BMC Medical Ethics

https://doi.org/10.1186/s12910-026-01549-6

Article in Press

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Received: 15 August 2025

Accepted: 23 June 2026

Published online: 23 July 2026

Cite this article as: Kihumuro R.B., Zhang C., Zaigham M. *et al.* Quality of informed consent for research participation obtained during labor versus mid-pregnancy in Uganda. *BMC Med Ethics* (2026). https://doi.org/10.1186/s12910-026-01549-6

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Title: Quality of informed consent for research participation obtained during labor versus mid-pregnancy in Uganda

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Abstract

Background: Obtaining high-quality informed consent for research is an ethical imperative and crucial for protecting participants' rights. For vulnerable populations, including pregnant women, this concern becomes even more paramount. We evaluated the quality of informed consent for research participation obtained at different times during pregnancy in Uganda.

Methods: This study was a nested prospective observational birth cohort study within the Placentas, Antibodies, and Child Outcomes (PACO) birth cohort. A total of 216 pregnant women were enrolled either during the second trimester (gestational weeks 16-24) or during labor at Mbarara Regional Referral Hospital and Kabwohe Clinical Research Centre in Uganda. The primary outcomes were objective (Quality of Informed Consent [QuIC]-A) and subjective (QuIC-B) informed consent scores. At the time of consent, we also assessed anxiety (Spielberger State-Trait Anxiety Inventory), pain (Wong-Baker Faces scale), and trust in medical researchers (Medical Researcher Trust scale, see Appendices for tools). We performed multivariable linear regression analyses to examine the association between consent timing and objective and subjective quality of informed consent for research participation.

Results: Of 216 participants, 134 (62%) were enrolled during mid-pregnancy and 82 (38%) during early active labor. Consent obtained during labor was associated with significantly lower objective (mean difference -12.9; 95% CI -18.3 to -7.4; $p<0.001$) and subjective (mean difference -10.1; 95% CI -18.3 to -2.0; $p=0.02$) informed consent scores compared to consent obtained mid-pregnancy. Higher anxiety score was significantly associated with lower objective ($p=0.009$) and subjective ($p=0.001$) consent scores. Both pain and trust in medical researchers were not associated with subjective or objective consent quality.

Conclusions: The quality of informed consent obtained during labor was significantly lower than consent obtained during mid-pregnancy, highlighting the need for strategies to optimize informed consent timing and processes.

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Keywords: Quality of Informed consent, Pregnancy, sub-Saharan Africa, Anxiety, Pain, Mbarara, Labor

Introduction

Informed consent is essential for participation in clinical research. High-quality informed consent ensures that participants understand the study's purpose, procedures, risks, and benefits before agreeing to participate(1,2). While the Declaration of Helsinki provides a structure and framework for informed consent, obtaining high-quality consent for research, particularly in low-resource settings and with vulnerable populations like pregnant women, can be challenging(3–5).

Historically, the desire to protect pregnant women and fetuses led to the exclusion of pregnant women from some types of clinical research, limiting their access to new medical advances(6). However, pregnant women need to be included in clinical research studies to advance both pregnancy-specific care and pre-existing conditions that continue during pregnancy. Informed consent for research participation should be obtained under conditions that optimize comprehension and voluntariness and minimize stress and external pressures.

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Pregnancy is associated with physiological and psychological changes, including periods of stress, anxiety and pain (7–9) that may compromise the quality of informed consent, especially if consent is obtained emergently or during stressful times, such as labor (10). In recognition of such challenges, deferred or two-stage consent processes have been developed which may be used in emergency settings such as intrapartum care, to balance the need for timely enrollment with ethical standards for participant understanding and autonomy(11). Two-stage consent includes obtaining provisional consent during an acute phase, followed by confirmation of participation or withdrawal of consent once the participant has recovered from the emergency(11). However, there is little published research on two-stage consent during labor. Understanding how consent timing affects the quality of informed consent during research participation is critical to ensure development of optimal methods for recruiting pregnant or laboring women.

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Despite the importance of ensuring high-quality informed consent for research participation, there is a dearth of research on the optimal timing of informed consent in pregnancy, with published studies presenting conflicting evidence on the optimal timing and methods for obtaining consent. Some studies from high-income settings suggest that pre-labor consent for research participation may lead to better understanding and voluntariness than consent during labor (12,13), but a recent review did not reach a consensus on the optimal timing of consent for research in pregnancy (14). There is a knowledge gap around consent quality and timing for research participation in pregnancy which is even greater in low-resource settings, including sub-Saharan Africa (sSA). The lack of empirical data highlights the need for investigation into the quality of informed consent obtained during different timing and settings during pregnancy, accounting for context and timing. This information is needed to optimize consent processes to be highly effective and meet strict ethical standards. Beyond meeting ethical standards, understanding these factors is essential for ensuring a person-centered approach to biomedical research during pregnancy and for supporting autonomous decision-making among potentially vulnerable participants. To address the gap in knowledge around the ideal timing of informed consent for research participation in pregnancy, we conducted a nested prospective study within the Placentas, Antibodies, and Child Outcomes (PACO) observational birth cohort study in Uganda to compare the quality of informed consent obtained during labor versus mid-pregnancy and to identify factors influencing the quality of consent obtained at each time point.

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Methods

Study design, area, and population

This was nested prospective observational sub-study conducted among 216 participants enrolled consecutively within the PACO study, a longitudinal birth cohort of 618 mother-baby dyads designed to evaluate the impact of HIV and antiretroviral medications on the placenta and child health outcomes. The nested sub-study enrolled participants from September 2021 to November 2023. Participants were pregnant women delivering at Mbarara Regional Referral Hospital (MRRH) or Kabwohe Clinical

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Research Centre (KCRC) in Uganda and aged at least 18 years. MRRH is a high-volume tertiary hospital and KCRC is a nearby local clinical research facility serving a largely rural population. All pregnant women presenting to MRRH for delivery, receiving antenatal care at the MRRH Maternal Child Health clinic, or receiving PrEP or HIV care at KCRC were screened for participation and were eligible if they spoke English or Runyankole (the local language) and were available by telephone for post-discharge contact. All pregnant women with HIV who reported taking antiretroviral therapy (ART) within the last 30 days and those taking pre-exposure prophylaxis to prevent HIV infection (PrEP) during pregnancy were enrolled, and the very next HIV-negative pregnant person was enrolled after each pregnant person taking PrEP or living with HIV. We adopted this recruitment approach from the parent PACO study, which was set up to compare placental and child health outcomes in women with different HIV and antiretroviral exposures.

