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Development of a Multi-state Markov Model for Labour Progression

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Development of a Multi-state Markov Model for Labour Progression

Original version

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This Dissertation, **"Development of a Multi-state Markov Model for Labour Progression"**, presented by Rodrigo de Souza Reis, and submitted to the Ribeirão Preto Medical School of the University of São Paulo, in Partial Fulfillment of the requirements for the degree of Master of Science in the Postgraduate Programme in Public Health, in the area of concentration of Quantitative Methods in Health, has been read and approved in ______ of ____________________ of _________ by:

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Abstract

SOUZA REIS, Rodrigo De. **Development of a Multi-state Markov Model for Labour Progression**. 2019. 89 p. Dissertation (Master of Science) – Ribeirão Preto Medical School, University of São Paulo, São Paulo, 2019.

This project aimed to develop a Multi-state Markov model for labour progression. The analysis was conducted as part of the World Health Organization Better Outcomes in Labour Difficulty project. The data employed was from a prospective, multi-centre, cohort study of women admitted for vaginal birth with single live fetus during early first stage of labour. It was conducted at 13 maternity hospitals in Nigeria and Uganda from December 2015 to November 2016. A multi-state continuous-time homogeneous Markov model was fitted to labour progression data for different groups of parity. The model was designed as an progressive model which consisted of one simple chain of 9 states. The states represented 2 to 10 centimetres, except 9 centimetres, of cervical dilatation and the vaginal birth. Parameters that define the labour progression model were estimated and these include transition intensities, mean sojourn times and total length of stay. The fitted model was used to simulate individual trajectories of labour progression. Estimated and observed prevalence of individuals in each state were plotted as time series for model assessment. The results obtained showed that the multi-state Markov model is robust to study labour progression.

Keywords: Labour progress. Cervical dilatation. Multi-state Markov model.

Resumo

REIS, Rodrigo de Souza. **Desenvolvimento de um Modelo Multi-estado de Markov para a Progressão do Trabalho de Parto**. 2019. 89 f. Dissertação (Mestrado em Ciências) – Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, São Paulo, 2019.

Este projeto teve como objetivo desenvolver um modelo multi-estado de Markov para a progressão do trabalho de parto. A análise foi realizada como parte do projeto *Better Outcomes in Labour Dificulty* da Organização Mundial de Saúde. Os dados utilizados foram de um estudo prospectivo multicêntrico de coorte de mulheres admitidas para parto normal com gravidez de um único feto vivo durante o periodo inicial da primeira fase do trabalho de parto. O coorte foi realizado em 13 maternidades na Nigéria e Uganda de dezembro de 2015 à novembro de 2016. Um modelo de multi-estado de Markov homogênio em tempo contínuo foi ajustado para os dados de progressão do trabalho de parto para diferentes grupos de paridade. O modelo foi concebido como um modelo progressivo que consistia em uma cadeia simples de 9 estados. Os estados representavam valores de dilatação cervical de 2 a 10 centímetros, com exceção de 9 centímetros, e o parto normal. Os parâmetros que definem o modelo da progressão do trabalho de parto foram estimados e incluem intensidades de transição, tempos médios de permanência e tempo total de permanência. O modelo ajustado foi utilizado para simular trajetórias de progressão do trabalho de parto individuais. As prevalências estimadas e observadas dos indivíduos em cada estado foram plotadas como séries temporais para avaliação do modelo. Os resultados obtidos mostraram que o modelo multi-estado de Markov é robusto para estudar a progressão do trabalho de parto.

Palavras-chaves: Progressão do trabalho de parto. Dilatação cervical. Modelo multi-estado de Markov.

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1 Introduction

Identifying women at high risk of complications, careful monitoring, and appropriate use of interventions during labour would avoid most maternal and neonatal adverse outcomes. For many women, intrapartum care is comprised of monitoring and a supportive approach. Others may require interventions to avoid complications. During this process, health professionals often have to acquire information, process it, and make the decision to keep monitoring, speed up labour or intervene.

Labour is a natural process that includes the onset of uterine contractions that increase in intensity and frequency, resulting in progressive effacement and dilation of the cervix. In this process, one of the most important indicators of progression is the cervical dilatation. The cervix represents the main impediment to the passage of the baby and its dilatation is the result of the main physiological mechanisms involved in the process (FRIEDMAN, 1959). Thus, many publications emphasise the importance of the graphical representation of cervical dilatation progression to the clinical management of labour.

Friedman (1954) was the first to publish a graphicostatistical analysis of labour progress composed of a series of cervical dilatation values over time. Labour progression has since been assessed on the basis of his work. He presented the cervical dilatation for nulliparous women as a sigmoid labour curve. Subsequently, based on Friedman's findings, Philpott and colleagues developed guidelines to assess labour progression (PHILPOTT; CASTLE, 1972b; PHILPOTT; CASTLE, 1972a). They proposed an alert line that represents a cervical dilatation rate of 1 cm/hr to detect abnormal labour. They also proposed an action line parallel to the alert line four hours to the right intended to trigger some action. After, O'DRISCOLL, Foley e MacDonald (1984) proposed a package of interventions to decrease the proportion of women with labour progression beyond the alert line. All these studies led to the creation of the World Health Organization (WHO) partograph presented in 1994 (KWAST; LENNOX; FARLEY, 1994). The partograph, has since been promoted as an essential tool for assessing labour progress and decision-making.

The partograph is a composite graphical record of key labour data over time. Its main feature is a cervicograph that displays labour time in hours, in the x axis, and cervical dilatation in centimetres, in the y axis. The principal attributes of the cervicograph are the alert and action lines, which act as triggers for interventions during labour. The alert line is linear and represents a cervical dilation rate of one centimetre per hour. The action line is parallel to the alert line and is displayed four hours to the right of the alert line. At first, 3 cm dilatation was believed to be the most frequent dilatation at which the transition takes place at the rate of 1 cm/hr and the cervicograph was marked accordingly. This marking was afterwards changed to 4 cm. The partograph has an underlying algorithm designed to identify women who are likely to present poor outcomes related to labour and which interventions or treatments to take. The active management of labour with the use of the partograph has been effective in reducing prolonged labour and adverse outcomes, but many elements of this approach are controversial.

The understanding of natural labour progression has regaining interest with the movement from a general approach of care to new approaches that are women-centred and more natural without too many interventions (OLADAPO *et al.*, 2018). There is growing evidence that the pattern of labour progression among low-risk women with spontaneous onset differs substantially from Friedman's reports of 1950 (ZHANG; TROENDLE; YANCEY, 2002; ZHANG *et al.*, 2010; OLADAPO *et al.*, 2018; ABALOS *et al.*, 2018). Changes in the characteristics of women and the current model of birth care are questionable factors of the use of normal labour curves based on Fridman's work (ZHANG *et al.*, 2010). In practice, identifying abnormally progressing labour that justifies a medical intervention is often challenging and it has become a leading indication for oxytocin augmentation and cesarean sections (BETRáN *et al.*, 2016).

Recently, Zhang *et al.* (2010) presented new labour progression curves based on records of more than 60,000 parturient women who had singleton births with spontaneous onset of labour, fetal cephalic presentation, vaginal delivery and normal perinatal outcome from 2002 to 2008. The curves encountered by Zhang and colleagues also differ from those previously described by Friedman. They argues that the rate of dilation from 4 cm to 6 cm is far slower than previously reported and that health professionals should wait longer before the 6cm dilation to make any decisions about the use of interventions. The American College of Obstetricians and Gynecologists, adhered to the labour curve proposed by Zhang and recommends its use instead of the curve based on Friedman's work (OBSTETRICIANS; GYNECOLOGISTS *et al.*, 2014).

These approaches have been extremely useful in assessing the labour progress retrospectively but not in predicting its course. When attempting to predict the course of labour, information on cervical dilatation should be quantitatively described in a sequential arrangement over time. For this purpose, we hypothesised that Markov processes could be useful in determining the actual labour progress. Markov process is based on the transition matrix with a probability structure (COX; MILLER, 1977). This matrix gives the probabilities by which one set of states is followed by another set of states. Thus, the transition matrix is a mathematical way of summarising the sequence of events over time. Therefore, using the transition matrix we could predict future states.

To our knowledge there is only one published work using Markov process to model labour progress. In 1988, Nagamatsu *et al.* (1988) developed a model based on Markov processes to predict the progress of labour, which made a huge contribution to the development of this project. In the mentioned study, when applying the Markov process, the progression of labour was divided into eight states of cervical dilatation. Based on collected data, a transition matrix was calculated, in which the value in each element presented the probability of progression from one state to another using a period of 30 minutes. The Markov process was reported as an effective analytical model for predicting labour. However, there are some limitations related to labour data that require some adaptations of their approach for fitting more realistic labour data.

The problems associated with the assessment and recording of cervical dilation during labour are important obstacles to study its progression (VAHRATIAN *et al.*, 2006). There is considerable variability between observers and the intermittent nature of the procedure does not allow an assessment of the whole dynamics of the cervix during labour. Pregnant women are usually evaluated on intermittent follow-up exams with time intervals greater than 30 minutes, every 2 or 4 hours. During these exams monitoring information is collected, but period information between the exams is not available. Also the exact time in which the labour starts is unknown. Thus, most transitions are likely to be missed.

In longitudinal medical studies, the analysis is often performed using multi-state models (MEIRA-MACHADO *et al.*, 2009). A multi-state model is a model for a continuous time stochastic process allowing individuals to move among a finite number of states. Different model assumptions can be made about the dependence of the transition rates on time. We assumed here the Markov property that the process depends only upon the present state, not on the sequence of events that preceded it. Therefore, we assumed labour can be represented as a state and time related phenomenon during a period ranging from the onset of labour to childbirth like Nagamatsu *et al.* (1988). In this way, the labour process can be considered as a mathematical model suitable for the application of the multi-state Markov model.

This master's dissertation proposes the application of mathematical and computational modelling techniques to develop a dynamic predictive model that could be used in decision support for professionals who assist women during labour. This work uses data from the prospective, multi-centre, cohort study of of the World Health Organization's Better Outcomes in Labour Difficulty (BOLD) project (SOUZA *et al.*, 2015). The project was submitted to the WHO Research Ethics Review Committee (WHO ERC) and approved in August 2014 (see **Appendix A**). One of the main objectives of the BOLD project is to develop innovative algorithms and tools for decision making during childbirth.

This is an article-based dissertation divided into four chapters. The first Chapter is an introductory section. In Chapter 2, the main article is presented. Chapter 3 contains three other articles related to the master's project. At last, a conclusion is presented.

2 Article

Multi-state Markov model for spontaneous labour progression with vaginal birth: a prospective cohort study in two sub-Saharan African countries

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Background

Intrapartum care is critical to the survival of pregnant women and their babies as the risk of serious morbidity and death increases during the period of birth (WORLD HEALTH ORGANIZATION, 2018). A substantial proportion of pregnancy-related life-threatening conditions and maternal deaths are attributed to complications that arise around the labour (KASSEBAUM *et al.*, 2014). These often include haemorrhage, obstructed labour or sepsis (ALKEMA *et al.*, 2016). Similarly, approximately half of all stillbirths and a quarter of neonatal deaths result from complications during labour and childbirth (LAWN *et al.*, 2016).

In obstetric practice, an important indicator used to assess labour progress and enable decision making during the intrapartum is the cervical dilatation. The cervix represents the major impediment to the passage of the baby and its dilatation is a result of the main physiological mechanisms involved in the labour process (FRIEDMAN, 1959). Therefore, the graphical presentation of cervical dilatation progression is an important feature of the partograph and has been the central measure for detecting abnormal progress. Those measures enable care providers have an understanding of which interventions are appropriated.

Despite decades of research and partograph use, the concept of normal progression and duration of cervix dilatation is neither universal nor standardised (ABALOS *et al.*, 2018). The problems associated with its measurement and recording during labour constitute major obstacles for the study of its progression. The intermittent nature of the process does not allow an assessment of the whole dynamics of the cervix. The identification of the exactly time of labour onset is very contentious. The changes of dilatation over time occur at unknown times which make it very difficult to study or mathematically model. Previously proposed models to estimate the rate of normal cervical dilatation are largely unpredictable (FERRAZZI *et al.*, 2015) and usually subject of intense debate (COHEN; FRIEDMAN, 2015b; COHEN; FRIEDMAN, 2015a; ZHANG *et al.*, 2015).

The theory of stochastic process is the mathematical tool to study situations of modelling complex systems where the probability distribution of random variables changes over time. Particularly when we work with longitudinal medical studies, the analysis are often performed using multi-state models (ANDERSEN; KEIDING, 2002; MEIRA-MACHADO *et al.*, 2009). It allows describing the transitions that a cohort of patients makes among a number of mutually exclusive and exhaustive states during a series of time intervals. Multi-state models for longitudinal or panel data are generally based on the Markov assumption that future evolution only depends on the current state. The supposition enables reasoning and computation with a model that would otherwise be intractable.

The goal of this study is to present the use of multi-state Markov modelling as alternative to model labour progression through the cervical dilation progress. The analysis performed here was conducted as part of the WHO's Better Outcomes in Labour Difficulty (BOLD) project (OLADAPO *et al.*, 2015). The project was primarily designed to identify the essential elements of labour monitoring that trigger the decision to use interventions aimed at preventing poor labour outcomes.

Methods

Data

The data employed in this article are from the World Health Organization (WHO) Better Outcome in Labour Difficult (BOLD) project. This was a prospective, multi-centre, cohort study of women admitted for vaginal birth with single live fetus during early first stage of labour. It was conducted at 13 maternity hospitals in Nigeria and Uganda from December 2015 to November 2016. The study protocol and detailed methodological considerations have been published elsewhere (SOUZA *et al.*, 2015). The information was collected on paper forms for individual study participants by trained research assistants at each health facility. Briefly, the data were collected on maternal admission characteristics, multiple assessments during labour monitoring, indication and timing of selected interventions and maternal and neonatal labour outcomes.

From the initial database we included births at term (between 37 weeks and 0 days and 41 weeks and 6 days) with vertex presentation, spontaneous labour onset and vaginal delivery. We excluded women who had labour induction, previous uterine scar, or elective cesarean. To examine the labour patterns in women with normal perinatal outcomes, we also excluded women whose labour resulted in severe adverse outcomes. The adverse outcomes was defined as occurrence of any of the following: stillbirths, early neonatal deaths, neonatal use of anticonvulsants, neonatal cardiopulmonary resuscitation, apgar at 5 minutes score < 6, maternal death or organ dysfunction with labour dystocia and uterine rupture. We further excluded women who gave birth to neonates with severe congenital malformation and those with fewer than two cervical dilatation assessments. The dataset used in this article has been published and made available elsewhere (OLADAPO *et al.*, 2018).

We grouped the selected women into three parity groups (para 0, 1 or 2+). Parity is the number of pregnancies carried to viable gestational age. A woman who has never carried a pregnancy beyond 20 weeks is nulliparous and is called a nullipara or "para 0". A woman who has given birth one or more times is a multiparous and can also be referred to as "para 1", "para 2", "para 3" and so on. Here we referred women who has given birth 2 or more times to as "para 2+".

The data were specified as a series of observations for each eligible participant. The variables selected for each observation indicate the time of observation in hours and either the observed cervical dilatation in centimetres or the occurrence of vaginal delivery. The first time the cervical dilatation reached 2 cm or more was marked as the starting point (time=0).

Multi-state Markov Modelling

A multi-state Markov model is a stochastic process $(X(t), t \in T)$ which assumes the markovian property (MEIRA-MACHADO *et al.*, 2009). $X(t)$ represents the state occupied from a finite state space $(S = 1, \ldots, N)$ at time t that varies over a period of time $(T = [0, \infty))$. With the evolution of the process over time, a history H_{s-} will be generated consisting of the observation of the process over the interval $[0, s)$. The multi-state Markov model is fully characterised through transition probabilities between states i and $j \in S$. Therefore, for any $s, t \in T$ with $0 \leq s < t$, we have:

$$p_{ij}(s,t) = (X(t) = j|X(s) = i, H_{s-}) = p(X(t) = j|X(s) = i),$$

Thus, the future states of the process after time s depends only on the state occupied at time s, not on the sequence of events that preceded it. The model can also be fully characterised through transition intensities:

$$q_{ij}(t) = \lim_{t \to 0} \frac{p_{ij}(t, t + \Delta t)}{\Delta t}$$

The intensity represents the instantaneous risk of moving from state i to state $j \neq i$. The set of intensities, q_{ij}, form a $R \times R$ matrix Q whose rows sum to zero. Any diagonal entries q_{ii} of Q are constrained to be minus the sum of all the other entries in the row.

For a time-homogeneous process, the set of transition probabilities $p_{ij}(s,t)$ (for $s, t \in T$ with $0 \leq s < t$) form the transition probability matrix $P(t)$. The (i, j) entry of $P(t)$, $p_{ij}(s,t)$, is the probability of being in state j at a time t, given the state i at time s. $P(t)$ can be calculated by taking the matrix exponential of the scaled transition intensity matrix.

$$P(t) = Exp(tQ).$$

To derive a Multi-state Markov model, we estimated the maximum likelihood for the transition intensity parameters (KALBFLEISCH; LAWLESS, 1985). The only information used was the observed states at a set of time. The sampling times were assumed to be non-informative. Also, the time of entry into the absorbing state was assumed as exactly observed. We estimated the likelihood from the transition probability matrix P using the Kolmogorov exponential intensity relationship. We used eigensystem decomposition to calculate the matrix exponential in case of distinct eigenvalues. When there were repeated eigenvalues, we used a method based on Padé approximants with scaling and squaring (MOLER; LOAN, 2003).

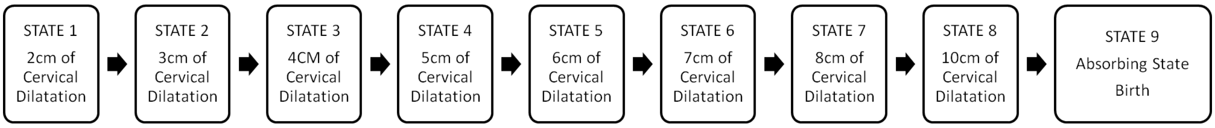
This process requires some simplifications and approximations. In this work we assumed that the behaviour of the underlying process is obeying a homogeneous Markov model. This assumption requires that the future evolution of the system depend only on its current state, not on the full history of the progression up to that point (COX; MILLER, 1965). To fit the Multi-state Markov models, all analysis was carried out using R version 3.0.1 (R Core Team, 2018) and the msm package (JACKSON, 2011). The package provides functions for multi-state modelling and it was designed for processes observed at arbitrary times in continuous time. The background to the method is explained in the package's documentation on which much of the explanation here is based.

Model Structure

The multi-state Markov model is a useful way of describing a process in which an individual moves through a series of states in continuous time where the exact times for state changes are unobserved. We can represent labour progression as a state and time related phenomenon during a period that range from onset spontaneous labour to full cervix opening until vaginal birth. In this manner, this process is suitable for the application of multi-state Markov modelling.

The structure of the multi-state Markov model for labour progression is illustrated in Figure 1. We designed it as an (unidirectional) progressive model which consists of one simple chain of 9 states similar to the presented by Nagamatsu *et al.* (1988). Thus, the model is more realistic to the scenario where parturient women had a vaginal delivery. The arrows show which transitions are possible between two states. Individuals can only progress through the states sequentially 1 to 8 (representing 2, 3, 4, 5, 6, 7, 8 and 10 centimetres of cervical dilatation) until the absorbing state 9 (the vaginal birth). There were no observations of 9 centimetres of cervical dilatation in our dataset, so we do not represent this state in our model.

Figure 1 – **State diagram for labour progression.** Unidirectional, progressive, 9-state model for labour progression. Paturients advances through the states sequentially 1 to 8 (2 to 10 cm of cervical dilatation) until the absorbing state 10 (the vaginal birth).



At a time t the parturient woman is in one of the described states. The next state to which the woman moves and the time of the change are governed by a set of transition intensities for each pair of states i and j. The transition intensity represents the instantaneous likelihood of moving from states i to state j. The full set of intensities for our proposed system form the matrix Q:

$$Q = \begin{pmatrix} q_{11} & q_{12} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & q_{22} & q_{23} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & q_{33} & q_{34} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & q_{44} & q_{45} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & q_{55} & q_{56} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & q_{66} & q_{67} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & q_{77} & q_{78} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & q_{88} & q_{89} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

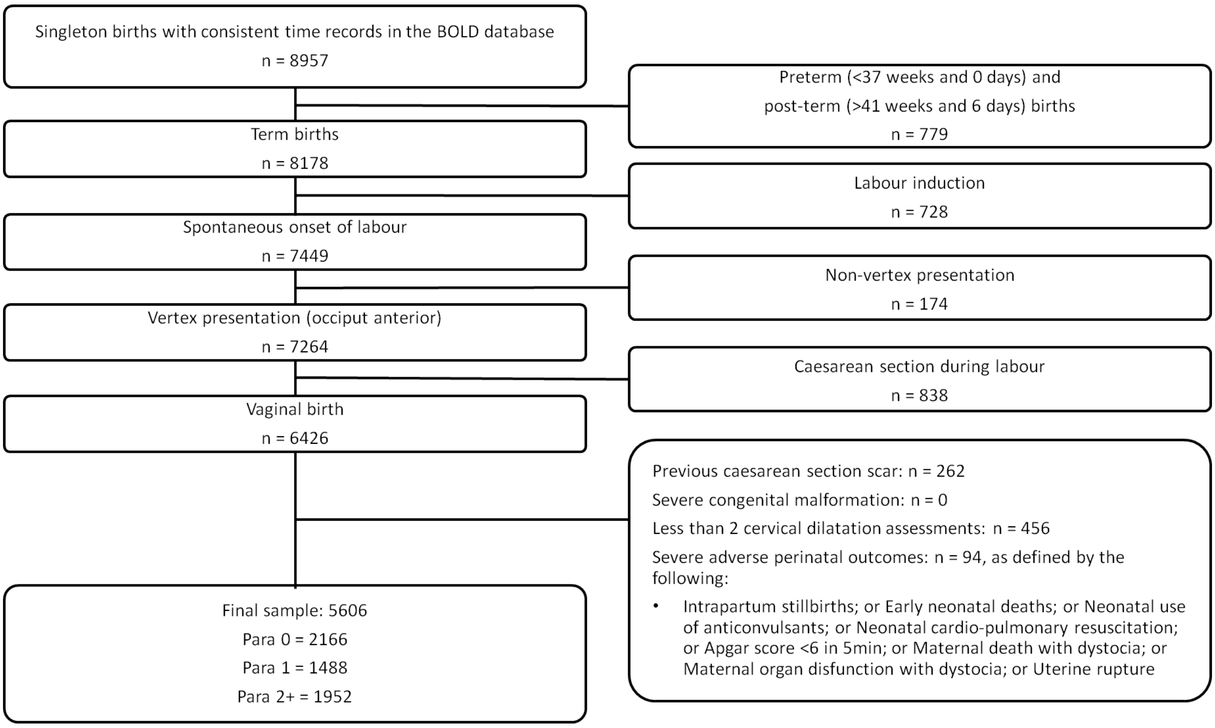
We may observe a patient moving from state 1 to state 3. However, we could still have a transition intensity from these states equal to 0 on the Q matrix. In this way, the proposed model specifies that the patient must have passed through state 2 in between, rather than jumping straight from state 1 to 3.

Results

From a total of 8,957 singleton births with consistent time records in the database, we restricted our analysis to 5,606 women based on the inclusion criteria described in

Figure 2. First, we excluded 779 preterm and post-term births. Then, we excluded 728 women who had labour induction and 714 who had non-vertex presentations. After that, we removed 838 women who had cesarean section during labour. Also, we excluded 262 women with previous uterine scar, 456 with less than 2 cervix assessments and 94 with adverse perinatal outcomes. The final sample consisted of 2.166 nulliparous women, 1.488 women who has given one birth and 1.952 who has given two or more births. The characteristics of selected women are presented by parity in **Table 1**.

Figure 2 – **Sample selection flow chart.**



In the selected sample, 54.7% of the women were from Uganda and 45.3% were from Nigeria. Nulliparous women were younger than the multiparous women, constituted over a third of the study sample, and were evenly balanced between the two countries. At labour admission, spontaneous rupture of the membranes had occurred in a quarter of nulliparous women and in about one-fifth of multiparous women. The cervix was well effaced (thin or very thin) in half of the nulliparous and in slightly higher proportions in the multiparous groups. The median cervical dilatation was 4 cm. The median number of vaginal examinations in the first stage was 3. The number of spontaneous vaginal birth with episotomy was higher in nulliparous women. The gestational age at birth was similar among the parity groups.

Table 1 – Labour characteristics and interventions by parity.

	Parity=0	Parity=1	Parity=2+
N total	2,166	1,488	1,952
Study population: N(%)			
Uganda	1,102 (50.9)	645 (43.3)	793 (40.6)
Nigeria	1,064 (49.1)	843 (56.7)	1,159 (59.4)
Age: years; mean(SD)	25.12 (4.17)	27.14 (4.05)	30.98 (4.64)
Cervix effacement at admission: N(%)			
Thick (<30%)	338 (15.6)	213 (14.31)	299 (15.32)
Medium (up to 50%)	745 (34.4)	422 (28.36)	585 (29.97)
Thin (up to 80%)	918 (42.38)	737 (49.53)	921 (47.18)
Very thin (>80%)	160 (7.39)	110 (7.39)	142 (7.27)
Unknown (non-response)	5 (0.23)	6 (0.4)	5 (0.26)
Amniotic membranes status at admission: N(%)			
Intact	1,630 (75.25)	1,189 (79.91)	1,530 (78.38)
Ruptured	534 (24.65)	295 (19.83)	420 (21.52)
Unknown (non-response)	2 (0.09)	4 (0.27)	2 (0.1)
Fetal station at admission: N(%)			
Above ischial spine	1,591(73.45)	1,056(70.97)	1,382(70.8)
At ischial spine	438(20.22)	316(21.24)	389(19.93)
Below ischial spine	136(6.28)	112(7.53)	173(8.86)
Unknown (non-response)	1(0.05)	4(0.27)	8(0.41)
Cervical dilatation at admission: median(10th; 90th)	4 (2;6)	4 (2;6)	4 (2;6)
Vaginal exams in first stage: median(10th; 90th)	3 (2;5)	3 (2;4)	3 (2;4)
Oxytocin use: N(%)	508 (23.5)	242 (16.3)	283 (14.5)
Labour analgesia: N(%)			
IV/IM Opioid	69 (3.2)	22 (1.5)	17 (0.9)
Epidural	0 (0.0)	1 (0.1)	0 (0.0)
Spinal	1 (0.0)	0 (0.0)	0 (0.0)
Other	31 (1.4)	17 (1.1)	21 (1.1)
Combined	0 (0.0)	1 (0.1)	0 (0.0)
Final mode of delivery: N(%)			
Spontaneous vaginal birth (without episiotomy)	849 (39.2)	1,218 (81.9)	1,798 (92.1)
Spontaneous vaginal birth (with episiotomy)	1,255 (57.9)	250 (16.8)	145 (7.4)
Operative vaginal birth (forceps or vacuum)	62 (2.9)	20 (1.3)	9 (0.5)
Maternal weight at delivery: kg; mean(SD)	71.84 (11.59)	73.82 (12.35)	76.37 (12.55)
Gestational age at birth: weeks; mean(SD)	38.74 (1.11)	38.74 (1.11)	38.77 (1.10)
Birth weight: grams; mean(SD)	3,139.72 (404.22)	3,277.48 (409.12)	3,348.28 (438.91)

We summarised the data by counting, for each state i and j, the number of times an observation of state i was followed by state j in **Table 2**. The resulting matrices are upper triangular matrices in which the entries below the main diagonal are all zero. In other words, there are no transitions returning from a state to an earlier one. The diagonal counts tends to decrease as states progress. This shows that in advanced states the transitions are faster.

