy as compared to the pattern of delivery of non-exposed women. The median gestational age at delivery in the exposed group of this study was 39.1 weeks as compared to 40.0 weeks in the non-exposed group (p < 0.001). Second, as a consequence of delivery earlier within the term period of pregnancy, AMOR-IPAT exposure promoted labor when fetuses tended to be smaller. In this study, the median birth weight was 3134 grams in the exposed group as compared to 3380 grams in the non-exposed group (p < 0.001). In addition, only 4% of exposed neonates weighed more than 4000 grams as compared to 9.7% of non-exposed neonates (RR 0.41, 95% CI [0.13–1.14], p=0.07). Possibly due to smaller average birth weight, women in the exposed group who delivered vaginally were significantly less likely to have a 3rd or 4th degree perineal injury as compared to women who delivered vaginally in the non-exposed group (7.7% vs. 16.9%, RR 0.41, 95% CI [0.18–0.95], p=0.04). Third, and also as a consequence of delivery earlier in the term period of pregnancy, AMOR-IPAT exposure may have promoted labor when the utero-placental unit was younger and healthier. In this study, the exposed group experienced repetitive late decelerations in only 8% of cases as compared to 21.3% in the non-exposed group (RR 0.38, 95% CI [0.25–0.81], p=0.002). In addition, the exposed group had thick meconium at rupture of membranes only 3% of the time, as compared to 15.6% in the non-exposed group (OR 0.19, 95% CI [0.06–0.60], p<0.001). Both findings suggest that fetuses in the exposed group may have been better supported by their placenta during labor.

We are very aware that many previous studies of labor induction have concluded that labor induction is associated with *increased* risks of cesarean delivery and other adverse birth outcomes (35–39). However, most previous studies of labor induction contain at least some potential flaws, the most significant of which is confounding by indication. If most “indicated” inductions are done in response to an identified complications of pregnancy (e.g., oligohydramnios, severe pre-eclampsia, failed antenatal testing), it is possible that the resultant cesarean section (or other untoward outcome) is due to the established complication of pregnancy rather than the induction per se. Furthermore, accurate assessment of the risks of preventive induction cannot be ascertained by comparing women with “indicated” inductions to women who generally have no complications and who enter labor spontaneously. Even when such studies include elective and preventative inductions in a cohort of “indicated” inductions, “indicated” inductions constitute the majority of the inductions, making it impossible to determine the relative impact of preventative inductions. Furthermore, we believe that evaluation of the impact of labor induction on birth outcomes can best be made through the use of population-based strategies that compare the outcomes of a group of women characterized by a high (and largely preventative) labor induction rate with the outcomes of a group of women characterized by a more standard (and largely “indicated”) labor induction rate (16,17).

This study has several potential limitations. First, although we identified and controlled for confounding factors in our analyses, and an indirect standardization suggested that the pre-38 week risk of cesarean delivery in the two study groups was similar, it is possible that unidentified factors may have accounted for some or all of the difference in outcomes between the exposed and non-exposed groups. Second, based on study design, we could not control for specialty of provider. It is well known that a variety of provider characteristics have a significant impact on group cesarean delivery rates. However, other than the use of preventive induction, type of prostaglandin for cervical ripening, and variable usage of epidural analgesia, there is little evidence that there were major differences in basic labor management. In addition, the obstetrics group made all decisions concerning the timing of cesarean delivery in both study groups. The possibility that AMOR-IPAT exposed women were subjected to longer, more difficult or more complicated vaginal delivery is refuted by both the finding of a shorter length of second stage in the exposed group, and a subtle pattern of more favorable APGAR scores in the exposed group. Third, the study took place in an urban setting, occurred at an academic institution and involved primarily African-American women. Hence, the generalizability of this study to other settings is unclear. However, a large recently-published retrospective study of Caucasian women in a rural setting also found a significantly lower cesarean delivery rate in nulliparous women (17).