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Informed consent process

In this sub-study, we assessed the quality of informed consent that participants gave to enroll in the parent PACO birth cohort study. There was no separate consent form for this nested quality-of-consent analysis; rather, the PACO parent study consent form was amended to incorporate the sub-study, and that amended consent form, was used for all participants enrolled from September 2021 through November 2023. Pregnant women were enrolled in either the 2nd trimester of pregnancy (gestational weeks 16 – 24) as part of a sub-study of how angiogenic factor levels changed across pregnancy trimesters, or during labor. The informed consent process for both the 2nd trimester and labor-enrolled participants was the same, except that 2nd trimester participants were recruited from outpatient or antenatal clinics, and laboring participants were recruited from the labor and delivery ward. Participants enrolled during labor were in the early active phase of labor. Prior to enrolling, the potential participant was asked to contact their partner/father of their child to discuss their potential enrollment. Potential participants were encouraged to request the support of the partner/father of the child, but it was not a requirement to enroll. PACO study nurses reassured participants during consenting that the decision to participate was completely voluntary, and

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there would be no negative consequences for the pregnant person's clinical care for non-participation. Participants were also reminded that they could refuse collection of any sample, at any time, for any reason (except for placental/umbilical cord samples) and still participate in the parent study. Study questionnaires were administered in a private, quiet room away from the clinical care area. Participants were reminded that the study was independent of their clinical care, that their answers would remain confidential, that their responses would not affect the care they received, and that there were no right or wrong answers. Study nurses were trained to administer tools neutrally and had received training in Good Clinical Practice (GCP) and Human Subjects Protection (HSP). For those enrolled in labor, after study eligibility was confirmed, a research nurse approached the potential participant during early-stage labor, in times of least distress, to provide them verbal and written information on the study and request their consent to enroll. All potential participants were allowed at least 24 hours to decide whether or not to enroll in the study, although they were no longer eligible for enrollment after they had delivered their placenta. Written informed consent was then obtained by a study nurse midwife in a private, quiet space from all participants. A witness was present to document the participant's consent for those who did not read or write.

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Inclusion and exclusion criteria

Exclusion criteria for the PACO parent study included multiple gestation pregnancy and inability to collect the participant's placenta. People living with HIV but not taking ART within the last 30 days were also excluded. The PACO study began enrolling in December 2019. The nested cohort study on informed consent was a pre-specified study objective that was launched in September 2021 after 402 PACO parent study participants had already been enrolled. All 216 participants who consented to participate in the PACO study from September 2021 to the end of PACO study enrollment in November 2023 were included in the nested cohort and this analysis.

Study variables

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Primary outcomes: Objective and subjective quality of informed consent, measured respectively by the Quality of Informed Consent (QuIC-A) and QuIC-B instruments. These were treated as independent outcomes, not a composite outcome.

Primary predictor (independent variable): Timing of informed consent (mid-pregnancy vs. labor).

Secondary predictors: Anxiety (Spielberger State-Trait Anxiety Inventory [STAI]), pain (Wong-Baker Faces Pain Scale), and trust in medical researchers (Medical Researcher Trust Scale [MRT]). Demographic and clinical factors were also considered, including maternal age, parity, marital status, education level, socioeconomic status, and HIV serostatus.

Sample size estimation

The PACO cohort enrolled 618 participants, and the sample size was calculated to achieve the power needed to determine differences in histologic placental findings by maternal HIV serostatus. For this nested informed consent sub-study, no power or sample size calculation was performed due to inadequate published literature on what difference in the outcomes (QuIC-A and QuIC-B) would be meaningful. All participants enrolled in the PACO parent study after the sub-study on informed consent was approved by the institutional review boards were included in the sub-study.

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Study procedures

After written informed consent was obtained, PACO study nurse midwives administered four standardized questionnaires to each participant: 1) the Quality of Informed Consent (QuIC) parts A ["objective"] and B ["subjective"], 2) the Medical Researcher Trust scale, 3) Wong-Baker Faces pain scale, and 4) the Spielberger State-Trait Anxiety Inventory(15–17). We also collected demographic and medical data on maternal age, parity, marital status, district of residence, level of education, asset index as a measure of socioeconomic status, antenatal care, household income, and maternal HIV serostatus. The asset index variable was calculated using an internal principal components analysis of household assets

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and ownership of durable goods, with the resulting index categorized into quartiles (“richest”, “richer”, “poorer”, “poorest”, according to the original category descriptions) representing socioeconomic levels(18).

For participants enrolled in the second trimester, we reminded them to attend antenatal care visits through regular phone calls throughout pregnancy. We also provided antenatal care services as part of the study, if the participant had not already received the eight antenatal care visits recommended by the World Health Organization and wished to have one or more antenatal visits with our team.

The Quality of Informed Consent (QuIC) questionnaire

We used the QuIC questionnaire, parts A and B, to measure the quality of informed consent in our cohort. QuIC-A is a 15-item questionnaire evaluating a participant's “objective” understanding of their research participation, including the contents of the informed consent document, the study purpose, risks/benefits, and data privacy (15). For each question, participants were asked to respond with "Agree," "Disagree," or "Unsure," and points were assigned for correct (100 points), incorrect (0 points) or unsure (50 points) responses. As designed in the original QuIC instrument, scoring for some questions is reversed to minimize agreement bias, with nine questions phrased positively (where “Agree” was the correct answer), and five phrased negatively (where “Disagree” was the correct answer). QuIC-B is a 13-item questionnaire evaluating a participant’s “subjective” understanding of their research participation, including participants' perception of how well they understood of the nature and purpose of the research, study procedures, the voluntary nature of participation, anticipated risks and discomforts, benefits to themselves and future patients, alternatives to participation, privacy and confidentiality measures, compensation for research-related injury, contacts for concerns, and their rights and welfare. For each question, participants were asked to respond with “Did not understand at all” (assigned 0 points), “Understood very little” (assigned 25 points), “Understood somewhat” (50 points), “Understood most” (75 points) or “Understood completely” (100 points). The sub-scale scores were averaged separately for

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QuIC-A and QuIC-B on a 100-point scale, where higher scores indicated greater objective (QuIC-A) and subjective (QuIC-B) understanding. For our observational study, we adapted QuIC-A and -B questions from their original format designed to assess understanding of clinical trial participation. For QuIC-A our adaptation included dropping questions 4, 5, 6, 7, and 18 from the original questionnaire due to limited relevance to our study design and setting. We then modified the wording of 12 of the remaining 15 questions to reflect our study design, changing “clinical trial” to “clinical research” or “study” and replacing references to “cancer” to “pregnancy” or “delivery” (see Appendices). For QuIC-B, we dropped, Question 7 (“Who will pay for treatment if you are injured or become ill because of participation in this clinical trial”). Of the remaining 13 questions retained in our final version, we modified the language of 9 questions to reflect our study design, changing “clinical trial” to “clinical research” or “study (see Appendices). To minimize bias, the study nurse midwife who administered the QuIC questionnaires was different from the study nurse midwife who performed the informed consent procedure.

Medical Researcher Trust Scale (MRT)

The MRT(16) was designed to assess participant trust in medical researchers. This four-item questionnaire evaluates trust across different domains, including researcher motivations, patient communication, and the treatment of research participants. Participants responded to each item on a 5-point Likert scale, ranging from "Strongly disagree" (1 point) to "Strongly agree" (5 points). The four items are: 1) "Doctors who do medical research care only about what is best for each patient," 2) "Doctors tell their patients everything they need to know about being in a research study," 3) "Medical researchers treat people like ʿguinea pigs'," and 4) "I completely trust doctors who do medical research." To minimize agreement bias, item 3, was reverse-scored. The total MRT score was calculated by summing the values of all responses for a score range of 4 – 20, with higher scores indicating greater trust in medical researchers.

