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Full length article

Management of the third stage of labor in second-trimester deliveries: How long is too long?☆

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ABSTRACT

Background: Retained placenta is the most common second-trimester delivery complication. As the optimal third stage of labor duration remains undefined, complications associated with retained placentas are difficult to study.

Objective(s): To determine the optimal third stage of labor duration in second-trimester deliveries based on estimates of time-specific probabilities of placental delivery, placental intervention, and postpartum complication.

Study design: We retrospectively studied adult women with singleton second-trimester vaginal deliveries. We identified third stage of labor duration, placental delivery method (spontaneous vs. manual/operative intervention), and indication for intervention. Postpartum complication was examined as a composite outcome. Differences among groups defined by delivery method and postpartum complication were tested using parametric and nonparametric tests. Probability curves describing the time-specific probabilities of placental delivery were derived using lifetable methods with group differences tested using the log-rank test. Probability of placental intervention and complication by time to placental delivery were examined using logistic regression with adjustment for confounders and other predictors.

Results: We identified 215 second-trimester placental deliveries (77% spontaneous, 23% intervention). Overall, 27% experienced postpartum complication, primarily hemorrhage (91%). Complication rates differed significantly between spontaneous placental deliveries (16%) and interventions (61%, $P < 0.01$). Both placental intervention and postpartum complication were strongly associated with longer time to placental delivery. Spontaneous placental deliveries occurred earlier than deliveries requiring intervention ($P < 0.01$). At 2 h, placental delivery rates were 93% in spontaneous deliveries and 39% in those requiring intervention. The overall postpartum complication rate for spontaneous placental deliveries (16%) was used as the threshold of tolerable risk and the criterion for placental intervention. Adjusted probability curves for deliveries of average gestational age (21.6 weeks) suggested that most patients (63.9%) may not require intervention until approximately 2 h following fetal delivery. Patients with PPROM would require intervention by 34 min, and those with intrapartum fever or delivery EBL ≥500 mL would already exceed the risk threshold at fetal delivery.

Conclusions: Our study suggests that an optimal third stage of labor duration of approximately 2 h maximizes probability of spontaneous delivery and minimizes complication risk. Timing of intervention may be further individualized for patients based on maternal characteristics and intrapartum conditions.

Introduction

Second-trimester abortions remain an essential component in the comprehensive care of women. Studies of medical abortions performed with misoprostol have suggested retained placenta may be the most common complication (21%) [1]. Despite the risk of retained placenta during the third stage of labor, no evidence-

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Table 1
Patient characteristics and postpartum outcomes overall and by placental delivery method and postpartum complication.

