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DEPARTAMENTO DE CIENCIAS CLÍNICAS
PROGRAMA DE DOCTORADO EN INVESTIGACIÓN APLICADA A LAS CIENCIAS SANITARIAS POR LA UNIVERSIDAD DE LAS PALMAS DE GRAN CANARIA, LA UNIVERSIDAD DE LEÓN Y UNIVERSIDAD DE TRÁS-OS-MONTES E ALTO DOURO

ESTUDIO DE LOS FACTORES RELACIONADOS CON LA MORBI-MORTALIDAD MATERNA Y NEONATAL PERIPARTO EN TETE (MOZAMBIQUE)

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Las Palmas de Gran Canaria, Marzo de 2024

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ESTUDIO DE LOS FACTORES RELACIONADOS CON LA MORBI-MORTALIDAD MATERNA Y NEONATAL PERIPARTO EN TETE (MOZAMBIQUE)

TESIS DOCTORAL PRESENTADA POR Dª. MARÍA NIEVES JAÉN SÁNCHEZ
DIRIGIDA POR EL DR. JOSÉ LUIS PÉREZ ARELLANO Y
LA DRA. CRISTINA CARRANZA RODRÍGUEZ

EL DIRECTOR **LA DIRECTORA** **EL DOCTORANDO**

Las Palmas de Gran Canaria, Marzo de 2024

D. José Luis Pérez Arellano, Catedrático de Universidad de Las Palmas de Gran Canaria y Dña. Cristina Carranza Rodríguez, Profesora Contratada Doctora de la Universidad de Las Palmas de Gran Canaria.

INFORMAN:

Que el trabajo de investigación titulado ***"Estudio de los factores relacionados con la morbi-mortalidad materna y neonatal periparto en Tete (Mozambique)",*** ha sido realizado por Dña. María Nieves Jaén Sánchez, en el Departamento de Ciencias Clínicas de la Universidad de Las Palmas de Gran Canaria, bajo su dirección y asesoramiento técnico y científico. Una vez revisada la presente Memoria, la encuentran apta para su defensa ante tribunal.

Y para que así conste y surta los efectos oportunos, extiende el presente certificado en Las Palmas de Gran Canaria a 12 de Marzo de 2024.

EL DIRECTOR **LA DIRECTORA**

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A mis padres porque sin ellos no hubiera sido posible.

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Abreviaturas

BPN: Bajo peso al nacer

CIR: Crecimiento intrauterino restringido

CSA: Condroitín sulfato A

INE: Instituto Nacional de Estadística

LMIC: Países de bajos y medianos ingresos (*Low- and middle-income countries*)

ODS: Objetivos de desarrollo sostenible

OMS: Organización Mundial de la Salud

PCR: Reacción en cadena de la polimerasa (*Polymerase chain reaction*)

PIGF: Factor de crecimiento placentario (*Placental growth factor)*

RMM: Razón de Mortalidad Materna

sFiT-1: Tirosina cinasa 1 soluble tipo Fms (*soluble Fms-like tyrosine kinase-1*)

TARGA: Tratamiento antirretroviral de gran actividad

VIH: Virus de la inmunodeficiencia humana

1. Introducción

1.1. Mortalidad materna en África Subsahariana

La Mortalidad Materna es definida por la Organización Mundial de la Salud (OMS) como "la muerte de una mujer durante su embarazo, parto o dentro de los 42 días después de su terminación por cualquier causa relacionada o agravada por el embarazo, parto o puerperio o su atención, pero no por causas accidentales o incidentales" [1,2]. En el año 2020, la razón de mortalidad materna, en países de ingresos altos fue de 12 por 100.000 nacidos vivos, mientras que en países de ingreso bajos fue de 430 por 100.000 nacidos vivos [3]. Las causas de mortalidad son en su mayoría prevenibles o tratables y se ha identificado la mortalidad materna como un indicador clave de desarrollo, así como una expresión de inequidad y desigualdad [1,3].

Durante el año 2020, se registraron aproximadamente 287.000 muertes maternas y cerca del 95% de ellas, ocurrieron en países de bajos y medianos ingresos (LMIC), alrededor del 70% se concentraron en África Subsahariana (202.000) [3]. Las elevadas tasas de muertes maternas en esta región se atribuyen a diversos factores interrelacionados, como las barreras socioeconómicas, las desigualdades de género y normas culturales arraigadas, las dificultades de accesibilidad de los servicios de atención de salud y situaciones humanitarias de conflictos, entre otros [4,5].

En Mozambique, estimaciones de la Razón de Mortalidad Materna (RMM) comparables a nivel internacional, realizadas por el Grupo Interinstitucional para la Estimación de la Mortalidad Materna, registró una RMM en el año 2020 de 127 por cada 100.000 nacidos vivos [6]. Sin embargo, uno de los Objetivos de Desarrollo Sostenible (ODS) 3 es reducir la tasa mundial de mortalidad materna a menos de 70 por cada 100.000 nacidos vivos para el año 2030 [7] por lo que es imprescindible implementar las medidas para lograr cifras aproximadas en el país.

En LMIC, la mortalidad materna genera consecuencias más graves con mayores impactos económicos y sociales en el hogar de la pérdida y en el entorno más cercano a la mujer fallecida. Las consecuencias de las complicaciones relacionadas con el embarazo y el parto son más drásticas Por cada muerte materna, hay otras 20 que se ven afectadas por infecciones o por lesiones graves como son la fístula obstétrica, y otras afecciones físicas, así como consecuencias psicológicas devastadora que puede causar la exclusión social [2].

1.2. Embarazo y adolescencia en África Subsahariana

En los países de África subsahariana, las mujeres contraen matrimonio a edades muy tempranas, inician la maternidad entre los 16 y los 24 años debido a los arraigados patrones culturales en estas comunidades [8,9,10]. El mayor número estimado de nacimientos de jóvenes de 15 a 19 años en 2021 tuvo lugar en África subsahariana (6.114.000) [11].

Mozambique tiene la décima tasa más alta de matrimonio infantil a nivel mundial, medida como la proporción de mujeres de 20 a 24 años que contrajeron matrimonio antes de cumplir los 18 años [12]. Además presenta la tasa de fecundidad adolescente más alta en la región meridional de África, un 38% de las adolescentes han tenido al menos un hijo. Se encuentra entre los seis países a nivel mundial en los cuales al menos una de cada diez niñas (14%) ha experimentado la maternidad antes de los 15 años, y el 57% lo ha hecho antes de cumplir los 18 años [13,14].

Las adolescentes embarazadas se enfrentan a un mayor riesgo de complicaciones que afectan tanto a la madre como al hijo [15,16]. Existe una alta probabilidad de que las mujeres adolescentes interrumpan su educación o abandonen la escuela por completo, incrementando así el riesgo de un estatus socioeconómico más bajo, pobreza e incluso mortalidad debido a complicaciones

relacionadas con el embarazo [17]. Las adolescentes son más propensas a recurrir a abortos inseguros y tienen menos posibilidades de recibir una atención especializada antes, durante y después del parto. Las complicaciones durante el embarazo y el parto son la principal causa de muerte entre las niñas de 15 a 19 años. En África subsahariana la mortalidad materna entre las adolescentes es muy elevada, con 36 muertes por cada 100.000 habitantes, seguida de 9, 7 y 3 muertes por cada 100 000 en los LMIC del Mediterráneo Oriental, del Asia Sudoriental y del continente Americano, respectivamente [18].

Los recién nacidos de madres adolescentes tienen mayor probabilidad de padecer bajo peso, nacimiento prematuro y afección neonatal grave [11]. Por las razones mencionadas, abordar las características del embarazo en mujeres adolescentes en Mozambique ha sido uno de los objetivos principales de este proyecto doctoral.