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The Spielberger State-Trait Anxiety Scale

The Spielberger State-Trait Anxiety (STAI) scale was used to assess participant anxiety. The STAI includes six items designed to evaluate participant emotional states. Participants were asked to rate how they felt “right now, at this moment” for each of six feelings: "I feel calm," "I feel tense," "I feel upset," "I feel relaxed," "I feel content," and "I feel worried." Responses were recorded on a four-point scale ranging from “not at all” (4 points) to “very much so” (1 point) with feelings “I feel tense," "I feel upset," and "I feel worried," reverse-scored. STAI values were summed for a total score between 6 – 24, where higher scores indicated higher anxiety levels.

The *Wong-Baker Faces Pain Scale*

The Wong-Baker Faces pain scale presents six facial expressions ranging from a happy face “no pain” to a crying face “severe pain” and was utilized to assess participant pain/discomfort levels. Although the scale consists of six illustrated faces, it is mapped onto a 0-10 numerical pain scale by assigning evenly spaced values. The first face, depicting a smiling expression “no pain” is assigned 0 points, while the last face, showing a crying face “worst pain possible” is assigned 10 points. Intermediate faces are assigned values at two-point intervals: a slight frown “mild pain” (2 points), a neutral expression “moderate pain” (4 points), a slight grimace “more pain” (6 points), and a frowning face “severe pain” (8 points). Participants were asked to select a face that best corresponded with their current pain level (see Appendices).

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Statistical analysis

Data were entered into a Research Electronic Capture (REDCap)(19) and analyzed using STATA version 16 and R version 4.3.1(20). We summarized the data using descriptive statistics, including mean and standard deviation (SD) for normally-distributed variables, median and interquartile range (IQR) for non-parametric data, and frequencies and proportions for categorical data. Our primary outcome measures

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were QuIC-A and QuIC-B scores, and our primary exposure variable was the timing of consent. We performed bivariate analyses using chi-square and t-tests and to assess associations between exposures and outcomes. We created separate multivariable linear regression models for QuIC-A and QuIC-B scores, adjusting for the MRT, STAI, pain scores, all exposure variables screened against the outcome with a *p*-value < 0.2 in bivariate analysis, and variables identified from previous studies as potential confounders influencing informed consent quality(6,10,21–26). In adjusted analyses, we considered all variables with *p*-values < 0.05 as statistically significant predictors. We also performed sensitivity analyses excluding QuIC-A Questions 4 and 8 because they did not adapt well to our observational study design. Question 4 "The monitoring I received is standard for women (receiving 2nd trimester antenatal care) or (who have undergone delivery)" posed challenges in defining what constituted "standard" monitoring. Similarly, Question 8 "Compared with standard ways of monitoring and treating women who are delivering their baby, my clinical research study does not carry any additional risks or discomforts" did not adapt well to our study based on an unclear definition of 'standard ways'. We also conducted a sensitivity analysis alternating excluding either Question 5 "In my study, one of the researchers' major purposes is to understand changes in the placenta that can affect a woman's baby" or 6 "In my clinical research study, one of the researchers' major purposes is to find out how changes in the placenta affect a woman's baby." due to their conceptual similarity. Our final models excluded Questions 4, 5, and 8. Due to non-normal distribution of the regression residuals for both QuIC-A and QuIC-B outcomes, we also conducted sensitivity analyses using both cubed and square root transformations for each outcome.

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Results

Overall, of 7,914 eligible pregnant women screened, 618 participants were enrolled in the parent PACO study. Participation was declined by approximately 5% of participants enrolled in the 2nd trimester group and 20% of participants enrolled in the labor group. Not all reasons for declining participation were captured, but common reasons included lack of support or agreement from the participant's partner/father of the baby, pain or discomfort at the time of consent, declining placenta collection, or lack of desire to

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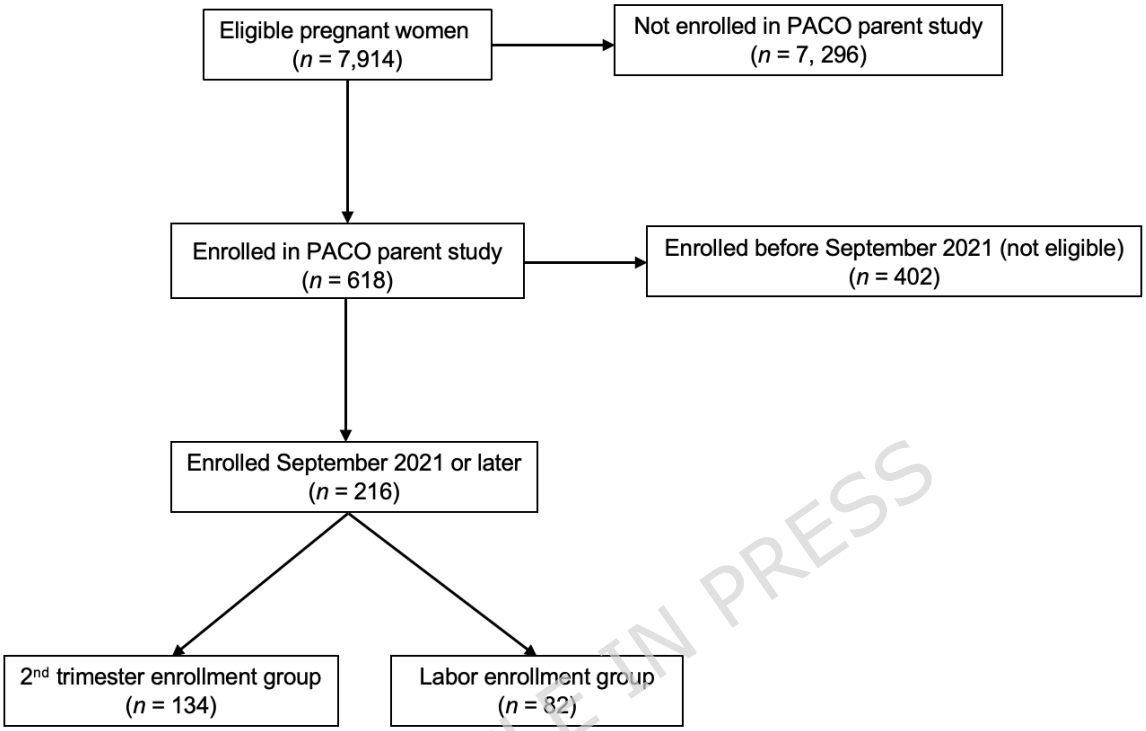
participate in study follow-up. Of these, 82/216 (38%) were consented during labor and 134/216 (62%) during the 2nd trimester of pregnancy (**Figure 1**).

Figure 1: Flow diagram for participant enrollment.



