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The association between the regular use of risk-based term IOL and improved birth outcomes in an Italian hospital: A retrospective cohort study

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Abstract

Objective: Associations have been recently reported between the regular use of risk-based term labor induction and improvements in birth outcomes. We wanted to study the use of this approach in an Italian hospital.

Design: Retrospective Cohort Study

Setting: The Mandic Hospital, in Merate, Italy, from March 2009 through July 2010.

Population: All pregnant women delivering at term who met study inclusion and exclusion criteria.

Methods: The "exposed" group was comprised of women cared for and delivered by providers who regularly offered risk-based term labor induction. The "non-exposed" group was comprised of women cared for and delivered by providers who followed the "expectant management" approach to risk. Prenatal, intrapartum and outcome data for the two cohorts were collected and compared.

Main outcome measures: Cesarean delivery rate and weighted Adverse Outcome Index (AOI) Score.

Results: The exposed group (n=120), as compared to the non-exposed group (n=159), had a higher induction rate, a lower cesarean rate (1.7% vs. 43.4%, aOR 0.04, CI [0.01-0.22]), and a numerically lower weighted Adverse Outcome Index Score (0.4 vs. 6.1, p=0.61). Two cases of term stillbirth occurred in the non-exposed group. No adverse birth outcome occurred with greater frequency in the exposed group.

Conclusion: In this Italian hospital, and consistent with previous studies, exposure to the regular use of risk-based term labor induction was associated with a more favorable set of birth outcomes. Randomised clinical trials are needed to further explore this alternative approach.

Introduction

Rates of cesarean delivery (CD) have increased dramatically in the USA [1], in Italy [2], and throughout the world [3]. Possible reasons include the modern option of patient-choice CD, medical-legal pressures to deliver "un-injured" babies, and an increasing number of medical indications for CD [4-6]. As compared to 30 years ago, pregnant women in developed countries now tend to be older, heavier, and more likely to have medical conditions linked to CD [7-9]. However, despite calls from various sectors to reverse rising CD rates [10,11], there has been little success in developing methods of care that *safely* reduce CD utilization [12,13].

The *safe* reduction of CD rates is desirable because CD, as compared to vaginal delivery, is linked to higher rates of post-partum infection [14,15], excessive blood loss [16], and neonatal intensive care unit (NICU) admission [17]. In addition, CD is associated with longer hospital stays for both mother and baby [18,19], increased frequency of serious complications during future pregnancies [18], and higher costs [20]. Despite suggestions that elective CD might improve maternal perineal health [21,22], its long-term benefits are unproven [16,23], and its long-term risks have probably been minimized [24,25]. Consequently, the identification of a method of care that could *safely* reduce CD remains an important goal [26].

Several published retrospective cohort studies described associations between exposure to an alternative method of care called the Active Management of Risk in Pregnancy at Term (AMOR-IPAT) and unusually low group CD rates (0.8% - 11%) [24,27-30]. AMOR-IPAT begins with the assessment of each pregnancy's pattern of common prenatal risk factors. This assessment is then used to estimate, for each pregnancy, an upper limit of the optimal time of delivery (UL-OTD)

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[24,28-31]. The greater a pregnancy's composite risk of CD for either cephalo-pelvic disproportion (CPD) or utero-placental insufficiency (UPI), the earlier the pregnancy's estimated UL-OTD [31]. Pregnant women at term who do not develop spontaneous labour as they near their UL-OTD are offered induction of labour (IOL). In contrast to an indicated IOL (i_IOL), where there is the identification of a specific high-risk state that justifies the IOL, a risk-based IOL (rb_IOL) is based on modeling of multiple intermediate-risk states. If the offer of a rb_IOL is accepted by a pregnant woman, then the IOL is scheduled so that the woman delivers on or just before her UL-OTD [32]. If a pregnant woman who is scheduled for a rb-IOL has an unfavorable uterine cervix (Bishop's score < 6), then pre-induction cervical ripening is recommended [32-34]. The purpose of this investigation was to see if the previously reported associations between AMOR-IPAT exposure and the *safe* reduction of CD rate could be replicated with the use of AMOR-IPAT in an Italian hospital.

