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Prediction of stillbirth low resource setting in Northern Uganda

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Abstract

Background: Women of Afro-Caribbean and Asian origin are more at risk of stillbirths. However, there are limited tools built for risk-prediction models for stillbirth within sub-Saharan Africa. Therefore, we examined the predictors for stillbirth in low resource setting in Northern Uganda.

Methods: Prospective cohort study at St. Mary's hospital Lacor in Northern Uganda. Using Yamane's 1967 formula for calculating sample size for cohort studies using finite population size, the required sample size was 379 mothers. We doubled the number (to > 758) to cater for loss to follow up, miscarriages, and clients opting out of the study during the follow-up period. Recruited 1,285 pregnant mothers at 16–24 weeks, excluded those with lethal congenital anomalies diagnosed on ultrasound. Their history, physical findings, blood tests and uterine artery Doppler indices were taken, and the mothers were encouraged to continue with routine prenatal care until the time for delivery. While in the delivery ward, they were followed up in labour until delivery by the research team. The primary outcome was stillbirth 24 + weeks with no signs of life. Built models in RStudio. Since the data was imbalanced with low stillbirth rate, used ROSE package to over-sample stillbirths and under-sample live-births to balance the data. We cross-validated the models with the ROSE-derived data using K (10)-fold cross-validation and obtained the area under curve (AUC) with accuracy, sensitivity and specificity.

Results: The incidence of stillbirth was 2.5%. Predictors of stillbirth were history of abortion (aOR = 3.07, 95% CI 1.11—8.05, $p = 0.0243$), bilateral end-diastolic notch (aOR = 3.51, 95% CI 1.13—9.92, $p = 0.0209$), personal history of preeclampsia (aOR = 5.18, 95% CI 0.60—30.66, $p = 0.0916$), and haemoglobin 9.5 – 12.1 g/dL (aOR = 0.33, 95% CI 0.11—0.93, $p = 0.0375$). The models' AUC was 75.0% with 68.1% accuracy, 69.1% sensitivity and 67.1% specificity.

Conclusion: Risk factors for stillbirth include history of abortion and bilateral end-diastolic notch, while haemoglobin of 9.5—12.1 g/dL is protective.

Keywords: Stillbirth, Risk factors, Prediction models, Uganda, Africa

Introduction

Stillbirth is the death of a fetus before birth after 20 weeks of gestation [1]. In the early twentieth century, stillbirth was any child who exhibits no sign of life by crying or

breathing, or by pulsation in the cord at its attachment to the body of the child, or by beating of the heart and measuring more than 13 inches in length from the top of head to the heel at birth [2]. In the late twentieth century stillbirth was defined as any baby born at 24 weeks of gestation without a sign of life [3]. It can be classified as an early (24 – 27 weeks), late (28 – 36 weeks), or term (37 weeks) stillbirth [4].

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The global prevalence of stillbirth is approximately 2% [5], with 0.3% occurring in the global north [6, 7], and more than 2% in the global south [5, 8–10]. Women of Afro-Caribbean and Asian origin are more at risk of stillbirths [7, 11–14] and this may be associated with racial disparities in accessing health care [12]. Incidence of stillbirth in Uganda is about 2.0%–3.6% [15, 16]. However, due to challenges in access to care and policies on death registration in the global south, most stillbirths are not registered [17].

When maternal obesity, smoking, chronic hypertension, antiphospholipid syndrome, type 2 diabetes, and insulin requirement are used in a prediction model risk calculator for stillbirth [18], it predicted stillbirths at 60–72% AUC at 75% sensitivity and close to 100% specificity [6, 7, 19]. When maternal history and fetal growth rates were added to maternal history without using the risk calculator, the discriminative performance of the model had a C-statistic of 0.80 [8].

There are limited number of tools built for risk-prediction models for stillbirth within sub-Saharan Africa. With the problems of access to hospital delivery and African ancestry being a risk factor for stillbirth, we set out to develop and validate a prediction model for stillbirth in Northern Uganda.

Materials and methods

Study design

A prospective cohort study at St. Mary's Hospital Lacor, which is one of the teaching hospitals of Gulu University. Using Yamane's 1967 formula for calculating sample size for cohort studies using finite population size, St. Mary's hospital Lacor delivers approximately seven thousand mothers per year. Since my study duration was 12 months for recruitment of the mothers, the finite population I could access was about 7,000 mothers. Yamane 1967 formula:

$$\text{Samplesize} = N/1 + Ne^2$$

where N is the finite population size 7,000 mothers.

Margin of error (e) 05%

Therefore $n = 7,000 / 1 + 7,000(0.05)^2$

$n = 379$.