As shown in Table 1, the mean age of all participants was 28 (SD = 6) years, and the group enrolled in labor was overall younger than the 2nd trimester enrollment group (mean 28.7, SD = 6.1 Vs mean 25.9, SD = 4.9, p=0.008). Most (113/216, 52%) participants had completed either no formal education or primary-level education, 94% (201/216) were married, and 88% (189/216) had attended at least four antenatal care visits during this pregnancy. Of those, 92.5% (124/134) in the 2nd trimester group attended 4 or more antenatal care visits, compared to 79.3% (65/82) in the labor group (p=0.008). Approximately 51% (111/216) of participants lived in the urban/semi-urban district of Mbarara. In bivariate analysis, participants enrolled in the 2nd trimester had significantly higher MRT scores (mean 17.4, SD=2.4) compared to those in labor (mean 15.8, SD=2.3, p<0.001). Anxiety levels were significantly lower among participants in the 2nd trimester (mean 0.3, SD=1.2) than those in labor (mean STAI score 6.4, SD=2.9, p<0.001). Similarly, pain levels were significantly lower in the 2nd trimester group (mean 6.9, SD=1.9)

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than the labor group (mean 14.5, SD=4.5, p<0.001). Participants enrolled in the 2nd trimester had significantly higher unadjusted QuIC-A (mean 78.9 vs 70.3, p< 0.001) and QuIC-B (mean 85.5 vs 67.3, p< 0.001) scores than those enrolled in labor (Table 1). Overall, there was a significant but modest positive association between QuIC-A and QuIC-B scores using Spearman's rank correlation (correlation coefficient = 0.30, p<0.001).

Table 1. Participant characteristics by pregnancy phase at consent, shown as median (IQR) or percentages.

Variable	**Timing of consent**		**P-value**
	2nd Trimester n = 134 n (%)	**Labor n = 82 n (%)**	
Age category, in years			**0.009**
<25	34 (25.4)	36 (43.9)	
25 – 29	51 (38.1)	30 (36.6)	
30 – 35	28 (20.9)	12 (14.6)	
>35	21 (15.7)	4 (4.9)	
Education level			0.91
No school/Primary	71 (53.0)	42 (51.2)	
Secondary or greater	63 (47.0)	40 (48.8)	
Residence location			0.58
Mbarara (urban/semi-urban)	67 (50.0)	37 (45.1)	
Rural	67 (50.0)	45 (54.9)	
Monthly income (USD $)	51.4 (28.6 to 85.7)	42.9 (20.0 to 71.4)	0.43
Marital status			0.74
Married	127 (94.8)	76 (92.7)	
Not-married	7 (5.2)	6 (7.3)	
Antenatal care attendance (≥4 visits)	124 (92.5)	65 (79.3)	**0.008**
Parity	3.0 (2.0 - 4.0)	2.0 (1.0 - 3.0)	0.13
HIV seropositive	47 (35.1)	23 (28.0)	0.36
Formally employed outside the home	68 (50.7)	32 (39.0)	0.09
Asset Index Quartile			**0.002**
Poorest	16 (11.9)	27 (32.9)	
Poorer	34 (25.4)	17 (20.7)	
Richer	42 (31.3)	23 (28.0)	
Richest	42 (31.3)	15 (18.3)	
MRT score	17.0 (16.0 - 20.0)	16.0 (15.0 - 17.0)	**<0.001**
STAI score	0.0 (0.0 - 0.0)	7.0 (4.0 - 9.0)	**<0.001**
Pain score	6.0 (6.0 - 7.0)	13.0 (11.0 -17.8)	**<0.001**
QuIC-A score	83.3 (79.2 - 91.7)	70.8 (62.5 - 82.3)	**<0.001**
QuIC-B score	86.5 (78.8 - 94.2)	69.2 (55.8 - 82.7)	**<0.001**

QuIC-A stands for Quality of Informed Consent Part A ("objective"), while QuIC-B is Part B ("subjective"). MRT stands for the Medical Researcher Trust scale, and STAI for the Spielberger State-Trait Anxiety Inventory.

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In our multivariable model to determine the association between research consent timing and QuIC-A (objective consent quality) score (Table 2), we adjusted for age, education level, residence, parity, antenatal care attendance, HIV serostatus, asset index quartile, MRT score, STAI score, and pain level. In this model, participants who consented during labor had average QuIC-A scores 12.9 points (95% CI: -18.3, -7.4, p<0.001) lower than those consented in the 2nd trimester. Being in the "richer" asset index quartile was also associated with an average QuIC-A score 4.6 (95% CI: –9.1, –0.2, p=0.04) points lower than the "poorest" asset index quartile, with no significant differences in the other two asset index quartiles. Additionally, higher STAI scores were associated with lower QuIC-A scores, with each one-point increase in STAI corresponding to a 0.62-point decrease in QuIC-A (95% CI: -1.1, -0.2, p=0.009, Table 2).

Table 2: Factors associated with objective understanding of informed consent (QuIC-A).

Variable	Mean (SD)	Coefficient (95% CI) (Unadjusted)	P-value	Coefficient 95% CI) (Adjusted)	P-value
Consent timing					
2nd trimester	84.4 (7.8)	-	-	-	-
Labor	70.4 (13.7)	-13.96 (-16.85 to -11.07)	p<0.001	-12.85 (-18.33 to -7.37)	**p<0.001**
Age (continuous) in Years	79.1 (12.4)	0.18 (-0.10 to 0.47)	p=0.21	0.02 (-0.34 to 0.39)	p=0.90
Education level					
No school/primary	77.9 (12.6)	-	-	-	-
Secondary/tertiary	80.4 (12.2)	2.45 (-0.89 to 5.79)	p=0.15	2.34 (-0.91 to 5.58)	p=0.16
Residence location					
Rural	78.4 (12.5)	-	-	-	-
Mbarara (urban/semi-urban)	79.7 (12.4)	1.20 (-2.15 to 4.55)	p=0.48	1.33 (-1.83 to 4.49)	p=0.41
Parity	79.1 (12.4)	-0.15 (-1.14 to 0.84)	p=0.76	-0.43 (-1.65 to 0.79)	p=0.49
Antenatal care					
4 or more	79.5 (12.1)	-		-	-
Less than 4	76.0 (14.3)	-3.49 (-8.61 to 1.63)	p=0.18	0.11 (-4.41 to 4.63)	p=0.96
HIV serostatus					
HIV negative	78.8 (12.3)	-		-	-
HIV positive	79.6 (12.8)	0.78 (-2.81 to 4.37)	p=0.67	0.48 (-2.71 to 3.66)	p=0.77
Formal employment Status					
No	78.0 (13.5)	-	-	-	-
Yes	80.3 (11.0)	2.22 (-1.13 to 5.57)	p=0.19	-	-
Asset index quartile					
Poorest	76.1 (14.5)	-	-	-	-

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Poorer	80.6 (12.0)	4.57 (-0.43 to 9.57)	p=0.07	-0.83 (-5.51 to 3.86)	p=0.73
Richer	76.9 (12.4)	0.84 (-3.92 to 5.60)	p=0.73	-4.63 (-9.09 to -0.17)	**p=0.04**
Richest	82.4 (10.3)	6.32 (1.44 to 11.20)	p=0.01	-1.16 (-6.08 to 3.77)	p=0.64
Marital status					
Married	79.2 (12.2)	-	-	-	-
Not married	76.9 (16.5)	-2.29 (-9.32 to 4.74)	p=0.52	-	-
MRT score	79.1 (12.4)	0.80 (0.13 to 1.48)	p=0.02	-0.07 (-0.68 to 0.53)	p=0.82
STAI score	79.1 (12.4)	-1.30 (-1.61 to -0.99)	p<0.001	-0.62 (-1.09 to -0.15)	**p=0.009**
Pain score	79.1 (12.4)	-1.52 (-1.96 to -1.09)	p<0.001	0.46 (-0.28 to 1.191)	p=0.22

QuIC-A stands for Quality of Informed Consent Part A ("objective"), while QuIC-B is Part B ("subjective"). MRT stands for the Medical Researcher Trust scale, and STAI for the Spielberger State-Trait Anxiety Inventory.

