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The Impact of the Active Management of Risk in Pregnancy at Term on Birth Outcomes: a randomized clinical trial

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Abstract

Objective—To compare birth outcomes resulting from the active management of risk in pregnancy at term (AMOR-IPAT) to those resulting from standard management.

Methods—Randomized clinical trial with 270 women of mixed parity. AMOR-IPAT used preventive labor induction to ensure delivery before the end of an estimated optimal time of delivery. Rates of four adverse obstetric events, and two composite measures, were used to evaluate birth outcomes.

Results—The AMOR-IPAT-exposed group had a similar cesarean delivery rate (10.3% vs. 14.9%, $p=0.25$), but a lower NICU admission rate (1.5% vs. 6.7%, $p=0.03$), a higher uncomplicated vaginal birth rate (73.5% vs. 62.8%, $p=0.046$), and a lower mean Adverse Outcome Index score (1.4 vs. 8.6, $p=0.03$).

Conclusion—AMOR-IPAT exposure improved the pattern of birth outcomes. Larger randomized clinical trials are needed to further explore the impact of AMOR-IPAT on birth outcomes and to determine the best methods of preventive labor induction.

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The study was conducted in Philadelphia, Pa. at two sites:

- 1) the Hospital of the University of Pennsylvania, by members of both the Department of Obstetrics and Gynecology and the Department of Family Medicine and Community Health, and
- 2) Pennsylvania Hospital, by members of the Department of Obstetrics and Gynecology

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Keywords

Adverse Outcome Index; Cesarean delivery; Neonatal Intensive Care Unit admission; Preventive labor induction; Uncomplicated Vaginal Delivery

INTRODUCTION

Over the past decade, the overall rate of cesarean delivery in the US steadily increased from 22% to 31.1% (1–3). Increases in cesarean delivery rates have occurred in all areas of the country and in most hospitals. The reasons for these increases are multi-factorial and include changing patient risk profiles (4–6), medico-legal pressures (7–8), and a growing interest in elective primary cesarean delivery (9–10). However, despite increases in cesarean delivery utilization, few improvements have been made in the overall quality of birth outcomes. US rates of term NICU admission have not significantly decreased (11), and rates of maternal and neonatal mortality have increased slightly (12). Currently, there is little research targeting either ways to reverse the current rising trend in cesarean delivery utilization, or ways to improve the overall pattern of birth outcomes.

Several recent retrospective studies have described an alternative method of obstetric care that has been associated with low cesarean delivery rates and improvement in the pattern of birth outcomes (13–14). This alternative method utilizes risk-based preventive labor induction to ensure that each pregnant woman enters labor at a gestational age that maximizes her chance for vaginal delivery. The alternative method is termed the Active Management of Risk in Pregnancy at Term (AMOR-IPAT). In addition to its association with lower cesarean delivery rates, AMOR-IPAT exposure has also been associated with lower NICU admission rates, decreased perineal trauma, and lower rates of low APGAR scores (13–17). However, the finding of previous AMOR-IPAT studies have been challenged based on retrospective study design (18), potential confounding by provider type, and inability to control for individual physician differences in labor management style apart from the variable use of labor induction (19). In response to these concerns, a randomized clinical trial was undertaken to more definitively evaluate the impact of AMOR-IPAT exposure on rates of cesarean delivery and other important birth outcomes.

The safe prevention of cesarean delivery is important because cesarean delivery, when compared to vaginal delivery, is associated with higher rates of post-partum hemorrhage, major post-partum infection and hospital readmission (20–23). In addition, cesarean delivery carries a greater likelihood for not only serious pulmonary morbidity for the neonate in the index pregnancy (24), but other major fetal complications, including fetal loss, in subsequent pregnancies (25–27). While several recent reports have presented elective primary cesarean delivery as a way to prevent vaginal delivery-related pelvic floor damage and resultant genitor-urinary morbidity (28–30), others have suggested that such benefits are neither clear-cut nor long lasting (31–32). There is currently no clear evidence that the risk/benefit ratio of elective primary cesarean delivery is equal to, or superior than, the risk/benefit ratio of the current standard of care that couples expectant management within the term period with attempted vaginal delivery. AMOR-IPAT was developed as a third option. It uses preventive labor induction relatively early in the term period of pregnancy to promote uncomplicated vaginal delivery and prevent a variety of adverse birth outcomes.

MATERIALS AND METHODS

Study Design

A randomized clinical trial design was used to evaluate the impact of AMOR-IPAT exposure on mode of delivery and other major birth outcomes. Pregnant women were invited to participate in the study between 32 and 37 1/2 weeks of gestation. There were three study inclusion factors: 1) accurate pregnancy dating (averaging of LMP and 8–22 week ultrasound data if the discrepancy was ≤ 6 days, or averaging of two 8–22 week ultrasounds if the discrepancy was ≤ 5 days); 2) fluency with the English language; and 3) at least one of six pre-identified risk factors for cesarean delivery: a) projected maternal age ≥ 35 at the time of delivery, b) maternal height ≤ 62 ", c) BMI ≥ 30 at conception, d) blood pressure (BP) elevation (any BP > 80 diastolic or > 120 systolic in the first trimester), e) first trimester hemoglobin < 11.0 mg/dl, and f) history of large fetus (> 8 lb 8oz). Although our method of pregnancy dating was unconventional, we believe that the merging of two good measurements improves the accuracy of EDC estimation. In turn, the safety of early term labor induction is improved if pregnancy dating is accurate. Additional risk factors beyond the six pre-identified risk factors were included in the AMOR-IPAT risk scoring model (Appendix 1). Exclusion factors included multiple gestation, prior cesarean delivery, placenta previa, positive HIV antibody titers, prior cervical cone biopsy, or any other fetal or maternal issue precluding a trial of labor. Women who provided informed consent, and who remained undelivered at 37 weeks 4 days of gestation, were randomized to either AMOR-IPAT or usual care. For logistical and clinical reasons, cervical Bishop Score was not determined prior to randomization nor was it part of the randomization scheme.