Table 2 – Number of observed transitions by parity.

Parity	**From To**	**2cm**	**3cm**	**4cm**	**5cm**	**6cm**	**7cm**	**8cm**	**10cm**	**Birth**
0	**2cm**	139	90	181	66	58	22	13	5	26
	3cm	0	97	147	73	53	31	14	10	23
	4cm	0	0	243	214	321	163	153	125	106
	5cm	0	0	0	89	128	118	141	165	135
	6cm	0	0	0	0	115	108	207	284	300
	7cm	0	0	0	0	0	18	35	179	235
	8cm	0	0	0	0	0	0	20	244	325
	10cm	0	0	0	0	0	0	0	6	1015
1	**2cm**	49	32	47	27	28	3	6	4	11
	3cm	0	36	76	41	38	14	12	3	20
	4cm	0	0	150	109	129	88	118	88	94
	5cm	0	0	0	67	55	81	103	121	121
	6cm	0	0	0	0	74	41	137	215	184
	7cm	0	0	0	0	0	10	17	104	110
	8cm	0	0	0	0	0	0	11	160	240
	10cm	0	0	0	0	0	0	0	3	705
2+	**2cm**	67	45	75	32	31	9	7	6	15
	3cm	0	73	109	50	42	25	22	10	24
	4cm	0	0	230	122	215	111	136	126	120
	5cm	0	0	0	117	103	87	93	175	143
	6cm	0	0	0	0	93	66	146	324	280
	7cm	0	0	0	0	0	9	23	136	142
	8cm	0	0	0	0	0	0	7	180	255
	10cm	0	0	0	0	0	0	0	2	969

In **Table 3** we presented all estimated non-zero transitions intensities q_{ij} of Q. The corresponding confidence interval is also given for each transition intensity. As shown, the transition rate of moving to the next state is inversely proportional to the intensity of staying at the same state. We can also observe that the transition rates increase as the states advance. Also showing faster transitions for greater values of cervical dilatation.

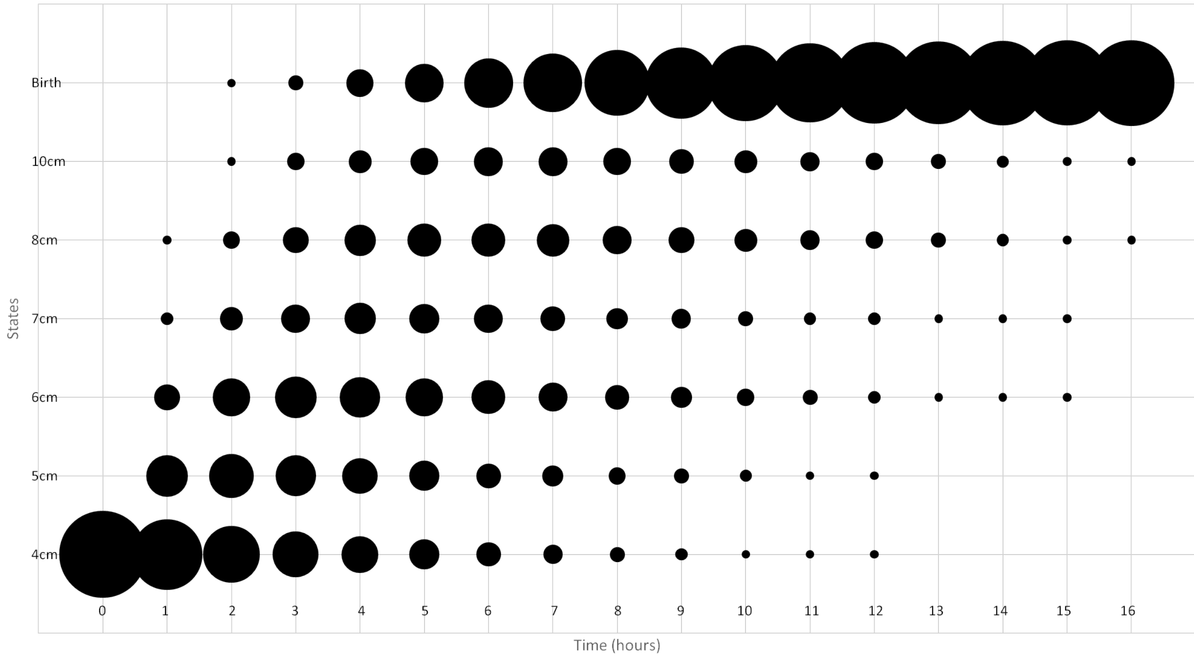
The probability distribution of women occupying each state within a 16-hour period by 1 hour cycle starting at 4cm of cervical dilatation is presented in **Figure 3**. The

Table 3 – Estimated transition rates with 95% confidence intervals for each model by parity.

	Parity 0	**Parity 1**	**Parity 2+**
2cm - 2cm	-0.2385 (-0.2650; -0.2146)	-0.1967 (-0.2339; -0.1655)	-0.2508 (-0.2928; -0.2148)
2cm - 3cm	0.2385 (0.2146; 0.2650)	0.1967 (0.1655; 0.2339)	0.2508 (0.2148; 0.2928)
3cm - 3cm	-0.3648 (-0.4025; -0.3306)	-0.3545 (-0.4084; -0.3077)	-0.3081 (-0.3450; -0.2752)
3cm - 4cm	0.3648 (0.3306; 0.4025)	0.3545 (0.3077; 0.4084)	0.3081 (0.2752; 0.3450)
4cm - 4cm	-0.4219 (-0.4498; -0.3957)	-0.4677 (-0.5106; -0.4284)	-0.4602 (-0.4954; -0.4275)
4cm - 5cm	0.4219 (0.3957; 0.4498)	0.4677 (0.4284; 0.5106)	0.4602 (0.4275; 0.4954)
5cm - 5cm	-0.7779 (-0.8345; -0.7251)	-0.8236 (-0.9035; -0.7507)	-0.8928 (-0.9761; -0.8166)
5cm - 6cm	0.7779 (0.7251; 0.8345)	0.8236 (0.7507; 0.9035)	0.8928 (0.8166; 0.9761)
6cm - 6cm	-0.6986 (-0.7432; -0.6566)	-0.8545 (-0.9346; -0.7813)	-0.8228 (-0.8898; -0.7608)
6cm - 7cm	0.6986 (0.6566; 0.7432)	0.8545 (0.7813; 0.9346)	0.8228 (0.7608; 0.8898)
7cm - 7cm	-1.1709 (-1.2674; -1.0818)	-1.6118 (-1.8111; -1.4344)	-1.9458 (-2.1851; -1.7328)
7cm - 8cm	1.1709 (1.0818; 1.2674)	1.6118 (1.4344; 1.8111)	1.9458 (1.7328; 2.1851)
8cm - 8cm	-0.8819 (-0.9455; -0.8226)	-1.0092 (-1.1165; -0.9122)	-1.1818 (-1.3186; -1.0591)
8cm - 10cm	0.8819 (0.8226; 0.9455)	1.0092 (0.9122; 1.1165)	1.1818 (1.0591; 1.3186)
10cm - 10cm	-1.1434 (-1.2229; -1.0690)	-1.1343 (-1.2308; -1.0453)	-1.1536 (-1.2545; -1.0608)
10cm - Birth	1.1434 (1.0690; 1.2229)	1.1343 (1.0453; 1.2308)	1.1536 (1.0608; 1.2545)
-2 * log-likelihood	21,743.7	13,525.32	17,704.05

bubble's size is proportional to each probability. At the start point the probability of being at 4cm is 1 (100%). Two hours after starting at 4cm, the probability of continuing in 4cm is 0.43 (43%) and the probability of being at 5cm, 6cm and 7cm are 0.26 (26%), 0.19 (19%) and 0.07 (7%) respectively. 16 hours later the probability of a nulliparous pregnant women reach the vaginal birth is 97%.

Figure 3 – **Bubble chart of transitions probabilities for nulliparous starting at 4cm of cervical dilatation with one hour cycle from 0 to 16 hours.**



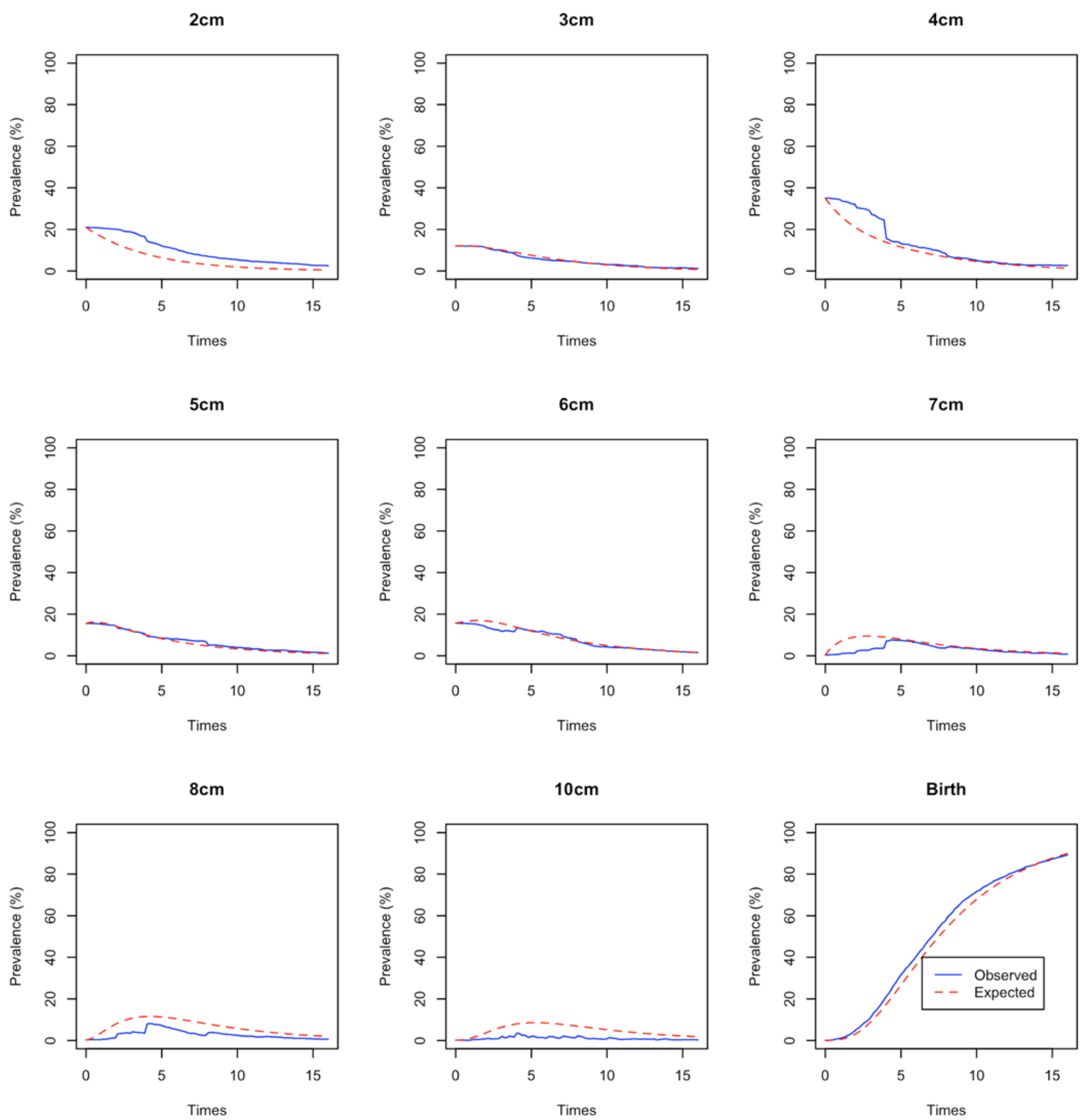
The results shown in **Table 4** describes the average time and their confidence limits an individual spends in each state in a single stay before she makes a transition to another state. The estimated mean sojourn times and expected total length of stay are equal as the model is progressive and once the individual leaves a state she cannot return. Smaller values of cervical dilatation had greater estimations of total length of stay and mean sojourn times. We also observe that the greater the dilation the narrower the confidence interval.

We present in **Figure 4** the estimations of the observed numbers of nulliparous occupying a state during the period of 16 hours. Forecasts from the fitted model are also plotted against these estimations. Individuals with 3cm, 5cm and 6cm of cervical dilatation appear to have a good fit. However, individuals predicted to have 2cm and 4cm are underestimated while those predicted to have 7cm, 8cm and 10cm are overestimated.

Table 4 – Estimation of the expected total length of stay in hours with 95% confidence intervals of multi-state Markov models by parity.

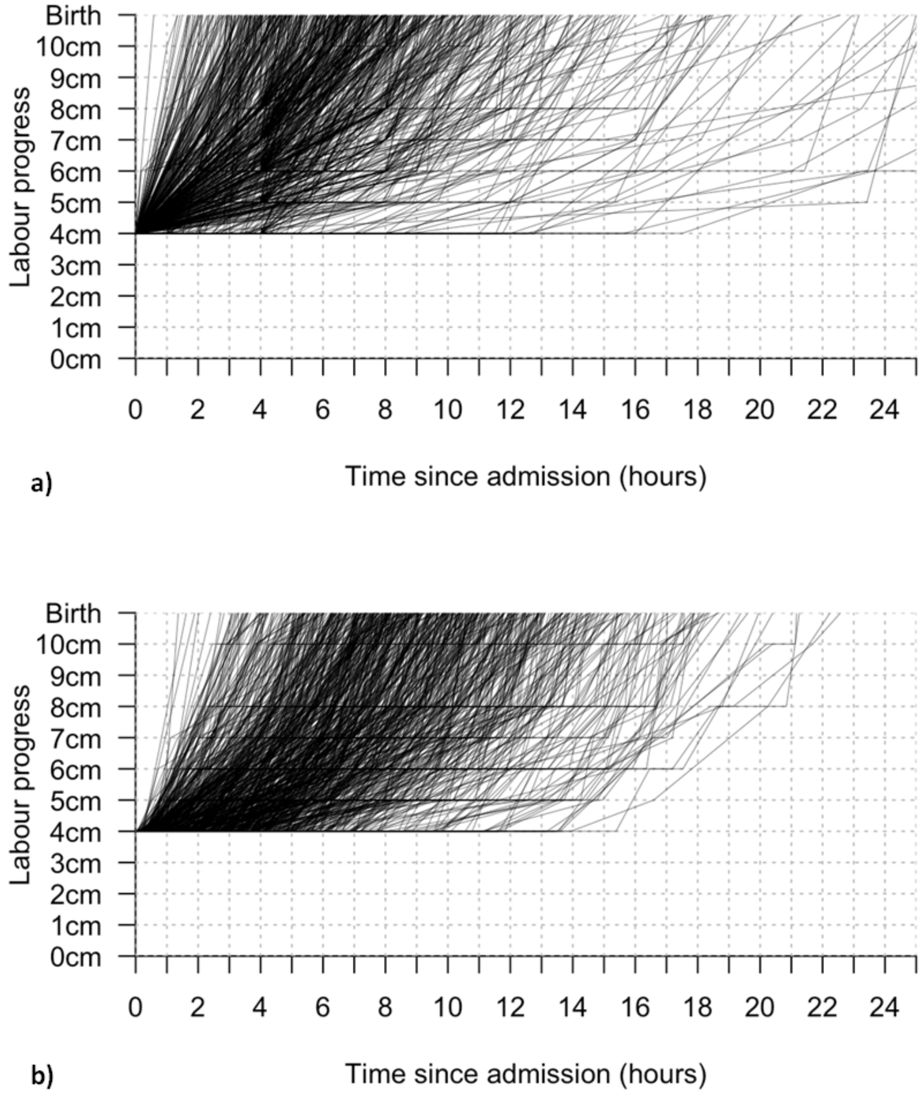
	Parity 0	**Parity 1**	**Parity 2+**
2cm	4.1936 (3.7734; 4.6607)	5.0827 (4.2748; 6.0433)	3.9871 (3.4147; 4.6554)
3cm	2.7413 (2.4845; 3.0247)	2.8211 (2.4486; 3.2503)	3.2455 (2.8986; 3.6339)
4cm	2.3703 (2.2231; 2.5272)	2.1382 (1.9586; 2.3343)	2.1731 (2.0187; 2.3393)
5cm	1.2855 (1.1983; 1.3792)	1.2142 (1.1068; 1.3321)	1.1200 (1.0245; 1.2246)
6cm	1.4315 (1.3455; 1.5230)	1.1703 (1.0700; 1.2800)	1.2154 (1.1239; 1.3144)
7cm	0.8540 (0.7890; 0.9244)	0.6204 (1.0700; 1.2800)	0.5139 (0.4576; 0.5771)
8cm	1.1339 (1.0577; 1.2157)	0.9909 (0.8957; 1.0962)	0.8462 (0.7584; 0.9442)
10cm	0.8746 (0.8177; 0.9354)	0.8816 (0.8125; 0.9566)	0.8669 (0.7972; 0.9427)
Birth	Inf	Inf	Inf

Figure 4 – **Estimated observed and expected proportions of nulliparous women at each state in 16 hours.** Observed prevalence are indicated as solid lines, expected prevalence as dashed lines.



We also display in **Figure 5** trajectories of nulliparous women from the BOLD cohort dataset and simulated trajectories from the multi-state Markov model for parity 0 with randomly placed observation times, both starting at 4cm.

Figure 5 – **Real and simulated trajectories of individual realisations of labour progress starting at 4cm for nulliparous women.** a) observed trajectories from BOLD's cohort data. b) simulated trajectories with randomly generated observation times from multistate Markov model



Discussion

From the analysis presented, it is possible to obtain a model that well represents labour progression during the time. In addition, it is possible to simulate new cohorts of labour progression similar to that studied. Understanding of the natural progression of labour presents unique challenges and it is important to identify elements of labour monitoring that trigger the decision to use interventions. Multi-state Markov modelling appears to be a good approach to model labour progress as it takes into account the main problems related to labour data: arbitrary observations times in continuous time and its large randomness. Distributions of potential outcomes are derived from a large number of simulations which reflect the random variation in the input. It shows not only the most likely estimate but what ranges are reasonable too.

Markov modelling has been applied to model labour progression in one study up to date (NAGAMATSU *et al.*, 1988). The computing resources at that time were more limited and the presented Markov model was in a discrete time with 30-minutes period cycle. They used 625 primiparas who went into spontaneous labour between 37 and 41 weeks of gestation with a single fetus of cephalic presentation starting at 4 cm of cervical dilatation. However, information on observation time was not reported. In our model, after 15 hours the probability of a nulliparous women starting at 4 cm reach a vaginal birth is 96%, while in their model 7 hours were needed to reach the same probability. According to recent studies, contemporary labour progress is slower than previously reported (ZHANG *et al.*, 2010; NEAL *et al.*, 2010). The differences may be related to the increasing maternal age, maternal and fetal body sizes and frequent obstetric interventions used in current obstetric practice (induction, epidural analgesia and oxytocin use).

The expected holding time in each state parallel those found in the literature. There is a recent systematic review on cervical dilatation patterns of 'low-risk' women with spontaneous labour and normal perinatal outcomes (OLADAPO *et al.*, 2018). They reported that the median time to advance by 1cm in nulliparous women was longer than 1 hour until a dilatation of 5cm was reached. They described a markedly rapid progress after 6 cm. Further, similar labour progression patterns were observed in multiparous women. Our results for nulliparous and multiparous women shows that smaller values of cervical dilatation had greater estimations of total length of stay much longer than 1 hour. We also observe that the greater the dilation smaller the expected holding time and narrower their confidence interval. This indicates faster transitions and more precise estimations for greater values of cervical dilatation. It is important to notice that as we do not represent 9cm of cervical dilatation in our model its holding time may be shared among other states.

Strengths of Markov modelling includes the possibility of modelling panel or longitudinal data with a variety of observation schemes from a cohort study. It provides a better representation of real life scenarios from more angles, including the incorporation of empirical observations in the mode of modelling. The different possibilities of model structure includes the use of covariates, piecewise-constant, censored states, misclassification models and competing death states. The model gives a distributions of potential outcomes and shows what ranges are reasonable too which can be more useful for decision making.

However, we also highlight some limitations. For a time-homogeneous Markov jump process, the holding time in a given state is modelled using exponential distributions. The exponential distributions is memoryless and may not be adequate for all real-life situations. Multi-state Markov models are also limited by computing resources as well simulation error. Other limitations includes the measurement of the cervix and data acquisition. A large number of transitions were likely to be missed as it is expected that the dilation progress sequentially. It is important to notice that there was no observation of 9 centimetres of cervical dilatation in our dataset and we did not represent this state in our model. A study argues that the frequency of vaginal examinations is once every 2 hours, and the median duration of labour between 9 and 10 cm is 0.5 hour. Thus the likelihood that a woman is observed at both 9 cm and promptly at 10 cm is very small and under the current practice, it is likely to be missed in the vast majority of women (ZHANG *et al.*, 2015).

Using the BOLD's dataset, we have already applied the multi-state Markov model to enable the study of the patterns of labour progression (OLADAPO *et al.*, 2018). The model was applied to determine how long it took the cervix to dilate by 1 cm from one level of dilatation to the next until full dilatation (10 cm). It was important in determining the time required for the cervix to achieve complete dilatation based on the dilatation at the time of labour admission. Also, we used the same method to obtain population average cervical dilatation time curves (labour curves) for the women in the sample. In that article, we conclude that averaged labour curves may not truly reflect labour progression and their use for decision-making in labour management should be deemphasized. The research among others had a practical implication on the WHO recommendations: "Intrapartum care for a positive childbirth experience" which will influence the intrapartum obstetric care for the next decades (WORLD HEALTH ORGANIZATION, 2018).

Conclusions

In this article a multi-state continuous-time homogeneous Markov model is fitted to labour progression data. The results obtained shows that multi-state Markov modelling is a robust method to study labour progression. In a future study, the applicability for decision-making in the management of labour for individual women will be analysed. We hope that the presented study generate ideas for new models in the field and that these models could be tested and applied to obstetric practice in the future.

3 Other Articles

During the Master's project, some articles have been published using the same framework.

We have applied multi-state Markov modelling to generate customised labour curves. Then, we assessed their accuracy compared with the WHO partograph lines in the identification of women at risk of developing severe adverse birth outcomes (SOUZA *et al.*, 2018). In that article, we hypothesised that cervical dilatation curves customised according to the obstetric characteristics of the population could have a better accuracy than the generic alert and action lines. The study population was stratified into mutually exclusive, totally inclusive obstetric groups according to the 10-group Robson classification. The results showed that labour is an extremely variable phenomenon, and the assessment of cervical dilatation curves and partograph lines are a poor predictor of severe adverse birth outcomes. The article is presented in the **Appendix B**.

Using the BOLD's dataset, we have also applied the multi-state markov model to enable the study of the patterns of labour progression (OLADAPO *et al.*, 2018). In the article presented in **Appendix C**, the model was applied to determine how long it took the cervix to dilate by 1 cm from one level of dilatation to the next until full dilatation (10 cm). It was important in determining the time required for the cervix to achieve complete dilatation based on the dilatation at the time of labour admission. Also, we used the same method to obtain population average cervical dilatation time curves (labour curves) for the women in the sample. In that article, we conclude that averaged labour curves may not truly reflect labour progression and their use for decision-making in labour management should be deemphasized. The research among others had a practical implication on the WHO recommendations Intrapartum care for a positive childbirth experience which will influence the intrapartum obstetric care for the next decades (WORLD HEALTH ORGANIZATION, 2018).

In a further related article, the development of a system for antenatal and labour care of pregnant women in the Brazilian private health system was presented. A partograph and an instrument for recording antenatal medical appointments were implemented as a software. The presented application would assist health professionals in the follow-up of women from the gestation period until delivery. The tool was intended to ease the burden of health professionals during labour and promote better management. The article is presented in **Appendix D**.

4 Conclusions

With the work presented in this dissertation, we conclude that multi-state Markov modelling can be a robust method to study labour progression. In a future study, the applicability of the model for decision-making in the management of labour could be better analysed. We hope that the presented study generate ideas for new models in the field and that these models could be tested and applied to obstetric practice.

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A WHO Research Ethics Review Committee Approval

World Health Organization

Research Ethics Review Committee (WHO ERC)

20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – HTTP://INTRANET.WHO.INT/HOMES/RPC/ERC – HTTP://WWW.WHO.INT/RPC/RESEARCH_ETHICS

WHO ERC
Review Summary

Protocol ID: A65879
Country: NA
Protocol Title: Development of a Simplified, Effective, Labour Monitoring-to-Action Tool (SELMA): a Cohort Study
Version: 3 **Dated:** 05/08/2014
WHO Responsible Staff Member: OLADAPO, O.T.
Responsible Unit: FWC/RHR
Meeting Date: NIL

Dear Dr. OLADAPO, O.T.,
Please find the review summary of the Protocol "Development of a Simplified, Effective, Labour Monitoring-to-Action Tool (SELMA): a Cohort Study", which was submitted to the Secretariat on 14/08/2014. This proposal underwent Expedited Review.

The outcome of the review is provided below. When responding, please submit the following:

1. A cover memorandum that addresses your responses, POINT BY POINT, to each of the queries in sections A and B.
   Section C contains Suggestions to improve the proposal but there is no obligation to follow them.

2. An Amended protocol including the responses in bold, highlighted or in track changes. The protocol should include all relevant documentation (ICF, study instruments, peer review, etc.) even if already submitted.

Please note that comments in the introductory paragraph are meant for the WHO Responsible Staff Member, though you may decide to share them with the PI.

PLEASE RESPOND TO THIS REVIEW SUMMARY WITHIN A three MONTH PERIOD, OR PROVIDE THE ERC SECRETARIAT A VALID JUSTIFICATION FOR THE DELAY.