Despite the limitations of this study, we believe that data presented here strongly suggest that the AMOR-IPAT method of care represents a potential strategy to safely improve birth health in nulliparous pregnant women at term. An adequately powered multi-site clinical trial will be essential to determine the impact of AMOR-IPAT on the birth outcomes of nulliparous women and their infants. If AMOR-IPAT is demonstrated to have positive effects on birth health in the context of a prospective randomized study, then it may be time to critically reevaluate the balance between the expectant management of pregnancy during the term period and the use of preventive labor induction.

Acknowledgments

none

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Figure 1.

Figure 1a: Delivery of Study Groups as a function of gestational age – This is a figure that shows in bar-graph form the distribution of timing of delivery by gestational age in the two study groups.

Figure 1b: Mode of Onset of Labor of Study Groups as a function of gestational age– This is a figure that shows in bar-graph form the distribution of induction of labor by gestational age in the two study groups.

Figure 1c: Route of Delivery of Study Groups as a function of gestational age– This is a figure that shows in bar-graph form the distribution of cesarean delivery by gestational age in the two study groups.

Figure 2. Survival Analysis of Timing of Delivery by Study Group: In weeks past 37 weeks 0 days gestation – This figure shows that exposure to AMOR-IPAT exposure results in a continuous impact on the timing of delivery

A. Utero-placental Factors: Odds Ratio Time Units

Hx chronic hypertension	1.8	6 days	_____
Gestational Diabetes	1.8	6 days	_____
Insulin Dependent Diabetes	2.4	10 days	_____
Sickle Cell Trait	1.5	3 days	_____
Elevated AFP	1.4	3 days	_____
Cigarette Use	1.3	2 days	_____
Size < Dates (<= 3 cm)	1.6	4 days	_____
Advanced Age (>= 35 years at delivery)	1.8	6 days	_____
Anemia (1 st Trimester <= 10.0)	1.6	4 days	_____

TOTAL UPI Time Units _____

ULOTD-upi = (41 weeks – Total UPI Time Units) = _____

B. Cephalo-Pelvic Factors: Odds Ratio Time Units

Elevated BMI (>=30)	1.3	2 days	_____
Short stature (<= 62")	1.8	6 days	_____
Excess Weight gain (>= 30 lbs)	1.8	6 days	_____
Size > dates (>= 3 cm)	1.7	4 days	_____
Gestational Diabetes	1.8	6 days	_____
Type I Diabetes	2.4	10 days	_____
History vacuum/forceps	2.2	9 days	_____
Prev. macrosomia (>4000 gm)	2.0	7 days	_____

TOTAL CPD Time Units _____

ULOTD-cpd = (41 weeks – Total CPD Time Units) = _____

FINAL ULOTD: Lower of the two ULOTD's (ULOTD-upi versus ULOTD-cpd), but the final ULOTD is always ≥ 38 weeks.

_____

Appendix 1.

AMOR-IPAT - UL-OTD Calculation Sheet – this figure describes how the timing of preventive labor induction was determined in the AMOR-IPAT exposed group