Unique sets of opaque envelopes were created for each parity group and each risk type at each of three recruitment sites (four sets of envelopes for each site). The three recruitment sites were: 1) the Hospital of the University of Pennsylvania Obstetrics Clinic (an obstetric residency training site), 2) the Pennsylvania Hospital Obstetrics Clinic (an obstetric residency training site), and 3) Penn Family Care (a family medicine residency training site). A block-size of four was used in the randomization scheme because subjects at each site were randomized based on both parity group (nulliparous vs. multiparous) and major risk type (UPI vs. CPD). A larger block design would have been more likely to lead to an imbalance of these factors, and study group assignment, between study groups. Because subjects provided informed consent weeks before their randomization, and because the exact ordering of consented women awaiting randomization could change at any time if a consented subject delivered prior to randomization, it was not possible to predict which envelope would be opened for any given subject at the time informed consent was obtained. All deliveries were intended to occur at either the Hospital of the University of Pennsylvania (Recruitment Site 1 and Recruitment Site 2) or Pennsylvania Hospital (Recruitment Site 3). The study was initially constructed to be a double-blinded trial, but because the active management of risk clearly involved the use of labor induction without an accepted indication, and because the scheduling of preventive labor induction required hospital admission earlier than most women anticipated, the study could not be completely blinded to either subjects or providers. Accordingly, approximately one-quarter of the way through the investigation all study subjects were informed of group assignment within one or two days of randomization. However, other than the identification of Active Group assignment of women receiving preventive labor induction, providers were not routinely informed of study group assignment, and the neonatal staff that made the determination of NICU admission remained functionally blinded.

The AMOR-IPAT method has been previously described (13,14,33). The risk-scoring system is attached as Appendix 1. 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 interfere with placental growth or accelerate placental aging) and/or 2) a cephalo-pelvic disproportion (CPD) category (i.e., factors that accelerate fetal growth or limit maternal pelvic size). We 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. 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 (13,14,33) (Appendix 1). We then subtracted the total number of days that any given subject 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 (34). The lower of the two category-specific UL-OTD's for each woman became her final UL-OTD, but a final UL-OTD could not be less than 38 weeks 0 days gestation. Although the process of UL-OTD determination may appear complicated, its determination requires only a one-page scoring sheet and simple addition and subtraction.

If a subject in the exposed group did not develop spontaneous labor as she approached her UL-OTD, then she was scheduled for preventive labor induction so that she would begin labor on, or 1–4 days before her UL-OTD. Within this four-day range, the exact timing of induction was often impacted by subject preference or labor floor space availability. If a woman was scheduled for labor induction, but had an unfavorable uterine cervix (modified Bishop's score < 6) (35), then she was provided with cervical ripening with dinoprostone or misoprostol prior to the start of oxytocin. For this study, labor was defined as the presence of regular contractions associated with cervical change, and labor induction was defined as the use of artificial agents to promote labor in a woman with intact membranes.

Consented study subjects who developed an accepted indication for labor induction were induced using standard protocols irrespective of gestational age, randomization status or study group assignment. Apart from the timing of preventive labor induction, no other study protocol changes were made in the labor management of women in the study. Data related to prenatal, intra-partum and post-partum events were collected from each mother and each baby.

Data Analysis

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 greater at the time of delivery. Dichotomous and categorical variables were compared using chi-squared techniques. We used relative risk as the main measure of comparison and defined statistical significance for all tests as a p-value ≤ 0.05 .

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. Some secondary analyses were based on mode-of-labor onset and parity groupings. The primary outcome of the study was mode of delivery. The trial was powered to show statistical significance if the exposed group had a cesarean delivery rate of 6% and the non-exposed group had a cesarean delivery rate of 18%. These rates were based on several previous retrospective investigations that studied women similar to those recruited into this study (13–15). In addition to the primary outcome “cesarean delivery”, three secondary outcomes were identified a priori: [1] major perineal injury (3rd or 4th degree tear), [2] neonatal intensive care unit admission (NICU), and [3] five-minute APGAR score less than seven. All decisions to admit neonates to the

NICU were made by members of the NICU staff. We used stepwise multivariate logistic regression to adjust for potential confounding in the association between AMOR-IPAT exposure and the primary and secondary outcomes. All potential prenatal variables, including all risk factors used for UL-OTD estimation, were added to the initial model. Variables that did not significantly impact the model were then deleted in stepwise fashion using likelihood ratio methodology and a p -value < 0.05 .

We also assessed the impact of AMOR-IPAT exposure on a variety of other birth outcomes using chi-squared methods (Fisher's exact test) for dichotomous outcomes and Wilcoxon rank-sum analysis for continuous outcomes. Flux in hemoglobin was determined by subtracting the lowest post-delivery hemoglobin from the pre-delivery hemoglobin. A composite outcome entitled "Fetal intolerance of labor, all types" was created that captured the presence of any of the four fetal heart tone a (FHT) abnormalities that can lead to cesarean delivery: repetitive late decelerations, severe variable decelerations, persistent bradycardia (FHT < 90) or persistent tachycardia (FHT > 170). We determined various labor-related time intervals for each group and made comparisons using Wilcoxon rank-sum methods. In addition, we 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. An analysis of the number needed to treat (NNT), or the number needed to harm (NNH), was done for all major outcomes present at statistically different levels in the two groups. We used bar graphs to present data related to the impact of gestational age on the frequency of three specific clinical events in the two study groups: 1) timing of delivery; 2) mode of onset of labor (spontaneous vs. induction); and 3) type of nursery admission (regular nursery vs. NICU admission).

