Perinatal Outcomes of Subjects Enrolled in a Multicenter Trial with a Waiver of Antenatal Consent

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Abstract

Objective This study aimed to determine whether outcomes differed between infants enrolled in the PREMOD2 trial and those otherwise eligible but not enrolled, and whether the use of waiver effected these differences.

Study Design The multicenter PREMOD2 (PREmature infants receiving Milking Or Delayed cord clamping) trial was approved for waiver of antenatal consent by six of the nine sites institutional review boards, while three sites exclusively used antenatal consent. Every randomized subject delivered at a site with a waiver of consent was approached for postnatal consent to allow for data collection. Four of those six sites IRBs required the study team to attempt antenatal consent when possible. Three sites exclusively used antenatal consent.

Results Enrolled subjects had higher Apgar scores, less use of positive pressure ventilation, a lower rate of bronchopulmonary dysplasia, and a less frequent occurrence of the combined outcome of severe intraventricular hemorrhage or death. A significantly greater number of infants were enrolled at sites with an option of waiver of consent (66 vs. 26%, risk ratio = 2.54, $p < 0.001$). At sites with an option of either approaching families before delivery or after delivery with a waiver of antenatal consent, those approached prior to delivery refused consent 40% (range 15–74% across six sites) of the time.

Conclusion PREMOD2 trial demonstrated analytical validity limitations because of the variable mix of antenatal consent and waiver of consent. A waiver of antenatal consent for minimal risk interventional trials conducted during the intrapartum period will be more successful in enrolling a representative sample of low and high-risk infants if investigators are able to enroll all eligible subjects.

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Keywords
- cord milking
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- waiver of consent

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Key Points

- Waiver of consent is when informed consent cannot be obtained prior to delivery.
- Cord milking is a procedure in which blood is pushed (stripped) two to four times towards the newborn.
- Delayed clamping means the umbilical cord is not clamped immediately after birth.

Recruitment for intrapartum research focusing on neonatal outcomes requires the consent of a highly vulnerable group, pregnant women. Substantial distress of imminent preterm delivery heightens uncertainty and risk. Maternal anxiety is compounded by labor, pain, analgesics, and unfamiliar personnel. Nonetheless, for peripartum studies, approaching expectant women prior to any intervention requires an informed, supportive discussion.

When informed consent cannot be obtained prior to delivery and equipoise exists for the treatment options, another possibility is waiting until after completion of the peripartum intervention. In the United States, this is a full waiver of consent and may be followed by postnatal informed consent for necessary maternal and neonatal data collection. Waiver of antenatal consent has been used in peripartum trials where the study interventions met standards for minimal risk, equipoise, and obtaining antenatal consent on all subjects prior to the intervention was not feasible.[1–4]

PREmature infants receiving Milking Or Delayed cord clamping (PREMOD2) was a noninferiority randomized clinical trial of preterm infants (23–31 weeks' gestation) conducted at nine university and private medical centers in four countries.[5] The planned enrollment was 750 subjects per study group. The study met the 45 Code of Federal Regulations 46.116(c) criteria for delayed consent based on the inability to conduct the trial without a waiver and the minimal risk of either intervention. When PREMOD2 began, there were no known major risks of delayed cord clamping or umbilical cord milking suggested in multiple studies and meta-analyses, and both were widely used as local standards of care. A safety signal comprising an imbalance in the number of severe intraventricular hemorrhage (IVH) events by study group was observed at the first interim analysis, so enrollment was stopped upon a recommendation from the Data Safety Monitoring Board.[6] We sought to determine whether outcomes differed between infants enrolled in the PREMOD2 trial and those otherwise eligible but not enrolled. In addition, we examined outcomes of those enrolled into the trial using waiver of consent enrollees versus antenatal consent.

Materials and Methods

The trial was approved for waiver of antenatal consent by six of the nine hospital's Institutional Review Boards (IRBs). Every randomized subject delivered at a site with a waiver of consent was approached for postnatal consent to allow for data collection. Four of those six sites' IRBs required the study team to attempt antenatal consent when possible. Three sites exclusively used antenatal consent.