Reviewers expressed three main concerns in relation to this protocol as follows:

1. The protocol states that "A major obstacle for improving birth outcomes is that intra-partum monitoring is a time consuming task….". This seems to indicate that the study intends to reduce the length of labour so as it is not so 'time consuming' for staff. Please note that this is not a women's centred approach. Monitoring women throughout labour <u>is</u> time consuming (it lasts the length of her labour until the birth of her child). Labour a complex situation requiring staff knowledge, skills, and time. The protocol does not reflect how SELMA would alleviate the burden of health professionals during labour without diminishing critical elements of quality of care.

2. SELMA is being developed to help health professionals to "…assess the clinical situation and prompt health care providers to either allow labour to progress with routine monitoring or perform interventions". However, well trained personnel would have the knowledge to assess the normal progress of labour and to identify complications. There seems to be a risk of providing the tool without training health personnel, particularly in the case of "less specialized health professionals".

3. The protocol states "The partogragh has an underlying algorithm aimed at identifying women who are likely to present labour related poor outcomes" which seems to be what SELMA is trying to achieve. It is stated as well that a possible reason for low partogragh use is that "…obtaining the information needed in a timely manner and plotting it is a complex task, particularly in busy –understaffed units". It is unclear how SELMA will change this and how SELMA compares with the partograph.

ERC Secretariat *Page 1 of 5* *Date:*

Protocol ID: A65879 /**Meeting Date**: NIL Review Summary (contd)

A. Amendments (Response and change required)

This section includes queries and comments on your protocol, study instruments or the informed consent form for which the ERC requires your response and where relevant, appropriate amendments to the protocol, study instruments or the informed consent.

1. Protocol

1.1. Please provide an amended proposal specifying the version number and/or date on each page.

1.2. It is well acknowledged that complications of labour are responsible for many poor maternal and fetal outcomes. The 'Simplified labour monitoring to action tool' does not seem to acknowledge the complex interactions and processes of normal labour and the need for continual support, engagement, and assessment by a health professional trained in caring for a woman in labour. The protocol should acknowledge that childbirth is a normal physiological process that can occur without complications and interventions and that labour outcomes are influenced by multiple factors (e.g. the health status and physiology of the mother, the health status and physical nature of the baby, the skills of the birth attendant, etc.)

1.3. Throughout the protocol the term 'labour difficulties' is used as a cause of mortality and morbidity. Labour is about 'labouring' and it is a challenging time for women (it is physically and mentally difficult) but this does not automatically mean poor outcomes. Is there a reason to refer to labour difficulties as a cause of poor outcomes rather than 'complications of labour'?

1.4. The protocol reflects that the BOLD project is aimed at increasing "efficiency" (page 13) whereas the improvement of health outcomes is not stated. Please address.

1.5. In relation to the Conceptual framework of the BOLD project (page 12), "Structure" and "Clinical Care Process" are considered as the elements that impact on positive outcomes of childbirth. Please consider including others, such as respectful care and social support.

1.6. In relation to target users of SELMA:

1.6.1. It is stated they "…are skilled birth attendants, particularly midwives and non-specialized clinicians" (Page 26). Please explain the involvement of these groups in the study design and project to date. Please also provide the definition of "non-specialized clinicians".

1.6.2. Please explain how it will be ensured that personnel are well trained and that the tool will not replace training. Please specify the additional benefits expected from the use of the tool.

1.6.3. SELMA intends to 'optimize task shifting" by providing a tool which can be used by less skilled staff. Please discuss the training that will be provided.

1.7. Please list the interventions that will be considered appropriate by the study team for the various complications of labour. It is important to specify what will be considered good midwifery practice and to state how this will be linked with the use of the tool during the regular assessments of the mother and the fetus.

1.8. In relation to the partograph:

1.8.1. "The partogragh has an underlying algorithm aimed at identifying women who are likely to present labour related poor outcomes" (page 4). This seems to be what SELMA is trying to achieve. Please explain the new tool differs from the partograph.

1.8.2. "Time constraints, staff shortages, lack of knowledge and negative attitudes among healthcare providers were some of the obstacles noted to hinder appropriate use of the partogragh". Please explain why these will not be obstacles with the use of the SELMA tool and/or how SELMA will address these challenges that have been identified as barriers to the use of the partogragh.

1.9. Please clearly differentiate between 'interventions' and 'monitoring'. They are different but this is not reflected in the document.

1.10. In relation to monitoring of women during labour:

1.10.1. The protocol states 'By improving the monitoring during labour and supporting the decision of health professionals during labour, this project hopes to contribute to improved birth outcomes' (page 3). Please explain how it is expected that this tool will improve monitoring. Monitoring involves being with the women throughout labour, observing her, and having the skills to assess normal progress of labour and acting on deviations of normal.

1.10.2. Please explain how the following tasks that are important aspects of monitoring women's progress in labour and assessing them holistically will be less complex by using SELMA: monitoring fetal heart rate, measuring decent of the head, cervical dilatation per vaginal examination, measuring contractions, pulse rate and bP of laboring woman, urine output and fluid intake of woman. These tasks are an important aspect of monitoring a womans progress in labour and assessing her holistically.

1.11. An example is given on predicting the probability of a woman having to have a c-section and focuses on the predicatability of other medical interventions (page 5). Please specify that non-medical interventions will be the first level of intervention of this tool and medical interventions will be the second level of intervention.

1.12. 'Candidate predictors' as presented in the protocol are mostly focused around the medical model of care (Page 11). Please provide details of the important non-medical elements of childbirth and social support from that promotes individualized and respectful care.

1.13. The protocol states "The quality of care can be improved through the use of SELMA within facilities" (Page 13) . Please substantiate and outline how this will be measured.

1.14. Inclusion criteria for health facilities:

1.14.1. Major health care facility that is not a primary health care unit. However, is stated that at the primary health care unit is where most of the deliveries take place. Please explain rationale for excluding them.

1.14.2. Includes access to medical interventions. However, access to good midwifery care is not considered. Please justify.

1.14.3. Intermittent fetal monitoring has been identified as good intra-partum care. Please specify other requirements of good intra-partum care.

1.15. Please explain inclusion of women in the study undergoing IOL as this is not classified as normal labour and often results in more interventions.

1.16. It is implied (Page 17) that staff may be working overtime to work on this study ("…he/she will only collect data outside his/her routine working hours). Please explain whether health staff will have two jobs.

1.17. Please clarify the statement 'Participants who decline to remain in the study will be discontinued'. It may be referring to participants that request to be withdrawn from the study and whose data will not be included in the analysis?

1.18. It is sated "…these projects will be translated into WHO guidelines on intrapartum care" (page 29). Is this for certain?

1.19. Under point 4.1.2 it is specified "…health providers will not know the identities of the women". Please explain how this will be achieved, it does not seem feasible.

1.20. Please elaborate on the security measures that will be put in place for data storage and data transference.

2. Study Instruments

2.1. Reference is made to Annex 1, form B (Page 17). Please ensure that forms are marked appropriately. No Annex 1, form B can be found, only Annex 1.

2.2. The study will use a set of forms that will enable data collection at individual and facility level". Please provide the data collections forms for ERC review when available.

2.3. Form 1: The collection of some of this data may be confidential (e.g. previous abortions). In case this has not already been captured on the antenatal records, please explain how the information will be obtained privately while ensuring that woman's needs are met (i.e. as a laboring woman in need of social support).

2.4. Form 3: Please elaborate on the 'expected multiple assessments and interventions to be performed during first stage of labour'. It seems that monitoring is required during the first stage of labour. The most intrusive 'intervention / assessment' is a vaginal examination. Please indicate the frequency of the proposed vaginal examinations and their rational.

Protocol ID: A65879 /**Meeting Date**: NIL Review Summary (contd)

3. Informed Consent Forms

NIL

B. Clarifications (Response required but change may not be required)

This section includes queries on your protocol, study instruments or the informed consent form for which the ERC requires a clarification, and it may not be mandatory for you to make changes to your protocol. Please consider the comments of the ERC and determine if you believe change is needed. If no change is made, the ERC will consider the response. If the judgement of the ERC is that a change should occur, the ERC will promptly notify you.

NIL

C. Suggestions

This section consists of suggestions for alternative scientific or technical approaches or methods for conducting the research but which do not raise critical, ethical issues. These are meant to be helpful to investigators and are presented as suggestions for you to consider incorporating into a revised protocol. No response from you is required for any comment in this section. If, however, you do make changes to the protocol as a result of these suggestions, please submit the revised protocol to the ERC.

1. It is suggested to revise the wording to ensure that the goals of the project are consistent with what the SELMA tool will be designed to do (page 8).
2. On page 33, please clarify if "…the way they are treated" is correct or whether 'treatment they receive' is more accurate.
3. Hospital capacity is going to be used in determining the baseline risk. It is unclear how will this 'capacity' be measured. As each facility and SBA will present with a different 'capacity – will these results be transferrable to other facilities.
4. Candidate predicators include characteristics of women, past obstetric and complications profile, the condition of the women and the hospital capacity (page 24). However, history of the current pregnancy (antenatal history) is not taken into account. This seems to be an omission.
5. Please explain how anemia status and hydration status will be ascertained during labour to ensure consistency.
6. Please provide a list of data items that will be collected which is part of routine care and what additional items will be collected for study participants and the rational for it.
7. It is stated that the use of a Doptone device may be considered to be a new intervention in service delivery for some hospitals (Page 17). Fetal monitoring whether by Doptone device or pinnards – is not an intervention. It is normal monitoring of labour. If this is a new device that is being introduced into the study sites –has it been considered that this could have been one of the barriers to being able to complete the Partogragh -is lack of access to equipment or lack of experience with it?

World Health Organization

Research Ethics Review Committee (WHO ERC)

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Protocol ID: A65879 /**Meeting Date**: NIL Review Summary (contd)

Based on the above comments, the Committee has the following recommendation(s) for this proposal:

[ ] The proposal is ***Approved as submitted.*** No modifications are required.

[X] The proposal is ***Conditionally Approved: requires amendments and/or clarifications.*** Final approval is contingent upon an adequate response by the Principal Investigator, to the satisfaction of the reviewers or the Chair on behalf of the ERC.

[ ] The proposal is ***Not approved; requires additional information and/or rewriting.*** A revised version of the proposal should be re-submitted by the WHO responsible staff member as a new submission to the ERC for re-review by Committee.

[ ] The proposal is ***Rejected***. The proposal is ethically unacceptable, for the reasons stated above. The Principal Investigator may submit a new proposal that takes into consideration the ethical issues raised by the Committee. If you do not agree with the Committee's assessment, please feel free to submit an appeal to the Chair of the ERC, through the Secretarait.

NOTE: Final Approval of the Proposal is contingent upon submission of the following:
[ ] Local ethics approval(s) [ ] Other relevant documents
The ERC would like to receive a copy of the recommendations of the local ethics committee when available.

IMPORTANT

1. *Any changes to the proposal or to the attachments (informed consent/study instruments etc.) should be approved by ERC before being implemented.*
2. *The approval for this proposal is valid for a period of **one year only.***
3. *Please resubmit this proposal for a Continuing Review at least 2 months before the next re-approval period.*

Chairperson ......[signature]...... **Date** 25.8.2014

Name: Melba Gomes/~~Alejandro Costa/Emilie Alirol~~

FINAL APPROVAL	**FOR THE SECRETARIAT**
Amendments and Clarifications to the proposal have been reviewed. The protocol (Version: 3 Date: 05/09/2014) and informed consent Forms (Dated: –) submitted on 10/09/2014 are approved by the ERC	Amendments and Clarifications to be reviewed: [ ] Electronically by ERC [ ] by Primary reviewers [ ] by Secretariat Amendments approved / Clarifications accepted on Local ERC approval(s) obtained on 05/11/2014, 25/07/2014 Relevant Documents submitted on NA Comments: NA
Chairperson ......[signature]...... **Name** MG/AC/EA NC Rollins **Date** 24/11/2014	Signature [signature] Date 24/11/2014

B Article - Cervical dilatation over time is a poor predictor of severe adverse birth outcomes: a diagnostic accurary study

BJOG An International Journal of Obstetrics and Gynaecology

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General obstetrics

Cervical dilatation over time is a poor predictor of severe adverse birth outcomes: a diagnostic accuracy study

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Objective To assess the accuracy of the World Health Organization (WHO) partograph alert line and other candidate predictors in the identification of women at risk of developing severe adverse birth outcomes.

Design A facility-based, multicentre, prospective cohort study.

Setting Thirteen maternity hospitals located in Nigeria and Uganda.

Population A total of 9995 women with spontaneous onset of labour presenting at cervical dilatation of ≤6 cm or undergoing induction of labour.

Methods Research assistants collected data on sociodemographic, anthropometric, obstetric, and medical characteristics of study participants at hospital admission, multiple assessments during labour, and interventions during labour and childbirth. The alert line and action line, intrapartum monitoring parameters, and customised labour curves were assessed using sensitivity, specificity, positive and negative likelihood ratios, diagnostic odds ratio, and the *J* statistic.

Outcomes Severe adverse birth outcomes.

Results The rate of severe adverse birth outcomes was 2.2% (223 women with severe adverse birth outcomes), the rate of augmentation of labour was 35.1% (3506 women), and the caesarean section rate was 13.2% (1323 women). Forty-nine percent of women in labour crossed the alert line (4163/8489). All reference labour curves had a diagnostic odds ratio ranging from 1.29 to 1.60. The *J* statistic was less than 10% for all reference curves.

Conclusions Our findings suggest that labour is an extremely variable phenomenon, and the assessment of cervical dilatation over time is a poor predictor of severe adverse birth outcomes. The validity of a partograph alert line based on the 'one-centimetre per hour' rule should be re-evaluated.

Funding Bill & Melinda Gates Foundation, United States Agency for International Development (USAID), UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), and WHO (A65879).

Keywords alert line, childbirth, diagnostic accuracy, partograph, receiver operating characteristic space.

Tweetable abstract The alert line in check: results from a WHO study.

Linked article This article is commented on by F Okonofua, p. 1000 in this issue. To view this mini commentary visit https://doi.org/10.1111/1471-0528.15213

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Introduction

Labour and childbirth are natural processes with a relatively low frequency of complications among healthy pregnant women.[1,2] Intrapartum maternal and fetal monitoring is used to further minimise risks, and is expected to enable the early identification and prompt treatment of complications. The assessment of cervical dilatation is part of intrapartum monitoring, and is conducted by healthcare providers to determine the adequacy of labour progress.

The observed cervical dilatation is usually compared with reference labour curves to estimate the risk of labour complications and to guide the use of interventions.[3–7]

The World Health Organization (WHO) partograph is a decision-making support tool designed to assist health providers in identifying women at risk of developing complications during labour, and to guide the use of interventions intended to mitigate any perceived risks.[6] With the partograph, the identification of certain patterns of cervical dilatation or other risk factors may prompt the transfer of the woman to a higher-level health facility, the intensification of intrapartum monitoring, the augmentation of labour, or delivery by caesarean section.[7] The WHO partograph is based on clinical principles, including the notion that 'normal' labour progress is defined by a cervical dilatation rate of not less than one centimetre per hour between 4 and 10 centimetres of cervical dilatation.[6] This concept is the basis for the partograph 'alert line', which was derived from average labour curves developed during the 1950s and 1960s.[8,9] Alternative and more recent labour curves have been developed to provide a reference for labour progress and to serve as the basis for new partograph designs.[5,10]

Although some observational studies and other empirical evidence point towards the benefit of using the WHO partograph, experimental, head-to-head comparisons failed to demonstrate an effect of the partograph in improving health outcomes related to labour and childbirth.[11] Furthermore, different studies have pointed to limitations in the 'one centimetre per hour rule' as a valid benchmark for assessing the adequacy of labour progress.[5,10,12] Our hypothesis is that if the partograph is unable to accurately identify women at risk of developing intrapartum complications, it will not be able to effectively guide labour management.

This article reports on findings of the WHO Better Outcomes in Labour Difficulty (BOLD) project. The present analysis assessed the diagnostic accuracy of the alert line, action line, and other parameters included in the WHO partograph as predictors of severe adverse birth outcomes. It also assessed the accuracy of customised labour curves to identify women at risk of developing severe adverse birth outcomes.

Methods

The BOLD project included quantitative, qualitative, and service-design research conducted in Nigeria and Uganda. The methodological details of the BOLD project have been described elsewhere.[13,14] This analysis is based on the quantitative component, a facility-based, multicentre, prospective cohort study. In brief, this study included women admitted for vaginal birth with single live fetuses during the early first stage of labour across 13 hospitals in both countries. Women with spontaneous onset of labour presenting at cervical dilatation of ≤6 cm and women undergoing induction of labour took part in the study. Women with multiple pregnancies, women with pregnancies with gestational ages of less than 34 weeks 0 days, women choosing elective caesarean section, and women who were incapable of giving consent because of labour distress or obstetric emergencies at arrival were excluded. Participating institutions had a minimum of 1000 deliveries per year, with stable access to caesarean section, augmentation of labour, and assisted vaginal birth. Midwives, obstetricians, or obstetric residents provided intrapartum health care to women in labour. Doptones were used to assess fetal vital status at hospital admission and for intermittent monitoring through labour and childbirth. Labour management protocol, as well as the number and timing of pelvic examinations, were not standardised across participating institutions. None of the institutions subscribed to the active management of labour protocol during the study period. Although the partograph was a standard element of medical records in all participating health facilities, its prospective application to guide labour management during the study period varied widely across the hospitals.

Eligible women were recruited into the study between December 2014 and November 2015. From the medical records, trained research nurses prospectively extracted detailed information on the sociodemographic, anthropometric, obstetric, and medical characteristics of the study participants at hospital admission, multiple assessments during labour monitoring, interventions performed throughout the first and second stages of labour, and maternal and neonatal labour outcomes. Attending staff were approached to complement medical records data when needed. Data collection was limited to hospital stay of the mother and baby, and there was no post-hospital discharge follow-up.

The current analysis was based on information on maternal baseline and admission characteristics, repeated assessments of cervical dilatation versus time, and maternal and neonatal outcome data. Severe adverse birth outcomes were defined as the occurrence of any of the following: stillbirths, intra-hospital early neonatal deaths, neonatal use of anticonvulsants, neonatal cardiopulmonary resuscitation, Apgar score of <6 at 5 minutes, uterine rupture, and maternal death or organ dysfunction with dystocia. Details of the sample size calculation are provided in the supporting information (Box S1).

Data analysis

Simple frequencies and proportions were used to describe the characteristics of the study population. Sensitivity, specificity, positive and negative likelihood ratios, diagnostic odds ratios, and the *J* statistic (Youden's index), with 95% confidence intervals, were used to estimate the diagnostic accuracy of the alert line and the action line in the identification of women who would develop a severe adverse birth outcome.[15–18] We used the true-positive rate (i.e. sensitivity) and the false-positive rate (i.e. 1 – specificity) to graphically represent the diagnostic accuracy of the partograph parameters in the receiver operating characteristic (ROC) space.[19] Each point estimate in the ROC space represents a classification result for binary parameters, and the interpretation of the ROC space is similar to the ROC curve: optimal results are associated with high true-positive rates combined with low false-positive rates. The *J* statistic summarises the performance of a binary classifier,[16] and also expresses the proportion of ideal performance of a diagnostic test (Box S2). The supporting information provides additional details related to the calculation and interpretation of these statistics (Tables S1–S3).

The alert line and the action line are classifiers currently applied to all women, regardless of their obstetric characteristics (e.g. nulliparous, multiparous, spontaneous or induced labour, or previous caesarean section). We hypothesised that cervical dilatation curves customised according to the obstetric characteristics of the population could have a better accuracy than the generic alert and action lines. The study population was stratified into mutually exclusive, totally inclusive obstetric groups according to the 10-group Robson classification:[20] group 1 (nulliparous, single cephalic pregnancy, 37 weeks of gestation or more, with spontaneous onset of labour); group 2 (nulliparous women, single cephalic pregnancy, 37 weeks of gestation or more, with induced onset of labour); group 3 (multiparous women without previous caesarean section, with single cephalic pregnancy, 37 weeks of gestation or more, with spontaneous onset of labour); group 4 (multiparous women without previous caesarean section, with single cephalic pregnancy, 37 weeks of gestation or more, with induced onset of labour); group 5 (all multiparous women with at least one previous caesarean section, single cephalic pregnancy, at 37 weeks of gestation or more); and group 10 (all women with singleton cephalic preterm pregnancy at less than 37 weeks of gestation at childbirth). As a result of the eligibility criteria, this study has no women from group 8 (multiple pregnancies) or with caesarean section before labour. Women with non-cephalic presentations (groups 6, 7, and 9) were grouped together. Groups 1–5 and 10, were further divided according to the use of augmentation of labour (present or absent), totalling 12 subgroups. Using data from women who did not have any severe adverse birth outcome, customised labour curves were generated for each of these 12 subgroups. Data from women pertaining to groups 6, 7, and 9 were not used to generate customised curves because of the small numbers involved. The customised cervical dilatation curves were created using a multi-state Markov model,[21,22] which represented the cervical dilation pattern through intermediate states from 2 cm to 10 cm, and childbirth by selected percentiles and obstetric group (i.e. one labour curve for each obstetric group and selected percentile). In this model, each centimetre of cervical dilatation represented an intermediate state, and childbirth was the final 'absorbing' state. The model was generated as a progressive unidirectional labour-to-childbirth model, and the time of state change was determined by a set of transition intensities. The transition intensity represents the instantaneous likelihood of moving from one state to another, and is generated as part of the multi-state Markov model. For each one of the 12 obstetric subgroups, the multi-state Markov model generated labour curves representing the progress of labour in women that was either faster or at the 50, 60, 70, 80, 90, and 95th percentiles.

Once the percentile curves were generated for each obstetric subgroup of women without severe adverse birth outcomes, women were classified as having crossed or not having crossed each of the percentile curves of their relevant obstetric subgroup. The study population was then consolidated and all women who crossed their relevant 50th percentile curves were grouped together (i.e. women in which labour progressed more slowly than the customised 50th percentile curve). Similarly, women were classified as having labour that progressed either slower or faster/equal to the relevant 60, 70, 80, 90, and 95th percentiles. We estimated the accuracies of the customised percentile curves in the identification of women who would develop a severe adverse birth outcome, by comparing women with labour progress that was slower than the specific percentile with women in which labour progressed faster or equal to that percentile. Sensitivity, specificity, positive and negative likelihood ratios, diagnostic odds ratios, with 95% confidence intervals, the *J* statistic, and ROC space plotting were used to estimate the accuracy of the percentile curves in the identification of women who would develop a severe adverse birth outcome.

Statistical analyses were carried in R and Microsoft EXCEL (2010).[23]

Results

The analysis flow is shown in Figure 1. Thirteen hospitals (nine from Nigeria and four from Uganda) and a total of 9995 women (4964 from Nigeria and 5031 from Uganda) took part in this study. The average age of the participants was 27.9 years (±5.0 years); 3.2% were younger than 20 years of age (320 women) and 11.0% were 35 years old or older (1100 women). The majority of the participants had a partner (97.6%, 9753 women); 5.2% of the participants had either incomplete primary education or no education (525 women), 5.6% had complete primary education (564 women), 42.5% had either complete or incomplete secondary education (4245 women), and 45.4% had either complete or incomplete post-secondary/tertiary education (4537 women). A total of 4076 nulliparous women took part in the study (40.8%), and among women with at least one previous birth (59.2%, 5919 women), 535 (5.4%) had had a previous caesarean section. A total of 667 women (6.7%) had no antenatal care visit, 4229 (42.3%) had between one and three antenatal care visits, and 5007 (50.6%) had four visits of more; 1228 women (12.3%) developed pre-labour complications during the current pregnancy. The majority of women initiated labour spontaneously (8984 women, 89.9%) at between 37 and 41 weeks of gestation (91.2%, 9111 women), with only 594 (5.9%) being referred from another health facility during labour. All women participating in this study had singleton pregnancies, 98.6% (9845 women) of which were in cephalic presentation. The mean number of cervical assessments between 4 and 10 cm was 2.22 (±1.02). Augmentation of labour was used in 3506 women (35.1%). Pharmacological analgesia was rarely used (2.0%, 196 women). Table 1 presents the distribution of the study population according to the 10-group Robson classification. The overall intrapartum caesarean section rate was 13.2% (1323 women), and the rate of severe adverse birth outcomes was 2.2% (223 women with severe adverse birth outcomes; Table S4). Nearly half of women with at least two assessments of cervical dilatation between 4 cm and childbirth crossed the alert line (49%; 4163/8489). Figure 2 illustrates the progress of labour in the study population. In the upper panel, each grey line represents the progress of an individual women without severe adverse birth outcomes, and each red line represents the progress of an individual woman with adverse outcomes. In the lower panel, the labour curves for women in the 95th percentile, without augmentation of labour, is displayed by obstetric group. Video S1 displays an animation of labour progress of all women in labour that reached at least 4 cm of cervical dilatation.

The sensitivity, specificity, positive and negative likelihood ratios, diagnostic odds ratio, and *J* statistic for the WHO partograph alert and action lines, and the 50, 60, 70, 80, 90, and 95th percentiles are presented in Tables 1 and S5. For all reference curves, women who crossed the curves tended to show a mild increase in the odds of severe adverse birth outcomes, when compared with women who did not cross the reference lines. All reference curves had a diagnostic odds ratio ranging from 1.29 to 1.60. All reference curves had positive likelihood ratios smaller than 1.5 and negative likelihood ratios greater than 0.85. The *J* statistic was less than 10% for all reference curves. Figure 3 presents the ROC space analysis, with all the aforementioned predictors showing a poor diagnostic performance.