Because of the importance of the estimation of the UL-OTD for each subject in the timing of preventive labor induction, we compared final UL-OTD estimations for women in each study group. Furthermore, we compared mean gestational age at delivery as a function of UL-OTD in the two study group. The study was not powered to differentiate rates of various study outcomes as a function of UL-OTD.

Finally, following all other data analysis, we assessed our study's findings using two composite outcomes. The first was the Adverse Birth Outcome Index (AOI). This previously published index (36) evaluates the outcomes of any given group based on a weighted scoring system of 10 specific adverse outcomes (Appendix 2). As in the study that introduced the AOI, we calculated and compared mean AOI scores. In addition, we compared the distributions of this outcome in the two study groups using Wilcoxon rank-sum testing. The second composite outcome was a construct entitled "uncomplicated vaginal birth" (UVB) (Appendix 3). A UVB identifies a vaginal delivery not impacted by any of five adverse outcomes: 1) mechanical assistance (vacuum or forceps), 2) severe shoulder dystocia (i.e., a shoulder dystocia that, according to the delivery note, appeared prolonged, required multiple maneuvers [McRobert's, suprapubic pressure, Woods screw, second level provider, knee chest positioning], and required considerable traction), 3) major perineal trauma (3rd or 4th degree tear), 4) post-partum hemorrhage (EBL > 500 cc's) or 5) NICU admission. We compared UVB rates using chi-squared methods, and an NNT analysis was done for the UVB composite outcome. All data were analyzed using the STATA Statistical Program (version 8, College Station, TX). The NICHD of the NIH and the IRB of the University of Pennsylvania approved the study protocol. The study was performed under a two Investigational New Drug numbers from the Federal Drug Administration due to the experimental use of both misoprostol and dinoprostone for cervical ripening prior to preventive labor induction.

RESULTS

The development of the two study groups is outlined in Figure 1. One hundred and thirty six women made up the exposed group, and 134 women made up the non-exposed group. Two hundred and one study subjects came from the obstetric clinic of the Hospital of the University of Pennsylvania (HUP) (74.4%), 61 subjects came from the obstetric clinic at Pennsylvania Hospital (22.6%), and 8 subjects came from the family medicine offices of HUP (3%).

The two final study groups were similar with reference to rates of common demographic, prenatal variables, and study risk factors (Table 1). Statistically significant differences in rates of previous abortion and anemia were probably due to chance. As expected based on study design (Table 2), the exposed group exhibited four clinical features: 1) earlier delivery within the term period of pregnancy (median gestational age of delivery 39.1 weeks vs. 40.0 weeks, $p < 0.001$), 2) higher labor induction rate (58% vs. 21.6%, $p < 0.001$), 3) lower median modified cervical Bishop's score on admission (3 vs. 5, $p = 0.001$), and 4) higher rate of cervical ripening using prostaglandins (PGE2 or PGE1) (40.4% vs. 17.2%, RR 2.36, $p < 0.001$) (Table 2). Survival analysis of time-to-delivery during the term period (Figure 2) demonstrates the continuous nature of the earlier delivery in the exposed group as compared to the non-exposed group. The Cox Proportional Hazard Ratio for the survival analysis was 2.30 (95% CI 1.78–2.98, $p < 0.001$). Graphic displays of gestational age at delivery (Figure 3a) and the timing and frequency of labor induction (Figure 3b) demonstrate very different distributions of these events in the two study groups.

The cesarean delivery rate of the exposed group was 10.3% as compared to 14.9% in the usual care group (RR 0.69, 95% CI [0.36–1.31], $p = 0.25$) (Table 3). Adjustment for parity and short stature changed these estimates only slightly (aOR 0.66, $p = 0.28$) (Table 4). Cesarean delivery rates in the nulliparous sub-group and the multiparous sub-group were 18.5% vs. 25.8% ($p = 0.32$) and 2.8% vs. 5.6% ($p = 0.41$), respectively. When examining the secondary outcomes, the infants of women in the exposed group were admitted to the NICU less frequently than the infants of women in the non-exposed group (1.5% vs. 6.7%, RR 0.22, 95% CI [0.05 – 0.99], $p = 0.03$) (Table 3). The statistical significance of this difference remained after adjustment sex of infant and site of prenatal care (aOR 0.18, $p = 0.037$) (Table 4). Figure 3c demonstrates the timing of NICU admissions as a function of gestational age at delivery in the two study groups. Rates of low Apgar score at five-minutes (< 7) and major perineal injury were not statistically different in the two study groups. All seven major perineal injuries were 3rd degree spontaneous tears and only one of these followed a 2nd degree episiotomy.

Table 5 reveals that the rate of high estimated blood loss was lower in the exposed group as compared to the usual care group (5.9% vs. 14.2%, $p = 0.02$). In addition, infants in the exposed group had significantly lower birth weights (3197 grams. vs. 3372 grams, $p = 0.005$) and were less likely to experience the outcome "Fetal Intolerance of Labor (all types)" ($p = 0.049$) (Table 2). While the exposed group had more infants with a birth weight of < 2500 grams, none of these relatively small infants required NICU admission. Two infants in the exposed group required NICU admission following labor induction (one for respiratory depression possibly due to intravenous narcotic dosage just prior to delivery, and one for possible sepsis), and two infants in the usual care group required NICU admission following labor induction (both infants required 7 days of antibiotic therapy for possible sepsis). There was one perinatal death in the control group, but the mother of this infant delivered at 37 weeks 4 days gestation and the death was probably not related to study group assignment.

