Risk factors and ramifications offailure to achieve cervical ripening with prostaglandins – Retrospective Cohort Study

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Abstract

Background Induction of labor (IOL) with prostaglandins is a common obstetric procedure. We aimed to assess baseline characteristics and evaluate the outcomes of women who failed to respond to labor induction.

Methods Retrospective cohort analysis of all women with singleton gestation who underwent induction of labor, due to prolonged pregnancy, with a slow release prostaglandin-E2 (PGE2) vaginal insert (PROPESS) for cervical ripening. During the study period (2012–2018), 1285 were analyzed. They were divided into 3 subgroups accordingly: a) responders – 1,202 (93.54%) - achieved ripening; b) partial responders – 39 (3.04%) – achieved partial ripening and proceeded to oxytocin augmentation; and c) non responders – 44 (3.42%) - required a second ripening method with extra amniotic foley catheter balloon (EAB). Baseline characteristics and labor outcomes were compared between the groups. Primary outcome was defined as intrapartum cesarean delivery (CD) rate. Secondary outcomes were defined as composite adverse maternal and composite adverse neonatal outcomes. A multivariant analysis was utilized to adjust outcomes to potential confounders.

Results Women in the responders' group were younger (30.03 vs. 32.13 and 31.32 years, $p = 0.005$), and had lower rates of primiparity (76.92% and 81.39% vs 50.99%, $p < 0.001$). Women in the responders group less frequently required intrapartum cesarean delivery (3.49% vs. 33.33% and 36.36%, $p < 0.001$). Failure to achieve a cervical ripening with PGE2 (both non-responders and partial responders) was found to be an independent risk factor for cesarean delivery following multivariate analysis (aOR 11.90, 95% CI 6.13–23.25).

Conclusion Women who fail to achieve cervical ripening with PGE2 are older, and more often primiparous. This group is associated with higher rates of intrapartum cesarean delivery and adverse outcomes.

Background

Induction of labor is a common obstetric procedure, performed in up to 25% of pregnant women (1) (2). When the cervix is unfavorable, referred to as *Bishop score* lower than 6, cervical ripening is indicated (3) (4). Slow release vaginal insert of prostaglandins E2 (PROPESS) is proven as an efficient and safe method for cervical ripening (5). Labor induction process and its' results have both medical and psychological impacts on pregnant women and medical consultants as well. Some women fail to respond to cervical ripening. Specific characteristics of those women have been previously described. They tend to be older, more primiparous and suffer from higher rates of overweight and obesity (6). The preferred management for these women is moot, with possible second line treatment by either extra-amniotic balloon (EAB) Foley catheter, repeated prostaglandin application or cesarean delivery (7)(8)(9)(10)(11). The lack of uniformity of evidence impairs clinicians' ability to offer evidence-based counseling. We aimed to better define the characteristics of women who fail to achieve cervical ripening with prostaglandins and evaluate their obstetric outcomes. Understanding the risk factors and outcomes of women who fail to achieve cervical ripening will assist clinicians in consulting these women better during the process of labor induction.

Methods

A retrospective cohort study was conducted in a single tertiary, university-affiliated medical center, between January 2012 and December 2018.

Study Population: All women presenting with an unfavorable cervix (Bishop score < 6) (3), who were admitted for cervical ripening with PROPESS due to prolonged gestation were included in the study.

The cohort was divided into three study groups according to evaluation at 24 hours of treatment: group A) responders - women who achieved cervical ripening (Bishop score ≥ 8); group B) partial responders - women who had some cervical response but did not reach a Bishop score ≥ 8.
Or those, who were diagnosed with membrane rupture during this timeframe; and group C) non responders - women who required an additional ripening method, because they did not achieve cervical ripening (Bishop score < 6).