The required sample size was 379 mothers. We doubled the number (to > 758) to cater for loss to follow-up, miscarriages, and clients opting out of the study during the follow-up period. Recruited 1,285 pregnant mothers 16 – 24 weeks from April 2019 to March 2020. Excluded all with lethal congenital anomalies diagnosed on ultrasound scan especially molar pregnancy, anencephaly, and cystic hygroma. A questionnaire was filled, and uterine artery Doppler sonography was done on all the mothers. The ultrasonography was done by

one trained obstetrician. A full foetal anatomical survey was done in addition to the uterine artery Doppler indices (pulsatility and resistive indices, end-diastolic notch). Blood samples were taken for complete blood count, liver and renal function tests, from one thousand (1,000) mothers. The mothers were encouraged to continue with routine antenatal care until the time for delivery. While admitted to the delivery ward, the mothers were followed up by the research team until delivery of the baby. The last mother was delivered at the end of September 2020.

Outcome

The Apgar score of zero within the first minute of birth at 24+ weeks was taken as stillbirth.

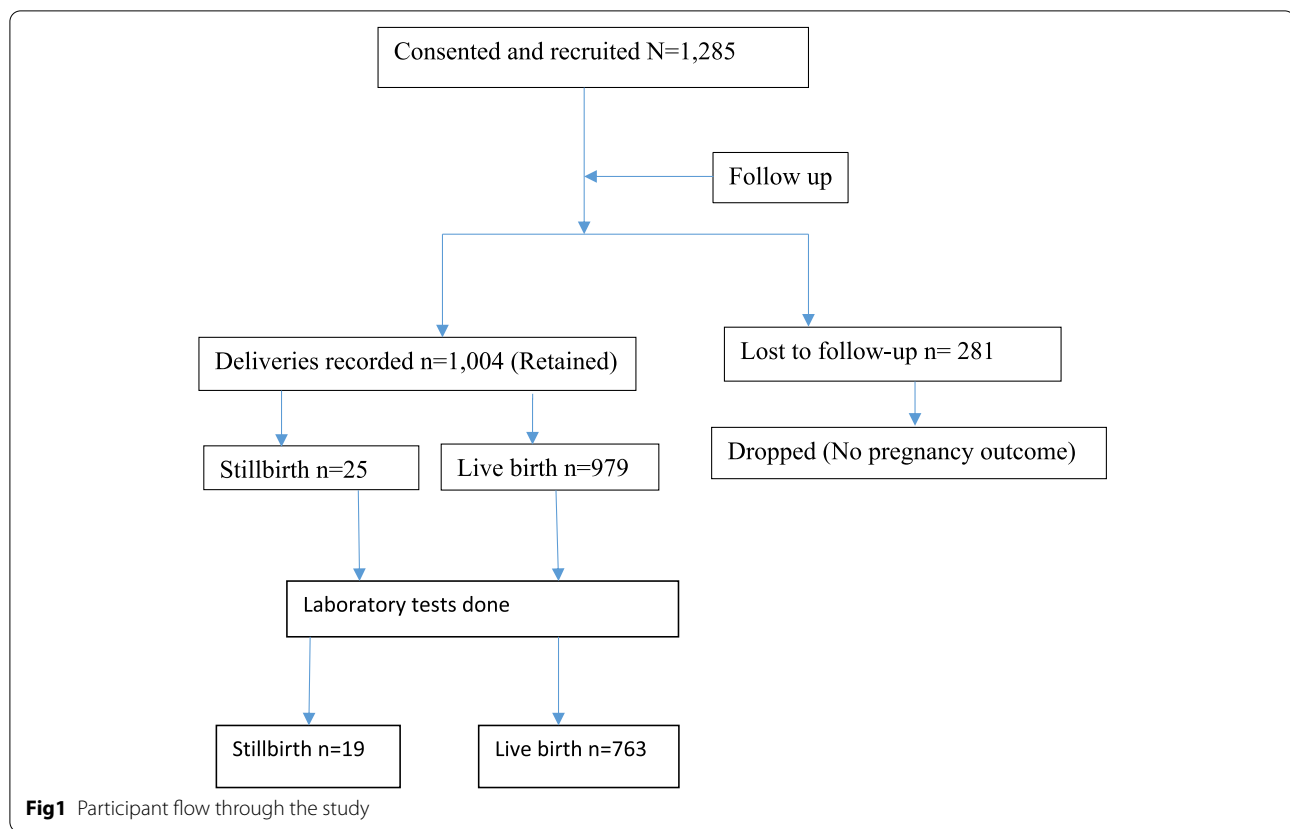
Statistical analysis

One thousand four (1,004) complete delivery records were obtained. Data were pre-processed using Stata 15.0 and built models using RStudio R version 4.1.1 (2021–08–10). Univariable analysis was done, and all variables with p-values ≤ 0.20 or were known risk factors for stillbirth like age and maternal comorbidities were put together into a logistic regression model. Since the data was imbalanced with few stillbirths, we applied the ROSE technique [20, 21] to create a new dataset by over-sampling stillbirths and under-sampling live births, and obtained a distribution of live births and stillbirth cases as 400 (51.1%) and 383 (48.9%), respectively. The ROSE-derived data set was fitted into a confusion matrix to evaluate the performance of our models (accuracy, sensitivity, specificity) using K-(10)-fold cross-validation. Variables were said to be independent risk factors of stillbirth if their p-value < 0.05 in the model. Six models were built.