In our multivariable model to determine the association between research consent timing and QuIC-B (subjective consent quality) score (Table 4), we adjusted for age, education level, residence, parity, HIV serostatus, antenatal care, asset index quartile, MRT score, STAI score, and pain level. In this model, participants who consented during labor had average QuIC-B scores 10.1 (95% CI: -18.3 to -2.0, p=0.02) points lower than those consented in the 2nd trimester. Higher STAI score was associated with lower QuIC-B scores, with each 1-point increase in STAI corresponding to a 1.2-point decrease in QuIC-B (95% CI: –1.0 to –0.5, p=0.001). MRT score, level of education, and location of residence were not associated with QuIC-B score in this model (Table 3).

Table 3: Factors associated with subjective understanding of informed consent (QuIC-B)

Variable	**Mean (SD)**	**Coefficient (95% CI) (Unadjusted)**	**P-value**	**Coefficient 95% CI) (Adjusted)**	**P-value**
Consent timing					
2nd Trimester	85.8 (10.2)	-		-	-
Labor	67.7 (22.3)	-18.05 (-22.46 to -13.64)	p<0.001	-10.13 (-18.30 to -1.96)	**p=0.02**
Age (continuous)	78.9 (18.2)	0.65 (0.24 to 1.06)	p=0.002	0.05 (-0.50 to 0.60)	p=0.86
Education level					
No School/Primary	78.2 (20.0)	-		-	-
Secondary/Tertiary	79.6 (16.0)	1.42 (-3.48 to 6.32)	p=0.568	3.60 (-1.28 to 8.48)	p=0.15
Residence location					
Rural	80.7 (17.2)	-		-	-
Mbarara (urban/semi-urban)	77.2 (18.9)	-3.57 (-8.44 to 1.31)	p=0.151	-2.14 (-6.89 to 2.62)	p=0.38
Parity	78.9 (18.2)	1.66 (0.24 to 3.09)	p=0.022	0.95 (-0.89 to 2.79)	p=0.31
Antenatal care					
4 or more	79.3 (17.5)	-		-	-
Less than 4	76.1 (22.9)	-3.14 (-10.64 to 4.35)	p=0.409	-	-

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HIV serostatus					
HIV negative	77.6 (18.6)	-		-	-
HIV positive	81.6 (17.1)	4.02 (-1.19 to 9.24)	p=0.130	1.66 (-3.13 to 6.45)	p=0.50
Formal employment Status					
No	77.2 (20.2)	-	-	-	-
Yes	80.8 (15.3)	3.65 (-1.23 to 8.53)	p=0.142	-	-
Asset index quartile					
Poorer	74.2 (18.7)	-		-	-
Poorest	80.1 (17.3)	5.93 (-1.45 to 13.31)	p=0.114	0.35 (-6.51 to 7.21)	p=0.92
Richer	78.2 (20.8)	4.02 (-3.01 to 11.05)	p=0.261	-1.66 (-8.22 to 4.91)	p=0.62
Richest	82.0 (14.6)	7.82 (0.62 to 15.02)	p=0.033	-0.38 (-7.69 to 6.93)	p=0.92
Marital status					
Married	78.8 (18.4)	-	-	-	-
Not-married	79.6 (14.0)	0.76 (-9.51 to 11.03)	p=0.884	-	-
MRT score	78.9 (18.2)	1.91 (0.95 to 2.87)	p<0.001	0.75 (-0.16 to 1.66)	p=0.10
STAI score	78.9 (18.2)	-1.92 (-2.37 to -1.47)	p<0.001	-1.18 (-1.88 to -0.48)	**P=0.001**
Pain score	78.9 (18.2)	-2.16 (-2.80 to -1.52)	p<0.001	0.40 (-0.71 to 1.50)	p=0.48

QuIC-A stands for Quality of Informed Consent Part A ("objective"), while QuIC-B is Part B ("subjective"). MRT stands for the Medical Researcher Trust scale, and STAI for the Spielberger State-Trait Anxiety Inventory.

The results of our sensitivity analyses using the cubic and square root transformations of the QuIC-A and QuIC-B outcomes were similar to our primary analysis results (see Appendices).

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Discussion

In a population of pregnant women living in semi-rural Uganda, the quality of informed consent for research participation was significantly higher when obtained during the 2nd trimester of pregnancy than during labor. Both “objective” (QuIC-A) and “subjective” (QuIC-B) measures of informed consent were lower in labor than in the 2nd trimester, and the relationship was stable after adjusting for potential confounders of this relationship. In our multivariable models, higher anxiety levels at the time of consent were associated with lower QuIC-A and QuIC-B scores, while higher asset index (wealth) and lower pain levels were associated with significantly lower QuIC-A scores.

Historically, many intrapartum research trials have excluded women in labor due to concerns that pain and anxiety limit the potential for fully informed research participation(27). In our study, we observed higher-quality informed consent in participants enrolled in the second trimester than in labor, consistent

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with other studies that found that labor negatively impacted the informed consent process(28,29). Lower scores for consent quality among laboring participants may reflect heightened stress and discomfort during labor. However, our findings persisted even after adjusting for self-reported pain and anxiety. This suggests that other unmeasured factors inherent to labor, such as cognitive overload, time constraints, or perceived urgency, may impair optimal engagement in the consent process. In other studies, obtaining informed consent during labor was impacted by physiological and psychological stressors not measured in our study, including fatigue and hormonal fluctuations, which may impair participants' capacity to process information and decrease the quality of informed consent(6,10,21–26). Some studies carried out in high-income settings report a participant preference for prenatal research recruitment over recruitment during labor, which may be related to some of these factors, as well as lower pain, stress, and anxiety(12,13). Because of the heightened stress experienced by laboring women, some studies have also raised concerns about high uptake of research participation in labor, noting that labor may increase the risk of coercion or perceived coercion (30,31).

The mean adjusted QuIC-A score in the laboring group was approximately 13 points lower than the 2nd trimester group, and the mean adjusted QuIC-B score in the laboring group was approximately 10 points lower than the 2nd trimester group. Although there is no established formal threshold for clinically meaningful differences in QuIC score between groups(15,32,33), some studies have considered 8- or 10-point differences as meaningful when evaluating interventions to improve informed consent(32,33). In our study, both QuIC-A and QuIC-B scores were >10 points lower in the labor group, which suggests that participants enrolled in the 2nd trimester of pregnancy likely had a clinically meaningful greater objective and subjective understanding of the study. However, given the logistical complexity and resource demands of enrolling participants early in pregnancy and retaining participants through labor and delivery, research programs must weigh the potential modest yet potentially meaningful improvements in consent quality through consent in 2nd trimester of pregnancy against the challenges of cohort retention and resource demands. The absence of clear benchmarks for clinically meaningful differences in QuIC

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scores between groups highlights the need for future studies to help contextualize what score differences are truly impactful for informed decision-making and research participation.