Methods

We employed a retrospective cohort study design to compare the outcomes of women exposed to the AMOR-IPAT method of care (hereinafter "the exposed group") to the outcomes of women who received usual obstetric care (hereinafter "the unexposed group"). All deliveries for this study occurred between March 2009 and July 2010 at Mandic Hospital in Merate, Italy. AMOR-IPAT exposure involved first the estimation of the UL-OTD for each exposed woman. A scoring sheet for UL-OTD estimation is included as Appendix A. To minimise the risk of iatrogenic neonatal pulmonary problems related to an incorrectly dated early-term risk-based IOL, ultrasound determination of pregnancy dating was obtained on all pateints in either the first trimester or the early second trimester. In this study, a gestational age of 37w 3d days was used as the lower limit of the optimal time of delivery (LL-OTD) for all exposed gravidas. If a woman exposed to AMOR-IPAT developed spontaneous labour before her UL-OTD, then her labour and delivery was managed in the usual manner. However, if spontaneous labour did not develop by 3-4 days prior to her UL-OTD, then she was offered rb_IOL so that she could deliver 1-3 days before her UL-OTD. In addition, if a woman was scheduled for a rb_IOL but her cervix was not favorable (i.e., modified cervical Bishop's score < 6[21]), then cervical ripening was promoted using Prostaglandin E2 pledget (Cervidil) and/or PGE2 gel (Propess). The protocol for cervical ripening and IOL used at Mandic Hospital is included as Appendix B. All women receiving rb_ IOL were counseled with regards to the potential increased risk of cesarean delivery following IOL, and women offered rb_IOL prior to 39 weeks 0 days gestation were counseled with regards to the potential increased risk of both fetal lung immaturity and NICU admission in the early-term period of pregnancy. Permission to perform this retrospective study was obtained from the Mandic Hospital and from the institutional review board of the University of Pennsylvania (Protocol #811046, approved 1/27/2011).

In this study, women in the exposed group received all of their pregnancy care (prenatal care and delivery care) from a group of three providers who routinely used the Del Boca AMOR-IPAT protocol (Appendix B). Women in the non-exposed group received all of their pregnancy care from a group of four obstetric physicians and/or eight midwives. Women who received no prenatal care, or whose care was provided by members of both groups, were excluded from the study. Inclusion criteria included singleton pregnancy, regular prenatal care with providers with clinical privileges at the study institution, and delivery on or after 37w 0d gestation. Exclusion criteria included prior cesarean delivery, any other previous transmural uterine surgery, HIV infection, major fetal anomaly, history of major pelvic injury, or any factor precluding a trial of labour.

Data concerning prenatal variables, intrapartum events, and clinical outcomes were abstracted from the charts of each identified mother-baby pair. The resulting data were then entered into an Excel database. Missing values were obtained by rechecking hospital records, or by contacting a woman's primary maternity care provider. Data were then transferred into the STATA Statistical Program (version 9, College Station, TX) for data analysis.

The Student's T test and the Wilcoxon rank-sum test were used to compare distributions of continuous demographic variables, past medical/surgical historical details, obstetric risk factors and outcomes present in the two study groups. Univariate chi-square tests were used to compare rates of various dichotomous prenatal risk factors, intrapartum variables, and birth outcomes in the two study groups. Statistical significance was determined by a p-value ≤ 0.05 for the primary outcome (cesarean delivery rate), and a p-value of ≤ 0.01 for all other comparisons and outcomes. Initially, analyses were performed comparing the two main study groups. In addition, some analyses were performed for each of two specific parity groups: nulliparous and multiparous. Data relating to the timing of delivery, mode of labour onset, and method of delivery were collated according to gestational age, collapsed into half-week sub-strata and encoded to enable graphic representation.

The strength of association between cesarean delivery and a variety of co-variates, including AMOR-IPAT exposure, were further assessed using multiple logistic regression. Clinical factors related to the use of AMOR-IPAT (e.g., birth weight, gestational age at delivery, indication for induction) were excluded from the final model due to concerns that they might lie in the causal chain between the lack of delivery before the UL-OTD and cesarean delivery.

To evaluate the possibility that exposure to AMOR-IPAT could have been associated with increased rates of various adverse outcomes, rates of multiple adverse birth outcomes for each group were determined and compared using both chi-square analysis and logistic regression. Rates of salient birth outcomes were also determined as a function of each of the two parity sub-groups. In addition, a summary outcome measurement called the weighted Adverse Outcome Index score (wAOI score) [35] was used to estimate the overall impact of AMOR-IPAT exposure on birth outcomes in the two study groups. Variables involved with the wAOI score are listed in Table 5 [35]. Finally, a "number needed to treat" (NNT) analysis was performed to estimate the number of women who would need to be exposed to the AMOR-IPAT method of care to prevent one cesarean delivery.