Eligibility was limited to women between 18 and 45 years of age with singleton gestations, who delivered a live birth neonate. Women with prior cesarean delivery, premature rupture of membranes at admission or known fetal anomaly were excluded from the study. Women who underwent cesarean delivery (due to non-reassuring fetal heart rate/ opted for CD), or those in whom cervical ripening was terminated prior to 24 hours evaluation (due to tachysystole, meconium stained amniotic fluid, intractable pain) were excluded as well.

Procedures and definitions

Gestational age was calculated according to last menstrual period and confirmed by a 1st trimester sonographic fetal crown-rump length measurement.

Postdate was defined as gestational age over 40 + 0 weeks (12).

According to our departmental protocol for postdate pregnancy, women carrying a low risk pregnancy are managed expectantly with non-stress test (NST) and biophysical profile twice weekly. When no contraindication for vaginal delivery exists and active labor is not observed, induction of labor is offered. Women opting for induction of labor undergo vaginal examination to assess cervical status - parameters of cervical dilatation, effacement, consistency, location and vertex position are determined to establish the Bishop score (4), and if 6 or below, cervical ripening is indicated. Cervical ripening by prostaglandins is performed in our center by a 10mg slow release vaginal insert of PGE2 Dinoprostone (PROPESS, Ferring Pharmaceuticals, Saint-Prex Switzerland). The vaginal insert is introduced into the posterior vaginal fornix and the woman is hospital admitted, for the following 24 hours. Women are evaluated upon regular contractions, rupture of membranes, suspected fetal compromise and routinely every 12 hours. The assessment includes NST and, if indicated, digital vaginal examination. The vaginal insert is removed upon the following scenarios: 1) Bishop score above 8, which denoted successful cervical ripening; 2) non reassuring fetal heart rate; 3) tachysystole, defined as more than 5 contractions in 10 minutes; 4) and upon completion of 24 hours from insertion.

Women who achieve cervical ripening (subgroup A, responders) or partial cervical ripening or rupture of membranes (subgroup B, partial responders) at or prior to completing 24 hours of treatment are transferred

to labor and delivery floor for further labor augmentation by oxytocin infusion and/or amniotomy, following removal of the vaginal insert. Women who do not achieve cervical ripening at 24 hours undergo a second line ripening method with an EAB (subgroup C, non-responders).

Cervical ripening by EAB is performed by transcervical insertion of a 22F Foley catheter under visualization, inflated with 80ml saline. The catheter is attached to the women's thigh with traction and removed after 24h, or earlier if spontaneous rupture of membranes or spontaneous EAB expulsion had occurred. After EAB removal or expulsion, the woman is transferred to labor and delivery floor, where oxytocin infusion and/or amniotomy are commenced if active labor had not occurred.

Data collection

Data was obtained from the medical electronic records including perinatal comprehensive database, maternal-fetal clinic records and delivery ward charts.

The following demographic and medical-obstetrical variables were recorded: maternal age, gravidity, parity, mode of conception, initial Bishop score, gestational age at delivery; and maternal co-morbidities including chronic hypertension, any thrombophilia, pre- gestational diabetes, and gestational diabetes. Body mass index (BMI) was calculated to account for overweight and obesity (BMI > 25kg/m^2).

Maternal and neonatal outcomes were collected from the medical records. Maternal measures included: mode of delivery, intrapartum fever, Obstetric Anal Sphincter Injuries (OASI), post-partum hemorrhage (PPH) and blood products transfusion. Neonatal measures included: gender, birthweight, 1st- and 5th-minute Apgar scores, neonatal intensive care unit (NICU) admission status, sepsis, asphyxia, seizures, hypoxic ischemic encephalopathy (HIE), transient tachypnea of the newborn (TTN), respiratory distress syndrome (RDS), oxygen enrichment, mechanical ventilation and meconium aspiration syndrome (MAS). Labor characteristics of epidural anesthesia or meconium stained amniotic fluid were recoded as well.