1.3. Causas de morbi-mortalidad materna en África Subsahariana

Las causas de muerte materna pueden dividirse en causas directas e indirectas. Las directas se encuentran relacionadas con complicaciones obstétricas durante el embarazo, el parto o el periodo posparto y son las hemorragias, las sepsis, la eclampsia, las obstrucciones durante el parto y las complicaciones derivadas de la práctica de abortos. Las causas obstétricas indirectas pueden ocurrir tanto como resultado de enfermedades preexistentes, o de enfermedades que surgen durante el embarazo y que no tienen una causa obstétrica directa pero que pueden agravarse debido a los efectos fisiológicos del embarazo. Entre ellas están la infección por VIH y la malaria, la anemia y las enfermedades cardiovasculares [2].

En líneas generales, aproximadamente el 80% de las muertes maternas se atribuyen a complicaciones directas, siendo la hemorragia, la sepsis y los trastornos hipertensivos las complicaciones más frecuentes [8,19,20]. En

Mozambique, diferentes autores han señalado que la eclampsia ocupa el tercer o incluso el segundo lugar como causa principal de muerte materna en el país [20,21]. En África Subsahariana como en el resto de LMIC, la morbilidad indirecta presenta diferencias en comparación con los países de altos ingresos, ya que la malaria y la infección por VIH son las causas más frecuentes de morbi-mortalidad indirecta [21]. El impacto de estas enfermedades durante el embarazo puede influir significativamente en la incidencia y características de las complicaciones directas [22].

1.4. Preeclampsia. Concepto y relevancia en la morbi-mortalidad materna en África Subsahariana

La preeclampsia puede definirse como la hipertensión de nueva aparición (presión arterial sistólica mantenida ≥140 mmHg o presión arterial diastólica mantenida en ≥90 mmHg, o ambas) con proteinuria o disfunción de órganos después de 20 semanas de gestación. Para el diagnóstico de eclampsia se requiere la presencia de convulsiones en pacientes con criterios de preclampsia [23].

La preeclampsia afecta alrededor del 3-5% de todos los embarazos y es responsable de alrededor de 42.000 muertes maternas anuales, mayormente concentrada en LMIC [23]. En estas regiones, el acceso a los servicios de atención obstétrica y planificación familiar es limitado en comparación con los países de altos ingresos. La incidencia de preeclampsia en países en vías de desarrollo presenta una variabilidad en los datos publicados, oscilando entre el 4,0% y el 12,3%. [24]. Es una de las principales causas de mortalidad y morbilidad materna y perinatal en estos países de medianos y bajos ingresos [23]. En el caso específico de Mozambique, la literatura describe una incidencia de preeclampsia que varía entre el 2% y el 4% [24].

La preeclampsia se presenta como una enfermedad multisistémica, caracterizada por el daño endotelial que precede al diagnóstico clínico. Este trastorno guarda relación con alteraciones en la placenta, específicamente un desequilibrio entre factores angiogénicos y anti angiogénicos. Se observan niveles elevados de tirosina cinasa 1 soluble similar al *fms* (sFlt-1), que actúa como inhibidor del factor de crecimiento endotelial, así como una disminución del factor de crecimiento placentario (PlGF), lo que da lugar a un aumento del cociente sFlt-1/PlGF [25]. Como consecuencia, la preclampsia condiciona una significativa morbi-mortalidad materna y neonatal, principalmente debido a la finalización pretérmino de la gestación y su asociación con el retraso del crecimiento intrauterino (CIR). Además de las complicaciones iniciales, secundarias al bajo peso al nacer y la prematuridad, esta condición también se asocia con un mayor riesgo de complicaciones a medio y largo plazo, como problemas en el desarrollo neurológico y otros problemas médicos en la edad adulta, incluyendo enfermedades de origen cardiovascular o diabetes mellitus [25].

1.5. Malaria y embarazo en África Subsahariana

En el año 2020, el número aproximado de casos de malaria fue de 241 millones, ocasionando en torno a 627.000 muertes, de los cuales el 95% tuvieron lugar en África subsahariana. Cuatro países africanos, Nigeria (3,9%), la República Democrática del Congo (13,2%), la República Unida de Tanzania (4,1%) y Mozambique (3,8%), representaron más de la mitad de todas las muertes por malaria a nivel mundial [26]. Según el informe mundial sobre el paludismo, se estimó que en el año 2020 alrededor de 11,6 millones de mujeres embarazadas en África subsahariana (equivalente al 35% de los embarazos en esa región) estaban infectadas por *Plasmodium* spp. En África Oriental y África Meridional, la prevalencia de exposición a la malaria durante el embarazo fue del 22% [27].

En Mozambique, la transmisión de la malaria se produce en todo el país, con una transmisión estacional baja en el sur y una transmisión holoendémica en el centro y norte del país [28,29]. La malaria es la cuarta causa de mortalidad en mujeres embarazadas y representa el 10,1% de las muertes [30].

Durante el embarazo, la infección por malaria puede tener una importante repercusión, tanto en la gestante como en el feto. La inmunodepresión secundaria al embarazo, junto con la presencia en la placenta de receptores como el condroitín sulfato A (CSA), que es un ligando de adhesión del parásito *Plasmodium falciparum*, aumenta la susceptibilidad de la madre a desarrollar malaria placentaria. Esta condición es más frecuente durante la primera gestación y se desarrolla cierto grado de inmunidad en las sucesivas gestaciones [31]. Es bien conocido que la malaria placentaria produce isquemia, un incremento en la producción de citocinas pro-inflamatorias y disfunción endotelial [32]. La malaria durante el embarazo da lugar a múltiples consecuencias negativas, como anemia materna, bajo peso al nacer, retraso en el crecimiento fetal, parto prematuro, aborto espontáneo, mortinatos, muerte neonatal y materna [33].

La infección subclínica por *P. falciparum* es más frecuente en África subsahariana que la infección sintomática [34]. En las mujeres embarazadas estas infecciones subclínicas pueden provocar infecciones placentarias [35,36] y provocar consecuencias en la salud de las madres y los recién nacidos [35,37]. Además, las mujeres embarazadas pueden actuar como reservorios del parásito, especialmente *P. falciparum,* lo que favorece la transmisión al resto de la población. Estas infecciones son con frecuencia submicroscópicas y tienen bajas cargas parasitarias, lo que dificulta su detección mediante métodos de diagnóstico convencionales como la microscopía y/o de diagnóstico rápido. Por esta razón, el diagnóstico molecular mediante la reacción en cadena de la polimerasa (PCR) es de particular importancia para detectar infecciones subclínicas [34,35,37,38].

1.6. Infección por VIH y embarazo en África Subsahariana

En el año 2020, en el continente africano, se registraron aproximadamente 37,7 millones de casos de VIH, que causaron alrededor de 1 millón de muertes en esta región [39]. En Mozambique, la prevalencia global de VIH en adultos de 15 a 49 años es del 12,6%, con un claro predominio en las mujeres (60%) [40]. Específicamente en las mujeres de la provincia de Tete (Mozambique) fue del 19% [10]. África subsahariana es la región con mayor proporción de mujeres embarazadas con infección por VIH en el mundo, representando el 85% de la carga global [41].

La infección por VIH se ha asociado con diversas complicaciones durante el embarazo y el parto [42-45]. Estas complicaciones incluyen: *i)* una mayor incidencia de anemia, especialmente anemia grave en el embarazo; *ii)* un aumento del sangrado antes del parto; *iii)* una mayor prevalencia de trastornos hipertensivos del embarazo; *iv)* un aumento de la sepsis puerperal y la endometritis; *v)* un mayor riesgo de parto prematuro; *vi)* un mayor riesgo de bajo peso al nacer (BPN) y *vii)* un mayor riesgo de muerte fetal. Sin embargo, los resultados de varios estudios individuales y metaanálisis son inconsistentes e incluso contradictorios, dependiendo, entre otros factores, del lugar de estudio o del uso del tratamiento antirretroviral.

