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Full Length Research Article

Factors Determining Birth Intervals: A Multilevel Mixed Effect Parametric Survival Approach

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ABSTRACT

Interval between births plays an important role in maternal health as well as child health. This study applies the methodology of Flexible parametric survival models to data on successive births among Nigeria women using the dataset from 2018 National Demographic Health survey. The flexible parametric survival model with Weibull baseline distribution was found to be the best among other fitted baseline distributions. The factors, zone of residence, educational qualification, religion, economic status and age at first birth were found to be significant in predicting the birth intervals. It was found that random effect parameter indicates that the interval between successive births is similar from the same woman.

Keywords: Birth intervals, Baseline hazard, Mixed effect, Flexible parametric model, AIC.

INTRODUCTION

In improving both the maternal and child health, birth spacing plays a crucial role and it is also an essential factor in family planning and fertility control (Adhikari, 2010). Birth interval is the period between successive live births (University of Florida, 2008; John and Kristin, 2019). World Health Organization (WHO) and other international organizations recommend a minimum of 2-3 years interval between pregnancies for the benefit of maternal health and reduction in child and infant mortality. United State Agency for International Development (USAID) suggests that a longer interval of 3-5years might be more beneficial (WHO, 2018).

Both very short and very long inter-birth intervals are associated with health challenges for both the mother and the child (Grundy and Kravdal, 2014). Findings have revealed that short birth intervals, which are less than 24 months are linked to health issues which include maternal morbidities such as uterine rupture and utero-placental bleeding disorders in the women and low birth weight, pre-term birth, small-for-gestational age, stunting growth in the babies (Kozuki *et al*., 2013; Kozuki and Walker, 2013; Fotso *et al*., 2013; Adekanmbi *et al*., 2012; Davanzo *et al*., 2008; Conde-Agudelo *et al*., 2006; Conde-Agudelo *et al*., 2007; Rustein, 2002). A very long birth interval influences increased risk of pre-eclampsia (Conde-Agudelo, 2012). Moreover, studies found that the risk of pre-eclampsia significantly increased between 10% to 12% for each 1-year increase in inter-pregnancy or birth interval since the first delivery (Skjaerven, *et al*., 2002). Aside from the health challenges that short birth interval poses, it also accelerates population growth and weakens developmental efforts. It limits the involvement of women in the economic development of their environment and their country at large thereby making them become less productive members of the society (Hailu *et al.*, 2014). The population of Nigeria as at November 2019 was estimated at 203,021,855 based on Worldmeters elaboration of the latest United Nations data which is equivalent to 2.6% of the total world population and fertility rate of 5.67 (Worldmeters, 2019). Fertility plays an important role in the component of population dynamics as it changes the size and structure of any population (Ayanaw, 2008; Yohannis *et al*., 2003). Hence, this study aimed to examine birth intervals and its associated factors among women of reproductive age in Nigeria using the parametric multilevel mixed-effect survival time model.

MATERIALS AND METHODS

Multilevel Mixed Effects Survival Models

In many practical settings, clustered survival data are often observed. A typical application is the case of a recurrent event, where an individual experienced the event of interest in multiple times in the course of the follow-up time (Gutierrez, 2002). In meta-analysis, analysing the individual patient data Individual patient data (IPD) simultaneously within a hierarchical structure allows a direct adjustment for factors and inclusion of non-proportional hazards in covariate effects (Tudur-Smith *et al*. 2005; Crowther *et al*., 2012; 2014). Other forms of clustering include the case of individuals living in the same area such as geographical location or patients treated in the same hospital or by the same medical practitioner. Such individuals may share the same unobserved features, such as environmental influence or medical care access (Charvat *et al*., 2016).

Multilevel Mixed Effect Parametric Survival Models

Consider the case of a study of G-independent clusters, $i = 1, \dots, G$ (e.g. individuals with repeated events or Hospital, study centres), with each cluster having $j = 1, \dots, n_i$ events or individuals. T_{ij} denotes the survival times for individual j from group i and C_{ij} is the corresponding right censoring time. Let T_{ij} be the observed survival time for the j^{th} individual or event in the i^{th} cluster or individual, assuming the censoring times are independent of the survival times, the observed times are $Y_{ij} = \min(T_{ij}, C_{ij})$ and the censoring indicator $\delta_{ij} = I_{\{T_{ij}, C_{ij}\}}$ which takes the value of 1 if the event has occurred and 0 if otherwise. For each subject, we observe the explanatory variable, x_{ij}.