The time intervals for various components of maternity admissions were somewhat different in the two study groups. The exposed group had a longer mean time between admission and onset of labor (6.2 hours vs. 3.6 hours, $p < 0.001$), but the length of the first stage of labor was not statistically different (7.3 hours vs. 6.4 hours, $p = 0.11$). The exposed group had a similar mean second stage of labor (41 min vs. 48 min, $p = 0.43$) and the similarity extended to both the nulliparous and multiparous sub-groups (data not shown). However, the median time from delivery to maternal discharge was significantly shorter in the exposed group (51.9 hours vs. 59.3 hours, $p = 0.02$), and the overall median hospital admission time was similar for exposed and non-exposed mothers (66.3 hours vs. 70.5 hours, $p = 0.07$). The neonates of exposed mothers experienced significantly shorter hospital stays (54.0 hours vs. 66.1 hours, $p = 0.01$).

The first composite outcome to be evaluated was the Adverse Outcomes Index (AOI). The raw AOI scoring data are attached as appendix 2. The exposed group experienced a significantly lower median AOI score (1.4 vs. 8.6, $p = 0.03$). Lower scores were also noted for nulliparous exposed women (1.8 vs. 8.1, $p = 0.03$), but were statistically similar for exposed multiparous women (1.1 vs. 8.6, $p = 0.28$) (Table 3). The second composite outcome was the Uncomplicated Vaginal Birth (UVB) Rate. Women in the exposed group achieved an uncomplicated vaginal birth 77.2% of the time, as compared to 62.7% in the usual care group. Following adjustment for parity group, this difference was statistically significant (aOR 1.7, 95% CI 1.01 – 2.94) $p = 0.046$) (Table 4). However, the higher rate of UVB was not statistically significant when analysis was limited to the nulliparous sub-group (63.1% vs. 49.2%, $p = 0.11$) or the multiparous sub-group (83.1% vs. 74.6%, $p = 0.22$) (Table 3).

Significant reductions in rates of both single and composite adverse outcomes, and trends toward reduction of rates of both cesarean delivery and fetal macrosomia were found in the exposed group despite a difference in median gestational age at delivery of only six days between the two study groups. For example, the impact of AMOR-IPAT on rate of macrosomia may be superficially puzzling, as a typical fetus gains only about 200 grams of weight per week during the term period. However, the key feature of AMOR-IPAT is that it differentially responds to each woman's overall constellation of risk. Using the macrosomia example, the more risk of cephalo-pelvic disproportion, the earlier preventive labor is recommended. Hence, exposed women at especially high risk for CPD (which usually included risk factors for macrosomia) were delivered more than 6 days before non-exposed women with similar risk profiles. Appendix 4 demonstrates that the greater the quantity of risk, the greater the discrepancy in gestational age at delivery in the two study groups. Within Appendix 4, one Yeager Unit = one day. Finally, the number needed to treat (NNT) to prevent one NICU admission was estimated to be 19.2 ($1/[0.067 - 0.015]$), while the NNT to obtain one uncomplicated vaginal delivery was 9.3 ($1/[0.735 - 0.627]$).

COMMENT

In this randomized clinical trial a high rate of preventive labor induction during the term period of pregnancy led to three important findings: 1) a significantly lower NICU admission rate, 2) a significantly higher uncomplicated vaginal birth rate, and 3) a significantly lower Adverse Outcome Index. Although the rate of cesarean delivery was not significantly lower in the exposed group, the greater use of preventive labor induction in the exposed group clearly did not increase its rate of cesarean delivery. Taken together, the findings of the study indicate that the active approach to obstetric risk during the term period of pregnancy, using preventive labor induction as needed, improved birth outcomes.

Our results are consistent with two previously completed retrospective investigations involving preventive labor induction. The first study (13) involved 400 urban primarily

African-American women and reported similar rates of NICU admission (9% vs. 14.3%, $p = 0.23$) but lower rates of cesarean delivery (4% vs. 16.7%, $p < 0.001$) in women exposed to AMOR-IPAT. The second study (14) involved 1869 rural primarily Caucasian women and reported lower rates of both NICU admission (2.3% vs. 4.2%, $p=0.03$) and cesarean delivery (5.3% vs. 11.7%, $p<0.001$) in women exposed to AMOR-IPAT. Both retrospective studies also found that the rates of other adverse outcomes were either unchanged or lower in the AMOR-IPAT-exposed groups.

Further support for the validity of the AMOR-IPAT approach may be found in a recent retrospective study of labor induction which defined the control group as those women expectantly managed beyond the gestational age of induction. In this study, induction of labor at 38 and 39 weeks of gestation was associated with lower cesarean delivery rates (37). In addition, multiple recent publications have demonstrated that deliveries which occur relatively early within the term period of pregnancy are associated with the lowest rates of a variety of adverse birth outcomes (34,38–41). Finally, multiple randomized clinical studies have demonstrated improved birth outcomes for low-risk women following routine labor induction at 41 weeks gestation as compared to expectant management beyond 41 weeks (42,43). AMOR-IPAT incorporates these two ideas by using preventive labor induction before 41 weeks gestation in a manner proportional to the amount of cumulative risk for cesarean delivery present in any given pregnancy. In keeping with the concept that AMOR-IPAT may promote labor when the cephalo-pelvic ratio is more favorable and the placenta is healthier, the AMOR-IPAT group in this randomized clinical trial had a lower average birth weight and a lower rate of major fetal heart tone abnormalities during labor.

In contrast to our findings, many previous retrospective studies have found an association between labor induction and higher rates of both NICU admission (44) and cesarean delivery (45–49). However, the majority of these retrospective studies failed to account for at least one of three methodological issues: 1) confounding by indication (50), 2) gestational age at delivery (51), and 3) the impact of a mode-of-labor-onset design vs. a group-oriented design (13, 14, and 33). Also in contrast to our findings, several randomized clinical trials have found a lack of benefit with labor induction as compared to expectant management. However, these studies all focused on women with already established problems such as oligohydramnios (52), macrosomia (53), and insulin dependent diabetes (54). In addition, several often-cited randomized clinical studies that did not find benefit with labor induction either took place before the availability of prostaglandin cervical ripening protocols or were not sufficiently powered to fully evaluate the full spectrum of birth outcomes (55–58). The prospective trials that have demonstrated improvement in birth outcomes related to labor induction were studies of women with mild-moderate risk profiles where labor induction was employed before the development of a recognized complication (59–61).