1.7. Relaciones entre malaria, infección por VIH y preeclampsia

1.7.1 Co-infección por malaria y VIH en el embarazo

La malaria y el VIH siguen siendo una importante amenaza para la salud pública en el África subsahariana. Durante el embarazo, ambas infecciones pueden tener un impacto significativo tanto en la madre como en el recién nacido. La salud materno-infantil, la malaria y la infección por el VIH son aspectos

prioritarios del Objetivo de Desarrollo Sostenible 3 (ODS3), cuyo objetivo es reducir la mortalidad materna y erradicar la malaria para 2030 [7].

En África subsahariana, se registra un alto número de co-infecciones por malaria y VIH. La malaria causa importante morbilidad y mortalidad entre las mujeres embarazadas infectadas con el VIH, con al menos 1 millón de casos de coinfección cada año [46]. Se han identificado diversas interacciones entre estas dos infecciones, como un aumento de la frecuencia de la parasitemia clínica y la malaria grave, así como un aumento de la carga viral y parasitaria, y una disminución de la inmunidad frente a la malaria [47,48].

1.7.2 Relación entre malaria y preeclampsia

En los países endémicos de malaria, se ha observado cierta evidencia que sugiere un posible vínculo entre la malaria placentaria y la preeclampsia basada en una variación estacional en la incidencia de preeclampsia coincidiendo con la estación de malaria en áreas de alta transmisión estacional. Esta asociación fue descrita por primera vez por Wickramasuriya et al, 1936 como “la epidemia toxémica del embarazo tras la malaria epidémica” [49]. Estudios más recientes realizados en Senegal [49,50] encontraron una disminución en el número de casos de anemia y eclampsia durante la estación seca, y un incremento durante las grandes lluvias y las bajas temperaturas. En otro estudio realizado en Gambia [51], se observó un incremento en el número de muertes maternas por eclampsia durante la temporada de mayor prevalencia de malaria. En Tanzania [52], se sugirió que tanto los mediadores inflamatorios como la disfunción endotelial podrían justificar la posible asociación entre la malaria placentaria y la hipertensión en primíparas. En general, la mayoría de las publicaciones sugieren que, en regiones endémicas de malaria, las mujeres expuestas a *Plasmodium* spp pueden tener un mayor riesgo de preeclampsia en comparación con aquellas regiones libres de malaria [32,50,52,53]. En 2020 Obiri et al. demostraron el incremento de riesgo de preeclamsia en mujeres con malaria placentaria, particularmente en mujeres primíparas [54].

1.7.3 Relación entre VIH y preeclampsia

El efecto de la infección por el VIH en el aumento del riesgo de aparición de preeclampsia ha sido ampliamente estudiada en la literatura, con resultados contradictorios [42,45,55-58]. Algunos estudios sugieren un efecto protector del VIH, disminuyendo el riesgo de preeclampsia en caso de infección por VIH, mientras que otros indican que aumenta la probabilidad de desarrollarla.

El trabajo de Suy et al, 2006 [55], encontró un incremento en el riesgo de preeclampsia y muerte fetal en embarazadas con infección VIH, y se asoció este aumento de riesgo con la exposición previa al tratamiento antirretroviral de alta eficacia (TARGA) antes del embarazo. En este trabajo se propusieron como mecanismos subyacentes potenciales la resistencia a la insulina y la inflamación endotelial. En cambio, en el estudio de Boyajian T. et al, 2012 [42], concluyó que no había diferencias significativas en el riesgo de preeclampsia entre embarazadas con infección por VIH en TARGA y aquellas sin infección VIH. Además, las tres embarazadas con infección por VIH que desarrollaron preeclampsia en ese estudio tenían factores de riesgo bien establecidos para dicha enfermedad. Estos resultados han sido corroborados por Browne JL et al [56], que no encontró una asociación significativa entre la infección por VIH y los estados hipertensivos del embarazo, incluida la preeclampsia.

2. Justificación

El Objetivo de Desarrollo Sostenible 3 (ODS) incluye una meta ambiciosa: «reducir la tasa mundial de mortalidad materna a menos de 70 por cada 100 000 nacimientos», sin que ningún país tenga una razón de mortalidad materna que sea superior al doble del promedio mundial [7].

Para ello, es preciso evaluar la influencia de los factores principales relacionados con este desenlace, para poder incidir sobre ellos y disminuir la morbimortalidad. En la introducción de este Proyecto Doctoral se han resumido los principales elementos relacionados: la disminución de la edad materna, la infección por VIH, la malaria, y la presencia de trastornos hipertensivos relacionados con el embarazo (preeclampsia y eclampsia). Todos estos elementos son especialmente relevantes en África subsahariana: *i)* el elevado número de embarazo en adolescentes [11,18], *ii)* la mayor proporción de mujeres embarazadas con infección por VIH en el mundo [41] y *iii)* la elevada prevalencia de infección por *Plasmodium falciparum* durante el embarazo [27]. En lo que respecta a la malaria, la información disponible es compleja, ya que los métodos diagnósticos convencionales presentan limitaciones debido a la frecuente presentación (subclínica y submicroscópica) [34,35,36]. Por ello, el empleo de técnicas más sensibles (como la reacción en cadena de la polimerasa) puede ser un instrumento útil en su diagnóstico [34,35, 36,37,38].

El análisis de los factores implicados en la mayor morbi-mortalidad materna y neonatal en África subsahariana es complejo, ya que además de su acción directa, existen interacciones entre ellos, así como en la aparición de preeclampsia/eclampsia como se resume en la **Figura 1.**

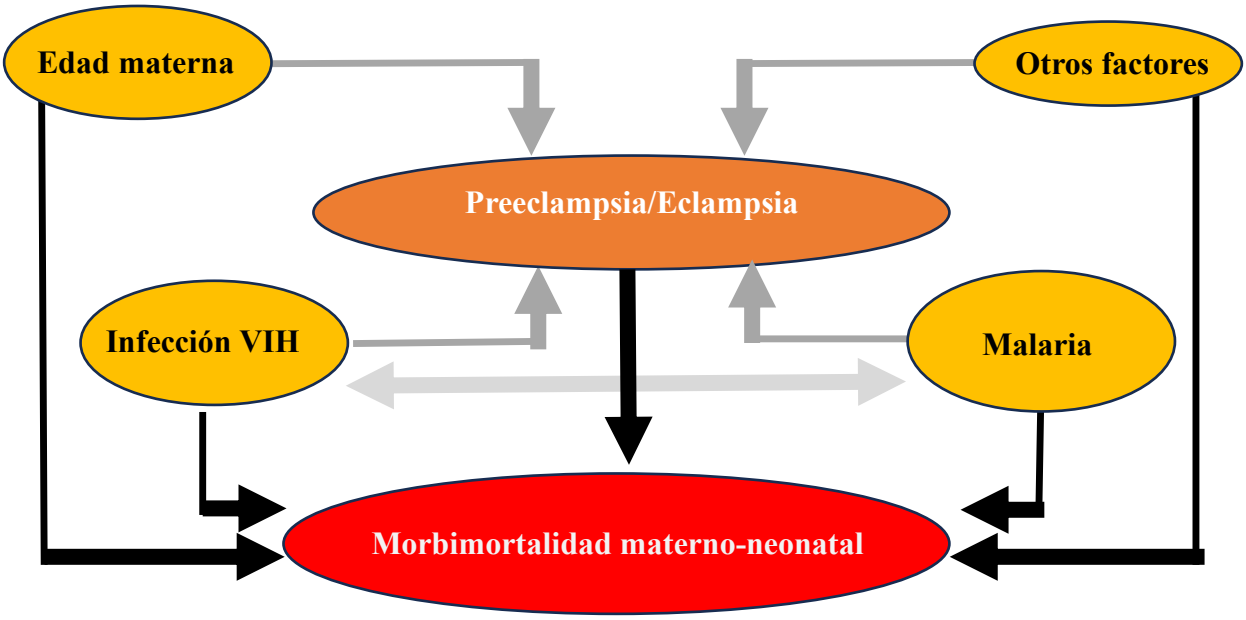

Figura 1: Factores relacionados con la morbi-mortalidad materna y neonatal.