Results

One thousand four (1004) complete delivery records were obtained at the end of the study period. Of these, seven hundred eighty two mothers had laboratory blood tests done with 2.4% (19) stillbirths and 97.6% (763) live-births. Prevalence of stillbirth was 2.5% (25 out of 1004). There was 979 (97.5%) live births. Seven (28%) out of the 25 deaths occurred intrapartum. Two (8%) of the 25 mothers who lost their babies had a history of previous stillbirth. Two hundred eighty-one mothers were lost to follow-up. Details are found in Fig. 1.

The incidence rates for stillbirth were higher at lower gestation ages, as outlined in Table 1. There were 273 stillbirths per 10⁴ women weeks at < 28 weeks while only 3 stillbirths per 10⁴ women weeks at ≥ 37 weeks.

**Table 1** Incidence of stillbirth

| Variables | Total Population | Number of stillbirth | % (95% CI) | Incidence of stillbirth per 10 ⁴ women weeks |
|--------------------------------|------------------|----------------------|---------------------|---|
| No stillbirth | 979 | 0 | 0% | 0 |
| Stillbirth occurred | 25 | 25 | 2.5% (1.6%—3.7%) | 6 (4—9) |
| Stillbirth occurred < 28 weeks | 9 | 6 | 66.7% (22.9%—92.5%) | 273 (94—379) |
| Stillbirth ≥ 28—< 37 weeks | 119 | 9 | 7.6% (3.5%—13.8%) | 22 (10—40) |
| Stillbirth ≥ 37 weeks | 876 | 10 | 1.1% (0.5%—2.1%) | 3 (1—6) |

Second trimester characteristics of the women who returned to deliver in hospital

Mean maternal age was 26.3 years while 316 participants were first time mothers. Details in Table 2.

Average body-mass index (BMI) was 24.7, and prevalence of multiple pregnancy was 2.4%. Only 0.6% (6) of participants had prenatal hypertension at the time of recruitment. Details in Table 3.

Prevalence of anaemia in pregnancy was high with a mean haemoglobin level of 10.7 g/dL and haematocrit levels of 32.6%. Details in Table 4.

Unadjusted logistic regression for stillbirth with demographic characteristics

Personal history of preeclampsia and any history of abortion were significantly related to stillbirth while being married or cohabiting was protective. Details in Table 5.

While for the clinical characteristics; systolic hypertension, end diastolic notch, pulsatility and resistive indices were significantly related to stillbirth. Details in table 6.

When laboratory characteristics were used, there were no significant relationship to stillbirth. Details in Table 7.

Table 2 Social demographic characteristics of the study population at recruitment

| Characteristics (n = 1,004) | Mean (sd) / Median (IQR) / Proportion (%) |
|---|---|
| Maternal age (years) mean (sd) | 26.3 (5.5) |
| Maternal age (years) median (IQR) | 26.0 (22.0—30.0) |
| Single | 17 (1.7%) |
| Married/Cohabiting | 987 (98.3%) |
| Nulliparity | 316 (31.5%) |
| Para 1–2 | 458 (45.6%) |
| Para > 2 | 230 (22.9%) |
| No history of abortion | 810 (80.7%) |
| Any history of abortion | 194 (19.3%) |
| Unemployed | 311 (31.0%) |
| Informal (casual labourer) | 620 (61.8%) |
| Formal (salaried job) | 73 (7.3%) |
| mean (sd) Gestation age at recruitment (weeks) | 20.4 (2.7) |
| median (IQR) Gestation age at recruitment (weeks) | 20.1 (18.6—22.1) |
| Previous history of preterm birth | 85 (12.4%) |
| No previous history of preterm birth | 603 (87.6%) |
| Personal history of preeclampsia | 14 (1.4%) |
| Not applicable (prime gravida) | 316 (31.5%) |
| No personal history of preeclampsia | 674 (67.1%) |
| Mean (sd) age at menarche (years) | 14.4 (1.4) |
| Median (IQR) age at menarche (years) | 14.0 (13.0—15.0) |
| History of fertility treatment | 9 (0.9%) |
| No history of fertility treatment | 995 (99.1%) |
| Family history of preeclampsia | 38 (3.8%) |
| No family history of preeclampsia | 966 (96.2%) |
| Presence of a chronic illness | 90 (9.0%) |
| No chronic illness | 914 (91.0%) |
| Tobacco use in a lifetime | 2 (0.2%) |
| No tobacco use in a lifetime | 1,002 (99.8%) |
| Living with a smoker in one house | 104 (10.4%) |
| No smoker in one house | 900 (89.4%) |
| Alcohol use in pregnancy | 56 (5.6%) |
| No alcohol use in pregnancy | 948 (94.4%) |