Characteristic or outcome	Overall N = 215	Placental delivery method			Postpartum complication		
		Spontaneous n = 166	Intervention[a] n = 49	*P* value	None n = 158	Any[b] n = 57	*P* value
Demographic and Pregnancy Characteristics							
Maternal race/ethnicity, n (%)							
White non-Hispanic	134 (62.3)	103 (62.1)	31 (63.3)	0.98	101 (63.9)	33 (57.9)	0.58
Black non-Hispanic	43 (20.0)	33 (19.9)	10 (20.4)		28 (17.7)	15 (26.3)	
Hispanic/Latina	26 (12.1)	21 (12.7)	5 (10.2)		20 (12.7)	6 (10.5)	
Other	12 (5.58)	9 (5.42)	3 (6.12)		9 (5.70)	3 (5.26)	
Maternal age (yr), mean (SD)	29.3 (0.39)	28.7 (0.43)	31.2 (0.83)	<0.01	29.5 (0.46)	28.8 (0.73)	0.42
Maternal age ≥35 yr, n (%)	38 (17.7)	25 (15.1)	13 (26.5)	0.06	30 (19.0)	8 (14.0)	0.40
BMI (kg/m^2), median (IQR)[c]	28.2 (9.90)	27.4 (10.0)	32.5 (9.00)	<0.01	27.9 (9.80)	32.0 (11.0)	0.03
Obese (BMI ≥ 30 kg/m^2), n (%)[c]	90 (42.3)	62 (37.8)	28 (57.1)	0.02	61 (39.1)	29 (50.9)	0.12
Previous pregnancy, n (%)							
0	62 (28.8)	56 (33.7)	6 (12.2)	0.01	48 (30.4)	14 (24.6)	0.67
1	60 (27.9)	43 (25.9)	17 (34.7)		44 (27.8)	16 (28.1)	
≥2	93 (43.3)	67 (40.4)	26 (53.1)		66 (41.8)	27 (47.4)	
Hx of abortion, n (%)	74 (34.4)	54 (32.5)	20 (40.8)	0.28	55 (34.8)	19 (33.3)	0.84
Hx of cesarean section, n (%)	32 (14.9)	20 (12.1)	12 (24.5)	0.03	19 (12.0)	13 (22.8)	0.05
Hx of D&C, n (%)	31 (14.4)	22 (13.3)	9 (18.4)	0.37	22 (13.9)	9 (15.8)	0.73
Pregestational diabetes present, n (%)	6 (2.79)	2 (1.20)	4 (8.16)	0.03	2 (1.27)	4 (7.02)	0.04
Hx of gestational diabetes, n (%)	7 (2.36)	5 (3.01)	2 (4.08)	0.66	5 (3.16)	2 (3.51)	1.00
Chronic hypertension present, n (%)	16 (7.44)	9 (5.42)	7 (14.3)	0.04	9 (5.70)	7 (12.3)	0.10
Hx of preeclampsia, n (%)	9 (4.19)	7 (4.22)	2 (4.08)	1.00	6 (3.80)	3 (5.26)	0.70
Gestational hypertension present, n (%)	10 (4.65)	9 (5.42)	1 (2.04)	0.46	9 (5.70)	1 (1.75)	0.30
Preeclampsia present, n (%)	5 (2.33)	4 (2.41)	1 (2.04)	1.00	2 (1.27)	3 (5.26)	0.12
Anemia present, n (%)	55 (25.7)	40 (24.2)	15 (30.6)	0.37	34 (21.7)	21 (36.8)	0.02
Delivery Characteristics							
Gestational age, mean (SD)	21.1 (0.21)	21.6 (0.23)	19.6 (0.48)	<0.01	21.2 (0.25)	21.1 (0.40)	0.60
Gestational age >20 weeks, n (%)	117 (54.4)	99 (59.6)	18 (36.7)	<0.01	85 (53.8)	32 (56.1)	0.76
NICU admission, n (%)	30 (14.0)	25 (15.1)	5 (10.2)	0.39	23 (14.6)	7 (12.3)	0.67
Fetal anomalies, n (%)	42 (19.5)	35 (21.1)	7 (14.3)	0.29	32 (20.3)	10 (17.5)	0.66
Fetal death, n (%)	189 (87.9)	143 (86.1)	46 (93.9)	0.14	137 (86.7)	52 (91.2)	0.37
PPROM present, n (%)	58 (27.0)	40 (24.1)	18 (36.7)	0.08	33 (20.9)	25 (43.9)	<0.01
Placental abruption occurred, n (%)	25 (11.6)	19 (11.5)	6 (12.2)	0.88	17 (10.8)	8 (14.0)	0.51
Placental previa present, n (%)	3 (1.40)	2 (1.20)	1 (2.04)	0.66	1 (0.63)	2 (3.51)	0.17
Indication, n (%)[d]	79 (36.7)	60 (36.1)	19 (38.8)	0.74	64 (40.5)	15 (26.3)	0.06
Fetal death	51 (23.7)	37 (22.3)	14 (28.6)	0.36	31 (19.6)	20 (35.1)	0.02
PPROM	19 (8.84)	16 (9.64)	3 (6.12)	0.57	15 (9.49)	4 (7.02)	0.57
Fetal anomaly	76 (35.4)	58 (34.9)	18 (36.7)	0.82	57 (36.1)	19 (33.3)	0.71
Preterm labor	22 (10.2)	16 (9.64)	6 (12.2)	0.60	14 (8.86)	8 (14.0)	0.27
Advanced dilation	16 (7.44)	14 (8.43)	2 (4.08)	0.53	9 (5.70)	7 (12.3)	0.10
Infection	6 (2.79)	4 (2.41)	2 (4.08)	0.62	2 (1.27)	4 (7.02)	0.02
Bleeding	3 (1.40)	3 (1.81)	0 (0.00)	1.00	1 (0.63)	2 (3.51)	0.11
Maternal indications	3 (1.40)	3 (1.81)	0 (0.00)	1.00	1 (0.63)	2 (3.51)	0.11
Other							
Labor induction, n (%)							
Spontaneous delivery without augmentation	87 (40.5)	64 (38.6)	23 (46.9)	0.57	63 (39.9)	24 (42.1)	0.84
Spontaneous delivery with augmentation	19 (8.84)	15 (9.04)	4 (8.16)		15 (9.49)	4 (7.02)	
Induction with/without augmentation	109 (50.7)	87 (52.4)	22 (44.9)		80 (50.6)	29 (50.9)	
Anesthesia, n (%)[d]							
None	32 (14.9)	23 (13.9)	9 (18.4)	0.44	28 (17.7)	4 (7.02)	0.05
Oral pain medication	38 (17.7)	30 (18.1)	8 (16.3)	0.78	25 (15.8)	13 (22.8)	0.24
IV pain medication	150 (69.8)	118 (71.1)	32 (65.3)	0.44	105 (66.5)	45 (79.0)	0.08
Epidural/spinal	49 (22.8)	37 (22.3)	12 (24.5)	0.75	31 (19.6)	18 (31.6)	0.07
Fever present intrapartum, n (%)[e]	30 (14.0)	25 (15.1)	5 (10.2)	0.39	16 (10.1)	14 (24.6)	<0.01
Chorioamnionitis present, n (%)	33 (15.4)	27 (16.3)	6 (12.2)	0.49	19 (12.0)	14 (24.6)	0.02
Delivery EBL ≥ 500 mL, n (%)[f]	17 (7.91)	9 (5.42)	8 (16.3)	0.01	5 (3.16)	12 (21.1)	<0.01
Postpartum Outcomes							
Time to placental delivery (min), median (IQR)	16.0 (70.0)	8.00 (25.0)	185 (234)	<0.01	8.50(33.0)	69.0(203)	<0.01
Placental delivery, n (%)							
Spontaneous	166 (77.2)	166 (100)	0 (0.00)	N/A	139 (88.0)	27 (47.4)	<0.01
Placental intervention	49 (22.8)	0 (0.00)	49 (100)		19 (12.0)	30 (52.6)	
By intervention method[g]							
Manual removal	19 (8.84)	0 (0.00)	19 (38.8)	N/A	5 (3.16)	14 (24.6)	<0.01
Operative removal	30 (14.0)	0 (0.00)	30 (61.2)		14 (8.86)	16 (28.1)	
By indication for intervention[h]							
Non-indicated	21 (9.77)	0 (0.00)	21 (42.9)	N/A	8 (5.70)	13 (22.8)	<0.01
Indicated	28 (13.0)	0 (0.00)	28 (57.1)		11 (6.33)	17 (29.8)	
Endometritis present, n (%)	2 (0.93)	2 (1.20)	0 (0.00)	1.00	0 (0.00)	2 (3.51)	N/A
Hemorrhage occurred, n (%)	52 (24.2)	23 (13.9)	29 (59.2)	<0.01	0 (0.00)	52 (91.2)	N/A
Transfusion performed, n (%)	7 (3.26)	3 (1.81)	4 (8.16)	0.05	0 (0.00)	7 (12.3)	N/A
Maternal ICU admission, n (%)	4 (1.86)	3 (1.81)	1 (2.04)	1.00	0 (0.00)	4 (7.02)	N/A
Hysterectomy needed, n (%)	1 (0.47)	1 (0.60)	0 (0.00)	1.00	0 (0.00)	1 (1.75)	N/A