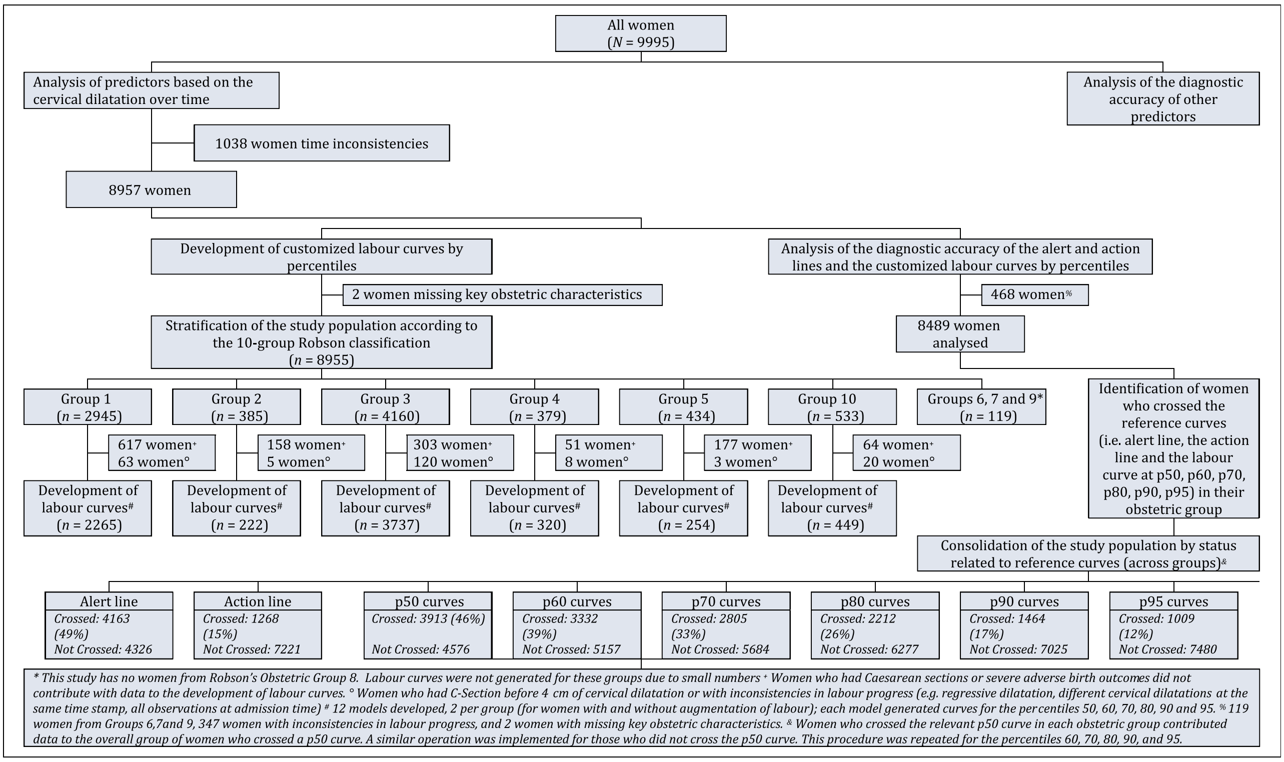

Figure 1. The analysis flowchart.

Table 1. Diagnostic accuracy of the alert line and the action line for severe adverse birth outcomes (n = 8603)

Clinical signs		Severe adverse birth outcomes		Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Diagnostic odds ratio (95% CI)	*J* statistic (Youden's index) (95% CI)
		Present	Absent						
Alert line	Crossed	110	4053	56.7% (49.7–63.5)	51.1% (50.1–52.2%)	1.16 (1.02–1.32)	0.85 (0.72–1.00)	1.37 (1.03–1.83)	7.8% (0.8–14.9)
	Not crossed	84	4242						
Action line	Crossed	38	1230	19.6% (14.6–25.7)	85.2% (84.4–85.9)	1.32 (0.99–1.77)	0.94 (0.88–1.01)	1.40 (0.98–2.01)	4.8% (−0.9 to 10.4)
	Not crossed	156	7065						

Figure S1 and Table S6 present the diagnostic accuracy of various predictors included in the partograph (the definitions of these predictors are presented in Table S7). Abnormal fetal heart rate, absence of fetal movements, significant moulding, significant caput succedaneum, meconium, and maternal hyperthermia (fever) were associated with mild to moderate increased odds of severe adverse birth outcomes. Similarly to the labour curves, the examined predictors presented poor performance in the prediction of severe adverse birth outcomes.

Discussion

Main findings

Labour is an extremely variable phenomenon, and our findings suggest that the assessment of cervical dilatation over time is a poor predictor of severe adverse birth outcomes. Labour curves depicting the cervical dilatation over time (including the WHO partograph alert and action lines) showed poor diagnostic accuracy to identify women at risk of severe adverse birth outcomes during labour. We draw one main inference from these findings: the validity of a partograph alert line based on the 'one-centimetre per hour' rule should be re-evaluated.

Strengths and limitations

These findings are relevant to the care provided in health facilities, particularly in sub-Saharan Africa, and have potential implications for clinical practice. Despite the procedures adopted to ensure appropriate study implementation and high quality data, some limitations need to be considered, however. The primary data source in this study was routine hospital records, complemented by information obtained from clinical staff. We opted for this approach to minimise any interference with the standard practice in health facilities, but acknowledge that it could be associated with irregular and, at times, incomplete and intermittent assessment and recording of maternal and fetal status during labour. Although unlikely given the clinical workload, the availability of Doptones provided by the study in the labour wards may have facilitated fetal monitoring and contributed to an increased identification of fetal distress, which could have affected the clinical management and outcomes. We were also able to determine the fetal vital status at arrival for all women, which resulted in an accurate assessment of intrapartum, intra-hospital fetal mortality. This assessment enabled the disentangling of pre-hospital fetal deaths from intra-hospital fetal deaths, and uncovered a low rate of intra-hospital fetal mortality, despite the constraints to optimal care in health facilities. None of the participating hospitals subscribed to a systematic implementation of the active management of labour; although this could contribute to a less standardised

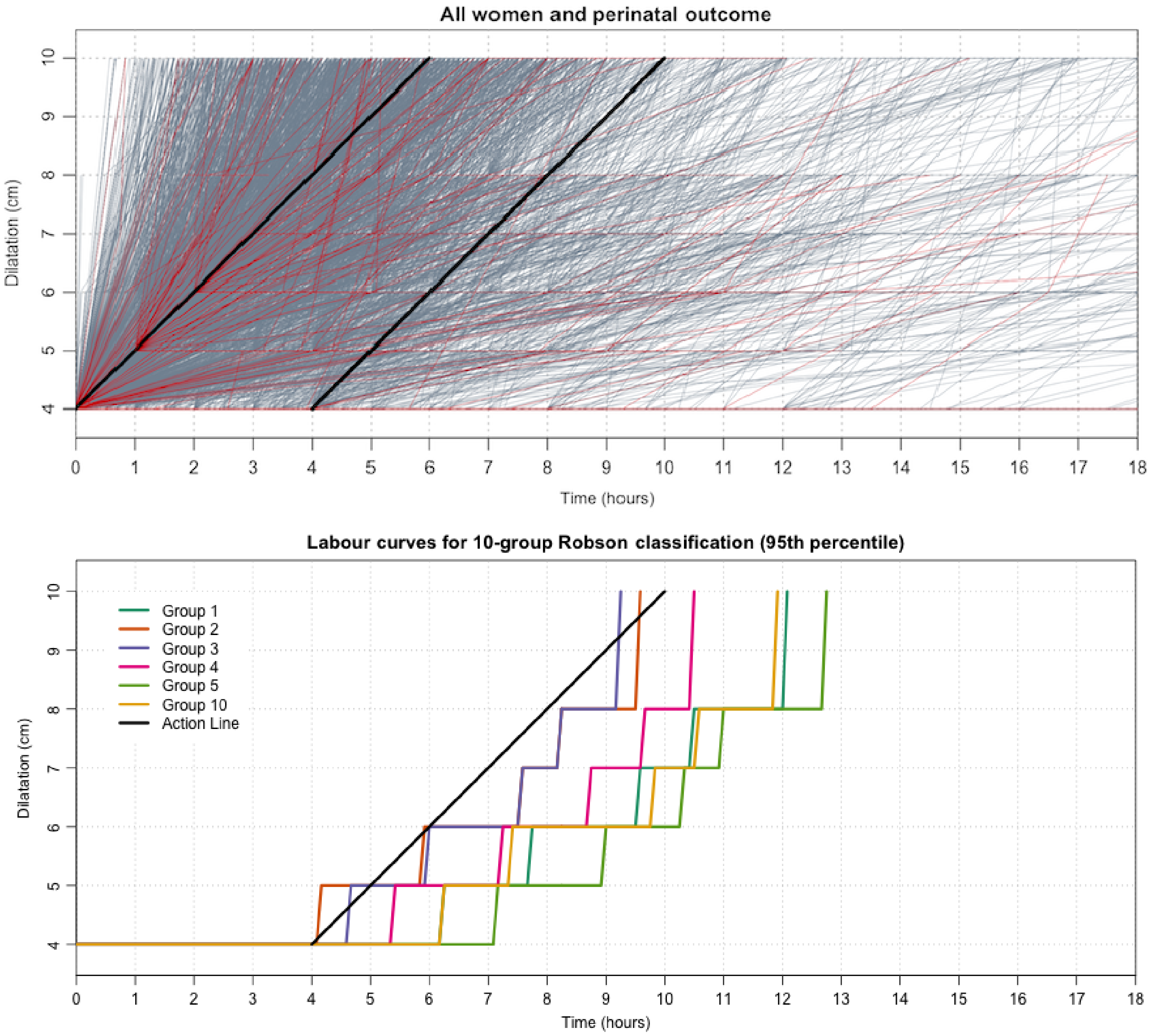

Figure 2. Upper panel: cervical dilatation over time (all women with at least two cervical dilatation assessments between 4 cm and childbirth). Grey lines denote labour progress of women without severe adverse birth outcomes; red lines denote labour progress of women with severe adverse birth outcomes. Lower panel: labour curves for selected groups of the 10-group Robson classification (95th percentile, women without augmentation of labour).

management of labour, it favoured a less interventionist approach and an intra-hospital labour progression that was more closely related to the natural progression in many women. Given the differences of workload and health-facility protocols, the standardisation of intrapartum maternal–fetal monitoring and recording was a challenging task. Several mechanisms were used to minimise methodological heterogeneity and to increase the quality of the data as much as possible (such as research assistant training, the use of a visual check of the data collection forms before data entry, automated queries, double-checking of selected medical records, and a thorough audit of unclear cases, especially those resulting in mortality). It should also be considered that crossing the alert or action lines could have prompted health providers to implement interventions in the current cohort population. These interventions could have modified the final outcome, either for good or bad.

Interpretation

Health facilities in low-resource settings often struggle with a shortage of human resources and life-saving commodities,

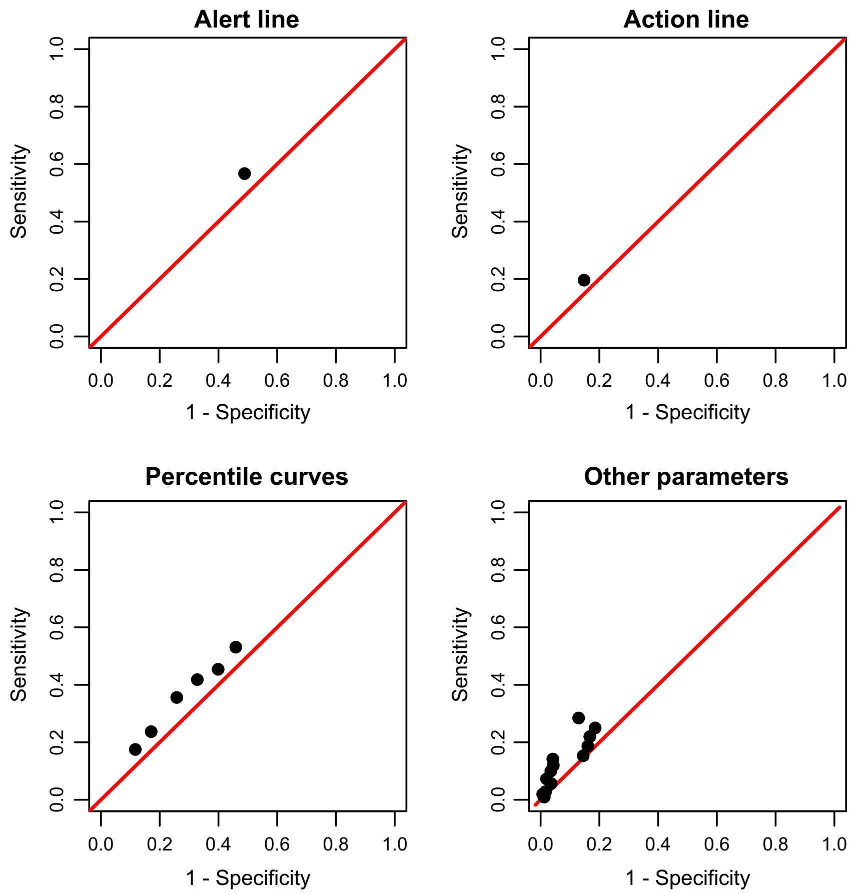

Figure 3. Analysis of the ROC space (alert and action line, customised percentile curves, and other parameters included in the partograph).

training resources, and health infrastructure, which limit the early identification and effective management of labour complications. Conversely, any overestimation of the risk of complications and over-medicalisation of care during labour and childbirth may lead to iatrogenic complications, avoidable suffering, and a waste of limited resources.[24] In an attempt to optimise intrapartum care, several organisations recommend the use of the WHO partograph to guide labour monitoring and management.[24] The 'one-centimetre per hour rule', as illustrated by the partograph alert line, has also (formally or informally) been used to prompt labour interventions in many settings around the world.[4,25] Global efforts to promote the use of the partograph in the last three decades have been met with mixed results. Although most healthcare providers working in maternity settings know about the partograph, it is frequently used retrospectively for recording purposes instead of providing prospective support for clinical decision making. Possible reasons for these shortcomings include difficulties in its use and interpretation.[26,27] Our findings suggest that the poor predictive performance of the partograph – and the consequent effect in supporting effective decision making – could contribute to the lack of interest in using the tool prospectively.

As countries navigate through the obstetric transition,[28] a marked trend towards the medicalisation of labour and childbirth is observed. Several determinants of the medicalisation of labour and childbirth are at play, including models of care based on the notion that a normal labour abides by the 'one-centimetre per hour' rule. This notion has been embedded in generations of healthcare providers across the world, and the implicit or explicit influence of this notion in obstetric and midwifery culture cannot be over-emphasised; however, as suggested by our findings, a cervical dilatation rate of 'one-centimetre per hour' may be unrealistically fast for a substantial proportion of women in labour. The mismatch between the unrealistic expectations of healthcare providers and the physiology of labour may give rise to the constructed 'need' for an intervention in a natural process that could otherwise be slower than currently expected but end well and naturally. The poor accuracy of the tool means on one hand that a high proportion of women would receive an intervention without a valid justification, and on the other hand women at risk would not be recognised in time to avoid the adverse outcome. The excessive use of interventions may also contribute to adverse outcomes. For example, the augmentation of labour is a well-established risk factor for fetal distress; unnecessary augmentation of labour, prompted by the 'one-centimetre per hour' rule, may be harmful, particularly in settings with limited capacity for providing appropriate, intermittent fetal monitoring. Another potential adverse effect of the above mismatch is increased tension, anxiety, and frustration among the staff, which could be a contributing factor to disrespect, abuse, and mistreatment of women during labour and childbirth. Allowing an increase in the average duration of labour in health facilities has a direct impact on the occupancy rate of labour-ward beds, however, which could further complicate the shortage of hospital beds and overcrowding of health facilities. Reducing the number of interventions during labour could reduce staff workload. Research to determine the short- and long-term consequences of a less invasive intrapartum care model at the individual and at the health-systems level is warranted.

The poor performance of the partograph and the customised labour curves may not be a surprising finding. The rationale for using the partograph for preventing labour problems goes back several decades, when it was introduced for the timely referral from peripheral health facilities to prevent the complications of obstructed labour.[9] Fetal and early neonatal outcomes are much more likely to be impacted by events that are not related to the cervical dilatation rate, such as placental abruption, cord compression, cord prolapse, meconium aspiration, and intrauterine growth restriction, among many other reasons. In South Africa, for example, only 6% of fetal and early neonatal deaths were associated with prolonged labour;[29] however, we should not overlook the finding that slower labours compared with faster labours (in different percentiles) tended to be associated with a mild increase in the risk of adverse outcomes. Nevertheless, this association alone can hardly provide a basis for a reliable classification tool because of the excessive number of false positives. For example, nearly half of the study population crossed the alert line, making the policy of transferring women who crossed the alert line to referral hospitals impractical. In this context, and given the limitations of static, paper-based diagnostic tools, the development and testing of more sophisticated, dynamic, easy-to-use tools for improved risk classification during labour is a priority. A cluster-randomised trial, comparing a static paper-based partograph with a dynamic, multivariable prediction model would be ideal research to be carried out next.

Conclusion

Our findings suggest that the validity of a partograph alert line based on the 'one-centimetre per hour' rule should be re-evaluated. Labour is an extremely variable phenomenon, and emphasis should be given to individualised, supportive, person-centered care during labour and childbirth.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

JPS, OTO, and AMG developed the research protocol, with input from members of the project steering committee and advisory group, Nigeria and Uganda research teams, data science team, and the project coordination and support team. The analysis plan was developed by JPS with input from OTO. Data analysis was carried out by RR, FBJ, LOC, and JPS. JPS drafted this article, with substantial contributions from OTO, BF, KM, RR, FBJ, LOC, DA, and AMG. All authors reviewed the draft manuscript for intellectual content and approved the final version for publication.

Details of ethics approval

Scientific and technical approval was obtained from the Review Panel on Research Projects (RP2) of UNDP/UNFPA/UNICEF/WHO/World Bank Special Program of Research, Development and Research Training in Human Reproduction (HRP). Ethical approval was obtained from the World Health Organization Ethical Review Committee (protocol A65879, approval date 25 August 2014), the Makerere University School of Health Sciences Research and Ethics Committee, Uganda (protocol #SHSREC REF 2014-058), University of Ibadan/University College Hospital Ethics Committee (UI/EC/14/0223), Federal Capital Territory Health Research Ethics Committee, Nigeria (protocol FHREC/2014/01/42/27-08-14), and Ondo State Government Ministry of Health Research Ethics Review Committee, Nigeria (AD 4693/160).

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. The analysis flowchart.

Table S1. Calculation of diagnostic accuracy statistics.

Table S2. Equivalence of diagnostic accuracy statistics.

Table S3. Suggested interpretation of diagnostic accuracy statistics.

Table S4. Distribution of the study population according to obstetric groups and the frequency of severe adverse birth outcomes.

Table S5. Diagnostic accuracy of customized labour curves by percentiles.

Table S6. Diagnostic accuracy of other predictors included in the partograph.

Table S7. Definitions of the predictors included in the Table S6 and Figure S1.

Box S1. Sample Size calculation.

Box S2. The J statistic in the ROC space

Video S1. All women and perinatal outcome ■

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Cervical dilatation over time is a poor predictor of severe adverse birth outcomes: a call for higher level evidence

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Linked article: This is a mini commentary on JP Souza et al., pp. 991–1000 in this issue. To view this article visit https://doi.org/10.1111/1471-0528.15205

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The article by Joao Paulo Souza et al. in this issue of BJOG makes interesting reading. It describes a study carried out in 13 maternity hospitals in Nigeria and Uganda that assessed the accuracy of the WHO parthograph for the identification of women at risk of severe adverse birth outcomes. The authors concluded that cervical dilatation over time is not a good predictor of severe birth outcomes, and that the current use of the '1-centimetre per hour' rule should be re-evaluated.

This conclusion is problematic for two main reasons. In the first place, parthography was never designed to be an accurate diagnostic tool for severe birth outcomes. It was intended to be used in primary healthcare settings to detect labour that is not progressing well (WHO. Managing prolonged and obstructed labour. http://whoqlidoc.who.int/publications/2008/978924156669_4_eng.pdf), so that early referrals can be made to centres where caesarean sections can be done. Secondly, not only were the studies reported in the paper conducted in secondary and tertiary health facilities where the use of the parthograph would be a moot point, the authors accepted that many of the facilities lacked the efficacy to use parthographic labour monitoring accurately. The authors state in the methods section of the paper that 'none of the institutions subscribed to the active management of labour protocol during the study period. Although the parthograph was a standard element of medical records in all participating health facilities, its prospective application to guide labour management during the study period varied widely across the hospitals'. It was therefore evident that the study reflected current suboptimal hospital practices rather than being a systematic process anchored in true experimental or quasi-experimental research design to answer the specific research question.

The true diagnostic accuracy of the parthograph can only be evaluated in centres practising parthographic labour monitoring correctly, and a randomised control trial would be better able to substantiate the effects of the parthograph. I therefore fully agree with the recommendations of the authors of the paper that more studies to validate parthographic monitoring of labour are needed.

In particular, since the '1-hour rule' on cervical dilatation has been taught to students of midwifery in Africa over the past decades, changing the practice should be based on rigorous scientific evidence. As reported elsewhere (Fawole et al. *Afr J Reprod Health* 2008;12:22–9), the present challenge in much of sub-Saharan Africa is the low use and poor understanding of parthographic labour monitoring of labour by healthcare 'providers. We believe that initial efforts should focus on rectifying this bottleneck, while simultaneously investigating its effects and methods of its application.

Disclosure of interests

Full disclosure of interests available to view online as supporting information. ■

C Article - Progression of the fisrt stage of spontaneous labour: A prospective cohort study in two sub-Saharan African countries

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RESEARCH ARTICLE

Progression of the first stage of spontaneous labour: A prospective cohort study in two sub-Saharan African countries

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Abstract

Background

Escalation in the global rates of labour interventions, particularly cesarean section and oxytocin augmentation, has renewed interest in a better understanding of natural labour progression. Methodological advancements in statistical and computational techniques addressing the limitations of pioneer studies have led to novel findings and triggered a re-evaluation of current labour practices. As part of the World Health Organization's Better Outcomes in Labour Difficulty (BOLD) project, which aimed to develop a new labour monitoring-

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Abbreviations: BOLD, Better Outcomes in Labour Difficulty; RP2, Review Panel on Research Projects.

to-action tool, we examined the patterns of labour progression as depicted by cervical dilatation over time in a cohort of women in Nigeria and Uganda who gave birth vaginally following a spontaneous labour onset.

Methods and findings

This was a prospective, multicentre, cohort study of 5,606 women with singleton, vertex, term gestation who presented at ≤ 6 cm of cervical dilatation following a spontaneous labour onset that resulted in a vaginal birth with no adverse birth outcomes in 13 hospitals across Nigeria and Uganda. We independently applied survival analysis and multistate Markov models to estimate the duration of labour centimetre by centimetre until 10 cm and the cumulative duration of labour from the cervical dilatation at admission through 10 cm. Multistate Markov and nonlinear mixed models were separately used to construct average labour curves. All analyses were conducted according to three parity groups: parity = 0 (n = 2,166), parity = 1 (n = 1,488), and parity = 2+ (n = 1,952). We performed sensitivity analyses to assess the impact of oxytocin augmentation on labour progression by re-examining the progression patterns after excluding women with augmented labours. Labour was augmented with oxytocin in 40% of nulliparous and 28% of multiparous women. The median time to advance by 1 cm exceeded 1 hour until 5 cm was reached in both nulliparous and multiparous women. Based on a 95th percentile threshold, nulliparous women may take up to 7 hours to progress from 4 to 5 cm and over 3 hours to progress from 5 to 6 cm. Median cumulative duration of labour indicates that nulliparous women admitted at 4 cm, 5 cm, and 6 cm reached 10 cm within an expected time frame if the dilatation rate was ≥ 1 cm/hour, but their corresponding 95th percentiles show that labour could last up to 14, 11, and 9 hours, respectively. Substantial differences exist between actual plots of labour progression of individual women and the 'average labour curves' derived from study population-level data. Exclusion of women with augmented labours from the study population resulted in slightly faster labour progression patterns.

Conclusions

Cervical dilatation during labour in the slowest-yet-normal women can progress more slowly than the widely accepted benchmark of 1 cm/hour, irrespective of parity. Interventions to expedite labour to conform to a cervical dilatation threshold of 1 cm/hour may be inappropriate, especially when applied before 5 cm in nulliparous and multiparous women. Averaged labour curves may not truly reflect the variability associated with labour progression, and their use for decision-making in labour management should be de-emphasized.

Author summary

Why was this study done?

- Dr Emmanuel Friedman's studies on normal and abnormal labour progression have defined how labour should be managed since the mid-1950s until today. Although Friedman's studies were conducted among pregnant women in the United States, the general belief that labour progression is the same in humans led to universal application of their findings, and the expectation that the cervix dilates by at least 1 cm/hour in all women during established labour.

- Since the early 2000s, however, researchers using new statistical methods to study labour found evidence to suggest that the patterns of labour progression as described by Friedman may not be accurate for the current generation of women giving birth. While these newer findings have informed changes in recommended labour practices in some settings, they have also generated a lot of controversy.
- As a result of persistent questions as to whether racial characteristics influence labour progression patterns, recent studies have been conducted among different populations, but not yet in any African population.

What did the researchers do and find?

- We conducted an analysis of prospectively collected observational data of 5,606 women who presented in early labour (at or before 6 cm of cervical dilatation) following spontaneous labour onset and gave birth vaginally in 13 maternity hospitals in Nigeria and Uganda. None of these women experienced serious adverse outcomes for themselves or their babies.
- We applied advanced statistical and computational methods (survival analysis and Markov techniques) to determine how long it took the cervix to dilate by 1 cm from one level of dilatation to the next until full dilatation (10 cm) and how long it took the cervix to reach full dilatation based on the dilatation at the time of labour admission. We also used two separate methods to plot population average cervical dilatation time curves (labour curves) for the women in our sample.
- Contrary to the generally held view, we found that labour progressed more slowly in our study population than previously reported. On average, the rate of cervical dilatation was less than 1 cm/hour for some women until 5 cm of cervical dilatation was reached among those undergoing their first, second, or subsequent labours.
- Labour was very slow in some women throughout the first stage, including the early part of the period that is traditionally known as the 'active phase', when the 'normal' cervical dilatation rate is expected to be at least 1 cm/hour or faster. While on average the labour progression in first-time mothers was generally similar to their counterparts in the US, China, and Japan, there are also important differences in the slowest-yet-normal (95th percentile) group of women in our study population.

What do these findings mean?

- The average labour curves derived from our study population are substantially different from those published from the pioneer work of Friedman. They also do not truly reflect the variations shown in the labour progression of individual women in our study.
- The application of population average labour curves could potentially misclassify women who are slowly but normally progressing as abnormal and therefore increase their chances of being subjected to unnecessary labour interventions. We propose that

averaged labour progression lines or curves are not used for decision-making in the management of labour for individual women.

- As labour may not naturally accelerate in some women until a cervical dilatation of 5 cm is reached, labour practices to address perceived slow labour progression should not be routinely applied by clinicians until this threshold is achieved, provided the vital signs and other observations of the mother and baby are normal.
- In the absence of any problems other than a slower than expected cervical dilatation rate (i.e., 1 cm/hour) during labour, it is in the interest of the woman that expectant, supportive, and woman-centred labour care is continued.

Introduction

From the mid-1950s until the 1980s, Dr Emmanuel Friedman published a series of landmark studies describing the patterns of labour progression in nulliparous and multiparous women [1–9]. The classic sigmoidal labour curve derived from his work has defined the fundamental basis of labour management for more than six decades. Although Friedman's studies were limited to obstetric populations in the US, the general notion that the labour progression pattern is largely consistent in humans has led to universal application of their findings and the expectation that the cervix dilates by at least 1 cm/hour in all women. This long-held assumption was the basis for the introduction of 'Active Management of Labour' protocols by O'Driscoll and colleagues in the 1970s [10], to 'normalize' women's labour patterns in accordance with the '1 cm/hour rule'. However, the escalating rates of unnecessary labour interventions over the last two decades, particularly oxytocin augmentation and cesarean section [11], have renewed interest in what constitutes normal labour progression.