All the variables with unadjusted p-value of ≤ 0.200 were taken for multivariable analysis to produce the models for prediction of stillbirth. Six models were built in R-studio. The variables are removed from the model in a stepwise manner to remain with the least number of variables with a high AUC. Those variables with $p < 0.1$ were retained in the model while those with $p < 0.05$ were taken as independent risk factors for stillbirth.

Models for prediction of stillbirth

Model 1 examined maternal history and physical examination (details in Table 8). The predictors of stillbirth

Table 3 Clinical characteristics of the study population at recruitment

| Characteristics n = 1,004 | Mean (Sd) / proportion (%) | Median (IQR) |
|--------------------------------|----------------------------|--------------------|
| Body mass index | 24.7 (3.9) | 23.9 (21.8—26.8) |
| Systolic blood pressure | 64.0 (10.4) | 63.0 (57.0—70.0) |
| Diastolic blood pressure | 105.7 (12.7) | 104.0 (97.0—113.0) |
| Prenatal hypertension | 6 (0.6%) | |
| No prenatal hypertension | 998 (99.4%) | |
| Singleton pregnancy | 980 (97.6%) | |
| Multiple pregnancy | 24 (2.4%) | |
| No diastolic notch | 734 (73.1%) | |
| Unilateral end diastolic notch | 156 (15.5%) | |
| Bilateral end diastolic notch | 114 (11.4%) | |
| Average Resistive index | 0.51 (0.11) | 0.50 (0.44—0.58) |
| Average pulsatility index | 0.81 (0.30) | 0.75 (0.61—0.96) |

Table 4 Laboratory characteristics of the population at recruitment

| Characteristics n = 787 | Mean (Sd) | Median (IQR) |
|--|--------------|---------------------|
| Serum ALT | 30.4 (27.7) | 25.0 (18.0—34.0) |
| Serum AST | 20.1 (23.2) | 14.0 (7.0—26.0) |
| Serum GGT | 21.6 (8.5) | 20 (15—29) |
| Serum ALP | 153.6 (49.9) | 146 (115—179) |
| Serum bicarbonate | 25.4 (2.2) | 25 (24—27) |
| Serum Albumin | 4.1 (2.9) | 3.9 (3.5—4.1) |
| Serum Urea | 25.3 (26.4) | 18 (14—25) |
| Serum sodium | 137.5 (4.0) | 137.3 (135.1—139.4) |
| Serum potassium | 4.3 (1.2) | 4.2 (3.9—4.5) |
| Serum chloride | 106.3 (4.3) | 105.0 (103.5—108.9) |
| Serum phosphorus | 1.3 (0.9) | 1.1 (0.9—1.4) |
| Serum calcium | 2.4 (1.2) | 2.2 (2.1—2.4) |
| Serum creatinine | 1.0 (0.6) | 0.9 (0.8—1.2) |
| Neutrophil count | 3.7 (2.2) | 3.5 (2.6—4.6) |
| Lymphocyte Count | 1.8 (0.9) | 1.6 (1.3—2.1) |
| Total White blood cell count | 6.3 (2.9) | 6.0 (4.9—7.4) |
| Platelet count | 223.9 (69.4) | 220 (178—267) |
| Haemoglobin level | 10.7 (2.0) | 10.9 (9.5—12.0) |
| Haematocrit | 32.6 (6.7) | 33.0 (28.5—33.0) |
| Mean corpuscular volume | 84.3 (7.8) | 84.5 (79.9—89.1) |
| Mean corpuscular haemoglobin concentration | 32.9 (2.5) | 32.8 (31.4—34.3) |

were parity, age ≥ 35 years, history of abortion and personal history of preeclampsia. Personal history of preeclampsia (aOR = 11.08, 95% CI 1.44—57.34, $p = 0.0075$) and history of abortion (aOR = 2.92, 95% CI 1.07—7.57, $p = 0.0293$) were independent risk factors for stillbirth.