based guidelines exist for providers regarding the acceptable length of expectant management.

Limited research has focused on third stage of labor duration and associated complications in the second-trimester. In 1974, a large study evaluating placental delivery following elective saline abortions proposed an interval of 2 h [2]. At 2 h, the complication rate associated with a retained placenta was greater than the complication rate associated with elective immediate surgical placental removal (4.3% vs. 4.0%, respectively) [2]. A 1989 elective dinoprostone abortion study found that the complication rate already reached 4% by 30 min and increased with expectant management up to 2 h [3]. More recently, a late second-trimester misoprostol abortion study expectantly managed placental deliveries for at least 4 h in the absence of excessive bleeding and no significant morbidity was identified [4]. Another induction abortion study evaluating placental delivery probability suggested that the likelihood of spontaneous expulsion beyond 2 h was only 2.7% [5]. Lastly, a retrospective review of all second-trimester vaginal deliveries suggested intervention before 60 min based on a composite endpoint [6].

Few studies have compared the risks associated with expectant management to those associated with intervention for retained placenta, and results have been generally inconsistent. Therefore, we aimed to compare these risks and determine the optimal third stage of labor duration in second-trimester deliveries based on estimates of time-specific probabilities of placental delivery, placental intervention, and postpartum complication.

Materials and methods

Study design

We retrospectively studied second-trimester deliveries within our large community-based hospital system, with study approval obtained by our Institutional Review Board. The study population included adult women with singleton second-trimester (13–26 weeks) vaginal deliveries during January 2011–June 2015. As data were extracted from the electronic medical record, patients were excluded if fetal or placental delivery times were not recorded. Third stage of labor duration, calculated as time from fetal to placental delivery, was the main factor of interest.

Primary outcomes in this study included placental intervention and postpartum complication. Placental intervention was defined as manual removal of the placenta with or without instrumentation and/or dilation and curettage. We also reviewed provider indication for placental intervention. Intervention was deemed non-indicated if the provider documented third stage of labor duration (i.e., prolonged time since fetal delivery) as the sole reason for placental removal or if no reason was provided. Intervention was considered indicated if one or more urgent clinical reasons for placental removal were provided, such as bleeding, infection, cord avulsion, partial placental passage, and maternal instability. Postpartum complication was assessed as a composite outcome including endometritis, hemorrhage, transfusion, maternal intensive care unit (ICU) admission, and/or hysterectomy. Endometritis was defined as a clinical diagnosis made by the physician. Hemorrhage was defined as postpartum EBL $\geq$ 500 mL or a decline in hemoglobin $\geq$2 mg/dL [3].

Statistical analysis

Patient characteristics and postpartum outcomes were described using frequencies with percentages, means with 95% confidence intervals (CIs), and medians with interquartile ranges (IQRs). Associations between patient characteristics, placental delivery method (spontaneous vs. intervention), and postpartum complication (none vs. any of five) were tested using the Pearson's chi-squared test of independence, Student's t-test, and Wilcoxon rank-sum test, as appropriate. *P* value adjustment for multiple testing was not performed given a priori hypotheses underlying the tests, the arbitrary number of tests ultimately performed, and our unwillingness to accept increased probabilities of type II error [7].

Cumulative probabilities of placental delivery by time since fetal delivery were derived using lifetable methods, with 30-minute intervals increasing to 2-h intervals across 10 h. Differences among patient groups defined by placental delivery method, indication for intervention, and postpartum complication were tested using the log-rank test; groups showing no difference were combined for recalculating probabilities. We also computed probabilities of placental intervention by time since fetal delivery (given precisely-documented intervention times) and postpartum complication by time to placental delivery (given unknown complication times but known placental delivery times). Lifetable methods were used to estimate overall intervention probabilities with censoring at spontaneous placental delivery; cumulative incidence functions accounted for indicated and non-indicated interventions as competing risks. Predicted probabilities of complication for the overall and stratified populations were computed using single-variable logistic regression incorporating time to placental delivery and multivariable regression incorporating time and placental delivery method with indication

Table 1 (*Continued*)

Characteristic or outcome	Overall N = 215	Placental delivery method			Postpartum complication		
		Spontaneous n = 166	Intervention[a] n = 49	*P* value	None n = 158	Any[b] n = 57	*P* value
Any of 5 complications, n (%)[b]	57 (26.5)	27 (16.3)	30 (61.2)	<0.01	0 (0.00)	57 (100)	N/A

Abbreviations: SD, standard deviation; BMI, body mass index; IQR, interquartile range; Hx, history; D&C, dilation and curettage; NICU, neonatal intensive care unit; PPROM, preterm premature rupture of membranes; IV, intravenous; EBL, estimated blood loss; N/A, not applicable; ICU, intensive care unit.