Since the late 1990s and early 2000s, there is increasing evidence to suggest that the descriptions of the relationship between the duration of first stage of labour and cervical dilatation patterns and the definitions of labour dystocia as earlier described may not be appropriate [12–16]. Labour interventions such as induction, oxytocin augmentation, and epidural anaesthesia are now more common, while instrumental and breech vaginal births are becoming rare. The generation of women giving birth in contemporary practice is older, and with increasing body mass index and fetal weight.

In addition, newer research has taken advantage of methodological advancements in computational techniques to address the limitations of studying labour progression and constructing labour curves in the 1950s and 1960s [17]. While these advancements have led to novel findings and new guidance on labour care [18], they are also a subject of intense debate [19–21]. Suggestions that there may be racial and ethnic differences in labour progression patterns as a result of differences in pelvic configurations and sociocultural aspects have promoted research in different obstetric populations [22]. While contemporary labour curves have been published for white, Hispanic, and Asian obstetric populations [14–16], no modern labour curves exist for sub-Saharan African women.

As part of the WHO's Better Outcomes in Labour Difficulty (BOLD) project, which aimed to develop an innovative and effective labour monitoring-to-action tool [23], we examined the patterns of labour progression in a prospective cohort of women in Nigeria and Uganda who gave birth vaginally without adverse birth outcomes following a spontaneous labour onset.

Methods

Ethics statement

Scientific and technical approval for this study was obtained from the Review Panel on Research Projects (RP2) of the UNDP/UNFPA/UNICEF/WHO/World Bank Special Program of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research, WHO. Ethical approval was obtained from the WHO Ethical Review Committee (protocol A65879), the Makerere University School of Health Sciences Research and Ethics Committee, Uganda (protocol #SHSREC REF 2014–058), University of Ibadan/University College Hospital Ethics Committee (UI/EC/14/0223), Federal Capital Territory Health Research Ethics Committee, Nigeria (protocol FHREC/2014/01/42/27-08-14), and Ondo State Government Ministry of Health Research Ethics Review Committee, Nigeria (AD 4693/160). The study was conducted according to the Declaration of Helsinki of the World Medical Association.

Design, setting, and population

The WHO BOLD research project was primarily designed to identify the essential elements of labour monitoring that trigger the decision to use interventions aimed at preventing poor labour outcomes, with the aim of developing a new labour monitoring-to-action tool. The study protocol and detailed methodological considerations have been published elsewhere [23]. In brief, this was a prospective, multicentre, cohort study of women admitted for vaginal birth with single live fetuses during early first stage of labour across 13 hospitals in Nigeria and Uganda. This included women undergoing induction of labour and those with spontaneous labour onset who presented at cervical dilatation of $\leq$ 6 cm. Women with multiple pregnancies, gestational age less than 34 weeks, elective cesarean section, and those who were unwilling to participate or incapable of giving consent due to obstetric emergencies were excluded. 9,995 women (56.1%) out of 17,810 women who were screened in all hospitals during the study period met these inclusion criteria and participated in the study.

Participating hospitals had a minimum of 1,000 deliveries per year with stable access to cesarean section, augmentation of labour, and instrumental vaginal birth. Estimation of gestational age at birth was in accordance with individual institutional practices, which relied upon the woman's first date of the last menstrual period in the majority of cases. Labour was managed by midwives or obstetric residents and/or obstetricians. Doppler fetal monitor was used to assess fetal vital status at hospital admission and for intermittent monitoring throughout labour. Labour management protocol, as well as the number and timing of pelvic examinations, were not standardized across participating institutions. None of the institutions subscribed to the 'Active Management of Labour' protocol during the study period. Although the partograph was a standard element in all labour protocols, adherence to its application for labour management during the study period varied widely across hospitals.

Study procedures

Eligible women were recruited into the study between December 2014 and November 2015. From the medical record, trained research nurses prospectively extracted detailed information on sociodemographic, anthropometric, obstetric, and medical characteristics of study participants at hospital admission, multiple assessments for labour monitoring and interventions performed throughout the first and second stages of labour, and maternal and neonatal outcomes following labour. Attending staff were approached to complement medical records data when needed. Data collection was limited to the hospital stay of the mother and baby, and there was no follow-up after hospital discharge.

The current study used information on maternal baseline and admission characteristics, repeated assessments of cervical dilatation over time, maternal and neonatal characteristics throughout labour, and perinatal outcome data. This analysis was focused on describing the labour patterns of women without adverse birth outcomes and not on determining correlation to clinical outcomes (See S1 STROBE Checklist). From a total of 8,957 singleton births with consistent time records in the database, we restricted our analysis to examine labour progression to 5,606 women on the basis of the following inclusion criteria (Fig 1): term births (between 37 weeks and 0 days and 41 weeks and 6 days) with vertex presentation and spontaneous labour onset. We excluded women who had labour induction, previous uterine scar, or

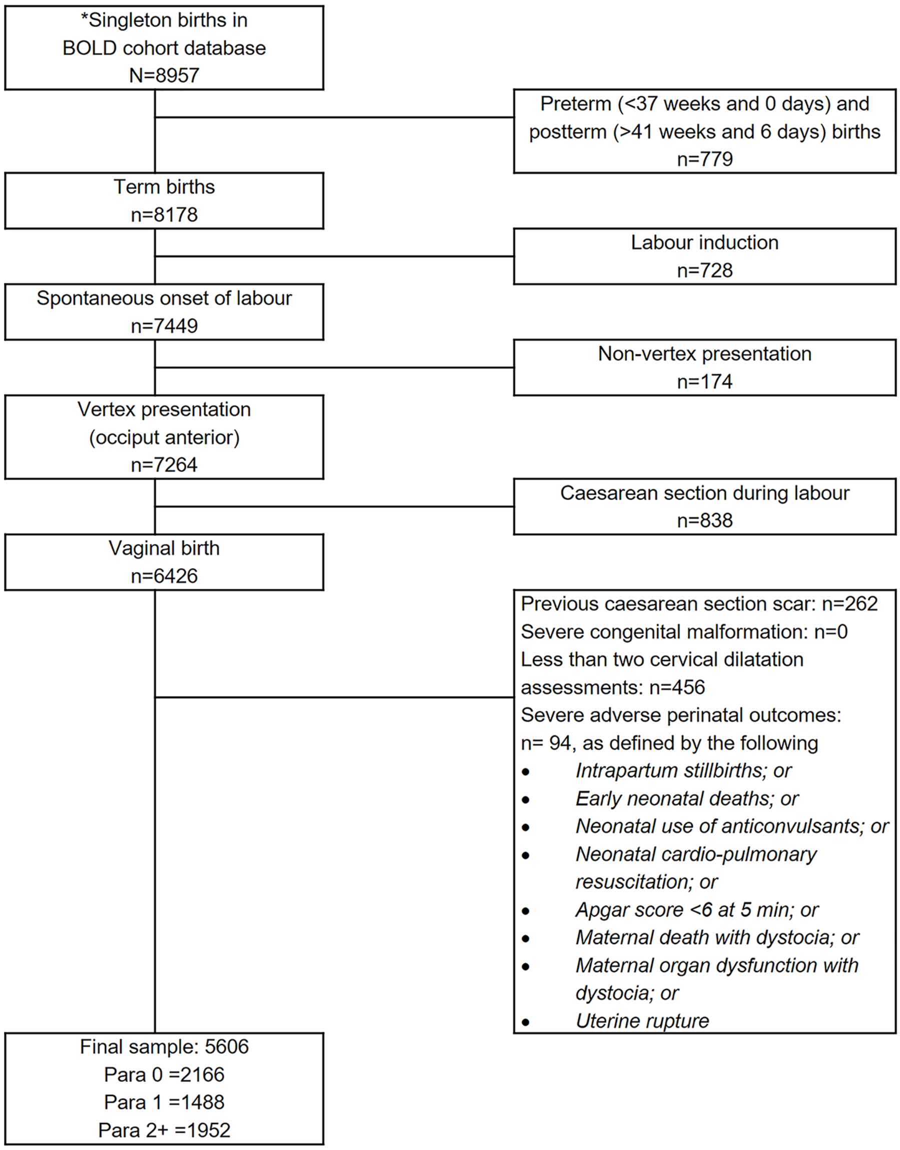

Fig 1. Sample selection flow chart. * Excluding significant outliers due to unusual rapidity, regression, or inconsistencies with time. BOLD, Better Outcomes in Labour Difficulty.

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intrapartum cesarean section. To examine the labour patterns in women with normal perinatal outcomes, we excluded women whose labour resulted in severe adverse outcomes, which was defined as occurrence of any of the following: stillbirth, early neonatal death, neonatal use of anticonvulsant, neonatal cardiopulmonary resuscitation, 5-minute Apgar score < 6, maternal death or organ dysfunction associated with labour dystocia, or uterine rupture. Furthermore, we excluded women who gave birth to neonates with severe congenital malformation and those with fewer than two cervical dilatation assessments during the first stage of labour (since a single data point cannot be used to generate a labour pattern for the individual woman).

Data analysis

We grouped women in the selected sample into three parity groups (0, 1, and 2+) to explore any differences in labour patterns according to parity. We used two independent approaches to analyse labour progression patterns and construct average labour curves for the selected sample. In the first approach, we performed survival analyses to estimate the time it took to progress from one level of cervical dilatation to the next (called 'sojourn time') (i.e., from 3 to 4 cm, 4 to 5 cm, 5 to 6 cm, until full dilatation [10 cm]). We used both complete (where available) and interval-censored times to estimate the distribution of times for progression from one integer centimetre of dilatation to the next, with an assumption that the labour data are log-normally distributed. Based on this model, the median, 5th, and 95th percentiles were calculated. We used the same approach to derive the cumulative duration of labour for women presenting at different cervical dilatations (3 cm, 4 cm, 5 cm, and 6 cm) to evaluate any potential differences in the patterns of labour progression. To illustrate the 'slowest-yet-normal' labour patterns, we plotted the 95th percentiles for the cumulative duration of labour based on the cervical dilatation at admission. To construct average labour curves, we applied a nonlinear mixed model that best fit our data instead of polynomial models used by previous authors [12–16, 24]. We expressed cervical dilatation for subject *i* in time *j* (y_{ij}) as a function of time (t_{ij}) according to the following three-parameter logistic growth model:

$$y_{ij} = \beta_0 + \frac{\beta_1}{1 + \exp(-(t_{ij} - (\beta_2 + b_i)))}$$

in which β_0 is dilatation value when $t_{ij} \rightarrow -\infty$, β_1 is the asymptotic curve height, and β_2 is the inflection point and at this time value when the dilatation reaches half of its height. For simplicity, we estimated β_0, β_1 as fixed effects and included the random term b_i in the inflection point and assumed that this term follows a normal distribution, i.e., $b_i \sim N(0, \sigma_b^2)$. Given that women in this analysis entered the cervical dilatation time curve at different dilatations but all ended at full dilatation (10 cm), the starting point (time = 0) on the x-axis was set at full dilatation (10 cm), which was reached by all women in the sample and then calculated backwards (e.g., 1 hour before 10 cm becomes −1 hour and so on). This x-axis (time) was then reverted to a positive value. For example, instead of $-12 \rightarrow 0$ hours, it became $0 \rightarrow 12$ hours. We used R-Cran version 3.2 for these statistical analyses [25].

In the second approach, we applied a multistate Markov modelling technique to examine the labour progression patterns in the same sample. This mathematical modelling technique from matrix algebra describes the transitions that a cohort of individuals make among a number of mutually exclusive and exhaustive health states during a series of short time intervals [26]. As cervical dilatation progression is a state- and time-related phenomenon during a period ranging from labour onset through to full cervical dilatation and birth of the baby (i.e., there is a finite set of states), the labour process can be considered a mathematical model that is suitable for the application of multistate Markov modelling. We therefore represented the sequence of labour progress as states based on every observed centimetre from 2 to 10 cm until birth of the baby—the 'absorbing state', as illustrated in S1 Fig. At a time t, the woman is in state $S(t)$. The model was designed as a progressive unidirectional model, which only allows a choice of a way out of a particular state, but once a woman has left a state she cannot return. The next state to which a woman moves and the time of the change are governed by a set of transition intensities for each pair of states r and s. The transition intensity represents the instantaneous likelihood of moving from state r to state s. The full set of intensities for the system form the matrix Q.

A Markov process is based on the transition matrix with a probability structure $P(u, t + u)$. The (r, s) entry (the elements of entire matrix) of $P(u, t + u)$, is the probability of being in state s at a time $t + u$, given the state at time u is r. $P(u, t + u)$ is calculated in terms of Q. Assuming that the transition intensity matrix Q is constant over the interval $(u, t + u)$, as in a time-homogeneous process, $P(u, t + u) = P(t)$ and the equations are solved by the matrix exponential of Q scaled by the time interval, $P(t) = Exp(tQ)$ (S1 Fig). We used msm package for R Project programming environment to fit the multistate Markov model [26]. We generated random observations of cervical dilatation based on the transition matrix $P(t)$ for the entire duration of labour (S2 Fig) to derive average labour curves according to parity and calculated the median, 5th, and 95th percentiles of sojourn times and cumulative duration of labour according to cervical dilatation at admission.

In order to assess the influence of oxytocin augmentation on the described labour patterns, we applied the survival analyses and multistate Markov models to perform sensitivity analyses comparing labour progression patterns of all women with that of a population excluding women with oxytocin augmentation (i.e., our entire study population versus study population excluding women with augmented labours).

The plan for the above survival analyses was first presented at an expert meeting convened by the WHO in November 2016, following which the analyses were started. In February 2017, after a review of the preliminary results of these analyses, the WHO study-coordinating unit requested an independent application of multistate Markov models to the same sample of women in order to determine whether the findings are consistent between the two analytical approaches. From June to July 2017, sensitivity analyses were conducted using the two analytical approaches to assess the influence of oxytocin augmentation on the described labour patterns for the study population, following the suggestions of the BOLD project technical advisory group and study co-authors.

Results

Baseline characteristics, labour observations, and interventions

A total of 5,606 women were included in these analyses. Table 1 presents the characteristics of these women by parity. In the selected sample, 54.7% of the women were from Uganda and 45.3% were from Nigeria. Nulliparous women were younger than the multiparous women, constituted over a third of the study sample, and were evenly balanced between the two countries. There was a slight increase in maternal body mass index at birth as parity increased. At labour admission, spontaneous rupture of the membranes had occurred in a quarter of nulliparous women and in about one-fifth of multiparous women. The cervix was well effaced (thin or very thin) in half of the nulliparous and in slightly higher proportions in the multiparous groups. Median cervical dilatation was 4 cm, and the fetal head was not engaged in over 90% of women in all parity groups. There was no caput succedaneum or moulding in over 99% of the women at the time of admission.

In terms of labour interventions, 40% of nulliparous women received oxytocin infusion for labour augmentation, compared with 28% of multiparous women. The median number of

Table 1. Labour characteristics and interventions by parity.

Demographic characteristics	Parity = 0	Parity = 1	Parity = 2+
Study population: *N* = 5,606	2,166	1,488	1,952
Country			
Nigeria	1,102 (50.88)	645 (43.35)	793 (40.62)
Uganda	1,064 (49.12)	843 (56.65)	1,159 (59.38)
Age: years, mean (SD)	25.12 (4.17)	27.14 (4.05)	30.98 (4.64)
Maternal height: cm, mean (SD)	159.88 (6.76)	159.96 (6.57)	160.43 (6.67)
Maternal weight at delivery: kg, mean (SD)	71.84 (11.59)	73.82 (12.35)	76.37 (12.55)
Maternal BMI at delivery: mean (SD)	28.09 (4.12)	28.86 (4.51)	29.66 (4.53)
Labour admission observations			
Amniotic membranes status: *N* (%)			
Intact	1,630 (75.25)	1,189 (79.91)	1,530 (78.38)
Ruptured	534 (24.65)	295 (19.83)	420 (21.52)
Unknown	2 (0.09)	4 (0.27)	2 (0.10)
Cervix effacement: *N* (%)			
Thick (<30%)	338 (15.60)	213 (14.31)	299 (15.32)
Medium (up to 50%)	745 (34.40)	422 (28.36)	585 (29.97)
Thin (up to 80%)	918 (42.38)	737 (49.53)	921 (47.18)
Very thin (>80%)	160 (7.39)	110 (7.39)	142 (7.27)
Unknown	5 (0.23)	6 (0.40)	5 (0.26)
Cervical dilatation: cm, median (10th, 90th percentiles)	4 (2, 6)	4 (2, 6)	4 (2, 6)
Fetal station: *N* (%)			
Above ischial spine	1,591 (73.45)	1,056 (70.97)	1,382 (70.80)
At ischial spine	438 (20.22)	316 (21.24)	389 (19.93)
Below ischial spine	136 (6.28)	112 (7.53)	173 (8.86)
Unknown	1 (0.05)	4 (0.27)	8 (0.41)
Caput succedaneum: *N* (%)			
None	2,158 (99.60)	1,486 (99.90)	1,949 (99.80)
Mild	7 (0.30)	1 (0.10)	3 (0.20)
Moderate	1 (0.00)	0 (0.00)	0 (0.00)
Severe	0 (0.00)	0 (0.00)	0 (0.00)
Unknown	0 (0.00)	1 (0.07)	0 (0.00)
Moulding: *N* (%)			
0 (none)	2,151 (99.30)	1,479 (99.50)	1,942 (99.50)
1+ (first degree)	13 (0.60)	8 (0.50)	10 (0.50)
2+ (second degree)	2 (0.10)	0 (0.00)	0 (0.00)
3+ (third degree)	0 (0.00)	0 (0.00)	0 (0.00)
Unknown	0 (0.00)	1 (0.07)	0 (0.00)
Intrapartum interventions and observations			
Total number of vaginal examinations in first stage: median (10th, 90th percentiles)	3 (2, 5)	3 (2, 4)	3 (2, 4)
Augmentation with oxytocin infusion: *N* (%)	866 (40.00)	444 (29.80)	522 (26.70)
Labour analgesia: *N* (%)			
IV/IM Opioid	69 (3.20)	22 (1.50)	17 (0.90)
Epidural	0 (0.00)	1 (0.10)	0 (0.00)
Spinal	1 (0.00)	0 (0.00)	0 (0.00)
Other	31 (1.40)	17 (1.10)	21 (1.10)
Combined	0 (0.00)	1 (0.10)	0 (0.00)

(*Continued*)

Table 1. (Continued)

Demographic characteristics	Parity = 0	Parity = 1	Parity = 2+
Presence of a labour companion*: *N* (%)			
0	1,053 (48.61)	661 (44.42)	808 (41.39)
1	304 (14.04)	300 (20.16)	414 (21.21)
2	371 (17.13)	276 (18.55)	400 (20.49)
≥3	429 (19.81)	240 (16.13)	316 (16.19)
Unknown	9 (0.42)	11 (0.74)	14 (0.72)
Oral fluid intake*: *N* (%)			
0	674 (31.12)	453 (30.44)	556 (28.48)
1	489 (22.58)	451 (30.31)	587 (30.07)
2	531 (24.52)	343 (23.05)	464 (23.77)
≥3	463 (21.38)	230 (15.46)	328 (16.80)
Unknown	9 (0.42)	11 (0.74)	17 (0.87)
Oral food intake*: *N* (%)			
0	1,698 (78.39)	1,187 (79.77)	1,561 (79.97)
1	273 (12.60)	207 (13.91)	255 (13.06)
2	118 (5.45)	52 (3.49)	92 (4.71)
≥3	67 (3.09)	29 (1.95)	27 (1.38)
Unknown	10 (0.46)	13 (0.87)	17 (0.87)
Caput succedaneum**: *N* (%)			
None	1,911 (88.23)	1,368 (91.94)	1,814 (92.93)
Mild	202 (9.33)	102 (6.85)	113 (5.79)
Moderate	44 (2.03)	10 (0.67)	16 (0.82)
Severe	0 (0.00)	0 (0.00)	0 (0.00)
Unknown	9 (0.42)	8 (0.54)	9 (0.46)
Moulding**: *N* (%)			
0 (none)	1,758 (81.16)	1,219 (81.92)	1,598 (81.86)
1+ (first degree)	332 (15.33)	225 (15.12)	312 (15.98)
2+ (second degree)	64 (2.95)	35 (2.35)	32 (1.64)
3+ (third degree)	2 (0.10)	1 (0.10)	1 (0.10)
Unknown	10 (0.46)	8 (0.54)	9 (0.46)
Birth outcomes			
Mode of birth: *N* (%)			
Spontaneous vaginal birth (without episiotomy)	849 (39.20)	1,218 (81.90)	1,798 (92.10)
Spontaneous vaginal birth (with episiotomy)	1,255 (57.90)	250 (16.80)	145 (7.40)
Operative vaginal birth (forceps or vacuum)	62 (2.90)	20 (1.30)	9 (0.50)
Gestational age at birth: weeks, mean (SD)	38.74 (1.11)	38.74 (1.11)	38.77 (1.10)
Birth weight: g, mean (SD)	3,139.72 (404.22)	3,277.48 (409.12)	3,348.28 (438.91)

*Frequency of observations during intrapartum assessments

**Most 'severe' observation during intrapartum assessments

https://doi.org/10.1371/journal.pmed.1002492.t001

vaginal examinations per woman throughout first stage was 3. Presence of a labour companion was observed at least on one occasion in more than half of the women and on two or more occasions in at least a third. While over two-thirds of the women were observed to have taken oral fluids at least once during labour, less than half of them were observed to have done so two or more times. In comparison, oral feedings were observed less frequently, although the observed pattern was similar across parity groups. Severe caput succedaneum and third-degree moulding of the fetal head were rarely seen in any of the parity groups. Labour analgesia and operative vaginal birth were used in less than 2% in the study population; a reflection of the current clinical practices in the study hospitals. While the gestational age at birth was similar across the parity groups, there was an average of a 100-g increase in birth weight with increasing parity.

Labour progression patterns (all women)

Table 2 presents the detailed analyses of labour progression based on the two analytical approaches and compares these with the findings of Zhang et al. [14]. The table shows that, based on survival analyses, the median time for the cervix to dilate by 1 cm was longer than the generally accepted limit of 1 hour until a cervical dilatation of 5 cm was achieved in nulliparous women and until 5 cm was achieved in multiparous women. In all parity groups, the median rate of progression doubles as the cervix reaches 6 cm with a median time shorter than 1 hour. Labour progression afterwards escalated more rapidly as it advanced towards 10 cm in all parity groups. Likewise, multistate Markov modelling shows that the median time needed to advance by 1 cm was more than 1 hour until 5 cm was achieved in both nulliparous and multiparous women, and labour progression became more rapid from 7 cm. The distribution of data from both analysis methods show a wide variability around the median for each level of advancement, though this was more pronounced in the survival analyses data. The 95th percentiles of the distribution of sojourn times indicate that labour could progress much more slowly for some women and still result in vaginal birth without adverse birth outcomes. The data show that it was not unusual for nulliparous women to spend more than 7 hours to advance from 4 to 5 cm and over 3 hours to advance from 5 to 6 cm. For some women, the 95th percentile data suggest that throughout the first stage of labour, it took more than 1 hour

Table 2. Duration of labour from one level of cervical dilatation to the next by parity and analysis method.

Parity	Parity = 0			Parity = 1			Parity = 2+		
Study	Current study	Current study	Zhang et al. [14]	Current study	Current study	Zhang et al. [14]	Current study	Current study	†Zhang et al. [14]
N	2,166	2,166	25,624	1,488	1,488	16,755	1,952	1,952	16,219
Cervical dilatation	Survival analysis†	Markov model	Survival analysis‡	Survival analysis†	Markov model	Survival analysis‡	Survival analysis†	Markov model	Survival analysis‡
3–4 cm	2.82 (0.60, 13.33)	1.83 (0.08, 8.17)	1.8 (8.1)	2.42 (0.41; 14.18)	1.92 (0.08, 8.33)	NA	2.35 (0.31; 17.85)	2.17 (0.08, 9.75)	NA
4–5 cm	1.72 (0.38, 7.83)	1.58 (0.08, 7.08)	1.3 (6.4)	1.37 (0.25; 7.65)	1.42 (0.08, 6.42)	1.4 (7.3)	1.18 (0.17; 8.05)	1.50 (0.08, 6.5)	1.4 (7.0)
5–6 cm	1.19 (0.23, 6.17)	0.83 (0.00, 3.83)	0.8 (3.2)	0.79 (0.13; 4.95)	0.83 (0.00, 3.58)	0.8 (3.4)	0.79 (0.10; 6.24)	0.75 (0.00, 3.33)	0.8 (3.4)
6–7 cm	0.66 (0.09, 4.92)	0.92 (0.00, 4.25)	0.6 (2.2)	0.33 (0.03; 3.67)	0.75 (0.00, 3.50)	0.5 (1.9)	0.31 (0.03; 3.29)	0.83 (0.00, 3.58)	0.4 (1.2)
7–8 cm	0.25 (0.02, 3.10)	0.58 (0.00, 2.50)	0.5 (1.6)	0.09 (0.00; 2.69)	0.42 (0.00, 1.83)	0.4 (1.3)	0.17 (0.01; 2.44)	0.33 (0.00, 1.50)	0.3 (0.9)
8–10 cm	0.87 (0.18, 4.19)	0.75 (0.00, 3.33)	0.5 (1.4)*; 0.5 (1.8)§	0.64 (0.11; 3.56)	0.67 (0.00, 2.92)	0.3 (1.0)*; 0.3 (0.9)§	0.68 (0.12; 3.77)	0.50 (0.00, 2.50)	0.3 (0.8)*; 0.3 (1.6)§

Current study data reported as median hours (5th, 95th percentiles).

Zhang et al. data reported as median hours (95th percentile).

† Survival analysis with complete and interval-censored values

‡ Survival analysis with interval-censored regression

* 8–9 cm.