Results

During the study period, 1080 deliveries occurred at the study hospital and the overall hospital cesarean delivery rate was 34.6%. 180 women delivered without having local prenatal care, 350 women had a uterine scar precluding a trial of labour, 70 women had some other problem precluding a trial of labour (breech presentation, fetal anomaly, placenta previa, herpes infection), 80 women delivered at or before 37 weeks 3 days of gestation, 100 women received obstetric care from both groups of providers, and 21 women had incomplete data. Of the remaining women, 120 were treated by providers who utilised AMOR-IPAT (the exposed group) and 159 were treated by providers who used the standard approach to prenatal risk (the non-exposed group).

Table 1 presents levels of prenatal risk factors present in the two study groups. The exposed group was more likely to be multiparous (51.7% vs. 23.9%, $p < 0.001$), was younger (median age 23 years vs. 25.9 years, $p < 0.001$), and had a lower preconception body mass index (BMI) (median BMI at conception 22.0 vs. 24.3 kg/m^2). Distributions of race and nationality were also statistically significantly different. Maternal height and gestational weight gain were similar in the two study groups. Table 2 presents levels of intrapartum factors in the two study groups. Women in the exposed group delivered earlier in the term period (38.4 weeks vs. 40.4 weeks, $p < 0.001$) and had a higher overall IOL rate (70.8% v. 33.3%, $p < 0.001$). The two groups had similar cervical Bishop's scores on admission (3.6 vs. 3.4, p=0.56).

Table 3 presents information concerning birth outcomes based on initial univariate analysis. The exposed group had a significantly lower cesarean delivery rate (1.7% vs. 43.4%), and significantly lower rates of cesarean delivery rates were associated with AMOR-IPAT exposure in both nulliparous and multiparous sub-groups. There were no NICU admissions in either group, but two cases of term stillbirth occurred in the nonexposed group (0% vs. 1.3%, p=0.22). Low APGAR scores at one and five minutes were rare and occurred at similar rates in the two groups.

Figure 1A shows the distribution of deliveries by week of gestational age in the two study groups. The exposed group delivered earlier in the term period. Figure 1B shows the frequencies of the types of labour onset as a function of gestational age in the two study groups. The exposed group experienced a more frequent overall use of IOL in general, and more frequent IOL in the 38th and 39th week. Figure 1C shows the incidence of vaginal delivery and CD as a function of gestational age in the two study groups. The exposed group experienced more frequent vaginal delivery.

Table 4 presents information from the final logistic regression modeling of the association between AMOR-IPAT exposure and CD. The final model included six factors: AMOR-IPAT exposure status (exposed vs. nonexposed), parity group (nulliparous or multiparous), high starting weight (≥ 80 kg), short stature (≤ 157 cm), excessive gestational weight gain (≥ 13 kg), and geographical origin. Adjustment for these important covariates did not alter the magnitude of association

Table 1. Prenatal Variables by Study Group.

Variable name	Exposed (n=120)	Non-Exposed (n=159)	Risk Ratio	95% CI	p value
Demographics					
Age, mean	31.6 yrs.	30.2 yrs.			<0.02
Advanced Age (≥ 35 years at delivery)	27.5%	22.6%	1.21	0.81-1.83	0.35
Geographical Designation:					
Arabian	8.3%	13.8%	0.60	0.30-1.22	0.15
African	5.8%	11.3%	0.52	0.22-1.19	0.11
Italian	77.5%	56.6%	1.37	1.16-1.62	<0.001
European, other	5.0%	13.2%	0.38	0.16-0.91	0.02
Asia (southern)	3.3%	3.8%	0.88	0.25-3.06	0.84
South American	0%	1.3%	-	-	0.22
Maternal Habitus					
Preconception weight, mean	61.3 kg	66.9 kg			<0.001* *
High Preconception weight ≥ 80 kg	7.1%	17.8%	0.40	0.19-0.84	0.01
Height, mean	1.65 m	1.64 m.			0.49*
Short stature (≤ 158 cm)	5%	10.7%	0.47	0.19-1.15	0.09
Preconception BMI, mean (kg/[m^2])	22.0	24.3			<0.001*
High BMI (≥ 30 kg/[m^2])	2.4%	11.5%	0.21	0.05-0.93	0.02
Index Pregnancy					
Nulliparous Status	48.3%	76.1%	0.64	0.52-0.78	<0.001*
Weight Gain during pregnancy, mean	12.9 kg	14.3 kg	---	---	0.02
Excess weight gain (≥ 13 kg)	43.4%	51.7%	0.84	0.64-1.1	0.18

*Calculated with the Mann Whitney rank-sum test

Table 2. Admission and Intrapartum Variables by Study Group.