[a] Placental intervention includes both manual and operative methods.

[b] Postpartum complications incorporated in the composite "any complication" variable include endometritis, hemorrhage, transfusion, maternal ICU admission, and subsequent hysterectomy.

[c] BMI was not available for 2 patients, both with spontaneous placental delivery and no documented complications.

[d] Individual patients may fall into more than one category.

[e] Intrapartum and postpartum fevers were recorded separately to avoid inclusion of other fever etiologies (e.g., chorioamnionitis or anesthesia).

[f] EBL during delivery was absent or recorded as minimal for 60 patients total (n = 45 with no complications, n = 15 with any complication, n = 43 with spontaneous placental delivery, and n = 17 with placental intervention).

[g] Intervention method represents the final (or most invasive) method used for removal of the placenta; 10 patients in the operative removal group first underwent physician attempts toward manual placental removal.

[h] Indicated placental intervention includes bleeding, infection, cord avulsion, partial placental passage, and maternal instability, while non-indicated includes interventions without documented reasons or with "time" recorded as the reason for intervention.

(spontaneous vs. indicated intervention vs. non-indicated intervention).

Single-variable and multivariable logistic regression models, respectively, were used to estimate unadjusted and adjusted odds ratios (ORs), describing proportional change in odds of placental intervention or postpartum complication with increasing time to placental delivery. From multivariable models, we also generated predicted probabilities of intervention and complication. Planned sensitivity analyses were performed. For intervention probability, we incorporated all placental deliveries (regardless of indication) and then re-ran the models excluding non-indicated interventions. For complication probability, we incorporated all placental deliveries (regardless of placental delivery method) and re-ran the models excluding all interventions, recognizing potential for bias in complication rates with their inclusion.

Important predictors in the multivariable models of placental intervention and postpartum complication were identified using stepwise variable selection procedures. Predefined selection specifications included: (1) entry of all variables hypothesized a priori to be important predictors and found to be individually associated with the outcome at the $P < 0.10$ level, followed by removal if $P \geq 0.10$, and (2) forced inclusion of time to placental delivery and all confounders of the time-to-placental-delivery effect, taking a purposeful selection approach [8]. Only the strongest predictor was allowed entry from any pair or cluster of highly-correlated variables (Pearson or Spearman |r| $\geq$0.70). Variables were confirmed as confounders only if $\geq$10% change in the adjusted effect size of time to placental delivery was observed following variable exclusion from the full model [9]. Analyses were performed using SAS statistical software (Version 9.4; SAS Institute Inc., Cary, NC).

Results

A total of 215 second-trimester placental deliveries were identified (77% spontaneous, 23% intervention; Table 1). A clinically-urgent indication for intervention was not provided in 43% of cases. Across all deliveries, 27% resulted in postpartum complication, primarily hemorrhage (91%). Overall complication rates were 16% for spontaneous placental deliveries versus 61% for placental interventions ($P<0.01$). Cervical laceration and uterine perforation were two potential but unobserved complications. Longer time to placental delivery was strongly associated with placental intervention and postpartum complication, while 16 other variables demonstrated associations with one or both primary outcomes ($P < 0.10$).

Estimated placental delivery probabilities demonstrated associations between time since fetal delivery, placental delivery method, indication for intervention, and postpartum complication (Fig. 1). Spontaneous placental deliveries occurred significantly earlier than deliveries requiring intervention ($P < 0.01$). The probability of spontaneous placental delivery depended on postpartum complication ($P < 0.01$), but probability of placental intervention did not ($P = 0.37$). However, the probability of placental intervention was significantly different when comparing indicated and non-indicated interventions ($P = 0.03$). At 2 h, placental delivery probabilities were 0.93 in spontaneous deliveries (0.96 without complication, 0.81 with complication) and 0.39 in placental interventions regardless of complication (0.50 when indicated, 0.24 when non-indicated; Table 2).

The cumulative probability of placental intervention increased steadily with time since fetal delivery (Table 3). Estimates for competing risks, however, revealed low incidence of non-indicated interventions through 4 h but steep incline for indicated interventions through 4 h. Complication probability also increased variably with time (Table 4). While no significant difference in