Application to Data on Birth Interval

Dataset on repeated five successive birth intervals for 11952 women, aged 15-49 from the 2018 Nigeria Demographic and Health Survey (NDHS) were analysed. Only women who already have five successive births were considered and therefore, there were no censored observations. The birth intervals were recorded in months and the methodology of Flexible parametric survival model was applied. Permission to use data from NDHS (2018) was obtained through online registration with Macro International Incorporation via the DHS website (www.measuredhs.com).

The outcome of interest is the interval between five successive births, each woman considered have experienced five consecutive births with four intervals resulting in a total of 47808 events. Each woman was considered as random because of the repeated birth intervals (events) measured. The geopolitical zone, religion, highest educational qualification, economic status and respondent age at first birth (demographic and economic factors) were considered as explanatory variables. In order to have three categories for the Economic Status variable, the “poorest‟ and “poorer”, from wealth index in NDHS data were combined as “poor”, “middle” remained as “middle” while “richer” and “richest” were combined as rich. The two major religions being practiced were considered as Christianity and Islam while the educational qualification was categorised as No education, Primary, Secondary and Higher. The geopolitical zones in the country are North-Central, North-East, North-West, South-East, South-South and South-West, respectively while the location of residence is classified as Urban and Rural. The age at first birth is a continuous variable

The overall aim is to fit the Flexible parametric survival model with different baseline parametric distribution. Model assessment was based on Akaike Information Criterion (AIC), (Akaike, 1974) given as:

$$AIC = -2logL + 2p$$

Where *logL* is the log likelihood and p is the number of parameters in the model. A model with lower AIC is preferred.

Ethical Approval

Permission to use data from NDHS 2018 was obtained through online registration with Macro International Incorporation via the DHS website (www.measuredhs.com). Respondent confidentiality was intact as no names and addresses were included in the data set and therefore the respondents cannot be identified by the researcher.

The Proportional Hazards Parametric Survival Model

The Cox proportional hazards mixed effect survival model is expressed as $h_{ij}(t) = h_0(t)exp(\beta^T x_{ij} + b_j^T z_{ij})$ (1) (Yamaguchi, 2002).

where $h_0(t)$ is the specified baseline hazard function of any of the distributions; exponential, Weibull or Gompertz, lognormal or log-logistic. β is the fixed effect and b_j is the random effect, the random effects are assumed to follow a multivariate normal distribution, with $b_j \sim N(0, \Sigma)$.

Flexible Parametric Model

Royston and Parmar (2002) provided the flexible parametric model as an alternative to the traditional proportional hazard. It has the potential for handling repeated event data. It was modelled on the cumulative hazard scale and extended by Crowther *et al.* (2014) to incorporate random effects. The flexible parametric model is given as;

$$H_{ij}(t) = H_0(t)exp[x_{ij}^T\beta + z_{ij}^T b_j] \quad (2)$$

If expressed in log, the model becomes;

$$\log[H_{ij}(t)] = \log[H_0(t)] + X_{ij}^T\beta + Z_{ij}^T b_j \quad (3)$$

Where β is the fixed effect, b_j is the random effect and $H_0(t)$ is the cumulative baseline hazard function. The spline basis is derived from the log cumulative hazard function of a Weibull proportional hazards model. The restricted cubic splines were used to relax the linear relationship with log time Royston and Parmar (2002) and Royston and Lambert (2011). Therefore, the restricted cubic spline function of $\log(t)$, with knots $\boldsymbol{k}_0$, as $s\{\log(t)|\gamma, \boldsymbol{k}_0\}$. With K knots if $w = \log(t)$ is written as:

$$s(w|\gamma, \boldsymbol{k}_0) = \gamma_0 + \gamma_1 v_1 + \gamma_2 v_2 + \cdots + \gamma_{m+1} v_{m+1} \quad (4).$$

with derived variables v_j(basic functions) and parameter vector γ, where;

$$v_i = w \quad (5)$$

$$v_j = (w - k_j)_+^3 - \lambda_j(w - k_{min})_+^3 - (1 - \lambda_j)(w - k_{max})_+^3 \quad (6).$$

for $j = 2, \ldots, m + 1$, $(w - k_j)_+^3$ is equal to $(w - k_j)^3$ if the value is positive and 0 elsewhere, and

$$\lambda_j = \frac{k_{max} - k_j}{k_{max} - k_{min}} \quad (7).$$

This is now substituted for the log cumulative baseline hazard in equation (3).