Variable name		Non-Exposed (n=300)	Risk Ratio	95% CI	p value
Woman Status on Admission					
Gestational age at delivery, all (median)	38.4 wks	40.4 wks	-	-	<0.0001*
Gest age on admission, nullip (median)	38.4 wks	40.4 wks	-	-	<0.0001
Gest age on admission, multip (median)	38.4 wks	40.69 wks	-	-	<0.0001
Post Dates Delivery (> 41 weeks)	0%	23.9%	-	-	<0.0001
Initial Bishop's Score (mean)	3.6	3.4	-	-	0.56*
Initial Bishop's Score (very low, *i.e.,* ≤ 1)	5.0%	6.9%	0.72	0.28-1.90	0.51*
Vertex Presentation	100%	100%	-	-	1.00
Intra-Partum Interventions					
Induction of labour, all	70.8%	33.3%	2.12	1.66-2.72	<0.0001
Induction of labour, nulliparous	69.0%	35.5%	1.94	1.44-2.61	<0.0001
Induction of labour, multiparous	72.6%	26.3%	2.76	1.59-4.80	<0.0001

*Mann Whitney rank-sum test

Table 3. Cesarean Delivery, Neonatal and AOI Score Information by Study Group.

	Exposed	Non-Exposed	Relative Risk	95% CI	p value
Overall Cesarean Delivery Rate					
All Study Subjects	1.7% (2/120)	43.4% (69/159)	0.04	0.01 - 0.15	<0.0001
CESAREAN DELIVERY RATE PARITY GROUP					
Nulliparous only **	1.7% (1/58)	52.1% (63/121)	0.03	0.01 - 0.23	<0.0001
Multiparous only **	1.7% (1/62)	15.8% (6/38)	0.10	0.01 - 0.82	0.007
Cesarean Delivery Rate By Mode Of Onset					
Spontaneous labour **	2.9% (1/35)	39.6% (42/106)	0.7	0.01 - 0.50	<0.0001
Induction of labour **	1.2% (1/84)	50.9% (27/53)	0.02	0.01 - 0.64	<0.0001
Cesarean Delivery Rate By Both Parity Group And Mode Of Onset					
Nulliparous and Spontaneous Labour **	5.6% (1/17)	47.4% (37/78)	0.06	0.02 - 0.80	0.001
Nulliparous and IOL **	0% (0/26)	60.5% (26/43)	_	_	<0.0001
Multiparous and Spontaneous Labour **	0% (0/17)	17.9% (5/28)	_	_	0.06
Multiparous and IOL **	2.2% (1/45)	10.0% (1/9)	0.22	0.02 - 3.26	0.23
Neonatal Intensive Care Unit Admission Rate					
Overall NICU Admission Rate	0%	0%	-	-	-
Term Fetal Mortality Rate					
Overall Term Fetal Mortality	0% (0/120)	1.3% (2/159)	_	_	0.22
Apgar Scoring					
1-Minute APGAR, mean	9.1	8.4	-	-	<0.001***
APGAR @ 1 minute ≤ 4	1.7% (2/120)	1.9% (3/159)	0.88	0.15 - 0.89	0.89
5-Minute APGAR, mean	9.7	9.3	-	-	<0.001***
APGAR @ 5 minutes ≤ 7	1.7% (2/120)	2.5% (4/159)	0.66	0.12 - 3.56	0.63
Cord Blood Gas Information					
Cord pH, mean	7.28	7.27	-	-	0.81***
Cord pH < 7.2	10.8% (13/120)	16.1% (25/155)	0.67	0.36 - 0.26	0.21
Cord pH < 7.1	2.5% (3/120)	3.9% (6/155)	0.65	0.16 – 2.53	0.53
WEIGHTED ADVERSE OUTCOME INDEX ("wAOI") SCORE (See Table 5)					
WEIGHTED ADVERSE OUTCOME INDEX ("wAOI") SCORE	0.4	6.1	_	_	0.61***

*when not specified, rates are based on entire study group
**rates calculated based on sub-strata
***by Wilcoxon rank-sum analysis

between AMOR-IPAT exposure and lower CD rate.