Our study has several potential limitations. First, it involved primarily African-American women who delivered at two hospitals that were part of the same health care system. Hence, its generalizability to other racial/ethnic groups and other settings is unclear. However, evidence of association between AMOR-IPAT exposure and improved rates of adverse birth outcomes was found in a rural non-academic population composed primarily of Caucasian women (14). Second, all study subjects were randomized by, and received all study communication from, the study research assistants or the principal investigator. In addition, all chart abstraction and data entry was performed by the principal investigator's research team, and this raises the possibility of information bias. However, the main prenatal issues involved with this study, and the main study outcomes, are dichotomous and relatively easy to determine. Hence the likelihood that information bias significantly affected the main study findings is low. Third, the use of both the AOI and the UVB rate were not a part of the original study design. Hence, the face validity of our findings related to these composite

outcomes is lessened somewhat. However, the study that introduced the AOI was not published until after our study was initiated. In addition, based on the potential importance of the AOI, we would have included AOI data even if the results had not been significant. The decision to use the rate of Uncomplicated Vaginal Birth was based on our interest in evaluating birth health as well as adverse birth outcomes.

The fourth limitation of this investigation was based on the nature of the intervention. Study group assignment could not be, and was not, completely blinded to either providers or study subjects. This raises the possibility of assessment bias on the part of the health care team managing each woman's delivery. We are aware that medical judgments related to many obstetric outcomes, including the decision to perform a cesarean delivery or admit an infant to the NICU, contain subjective elements that could be impacted by incomplete blinding. However, it is more likely that knowledge of study group assignment would have led to higher rates, rather than lower rates of NICU admission rates and cesarean delivery in the exposed group. Specifically, the NICU team would be unlikely to tolerate more neonatal respiratory insufficiency just because an infant was part of an investigation studying early term labor induction. As another example, an obstetric team would be unlikely to tolerate more fetal intolerance or longer periods of dystocia just because a woman was undergoing preventive labor induction. In addition, any intentional delay of cesarean delivery in the active management group should have resulted in longer labor times and more neonatal complications at delivery in the exposed group. However, neither the range of, or the mean duration of, the second stage of labor were longer in the exposed group, and overall neonatal outcomes were better in the AMOR-IPAT exposed group. Hence, while the lack of blinding could have theoretically affected study outcomes, the pattern of outcomes actually observed in this clinical trial are not consistent with assessment bias.

In summary, we found that exposure to AMOR-IPAT, through the frequent use of preventive labor induction, significantly reduced neonatal intensive care unit admission rates in women with increased risk for cesarean delivery. Furthermore, the use of the composite outcomes "Adverse Outcomes Index" and "Uncomplicated Vaginal Birth" strongly suggests that exposure to AMOR-IPAT lead to significant improvements in overall birth health. The finding that AMOR-IPAT exposure did not increase the rate any major adverse birth outcome requires a reconsideration of the belief that labor induction necessarily leads to adverse birth outcomes. Larger randomized clinical trials in more diverse populations are needed to further study the impact of this alternative method of obstetric care on both single and composite measures of birth health.

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Figure 1.
Study Group Development – *This figure demonstrates the flow of subjects throughout the study.*

Figure 2.

Survival Analysis of Timing of Delivery by Study Group: Number of weeks beyond 37 weeks 0 days gestation at the time of delivery – *This figure demonstrates the continuous nature of earlier gestational age at delivery in the exposed group as compared to the non-exposed group.*

Figure 3a: Distribution of gestational age at delivery by study group

Figure 3b: Distribution of mode of labor onset by gestational age and study group

Figure 3c: Distribution of type of nursery admission by gestational age and study group

Figure 3.

Figure 3a. Distribution of gestational age at delivery by study group – *This figure demonstrates the timing of delivery by half weeks of gestation in the two study groups.*

Figure 3b. Distribution of mode of labor onset by gestational age and study group - *This figure demonstrates the timing of labor induction and spontaneous labor by half weeks of gestation in the two study groups.*

Figure 3c. Distribution of type of nursery admission by gestational age and study group - *This figure demonstrates the timing of NICU admission by half weeks of gestation in the two study groups.*

A. Utero-placental Factors: Odds Ratio Time Units

History of 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 Alpha Feto-Protein (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 outlines the scoring sheet used to estimate, for each study subject, the upper limit of the optimal time of delivery.*

Key:

- Yeager Group 1: 1-3 Yeager units
- Yeager Group 2: 4-6 Yeager units
- Yeager Group 3: 7-9 Yeager units
- Yeager Group 4: 10-12 Yeager units
- Yeager Group 5: 13-15 Yeager units
- Yeager Group 6: 16-18 Yeager units
- Yeager Group 7: 19-21 Yeager units
- Yeager Group 8: > 21 Yeager units

Appendix 4.