Outcome measures: Primary outcome was defined as the rate of intrapartum cesarean delivery due to labor dystocia. Secondary outcomes were defined as maternal composite adverse outcomes including any of the following: intrapartum fever, OASI, PPH and blood products transfusion and neonatal composite adverse outcomes including any of the following: TTN, RDS, oxygen enrichment, mechanical ventilation, and MAS, 5-minutes Apgar score < 7, asphyxia, seizures or HIE.

Statistical analysis: Statistical analysis was performed using the SAS software (Version 9.4, SAS Institute, North Carolina, USA). Comparison between continuous variables was performed with Student's t-test and categorical data was compared using $\chi 2$ test. A probability value < 0.05 was considered significant. A multivariate logistic regression was performed to detect independent risk factors for cesarean delivery after controlling for possible confounders including maternal age, overweight and obesity and primiparity. We constructed a predictive model accounting for the following: responsiveness to prostaglandins, age, overweight and obesity and primiparity to predict the risk of cesarean delivery, using a receiver operating characteristic (ROC) analysis.

Results

Overall, 1,377 women meeting the inclusion criteria were admitted for cervical ripening using PGE2 vaginal insert, due to post-date pregnancy. Of those, 92 (6.68%) were excluded from the study. 29 (2.11%) underwent cesarean delivery during the 24 hours of cervical ripening process and before achieving cervical ripening, and for 63 (4.58%) PGE2 treatment was halted prior to completion. Thus, 1,285 women were included in the final analysis. These women were allocated accordingly: group A, responders - 1202 (93.54%), group B, partial responders - 39 (3.04%) and group C, non-responders - 44 (3.42%) (Figure 1).

Our results demonstrate that women in the responders' group were younger (30.03 years vs 32.13 and 31.3, p=0.04 and 0.005 respectively), and had lower primiparity rates (50.99% vs 76.92% and 81.39%, p<0.001) compared to partial-responders and non-responders. These women tended to be less overweight/obese as well (27.37% vs 36.14% and 34.88%, p=0.11), (Table 1). Labor parameters including epidural analgesia and meconium stained amniotic fluid did not differ between the groups (Table 2).

The rate of cesarean delivery was significantly higher among partial responders and non-responders compared to responders (33.33% and 36.36% vs 3.49%, respectively, p<0.001). PPH rates were higher among the partial-responders group compared to non- responders and responders (23.07% and 11.36% vs 9.48%) (Table 2).

Maternal composite adverse outcomes were higher among partial responders and non-responders compared to responders (30.77% and 18.18% vs 12.8%, p=0.019 and 0.031), mostly attributed to PPH.

For neonatal adverse outcomes, we found a higher rate of composite respiratory complications among the partial responders compared to responders (7.69% vs 1.33%, p=0.01). Groups did not differ in any other neonatal parameters including NICU admission, birthweight, 5-minutes Apgar score, asphyxia, sepsis and the composite neonatal outcome (Table 2).

A multivariate logistic regression analysis controlling for maternal age, primiparity, and overweight-obese showed that being a partial-responder or non-responder is an independent risk factor for intrapartum cesarean delivery (adjusted Odds Ratio [aOR] 11.90, 95% CI 6.13-23.25, p<0.001) (Table 3).

We constructed a predictive model accounting for non-responsiveness to PGE2 (non- and partial responders), maternal age, overweight and primiparity to predict the risk for cesarean delivery with an area under the curve in a ROC analysis of 0.73 (Figure 2). Primiparous women, older than 30 with BMI>25kg/M^2, who fail to achieve cervical ripening had a 60% chance for undergoing an intrapartum cesarean delivery accounted for labor dystocia (Table 4).

Discussion

Main Findings: Our main findings demonstrate that women who failed to achieve cervical ripening have independently significant higher rates of intrapartum cesarean delivery. These women tend to be older, more frequently primiparous and have tendency towards higher BMIs.