At the onset of the PREMOD2 trial, all sites obtained IRB approval for the collection of deidentified data on perinatal and neonatal outcomes for eligible nonenrolled infants. The nonenrolled group included infants whose parents declined antenatal consent, infants whose parents declined postnatal consent, and those who were never approached due to precipitous delivery, staffing, or other site-specific reasons. Each institution had an existing internal quality improvement database which collected outcome data on their maternal and neonatal population. Seven of these sites are members of the Vermont Oxford Network database which provided a standardized deidentified dataset. The remaining two sites utilized their internal databases with all personal identifiers removed and extracted equivalent data regarding baseline characteristics and short-term outcomes. These data did not allow for determining if nonenrolled subjects who were eligible were ever approached for consent at any of the study sites.

Each institution's database analyst worked with site coordinators and provided information on nonenrolled infant outcomes. Inclusion and exclusion criteria from the original study (e.g., congenital anomalies, placental abruption, monochorionic twins, outborn) were applied. The data of eligible nonenrolled infants were compared with enrolled infants in the PREMOD2 trial (June 2017 to September 2018). A comparison of infants enrolled with and without waiver of consent was performed.

Summary statistics were calculated for baseline characteristics and outcome measures using means (standard deviation), medians (interquartile range), and percentages depending on the data type. These were presented comparing the two consent types for those enrolled in PREMOD2, and for enrolled infants compared with nonenrolled infants irrespective of consent status. Statistical hypothesis tests were used to assess differences associated with type of consent and enrollment status. Two-sample *t*-tests were used for continuous measures, and chi-square tests or Fisher's exact tests were used for categorical measures. Recruitment was compared between sites with and without postnatal consent available using a chi-square test. Analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

Data from 482 nonenrolled mother and infant pairs meeting PREMOD2 inclusion criteria were collected (►**Table 1**). These data were compared with the 474 enrolled mothers in the PREMOD2 trial. Out of 1,717 mothers screened for PREMOD2, 585 were eligible and provided prenatal consent; of which 83 mothers were subsequently excluded for reasons unrelated to the consenting process (clinical team unaware of consented subject at delivery, emergent c-section, etc.). Of the 474 enrolled mothers, 219 were enrolled via antenatal consent and 255 were enrolled via waiver of antenatal consent. Prenatal care, cesarean delivery, antenatal steroid administration, and clinical chorioamnionitis were more

Table 1 Baseline demographics for those enrolled and those not enrolled in PREMOD2

	Enrolled in PREMOD2 ($N = 474$)	Not enrolled in PREMOD2 ($N = 482$)	*p*-Value
Birth GA, wk: mean (SD)	28.4 (2.4)	28.0 (2.5)	0.045
Prenatal care	462 (97%)	450 (93%)	0.008
Female infant gender	219 (46%)	244 (51%)	0.144
Cesarean section delivery	339 (72%)	304 (63%)	0.004
Maternal chorioamnionitis	153 (32%)	112 (23%)	0.004
Antenatal steroids[a]	465 (98%)	447 (93%)	0.001
Antenatal magnesium sulfate	391 (82%)	370 (77%)	0.976
Compressions in delivery room	15 (3%)	13 (3%)	0.614
PPV in delivery room	325 (69%)	370 (77%)	0.015
Apgar score at 1 min: median (Q_1, Q_3)	6 (4, 7)	5 (2, 7)	<0.001
Apgar score at 5 min: median (Q_1, Q_3)	8 (7, 8)	7 (6, 8)	<0.001
Oxygen at 36 wk	93 (20%)	137 (28%)	<0.001
ROP stage 3 or more	28 (6%)	19 (4%)	0.462
ROP requiring treatment	29 (6%)	15 (3%)	0.199
Any grade IVH	109 (23%)	92 (19%)	0.395
Severe IVH or death	50 (11%)	80 (17%)	0.001
Severe IVH	28 (6%)	33 (7%)	0.359
Infant death	33 (7%)	62 (13%)	0.002

Abbreviations: GA, gestational age; IVH, intraventricular hemorrhage; PREMOD2, PREmature infants receiving Milking Or Delayed cord clamping; PPV, positive pressure ventilation; ROP, retinopathy of prematurity; SD, standard deviation; Severe IVH, grade III or IV intraventricular hemorrhage.
[a]Partial versus full course of antenatal steroids could not be determined using the Vermont Oxford Network database.

frequent in enrolled mothers. Enrolled infants were distinguished by higher Apgar scores, less use of positive pressure ventilation (PPV), a lower rate of bronchopulmonary dysplasia (BPD), and a less frequent occurrence of the combined outcome of severe IVH or death.