Average gestational age at delivery as a function of Yeager Group - *This figure demonstrates the relationship between magnitude of risk of cesarean delivery (measured in Yeager Units [or days subtracted from 41 weeks 0 days gestation] and mean gestational age at delivery in the two study groups In the exposed group, greater risk resulted in earlier mean gestational age at delivery than in the non-exposed group.*

Table 1

Levels of Pre-Delivery Risk Factors by Study Group – This table presents information about prenatal variables (demographics, prenatal risk factors) in the two study groups

VARIABLE NAME	Exposed n=136	NonExp n=134	Risk Ratio	95% CI	p value
DEMOGRAPHICS					
Age, median	23.4 years	23.3 yrs	–	–	0.91 *
Advanced Age (>= 35 years at delivery)	4.4%	3.7%	1.18	0.37 – 3.78	0.78 **
African-American	89.7%	86.6%	1.04	0.95 – 1.13	0.42
Medicaid Insurance	92.6%	91.8%	1.01	0.94 – 1.08	0.79
Married	14.7%	15.7%	0.95	0.54 – 1.67	0.87
PAST MEDICAL					
Previous SAB	21.3%	26.9%	0.79	0.52 – 1.22	0.29
Previous TAB	23.5%	42.5%	0.55	0.39 – 0.79	<0.001
Any blood pressure elevation in first trimester (diastolic > 80 or systolic > 120)	39%	34.3%	1.14	0.83 – 1.56	0.43 **
Chronic Hypertension	10.3%	7.5%	0.67	0.64 – 3.00	0.41 ***
Asthma	19.4%	17.6%	0.91	0.55 – 1.50	0.71
Cigarette Use	18.1%	17.7%	1.02	0.59 – 1.75	0.94 ***
Marijuana abuse	9.7%	6.7%	1.44	0.60 – 3.47	0.40
PAST OBSTETRICAL					
History baby > 8lbs 8 oz	11.8%	19.4%	0.61	0.34 – 1.08	0.08 **
History vacuum or forceps	3.7%	5.2%	0.70	0.23 – 2.16	0.54 ***
LABORATORY					
1 hr Glucola ≥ 135	8.1%	10.4%	0.77	0.36 – 1.64	0.50
Hemoglobin (1 st trimester) (mean)	11.8 mg/dl	12.1 mg/dl			0.03
Hemoglobin (2 nd trimester) (mean)	10.7 mg/dl	11.2 mg/dl			0.02
Anemia (1 st trimester hgb < 11.0 mg/dl or 2 nd trimester hgb < 10.0 mg/dl)	34.6%	23.1%	1.49	1.02 – 2.20	0.04 **
Sickle Trait	3.7%	8.2%	0.45	0.16 – 1.25	0.11 ***
Group B Strep culture positive	35.3%	42.5%	0.83	0.61 – 1.12	0.22

VARIABLE NAME	Exposed n=136	NonExp n=134	Risk Ratio	95% CI	p value
MATERNAL HABITUS					
Height (mean)	64.1 in	63.6 in			0.22*
Short stature (height $\leq 5' 2''$)	33.1%	40.3%	0.82	0.60 – 1.13	0.22
Preconception weight (mean)	172.3 lbs	167.8 lbs			0.68*
Preconception BMI (kg/[m ² * m]) (mean)	29.3 kg/m ²	28.9 kg/m ²			0.92*
Preconception BMI > 30	42.7%	41.8%	1.02	0.77 – 1.35	0.89**
INDEX PREGNANCY					
Weight Gain during pregnancy (mean)	31.8 lb	30.5 lb			0.61***
Female Fetal sex	52.9%	50.8%	0.96	0.75 – 1.22	0.72

* calculated with the Mann Whitney rank-sum test

** Study risk factors used in subject selection

*** Other risk factors used for risk-scoring

Table 2

Levels of Intrapartum Factors by Study Group – This table presents information about intrapartum factors (status on admission, labor induction activity, anesthesia) and duration of various events in the two study groups

VARIABLE NAME	Exposed N=136	Non-Exposed n=134	Risk Ratio	95% CI	p value
SUBJECT STATUS ON ADMISSION					
Nulliparous	47.8%	47.0%	1.02	0.79 – 1.31	0.80
Gestational age at delivery, (median)	39.1 wks	40.0 wks			< 0.001
Ruptured Membranes on admission	14%	25.4%	0.55	0.33 – 0.92	0.02
Initial Bishop's Score (median)	3	5	-	-	0.001
Initial Bishop's Score ≤ 5	79.4%	69.4%	1.14	0.99 – 1.14	0.06
INTRA-PARTUM EVENTS					
Spontaneous labor	22.1%	45.5%	0.48	0.34 – 0.70	< 0.001
Induction of labor	58.1%	21.6%	2.68	1.89 – 3.82	< 0.001
Augmentation (following premature rupture of membranes, or ineffective spontaneous labor)	19.8%	32.8%	0.62	0.40–0.92	0.02
Prostaglandin (any use)	40.4%	17.2%	2.36	1.54 – 3.60	< 0.001
Prostaglandin E1 (any antepartum use)	32.4%	11.9%	2.71	0.61 – 4.56	< 0.001
Prostaglandin E2 (any antepartum use)	11.0%	5.2%	2.11	6.20 – 19.89	< 0.001
Use of Pitocin (any)	76.5%	64.2%	1.19	1.02 – 1.39	0.03
Artificial Rupture of Membranes	72.1%	64.9%	1.11	0.94 – 1.31	0.21
Epidural Analgesia	81.6%	84.3%	0.97	0.87 – 1.08	0.55
INTRAPARTUM FINDINGS					
Thick Meconium at ROM	3.7%	8.2%	0.45	0.16 – 1.25	0.11
Fetal Intolerance to Labor (all types)**	22.8%	33.6%	0.68	0.46 – 1.00	0.049
Severe variable decelerations	13.2%	16.4%	0.81	0.45 – 1.43	0.46
Repetitive late decelerations	15.4%	20.9%	0.73	0.44 – 1.23	0.24
Persistent non-terminal bradycardia (<100 beats per minute [bpm])	1.5%	2.2%	0.66	0.11 – 3.87	0.64
Persistent Tachycardia (> 170 bpm)	0.8%	0.7%	0.99	0.06 – 15.6	0.99
Maternal Temperature (median)	98.6 F	98.6 F	-	-	0.86
Maternal Fever prior to delivery(Temp > 100.4)	4.4%	3.0%	1.48	0.43 – 5.12	0.53
LABOR and DELIVERY TIMING					