Teniendo en cuenta este contexto y ante la presencia de infraestructuras sanitarias básicas en la provincia de Tete (Mozambique), así como, a la existencia de un convenio de colaboración docente entre la Facultad de Ciencias de la Salud de la Universidad de Zambeze y la ULPGC (Universidad de las Palmas de Gran Canaria) esta región se presenta como un lugar idóneo de estudio de las causas de morbilidad directa e indirecta en mujeres embarazadas. Los resultados de esta investigación pueden proporcionar información relevante para contribuir y para elaborar estrategias de prevención y abordaje precoz con el fin de disminuir la morbilidad materna y neonatal.

3. Objetivos

El **objetivo principal** de este Proyecto Doctoral consistió en evaluar la morbilidad materna directa e indirecta en el Hospital Provincial de Tete (Mozambique) y su repercusión en los recién nacidos.

Los **objetivos específicos** responden a las principales cuestiones identificadas en la Introducción y son los siguientes:

- Estudiar la prevalencia de embarazos en adolescentes, las consecuencias sobre la madre y el recién nacido así como los factores implicados.
- Examinar los efectos de la malaria clínica, la infección por VIH y la coinfección en la salud materna y neonatal en un entorno de alta prevalencia.
- Describir la incidencia de preeclampsia/eclampsia en esta población, así como la influencia de la malaria clínica, la infección por VIH y de la coinfección en su aparición.
- Evaluar la prevalencia de la infección subclínica por *Plasmodium falciparum* en las mujeres embarazadas en el HPT (Mozambique).y su asociación con la morbimortalidad materna y perinatal.

4. Artículos de Investigación

Los resultados de este trabajo doctoral vienen estructurados como artículos originales, que dan respuesta a los diferentes objetivos previamente referidos

Inicialmente se indicará el resumen del artículo, posteriormente se adjuntará la publicación aceptada a la que dio lugar y, finalmente los Indicios de calidad y relevancia de las aportaciones.

4. Resúmenes de los artículos

4.1. Artículo Primero

Título: Maternidad adolescente en Mozambique. Consecuencias en las mujeres embarazadas y los recién nacidos.

Objetivo: Identificar los factores asociados a la maternidad adolescente en Tete (Mozambique).

Metodología: Se realizó un estudio transversal que incluyó a 821 mujeres embarazadas (255 adolescentes) que ingresaron en el servicio de maternidad del Hospital Provincial de Tete entre marzo y octubre de 2016. La encuesta incluyó datos clínicos de la madre y del recién nacido.

Principales resultados: La prevalencia general de partos en adolescentes fue del 31,8 % (IC del 95 %: 27,9 % - 34,2 %). . El análisis multivariante mostró que los factores independientes asociados con la maternidad adolescente fueron: el número de embarazos (OR 0,066; IC 95% 0,040-0,110), el seguimiento del embarazo (OR 0,29; IC 0,173-0,488) y los abortos previos (OR 4,419; IC 95% 1,931-10,112). Cuando la edad de la madre se analizó como una variable continua, los factores positivamente asociados fueron el índice de masa corporal, la hipertensión arterial, la infección por VIH, el seguimiento del embarazo, y el peso del recién nacido. Los factores asociados negativamente fueron la episiotomía y el distrés respiratorio del recién nacido.

Conclusiones: La maternidad adolescente es un grave problema de salud pública en Mozambique. Es necesaria la intensificación de la planificación de la salud sexual y reproductiva de las mujeres adolescentes.

PLOS ONE

RESEARCH ARTICLE

Adolescent motherhood in Mozambique. Consequences for pregnant women and newborns

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Abstract

Introduction

In sub-Saharan Mozambique, high adolescent fertility rates are a significant public health problem. Understanding the consequences of teenage pregnancies facilitates effective strategies for improving the quality of care of both mother and the newborn.

Aims

To identify the factors associated with adolescent motherhood in Tete (Mozambique).

Methods

This was a cross-sectional study including 821 pregnant women (255 teenagers) admitted to the general maternity ward of the Provincial Hospital between March and October 2016. The survey included clinical data of the mother and newborn.

Results

The overall prevalence of adolescent deliveries was 31.8% (95% CI 27.9% - 34.2%). Multivariate analysis showed that independent factors associated with teenage motherhood were: number of pregnancies (OR 0.066; 95% CI 0.040–0.110), pregnancy follow-up (OR 0.29; CI 0.173–0.488) and previous abortions (OR 4.419; 95% CI 1.931–10.112). When the age of the mother was analysed as a continuous variable, positively associated factors were body mass index, arterial hypertension, HIV infection, previous abortions, pregnancy follow-up, and the weight of the newborn. Negatively associated factors were episiotomy and respiratory distress in the newborn.

Conclusion

Teenage motherhood is a serious public health problem in Mozambique. Intensive sexual and reproductive health planning for adolescents is needed.

Background

The adolescent population includes individuals in the 10–19 years group [1], representing those in the transitional phase between childhood and adulthood. This life period is marked by intense physical, psychological, emotional, and economic changes [1, 2]. In many cultures, this developmental phase does not exist or is relatively brief, particularly when controlled by initiation rites [3].

Approximately 16 million girls aged 15–19 years and 2.5 million girls under 16 years of age give birth every year in developing regions [4]. The maternal mortality rate among girls aged 15–19 years in low- and middle-income countries (LMICs) in the African region is very high (36 per 100,000 population), followed by 9, 7, and 3 deaths per 100,000 in the LMICs of the Eastern Mediterranean, South-East Asia and the Americas region, respectively [1].

Interventions to reduce the prevalence of adolescent pregnancies in developing countries is therefore a public health imperative, aimed at achieving sustainable development goals by 2030 [5].

In Mozambique, 38% of adolescent girls have given birth to a live child. This is the highest adolescent fertility rate in the countries of the Southern African Development Community, with a rising trend between 1997 and 2015 [6]. Furthermore, Mozambique is one of six countries in the world where at least one in ten girls (14%) has had a child before the age of 15, and 57% before age 18 [6, 7]. Mozambique has the 10th highest rate of child marriage in the world, measured as the proportion of women aged 20–24 who married in childhood (under 18 years old). Rates of child marriage are much higher than the averages in Eastern and Southern African sub-regions and are exceeded only by another Southern African country, Malawi [8]. According to data from the Demographic and Health Survey (DHS), in 2011 48% of women aged 20–24 were married before the age of 18, and 14% even before the age of 15 [9].

Both mother and child are at increased risk of adverse outcomes in adolescent pregnancies [10, 11]. There is also a high probability that the young mother will interrupt her education or drop out of school altogether, increasing the risk of lower socio-economic status, poverty, and even death from pregnancy-related complications [12].

In many African countries, it is common for people to be born, grow up, and die without being officially registered. In Africa, only Mauritius and the Seychelles have complete registrations of births, deaths, and causes of death [13] (the data from the most recent survey published in Mozambique indicates that childbirth increased from 48% to 55% between 2011 and 2015) [6].

Reliable statistics on maternal and perinatal morbidity and mortality are scarce in low- and middle-income countries, particularly in rural areas like Mozambique [14]. This information is crucial for developing effective national and global health policies concerning maternal and child health.

Data and methods

Study setting and participants

The data was collected from the maternity department of the Provincial Hospital of Tete (PHT), between March and October 2016. The province of Tete is located in the central region of Mozambique sharing a border with Zambia to the northwest and Zimbabwe to the southwest

(Fig 1). According to the 2017 National Institute of Statistics Annual Report for 2017, the population of the province of Tete was 2,764,169 and 13.6% lived in urban areas [15]. The number of births during this period was 2,906. Eight hundred and twenty-one women aged between 13 and 45 years from different districts in Tete province were randomly selected (Fig 2).

Study procedures

To minimize errors, the person responsible for collecting the data and a supervisor took part in a two-day training session focused on aspects associated with the ques-tionnaire, physical examination, and anthropometric measurements. The data was collected by completing a survey based on the pregnancy chart, which included personal details, as well as the obstetric history of the women included in the study, with information on the current gestation, events associated with the delivery, and data about the newborn.