Table 1

Levels of Risk Factors by Study Group

VARIABLE NAME	Exposed n=100	NonExp n=352	Risk Ratio	95% CI	p value
DEMOGRAPHICS					
Age, median	20 years	23 yrs			<0.001*
Advanced Age (> = 35 years at delivery)	3%	8.2%	0.36	0.11–1.17	0.07
African-American	76%	60.8%	1.25	1.09–1.44	0.005
Medicaid Insurance	62%	44.6%	1.39	1.15–1.69	0.002
Single Marital Status	81%	64.2%	1.26	1.12–1.43	0.002
PAST MEDICAL					
Previous TAB	63%	59.4%	1.06	0.89–1.26	0.51
Previous SAB	8%	17.6%	0.45	0.23–0.97	0.02
Chronic Hypertension	2%	3.4%	0.59	0.13–2.58	0.47
Asthma	17%	13.9%	1.22	0.74–2.02	0.44
Previous UTI	9%	7.1%	1.27	0.61–2.63	0.53
Previous atypical PAPS	10%	19.9%	0.50	0.27–0.94	0.02
Cigarette Use	18%	9.9%	1.81	1.07–3.06	0.03
Alcohol Use	4%	2.0%	2.01	0.60–6.73	0.25
Cocaine abuse	4%	1.7%	2.35	0.68–8.15	0.17
LABORATORY					
□ 1 hr Glucola ≥ 135	3%	10.2%	0.29	0.09–0.93	0.02
Hemoglobin (1 st or 2 nd trimester <= 11)	16%	11.9%	1.34	0.79–2.28	0.28
Group B Strep culture positive	40%	26.4%	1.51	1.13–2.04	0.008
MATERNAL HABITUS					
Preconception weight, median	138 lbs	138.5 lbs			0.60*
Preconception weight > 160 lbs	32%	28.4%	1.13	0.81–1.57	0.49
Height, mean	64 in	64 in			1.00*
Height < 62 inches	16%	9.9%	1.61	0.93–2.78	0.09
Preconception BMI, median (kg/m ² ml)	23.8 kg/m ²	23.4 kg/m ²			0.60*

VARIABLE NAME	Exposed n=100	NonExp n=352	Risk Ratio	95% CI	p value
Preconception BMI > 30	16%	16.8%	0.97	0.58–1.61	0.91
INDEX PREGNANCY					
Weight Gain during pregnancy, median	30.5 lb	33 lb			0.07*
Excess Weight Gain (>= 30 lbs)	57%	62.8%	0.91	0.75–1.10	0.29
Gestational Diabetes	3%	2.6%	1.17	0.32–4.25	0.81
Size > Dates (by at least 3 cm)	24%	5.4%	4.45	2.54–7.78	<0.001
Size < Dates (by at least 3 cm)	6%	4.6%	1.32	0.53–3.28	0.55

* calculated with the Mann Whitney rank-sum test

Table 2

Levels of Intrapartum Variables/Factors by Study Group

VARIABLE NAME	Exposed N=100	Non-Exposed n=352	Risk Ratio	95% CI	p value
SUBJECT STATUS ON ADMISSION					
Gestational age on admission, (median)	39.1 wks	40.0 wks			< 0.001
Ruptured Membranes on admission	22%	29.8%	0.74	0.49–1.10	0.12
Initial Bishop's Score, median	3.8	4.6	–	–	0.01
Initial Bishop's Score ≤ 5	73%	56.2%	1.30	1.12–1.51	0.002
Median Arterial Pressure on admission (MAP – mmHg))	90	91			0.30
Arterial Pressure (MAP) on admission >= 105	9%	9.7%	0.69	0.3170–1.30	0.42
Median Arterial Pressure at one hour (MAP – mmHg))	85	81			0.07
Arterial Pressure (MAP) at one hour >= 105	7%	9.4%	0.75	0.34–1.64	0.46
Vertex Presentation	100%	97.7%	–	–	0.13
INTRA-PARTUM EVENTS					
Spontaneous labor	22%	23.1%	0.96	0.63–1.45	0.83
Induction of labor	47%	24.2%	1.95	1.47–2.57	< 0.001
Augmentation (following premature rupture of membranes or ineffective spontaneous labor)	31%	51.7%	0.60	0.44–0.82	< 0.001
Elective Cesarean	0%	1.4%	–	–	0.23
Prostaglandin (any use)	45%	23.9%	1.89	1.42–2.51	< 0.001
Prostaglandin E1 (any antepartum use)	6%	21.6%	0.28	0.12–0.62	< 0.001
Prostaglandin E2 (any antepartum use)	41%	3.7%	11.1	6.20–19.89	< 0.001
Use of Pitocin (any)	71%	70.5%	1.01	0.87–1.16	0.92
Artificial Rupture of Membranes	46%	54.3%	0.85	0.67–1.07	0.14
Epidural Analgesia	66%	89.8%	0.74	0.64–0.85	< 0.001
Placement of Fetal Scalp Electrode	39%	45.7%	0.85	0.65–1.12	0.23
Placement of IUPC	19%	38.9%	0.49	0.32–0.75	< 0.001
Assisted Vaginal Delivery (all types)	22%	16.2%	1.36	0.88–2.11	0.18
Use of Vacuum	21%	7.7%	2.74	1.62–4.63	< 0.001
Use of Forceps	1%	8.5%	0.12	0.02–0.87	0.01