Table 5 shows that the wAOI score was lower in the exposed group (0.4 vs. 6.1, p=0.61), but this finding was heavily influenced by the occurrence of two term stillbirths in the non-exposed group (one at 40w 1d and one at 41w 4d). Both stillbirths delivered well after their pregnancy's estimated UL-OTD and were therefore theoretically preventable. The NNTs for exposure to AMOR-IPAT to prevent one CD were 2.4 for the entire group, 2.0 for nulliparous women and 7.1 for multiparous women.

Discussion

Main findings

Exposure of pregnant women at term to the regular use of risk-based IOL (AMOR-IPAT) was associated with a significantly lower CD rate (1.7%) as compared to women receiving usual care (43.4%). Exposure

Table 4. Logistic Regression Modeling of AMOR-IPAT exposure on cesarean delivery.

Variables*	Unadjusted RR	Adjusted OR's	Adjusted 95% Confidence Intervals
AMOR-IPAT exposure	0.04	0.04	(0.01 – 0.16)
Nulliparity	5.11	6.04	(2.11 – 17.30)
High Starting Weight (≥ 80 kg)	1.56	1.61	(0.62 – 4.19)
Short Stature (≤ 62")	1.62	1.64	(0.51 – 5.29)
Excess Weight Gain (≤ 13 kg)	1.40	1.32	(0.64 – 2.70)
Arabian	1.00	1.00	(1.17 – 3.04)
African	2.89	1.17	(1.17 – 3.04)
Italian	1.33	0.60	(0.60 – 7.89)
European	1.82	0.50	(0.40 – 10.50)
Asia (southern)	1.85	0.33	(0.33 – 35.84)
South America	4.33	0.08	(0.08 – 39.18)

*Listed according to decreasing significance within the final logistic model
**Statistically significant (p < 0.05)

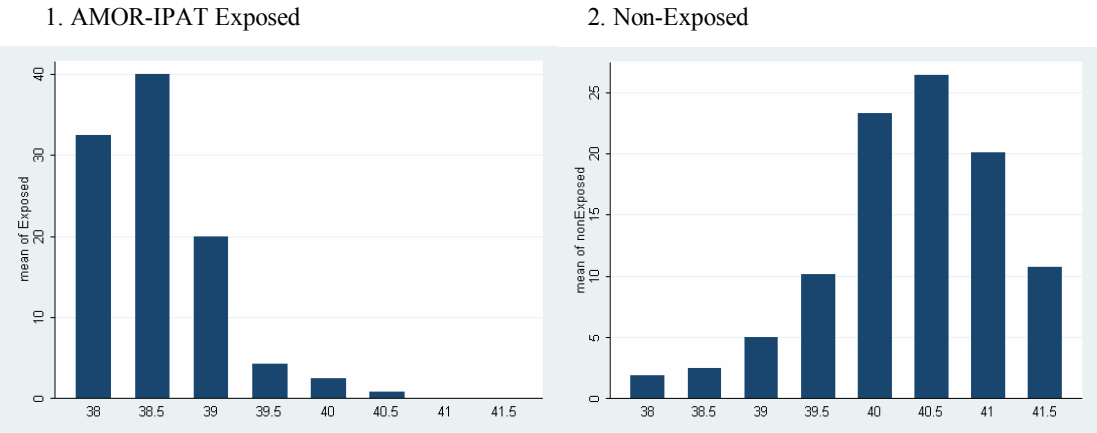

Figure 1A. Distribution of timing of delivery, as a function of gestational age, by study group.