Separate comparisons examined whether rates of study enrollment differed between sites with antenatal consent and waived consent, and whether outcomes differed between antenatally consent and waived consent. A significantly greater number of infants were enrolled at sites with an option of waiver of consent (66 vs. 26%, risk ratio = 2.54, $p < 0.001$). At sites with an option of either approaching families before delivery or after delivery with a waiver of antenatal consent, those approached prior to delivery refused consent 40% (range 15–74% across six sites) of the time. At these waiver hospitals ($N = 6$), families not approached antenatally but randomized and enrolled after delivery refused postnatal consent 3% of the time. At sites with antenatal consent only, 49% of those who were approached before delivery refused consent (range 39–61%). ►Table 2 lists the baseline characteristics, demographics, and neonatal morbidities for PREMOD2, comparing participants randomized using waiver/postnatal consent with those with antenatal consent. There were 474 infants enrolled in PREMOD2—255 using waiver of antenatal consent and 219 with antenatal consent. Duration of rupture of membranes, receipt of full course of antenatal steroids, infant sex, and retinopathy of prematurity requiring treatment were different between the two groups.

Discussion

Antenatal waiver of consent in the PREMOD2 trial significantly increased enrollment when compared with sites without waiver. Contrary to our hypothesis, waiver of consent did not eliminate differences between enrolled and nonenrolled subjects. Infants not enrolled had suboptimal outcomes: less maternal prenatal care, increased need for PPV at delivery, lower Apgar scores, increased BPD, increased severe IVH, and/or death before discharge. Differences in neonatal outcomes in eligible enrolled infants versus eligible not enrolled were highlighted in a post hoc analysis of the SUPPORT (Surfactant, Positive Pressure, and Oxygenation Randomized) trial.[7] This 2×2 factorial design study compared high versus low oxygen targets after birth and the use of early continuous positive airway pressure versus early intubation and administration of surfactant. The trial only allowed for antenatal consent, but data on eligible but nonenrolled subjects born in the same period were collected prospectively. Infants enrolled in SUPPORT were less likely to die before discharge, and/or have severe IVH or periventricular leukomalacia and BPD than those eligible but not enrolled.[8] The results of this post hoc analysis supports the justification of waiver of antenatal consent for delivery room trials considered minimal risk. The use of a waiver of antenatal consent would presumably allow enrollment of a more representative sample of subjects than traditional methods, due to various factors such as imminent delivery or maternal compromise.

Table 2 Demographics by type of consent in the PREMOD2 sample

	Enrolled via waiver of antenatal consent ($N = 255$)	Enrolled via antenatal consent ($N = 219$)	*p*-Value
Birth GA, wk: mean (SD)	28.3 (2.5)	28.4 (2.4)	0.567
Compressions in delivery room	8 (3%)	7 (3%)	0.921
PPV in delivery room	178 (70%)	147 (67%)	0.902
Prenatal care	245 (96%)	217 (99%)	0.058
Female infant gender	116 (45%)	103 (47%)	0.737
Rupture of membranes duration, h: median (Q_1, Q_3)	39 (7, 154)	190 (23, 512)	<0.001
Cesarean section delivery	180 (71%)	159 (73%)	0.628
Maternal chorioamnionitis	90 (35%)	63 (29%)	0.122
Full course of antenatal steroids[a]	170 (67%)	196 (89%)	<0.001
Antenatal magnesium sulfate	207 (81%)	184 (84%)	0.470
Apgar score at 1 min: median (Q_1, Q_3)	5 (4, 7)	6 (4, 7)	0.504
Apgar score at 5 min: median (Q_1, Q_3)	8 (7, 8)	8 (7, 9)	0.543
Oxygen at 36 wk	46 (18%)	47 (21%)	0.348
ROP stage 3 or more	18 (7%)	10 (5%)	0.235
ROP requiring treatment	22 (9%)	7 (3%)	0.014
PVL	12 (5%)	14 (6%)	0.456
Any grade IVH	60 (24%)	49 (22%)	0.766
Severe IVH or death	26 (10%)	24 (11%)	0.788
Severe IVH	16 (6%)	12 (5%)	0.714
Infant death	17 (7%)	16 (7%)	0.785

Abbreviations: GA, gestational age; IVH, intraventricular hemorrhage; PREMOD2, PREmature infants receiving Milking Or Delayed cord clamping; PPV, positive pressure ventilation; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; SD, standard deviation; Severe IVH, grade III or IV intraventricular hemorrhage.
[a]Full course of antenatal steroids were considered as two or more doses prior to delivery.