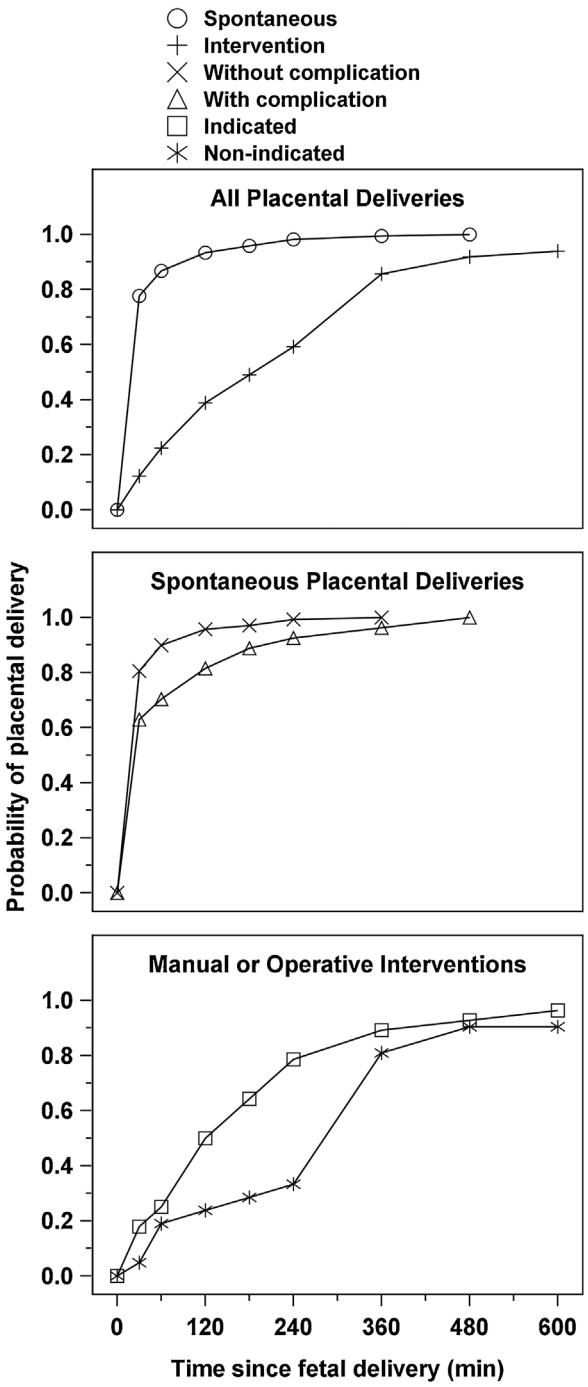

Fig. 1. Lifetable estimates of placental delivery probability by time since fetal delivery and placental delivery method (top graph), with spontaneous delivery stratified by occurrence of complication (middle graph) and manual/operative intervention stratified by indication (bottom graph).

overall complication rates was observed between indicated (61%) and non-indicated (62%) interventions (Table 1), predicted probability curves suggested relative temporal stability in complication risk across 10 h for indicated interventions (increasing from 0.60 to 0.69) but dramatic increases in risk for non-indicated interventions (from 0.33 to 0.82) and spontaneous placental deliveries (from 0.13 to 0.91).

Based on single-variable logistic regression, the unadjusted odds of placental intervention increased 2.2–2.5 times per hour of undelivered placenta, considering all deliveries (OR 2.56, 95% CI 1.93–3.40) or when excluding non-indicated interventions (OR

Table 2
Lifetable estimates of placental delivery probability overall and by placental delivery method, with stratification of spontaneous deliveries by occurrence of complication and stratification of manual/operative deliveries by indication for intervention.

Time since fetal delivery (min)[a]	Overall		Placental delivery method							
			Spontaneous				Intervention			
			Overall		No complications	Complications	Overall		Non-indicated	Indicated
	n[b]	Prob (95% CI)	n[b]	Prob (95% CI)	Prob (95% CI)	Prob (95% CI)	n[b]	Prob (95% CI)	Prob (95% CI)	Prob (95% CI)
30	215	0.63 (0.56–0.69)	166	0.77 (0.71–0.84)	0.81 (0.74–0.87)	0.63 (0.45–0.80)	49	0.12 (0.06–0.25)	0.05 (0.01–0.29)	0.18 (0.08–0.38)
60	80	0.72 (0.66–0.78)	37	0.87 (0.81–0.91)	0.90 (0.84–0.94)	0.70 (0.53–0.86)	43	0.22 (0.13–0.37)	0.19 (0.08–0.43)	0.25 (0.13–0.45)
120	60	0.81 (0.75–0.86)	22	0.93 (0.89–0.96)	0.96 (0.92–0.98)	0.81 (0.65–0.93)	38	0.39 (0.27–0.54)	0.24 (0.11–0.48)	0.50 (0.33–0.69)
180	41	0.85 (0.80–0.89)	11	0.96 (0.92–0.98)	0.97 (0.93–0.99)	0.89 (0.74–0.97)	30	0.49 (0.36–0.64)	0.29 (0.14–0.53)	0.64 (0.47–0.81)
240	32	0.89 (0.85–0.93)	7	0.98 (0.95–0.99)	0.99 (0.96–0.99)	0.93 (0.79–0.99)	25	0.59 (0.46–0.73)	0.33 (0.17–0.57)	0.79 (0.62–0.91)
360	23	0.96 (0.93–0.98)	3	0.99 (0.97–1.00)	1.00 (1.00–1.00)	0.96 (0.84–0.99)	20	0.86 (0.75–0.94)	0.81 (0.63–0.94)	0.89 (0.75–0.97)
480	8	0.98 (0.96–0.99)	1	1 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	7	0.92 (0.82–0.97)	0.90 (0.74–0.98)	0.93 (0.80–0.99)
600	4	0.99 (0.96–1.00)	0	1 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	4	0.94 (0.85–0.98)	0.90 (0.74–0.98)	0.96 (0.85–0.99)

Abbreviations: CI, confidence interval; Prob, probability.
[a] Represents the upper bounds of the time interval.
[b] Represents the effective sample size (or average number of patients available for placental delivery during the time interval).

Table 3
Lifetable estimates of placental intervention probability, with and without accounting for the competing risks of non–indicated and indicated interventions.