Study design

This was a cross-sectional study that included 821 pregnant women living in Tete (Mozambique), 255 of whom were teenagers. The subject was considered a teenager if she was under 20 years of age.

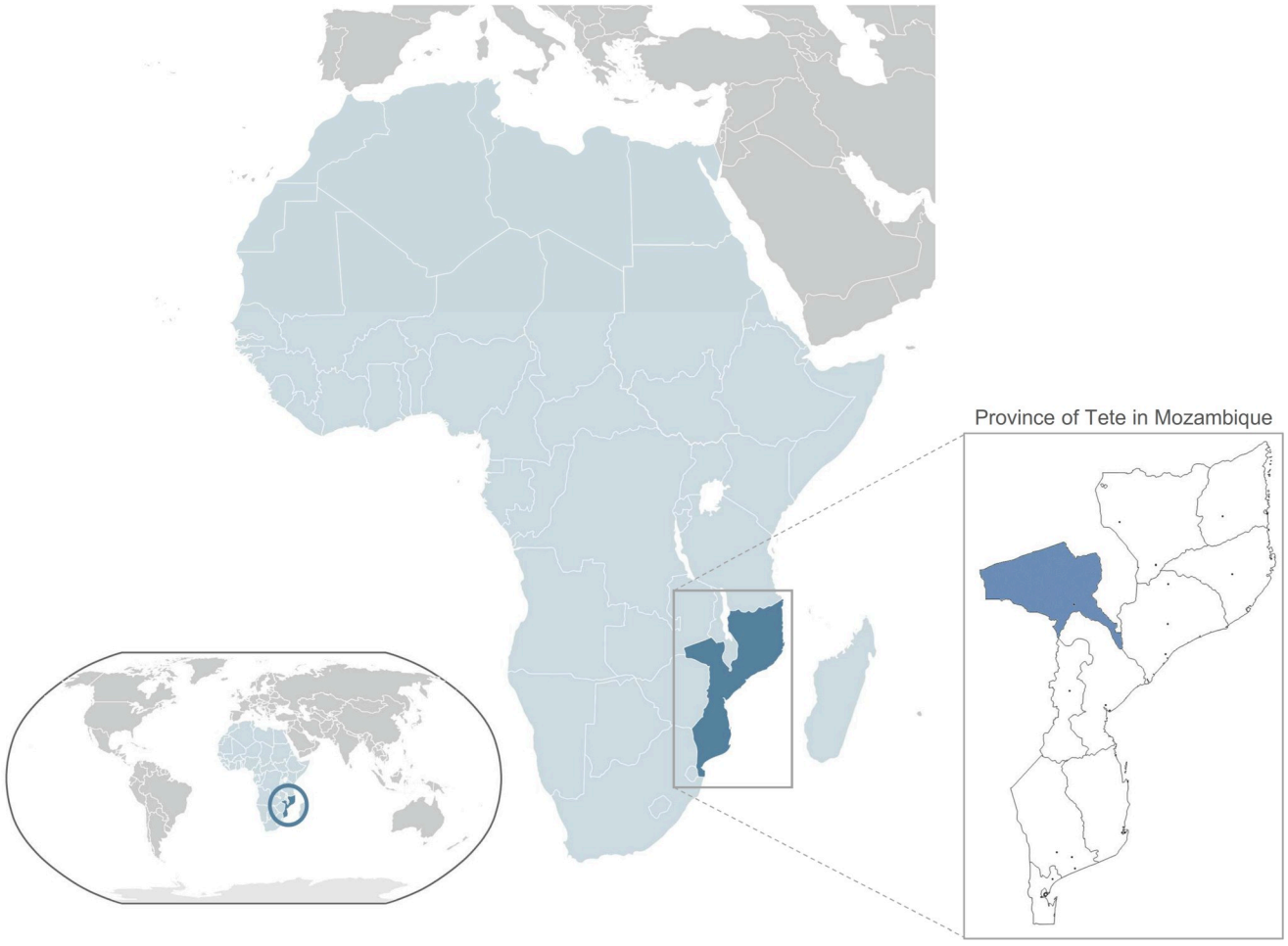

Fig 1. Geographical situation of the study area.

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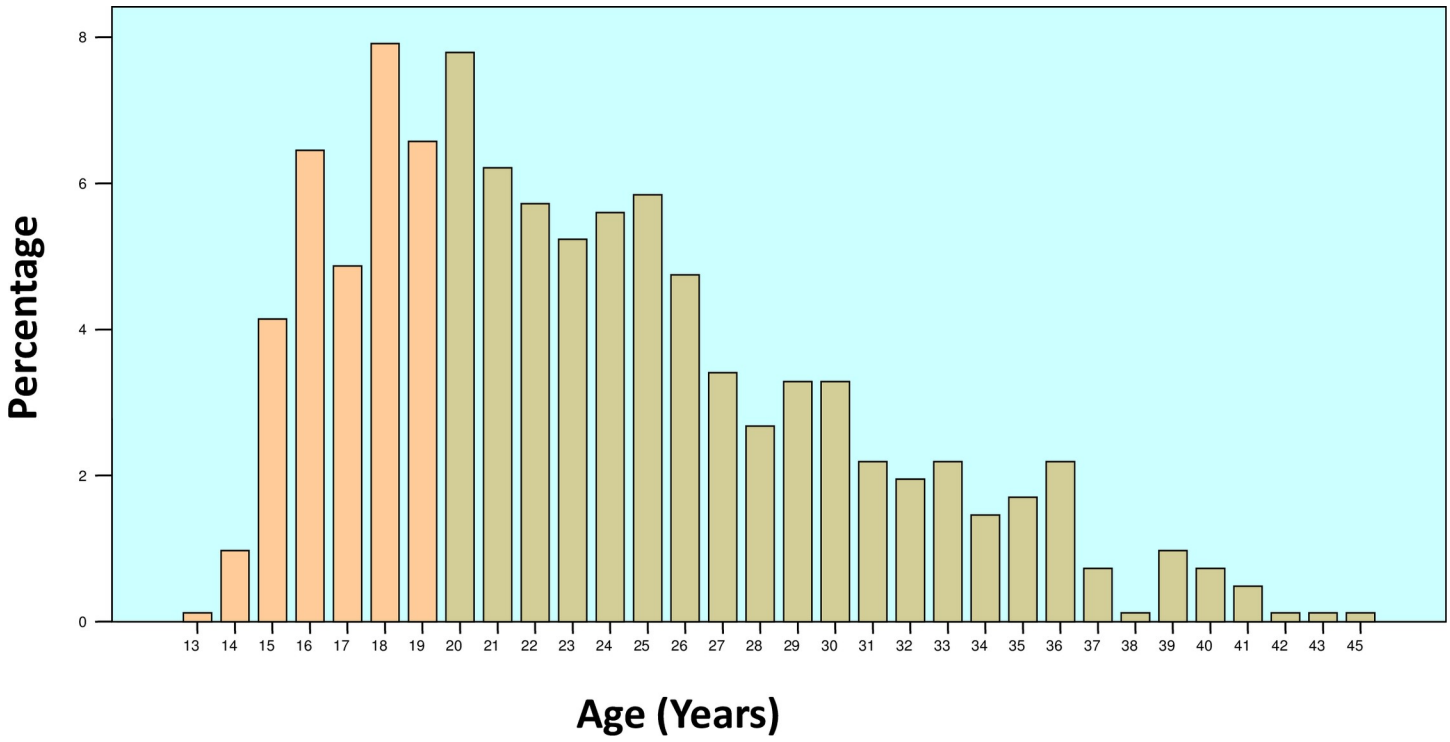

Fig 2. Distribution of study subjects according to their age.

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Variables

The following variables were included in this study: age, prenatal follow-up, anthropometric measurements, such as body mass index, arterial hypertension, HIV or syphilis infection, and pregnancy and intrapartum variables. Data about the newborn was also collected, including weight, Apgar score, neonatal respiratory distress (NRD), and mortality.