Induction of labor occasionally fails at the initial phase of cervical ripening. In our study we report a failure rate of 6.46%, lower than the 10% to 30% reported in the literature (8)(13) (14). A possible explanation to our low failure rate might be related to single ripening method (PROPESS) and more importantly to a single indication for cervical ripening (postdate), with a clear and clinically relevant definition of failed ripening. While some studies define the outcome of ripening as failure to deliver vaginally within 24 hours following induction initiation, we defined it as failure to achieve a minimal Bishop score (at least 8) within 24 hours of treatment onset.

Several studies have previously described the predictors for cervical ripening failure. Melamed et al. (6) and Pevzner et al. (15) - in concordance to our results - demonstrated that older, primiparous, overweight women have higher PGE2 failure rates.

An important issue rarely addressed, is the pharmacokinetics of prostaglandins when used for labor induction. Prostaglandins are detected in the plasma after vaginal administration, thus exhibiting systemic absorption via vaginal mucosa, with different distribution for gel or tablet administration (16). Current treatment protocols and dosage are based on clinical response (i.e. cervical softening, dilatation, and uterine contractions), rather than plasma levels titrations. Moreover, the slow release vaginal insert used in our study lacks the option of dosage adjustment according to clinical response as accepted in PGE2 gel and tablets.

Hence, a possible explanation to the difference in response to cervical ripening by prostaglandins is hinged on differences in absorption, distribution, and excretion, all of which may all be influenced by maternal age and weight.

It is well established that primiparity is a risk factor for prolonged labor (17), need for operative vaginal delivery and intrapartum cesarean delivery (18)(19)(20). Our results support these findings and perhaps imply that the treatment protocol to these patients should be modified, allowing a longer exposure to the medications or usage of a combined method for cervical ripening.

Other prior studies tried to offer the adequate treatment when such an event of cervical ripening failure occurs. These studies were inconclusive in their results and offered variable possible second line treatments as Extra-Amniotic balloon (EAB) Foley catheter, repeated prostaglandin application or cesarean delivery (7)(8)(9)(10)(11). Our study found that primiparous, older (>30) and overweight women (>25 BMI) who fail to respond or partially respond to cervical ripening have as much as 60% chance ending up in an intrapartum cesarean delivery. This finding should be accounted for, when counseling those women for induction continuation or cessation, at the decision-making point.

Our study is limited by its retrospective nature. First, we could not account for some probable confounders, as gestational weight gain. Second, the decision of partial response versus complete non-response was made by different physicians and could lead to selection bias. Third, when comparing between non- and partial responders we could not detect differences due to small sample size. Having said that, our study has several strengths', as a large cohort undergoing a standard practice for a solitary indication, with a single pharmacological agent, in a single tertiary center. We focus on a common, but not well answered dilemma regarding the outcomes of failed cervical ripening.

Conclusion

Women at post-date who fail to achieve cervical ripening within 24 hours of PGE2 treatment onset, have not only higher rates of cesarean deliveries, but also an increased risk for maternal adverse outcomes. This is particularly significant in older, primiparous women.

List Of Abbreviations

IOL: Induction of Labor

PGE2: Prostaglandin-E2

EAB: Extra Amniotic Balloon

CD: Cesarean Delivery

NST: Non-Stress Test

BMI: Body Mass Index

OASI: Obstetric Anal Sphincter Injuries

PPH: Post-partum hemorrhage

NICU: Neonatal Intensive Care Unit

HIE: Hypoxic Ischemic Encephalopathy

TTN: Transient Tachypnea of the Newborn

RDS: Respiratory Distress Syndrome

MAS: Meconium Aspiration Syndrome

Declarations

Ethics approval and consent to participate: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by local institutional review board at Rabin medical center (Approval number RMC-0224-18). Informed consent was waived due to the retrospective design of the study, by Rabin medical center IRB Helsinki committee.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

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Authors' contributions: Alexandra Berezowsky: protocol development, data analysis, and manuscript writing. Gil Zeevi: data collection and data analysis. Eran Hadar: protocol development and manuscript editing. Eyal Krispin: protocol development, data management and analysis, and manuscript editing