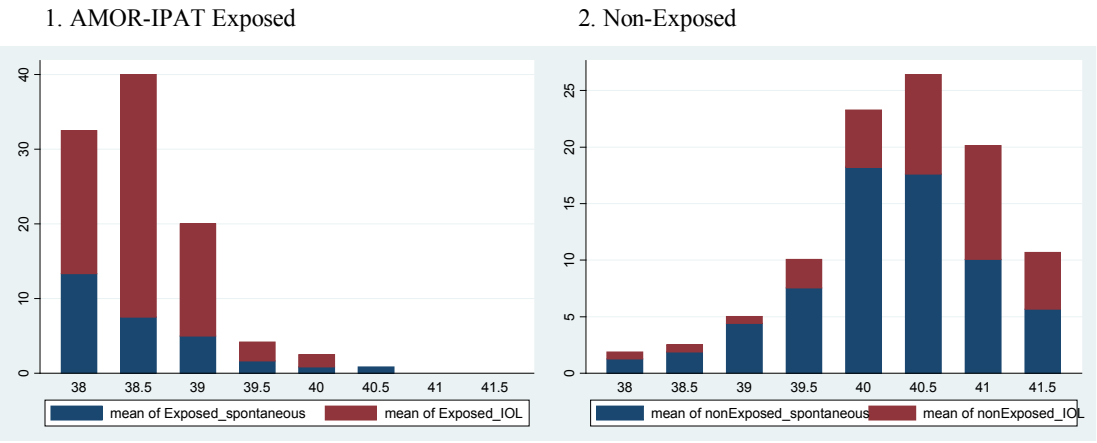

Figure 1B. Spontaneous vs. induced labour, as a function of gestation age, by study group.

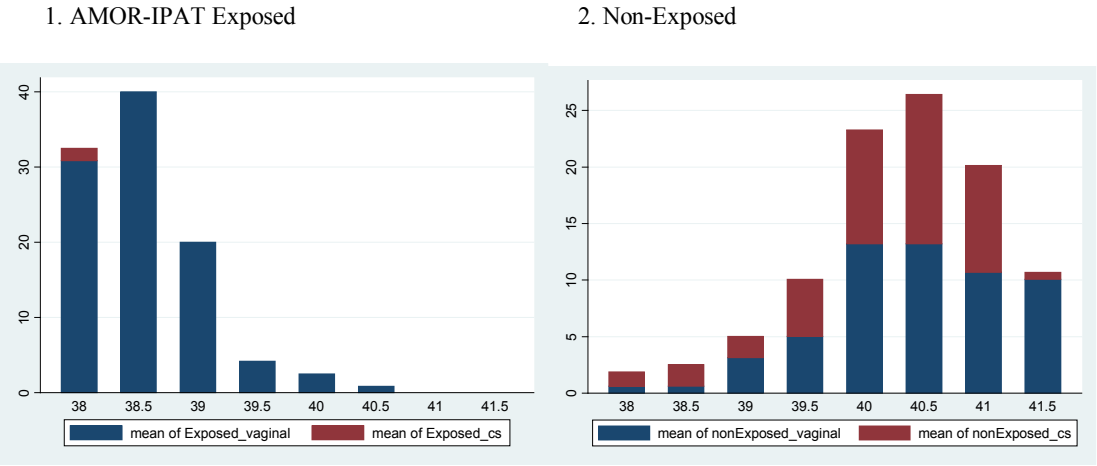

Figure 1C. Vaginal vs. cesarean delivery, as a function of gestational age, by study group.

was also associated with either significantly lower, or unchanged, rates of other adverse birth outcomes. The occurrence of two cases of stillbirth in the non-exposed group (one full-term term and one late-term) highlights an area where the use of AMOR-IPAT might provide an extremely important benefit [36,37]. Recent evidence suggests that the recent adoption of a policy to delay all "non-indicated" deliveries until at least 39 weeks has been associated with a significant increase in the rate of term stillbirth in the USA [38].

Strengths and limitations

The strength of this study, and its importance, rests in both the history of its own development and in the general concept of translation of new ideas into clinical use. The providers caring for the women in the exposed group read published papers describing AMOR-IPAT, and applied this method of care to their own patient population. Whereas the original papers describing risk-based term IOL involved women

Table 5. Adverse Outcome Index Information.

Variable name	Exposed (n=120)	Non-Exposed (n=159)	AOI Points	Exposed Points	Non-Exposed Points
Maternal Death	0	0	750	0	0
Term Stillbirth/Intrapartum/Perinatal Death	0	2	400	0	800
Uterine Rupture	0	0	100	0	0
Maternal Intensive Care Unit Admission	0	0	65	0	0
Infant Birth Trauma	0	2	60	0	120
Return to Operating Room	0	0	40	0	0
Neonatal Intensive Care Unit Admission	0	0	35	0	0
APGAR Score @ 5 min < 7	2	2	25	50	50
Maternal Blood Transfusion	0	0	20	0	0
Third or Fourth Degree Perineal Injury	0	0	5	0	0
Total points	-	-	-	50	970
Mean AOI Score	-	-	-	**0.4**	**6.1**

*Calculated with the Mann Whitney rank-sum test

from the Northeastern region of the USA, this paper describes the application of AMOR-IPAT to patients in Italy. As such, the apparent benefit found in this study provides evidence that the use of risk-based term IOL may be beneficial in multiple populations. Furthermore, the unusually low adjusted Odds Ratio (aOR) found for the association between "exposure" and CD rate (0.04) indicates the strong possibility of an underlying causal relationship [39]. Such a possibility is also suggested by the unusually strong aORs noted in previous AMOR-IPAT observational studies [24,27-30].