Table 5 Unadjusted regression analysis for demographic characteristics for prediction of stillbirth

| Variable | OR (95% CI) | p-value |
|-----------------------------------|-------------------|--------------|
| Maternal age (years) ≥ 35 | 1.80 (0.63—5.14) | 0.271 |
| Married/Cohabiting | 0.20 (0.50—0.77) | 0.020 |
| Nulliparity | 1.82 (0.58—5.73) | 0.307 |
| Para 1–2 | 1.38 (0.44—4.29) | 0.577 |
| Any history of abortion | 2.78 (1.30—6.10) | 0.011 |
| Informal (casual labourer) | 0.67 (0.28—1.57) | 0.356 |
| Formal (salaried job) | 1.89 (0.60—5.98) | 0.277 |
| Previous history of preterm birth | 1.09 (0.25—4.76) | 0.907 |
| Personal history of preeclampsia | 6.15 (1.60—23.62) | 0.008 |
| age at menarche ≥ 15 years | 0.53 (0.16—1.77) | 0.305 |
| Family history of preeclampsia | 1.06 (0.15—7.63) | 0.954 |
| Presence of a chronic illness | 0.42 (0.06—3.09) | 0.397 |
| Living with a smoker in one house | 0.75 (0.18—3.15) | 0.697 |
| Alcohol use in pregnancy | 1.47 (0.36—6.09) | 0.594 |

Table 6 Unadjusted regression analysis for clinical characteristics for prediction of stillbirth

| Variable | OR (95% CI) | p-value |
|--|-------------------|--------------|
| Body mass index > 25 kg/m ² | 0.76 (0.33—1.74) | 0.511 |
| Systolic blood pressure ≥ 140 mmHg | 5.94 (0.93—38.05) | 0.060 |
| Diastolic blood pressure ≥ 90 mmHg | 1.70 (0.24—12.08) | 0.595 |
| Multiple pregnancy | Too few | |
| Lateral placental location | 1.22 (0.29—5.05) | 0.788 |
| Unilateral end diastolic notch | 1.01 (0.29—3.47) | 0.990 |
| Bilateral end diastolic notch | 3.68 (1.58—8.58) | 0.003 |
| Average Resistive index > 0.65 (90th percentile) | 3.75 (1.65—8.49) | 0.002 |
| Average pulsatility index > 1.19 (90th percentile) | 3.82 (1.69—8.66) | 0.001 |

Model 2 examined the uterine artery Doppler indices (details in Table 9). The predictor of stillbirth was presence of end diastolic notch on the uterine artery Doppler flow tracing. Bilateral end diastolic notch (aOR = 4.28, 95% CI 1.54—11.19, $p = 0.0035$) was an independent risk factor for stillbirth.

Model 3 examined the combination of maternal history, physical examination and uterine artery Doppler indices (models 1 and 2) (details in Table 10). The predictors of stillbirth were history of abortion and end-diastolic notch on the uterine artery Doppler flow tracing. The history of abortion (aOR = 3.29, 95% CI 1.24—8.41, $p = 0.0134$) and bilateral end-diastolic notch (aOR = 4.49, 95% CI 1.60—11.88), $p = 0.0029$) were independent risk factors for stillbirth.

Model 4 examined maternal laboratory blood tests (details in Table 11). The predictors of stillbirth were

platelet neutrophil ratio, neutrophil count and haemoglobin level. The independent risk factors for stillbirth was platelet neutrophil ratio of > 83.95 (aOR = 5.76, 95% CI 1.12—35.90, $p = 0.0437$). Haemoglobin level of 9.5 – 12.1 g/dL (aOR = 0.32, 95% CI 0.11—0.89, $p = 0.0287$) was protective against stillbirth.

Model 5 examined the combination of maternal history and laboratory tests (models 1 and 4) (details in Table 12). The predictors of stillbirth were history of abortion, parity, age ≥ 35 years and haemoglobin level. The independent risk factors for stillbirth was history of abortion (aOR = 3.10, 95% CI 1.11—8.26), $p = 0.0254$). Haemoglobin level of 9.5 – 12.1 g/dL (aOR = 0.33, 95% CI 0.109—0.95, $p = 0.0411$) was protective against stillbirth.

Model 6 examined the combination of maternal history, physical examination, uterine artery Doppler indices and laboratory tests (models 1, 2 and 4) (details in Table 13). The predictors of stillbirth were personal history of preeclampsia, history of abortion, end-diastolic notch and haemoglobin level. The history of abortion (aOR = 3.07, 95% CI 1.11—8.05, $p = 0.0243$) and bilateral end diastolic notch (aOR = 3.51, 95% CI 1.13—9.92, $p = 0.0209$) were independent risk factors for stillbirth while haemoglobin level of 9.5 – 12.1 g/dL (aOR = 0.33, 95% CI 0.11—0.93, $p = 0.0375$) was protective.

Evaluation of the models of stillbirth

The models AUC ranges from 66.8% to 75.0%, with accuracies of 63.9% to 68.1%. Details in Table 14.