§ 9–10 cm.

https://doi.org/10.1371/journal.pmed.1002492.t002

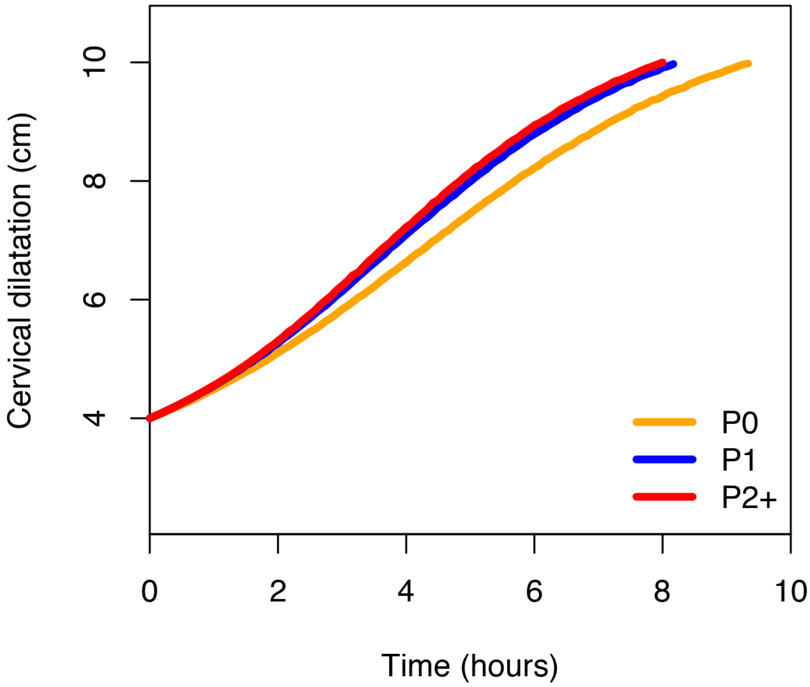

Fig 2. Average labour curves by parity based on multistate Markov models. P0, nulliparous women; P1, parity = 1 women; P2+, parity = 2+ women.

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for cervical dilatation to advance by 1 cm irrespective of the parity groups. The table also shows that the pattern of median times to advance from early to advanced first stage of labour is largely consistent with the findings of Zhang et al. [14], although our 95th percentiles show even wider variability.

Fig 2 shows that the 'average labour curves' derived from multistate Markov models for both nulliparous and multiparous women progressed gradually from 4 cm with fairly linear trajectories as they advanced towards 10 cm. The slopes of the curves for multiparous women were steeper than that of the nulliparous women.

The nonlinear mixed models, however, produced smooth labour curves for both nulliparous and multiparous women, which proceeded gradually with a slight upward inclination from around 5 cm and no clear inflection points through 10 cm (S3 Fig). Inflection points appear outside the normal range of observations. Within the range of observed data for cervical dilatation, the curves appear to accelerate from 5 cm, with steeper slopes as they advanced towards 10 cm in multiparous compared to nulliparous women.

S1 Video, S2 Video, S3 Video, and S4 Video are video displays comparing actual plots of cervical dilatation pattern of individual women (starting from 4 cm) with (1) the average labour curves constructed from our study population and (2) the 1 cm/hour alert line of the partograph. The videos show that a substantial proportion of nulliparous and multiparous women crossed the 1 cm/hour alert line as they progressed during labour. The videos also show that substantial differences exist between actual plots of labour progression for individual women and the population average curves.

Table 3 shows the cumulative duration of labour from the cervical dilatation observed at admission (e.g., at 3 cm, 4 cm, 5 cm, or 6 cm) to the next centimetre until 10 cm. The table shows that the median times estimated by the two analysis methods are mostly consistent but also have wide variability in data distribution expressed by their corresponding 5th and 95th

Table 3. Cumulative duration of labour in Para 0, 1, and 2+ based on the cervical dilatation at admission.

Parity = 0								
	Survival analysis	Markov model	Survival analysis	Markov model	Survival analysis	Markov model	Survival analysis	Markov model
Cervical dilatation at:	Adm. at 3 cm (*N* = 249)	Adm. at 3 cm (*N* = 249)	Adm. at 4 cm (*N* = 715)	Adm. at 4 cm (*N* = 715)	Adm. at 5 cm (*N* = 316)	Adm. at 5 cm (*N* = 316)	Adm. at 6 cm (*N* = 322)	Adm. at 6 cm (*N* = 322)
Adm. to 3 cm								
Adm. to 4 cm	2.76 (0.58, 13.10)	1.83 (0.08, 8.17)						
Adm. to 5 cm	4.49 (1.17, 17.17)	4.25 (0.83, 12.08)	1.71 (0.37, 7.96)	1.58 (0.08, 7.08)				
Adm. to 6 cm	5.65 (1.65, 19.40)	5.58 (1.67, 13.67)	3.02 (0.86, 10.60)	2.92 (0.58, 8.92)	1.29 (0.28, 6.05)	0.83 (0.00, 3.83)		
Adm. to 7 cm	6.50 (1.99, 21.26)	7.08 (2.50, 15.50)	4.15 (1.41, 12.19)	4.42 (1.33, 10.83)	2.10 (0.51, 8.66)	2.25(0.42, 6.42)	0.78 (0.11, 5.46)	0.92 (0.00, 4.25)
Adm. to 8 cm	7.19 (2.34, 22.14)	7.92 (3.17, 16.58)	4.97 (1.87, 13.24)	5.33 (1.92, 12.00)	3.06 (0.93, 10.14)	3.08 (0.92, 7.50)	1.76 (0.42, 7.44)	1.83 (0.33, 5.50)
Adm. to 10 cm	8.37 (2.98, 23.51)	9.08 (4.00, 17.83)	5.92 (2.42, 14.48)	6.50 (2.67, 13.25)	4.30 (1.64, 11.30)	4.25 (1.58, 9.17)	2.86 (0.88, 9.30)	3.00 (0.92, 7.25)
Parity = 1								
Cervical dilatation at:	Adm. at 3 cm (*N* = 164)	Adm. at 3 cm (*N* = 164)	Adm. at 4 cm (*N* = 491)	Adm. at 4 cm (*N* = 491)	Adm. at 5 cm (*N* = 292)	Adm. at 5 cm (*N* = 292)	Adm. at 6 cm (*N* = 320)	Adm. at 6 cm (*N* = 320)
Adm. to 3 cm								
Adm. to 4 cm	2.05 (0.29, 14.50)	1.92 (0.08, 8.33)						
Adm. to 5 cm	3.43 (0.63, 18.55)	4.08 (0.83, 11.75)	1.34 (0.24, 7.51)	1.42 (0.08, 6.42)				
Adm. to 6 cm	4.77 (1.10, 20.63)	5.42 (1.58, 13.33)	2.31 (0.55, 9.66)	2.75 (0.50, 8.08)	0.80 (0.14, 4.72)	0.83 (0.00, 3.58)		
Adm. to 7 cm	5.91 (1.65, 21.17)	6.58 (2.33, 14.75)	2.99 (0.80, 11.18)	3.92 (1.17, 9.67)	1.47 (0.33, 6.54)	1.92 (0.42, 5.58)	0.43 (0.05, 3.50)	0.75 (0.00, 3.50)
Adm. to 8 cm	6.61 (1.97, 22.20)	7.25 (2.83, 15.42)	3.78 (1.19, 11.97)	4.58 (1.58, 10.42)	2.31 (0.61, 8.69)	2.58 (0.75, 6.42)	1.13 (0.22, 5.81)	1.42 (0.25, 4.33)
Adm. to 10 cm	7.55 (2.48, 23.05)	8.25 (3.58, 16.58)	4.63 (1.66, 12.96)	5.58 (2.25, 11.67)	3.43 (1.17, 10.06)	3.58 (1.25, 7.83)	2.19 (0.64, 7.53)	2.42 (0.67, 5.92)
Parity = 2+								
Cervical dilatation at:	Adm. at 3 cm (*N* = 231)	Adm. at 3 cm (*N* = 231)	Adm. at 4 cm (*N* = 626)	Adm. at 4 cm (*N* = 626)	Adm. at 5 cm (*N* = 385)	Adm. at 5 cm (*N* = 385)	Adm. at 6 cm (*N* = 414)	Adm. at 6 cm (*N* = 414)
Adm. to 3 cm								
Adm. to 4 cm	2.19 (0.29, 16.32)	2.17 (0.08, 9.75)						
Adm. to 5 cm	3.54 (0.61, 20.75)	4.42 (0.92, 12.92)	1.25 (0.19, 8.14)	1.50 (0.08, 6.50)				
Adm. to 6 cm	4.82 (1.04, 22.38)	5.58 (1.67, 14.25)	2.24 (0.48, 10.48)	2.67 (0.50, 8.00)	0.76 (0.10, 5.80)	0.75 (0.00, 3.33)		
Adm. to 7 cm	5.55 (1.34, 22.96)	6.92 (2.42, 15.75)	3.08 (0.82, 11.52)	3.92 (1.17, 9.75)	1.34 (0.24, 7.46)	1.92 (0.33, 5.50)	0.52 (0.07, 3.65)	0.83 (0.00, 3.58)
Adm. to 8 cm	6.17 (1.63, 23.31)	7.42 (2.92, 16.33)	3.83 (1.18, 12.41)	4.42 (1.50, 10.25)	1.94 (0.40, 9.35)	2.50 (0.67, 6.08)	1.20 (0.26, 5.52)	1.33 (0.25, 4.25)
Adm. to 10 cm	7.24 (2.17, 24.18)	8.25 (3.50, 17.25)	4.71 (1.71, 13.02)	5.33 (2.08, 11.33)	3.07 (0.87, 10.83)	3.33 (1.17, 7.25)	2.39 (0.77, 7.42)	2.25 (0.67, 5.50)

Data presented as median hours (5th, 95th percentiles).

Abbreviation: Adm., Admission

https://doi.org/10.1371/journal.pmed.1002492.t003

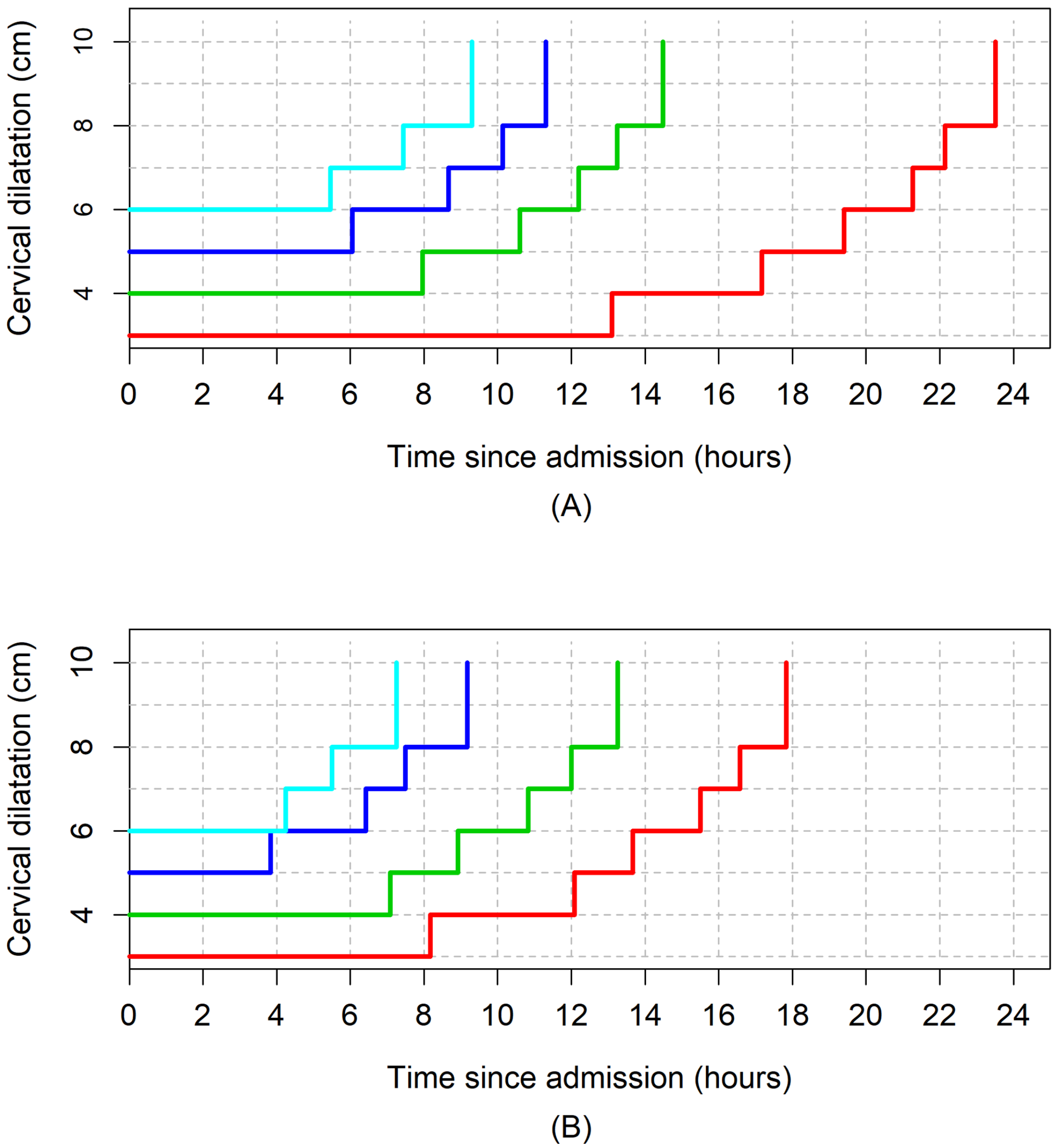

Fig 3. The 95th percentiles of cumulative duration of labour among nulliparous women. (A) Survival analysis. (B) Multistate Markov analysis.

https://doi.org/10.1371/journal.pmed.1002492.g003

percentiles. The rapid progression of cervical dilatation in advanced labour as shown by the sojourn times (in Table 2) is also expressed by the progressively shorter cumulative duration of labour as cervical dilatation on admission increased from 4 to 6 cm. The median rates of 'linear dilatation' increased from 1 cm/hour for nulliparous women admitted at 4 cm to 1.3 cm/hour for those admitted at 6 cm. While the median times for nulliparous women admitted at 4, 5, and 6 cm to achieve full dilatation were within the same time frame for dilatation progressing at ≥1 cm/hour, their 95th percentiles show that it was not uncommon to have labours lasting up to 14, 11, and 9 hours in the same categories of women, respectively. The observed cumulative duration of labour in women arriving in labour before 4 cm shows that some of these

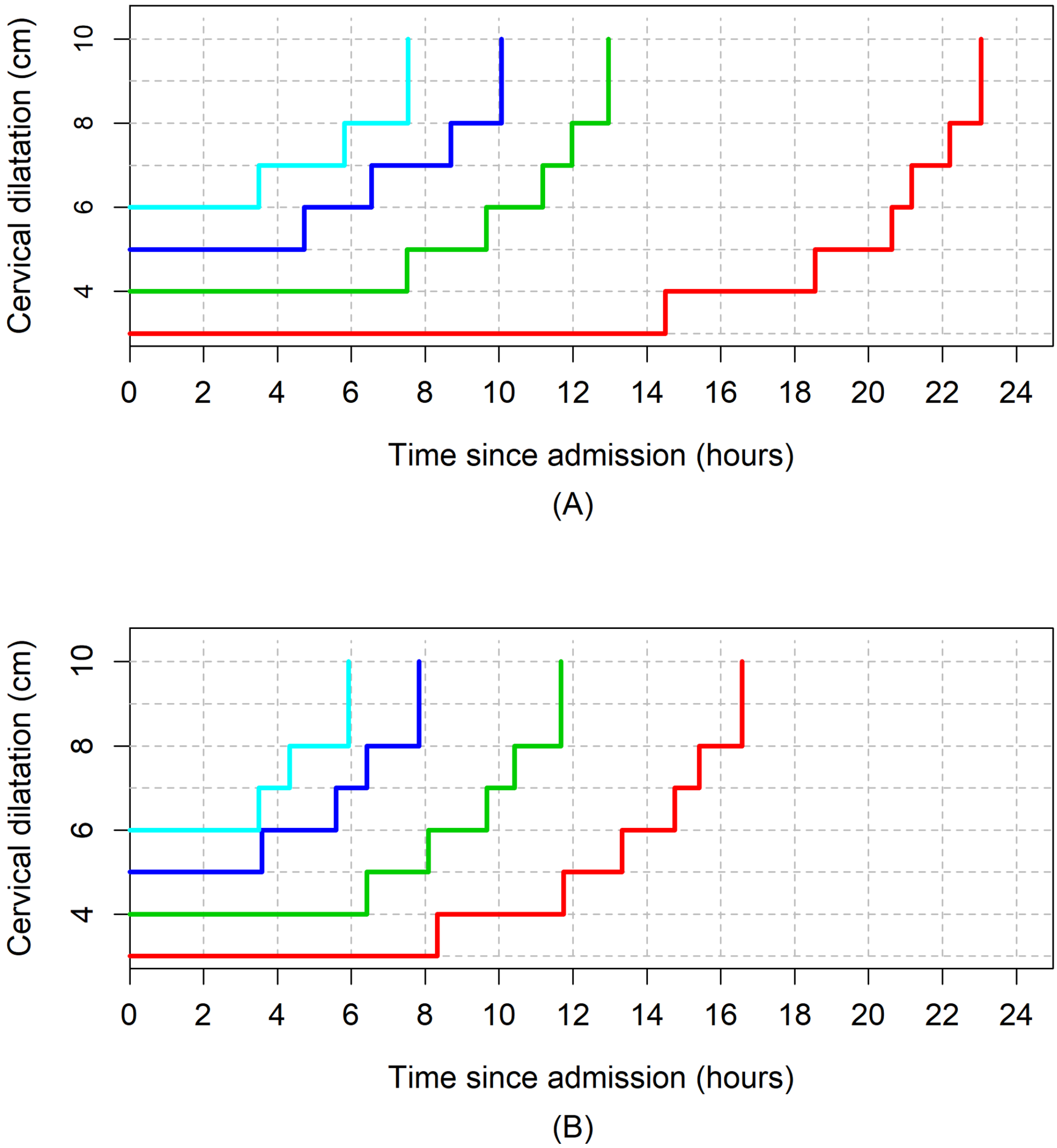

Fig 4. The 95th percentiles of cumulative duration of labour among parity = 1 women. (A) Survival analysis. (B) Multistate Markov analysis.

https://doi.org/10.1371/journal.pmed.1002492.g004

women did not deliver vaginally until almost 24 hours after admission. The overall patterns are similar for multiparous women, although the medians and their corresponding 95th percentiles were generally shorter than for nulliparous women.

Fig 3, Fig 4, and Fig 5 illustrate the 95th percentiles (in Table 3) plotted as connected staircase lines with specified dilatation at admission having its own corresponding line. Based on the dilatation at admission, women falling to the right of these lines (or thresholds) can be regarded as having protracted or unusually slow labour. From the survival analysis data, for example, if a nulliparous woman who was admitted at 4 cm takes longer than 10 hours to reach 6 cm. Likewise, a nulliparous woman admitted at 6 cm can be considered to be experiencing a protracted

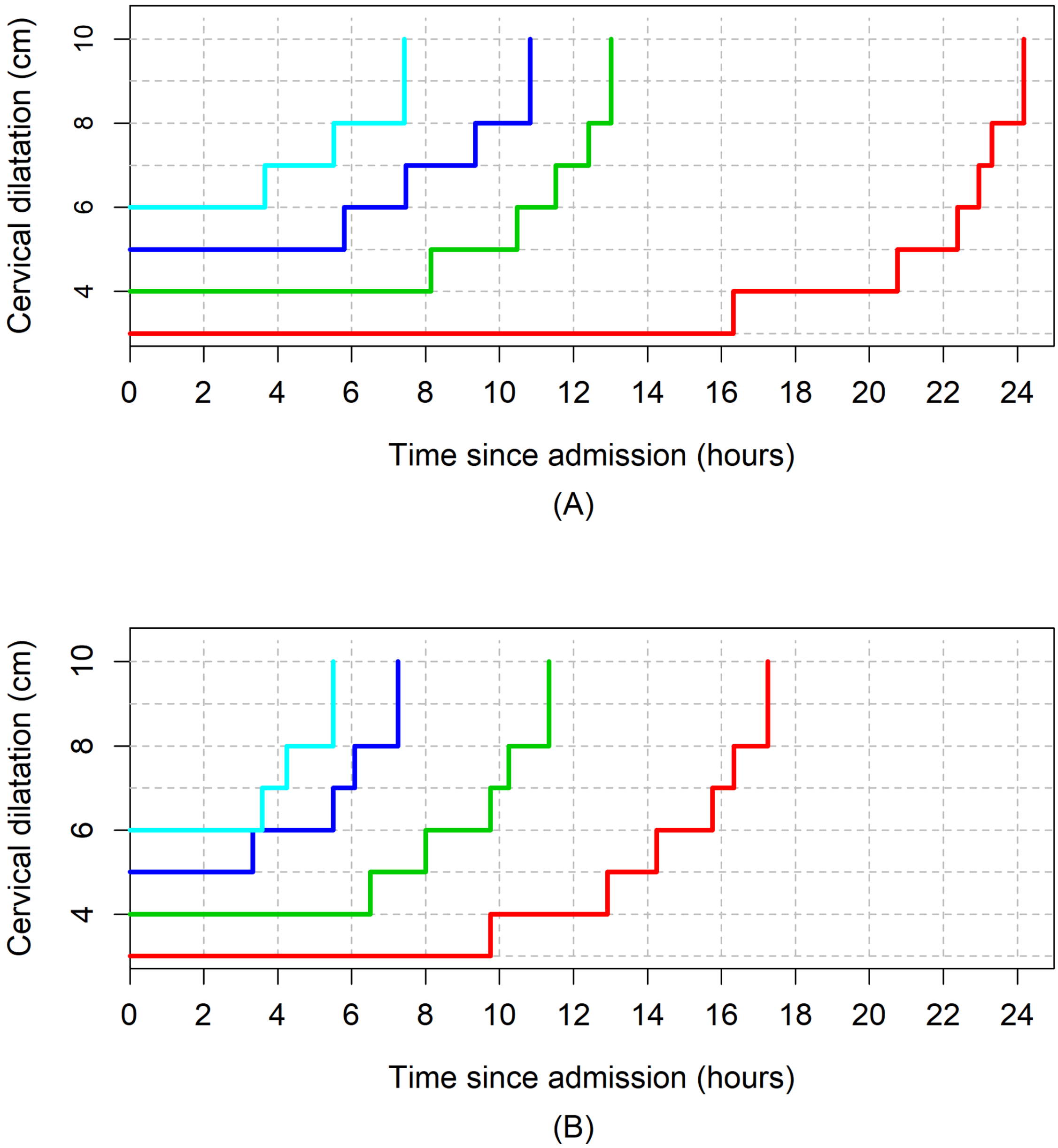

Fig 5. The 95th percentiles of cumulative duration of labour among parity = 2+ women. (A) Survival analysis. (B) Multistate Markov analysis.

https://doi.org/10.1371/journal.pmed.1002492.g005

labour if she takes longer than 7 hours to reach 8 cm or longer than 9 hours to reach 10 cm. The patterns of cumulative labour duration are similar for all parity groups until 6 cm, when the staircase lines become steeper for multiparous compared to nulliparous women.

Labour progression patterns (excluding women with oxytocin augmentation)

Table 4, Table 5, and Table 6 show the results of the sensitivity analyses of labour progression based on our two analytical approaches. As shown in Table 4, the median, 5th, and 95th percentile times to advance by 1 cm were generally shorter when women who had oxytocin were

Table 4. Duration of labour from one level of cervical dilatation to the next with and without augmented labours.

	All women	All women w/o oxytocin	Difference in median times	All women	All women w/o oxytocin	Difference in median times
Parity = 0						
N	**2,100**	**1,300**		**2,166**	**1,300**	
Cervical dilatation	**Survival analysis†**	**Survival analysis†**		**Markov model**	**Markov model**	
3–4 cm	2.82 (0.60, 13.33)	2.47 (0.47, 13.14)	0.35	1.83 (0.08, 8.17)	1.75 (0.08, 7.67)	0.08
4–5 cm	1.72 (0.38, 7.83)	1.35 (0.24, 7.57)	0.37	1.58 (0.08, 7.08)	1.67 (0.08, 7.25)	−0.09
5–6 cm	1.19 (0.23, 6.17)	1.01 (0.19, 5.38)	0.18	0.83 (0.00, 3.83)	0.75 (0.00, 3.42)	0.08
6–7 cm	0.66 (0.09, 4.92)	0.46 (0.05, 4.12)	0.20	0.92 (0.00, 4.25)	0.92 (0.00, 4.00)	0.00
7–8 cm	0.25 (0.02, 3.10)	0.16 (0.01, 2.84)	0.09	0.58 (0.00, 2.50)	0.58 (0.00, 2.50)	0.00
8–10 cm	0.87 (0.18, 4.19)	0.76 (0.14; 4.20)	0.11	0.75 (0.00, 3.33)	0.75 (0.00, 3.50)	0.00
Parity = 1						
N	**1,488**	**1,044**		**1,488**	**1,044**	
Cervical dilatation	**Survival analysis†**	**Survival analysis†**		**Markov model**	**Markov model**	
3–4 cm	2.42 (0.41, 14.18)	2.39 (0.50, 11.49)	0.03	1.92 (0.08, 8.33)	1.83 (0.08, 7.92)	0.09
4–5 cm	1.37 (0.25, 7.65)	0.82 (0.11, 6.38)	0.55	1.42 (0.08, 6.42)	1.17 (0.08, 5.33)	0.25
5–6 cm	0.79 (0.13, 4.95)	0.64 (0.10, 4.17)	0.15	0.83 (0.00, 3.58)	0.75 (0.00, 3.17)	0.08
6–7 cm	0.33 (0.03, 3.67)	0.30 (0.03, 3.15)	0.03	0.75 (0.00, 3.50)	0.75 (0.00, 3.42)	0.00
7–8 cm	0.09 (0.00, 2.69)	0.05 (0.00, 2.48)	0.04	0.42 (0.00, 1.83)	0.33 (0.00, 1.75)	0.09
8–10 cm	0.64 (0.11, 3.56)	0.62 (0.12, 3.23)	0.02	0.67 (0.00, 2.92)	0.58 (0.00, 2.58)	0.09
Parity = 2+						
N	**1,952**	**1,430**		**1,952**	**1,430**	
Cervical dilatation	**Survival analysis†**	**Survival analysis†**		**Markov model**	**Markov model**	
3–4 cm	2.35 (0.31, 17.85)	1.90 (0.27, 13.50)	0.45	2.17 (0.08, 9.75)	1.75 (0.08, 7.58)	0.42
4–5 cm	1.18 (0.17, 8.05)	0.83 (0.11, 6.54)	0.35	1.50 (0.08, 6.50)	1.33 (0.08, 5.83)	0.17
5–6 cm	0.79 (0.10, 6.24)	0.61 (0.07, 5.51)	0.18	0.75 (0.00, 3.33)	0.67 (0.00, 2.92)	0.08
6–7 cm	0.31 (0.03, 3.29)	0.25 (0.02, 2.71)	0.06	0.83 (0.00, 3.58)	0.75 (0.00, 3.50)	0.08
7–8 cm	0.17 (0.01, 2.44)	0.16 (0.01, 2.52)	0.01	0.33 (0.00, 1.50)	0.33 (0.00, 1.58)	0.00
8–10 cm	0.68 (0.12, 3.77)	0.69 (0.12, 4.15)	−0.01	0.50 (0.00, 2.50)	0.50 (0.00, 2.42)	0.00

Data presented as median hours (5th, 95th percentiles).