$$\log[H_{ij}(t)] = \eta_{ij} = s(\log(t)\,|\gamma, k_0) + X_{ij}^T\beta + Z_i^T b_i \quad (8)$$

Transforming the hazard and survival scales, we have;

$$h_{ij}(t) = \left[\frac{1}{t}\frac{ds(\log(t)|\gamma, k_0)}{d\log(t)}\right] exp(\eta_{ij}),$$
$$s_{ij}(t) = exp[-exp(\eta_{ij})] \quad (9)$$

The proportional cumulative hazard is assumed in equation (3). Crowther *et al*. (2014).

Table 1 presents some probability distributions with their survival, hazard and cumulative survival functions.

Table 1: Probability distribution, survival, hazard and cumulative hazard functions of the parametric distributions

DISTRIBUTIONS	PROBABILITY DISTRIBUTION FUNCTIONS	SURVIVAL FUNCTIONS	HAZARD FUNCTIONS	CUMULATIVE HAZARD FUNCTIONS
Exponential	$\lambda e^{-\lambda t}$	$e^{-\lambda t}$	λ	λt
Weibull	$\lambda\gamma t^{\gamma-1}e^{-\lambda t^{\gamma}}$	$e^{-\lambda t^{\gamma}}$	$\lambda\gamma t^{\gamma-1}$	λt^{γ}
Gompertz	$ae^{bt}e^{-\frac{a}{b}(e^{bt}-1)}$	$e^{-\frac{a}{b}(e^{bt}-1)}$	ae^{bt}	$\frac{a}{b}(e^{bt}-1)$
Log-logistic	$\frac{ab(at)^{b-1}}{(1+(at)^{b})^{2}}$	$\frac{1}{1+(at)^{b}}$	$\frac{ab(at)^{b-1}}{1+(at)^{b}}$	$\ln(1+(at)^{b})$
Lognormal	$\frac{1}{\sqrt{2\pi st}}e^{-\frac{(\ln(t)-m)^{2}}{2s^{2}}}$	$1-\Phi\left(\frac{\log(t)-m}{s}\right)$	$\frac{\frac{1}{st}\Phi\left(\frac{\log(t)-m}{s}\right)}{1-\Phi\left(\frac{\log(t)-m}{s}\right)}$	
Gamma	$\frac{\lambda^{k}t^{k-1}\lambda^{-\lambda t}}{\Gamma(k)}$	$1-\mathrm{I}_{k}(\lambda t)$	$\frac{\lambda^{k}t^{k-1}e^{-\lambda t}}{\left(1-\mathrm{I}_{k}(\lambda k)\right)\Gamma(k)}$	

Likelihood and estimation

Under the mixed effect survival models, the likelihood for the i^{th} cluster is defined as;

$$L_i = \int_{-\infty}^{\infty}\left[\prod_{j=1}^{n_i} p\left(T_{ij},\delta_{ij}|b_i,\boldsymbol{\theta}\right)\right]p(b_i|\boldsymbol{\theta})db_i \quad (10)$$

With parameter vector θ, under a hazard model

$$p\left(T_{ij},\delta_{ij}|b_i,\theta\right) = h\left(T_{ij}\right)^{\delta_{ij}} exp\left[-\int_0^{T_{ij}} h\left(T_{ij}\right)\right] \quad (11).$$

With $h()$defined in eq. (1). Assuming proportional hazards under the flexible parametric survival model;

$$p\left(T_{ij},\delta_{ij}|b_i,\theta\right) = \left[\left\{\frac{1}{T_{ij}}\frac{ds\left(\log\left(T_{ij}\right)|\gamma,\mathrm{K}_0\right)}{d\log\left(T_{ij}\right)}\right\}exp\left(\eta_{ij}\right)\right]^{\delta_{ij}} exp\left\{-exp\left(\eta_{ij}\right)\right\} \quad (12)$$

The random effects are assumed to follow a multivariate normal distribution

$$p(b_i|\theta) = (2\pi|\boldsymbol{V}|)^{-q/2} exp\left\{-\frac{b_i'\boldsymbol{V}'b_i}{2}\right\} \quad (13).$$

Where V is a variance-covariance matrix and q is the number of random effects. Due to possibly multi-dimensional integral, the integral in equation (10) is analytically intractable and therefore, requires numerical techniques for its evaluation.