Waiver of consent has been used in neonatal trials[4,9,10] where the interventions being studied are deemed low risk and/or standard of care, but the question of how parents feel about waived or delayed consent has not been fully answered. A prior survey of parents enrolled in the original pilot trial (PREMOD1) demonstrated that the majority of responding parents with a waiver of consent process had a positive response to participation in the study.[11]

Previous studies have demonstrated that subjects enrolled with postnatal consent are different from those enrolled with antenatal consent. Songstad et al[10] performed a secondary analysis of the HIPSTER trial comparing nasal high flow with nasal continuous positive airway pressure for primary respiratory support in preterm infants. There was both a period of antenatal and postnatal consents and mothers enrolled in the postnatal consent-only cohort were less likely to have received a full course of antenatal steroids and antibiotics. Our study also found that fewer subjects enrolled by a waiver of consent received a complete course of antenatal steroids.

Theoretically, a waiver of antenatal consent allows the inclusion of pregnant women whose infants might be at higher risk for morbidity and mortality, yet our PREMOD2 trial failed to demonstrate this crucial reduction of possible bias. There are several reasons why this may have occurred. First, the application of the waiver of consent was variable across sites. The use of a waiver may only be useful and valid in research settings where providers agree that all eligible infants can, and will, be randomized 24 hours a day. Continued education and dialog between the research investigators and obstetrical and neonatal providers is necessary to ensure that there is a willingness and understanding that including all subjects reduces bias and enhances external validity. Important reminders such as posting of signs with clear inclusion and exclusion criteria, reminders in labor wards and operating rooms, as well as easily accessible randomization mechanisms may help providers remember the utility of waiver of consent. Involvement of ancillary staff, operating room technicians, and labor and delivery room nurses may increase the use of the waiver of antenatal consent.

Second, higher morbidity and mortality in the nonenrolled subjects suggest that some of these deliveries occurred in emergent situations. It is possible that perinatal care providers may not prioritize pulling a randomization card and performing an assigned procedure in urgent situations despite IRB approval for a waiver of consent.

Third, conducting our randomized intervention, which required pulling a randomization card and efficient interprovider communication to correctly apply the assigned arm, during urgent or precipitous deliveries was not always feasible. An alternative design is the cluster-randomized

crossover whereby subjects are randomized by hospital.[12,13] Each institution is randomized to distinct arms for a finite period sequentially, thus reducing institutional and selection bias and minimizing site differences. Cluster randomization may enhance external validity because treatments occur in a more realistic delivery room setting reflective of real-world clinical settings and allows for recruitment of every eligible subject. It simplifies the consent process because eligible subjects receive the same intervention during each epoch.

There are limitations to our trial design analysis. Each site IRB determined whether the study required antenatal consent, a waiver of consent when antenatal consent was not possible, or exclusively postnatal consent. The mix of consent approaches may have limited the effectiveness of the application of waiver in our trial. The mixed approach did not allow us to distinguish between nonenrolled infants whose parents were approached for antenatal consent but declined participation versus those who were never approached due to precipitous delivery, staffing, or other site-specific reasons.

Conclusion

In conclusion, our PREMOD2 trial demonstrated analytical validity limitations because of our variable mix of antenatal consent and waiver of consent. Our trial highlights the challenges of using a mixed approach of waiver and nonwaiver consents, and the difficulty ensuring subjects consented with waiver can be enrolled during urgent deliveries. A waiver of antenatal consent for minimal risk interventional trials conducted during the intrapartum period will be more successful in enrolling a representative sample of low- and high-risk infants if investigators are able to enroll all eligible subjects.

Authors' Contributions

A.C.K. conceptualized and designed the study, drafted the initial manuscript, designed the data collection instruments, coordinated and supervised data collection, and approved the final manuscript as submitted. J.E., J.K., E.D., G.M.S., M.V., F.V., W.C., T.Y., and S.B. performed the initial analyses, and coordinated and supervised data collection, reviewed and revised the manuscript, and approved the final manuscript as submitted. K.A., P.A., W.R., and J.M.S. collected the data, performed the initial analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Conflict of Interest

None declared.

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