Three other recent studies highlight the concept that risk-based non-indicated IOL might be beneficial. First, a recent meta-analysis of all RCTs involving non-indicated IOL found that non-indicated IOL, as compared to expectant management, led to a lower cesarean delivery rate [40]. Second, a recent large retrospective study of Scottish women evaluated birth outcomes in women following non-indicated IOL at various weeks in the term period compared to expectant management and delivery later [41]. Non-indicated term IOL was associated with clinically meaningful and statistically significant decreased odds of term perinatal mortality at all weeks of gestation prior to the estimated date of confinement (EDC, or due date). Finally, a recent large retrospective study of Californian women, using the same approach as the Scottish study, found clinically meaningful and statistically significant decreased odds of CD with non-indicated IOL at every week of the term period, including the early term weeks [42]. Hence, the findings of this Italian study are consistent with a growing body of evidence suggesting that non-indicated IOL might be more beneficial than harmful. This study focuses on risk-based IOL, which, while currently considered a "non-ndicated" type of IOL, might be now viewed as an acceptable "modeled indication" for early-term labor induction.

In contrast to our findings, many previous observational studies reported associations between delivery following IOL, as compared to delivery following spontaneous labour, and higher rates of various adverse birth outcomes [43-49]. However, studies comparing the outcomes of "indicated" IOL to the outcomes of spontaneous labour provide little useful information because, in the presence of an accepted indication, there is generally no choice but to initiate IOL [49,50]. Furthermore, even for women having a "non-indicated" IOL, there usually exist one or more risk factors that underlie the recommendation, or the request, for the IOL [51]. If women delivering after the spontaneous onset of labour are less likely to have risk factors than women having a "non-indicated" IOL, then the observational studies comparing the outcomes following IOL to the outcomes following spontaneous labour probably contain significant "confounding by indication" [52,53]. Finally, most of the observational studies that compared "non-indicated" IOL to spontaneous labour failed to correctly model the actual impact of ni_IOL on the flow of term pregnancy. Specifically, in deciding to perform a ni_ IOL, the actual choice is between delivery now (by "non-indicated" IOL) and delivery later (by either spontaneous labour, some type of IOL at a later date or pre-labour CS) [41,42,54]. Several recent cohort studies that used the correct modeling found that "non-indicated" IOL, as compared with expectant management to a later gestational age, was associated with lower rates of adverse birth outcomes including CD and term stillbirth [40-42,55].

We acknowledge that this study contains a number of limitations. First, it was retrospective and therefore potentially influenced by unknown confounders. Although logistic regression demonstrated that adjustment for known confounding variables did not alter the strength of study associations, it is possible that hidden confounders might have caused alterations in those associations. Second, this study occurred at a single Italian hospital and it is unclear whether our results are generalizable to other types of institutions, patient populations or geographic areas. However, the study population was of mixed ethnic and racial types, and its results are similar to other recently published studies of AMOR-IPAT that involved women of mixed ethnic and racial types. Third, the difference in the types of providers in the exposed group (obstetricians) and non-exposed group (obstetricians and midwives) raises the possibility of selection bias, information bias, and differences in practice style including threshold for CD. This type of bias, if present, could not be eliminated through the use of logistic regression. However, the presence of midwife providers in the non-exposed group would be expected to lower, not raise, the CD rate of that group [56]. Fourth, the study was not powered to evaluate the association between AMOR-IPAT exposure and infrequent adverse outcomes such as neonatal hyaline membrane disease, meconium aspiration syndrome, or neonatal mortality. However, there were no worrisome trends or "near misses" in the outcome data suggesting that maternal or neonatal outcomes would have been less favorable in the exposed group if the study had been larger. In fact, the opposite trends were present. Finally, the providers of AMOR-IPAT did not routinely perform amniocentesis prior to risk-based IOL in the early-term period of pregnancy [57]. However, a similar use of AMOR-IPAT in the setting of an RCT reported that AMOR-IPAT exposure led to a significantly lower NICU admission rate as compared to usual care.[30] In addition, all observational studies of AMOR-IPAT have included risk-based IOL in the early-term period (i.e., the 37th and 38th weeks

of gestation) and all have reported either lower or unchanged rates of NICU admission following AMOR-IPAT exposure [18,20].