Time since fetal delivery (min)[a]	Overall		Competing risks	
	n[b]	Prob (95% CI)	Non–indicated Prob (95% CI)	Indicated Prob (95% CI)
30	150.5	0.04 (0.02–0.09)	0.01 (0.00–0.05)	0.04 (0.01–0.09)
60	72.5	0.11 (0.06–0.19)	0.05 (0.02–0.12)	0.08 (0.04–0.16)
120	54.5	0.24 (0.15–0.36)	0.07 (0.02–0.15)	0.18 (0.10–0.28)
180	39.0	0.34 (0.23–0.47)	0.09 (0.03–0.17)	0.26 (0.16–0.38)
240	30.0	0.45 (0.33–0.59)	0.11 (0.05–0.21)	0.35 (0.23–0.48)
360	22.0	0.77 (0.64–0.88)	0.36 (0.22–0.50)	0.43 (0.28–0.56)
480	7.5	0.86 (0.74–0.95)	0.42 (0.27–0.57)	0.45 (0.31–0.59)
600	4.0	0.90 (0.77–0.97)	0.42 (0.27–0.57)	0.48 (0.33–0.62)

Abbreviations: CI, confidence interval; Prob, probability.
[a] Represents the upper bounds of the time interval.
[b] Represents the effective sample size (or average number of patients available for placental delivery during the time interval).

Table 4
Predicted probabilities of complication across all patients and by placental delivery method with indication for intervention.

Time to placental delivery (min)		Placental delivery method with intervention indication		
	Overall Prob (95% CI)	Spontaneous Prob (95% CI)	Non-indicated intervention Prob (95% CI)	Indicated intervention Prob (95% CI)
30	0.21 (0.15–0.27)	0.16 (0.11–0.23)	0.35 (0.24–0.48)	0.61 (0.37–0.80)
60	0.24 (0.19–0.31)	0.19 (0.13–0.26)	0.38 (0.27–0.49)	0.61 (0.40–0.79)
120	0.32 (0.25–0.40)	0.26 (0.17–0.38)	0.43 (0.33–0.54)	0.62 (0.43–0.78)
180	0.41 (0.31–0.52)	0.35 (0.20–0.54)	0.49 (0.38–0.60)	0.63 (0.45–0.78)
240	0.51 (0.37–0.65)	0.45 (0.23–0.69)	0.55 (0.41–0.67)	0.64 (0.44–0.80)
360	0.70 (0.49–0.85)	0.65 (0.28–0.90)	0.65 (0.46–0.81)	0.65 (0.37–0.86)
480	0.83 (0.60–0.94)	0.81 (0.34–0.97)	0.75 (0.49–0.90)	0.67 (0.28–0.92)
600	0.92 (0.70–0.98)	0.91 (0.40–0.99)	0.82 (0.52–0.95)	0.69 (0.20–0.95)

Abbreviations: CI, confidence interval; Prob, probability.

2.24, 95% CI 1.67–3.16). Adjustment for confounders and other predictors led to little change in the magnitude of the time-to-placental-delivery effect but affirmed the significance of maternal age, gravidity, and postpartum hemorrhage as predictors when considering all placental deliveries (Table 5). The odds of intervention for all placental deliveries increased 3 times per 10-year maternal age increase, 5–7 times for multigravida women, and 9 times if postpartum hemorrhage occurred. When excluding non-indicated interventions, however, the model reflected the reduced influence of time and expected greater influence of intrapartum characteristics. Adjusted probability curves reflected

Table 5
Adjusted odds ratios derived from multivariable models of placental intervention and postpartum complication.

Predictor[a]	Outcome: Placental intervention				Outcome: Any postpartum complication			
	Including all deliveries		Excluding non-indicated interventions		Including all deliveries		Excluding all interventions	
	AOR (95% CI)	*P* value	AOR (95% CI)	*P* value	AOR (95% CI)	*P* value	AOR (95% CI)	*P* value
Time to placental delivery[b]	2.34 (1.75–3.13)	<0.0001	2.03 (1.47–2.81)	<0.0001	1.69 (1.35–2.11)	<0.0001	1.79 (1.16–2.77)	0.0091
Maternal age[c]	3.00 (1.23–7.33)	0.0157	5.13 (1.75–15.1)	0.0029				
Previous pregnancy								
0	Reference	0.0405						
1	6.75 (1.44–31.5)							
≥2	5.41 (1.26–23.2)							
Gestational age[d]					1.22 (1.05–1.40)	0.0084	1.24 (1.01–1.51)	0.0387
Hx of cesarean section								
No			Reference	0.0625	Reference	0.0512		
Yes			3.52 (0.94–13.3)		2.51 (1.00–6.34)			
PPROM present								
No					Reference	0.0183	Reference	0.0591
Yes					2.57 (1.17–5.64)		2.66 (0.96–7.35)	
Pregestational diabetes present								
No			Reference	0.0992	Reference	0.0846		
Yes			7.31 (0.69–77.7)		4.84 (0.81–29.1)			
Intrapartum fever present								
No			Reference	0.0789	Reference	0.0063	Reference	0.0073
Yes			0.20 (0.03–1.21)		3.86 (1.47–10.2)		4.54 (1.50–13.7)	
Delivery EBL ≥ 500 mL								
No			Reference	0.0085	Reference	<0.0001	Reference	0.0007
Yes			8.63 (1.73–43.0)		13.3 (4.05–43.6)		15.3 (3.14–74.3)	
Hemorrhage occurred								
No	Reference	<0.0001	Reference	0.0034	N/A		N/A	
Yes	9.28 (3.38–25.5)		6.21 (1.83–21.1)					

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; EBL, estimated blood loss; PPROM, preterm premature rupture of membranes; N/A, not applicable.
[a] Following single-variable modeling, one variable from each of 3 pairs of correlated predictor variables were selected for possible inclusion in multivariable modeling, including: continuous (vs. categorical) maternal age, continuous (vs. categorical) body mass index, and continuous (vs. categorical) gestational age.
[b] Odds ratios computed as the proportional increase in probability of outcome per 1-hour increase in time.
[c] Odds ratios computed as the proportional increase in probability of outcome per 10-year increase in age.
[d] Odds ratios computed as the proportional increase in probability of outcome per 1-week increase in gestational age.

the different combinations of imposed risk defined in the model (Fig. 2).