In our study, higher anxiety level, as measured by the STAI, was associated with lower "objective" QuIC-A, and "subjective" QuIC-B scores. This association suggests that anxiety is an independent risk factor impeding the participant comprehension of the research and subjective feeling of being informed. To date, very little has been published on the influence of anxiety on the quality of informed consent for research studies obtained in pregnancy. However, studies in non-pregnant populations have documented that high anxiety levels interfere with comprehension and retention of detailed information and diminish willingness to participate in studies(34–39). In contrast, some studies in clinical care settings have shown that individuals with high anxiety levels still expressed a desire to engage in research despite their difficulties in processing information(34,38,39). This apparent contradiction could reflect differences in perceived benefits in clinical settings – where informed consent is a gateway to accessing care – versus observational research settings, where there is no direct benefit to participants. In both settings, anxiety levels may also be influenced by the amount of information provided by the person obtaining consent.

Medical researcher trust (MRT) and pain scores were not significantly associated with QuIC-A and QuIC-B scores after adjusting for other variables. Trust in medical professionals is considered crucial for fostering open communication and facilitating informed decision-making(40), and prior studies have found that high trust in medical researchers was consistently associated with higher quality informed consent. In some parts of sSA, medical care has been characterized as paternalistic,(41) which may diminish the role of personal trust in the consent process, as participants may follow healthcare providers' recommendations regardless of how much trust they personally feel. However, the lack of association we observed between MRT and QuIC scores suggests that trust may play a different role in higher-stress scenarios like labor(42–44). Furthermore, in our study, we also found that pain was not significantly associated with quality of informed consent, which differs from prior research suggesting that pain impairs cognitive functions essential for informed consent(45–48). This discordant finding may also point

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to a different mechanism for the impact of pain on consent quality in the setting of labor, where pain may heighten awareness or understanding.

Additionally, whereas our study concentrated on individual level factors such as trust, pain and anxiety, previous studies have reported informed consent as also context driven and influenced by the wider political, economic, and social environment in which research takes place. Some studies have shown that decisions about research participation in sub-Saharan Africa often involve family members and partners(49,50). In Uganda and similar sub-Saharan African settings, the organization and financing of maternal health services, the history of biomedical research in the region, gender and household power dynamics, economic precarity, and the local regulatory environment can all influence how pregnant women perceive research and engage with the consent process(50–54). Our study invited women to discuss enrollment with a partner or the father of the child, but we did not systematically record whether these conversations took place.

The strengths of our study include inclusive recruitment of diverse participants, study setting in a low-resource environment where to date there has been little prior empirical data on consent quality, and the use of validated tools to assess informed consent quality, anxiety, pain, and trust. Limitations of our study include the lack of formal validation of the QuIC tool in Uganda, although it has previously been used in Uganda to assess the quality of informed consent(55). In addition, the QuIC tool has been largely used in clinical trial settings, rendering some items less applicable to our observational cohort study. We mitigated this limitation by adapting the original tool to an observational study by rephrasing some questions; however, the adapted items were not formally re-validated or piloted prior to use in this cohort. To partially address this, we performed sensitivity analyses where we removed items that seemed redundant or less applicable to an observational study, demonstrating the robustness of our results to whether these items were included or excluded. The other tools we used to evaluate factors that may influence informed consent quality have been widely used in Uganda but may not be fully adapted to this context and may have impacted our ability to reliably estimate the impact of anxiety, trust, and pain on

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the consent process in this setting. In addition, despite a large sample size, the group consented in labor was relatively small, limiting statistical power to detect more subtle associations. In addition, approximately 20% of participants approached for enrollment during labor and approximately 5% approached during the 2nd trimester of pregnancy declined participation. These individuals may have had higher pain and/or anxiety levels which may have affected the observed associations between pain and anxiety levels and consent quality. Participants who were in late-stage labor were also not eligible for enrollment, limiting the generalizability of our results to that group. The study's cross-sectional assessment of consent quality did not allow us to assess long-term retention of informed consent information over time. Additionally, the quantitative nature of our study doesn't capture pregnant women's own perspectives on the factors that influence the experience and meaning of consent during pregnancy and labor and may also have missed contextual or experiential influences that only emerge through in-depth interviews.

Our findings demonstrate that the timing of informed consent during pregnancy impacts the quality of consent for research participation and highlight a need to optimize consent quality. Where possible, researchers should consider non-labor consent timing or alternative methods for obtaining consent during pregnancy. Such methods could include pre-labor consent, with re-confirmation of interest in research participation in early labor(27). Where consent during labor is the only feasible option, laboring women could also be approached in early labor at times of lower pain and stress to obtain verbal assent or preliminary consent for participation, followed by the full informed consent process after labor is complete. Such a two-stage or deferred consent approach may be lead to higher-quality consent and more informed research participation(11,27). Innovative approaches leveraging more engaging formats to deliver research study information, such as artificial intelligence (AI)-based chatbots,(56) slideshows, and videos(55) have also been leveraged in some studies to enhance the consent process and promote retention of key information and could be explored in addition to other methods of optimizing the consent timing(42–44,57). Regardless of the setting, additional factors should be considered and optimized

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including participant trust, pain, and anxiety levels, and rigorous training and close supervision throughout the informed consent process to improves the quality of consent obtained(58).

Future research should focus on understanding factors affecting consent from the perspective of pregnant women; as well as the quality of informed consent across different populations and contexts, both during and outside of pregnancy including in diverse healthcare environments in high- and low-income settings. Strategies should also be developed to improve the quality and feasibility of performing informed consent earlier in pregnancy. Additionally, it would be valuable to measure the long-term retention of information provided during the informed consent process in longitudinal studies, particularly to assess whether the initial quality of consent impacts long-term trust and engagement in medical research. Finally, improved tools should be developed or adapted to assess consent quality, particularly in low-resource settings.

Conclusion

Our study highlights lower quality of informed consent when performed in labor compared to the 2nd trimester of pregnancy, emphasizing the need for targeted interventions to support informed decision-making during critical moments in research.

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List of abbreviations

ACOG: American College of Obstetricians and Gynecologists

ART: Antiretroviral therapy

HIV: Human immunodeficiency virus

MRRH: Mbarara Regional Referral Hospital

MUST: Mbarara University of Science and Technology

PACO: Placentas, Antibodies, and Child Outcomes

PrEP: Pre-exposure prophylaxis against HIV infection

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QuIC: Quality of Informed Consent

REDCap: Research Electronic Data Capture

STAI: Spielberger State-Trait Anxiety Inventory

MRC score: Medical Researcher Trust score

DECLARATIONS

Ethics approval and consent to participate

The study received ethical approval from the MUST Research Ethics Committee (10/06-19), the Uganda National Council of Science and Technology (HS/2697), and Partners (now Mass General Brigham) IRB (2019P003248). The study was conducted according to ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. No samples or data were collected from prisoners, and all participants provided written informed consent to participate before data collection.

Consent for publication: Not applicable.

Availability of data and materials: The data set used in this manuscript is available upon reasonable request to the corresponding author and execution of a data use and sharing agreement.