† Survival analysis with complete and interval-censored values

Abbreviation: w/o, without.

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excluded from the study population. The differences between the median times were generally small, less than half an hour in nearly all cases, and mostly confined to the early part of labour (i.e., between 3 and 5 cm). For nulliparous women, the differences in median times ranged from 5 to 22 minutes, while for parity = 1 and parity = 2+ women, it ranged from 1 to 33 minutes and from less than 1 minute to 27 minutes, respectively. The differences in median times centimetre by centimetre became insignificant as labour advanced.

Table 5 and Table 6 show the cumulative duration of labour from the cervical dilatation observed at admission to the next centimetre until 10 cm, excluding women who had oxytocin augmentation. The slightly faster progression of cervical dilatation in the absence of oxytocin augmentation as shown by the sojourn times (in Table 4) is also expressed by the shorter median cumulative duration of labour in all scenarios. For example, considering the cumulative duration of labour for 3 to 10 cm, 4 to 10 cm, 5 to 10 cm, and 6 to 10 cm, the differences in median times were all less than 1 hour regardless of the analysis method used, and the faster

Table 5. Cumulative duration of labour in Para 0, 1, and 2+ based on the cervical dilatation at admission by use of oxytocin augmentation (survival analysis).

Parity = 0								
	All women	w/o oxytocin	All women	w/o oxytocin	All women	w/o oxytocin	All women	w/o oxytocin
Cervical dilatation at:	Adm. at 3 cm (*N* = 249)	Adm. at 3 cm (*N* = 158)	Adm. at 4 cm (*N* = 715)	Adm. at 4 cm (*N* = 384)	Adm. at 5 cm (*N* = 316)	Adm. at 5 cm (*N* = 191)	Adm. at 6 cm (*N* = 322)	Adm. at 6 cm (*N* = 201)
Adm. to 3 cm								
Adm. to 4 cm	2.76 (0.58, 13.10)	2.54 (0.48, 13.54)						
Adm. to 5 cm	4.49 (1.17, 17.17)	4.07 (0.90, 18.38)	1.71 (0.37, 7.96)	1.32 (0.25, 7.14)				
Adm. to 6 cm	5.65 (1.65, 19.40)	5.27 (1.36, 20.46)	3.02 (0.86, 10.60)	2.58 (0.66, 10.07)	1.29 (0.28, 6.05)	0.86 (0.15, 4.98)		
Adm. to 7 cm	6.50 (1.99, 21.26)	6.09 (1.67, 22.22)	4.15 (1.41, 12.19)	3.65 (1.11, 11.97)	2.10 (0.51, 8.66)	1.74 (0.40, 7.56)	0.78 (0.11, 5.46)	0.51 (0.06, 4.42)
Adm. to 8 cm	7.19 (2.34, 22.14)	6.81 (2.03, 22.88)	4.97 (1.87, 13.24)	4.51 (1.55, 13.15)	3.06 (0.93, 10.14)	2.69 (0.76, 9.47)	1.76 (0.42, 7.44)	1.46 (0.31, 6.81)
Adm. to 10 cm	8.37 (2.98, 23.51)	7.98 (2.61, 24.42)	5.92 (2.42, 14.48)	5.42 (2.06, 14.25)	4.30 (1.64, 11.30)	4.00 (1.46, 10.97)	2.86 (0.88, 9.30)	2.56 (0.75, 8.75)
Parity = 1								
Cervical dilatation at:	Adm. at 3 cm (*N* = 164)	Adm. at 3 cm (*N* = 123)	Adm. at 4 cm (*N* = 491)	Adm. at 4 cm (*N* = 304)	Adm. at 5 cm (*N* = 292)	Adm. at 5 cm (*N* = 211)	Adm. at 6 cm (*N* = 320)	Adm. at 6 cm (*N* = 256)
Adm. to 3 cm								
Adm. to 4 cm	2.05 (0.29, 14.50)	1.98 (0.35, 11.15)						
Adm. to 5 cm	3.43 (0.63, 18.55)	3.24 (0.79 13.34)	1.34 (0.24, 7.51)	0.82 (0.11, 6.25)				
Adm. to 6 cm	4.77 (1.10, 20.63)	4.50 (1.32, 15.35)	2.31 (0.55, 9.66)	1.79 (0.35, 9.19)	0.80 (0.14, 4.72)	0.66 (0.11, 4.03)		
Adm. to 7 cm	5.91 (1.65, 21.17)	5.41 (1.78, 16.46)	2.99 (0.80, 11.18)	2.54 (0.60, 10.84)	1.47 (0.33, 6.54)	1.15 (0.23, 5.73)	0.43 (0.05, 3.50)	0.36 (0.05, 2.68)
Adm. to 8 cm	6.61 (1.97, 22.20)	6.05 (2.08, 17.61)	3.78 (1.19, 11.97)	3.3 (0.95, 11.51)	2.31 (0.61, 8.69)	1.98 (0.49, 8.04)	1.13 (0.22, 5.81)	0.96 (0.19, 4.93)
Adm. to 10 cm	7.55 (2.48, 23.05)	6.92 (2.53, 18.91)	4.63 (1.66, 12.96)	4.08 (1.36, 12.28)	3.43 (1.17, 10.06)	3.17 (1.04, 9.70)	2.19 (0.64, 7.53)	2.03 (0.60, 6.84)
Parity = 2+								
Cervical dilatation at:	Adm. at 3 cm	Adm. at 3 cm	Adm. at 4 cm	Adm. at 4 cm	Adm. at 5 cm	Adm. at 5 cm	Adm. at 6 cm	Adm. at 6 cm
	(*N* = 231)	(*N* = 163)	(*N* = 626)	(*N* = 446)	(*N* = 385)	(*N* = 283)	(*N* = 414)	(*N* = 333)
Adm. to 3 cm								
Adm. to 4 cm	2.19 (0.29, 16.32)	1.84 (0.27, 12.76)						
Adm. to 5 cm	3.54 (0.61, 20.75)	2.97 (0.52, 16.87)	1.25 (0.19, 8.14)	0.91 (0.12, 6.84)				
Adm. to 6 cm	4.82 (1.04, 22.38)	4.09 (0.89, 18.89)	2.24 (0.48, 10.48)	1.85 (0.37, 9.33)	0.76 (0.10, 5.80)	0.54 (0.06, 5.28)		
Adm. to 7 cm	5.55 (1.34, 22.96)	4.82 (1.18, 19.74)	3.08 (0.82, 11.52)	2.66 (0.66, 10.64)	1.34 (0.24, 7.46)	1.10 (0.17, 7.17)	0.52 (0.07, 3.65)	0.44 (0.06, 3.06)
Adm. to 8 cm	6.17 (1.63, 23.31)	5.46 (1.51, 19.82)	3.83 (1.18, 12.41)	3.46 (1.01, 11.82)	1.94 (0.40, 9.35)	1.67 (0.30, 9.18)	1.20 (0.26, 5.52)	1.06 (0.23, 4.87)
Adm. to 10 cm	7.24 (2.17, 24.18)	6.53 (2.03, 21.01)	4.71 (1.71, 13.02)	4.38 (1.54, 12.41)	3.07 (0.87, 10.83)	2.83 (0.73,10.93)	2.39 (0.77, 7.42)	2.24 (0.71, 7.11)

Data presented as median hours (5th, 95th percentiles).

Abbreviation: Adm., Admission

https://doi.org/10.1371/journal.pmed.1002492.t005

Table 6. Cumulative duration of labour in Para 0, 1, and 2+ based on the cervical dilatation at admission by use of oxytocin augmentation (Markov analysis).

	All women	w/o oxytocin	All women	w/o oxytocin	All women	w/o oxytocin	All women	w/o oxytocin
Parity = 0								
Cervical dilatation at:	Adm. at 3 cm (*N* = 249)	Adm. at 3 cm (*N* = 158)	Adm. at 4 cm (*N* = 715)	Adm. at 4 cm (*N* = 384)	Adm. at 5 cm (*N* = 316)	Adm. at 5 cm (*N* = 191)	Adm. at 6 cm (*N* = 322)	Adm. at 6 cm (*N* = 201)
Adm. to 3 cm								
Adm. to 4 cm	1.83 (0.08, 8.17)	1.75 (0.08, 7.67)						
Adm. to 5 cm	4.25 (0.83, 12.08)	4.17 (0.83, 11.75)	1.58 (0.08, 7.08)	1.67 (0.08, 7.25)				
Adm. to 6 cm	5.58 (1.67, 13.67)	5.33 (1.58, 13.17)	2.92 (0.58, 8.92)	2.83 (0.58, 8.83)	0.83 (0.00, 3.83)	0.75 (0.00, 3.42)		
Adm. to 7 cm	7.08 (2.50, 15.50)	6.75 (2.42, 15.00)	4.42 (1.33, 10.83)	4.25 (1.25, 10.67)	2.25(0.42, 6.42)	2.08 (0.42, 5.92)	0.92 (0.00, 4.25)	0.92 (0.00, 4.00)
Adm. to 8 cm	7.92 (3.17, 16.58)	7.58 (3.08, 15.83)	5.33 (1.92, 12.00)	5.17 (1.83, 11.67)	3.08 (0.92, 7.50)	2.92 (0.83, 7.08)	1.83 (0.33, 5.5)	1.75 (0.33, 5.25)
Adm. to 10 cm	9.08 (4.00, 17.83)	8.93 (3.92, 17.33)	6.50 (2.67, 13.25)	6.33 (2.58, 13.17)	4.25 (1.58, 9.17)	4.08 (1.50, 8.75)	3.00 (0.92, 7.25)	2.92 (0.83, 7.08)
Parity = 1								
Cervical dilatation at:	Adm. at 3 cm (*N* = 164)	Adm. at 3 cm (*N* = 123)	Adm. at 4 cm (*N* = 491)	Adm. at 4 cm (*N* = 304)	Adm. at 5 cm (*N* = 292)	Adm. at 5 cm (*N* = 211)	Adm. at 6 cm (*N* = 320)	Adm. at 6 cm (*N* = 256)
Adm. to 3 cm								
Adm. to 4 cm	1.92 (0.08, 8.33)	1.83 (0.08, 7.92)						
Adm. to 5 cm	4.08 (0.83, 11.75)	3.67 (0.75, 10.58)	1.42 (0.08, 6.42)	1.17 (0.08, 5.33)				
Adm. to 6 cm	5.42 (1.58, 13.33)	4.75 (1.42, 11.92)	2.75 (0.5, 8.08)	2.33 (0.42, 6.92)	0.83 (0.00, 3.58)	0.75 (0.00, 3.17)		
Adm. to 7 cm	6.58 (2.33, 14.75)	6.00 (2.17, 13.33)	3.92 (1.17, 9.67)	3.50 (1.00, 8.50)	1.92 (0.42, 5.58)	1.83 (0.33, 5.33)	0.75 (0.00, 3.50)	0.75 (0.00, 3.42)
Adm. to 8 cm	7.25 (2.83, 15.42)	6.58 (2.58, 14.08)	4.58 (1.58, 10.42)	4.08 (1.42, 9.25)	2.58 (0.75, 6.42)	2.42 (0.67, 6.00)	1.42(0.25, 4.33)	1.42 (0.25, 4.25)
Adm. to 10 cm	8.25 (3.58, 16.58)	7.50 (3.25, 15.17)	5.58 (2.25, 11.67)	5.00 (2.00, 10.33)	3.58 (1.25, 7.83)	3.33 (1.17, 7.33)	2.42 (0.67, 5.92)	2.25 (0.67, 5.67)
Parity = 2+								
Cervical dilatation at:	Adm. at 3 cm	Adm. at 3 cm	Adm. at 4 cm	Adm. at 4 cm	Adm. at 5 cm	Adm. at 5 cm	Adm. at 6 cm	Adm. at 6 cm
	(*N* = 231)	(*N* = 163)	(*N* = 626)	(*N* = 446)	(*N* = 385)	(*N* = 283)	(*N* = 414)	(*N* = 333)
Adm. to 3 cm								
Adm. to 4 cm	2.17 (0.08, 9.75)	1.75 (0.08, 7.58)						
Adm. to 5 cm	4.42 (0.92, 12.92)	3.75 (0.75, 10.67)	1.50 (0.08, 6.50)	1.33 (0.08, 5.83)				
Adm. to 6 cm	5.58 (1.67, 14.25)	4.75 (1.33, 11.92)	2.67 (0.50, 8.00)	2.33 (0.42, 7.17)	0.75 (0.00, 3.33)	0.67 (0.00, 2.92)		
Adm. to 7 cm	6.92 (2.42, 15.75)	5.92 (2.08, 13.42)	3.92 (1.17, 9.75)	3.58 (1.08, 8.92)	1.92 (0.33, 5.50)	1.75 (0.33, 5.17)	0.83 (0.00, 3.58)	0.75 (0.00, 3.50)
Adm. to 8 cm	7.42 (2.92, 16.33)	6.50 (2.58, 14.00)	4.42 (1.50, 10.25)	4.08 (1.42, 9.50)	2.50 (0.67, 6.08)	2.33 (0.67, 5.83)	1.33 (0.25, 4.25)	1.33 (0.25, 4.25)
Adm. to 10 cm	8.25 (3.50, 17.25)	7.33 (3.17, 14.92)	5.33 (2.08, 11.33)	4.92 (2.00, 10.50)	3.33 (1.17, 7.25)	3.17 (1.17, 6.92)	2.25 (0.67, 5.50)	2.17 (0.67, 5.42)

Data presented as median hours (5th, 95th percentiles).

Abbreviation: Adm., Admission

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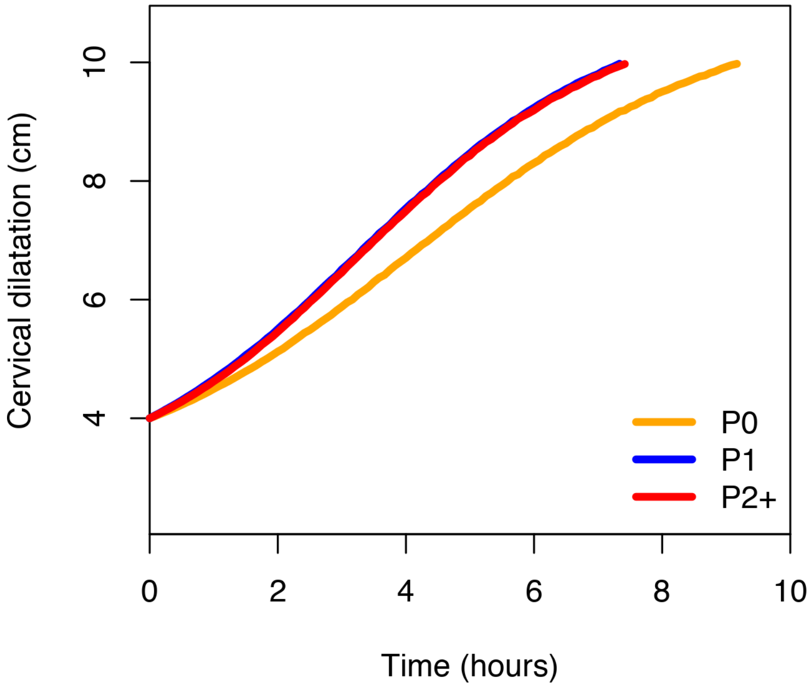

Fig 6. Average labour curves by parity after excluding women with augmented labours. P0, nulliparous women; P1, parity = 1 women; P2+, parity = 2+ women.

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progressions were more obvious in women arriving early in labour (i.e., at 3 and 4 cm cervical dilatation).

Fig 6 shows the average labour curves by parity groups after excluding women with oxytocin augmentation. Excluding women who received oxytocin augmentation did not lead to any major change in the pattern or the trajectories of the curves for any parity group. However, the small difference in the labour curves of multiparous groups (as shown in Fig 2) disappeared when women who received oxytocin augmentation were excluded from the analysis. Fig 7, Fig 8, and Fig 9 illustrate the changes in the 95th percentiles (in Table 5 and Table 6) plotted as connected staircase lines for women who received oxytocin augmentation compared to all women. The shorter cumulative labour duration is also reflected in the 95th percentiles for all parity groups regardless of the dilatation at admission, except for nulliparous women admitted at 3 cm, which showed more variability.

Discussion

Main findings

Understanding the natural progression of labour presents unique challenges in current obstetric practice. Nevertheless, a gradual shift towards approaches to reduce labour interventions deserves evidence-based information on the upper limits of normal labour to guide practice, especially now that modern analytical methods are available. Contrary to the generally held view, our study shows that in this obstetric population, labour appears to progress more slowly than previously reported [1–3, 27, 28]. The median time needed for the cervix to dilate by 1 cm exceeded 1 hour until dilatation was at least 5 cm in both nulliparous and multiparous women. Labour tended to progress more slowly in the early part of traditional active phase and more rapidly after 6 cm. Considerable variability exists in the distribution of times needed to advance by 1 cm and the

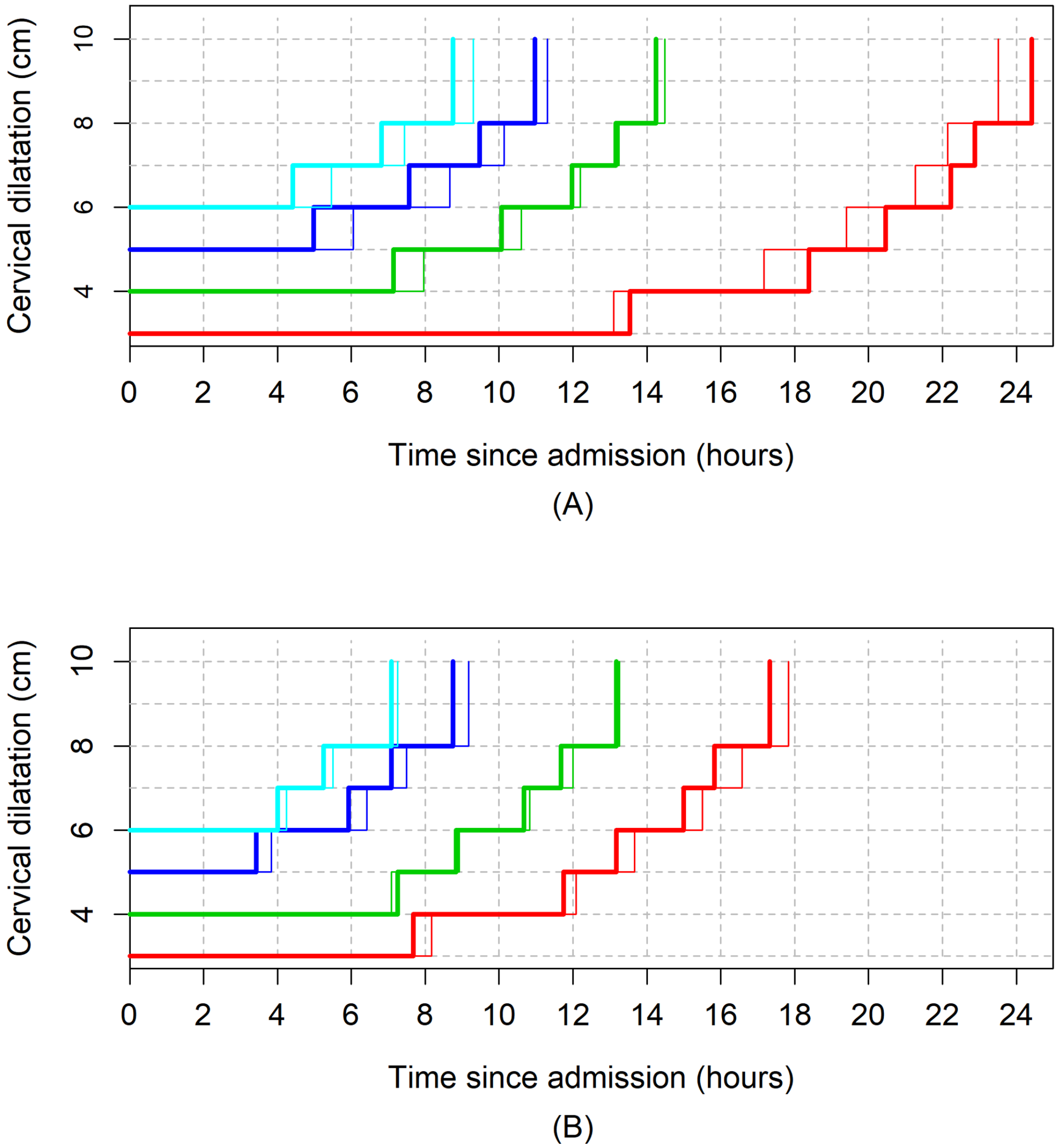

Fig 7. The 95th percentiles of cumulative duration of labour in nulliparous women by augmentation. (A) Survival analysis. (B) Multistate Markov analysis. Thin lines: all women. Thick lines: women with oxytocin augmentation excluded.

https://doi.org/10.1371/journal.pmed.1002492.g007

duration of labour among women who gave birth vaginally without adverse birth outcomes. For instance, based on 95th percentile thresholds, some nulliparous women took more than 7 hours to advance from 4 to 5 cm, and more than 3 hours to advance from 5 to 6 cm. This pattern of progression was observed irrespective of the analysis method we applied.

While the cumulative duration of labour indicates that a substantial proportion of nulliparous women admitted in labour at 4, 5, and 6 cm achieved full dilatation within an expected time frame if the dilatation rate was $\geq$ 1 cm/hour, their 95th percentiles show that labour in these women could last up to 14, 11, and 9 hours, respectively, and still lead to a vaginal birth without untoward effects on the mother and baby. Labour could be considerably slow to

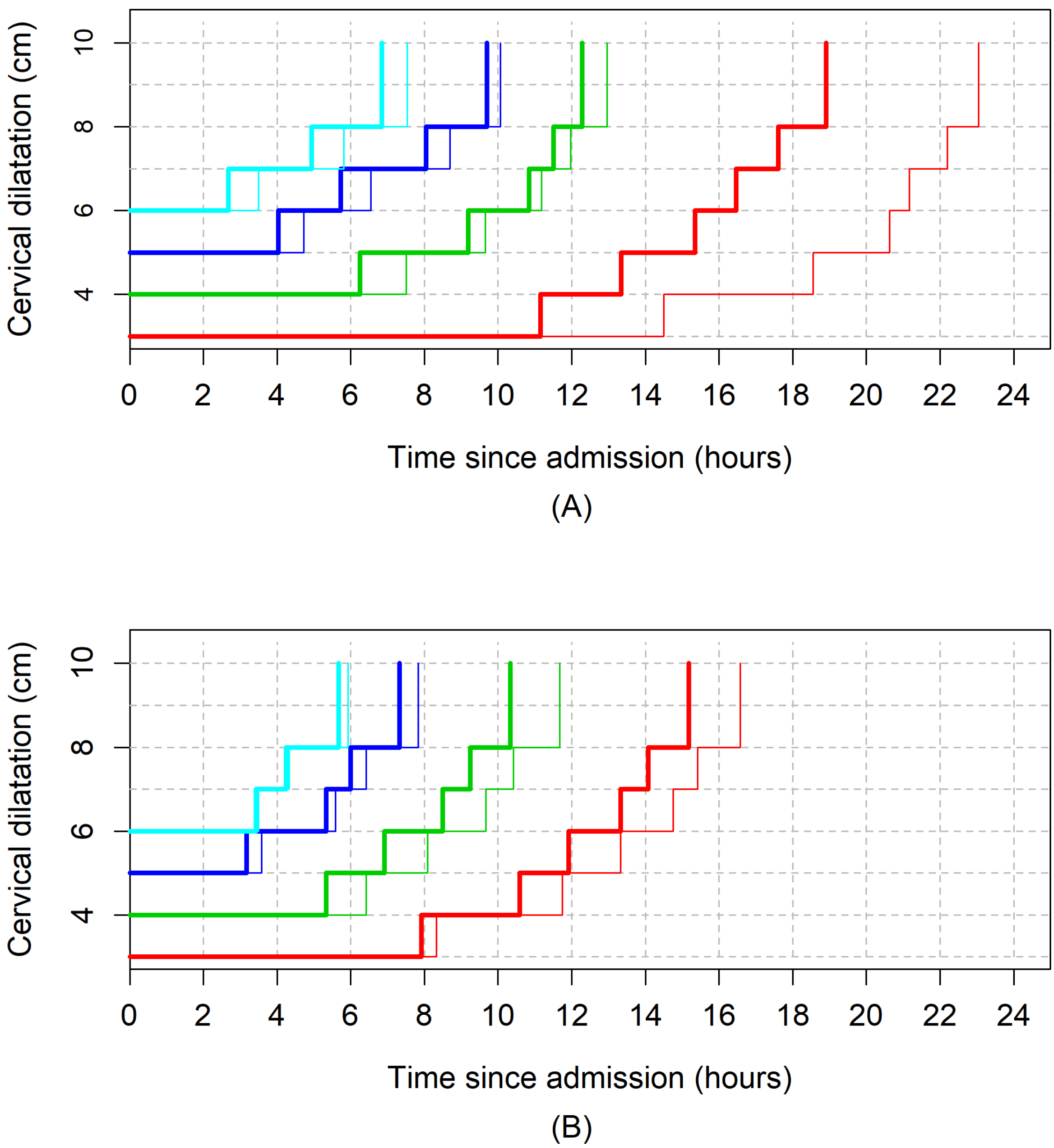

Fig 8. The 95th percentiles of cumulative duration of labour in parity = 1 women by augmentation. (A) Survival analysis. (B) Multistate Markov analysis. Thin lines: all women. Thick lines: women with oxytocin augmentation excluded.

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advance from 3 to 4 cm, and women admitted before 4 cm could have long labours that ultimately end in uncomplicated vaginal birth. Substantial differences exist between actual plots of cervical dilatation over time for individual women and the 'average labour curves' derived from our population-level data.