Regarding postpartum complication, single-variable logistic regression revealed that odds of complication increased 65% per hour of undelivered placenta, whether considering all deliveries or excluding interventions (OR 1.65, 95% CI 1.14–2.47). Adjustment for confounders and other predictors produced a larger time-to-placental-delivery effect size, suggesting complication odds increased 69% per hour of undelivered placenta when considering all placental deliveries (Table 5). Complication odds also increased 22% per 1-week increase in gestational age, 2.5 times with a history of cesarean section, nearly 3 times with PPROM, 5 times with pregestational diabetes, 4 times with intrapartum fever, and over 13 times with delivery EBL ≥ 500 mL. When excluding all interventions, a reduced model was developed, showing increased influence of time (79% per hour of undelivered placenta). Again, adjusted probability curves reflected the different combinations of imposed risk (Fig. 2).

The overall postpartum complication rate for spontaneous placental deliveries (16%) was used as an upper threshold of tolerable risk and the criterion for placental intervention. Adjusted probability curves for deliveries of average gestational age suggested that most patients may not require intervention until approximately 2 h following fetal delivery (Table 6). However, patients with PPROM would require earlier intervention, and those with intrapartum fever or delivery EBL ≥ 500 mL would already exceed the risk threshold at fetal delivery.

Comment

In this study, we aimed to determine the optimal third stage of labor duration in second-trimester deliveries and recommend a time for intervention using estimated probability curves for placental intervention and postpartum complication. We found that spontaneous placental deliveries occurred significantly earlier than deliveries requiring intervention and >40% of interventions were performed without a clinically-urgent indication. Furthermore, postpartum complication was strongly associated with increasing third stage of labor duration, showing 79% increased complication odds per additional hour of undelivered placenta. Our findings highlight the importance of establishing a time-frame for expectant management of the third stage of labor in order to decrease maternal morbidity and instill consistency in provider practice.

Our overall retained placenta rate of 23% was consistent with previous studies [1–3,5,6]. However, Green and colleagues reported a lower rate of retained placenta (6%) among elective second-trimester induction abortions at 18–23 weeks gestation [4]. Previous studies have demonstrated increased retained placenta rates among earlier gestational ages [2,3,5]. Our population included earlier gestational ages (13–26 weeks) with 46% of our patients delivering at a gestational age ≤20 weeks. Therefore, higher rates of retained placenta were expected. Our mean gestational age was significantly lower for women requiring placental intervention compared to women delivering spontaneously. Also in contrast to Green's study, our patient population included deliveries with numerous maternal and fetal indications and excluded solely elective inductions per health system policy. Consequently, patients in the former study likely showed greater propensity for normal placental and fetal pathology than our patients.

Previous studies have recommended various thresholds for intervention of retained placenta, with most studies including only induction abortions. The approaches used to derive these

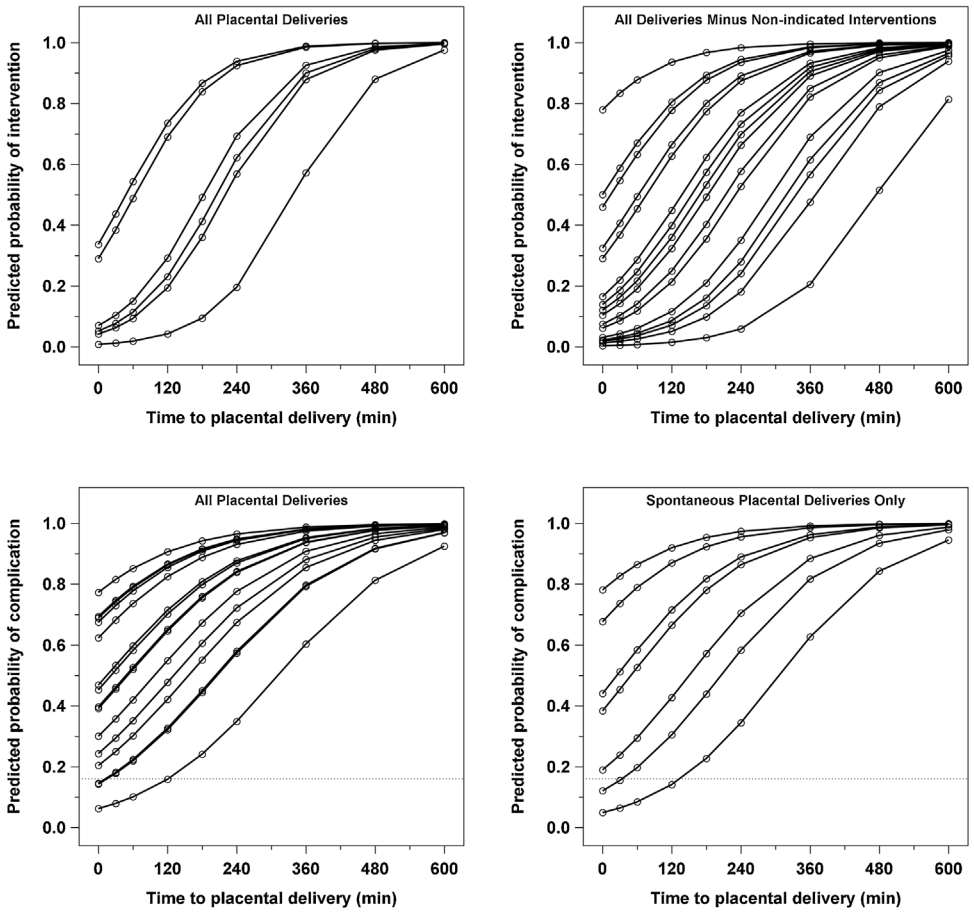

Fig. 2. Predicted probabilities of placental intervention (top graphs) and postpartum complication (bottom graphs) by time to placental delivery.
Description: The multiple probability curves in each graph reflect different combinations of imposed risk, as defined by model predictors. The horizontal reference line in the lower graphs represents the overall postpartum complication rate of 16% for spontaneous deliveries and an upper threshold of tolerable risk.