	Exposed N=100	Non-Exposed n=352	Risk Ratio	95% CI	p value
INTRAPARTUM FINDINGS					
Thick Meconium at ROM	3%	15.6%	0.19	0.06–0.60	< 0.001
Fetal Intolerance to Labor – (repetitive late decelerations)	8.0%	21.3%	0.38	0.25–0.81	0.002
Maternal Fever prior to delivery (Temp > 100.4)	9.0%	6.0%	1.50	0.71–3.19	0.28
LABOR and DELIVERY TIMING					
Admission – Delivery, (median)	16 hrs	12 hrs			0.04*
Admission – Delivery > 24 hrs	19%	15.9%	1.19	0.75–1.91	0.46
Admission – Delivery > 48 hrs	3%	2.6%	1.17	0.32–4.25	0.82
Admission – Labor Onset, (median)	6.0 hrs	2.4 hrs			< 0.001*
Admission – Labor Onset > 6 hrs	50%	26.4%	1.89	1.46–2.46	< 0.001
1 st stage, (median)	8 hr	7.1 hr			0.19*
1 st stage > 12 hrs	18.0%	13.6%	1.32	0.81–2.16	0.28
2 nd stage, (median)	42 min	53 min			0.05*
2 nd stage ≥ 1 hr	28%	36.4%	0.77	0.28–1.00	0.04
2 nd stage ≥ 2 hr	10%	18.8%	0.53	0.24–0.91	0.02
2 nd stage ≥ 3 hr	5%	9.4%	0.47	0.21–1.33	0.16
2 nd stage ≥ 4 hr	2%	4.6%	0.44	0.10–1.88	0.25

* Mann Whitney rank-sum test

Table 3

Induction of Labor and Major Birth Outcome Information: Overall Rates and Indications*

VARIABLES:	Exposed n=100	Non-exposed n=352	Risk Ratio	95% CI	p value
INDUCTION OF LABOR INFORMATION:					
Induction of Labor Rate, overall	47%	24.2%	1.95	1.47–2.57	< 0.001
(Indicated Induction)	(11%)	(23.1%)	(0.52)	(0.14–73)	(0.008)
(Preventive Induction)	(36%)	(1.1%)	(31.7)	(11.6–86.9)	(< 0.001)
Use of PGE1 with labor induction	4%	16.2%	0.25	0.09–0.66	0.002
Use of PGE2 with labor induction	40%	3.4%	11.7	6.4–21.5	< 0.001
Reasons for Indicated Labor Induction					
> 41 weeks	3%	10.2%	0.29	0.09–0.93	0.02
> 42 weeks	0%	2.0%	–	–	0.13
Oligohydramnios/IUGR	7%	4.3%	1.64	0.69–3.92	0.26
Severe PreEclampsia	1%	3.4%	0.29	0.04–2.23	0.20
Other*	0%	3.1%	–	–	0.16
Reasons for Preventive Labor Induction					
Impending Cephalo-Pelvic Disproportion	14%	0%	–	–	< 0.001
Impending PreEclampsia	12%	0.3%	14.1	4.05–48.9	< 0.001
Impending IUGR or Oligohydramnios	6%	0%	17.6	2.08–149	< 0.001
Impending Utero-Placental Insufficiency	2%	0%	–	–	0.008
Social/Miscellaneous	2%	0.8%	2.35	0.40–13.9	0.33
CESAREAN DELIVERY INFORMATION:					
Cesarean delivery Rate**	9%	25.8%	0.35	0.18–0.67**	<0.001**
Indications for C-section:					
Failure to Progress	5%	11.9%	0.42	0.17–1.03	0.045
Fetal Intolerance	4%	10.8%	0.37	0.14–1.01	0.039
Non-reassuring fetal heart tracing	0%	4.0%	–	–	0.04
Acute Fetal Intolerance	4%	6.8%	0.59	0.21–1.65	0.30
Malpresentation (breech)	0%	1.1%	–	–	0.28