Statistical analysis

Categorical variables were expressed as frequencies and percentages, and continuous variables as means and standard deviation (SD) when the data was normally distributed, and as median and interquartile range (IQR = 25th– 75th percentile) when the data was not normally distributed. Percentages were compared using the chi-square ($\chi 2$) test or the Fisher's exact test as appropriate; the t-test was used to compare means, and the Mann-Whitney test was used for independent data.

Multivariate binomial regression analysis was performed to identify factors independently associated with teenage motherhood. Variables significantly associated with the outcome (teenage motherhood) in univariate analysis were entered into multivariate logistic analysis. Variable selection was based on the best subset regresson and Akaike Information Criterion (AIC) was then performed. The model was summarized as coefficients (SE), p-values and odds ratios, estimated using a 95% confidence interval.

Additive models. We performed a multivariate analysis for the age of the pregnant. We carried out a selection of variables The modes were summarized as coefficients (SE). Data were analysed using the R package, version 3.3.1 (R Development Core Team, 2019) [16].

Ethics

The study was conducted according to the criteria established by the Declaration of Helsinki [17], and approved by the National Committee for Bioethics in Health of Mozambique´s Ministry of Health. An interview was conducted only if the respondent provided their verbal consent in response to being read out an informed consent statement by the interviewer. Eligible participants provided written informed consent, which was documented in writing or with a fingerprint and witness signature prior to beginning the survey. The consent was signed by parent/guardian if the participant is under 18 years of age.

The authors declare that there are no conflicts of interest with respect to this study.

Results

The percentage of adolescents giving birth was 31.8% (95% CI 27.9% - 34.2%). Body mass index (Table 1), was significantly lower in adolescent mothers ($p = 0.001$).

Teenage mothers had fewer previous pregnancies and abortions ($p < 0.001$ in both cases) (Table 1). However, these data were reversed when women were pregnant with their second child, pregnant teenage had suffered more abortions (39.5%) than adult women (13.6%, $p < 0.001$). Follow-up of pregnancy (Table 2) was significantly lower among adolescents (42.6% vs 63.0%; $p < 0.001$) and HIV infection ($p < 0.001$) (Table 2).

With respect to the newborns, the weights and first-minute Apgar score of those born to teenage mothers were significantly lower ($p<0.001$, $p = 0.047$ respectively) than those born to older mothers. Neonatal respiratory distress was more frequently detected in the babies of adolescent mothers ($p = 0.007$), regardless of gestational age (Table 3).

Multivariate analysis found that being a teenage mother was statistically significantly associated with having had fewer pregnancies (OR per unit = 0.057; 95% CI = 0.033–0.098), receiving less prenatal follow-up (OR = 0.290; 95% CI = 0.173–0.488) and being at greater risk of miscarriage (OR = 5.889; 95%CI = 2.365–14.661) (Table 4).

An analysis of the age of the mother as a continuous variable (Table 5) revealed that BMI (Fig 3A) was low in the early years of adolescence and then increased until the mother was around 32 years of age ($p < 0.001$). Arterial hypertension (Fig 3B) was observed to increase with the age of the mother ($p < 0.001$). Prevalence of HIV infection (Fig 3C) was low at younger ages, increased until age 35, and then stabilized ($p < 0.001$). The abortion rate (Fig 3D) rose from the early years of adolescence until age 25, when it declined sharply ($p = 0.023$). Follow-up during pregnancy (Fig 4A) was less common among adolescents but increased

Table 1. Characteristics of the mothers.

		Teenage motherhood		
	Overall N = 821	***No N = 566***	***Yes N = 255***	***p***
Age, years	23.5 ± 6.3	26.5 ± 5.4	17.1 ± 1.5	< .001
Body mass index, kg/m^2	24.4 ± 4.2	25.0 ± 4.4	23.2 ± 3.7	0.001
Living area				0.280
Urban	669 (89.0)	466 (90.0)	203 (86.8)	
Peri-urban	35 (4.7)	20 (3.9)	15 (6.4)	
Rural	48 (6.4)	32 (6.2)	16 (6.8)	
Number of pregnancies	2 (1;3)	3 (2;4)	1 (1;1)	< .001
Previous abortion	134 (16.3)	117 (20.7)	17 (6.7)	< .001

Data are presented as means ± SD and frequencies (%)

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Table 2. Characteristics of the pregnancies and deliveries.

		Teenage motherhood		
	Overall = 821	**No N = 566**	**Yes N = 255**	***p***
Pregnancy follow-up	348 (56.9)	271 (63.0)	78 (42.6)	< .001
Malaria during pregnancy	92 (11.2)	64 (11.3)	28 (11.0)	0.899
Syphilis	9 (1.1)	6 (1.1)	3 (1.2)	1
HIV infection	101 (12.5)	89 (16.0)	12 (4.8)	< .001
Systolic blood pressure, mmHg, mmHg	125 (117;139)	124 (118;138)	128 (117;140)	0.236
Diastolic blood pressure, mmHg, mmHg	80 (70;90)	80 (70;90)	80 (70;90)	0.697
Malaria at delivery	15 (1.8)	9 (1.6)	6 (2.4)	0.574
Placental abruption	32 (3.9)	23 (4.1)	9 (3.6)	0.731
Peripartum Urinary Tract Infection	48 (5.9)	36 (6.4)	12 (4.7)	0.351
Maternal fever at delivery	33 (4.1)	23 (4.1)	10 (4.0)	0.930
Intra-partum hemorrhage	101 (13.2)	76 (14.5)	25 (10.3)	0.108
Episiotomy	32 (6.9)	11 (3.4)	21 (14.7)	< .001
Hypertensive disorders of pregnancy				0.255
Normal	697 (84.9)	483 (85.3)	214 (83.9)	
Preeclampsia	84 (10.2)	60 (10.6)	24 (9.4)	
Eclampsia	40 (4.9)	23 (4.1)	17 (6.7)	
Gestation				0.588
Pre-term	107 (13.2)	72 (12.9)	35 (13.9)	
Post-term	9 (1.1)	5 (0.9)	4 (1.6)	
At term	694 (85.7)	481 (86.2)	213 (84.5)	
Gestation type				0.080
Single	793 (96.8)	543 (96.1)	250 (98.4)	
Multiple	26 (3.2)	22 (3.9)	4 (1.6)	
Type of delivery				0.349
Eutocic	555 (68.0)	374 (66.5)	181 (71.3)	
Caesarean section	235 (28.8)	168 (29.9)	67 (26.4)	
Vacuum	26 (3.2)	20 (3.6)	6 (2.4)	

Data are presented as means ± SD and frequencies (%)

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significantly with age until around 23 years, when it stabilized ($p < 0.001$). A quasi-linear progression was observed between episiotomy rate and age (Fig 4B), being very frequent among

Table 3. Characteristics of the newborns.

		Teenage motherhood		
	Overall N = 821	**No N = 566**	**Yes N = 255**	***p***
Sex male	252 (44.1)	185 (46.7)	67 (38.1)	0.054
Weight at birth, kg	3.0 (2.6; 3.3)	3.0 (2.7; 3.3)	2.9 (2.6; 3.1)	< .001
Height at birth, cm	47 (43; 49)	47 (43; 49)	47 (43; 49)	0.839
Cephalic perimeter at birth, cm	33 (32; 35)	33 (32; 35)	33 (32; 34)	0.994
One-minute Apgar score	9 (8; 9)	9 (8; 9)	8 (7; 9)	0.047
Respiratory distress	48 (6.2)	25 (4.6)	23 (9.7)	0.007
Death	60 (7.3)	39 (6.9)	21 (8.2)	0.493

Data are presented as medians (IQR) and frequencies (%)

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Table 4. Multivariate binomial regression for the teenage motherhood.