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

Funding

This work was supported by a career development award from the National Institute of Allergy and Infectious Diseases [grant number K23AI138856 to LMB], and the Massachusetts General Hospital Center for Global Health Finish Line Grant (to RBK). BG contributed to this work as part of his official duties as an employee of the United States Federal Government. The sponsors had no role in study design, data collection, analysis or interpretation, writing the report, or the decision to submit the article

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for publication. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or Massachusetts General Hospital.

Authors' contributions

RBK, CZ, and LMB analyzed the data, drafted the initial manuscript, and reviewed and edited subsequent. MZ, JEH, AB, ET, SA, BG, FB, JN, and AAB critically reviewed and edited manuscript versions. LMB, AAB, and JN conceptualized the study. LMB and JN supervised data collection and analysis. All authors read and approved of the final manuscript.

Acknowledgements

We are grateful to the PACO study participants and staff for their contributions to this research. We are also grateful to the faculty and staff at Mbarara University of Science and Technology (MUST), Mbarara Regional Referral Hospital, and Kabwohe Clinical Research Centre for their partnership in this research. We also thank Dr. Kathryn Barger for her statistical advice.

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Appendix 1: Medical researcher trust scale

1. Doctors who do medical research care only about what is best for each patient.
    a. Strongly disagree
    b. Disagree
    c. Neither agree nor disagree
    d. Agree
    e. Strongly agree
2. Doctors tell their patients everything they need to know about being in a research study.
    a. Strongly disagree
    b. Disagree
    c. Neither agree nor disagree
    d. Agree
    e. Strongly agree
3. Medical researchers treat people like “guinea pigs”.
    a. Strongly disagree

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b. Disagree

c. Neither agree nor disagree

d. Agree

e. Strongly agree

4. I completely trust doctors who do medical research.

a. Strongly disagree

b. Disagree

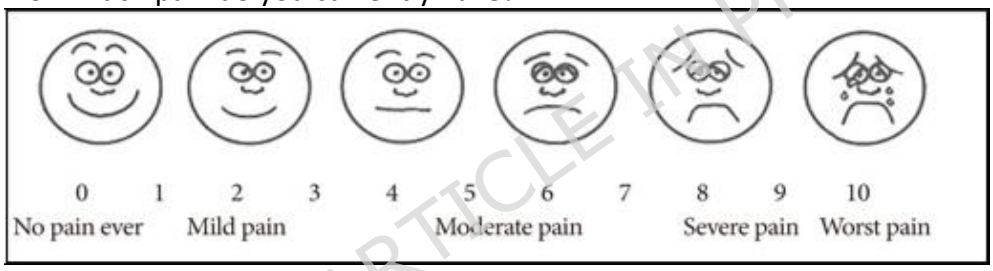
c. Neither agree nor disagree

d. Agree

e. Strongly agree

Appendix 2: Wong-Baker Faces Pain Scale

How much pain do you currently have?



Appendix 3: Spielberger State-Trait Anxiety Inventory

Please indicate how much you agree with each of these statements

- I feel calm
- I am tense
- I feel upset
- I feel relaxed
- I feel content
- I am worried

□ Not at all □ Moderately so

□ Somewhat □ Very much so

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Appendix 4: Modified version of QuIC-A used for this study

QuIC-A questions	
Question1	When I signed the consent form for PACO, I knew I was agreeing to participate in a clinical research study.
Question2	The main reason clinical research studies are done is to improve the treatment of future patients
Question3	I was informed how long I would participate in this research study
Question4	The monitoring I received is standard for women receiving 2nd trimester antenatal care
Question5	In my study, one of the researchers' major purposes is to understand changes in the placenta that can affect a woman's baby
Question6	In my clinical research study, one of the researchers' major purposes is to find out how changes in the placenta affect a woman's baby.
Question7	The questions being researched in my clinical research study have already been answered in other studies
Question8	Compared with standard ways of monitoring and treating women who are delivering their baby, my clinical research study does not carry any additional risks or discomforts
Question9	There may not be direct medical benefit to me from my participation in this clinical research study.
Question10	By participating in this clinical research study, I am helping the researchers learn information that may benefit other women delivering their babies.
Question11	Because I am participating in a clinical research study it is possible that the study sponsor, various government agencies or others who are not directly involved in my care could review my medical records
Question12	My doctors did not offer me any alternatives besides participating in this clinical research study
Question13	The consent form I signed lists the name of the person (or persons) whom I should contact if I have any questions or concerns about the clinical research study
Question14	If I had not wanted to participate in this clinical research study, I could have declined to sign the consent form
Question15	I had to remain in the clinical research study even if I decided I wanted to withdraw.

Appendix 5: Modified version of QuIC-B used for this study

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Please rate your understanding of each of the following aspects of the clinical research study. For each statement, choose one of the following:

- Did not understand at all
- Understood very little
- Understood somewhat
- Understood most
- Understood completely

1. The fact that the participation in the clinical research study is voluntary
2. What the researchers are trying to find out in the clinical research study
3. How long you would be in the clinical research study
4. The procedures you would undergo
5. Which of these procedures are experimental?
6. The possible risks and discomforts of participating in the clinical research study
7. The possible benefits to you of participating in the clinical research study
8. How your participation in this clinical research study may benefit future patients
9. The alternatives to participation in the clinical research study
10. The effect of the clinical research study on the confidentiality of your medical records
11. Whom you should contact if you have questions or concerns about the clinical research study
12. Overall, how well did you understand your clinical research study when you signed the consent form
13. The fact that the measurements and samples you had involve research

Appendix 6: Cubed transformation multivariableanalysis: QuIC A

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Variable	Coefficient (95% CI) (Unadjusted)	P-value	Coefficient 95% CI) (Adjusted)	P-value
Consent timing				
2nd Trimester	-		-	-
Labor	-226230.58 (-275937.86 to -176523.31)	p<0.001	-282202.75 (-381645.86 to -182759.64)	**p<0.001**
Age (continuous)	2418.25 (-2398.66 to 7235.16, p=0.324)	p=0.32	419.20 (-5666.72 to 6505.12)	p=0.89
Education level				
No School/Primary	-		-	-
Secondary/Tertiary	40931.62 (-15317.34 to 97180.57)	p=0.15	52057.73 (-2673.69 to 106789.15)	p=0.06
Residence location				
Rural	-		-	-
Mbarara (urban/semi-urban)	23868.38 (-32536.86 to 80273.62)	p=0.41	8866.74 (-43176.52 to 60909.99)	p=0.74
Parity	-4323.24 (-20974.50 to 12328.02)	p=0.61	-6144.09 (-26614.20 to 14326.02)	p=0.56
Antenatal care				
4 or more	-		-	-
Less than 4	-59707.56 (-144684.19 to 25269.06)	p=0.17	-13006.11 (-87019.74 to 61007.53)	0.73
HIV status				
HIV negative +/- PrEP	-		-	-
HIV positive	5773.99 (-54764.40 to 66312.38)	p=0.85	-22294.80 (-76184.70 to 31595.11)	p=0.42
Employment Status				
No	-	-	-	-
Yes	30139.60 (-26328.18 to 86607.38)	p=0.30	-	-
Asset Index Quartile				
Poorer	-		-	-
Poorest	72602.95 (-11261.93 to 156467.84)	p=0.09	-28566.17 (-106787.14 to 49654.80)	p=0.47
Richer	694.53 (-78511.42 to 79900.48)	p=0.99	-103741.90 (-176897.15 to -30586.65)	**p=0.006**
Richest	108884.07 (27149.23 to 190618.91)	p=0.009	-29378.61 (-110701.59 to 51944.38)	p=0.48
Marital status				
Married	-	-	-	-
Not-married	-18068.86 (-136738.29 to 100600.58)	p=0.76	-	-
MRT score	12049.46 (674.96 to 23423.96)	p<0.03	-4050.71 (-14059.58 to 5958.16)	p=0.43
STAI score	-20452.68 (-25717.51 to -15187.84)	p<0.001	-6580.96 (-14497.33 to 1335.40)	P=0.103
Pain score	-25306.72 (-32605.91 to -18007.53)	p<0.001	12114.83 (-458.54 to 24688.20)	p=0.06