VARIABLES:	Exposed n=100	Non-exposed n=352	Risk Ratio	95% CI	p value
Active Herpes	0%	0.3%	–	–	0.59
Acute vaginal bleeding	0%	0.3%	–	–	0.59
Occurrence of Cesarean Delivery by Mode of Labor Onset **					
Spontaneous labor	0%	18.5%	–	–	<0.001
Induction of labor (all)	12.8%	43.5%	0.29	0.13–0.64	<0.001
Indicated Induction of Labor	7.7%	43.2%	0.18	0.03–1.19	0.01
Preventive Induction of Labor	14.7%	50.0%	0.29	0.08–1.05	0.08
Augmentation of labor	9.7%	18.8%	0.52	0.17–1.57	0.22
Elective Cesarean	– (0/0)	100%	–	–	–
NEONATAL INTENSIVE CARE					
NICU Admission (overall)	5%	11.9%	0.42	0.17–1.03	0.045
Sepsis – suspect or actual	5%	9.7%	0.52	0.21–1.29	0.14
Respiratory disorders requiring NICU Admission§	2%	6.0%	0.34	0.08–1.41	0.11
□□ Blood sugar-minima ≤ 50	4%	4.3%	0.94	0.32–2.77	0.91
COMPOSITE OUTCOMES					
Adverse Outcome Index (mean)	3.1	6.3	–	–	0.026***
Uncomplicated Vaginal Birth Rate	59%	47.4%	1.24	1.02–1.51	0.041

* Failed Testing (1), Polyhydramnios (1), Gestational Diabetes (2), Chronic Hypertension (3), and Unstable Lie (2). When not specified, rates are based on entire study group

** Confidence interval and p-value listed here are based on univariate analysis. Confidence interval and p-value determined by logistic regression modeling may be found in the text and in the abstract.

*** Rank-sum analysis

Table 4

Outcomes based on AMOR-IPAT exposure status

VARIABLE	Exposed n=100	Non-Exposed n=352	Risk Ratio	95% CI	p-value
MATERNAL – Delivery					
Assisted Vaginal Delivery, all	22%	16.5%	1.33	0.86–2.07	0.20
3 rd or 4 th Degree Perineal Injury, all	7%	12.5%	0.56	0.26–1.20	0.12
3 rd or 4 th Degree Perineal Injury, vaginal only	7.7%	16.9%	0.41	0.18–0.95	0.04
Estimated Blood Loss, all	411cc ± 258	514cc ± 277	–	–	<0.001*
Excess Blood Loss (>500 cc), all	19.0%	29.0%	0.66	0.42–1.01	0.05
Estimated Blood Loss, vaginal only	370 cc ± 157	399cc ± 223			0.007
Excess Blood Loss (>500cc), vaginal only	13.2%	8.8%	0.04	(–0.03)–(0.12)	0.23
MATERNAL - Post-Partum					
Maternal fever (>100.4)	9.0%	8.5%	1.06	0.52–2.15	0.88
Post Partum hemoglobin, median	9.6 ± 1.4	10.0 ± 1.4	–	–	0.04
Post Partum anemia (Hgb<8)	13%	7.7%	1.69	0.91–3.16	0.10
Flux in hemoglobin with delivery	1.6 gms ± 1.7	1.8 gms ± 1.5	–	–	0.80*
NEONATAL					
Male Infant	45%	47%	0.96	0.72–1.28	0.77
Minor congenital problem**	4%	1.7%	2.35	0.68–8.15	0.17
Significant congenital problem†	0%	0.6%	–	–	0.46
Minor respiratory disorders‡	7%	3.1%	2.24	0.89–5.63	0.08
Bilirubin, median (if checked)	9 mg/dl	10 mg/dl			0.79*
Cephalo-hematoma	3%	8.8%	0.34	0.11–1.09	0.05
Birth weight	3134 gm ± 457	3380 gm ± 453	–	–	<0.001*
Large (>4000 gm)	4.0%	9.7%	0.41	0.13–1.14	0.07
Small (<2500 gm)	8.0%‡‡	1.1%	7.04	2.16–22.9	<0.001
Head circumference	33.4 cm ± 1.7	34.1 cm ± 1.9	–	–	0.001*
Venous Cord Blood pH < 7.2	5.0%	8.0%	2.2	0.74–6.58	0.15