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Tables

Table 1: Maternal baseline characteristics

	Responders (A 1202, 93.54%)	Partial Responders (B 39, 3.04%)	Non-Responders (C 44, 3.42%)	p value a vs. b	p value a vs. c
Age, Years	30.05±5.02	32.13±5.86,	31.32±3.96	**0.005**	**0.04**
GA at birth, weeks	41.21±0.50	41.39±0.49,	41.27±0.55	**0.015**	0.42
Nulliparity	613 (50.99)	30 (76.92),	35 (81.39)	**<0.001**	**< 0.001**
BMI>25kg/M^2	329 (27.37)	16 (36.14),	15 (34.88)	0.112	0.12
ART	28 (2.33)	1 (2.56),	0 (0.0)	1.0	0.88
GDM	71 (5.91)	1 (2.56),	3 (6.98)	1.0	0.738
Epidural, n (%)	776 (64.56)	26 (66.67)	30 (68.18)	0.411	0.574

1. Data presented as mean ± standard deviation for continuous variables and n(%) for categorical variables
2. p-values are versus the responders' group
3. GA: Gestational Age
4. ART: Assisted Reproductive Technology
5. GDM: gestational diabetes mellitus

Table 2: Maternal and Neonatal Outcomes					
	Responders (A 1202, 93.54%)	Partial Responders (B 39, 3.04%)	Non-Responders (C 44, 3.42%)	p value a vs. b	p value a vs. c
Labor Characteristics					
Meconium stained amniotic fluid, n (%)	198 (16.47)	4 (10.26)	9 (20.45)	1.0	0.336
NVD, n (%)	966 (80.37)	19 (48.72)	26 (59.09)	**0.001**	**<0.001**
OVD, n (%)	194 (16.14)	8 (20.51)	3 (6.82)	0.641	0.106
CD, n (%)	42 (3.49)	13 (33.33)	16 (36.36)	**<0.001**	**<0.001**
Failed induction, n (%)	6 (14.29)	6 (46.15)	10 (62.5)	**<0.001**	**<0.001**
Arrest of dilation, n (%)	19 (45.24)	3 (23.07)	3 (18.75)	**0.002**	**0.001**
Arrest of descent, n (%)	11 (26.19)	2 (15.38)	3 (18.75)	**0.001**	**0.002**
Other, n (%)	6 (14.29)	2 (15.38)	0 (0.0)	0.066	0.061
Maternal outcomes					
Maternal Composite	154 (12.8)	12 (30.77)	8 (18.18)	**0.019**	**0.031**
OASIS, n (%)	10 (0.86)	1 (3.70)	0 (0.0)	0.555	1.0
PPH, n (%)	114 (9.48)	9 (23.07)	5 (11.36)	**0.045**	0.797
Transfusion, n (%)	11 (0.92)	1 (2.56)	1 (2.27)	0.229	0.376
Intrapartum Fever, n (%)	19 (1.58)	1 (2.56)	2 (4.55)	0.194	0.191
Neonatal outcomes					
Neonatal composite	131 (10.89)	8 (20.51)	8 (18.18)	0.504	0.639
Gender male, n (%)	581 (48.34)	23 (58.97)	21 (47.73)	0.571	0.878
BW, grams	3464.94±382.04	3480.36±351.04	3438.80±329.61	0.72	0.59
5-min Apgar < 7, n (%)	8 (0.66)	1 (2.56)	0 (0.0)	0.375	1.0
PH<7.2, n (%)	63 (5.24)	1 (2.56)	3 (6.82)	0.814	1.0
Asphyxia, n (%)	3 (0.25)	0 (0.0)	0 (0.0)	0.918	0.872
NICU, n (%)	34 (2.83)	2 (5.13)	2 (4.55)	0.304	0.356
Respiratory comp, n (%)	16 (1.33)	3 (7.69)	2 (4.55)	**0.01**	0.126
Phototherapy, n (%)	7 (0.58)	1 (2.56)	1 (2.27)	0.110	0.246