Model 1 examined maternal history and physical examination (details in Table 8). The predictors of stillbirth were parity, age ≥ 35 years, history of abortion and personal history of preeclampsia. This predicted stillbirth with 65.8% accuracy, 82.4% sensitivity, 48.4% specificity and 71.9% AUC. The details for the models are found in Table 14.

Discussion

From demographic characteristics of our participants, the predictors of stillbirth were parity, age ≥ 35 years, history of abortion and personal history of preeclampsia. This predicted stillbirth with 65.8% accuracy, 82.4% sensitivity, 48.4% specificity and 71.9% AUC. In Niger state Nigeria, the predictors of stillbirth were maternal comorbidity, rural place of residence, multipara, bleeding during pregnancy, and non-cephalic fetal presentation [8]. Maternal employment was protective of stillbirth [8]. They predicted stillbirth with a C-statistic basic model = 0.80 (95% CI 0.78—0.83), and when ultrasound parameters were added the extended C-statistic model improved slightly to 0.82 (95% CI 0.80—0.83)[8]. In a case–control study in southern Ethiopia, the predictors of stillbirth were women with multiple pregnancy

Table 7 Unadjusted regression analysis for laboratory characteristics for prediction of stillbirth

| Variable | OR (95% CI) | p-value |
|--|-------------------|--------------|
| Serum ALT 19—25 IU | 2.52 (0.79—8.04) | 0.120 |
| Serum ALT > 25 IU (> 90th percentile) | 0.84 (0.24—2.96) | 0.792 |
| Serum AST 4—40 IU (10th—90th percentile) | 0.81 (0.19—3.49) | 0.782 |
| Serum AST > 40 IU (> 90th percentile) | 0.95 (0.14—6.55) | 0.756 |
| Serum GGT ≤ 30 IU (Normal lab range) | 1.34 (0.39—4.54) | 0.639 |
| Serum ALP ≤ 98 IU (low lab range) | 1.44 (0.20—10.45) | 0.717 |
| Serum bicarbonate 24—27 (25th—75th percentile) | 4.10 (0.54—30.93) | 0.172 |
| Serum bicarbonate > 27 (> 75th percentile) | 3.77 (0.43—33.36) | 0.233 |
| Serum albumin 3.5—4.1 g/dL | 0.46 (0.15—1.42) | 0.180 |
| Serum Albumin < 3.5 g/dL | 1.27 (0.43—3.70) | 0.667 |
| Serum urea 14—25 mg/dL (25th—75th percentile) | 1.50 (0.42—5.40) | 0.534 |
| Serum urea > 25 mg/dL (> 75th percentile) | 1.85 (0.47—7.30) | 0.379 |
| serum creatinine 0.61—1.50 mg/dL (10th—90th percentile) | 0.62 (0.21—1.86) | 0.395 |
| Serum creatinine > 1.50 mg/dL | 0.35 (0.40—3.07) | 0.343 |
| Neutrophil count 2.63—4.54 cells/microlitre | 0.92 (0.31—2.71) | 0.881 |
| Neutrophil count > 4.54 cells/microlitre | 1.00 (0.29—3.40) | 1.000 |
| Lymphocyte Count 0.9—3.9 cells/microlitre | 0.33 (0.10—1.12) | 0.075 |
| Lymphocyte Count > 3.9 cells/microlitre | 1.89 (0.34—10.42) | 0.465 |
| Total White blood cell count 4000—11,000 cells / microlitre | 1.10 (0.26—4.70) | 0.900 |
| Total White blood cell count > 11,000 cells / microlitre | 2.91 (0.28—30.25) | 0.372 |
| platelet count 178—266 cells / microliter (25th—75th percentile) | 1.60 (0.45—5.76) | 0.470 |
| Platelet count > 266 cells / microliter (> 75th percentile) | 1.93 (0.49—7.60) | 0.348 |
| Haemoglobin level < 9.5 g/dL (< 25th percentile) | 2.78 (0.76—10.12) | 0.120 |
| Haemoglobin level 9.5—12.1 g/dL (25th—75th percentile) | 1.02 (0.27—3.89) | 0.981 |
| Haematocrit 30—39.9% (25th—75th percentile) | 0.50 (0.20—1.25) | 0.140 |
| Haematocrit ≥ 40% (> 75th percentile) | 0.49 (0.06—3.83) | 0.501 |
| Mean corpuscular volume 79.9—89.2 fl (25th—75th percentile) | 1.30 (0.42—4.04) | 0.647 |
| Mean corpuscular volume < 79.9 fl (< 25th percentile) | 0.97 (0.25—3.82) | 0.965 |
| Mean corpuscular haemoglobin concentration 31.5—34.4 g/dL | 1.05 (0.40—2.75) | 0.923 |
| Mean corpuscular haemoglobin concentration < 31.5 g/dL | 0.18 (0.22—1.47) | 0.110 |