VARIABLE	Exposed n=100	Non-Exposed n=352	Risk Ratio	95% CI	p-value
APGAR @5 < 7	1.0%	1.7%	0.59	0.07–4.82	0.61

* calculated with the Mann Whitney rank-sum test

** polydactyly, umbilical hernia, undescended testes, pyelectasis

† major cardiac anomalies

§ pneumonia, meconium aspiration, or hypoxia requiring ventilation

‡ assisted ventilation at birth, or transient tachypnea, without need for NICU admission

†† none of these neonates required admission to the NICU

§§ cesarean delivery, 3rd/4th degree perineal injury, NICU admission, APGAR @ 1 < 4, APGAR @ 5 < 7

Appendix 2

Development of Adverse Outcome Index by Group

VARIABLE NAME	Exposed, n=100 number (rate)	NonExp, n= 352 number (rate)	Weights
Maternal Death	0 (0%)	0 (0%)	750
Intrapartum or neonatal death	0 (0%)	1 (0.75%)	400
Uterine rupture	0 (0%)	0 (0%)	100
Maternal ICU admission	0 (0%)	2 (0.6%)	65
Infant Birth Trauma (Erbs palsy, vacuum or forceps injury)	0 (0%)	3 (0.8%)	60
Return to operating room of labor and delivery unit	0 (0%)	2 (1.5%)	40
Admission to NICU	5 (5%)	42 (11.9%)	35
Apgar score less than 7 at 5 minutes	1 (1%)	6 (1.7%)	25
Maternal blood transfusion	0 (0%)	4 (1.1%)	20
Third- or fourth-degree perineal tear	7 (7%)	44 (12.5%)	5
Mean Adverse Outcome Index Score	3.1	6.3	0.026
Overall Frequency of at least one adverse outcome	13 (13%)	82 (23.3%)	P=0.03

3.1, as compared to 6.3 in the non-exposed group ($p = 0.026$).

Appendix 3

Development of the Uncomplicated Vaginal Delivery Rate by Group

VARIABLE NAME	Exposed, n=100 number (rate)	NonExposed, n= 352 number (rate)
Cesarean Delivery	9 (9%)	91 (25.8%)
Assisted Vaginal Delivery (vacuum or forceps)	21 (21%)	27 (7.7%)
Shoulder dystocia (severe)	3 (3%)	4 (1.1%)
Major perineal trauma (3 rd - or 4 th - degree injury)	7 (7%)	44 (12.5%)
Post-partum hemorrhage (vaginal delivery, EBL > 500 cc's)	19 (19%)	102 (29%)
NICU Admission	5 (5%)	42 (11.9%)
Overall frequency of complicated vaginal delivery(at least one complication)	41 (41%)	185 (52.6 %)
Overall frequency of uncomplicated vaginal delivery (none of the five identified adverse outcomes)	59 (59%)	167 (47.4%) p = 0.041