1. Data presented as mean ± standard deviation and n (%)
2. p-values are versus the responders' group
3. NVD: Normal Vaginal Delivery

4. OVD: Operative Vaginal Delivery
5. CD: Cesarean Delivery
6. OASIS: Obstetric Anal Sphincter Injuries
7. PPH: Postpartum Hemorrhage
8. Maternal Composite of OASIS, PPH, need for blood transfusion and Intrapartum Fever
9. Neonatal Composite of 5-min APGAR<7, PH<7.2, Asphyxia, NICU, Respiratory composite and phototherapy
10. BW: Birth Weight
11. NICU: Neonatal Care Unit
12. Respiratory Composite of neonatal apnea, TTN, RDS, oxygen enrichment, mechanical ventilation and meconium aspiration syndrome

Table 3: Adjusted odds ratio for cesarean delivery

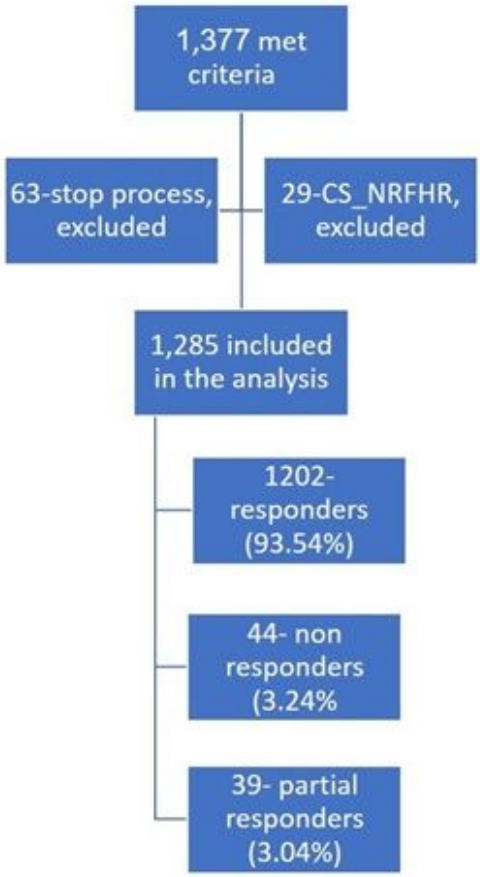
	Adjusted odds ration	95% confidence interval	p Value
Both Partial and Complete- non responders	11.90	6.13-23.35	<0.001
Age > 30	2.30	1.24-4.27	0.008
BMI> 25 kg/M^2	1.08	0.45-1.91	0.83
Primiparity	9.90	4.13-23.81	<0.001

1. BMI: Body Mass Index

Table 4: cesarean delivery rates according to maternal characteristics

Group	Age	Parity	BMI> 25kg/m^2	All	Cesarean	%
Responders	≤30	≥1	<25	114	0	0
			≥25	64	0	0
		0	<25	274	8	2.92
			≥25	95	4	4.21
	>30	≥1	<25	170	2	1.18
			>25	122	2	1.64
		0	<25	98	4	4.08
			≥25	48	5	10.42
All non-responders	≤30	≥1	<25	1	0	0
			≥25	2	0	0
		0	<25	21	6	28.57
			≥25	13	6	46.15
	>30	≥1	<25	6	1	16.67
			≥25	6	1	16.67
		0	<25	15	7	46.67
			≥25	10	6	60

Figures



Overall, 1,377 women at 40+0 to 42+6 weeks of gestation were admitted due to post-term gestation for cervical ripening using a slow release vaginal insert (PROPESS). Of those, 92 (6.68%) were excluded from the study - 29 (2.11%) were operated due to non-reassuring fetal heart rate tracings before achieving cervical ripening; 63 (4.58%) because the process was ceased prior to ripening due to tachysystole, meconium stained amniotic fluid or intractable pain, they were forward induced with EAB or Oxytocin. Thus, 1,285 parturients were included in the statistical analysis. Of those, 1202 (93.54%) achieved cervical ripening with PROPESS and 83 (6.46%) did not. Of the 83 who did not achieve cervical ripening - 44 (3.42% of initial cohort) were complete non-responders, and required a second method of cervical ripening, with EAB; 39 were partial responders and continued induction with Oxytocin