VARIABLE NAME	Exposed N=136	Non-Exposed n=134	Risk Ratio	95% CI	p value
Admission – Labor Onset (mean), all	6.2 hrs	3.6 hrs			< 0.001 *
1 st Stage (mean), all	7.3 hrs	6.4 hrs			0.11 *
1 st Stage (mean), nulliparous	8.6 hrs	8.3 hrs			0.69 *
1 st Stage (mean), multiparous	6.3 hrs	5.0 hrs			0.13 *
2 nd stage (mean), all	41 min	48 min			0.43 *
First Stage (mean), nulliparous	58 min	77 min			0.20 *
First Stage (mean), multiparous	28 min	27 min			0.73 *
2 nd stage > 2 hours, nulliparous	8.1%	6.7%	1.20	0.50 – 2.81	0.67 *
2 nd stage > 1 hours, multiparous	11.4%	5.8%	1.97	0.62 – 6.25	0.24
Delivery – Discharge, mom (mean), all	51.9 hrs	59.3 hrs			0.02 *
Overall admission, mom (mean), all	66.3 hrs	70.5 hrs			0.70 *
Overall admission, baby (mean), all	54.0 hrs	66.1 hrs			0.01 *

* Mann Whitney rank-sum test

** At least one of the four types of fetal heart tone abnormalities

Table 3

Major Study Outcomes: Rates and Indications of Cesarean Delivery and NICU Admission; Secondary Outcomes; and Composite Outcomes – *This table presents information about rates of adverse outcomes and Composite Outcome data in the two study groups*

VARIABLE NAME	Exposed n=136	Non-exposed n=134	Risk Ratio	95% CI	p value
CESAREAN DELIVERY INFORMATION:					
Cesarean delivery Rate (all)	10.3%	14.9%	0.69	0.36 – 1.31	0.25
Primigravidas	18.5%	25.8%	0.72	0.37 – 1.39	0.32
Multiparas	2.8%	5.6%	0.51	0.10 – 2.68	0.41
Indications for C-section:					
Failure to Progress	3.7%	8.2%	0.45	0.16 – 1.25	0.11
Fetal Intolerance	6.6%	6.0%	1.11	0.4 – 2.79	0.83
Elective (history of shoulder dystocia)	0%	0.8%	-	-	0.31
Occurrence of Cesarean Delivery by Mode of Labor Onset					
Spontaneous labor	6.7%	8.2%	0.81	0.17 – 3.95	0.80
Induction of labor (all)	11.4%	24.1%	0.47	0.19 – 1.15	0.10
Augmentation of labor	11.1%	18.2%	0.61	0.18 – 2.1	0.42
NICU ADMISSION INFORMATION					
NICU Admission (overall) (n)	1.5% (2)	6.7% (9)	0.22	0.05 – 0.99	0.03
Sepsis – suspect or actual (n)	0.75% (1)	4.5% (6)	0.16	0.02 – 1.34	0.053
Respiratory disorders requiring NICU Admission (n)	0.75% (1)	1.5% (2)	0.49	0.04 – 5.37	0.55
High serum bilirubin (n)	0% (0)	0.8% (1)	-	-	0.31
OTHER SECONDARY OUTCOMES					
Perineal Injury, any	41.9%	38.8%	1.08	0.81 – 1.44	0.60
Perineal Injury, first degree	17.6%	15.7%	1.13	0.66 – 1.92	0.66
Perineal Injury, second degree	20.6%	21.6%	0.83	0.60 – 1.51	0.83
Perineal Injury, third degree	3.7%	1.5%	0.26	0.49 – 12.5	0.26
5-minute APGAR Scores					
APGAR@ 5 minutes (mean)	8.92	8.90	-	-	0.91*
APGAR@ 5 minutes < 7 (n)	0.0% (0)	0.8% (1)	0	-	0.31
COMPOSITE OUTCOMES					

VARIABLE NAME	Exposed n=136	Non-exposed n=134	Risk Ratio	95% CI	p value
Adverse Outcome Index (AOI) (mean)	1.4	8.6			0.03*
AOI - Nulliparous	1.8	8.1			0.03
AOI - Multiparous	1.1	8.6			0.28*
Uncomplicated vaginal birth(UVB)**	73.5%	62.7%	1.78	1.01 – 3.13	0.046***
UVB - Nulliparous	63.1%	49.2%	1.28	0.94 – 1.75	0.11
UVB - Multiparous	83.1%	74.6%	1.11	0.94 – 1.32	0.22

* calculated with the Mann Whitney rank-sum test

** Vaginal delivery without mechanical assistance, major perineal tear, severe shoulder dystocia, EBL > 500 cc or NICU admission

*** adjusted for parity group

Table 4

Logistic Regression Models for Cesarean Delivery and NICU admission – *This table presents information about the logistic regression models used to evaluate the outcomes “cesarean delivery” and “NICU admission.”*

	Unadjusted OR	p-value	Adjusted OR	Adjusted p-value
CESAREAN DELIVERY				
Exposure to AMOR-IPAT	0.65	0.25	0.66	0.28
Multiparous (previous vaginal birth)	0.16	< 0.001	0.16	< 0.001
Short Stature ($\leq 62''$)	2.47	0.015	2.25	0.04
NICU ADMISSION				
Exposure to AMOR-IPAT	0.21	0.047	0.18	0.037
Male sex of fetus	2.99	0.11	3.20	0.10
Location of Prenatal Care				
HUP OB Clinic	1.00	-	1.00	–
Penn Family Care	7.07	0.098	10.51	0.06
Pa Hosp OB Clinic	5.50	0.01	5.91	0.01
UNCOMPLICATED VAGINAL BIRTH				
Exposure to AMOR-IPAT	0.60	0.057	0.58	0.046
Multiparous (previous vaginal birth)	0.16	< 0.001	0.34	< 0.001

Table 5

Maternal and Neonatal Outcomes based on AMOR- IPAT exposure status – *This table presents information about univariate maternal and neonatal outcomes in the two study groups*