	Coefficient (SE)	*p*	OR (95% CI)
(Intercept)	1.638(0.211)	< .001	
Number of pregnancies, per subject	-1.805 (0.204)	< .001	0.164 (0.110; 0.245)
Previous abortion	1.286 (0.312)	< .001	3.617 (1.962; 6.667)
Pregnancy follow-up	-0.354 (0.088)	< .001	0.702 (0.591; 0.833)

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younger mothers, then decreasing steadily with age ($p = 0.007$). The mean weight of the newborn (Fig 4C) was very low in the younger mothers and increased until age 23, at which point a decrease in mean weight was observed until the age of 30, when another increase was observed until the mother reached 35 ($p = 0.052$). Neonatal respiratory distress showed a linear decrease (Fig 4D) and was most frequently observed in younger mothers, decreasing with age ($p = 0.011$).

Discussion

In Mozambique, adolescents are the fastest growing segment of the population [18]. The fertility rate in 2015 was 5.3 children per woman and only 27% of these used some type of family planning method. Compared with currently married women, almost twice the percentage of those who were unmarried and sexually active used some family planning method [6]. Twenty-five percent of married women used modern methods and two percent traditional methods. The most commonly method used by unmarried, sexually-active women was male condoms, followed by contraceptive injection and oral [6].

Mozambique has the highest adolescent fertility rate of all the countries in the Southern African Development Community [3, 6, 7]. The 2015 IMASIDA survey indica-ted that 38% of adolescents had a child and, in the province of Tete in particular, the incidence was 46% [6].

There is a significant association between adolescent pregnancy and lower BMI and follow-up during pregnancy, similar to that reported in other publications with sub-Saharan African populations [19, 20]. Although the median weight of the newborns was significantly lower, there were more episiotomies and lower first-minute Apgar scores.

The percentage of previous abortions among adolescents in the Provincial Hospital of Tete was slightly higher than that reported in the Demographic and Health Survey (DHS) 2011 [9]. In this sample, although previous abortions among adolescents were significantly lower, after

Table 5. Additive models for the effects of the age on several factors.

Dependent variable	*p*-value	Co-variable
Body mass index[a], Kg/m^2	< 0.001	None
Arterial hypertension[b]	< 0.001	None
HIV infection[b]	< 0.001	None
Previous abortions[b]	0.023	*Number of pregnancies*
Control of pregnancy[b]	< 0.001	None
Episiotomy[b]	0.007	None
Weight of newborn[a], Kg	0.052	*Gestation week*
Respiratory distress[b]	0.011	None

[a]For continuous dependent variables, data were fitted by an ordinary additive model.

[b]For binary dependent variables, data were fitted by a logistic additive model.

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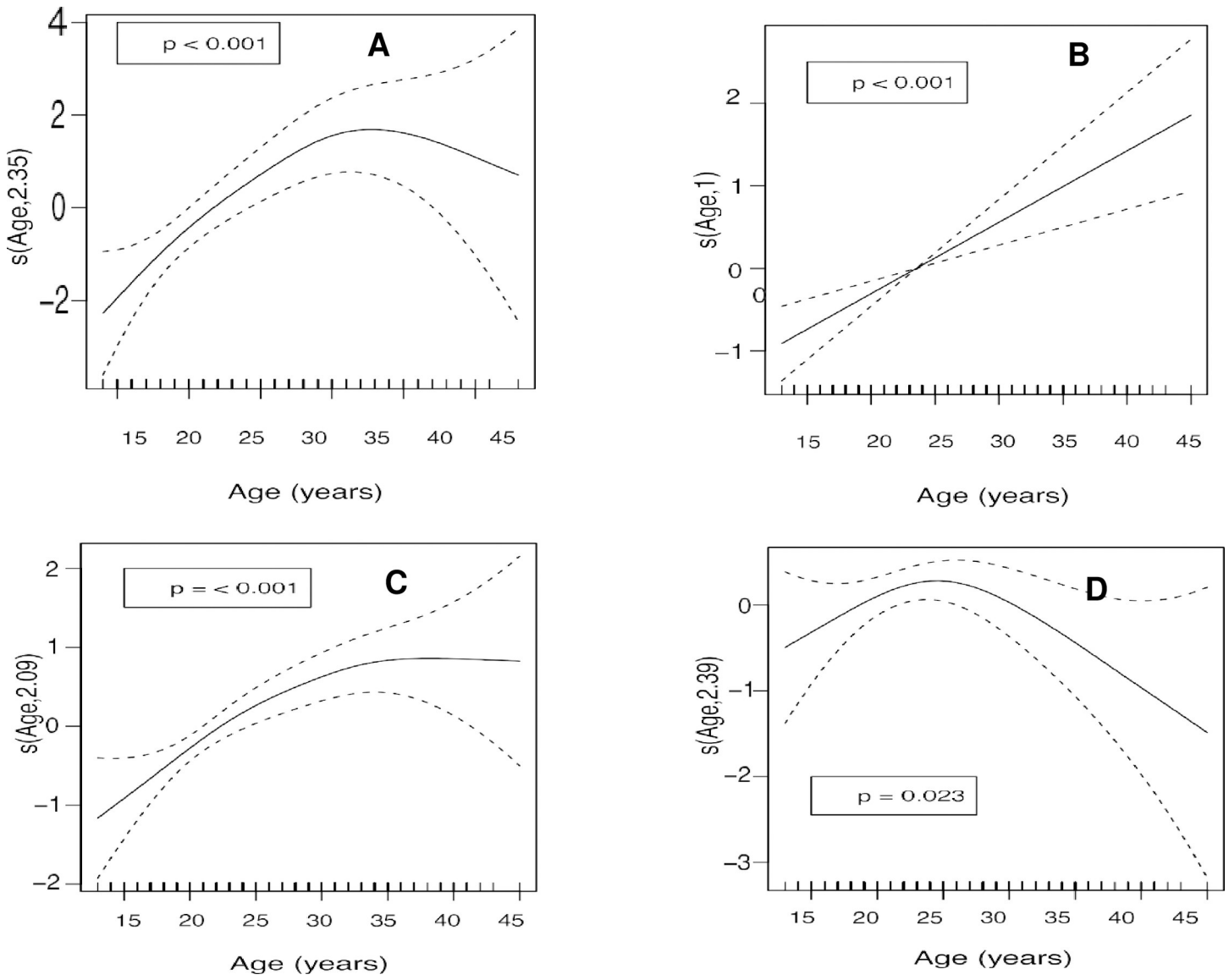

Fig 3. Analysis of the age of the mother versus A) Body mass index, B) Arterial hypertension, C) HIV infection, D) Previous abortions. Adjusted by the number of gestation.

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adjusting for number of gestations, the rate of previous abortions in second pregnant women was significatively higher compared with adult women.

According to the data from the last national survey carried out in Mozambique, 93% of pregnant women had one pre-natal visit and 55% had four or more [6]. However, in our study, 63% of adult women received follow-up during pregnancy (minimum four visits per pregnancy) and only 42.6% of adolescents [21, 22]. This rate of follow-up during pregnancy in Mozambique correlates with increased maternal mortality as cause of death; 24% of adolescent deaths are associated with maternity, declining to 16% in women aged 25–29, and 8% in women aged 45–49 [3, 23].