Table 8 Model 1 using maternal history for prediction of stillbirth

| Variable | OR (95% CI) | p-value |
|-----------------------------------|--------------------|---------------|
| Personal history of pre-eclampsia | 11.08 (1.44—57.34) | 0.0075 |
| History of abortion | 2.92 (1.07—7.57) | 0.0293 |
| Age ≥ 35 years | 4.29 (0.72—20.72) | 0.0851 |
| nullipara | 5.37 (1.10—36.24) | 0.0576 |
| para 1—2 | 2.28 (0.48—13.67) | 0.3284 |
| Intercept | 0.005 (0.001—0.02) | 0.0000 |

[aOR = 2.98, 95%CI: 1.39–6.36], having preterm birth [aOR = 2.83, 95%CI: 1.58–5.08], having cesarean mode of delivery [aOR = 3.19, 95%CI: 1.87–5.44], having no ANC visit [aOR = 4.17, 95%CI: 2.38–7.33], and being hypertensive during pregnancy [aOR = 3.43, 95%CI: 1.93–6.06].

Table 9 Model 2 using uterine artery Doppler indices for prediction of stillbirth

| Variable | OR (95% CI) | p-value |
|------------|-------------------|---------------|
| Unilateral | 0.40 (0.02—2.09) | 0.3843 |
| Bilateral | 4.28 (1.54—11.19) | 0.0035 |
| Intercept | 0.02 (0.01—0.03) | 0.0000 |

Table 10 Model 3 using combination of maternal history and uterine artery Doppler indices for prediction of stillbirth

| Variable | OR (95% CI) | p-value |
|---------------------|-------------------|---------------|
| History of abortion | 3.29 (1.24—8.41) | 0.0134 |
| Unilateral | 0.38 (0.02—2.01) | 0.3618 |
| Bilateral | 4.49 (1.60—11.88) | 0.0029 |
| Intercept | 0.01 (0.006—0.03) | 0.0000 |

Table 11 Model 4 using maternal laboratory tests for prediction of stillbirth

| Variable | OR (95% CI) | p-value |
|--|-------------------|---------------|
| Platelet neutrophil ratio of 47.04—83.95 | 1.80 (0.46—9.00) | 0.4232 |
| Platelet neutrophil ratio of > 83.95 | 5.76 (1.12—35.90) | 0.0437 |
| Neutrophil count of (2.63—4.54) *1000 | 2.14 (0.60—8.12) | 0.2453 |
| Neutrophil count of (>4.54) *1000 | 4.16 (0.77—22.81) | 0.0958 |
| Haemoglobin level of 9.5—12.1 g/dL | 0.32 (0.11—0.89) | 0.0287 |
| Haemoglobin level of > 12.1 g/dL | 0.33 (0.07—1.14) | 0.1027 |
| Intercept | 0.01 (0.001—0.06) | 0.0000 |

Table 12 Model 5 using combination of maternal history and laboratory tests for prediction of stillbirth

| Variable | OR (95% CI) | p-value |
|------------------------------------|--------------------|---------------|
| History of abortion | 3.10 (1.11—8.26) | 0.0254 |
| Age ≥ 35 years | 4.87 (0.79—24.57) | 0.0677 |
| nullipara | 5.09 (1.02—35.71) | 0.0715 |
| para 1—2 | 2.51 (0.52—15.59) | 0.2831 |
| Haemoglobin level of 9.5—12.1 g/dL | 0.33 (0.109—0.95) | 0.0411 |
| Haemoglobin level of > 12.1 g/dL | 0.27 (0.06—0.99) | 0.0656 |
| Intercept | 0.01 (0.001—0.005) | 0.0000 |

Table 13 Model 6: Combination of maternal history, uterine artery Doppler indices and laboratory tests for prediction of stillbirth

| Variable | OR (95% CI) | p-value |
|----------------------------------|-------------------|---------------|
| Personal history of preeclampsia | 5.18 (0.60—30.66) | 0.0916 |
| History of abortion | 3.07 (1.11—8.05) | 0.0243 |
| Unilateral | 0.37 (0.02—1.98) | 0.3507 |
| Bilateral | 3.51 (1.13—9.92) | 0.0209 |
| Haemoglobin level 9.5—12.1 g/dL | 0.33 (0.11—0.93) | 0.0375 |
| Haemoglobin level > 12.1 g/dL | 0.30 (0.06—1.07) | 0.0850 |
| Intercept | 0.03 (0.01—0.07) | 0.0000 |