VARIABLE NAME	Exposed n=136	Non-Exposed n=134	Risk Ratio	95% CI	p-value
MATERNAL – Delivery					
Assisted Vaginal Delivery (all types)	5.9%	9.7%	0.61	0.26 – 1.42	0.24
Use of Vacuum	1.5%	6.0%	0.25	0.05 – 1.14	0.05
Use of Forceps	4.4%	3.7%	1.18	0.37 – 3.78	0.78
Shoulder dystocia, severe	0%	1.5%	–	–	0.15
Episiotomy (1 st or 2 nd Degree)	1.5%	1.5%	0.98	0.14 – 6.89	0.99
Estimated Blood Loss, mean	403cc + 236	485cc + 416	–	–	< 0.001*
High EBL, vaginal (> 500 cc)	6.6% (8/122)	10.5% (12/114)	0.62	0.26 – 1.47	0.27
High EBL, cesarean (> 1000 cc)	0% (0/14)	35% (7/20)	–	–	0.01
MATERNAL - Post-Partum					
Maternal temperature, mean	98.8	98.9			0.048
Maternal fever (>100.4)	5.2%	5.2%	0.98	0.36 – 2.7	0.98
Post Partum hemoglobin, mean	10.0 + 1.51	10.0 + 1.58	–	–	0.90
Post Partum anemia (Hgb<8)	9.3% (8/86)	10.3% (10/97)	0.90	0.37 – 2.18	0.82
Flux in hemoglobin with delivery	1.19 gms+ 0.87 (n = 80)	1.68 gms+ 1.19 (n=92)	–	–	0.007
Maternal Transfusion	1.5% (2)	3.0% (4)	0.49	0.09 – 2.64	0.40
Post-partum septic pelvic thrombophlebitis	0%	1.5% (2)	–	–	0.15
NEONATAL					
Male Infant	47.4%	50%	0.95	0.74 – 1.21	0.67
Abnormal Nursery Course	1.5%	8.2%	0.18	0.04 – 0.79	0.01
NICU Admission (overall) (n)	1.5% (2)	6.7% (9)	0.22	0.05 – 0.99	0.03
Special Care Nursery	0%	0.75% (1)	–	–	–
Neonatal Death	0%	0.75% (1)	–	–	–
Birth weight (mean)	3197 gm + 497	3372 gm + 425	–	–	0.005*
Large (> 4000 gm)	2.9%	7.5%	0.39	0.13 – 1.23	0.09

VARIABLE NAME	Exposed n=136	Non-Exposed n=134	Risk Ratio	95% CI	p-value
Small (< 2500 gm) **	5.2%	1.5%	3.4	0.73 – 16.3	0.09
Head circumference	33.6 cm + 1.5	33.9 cm + 1.6	–	–	0.25
Discordant Discharge ($\geq$ one day)	2.9%	7.5%	0.39	0.13 – 1.23	0.09

* calculated with the Mann Whitney rank-sum test

** no neonate weighing < 2500 grams required admission to the NICU

Appendix 2

Adverse Outcome Index by Study Group – *This appendix provides detailed information about the generation of the Adverse Outcome Index (AOI) in the two study groups.*

VARIABLE NAME	Exposed, n=136 number (rate)	NonExp, n= 134 number (rate)	Weights
1. Maternal Death	0 (0%)	0 (0%)	750
2. Intrapartum or neonatal death	0 (0%)	1 (0.75%)	400
3. Uterine rupture	0 (0%)	0 (0%)	100
4. Maternal ICU admission	0 (0%)	0 (0%)	65
5. Infant Birth Trauma (Erbs palsy, vacuum or forceps injury)	0 (0%)	4 (3.0%)	60
6. Return to operating room of labor and delivery unit	0 (0%)	2 (1.5%)	40
7. Admission to NICU	2 (1.5%)	9 (6.7%)	35
8. Apgar score less than 7 at 5-minutes	0 (0%)	1 (.75%)	25
9. Maternal blood transfusion	2 (1.5%)	4 (3%)	20
10. Third- or fourth-degree perineal tear	5 (3.7%)	2 (1.5%)	5
Overall Frequency of at least one adverse outcome	9 (4.4%)	19 (14.2%)	p = 0.04 **
Mean AOI Score	1.4	8.6	p = 0.03 ***

* from: Nielsen PE, Goldman MB, Mann S, Shapiro DE, Marcus RG, Pratt SD, et al. Effects of teamwork training on adverse outcomes and process of care in labor and delivery. *Obstet Gynecol* 2007;109:48-55.

** p-value based on chi-square (Fisher's Exact test) of proportions

*** p-value based on Wilcoxon Rank-Sum analysis

Appendix 3

Uncomplicated Vaginal Birth by Study Group – *This appendix provides detailed information about the generation of the Uncomplicated Vaginal Birth (UVB) rate in the two study groups.*

VARIABLE NAME	Exposed, n=136 number (rate)	NonExp, n= 134 number (rate)
1. Cesarean Delivery	14 (10.3%)	20 (14.9%)
2. Assisted Vaginal Delivery(vacuum or forceps)	8 (5.9%)	13 (9.7%)
3. Shoulder dystocia (severe)	0 (0%)	2 (1.5%)
4. Major perineal trauma (3 rd - or 4 th - degree tear)	5 (3.7%)	2 (1.5%)
5. Post-partum hemorrhage(vaginal and cesarean)	21 (15.4%)	30 (22.4%)
6. Neonatal Intensive Care Unit(NICU) Admission	2 (1.5%)	9 (6.7%)
Overall frequency of complicated trial of labor (at least one of the six complications)	36 (26.5%)	50 (37.3%)
Overall frequency of uncomplicated vaginal birth (none of the six identified adverse outcomes)	100 (73.5%)	84 (62.8%)