RESULTS AND DISCUSSION

Firstly, the Flexible parametric survival model was fitted with exponential, Weibull, lognormal, loglogistic and gamma baseline distributions. The results showing values of AIC of the models are presented in Table 2.

Table 2: The values of the AIC for Flexible parametric survival models with different baseline distribution

BASELINE HAZARD DISTRIBUTION	LOG LIKELIHOOD	AIC
Exponential	-214910.5	429847.1
Weibull	-34800.38	69630.75
Lognormal	-192239.7	384509.3
Log logistic	-191798.9	383627.8
Gamma	-193777.2	387584.3

As observed from Table 2, Flexible parametric survival model with Weibull baseline hazard distribution has the least AIC value and therefore performed best compared to other baseline hazard distributions. Further discussions of effects of the observed factors on birth intervals are therefore based on the model with the least AIC value.

The estimates of the hazard ratio and p-values for Flexible parametric survival model with Weibull baseline hazard distribution are presented in Table 3. From the p-values, all the factors considered were found to be significant in explaining the variation in the interval of successive births in women. The birth intervals were measured in months, therefore, the hazards increased or decreased by the hazard ratio in months. It was observed that the hazard ratio increased with 0.0271 as the age increased. Findings from EDHS showed similar conclusion (EDHS, 2011). For the different zones of residence, hazard increased with 0.2053, 0.3011, 0.3191 and 0.0813 for women from North-east, Northwest, South-east and South-south, respectively compared to women from the North-central but the hazard decreased by 0.1454 for women in the South-west compared to women from the North-central.

Also, for the highest educational qualification, the hazard for women with secondary education increased by 0.0447 compared to women with no education while the hazard decreased for women with primary and higher education with 0.046 and 0.1196 respectively compared to women with no education. The findings on the educational qualification as a determinant of birth interval are consistent with findings of Abdurrahman and Majid (2007), Youssef (2005) and Yohannes *et al.* (2011). The economic status shows that the hazard of women decreased by 0.0463 and 0.095 for women whose economic status was middle and rich, respectively compared to women whose economic status was poor. The findings on economic status are similar with the result of the study conducted in Ethiopia which revealed that the length of birth interval increased with increasing economic status (Yohannes *et al.* 2011). The hazard of Christian women decreased by 0.1959 compared to Muslim women.

The estimated frailty standard deviation is 0.5699 (95% CI: 0.5545, 0.5858), indicating a non-heterogeneous baseline hazard function which implies that the interval between repeated births from a woman is similar.

CONCLUSION

Findings of this study reveal Akaike Information Criterion (AIC) indicate Flexible parametric survival model with Weibull baseline hazard distribution was best to describe the recurrence of birth in individual woman. All the factors considered were found to influence the interval between births. In estimating the random effect parameter, it was revealed that the intervals between successive births are similar from the same woman, which implies that repeated birth intervals from the same woman are homogenous. Therefore, the childbirth spacing is dependent on the individual woman and the intervals between successive births from the same woman are similarly spaced.

Table 3: Hazard ratio, p-value and 95% confidence interval of the hazard ratio of flexible parametric survival model with Weibull baseline

FACTORS	HAZ. RATIO (S.E)	P-VALUE	95% C.I	
Age at first Birth				
Age	1.0271(0.0022)	<0.0001	1.0227	1.0314
Zone				
North-East	1.2053(0.0295)	<0.0001	1.1488	1.2646
North-West	1.3011(0.0308)	<0.0001	1.2422	1.3629
South-East	1.3191(0.0399)	<0.0001	1.2431	1.3997
South-South	1.0813(0.0348)	0.0150	0.8041	0.9082
South-West	0.8546(0.0265)	<0.0001	0.8042	0.9082
Highest Educational Qualification				
Primary	0.9540(0.0197)	0.0230	0.9161	0.9935

Secondary	1.0447(0.0256)	0.0750	0.9956	1.0962
Higher	0.8804(0.0363)	0.0020	0.8121	0.9545
Economic Status				
Middle	0.9537(0.0182)	0.0130	0.9186	0.9901
Rich	0.9050(0.0185)	<0.0001	0.8694	0.9421
Religion				
Christian	0.8041(0.0183)	<0.0001	0.7691	0.8407
Constant	0.0001(0.0000)	<0.0001	0.0001	0.0001
Random Effects				
Random Effects Parameters	**Estimate**	**Std. Error**	**95% C.I**	
Woman	0.5699	0.008	0.5545	0.5858

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