Strengths and limitations

To our knowledge, this is the first attempt to employ modern statistical and computational mathematical methods to assess the patterns of labour in any African population. We used two

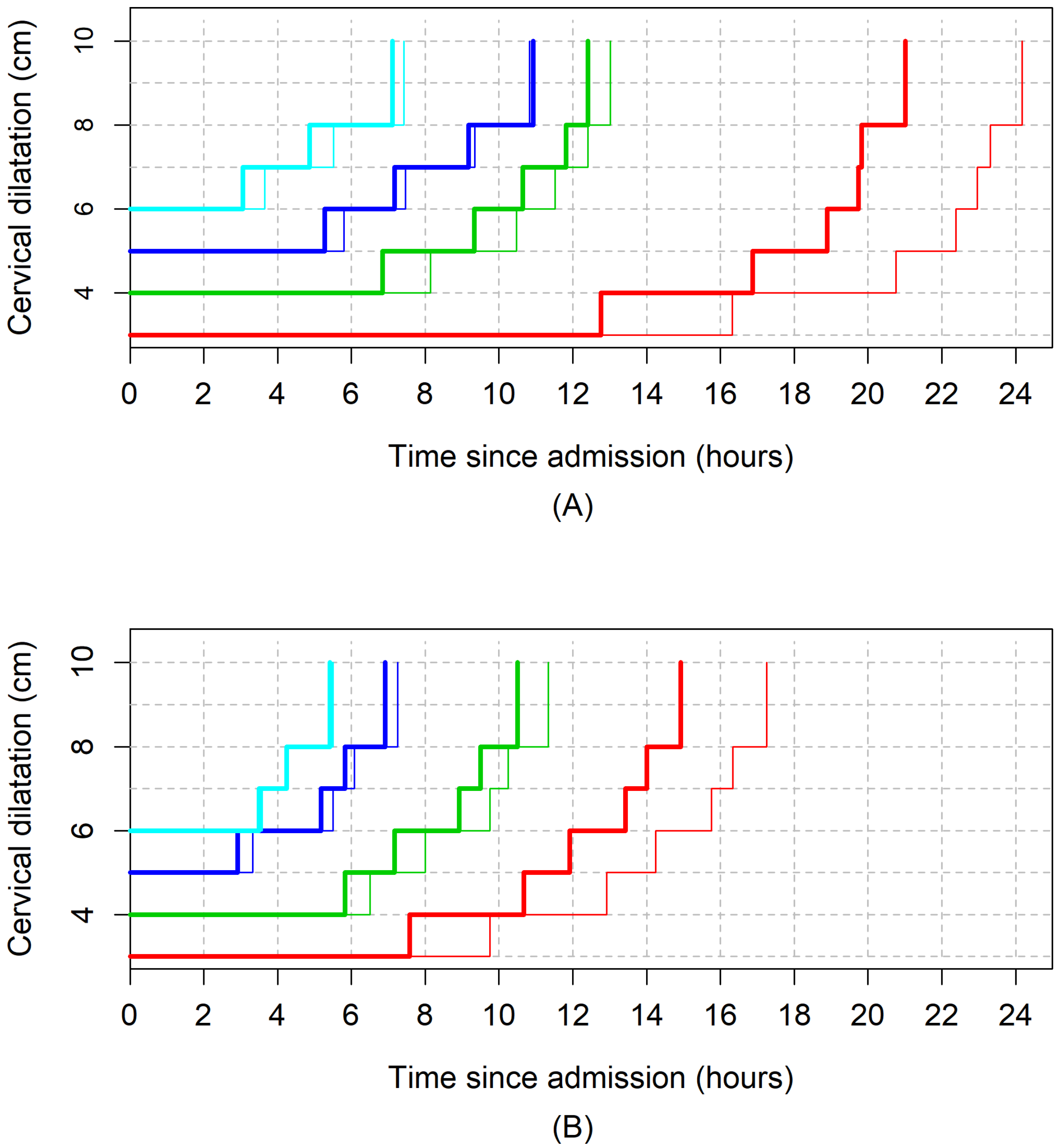

Fig 9. The 95th percentiles of cumulative duration of labour in parity = 2+ women by augmentation. (A) Survival analysis. (B) Multistate Markov analysis. Thin lines: all women. Thick lines: women with oxytocin augmentation excluded.

https://doi.org/10.1371/journal.pmed.1002492.g009

analytical approaches to determine labour progression and construct labour curves from the same sample in an attempt to explore whether the resulting patterns are independent of analysis methods. We applied these methods to a relatively large and prospectively collected data set from two sub-Saharan African countries comprising multiethnic groups. However, two main limitations need to be highlighted.

First, our study is prone to selection bias that is inherent in the designs of studies of labour patterns in current obstetric practice [17]. Women excluded from our analysis due to cesarean section during the first or second stage of labour may have a different pattern of labour progression compared with women who had vaginal births. Our perception is that this will not impact our study findings, not only because such women constituted 12% of women in whom vertex delivery was anticipated, but also because the inclusion of women who had cesarean sections as a result of labour dystocia during the first stage or failed operative vaginal birth during the second stage could have biased our results towards even longer labours. Additionally, construction of our labour curves was dependent on using 10 cm as the starting point through a reverse approach, and therefore, it was essential that all women in our study sample reached full dilatation. Nevertheless, the exclusion of women whose labours were induced and those with nonvertex presentation implies that our findings may not be applicable to these women. Our findings also need to be interpreted within the context of non- or low use of epidural anaesthesia and instrumental vaginal birth. As these interventions tend to be associated with slower labours, it is reasonable to assume that their low rates in this population would have biased the current findings towards shorter rather than longer labour duration.

Second is the measurement bias that could have been introduced due to inherent subjectivity in cervical dilatation assessments and a lack of standardization of frequency of pelvic examinations across participating hospitals. Additionally, clinical assessments of cervical dilatation can only be estimates that are rounded up to the nearest centimetre. Given the total number of women analysed for each parity group, any bias from intra- and inter-observer variations is likely to be random with potential impact on the data spread but with minimal effects on the point estimates. However, it is possible that the accuracy of our estimations could have been affected by smaller sample sizes in the subgroups that were used to explore various obstetric characteristics. For example, fewer women in our analysed sample presented to the labour ward at 3 cm or less compared to 4 cm and above in all parity groups. While this reflects the prevailing practices in the study hospitals and most maternity units around the world, it is possible that smaller numbers of women did not permit an equally robust analysis of the passive phase of labour and could have contributed to even wider variability in cervical dilatation profiles during this stage.

Interpretation

Our findings provide new data from the perspective of a sub-Saharan African population to support the observations reported in similar studies by Zhang [12–14], Suzuki [16], Shi [15], and their colleagues, which suggest that labour progresses more slowly than previously thought. Similar to these studies, our study reveals that the variability of labour progress in a cohort of nulliparous and multiparous women with vaginal birth is greater than generally appreciated. This variability is apparent even in an obstetric population as selected as ours and is independent of our analysis methods, centimetre of cervical dilatation, or cervical dilatation of the woman at admission.

Despite the general similarities in the nulliparous labour progression pattern between our study and those by Zhang [14], Suzuki [16], and Shi [15] et al., there are important differences in the 95th percentiles reported for sojourn times and cumulative durations of labour. Our 95th percentile times indicate that labour can even be slower than what was reported by Zhang [14] and Shi et al. [15], in their American and Chinese populations, respectively, but not as long as Suzuki et al. [16] reported for Japanese women. While this may be due to the differences in the methods for analysing labour progression, a more logical explanation is the heterogeneity in these study populations in terms of labour interventions and demographic characteristics. For instance, oxytocin augmentation among nulliparous women was more common in the US population (47%) studied by Zhang et al. [14] and our study population (40%), but infrequent (6.5%) in the Japanese population studied by Suzuki et al. [16].

The described patterns of labour progress from our study deviate substantially from what Friedman's curve indicates [1–3]. The classic sigmoidal pattern was not observed in our average labour curves. This may be due to the fact that the majority of the women in our study were not admitted early enough in labour to substantially reflect the pattern of the passive phase of labour and because of the lack of documented assessment of 9-cm dilatation in our cohort, which precluded exploration of any deceleration between 9 and 10 cm. In his series of 500 nulliparous women [2], Friedman used the mean values of the four separate phases of individually plotted sigmoid curves to derive the mean labour curve and reported 1.2 cm/hour as the minimum value of 'phase of maximum slope' based on the 95th percentile point on the distribution curve. The nulliparous average curves from our cohort are less steep, and the 95th percentile values from one level of dilatation to the next during the traditional active phase yielded median rates between 0.1 and 0.5 cm/hour between 4 and 10 cm. It remains unclear to what extent an average labour curve depicts the variability associated with individual women's labour progress, and its value in clinical practice is becoming increasingly questioned. The differences illustrated by the video displays of individual labour profiles, compared to the average labour curves for this cohort, indicate how unreliable a population average curve is in representing an individual woman's labour progression profile.

In an attempt to overcome the shortcomings of Friedman's labour curves, Zhang et al. [12] proposed the use of repeated measures analysis with polynomial modelling as a superior method for constructing labour curves, given its flexibility to fit labour data. Other investigators using the same statistical method have confirmed a similar pattern of labour curves published by Zhang et al [12–14]. However, we found that the polynomial model was not appropriate for our data, as it presents a behaviour that is incompatible with labour curve modelling. Rather, we applied multistate Markov modelling to overcome the unpredictable nature of cervical dilatation [29], since its models can accommodate the inherent randomness in cervical dilatation over time [30] and it has the advantage of providing a better representation of real life scenarios from more angles by including empirical observations. We also applied a nonlinear mixed model because of its advantages in terms of interpretability, parsimony, and validity [31]. Although the curves obtained from our nonlinear mixed models are similar to those constructed through polynomial models by previous authors [12, 14, 15], they should be interpreted with caution, as the model appears dependent on extrapolation beyond the normal range of observations for women in the sample.

An interesting finding in our study is the median cumulative duration of labour (e.g., from 4 to 10, 5 to 10, and 6 to 10 cm), which, when considered linearly, suggests that the cervix was dilating at $\geq$ 1 cm/hour. However, such interpretation hides the nonlinearity of labour progression patterns for most women and does not account for slower progress at the beginning of the traditional active phase and faster progress when active phase is advanced. This implies that some women within the 95th percentile boundary as shown in our study will be categorised as having protracted labour if current labour standards were applied. For instance, a woman with reassuring maternal and fetal conditions who remains at 4 cm for 4 hours may be subjected to oxytocin augmentation when she could still be within her normal limits before advancing to 5 cm. Application of interventions too soon when a woman is still within the boundaries of her normality probably accounts for escalating rates of interventions to expedite labour globally.

One subject of debate in the analysis of labour progression patterns in contemporary practice is the potential impact of oxytocin augmentation on observed labour patterns. A widely held view is that the inclusion of women with augmented labour is likely to produce faster labour progression profiles, and the restriction of analysis to women without labour augmentation will generate labour profiles that reflect natural labour progression. However, we found the contrary, as the exclusion of women with augmented labours from our study population resulted in generally faster labour progression patterns. Although unexpected, this finding was not surprising, as it reflects the impact of Friedman's original curves and their derivative tools on labour management even today. Women with augmented labours were those assessed by labour attendants as having slower than normal progression based on a preconceived expectation of 1 cm/hour cervical dilatation. Therefore, their exclusion from the analysed study population leaves a highly selected population of women whose labour progression, by the assessment of the labour attendants, conformed to this preconceived expectation and did not require labour augmentation. While the overall clinical implications of the altered progression in terms of labour duration are minimal, our findings support the inclusion of women with augmented labours in the analysis of labour progression in the context where use of oxytocin is the norm so as to facilitate applicability of their findings.

Conclusions and recommendations

We acknowledge that the described labour patterns from this cohort may be related to the demographic characteristics and prevailing clinical practices in our study settings. Nevertheless, a number of clear messages emerged from our study. First, population average labour curves are at best estimates that may not truly reflect the variability associated with labour progress and could potentially misclassify individual women. It appears that average labour curves are dependent on the underlying assumptions and principles governing the statistical methods from which they are derived. We conclude that population average labour curves are merely useful for illustrative purposes.

Secondly, our labour progression data clearly demonstrate that a minimum cervical dilatation rate of 1 cm/hour throughout the period traditionally described as active phase may be unrealistically fast for some women and should therefore not be universally applied as a threshold for identifying abnormally progressing labour. Likewise, for most nulliparous and multiparous women, labour may not accelerate until a threshold of at least 5 cm is reached. The implication is that a cervical dilatation rate slower than 1 cm/hour throughout the first stage of labour, especially before 5 cm, should not be an indication for interventions to expedite labour provided maternal and fetal vital signs and other observations are normal. It would be useful for labour care providers to consider the upper boundaries reported in this cohort when reviewing whether an intervention is justified. It is important to note, however, that the presented percentile values are insufficient to define abnormal labour that requires interventions to avert adverse outcomes. As this is a selected sample of women without adverse birth outcomes, we cannot conclude from the current analysis whether women with cervical dilatation progressing beyond our percentile values (or other specific boundaries) have comparatively higher risk of adverse birth outcomes. As cervical dilatation is a reflection of a complex interaction of biological, physical, and psychological factors during the course of labour, it is imperative that women with a suspicion of protracted labour be carefully evaluated to exclude developing complications (e.g., cephalopelvic disproportion) and to ensure that the woman's physical and emotional needs are being met. In the absence of any problems other than a slower than expected cervical dilatation (i.e., 1 cm/hour), it is in the interest of the woman that expectant, supportive, and woman-centred labour care is continued.

We propose that averaged lines or curves are not used for decision-making in the management of labour for individual women. Efforts should focus on developing individualised (or personalised) labour management algorithms that optimize woman-centred health outcomes. Decision-analysis models and machine learning technologies that are available today can assist in achieving this objective.

Supporting information

S1 STROBE Checklist.
(DOC)

S1 Fig. States and matrix of possible transitions of cervical dilatation. (a) Schematic representation of possible states from 2 cm to 10 cm of cervical dilatation until birth (absorbing state). (b) Matrix representation of all possible transitions between states of cervical dilatation.
(TIF)

S2 Fig. 3D graphical illustration of transition (matrix) model. The temporal evolution of the distribution representing the theoretical cohort entering labour at 2 cm of cervical dilation. Example of graphical representation of the transition (matrix) model for a simple case study where each state (2, 3, 4, 5, 6, 7, 8, 10) is modelled as the possible next cervical dilatation until the delivery state (D). Simulation was for a period cycle of 1 hour between transitions for the sake of simplicity.
(TIF)

S3 Fig. Average labour curves by parity based on nonlinear mixed models. P0, nulliparous women; P1, parity = 1 women; P2+, parity = 2+ women.
(TIFF)

S1 Video. Individual plots of cervical dilatation, average labour curve (from Markov models), and alert line for nulliparous women.
(MP4)

S2 Video. Individual plots of cervical dilatation, average labour curves (from Markov models), and alert line for multiparous women.
(MP4)

S3 Video. Individual plots of cervical dilatation, average labour curve (from nonlinear mixed models), and alert line for nulliparous women.
(MP4)

S4 Video. Individual plots of cervical dilatation, average labour curves (from nonlinear mixed models), and alert line for multiparous women.
(MP4)

S1 Data. Data set.
(CSV)

S2 Data. Data dictionary.
(XLSX)

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The manuscript presents the views of the named authors only.

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D Article - Development of a system for antenatal and labour care of pregnant women in the Brazilian private health system

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Development of a system for antenatal and labour care of pregnant women in the Brazilian private health system

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Abstract

Brazil is the second country with the highest rate of caesarean sections worldwide which has a negative impact on maternal and neonatal mortality and morbidity rates. In order to stimulate normal vaginal delivery and reduce the number of unnecessary caesarean surgeries, the National Agency of Supplementary Health established a Normative Resolution. It states the right to access the cesarean surgeries and normal deliveries percentation per operator, health facility and physician, ensure partogram use during labour, antenatal care card and the information letter to the pregnant woman within the scope of supplementary health. Aiming at providing quality information to the parturient which would allow her to choose the most suitable type of birth, assisting the health professionals, and facilitating the adaptation of health operators to the new law, a system has been developed. The requirements gathering was done through online questionnaires and interviews with health professionals, which increases their chances of having a good acceptance by the users. The system was developed using the framework CakePHP. As next steps, we intend to develop some more functionalities and implant the system in maternity wards to validate the tool.

Keywords: Antenatal Care; Labour Care; Supplementary Health.

1. Introduction

According to a research conducted in 2014 by the World Health Organization (WHO), Brazil is the second country with the highest rate of deliveries by caesarean section (CS) in the world (55.6%)[1].

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According to data from the National Agency of Supplementary Health (in Portuguese: Agência Nacional de Saúde Suplementar - ANS), responsible for regulating the Brazilian private health sector, the situation is even more worrying in the private health sector. In 2015, 84.6% of deliveries in supplementary health were performed by cesarean section[2]. WHO suggests that populational rates of caesarean sections above 10% do not contribute to the reduction of maternal, perinatal or neonatal mortality. Considering the characteristics of Brazil, the reference rate adjusted by the instrument developed by the WHO would be between 25% and 30%[3].

CS without medical indication increases risks to the woman and neonatal health. Because it is a surgery, it presents complications risks such as infections and hemorrhage to the mother that may result in maternal death[4, 5, 6]. As for the newborn, lesions can occur at the time of delivery or other complications after birth such as infections, pneumonias, prematurity or Intensive Care Unit (ICU) admission, in cases in which surgery is performed before 39 weeks of gestation[7, 8, 9]. In addition, cesarean delivery increases the infant's chance of respiratory distress by 120 times when the surgery is performed between 37 and 38 weeks[10].

In order to stimulate normal vaginal delivery and reduce the number of unnecessary caesarean surgeries, ANS established the Normative Resolution (RN) 368, of January 6, 2015. With its entry into force, health plan operators, whenever requested, must disclose the percentages of cesarean surgeries and vaginal deliveries per health facility and physician. The operators will also be obliged to provide the antenatal care card, in which all the antenatal information must be recorded. In addition, they must require the use of the Partogram, a graphic document where the entire evolution of labor is recorded and will be considered an integral part of the process for payment of the procedure [11].

This article aims to present the development of a system for antenatal care follow-up and labor management at the supplementary health care. The system will allow health professionals to store and organize pregnant women information from the antenatal care facility until delivery. The system will respond to the RN 368, integrating the information on percentages of normal and cesarean deliveries, the antenatal care card and the Partogram in a digital form with easy access. Consequently, it is hoped that the system may contribute to reducing the number of cesarean deliveries performed in the private health sector.

In the next section, we will present some concepts used as reference background for the construction of the proposed system. Then, in the third section, we will describe the steps planned to build the system. In the section four, we will present the results and a brief discussion of the importance of such work. At last, we will present the conclusion and propose future works.

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2. Background

2.1. Supplementary health

The Brazilian health system consists of at least two subsystems: a public health system, the Unified Health System (SUS - Sistema Único de Saúde) and a private health system, the Supplementary Health Care System (SSAM - Sistema Supletivo de Assistência Médica)[12]. The Supplementary Health in Brazil is the activity that involves the operation of private health insurance plans and insurance[13]. This operation is regulated by the ANS that represents the public power and was created to act in the regulation, creation and implementation of norms, control and inspection of the activities of the segment. The supplementary health operators include health insurers, group medicines, cooperatives, philanthropic institutions and self-suggestions. According to the ANS, of 2.905.789 births a total of 589.188 were performed at the Supplementary Health system in 2015.

2.2. Antenatal care card

The antenatal care card, created in Brazil in 1988, is a paper instrument for recording antenatal medical appointments that contains the main data of the pregnant woman's follow-up[14]. Because it is a paper record, the custody of the card may be vulnerable to loss, which may make it difficult to perform any procedure in an emergency situation. The card must be provided to all pregnant women, both in the public and private health care, at the first prenatal visit and must be filled in regularly with information such as the weight of the pregnant woman, vaccination, obstetric characteristics, medical conditions, results of each medical appointment and symptoms presented in the period. The card is also important for recording uterine height measurement, an examination that helps to monitor the development of the baby[15].

The pregnant woman must ask her doctor for the correct and legible filling of the card information and carry it with her all the time, especially on trips, because if she needs emergency care, any health professional can review the information and act safely. It is also important to take the Pregnant Woman's Card to hospital admission during labour[15]. Women with gestational diabetes, for example, can not take glucose serum, that is, through the antenatal care card, before performing any procedure, doctors can analyze and act safely for the mother and the baby[16].

2.3. Partograph

The partograph is a graphic tool where the progression of labor and conditions of the mother and fetus are recorded[17]. It was idealized by WHO in 1992 and became mandatory in maternity hospitals in 1994[18]. It mainly records the frequency of uterine contractions, fetal heart rate, and maternal cervical dilatation. With these records the doctor can assess whether labor is within normal standards and

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whether interventions should be performed. Through the partograph it can be possible to verify if a cesarean was performed unnecessarily.

3. Methods

To gather important information to identify and analyse users' wants, needs and beliefs, we applied online questionnaires. This kind of strategy, also known as market research, is beneficial in providing a better understanding of users' demands and behaviour, thus, helping in product design. Also, interviews with a gynecologist-obstetrician doctor were conducted. Therefore, the requirements (functional and nonfunctional) were raised from both strategies. Consultations were also held on related work and demonstrations of related systems. In this way, our intention was to guarantee consistency, completeness and correctness of the product during the development phase.

The web-based system was designed following the model-view-controller (MVC) pattern[19]. The MVC architecture organizes the application into three interconnected parts: the first (the model) represents an object carrying data; the second (the view) represents the presentation layer; and the last (the controller) acts on both, model and view, controlling the data flow updating the view whenever data changes. This pattern permits a better organization of the code and allows the development of multiple views for a model. The system will provide interoperability by a web service application program interface (API) that adhere to the representational state transfer (REST) architecture[20]. REST is a great way to facilitate the access to the logic of the application and the integration with other systems. The API and the web tool was implemented using the PHP framework CakePHP that makes building web applications using the MVC patterns and implementing REST services simpler, faster, while requiring less code[21]. The presentation layer was developed using HTML5, CSS and JavaScript. Also, a mobile application was developed consuming the RESTful API, so the parturient can always be with her antenatal information when it is needed.

4. Results and Discussion

A total of 15 women (who was pregnant or had already given at least one birth) answered an online questionnaire. The results showed that 66.7% of the women would like to exchange the paper version for a digital one of the pregnant antenatal care card, and 93.3% was interested in a system that provides information such as feeding, proper exercises, baby development and care to be taken during pregnancy. Also, 2 health professionals responded to a different online questionnaire and both would like to use a tool to help their patients with useful information that contains the antenatal care card and the partograph digitally. The participants, women and the health professional, suggested some functionalities to the system in the survey, and although it was a low number of interviewed people, their answers were essential to the software development.

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In addition, a third health professional, an experienced gynecologist and obstetrician doctor, participated in the system development through interviews. In particular, she was crucial at informing the functioning and flow of the process of antenatal care at the supplementary health system. She also suggested some desired functionalities to speed up and facilitate the work of health professionals during antenatal and labour care. We recognize that health professionals may have different perceptions and only one is a very low number. Therefore, further tests and improvements are needed, but it was important to obtain the first version of the system.

The developed system fulfills the requirements of the RN 368 in a digital manner through a web-based multi platform architecture. The model adopted for the development of the application is based on the client-server model, where several clients can simultaneously access the server, which searches for information in a database, to respond to customer requests. The system allows health professionals to register pregnant women and, from then on, to monitor their antenatal care. When starting the labor, the health professional counts on the aid of a digital partogram, a tool much more practical and easy to use than its paper version. The pregnant woman can have access to the information on the Antenatal Care Card and also useful information during pregnancy and the postpartum period, such as feeding, adequate exercise, baby development, etc. In Fig. 1. are presented screenshots of the mobile version developed for pregnant women and in Fig. 2. is shown the digital partogram developed for health professionals.

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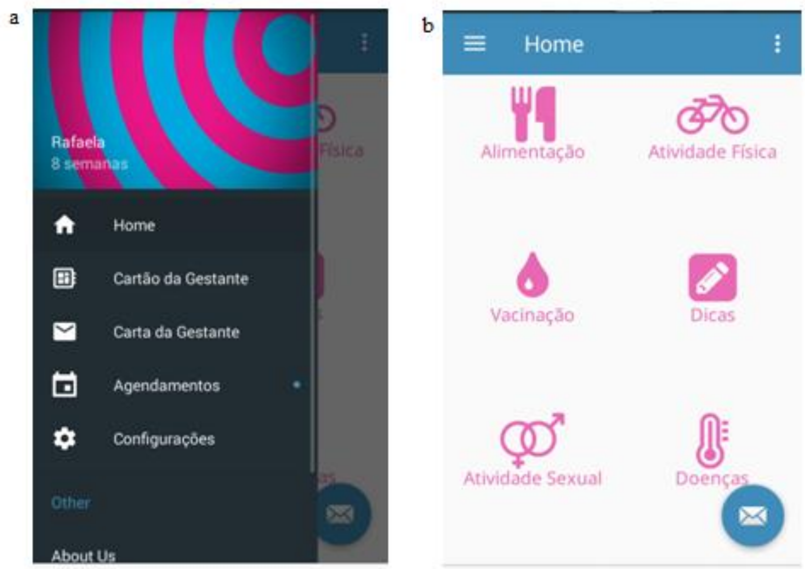

Fig. 1. Mobile interfaces of the system for pregnant women

Fig. 2. Digital Partogram (version of system for health professionals)

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Some similar systems have already been developed. One of them is QUALMAT, a software that aims to improve the performance and motivation of rural health workers and ultimately quality of primary maternal health care services in three African countries Burkina Faso, Ghana, and Tanzania. QUALMAT Clinical Decision Support System provides computerized guidance and clinical decision support for antenatal care, and care during delivery and up to 24 hours post delivery[22]. However, the system does not support the interaction between health professionals and parturients and it is designed for a different scenario.

Childbirth is often one of the most special moments in the lives of many women and their families. In addition, it is important to understand the life risks caused by gestation, which are even greater when a CS is performed. The parturient must have the right to quality information and to have a humanized labour, without any abuse, disrespect or mistreatment for both mother and baby. In the current model of delivery and birth care in the private sector in Brazil, we could say that this may does not always occur due to the high number of SC that increases the risk of complications. A system that allows the women to consult information on the number of cesarean deliveries and normal births of each doctor and health unit would empower the woman to make the best choice on where to get a better antenatal and labour care.

On the other hand, the application will assist health professionals in the follow-up of women from the gestation period until delivery. The tool is expected to ease the burden of health professionals during labor, promote better management, and support decision-making by health professionals. The application could help increase the efficiency of the care process and ultimately improve the outcomes of labor.

Therefore, the application will have a positive impact on both the private health sector, helping the workflow and adjustment to the RN 368, as well as the pregnant woman, making her feel more confident about the procedures performed during her pregnancy. Also, the system could have a positive impact on public health too.

5. Conclusion

The purpose of this article was to present a solution that could help to reduce the number of unnecessary caesarean surgeries, keeping the pregnants informed about her and her baby's health and helping the health professionals at daily work routine to accomplish the RN 368. We proposed a web-based solution that was developed using the MVC patterns.

By being an intuitive system, available on multiple platforms, modeled and developed together with healthcare professionals, it is believed the software will have good acceptance of the users. Regarding this, we aim to strengthen the cooperation and involvement with Brazilian healthcare institutions, in order to make tests and improve our solution toward an effective implementation to its users. We also aim to add more functionalities to our system, like a chat to enable the pregnant and her health

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professional to communicate and an intelligent algorithm to help health professionals to make their decisions at deliveries.

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