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Appendix 7: Cubed transformation multivariable analysis: QuIC B

Variable	Coefficient (95% CI) (Unadjusted)	P-value	Coefficient 95% CI) (Adjusted)	P-value
Consent timing				
2nd Trimester	-		-	-
Labor	-257328.46 (-326947.85 to -187709.07)	p<0.001	-175016.50 (-317810.48 to -32222.51)	**p=0.017**
Age (continuous)	10355.18 (4068.48 to 16641.88)	p=0.001	1256.06 (-7517.08 to 10029.20)	p=0.79
Education level				
No School/Primary	-		-	-
Secondary/Tertiary	-7673.32 (-83053.19 to 67706.54)	p=0.84	40130.25 (-38651.98 to 118912.49)	p=0.32
Residence location				
Rural	-		-	-
Mbarara (urban/semi-urban)	-57738.33 (-132693.50 to 17216.83)	p=0.13	-43271.01 (-118277.33 to 31735.31)	p=0.26

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Parity	30267.18 (8520.38 to 52013.97)	p=0.007	19841.19 (-9652.53 to 49334.91)	p=0.19
Antenatal care				
4 or more	-		-	-
Less than 4	-35565.80 (-149317.05 to 78185.46)	p=0.54	-	-
HIV status				
HIV negative +/- PrEP	-		-	-
HIV positive	58817.02 (-21548.43 to 139182.46)	p=0.15	-6846.28 (-84520.29 to 70827.74)	p=0.86
Employment Status				
No	-	-	-	-
Yes	39693.47 (-35630.47 to 115017.40)	p=0.30	-	-
Asset Index Quartile				
Poorer	-		-	-
Poorest	83064.23 (-30907.07 to 197035.54)	p=0.15	1056.47 (-109107.29 to 111220.24)	p=0.99
Richer	70191.34 (-37448.53 to 177831.21)	p=0.20	997.97 (-102614.68 to 104610.62)	p=0.99
Richest	118908.20 (7831.60 to 229984.80)	p=0.04	3443.13 (-112082.91 to 118969.17)	p=0.96
Marital status				
Married	-	-	-	-
Not-married	-11391.43 (-169703.47 to 146920.60)	p=0.884	-	-
MRT score	32554.12 (17869.71 to 47238.53)	p<0.001	14460.73 (58.43 to 28863.04)	**p=0.049**
STAI score	-27071.60 (-34192.43 to -19950.77)	p<0.001	-15930.50 (-27331.07 to -4529.94)	**P=0.006**
Pain score	-30704.41 (-40793.42 to -20615.39)	p<0.001	10892.22 (-7229.31 to 29013.76)	p=0.23

Appendix 8: CONSORT diagram for screening and enrollment

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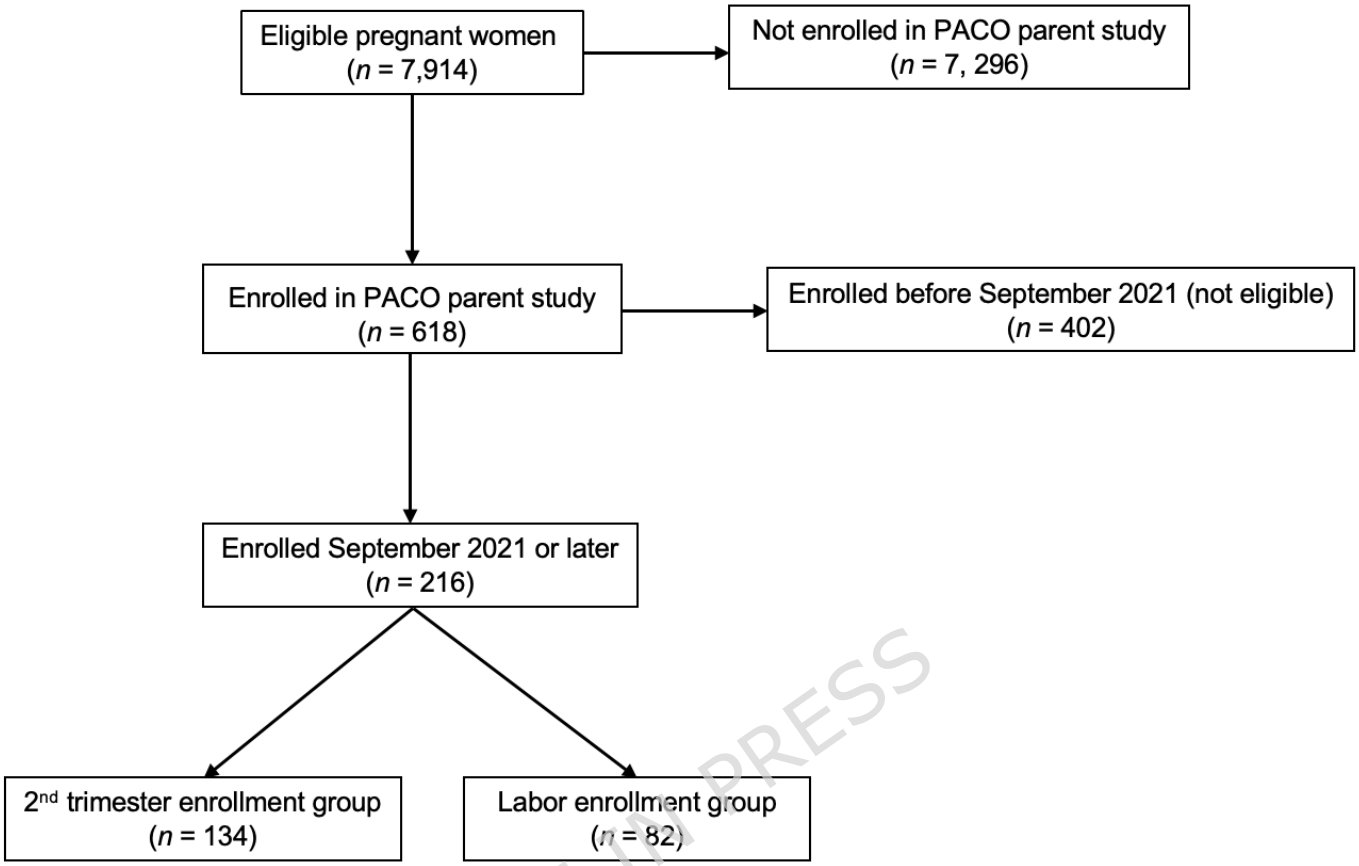

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