Table 6
Postpartum complication risk levels for patients with vaginal deliveries of average gestational age (21.6 weeks) and spontaneous placental delivery (N = 166).

Risk level	Patient group characteristics	Percentage of the population	Upper threshold for length of time in expectant management[a]
Lowest	No PPROM, no fever intrapartum, delivery EBL < 500 mL	63.9%	2 hr 15 min
	PPROM present, no fever intrapartum, delivery EBL < 500 mL	17.5%	34 min
	No PPROM, fever present intrapartum, delivery EBL < 500 mL	7.83%	0 min
	PPROM present, fever present intrapartum, delivery EBL < 500 mL	5.42%	0 min
	No PPROM, no fever intrapartum, delivery EBL ≥ 500 mL	2.41%	0 min
	PPROM present, no fever intrapartum, delivery EBL ≥ 500 mL	1.20%	0 min
Highest	No PPROM, fever present intrapartum, delivery EBL ≥ 500 mL	1.81%	0 min

Abbreviations: EBL, estimated blood loss; PPROM, preterm premature rupture of membranes.
[a] Based on the study population's overall postpartum complication rate of 16% for spontaneous deliveries, representing the upper threshold of tolerable risk and the time criterion for placental intervention.

thresholds have also varied. For example, Berger and colleagues compared the complication rate of expectant management (incorporating emergent surgical placental removal) to that of elective immediate placental removal. At 2 h the risk of complication was similar between groups (4.3% vs. 4.0%, respectively) and intervention was recommended without comparison to the overall complication rate [2]. Kirz and Haag found that 64% of placentas delivered spontaneously before or at 30 min, with an overall complication rate of 4.2%, suggesting a 30 min third stage of labor duration [3]. Similar to Berger, Dickinson and colleagues suggested a 2-h threshold for expectant management but based recommendations on the spontaneous placental delivery rate rather than complication rate [5]. Finally, Childress and colleagues included all second-trimester deliveries and recommended a third stage of labor duration <60 min based on a composite endpoint (chorioamnionitis, endometritis or manual/instrumental placenta delivery) [6].

As there is limited evidence to support an acceptable complication rate with expectant management for retained placenta, we chose to use our overall complication rate for spontaneous placental deliveries only (16%) as an acceptable threshold for postpartum complication. This population is at lowest risk for complication and is not impacted by a provider's clinical decision to intervene. Therefore, it seems prudent to consider placental intervention when the complication rate reaches this threshold of 16%. Our complication rate is higher

than previously reported and was primarily driven by hemorrhage. Other studies of retained placenta have also identified hemorrhage as the most common postpartum complication. Our higher complication rate may be reflective of the maternal and delivery characteristics of our population and inclusivity of our definition of hemorrhage [2,3].

To our knowledge, previous studies have not evaluated the indication for placental intervention. Our study identified that >40% of interventions were performed without a clinically-urgent indication, other than the perception of prolonged third stage of labor. The timing of non-indicated interventions ranged from 24 min to 17 h, likely reflecting the diversity in provider practices and validating the need for a standardized definition of retained placenta. Despite a wide variation in time to intervention, we observed no difference in overall complication rates between indicated and non-indicated placental interventions (61% and 62%, respectively). However, the probability of complication increased nearly threefold across 10 h for non-indicated interventions, while remaining stable for indicated interventions. Potentially, continued expectant management in non-indicated interventions may be associated with increasing complication risk.

Our study has both strengths and limitations. Most notably, our study may be more generalizable and relevant to the general obstetrician who encounters diverse presentations and indications for second-trimester deliveries. Previous studies have largely focused on elective second-trimester induced abortions, which may not include other emergent indications. Moreover, our study included all gestational ages between 13–26 weeks, while previous studies focused on various ranges within the second-trimester. Our study was principally limited by its retrospective design, wherein indication for and timing of intervention were uncontrolled. Medication regimens used for labor induction and postpartum management were also uncontrolled, heterogeneous, and difficult to incorporate into our analysis.

As placental interventions are frequently performed without clinically-urgent indications and complication risk increases significantly per hour of undelivered placenta, standard guidelines are needed for determining the appropriateness and timing of intervention. Using our overall complication rate for spontaneous placental deliveries as an acceptable complication threshold, our study suggests that an optimal third stage of labor duration of approximately 2 h maximizes the probability of spontaneous placental delivery and minimizes the risk of complication for most patients. However, the timing of intervention may also need to be individualized based on maternal characteristics and intrapartum conditions. Randomized controlled trials are needed to (1) evaluate the risks associated with a range (e.g., 30 min, 1 h, etc.) of planned intervention times, (2) further assess the impact of maternal risk factors and delivery characteristics on complications associated with retained placenta, (3) examine the influence of medications on the third stage of labor, and (4) confirm or refute our recommended 2-hour duration for the third stage of labor as a standard definition for retained placenta in the second-trimester.

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Conflict of interest statement

The authors report no conflict of interest.

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