Table 14 Evaluation of the models for stillbirth

| Model | Accuracy | Sensitivity | Specificity | AUC |
|--|----------|-------------|-------------|------|
| Model 1 (Maternal history and exam) | 65.8 | 82.4 | 48.4 | 71.9 |
| Model 2 (Uterine artery Doppler indices) | 63.9 | 88.7 | 37.9 | 66.8 |
| Model 3 (History and uterine artery Doppler indices) | 67.6 | 75.9 | 59.0 | 69.9 |
| Model 4 (lab tests) | 65.3 | 71.6 | 58.7 | 69.7 |
| Model 5: (combination of history and laboratory tests) | 68.0 | 67.1 | 69.0 | 74.4 |
| Model 6: (combination of maternal history, Doppler indices and laboratory tests) | 68.1 | 69.1 | 67.1 | 75.0 |

[22]. However, these women were recruited after they had given birth. In clinical settings in low resource settings one can use the demographic characteristics above as predictors to identify up to two-thirds of mothers at risk of having stillbirth. Despite the model's sensitivity of 82.4%, the model's specificity of 48.4% is low. One will have to put more than twice the number of women identified as at risk of stillbirth in order to get the two thirds of women who will actually get stillbirth.

Combination of uterine artery Doppler indices and maternal history predicted stillbirth by 67.6% accuracy, 75.8% sensitivity and 69.9% AUC. This may be comparable to Akolekar et al. [19] who predicted 55% of all stillbirths, including 75% of those due to impaired placentation and 23% of those that were unexplained or due to other causes, at a false-positive rate of 10% using maternal history and uterine artery Doppler indices. Ultrasound examination is not compulsory in Uganda [23]. It is reserved for a few referral centers, teaching hospitals and private hospitals [24, 25]. Majority of the mothers go through their gestation period without performing a single ultrasound scan.

We predicted stillbirth by 75.0% AUC with 68.1% accuracy, 69.1% sensitivity and 67.1% specificity. This was comparable to the stillbirth-risk calculator [18] validated in Austria at 72% AUC [6]. In the United Kingdom, stillbirth detection rates ranged from 28 to 48% with an AUC of 55.0% to 65.8% even after allowing a 10% false positive rate [7, 19]. In Australia, the detection rate for stillbirth was 45%, with an AUC ranging from 59 to 84% [26]. Similarly, in the United States of America, the detection rate for stillbirth has been 64%—66% AUC [27].

Mastrodima et al. [28] used maternal factors, PAPP-A, Doppler pulsatility index and ductus venosus pulsatility index for veins (DV-PIV), and predicted 40% of all stillbirths and 55% of those due to impaired placentation, at a false-positive rate of 10%. Within the impaired-placentation group, the detection rate of stillbirth < 32 weeks' gestation was higher than that of stillbirth ≥ 37 weeks (64% vs 42%). This makes the study compare favorably to those

conducted in global north. Perhaps the differences seen is due to the differences in the population itself and the technology used for the prediction of stillbirth.

Research implications

These models may be used in several clinics. Future studies may include a larger number of participants from several locations to validate the models to ensure generalizability.

Strengths and limitation

This study was a baseline study in Northern Uganda to find out the predictors of stillbirths and to pave way for more research. There was a high number of mothers lost to follow-up.

Conclusion

In places where ultrasound or laboratory services are not available, the predictors of stillbirths are history of abortion, personal history of preeclampsia, maternal age ≥ 35 years and parity. These variables predict stillbirth by 71.9% AUC with 68.5% accuracy, 82.4% sensitivity and 48.4% specificity.

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Authors' contributions

Silvia Awor is a Ph.D. student who wrote the proposal, collected data and drafted the manuscript. Annetee Nakimuli, Jaspar Ogwal-Okeng and Dan Kabonge Kaye are doctoral supervisors who guided the writing of the manuscript. Rosemary Byanyima, Paul Kiondo and Christopher Garimoi-Orach are doctoral committee members who gave technical advice during the data collection and manuscript writing. Benard Abola, a mathematician, helped develop and validate the model and participated in data analysis. The author(s) read and approved the final manuscript.

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Availability of data and materials

The corresponding author Dr. Silvia Awor or Makerere University Directorate of Research and Graduate training can be contacted to request for the data and other materials.

Declarations

Competing interests

The authors declare no competing interests.

Ethical approval and consent to participate

The study was approved by the Research and Ethics Committee of Makerere University School of Medicine (Reference number 2018–105), Uganda National Council for Science and Technology (Reference number HS258ES),

and administrative clearance from St. Mary's hospital Lacor (Reference number LHIREC Adm 009/11/18). Written informed consent was sought from every participant. All methods were carried out according to the "Declaration of Helsinki" guidelines [29].

Consent for publication

Not applicable.

Conflict of interest

The authors have declared no competing interest.

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