Figure 1

Study Design

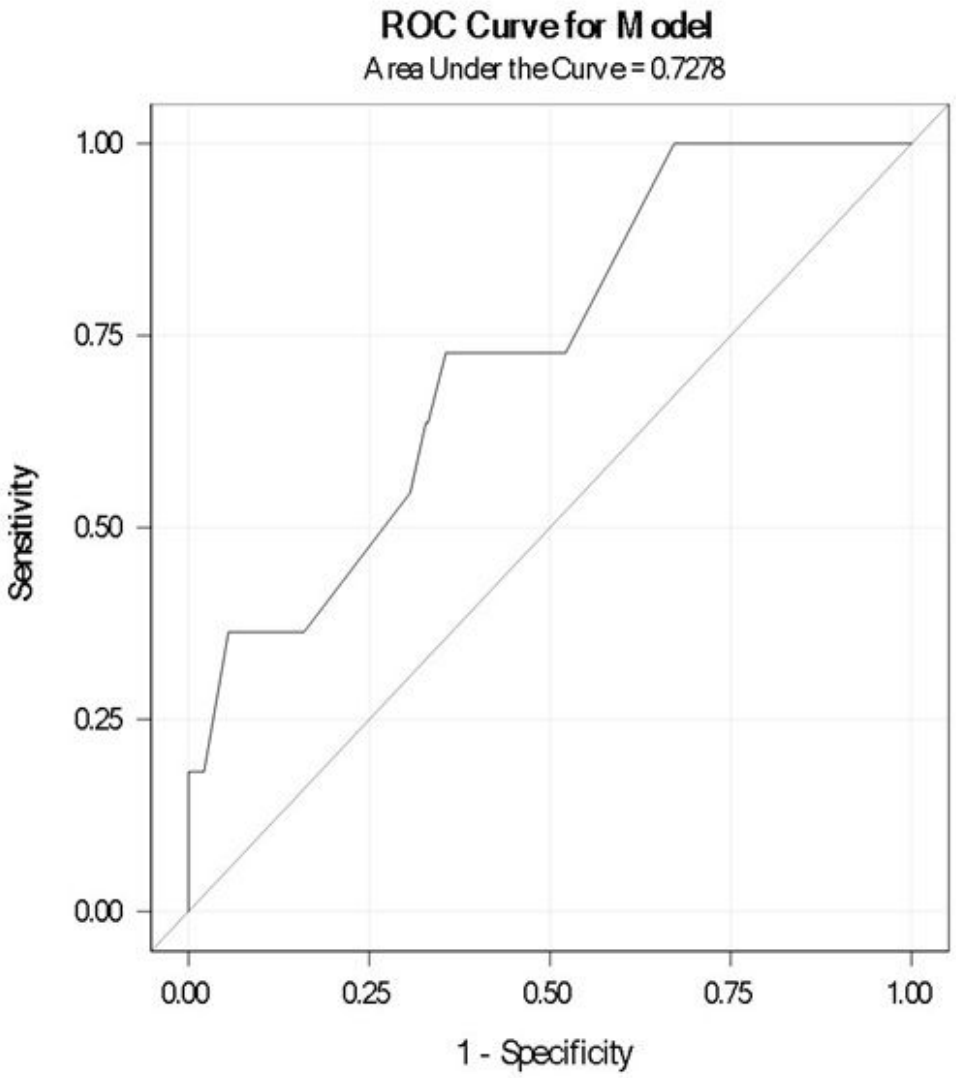


Figure 2

aOR of 18.18 for cesarean delivery (95% CI 2.38-142) calculated for Compete non-responders, Age>30, BMI>25 and primiparous parturiens