Interpretation

The estimation of individual UL-OTD and the regular use of risk-based IOL may enable women to avoid cesarean delivery in two ways: 1) the fetus may be slightly smaller and therefore better able to fit through the maternal pelvis, and 2) the placenta may be healthier and therefore better able to support the fetus during labor. The issue of a low pre-induction cervical Bishop's score may be addressed with the regular use of prostaglandin medication (PGE1 or PGE2) and/or Foley balloon catheters. By the 38th week of gestation the human fetus may be ready for extra-uterine life if delivery is preceded by labor (i.e. following labour induction). Transition to extrauterine life in the 38th week may be more difficult if delivery occurs via pre-labour cesarean section. .

Conclusion

This study found that the regular use of AMOR-IPAT, with its high rates of cervical ripening and risk-based IOL, as compared to usual care that involves expectant management until 41-42 weeks of gestation, was associated with a significantly lower group CD rate. Rates of other major adverse birth outcomes were not increased following exposure to AMOR-IPAT. In this study, the rate of perinatal mortality and the pattern of AOI scores trended higher in the usual care group, but did not reach statistical significance. AMOR-IPAT may represent a strategy able to provide for the safe reduction of group CD rates through the use of risk-based IOL. If there is serious interest in reducing high global rates of term cesarean delivery, then adequately powered, multi-site, prospective randomised clinical trials are needed that compare the outcomes following the regular use of risk-based "non-indicated" IOL to the outcomes of the expectant management of risk.

Disclosure of interests - Dr. Nicholson has provided grand rounds presentation on the topic of AMOR-IPAT at several academic institution , and was provided standard compensation for that activity. He also works with the Star Legacy Foundation. The Star Legacy Fouundation is a stillbirth advocacy group. Dr. Nicholson has been provided travel and lodging to several meetings organized by this foundation over the past three years. Otherwise, the authors have no conflict of interest to report with regard to this publication.

Authorship criteria –

1. Gergorio DEL BOCA – Dr. DEL BOCA is currently the "Primario" of the Obstetrics Department at the Mandic Hospital. He was an active member of the 3-person OB group that used AMOR-IPAT during the 18 month period of clinical activity reported by this manuscript. Dr. DEL BOCA developed the DEL BOCA Method that is described in the manuscript (the Italian version of AMOR-IPAT). He was involved with the conceptualization of the study and was involved with data abstraction, drafting of several original versions of the study and reviewed multiple version of the manuscript. He has provided final approval of the version of the manuscript that is being submitted.

2. Anna Biffi, MD – Dr. Biffi was an active member of the 3-person OB group that used AMOR-IPAT during the 18 month period of clinical activity reported by this manuscript. Dr. Biffi was the individual who connected the Italian team with USA AMOR-IPAT providers. She was involved with the conceptualization of the study and was involved with data abstraction, drafting of several original versions of the study and reviewed multiple version of the manuscript. She has provided final approval of the version of the manuscript that is being submitted.

3. Roberto Zagni, MD – Dr. Zagni was the "Primario" of the Obstetrics Department at the Mandic Hospital during the time period the clinical portion of this study occurred. He was also the senior member of the 3-person group during that time. He was involved with the conceptualization of the study and was involved with data abstraction, drafting of several original versions of the study and reviewed multiple version of the manuscript. He has provided final approval of the version of the manuscript that is being submitted.

4. Antonio Montanari, M.D. – Dr. Montanari is an anesthesiologist who worked at the Mandic Hospital during the time the clinical activity for the Italian study was taking place. He helped with data abstraction and was involved with drafting and editing the study manuscript. He has provided final approval of the version of the manuscript that is being submitted.

5. James Nicholson, M.D., M.S.C.E. - Dr. Nicholson was invited by the primary study group to assist with the development and publication of this study. He assisted with confirmation of data integrity, statistical analysis, and manuscript generation. He has provided final approval of the version of the manuscript that is being submitted.

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