Sub-Saharan Africa remains the region with the highest percentage of pregnant women living with HIV, accounting for nearly 85% of the global burden of HIV [24]. According to

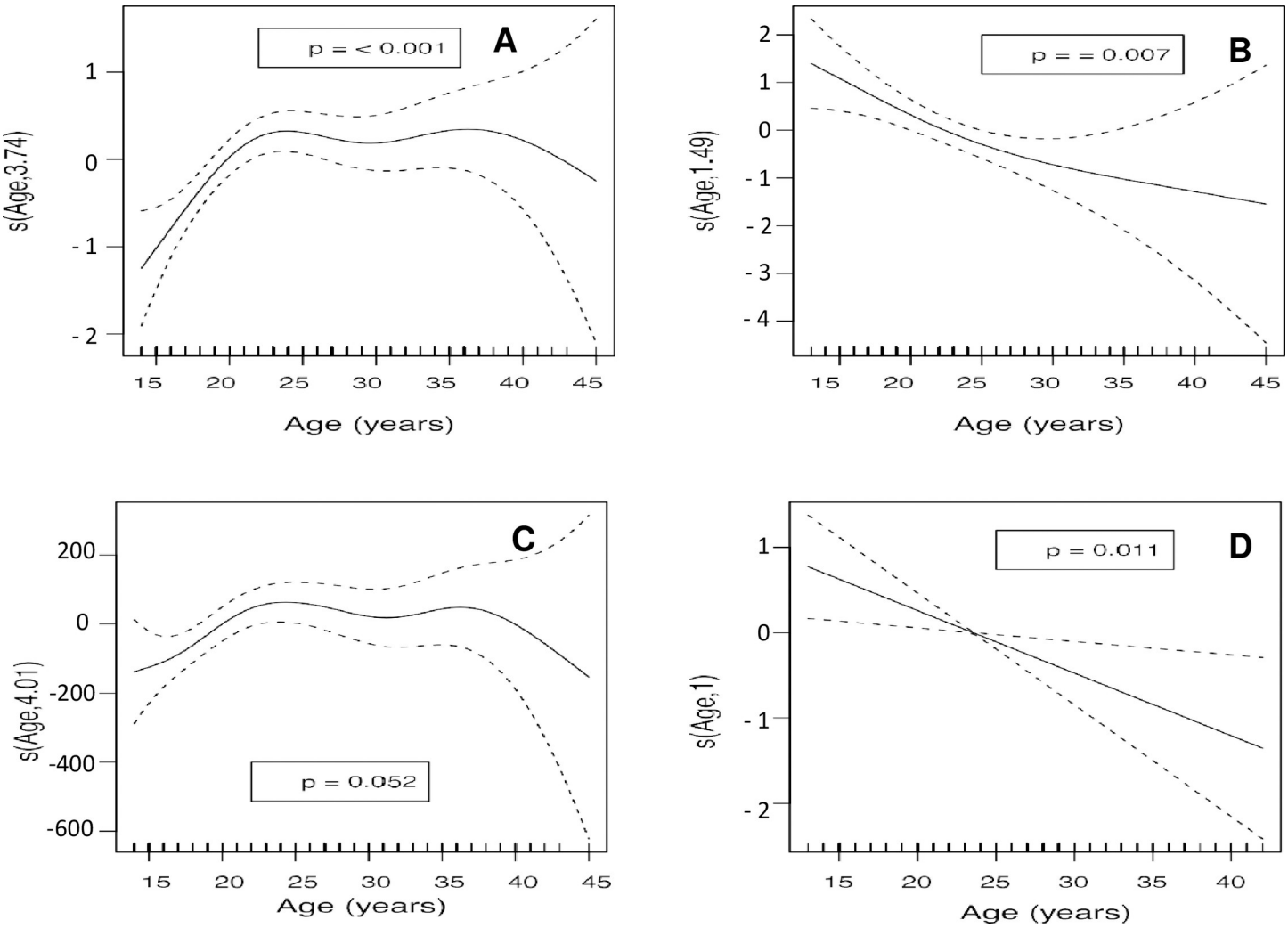

Fig 4. Analysis of the age of the mother versus A) follow-up of the pregnancy, B) episiotomy, C) weight of the newborn. Adjusted to the gestation week, D) neonatal respiratory distress.

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UNAIDS 2017, the estimated prevalence of HIV among people aged 15–49 is 12.5% [25]. In this study, 12.5% of women sampled were HIV-positive, which is twice the 2015 number reported by IMASIDA (5.2%) for the province of Tete [6]. As in other areas of the country, the prevalence of HIV is significantly correlated with the age of the mother; the prevalence in adolescence is significantly lower, increases until age 35 and then stabilizes although in other areas of the country it decreases [26].

Caesarean section rates are used as indicators of the availability and use of life-saving obstetric services in developing countries. In the PHT, the percentage of caesarean sections was 28.8% with no significant differences in adolescents. The proportion of caesarean sections is higher than that published for public hospitals in the southern area of Mozambique between 2009 and 2011, when the highest percentage was 20.6% [27].

The incidence of preterm births in this sample was slightly lower than the figure reported in another publication on Mozambique, which pointed out that it was in the top 10 of countries in the world with the highest rates of preterm births [28]. Unlike other publications, no significant increases were observed in pre-term births or neonatal mortality in pregnant adolescents [21, 22].

The main limitations of this study are the underestimation of the prevalence of adolescent pregnancies in the central region of Mozambique and that little attention has been paid to sociodemographic factors in adolescent pregnancies [29, 30].

As an example of the reflection of this data The Mozambican Association for Family Development (AMODEFA) has a clinic that offers sexual and reproductive health services, including safe abortions. Unpublished AMODEFA data indicate that 70,895 women underwent induced abortions in their clinic between 2010 and 2016, and that 43% of these women were between 15 and 24 years old. Of the 1,500 women who had induced abortions in the AMODEFA clinic in the first three months of 2017, 27.9% were also in this age group [29, 30]. These data are indicative of the high demand for (safe) abortions among young women in the country.

In summary, this analysis highlights some of the immediate challenges facing Mozambique, trade-and emphasizes the need to improve more sexual and reproductive health services for adolescents. [31].

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4.2 Artículo Segundo

Título: Efectos de la infección por VIH y/o la malaria en la salud materna y neonatal en un entorno de alta prevalencia.

Objetivo: El objetivo principal fue analizar las consecuencias obstétricas y perinatales de la malaria, la infección por VIH y la confección VIH/malaria en mujeres embarazadas y recién nacidos.

Metodología: Se realizó un estudio transversal en el Servicio de Maternidad de la Hospital Provincial de Tete Mozambique, que implica la realización de un cuestionario estructurado que incluía datos demográficos e información sobre el embarazo actual parto y el recién nacido. En total, 819 mujeres (13–45 años) en el entorno inmediato posparto se incluyeron entre marzo y octubre de 2016.

Principales resultados: La prevalencia global de VIH y malaria en mujeres embarazadas, consideradas por separado, fue del 12% (103 mujeres con VIH y 101 con malaria). Solo una quinta parte de las mujeres infectadas por el VIH conocían su estado serológico antes del embarazo. Significativamente una mayor proporción de mujeres con VIH asistieron a cuatro o más visitas de atención prenatal en comparación con las mujeres sin VIH. La cesárea fue menos frecuente en pacientes con VIH y la infección urinaria periparto fue más frecuente que en mujeres seronegativas (13/103 [12,6 %] frente a 34/716 [4,7 %]). La coinfección VIH/malaria fue de 17/819 (2%), se asoció significativamente con un aumento de las infecciones del tracto urinario periparto. Con respecto al recién nacido, la coinfección aumentó la frecuencia de muerte neonatal temprana.

Conclusiones: En Mozambique, la prevalencia de malaria e infección por VIH en mujeres de edad fértil continúa siendo alta y contribuye de manera adicional a las complicaciones durante el embarazo y el parto, y en el recién nacido. Por lo tanto, integrar el VIH, la malaria y los servicios de salud reproductiva son esenciales si los resultados maternos y fetales son para mejorar.

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RESEARCH ARTICLE

Effects of HIV infection and/or malaria on maternal and neonatal health in a high-prevalence setting

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Abstract

Objective: HIV infection and malaria have been associated with different complications during pregnancy and delivery. HIV-positive pregnant women are at increased risk for all adverse outcomes of malaria during pregnancy. The main objective was to analyse the obstetric and perinatal consequences of malaria, HIV infection and HIV/malaria co-infection in pregnant women and newborns, which has been less well evaluated.

Methods: A cross-sectional study was carried out in the Maternity Service of the Provincial Hospital of Tete Mozambique, involving completion of a structured questionnaire that included demographic data, and information on the current pregnancy, delivery and the newborn. In total, 819 women (13–45 years old) in the immediate postpartum period were enrolled between 1 March and 31 October 2016.

Results: The overall prevalence of HIV and malaria, considered separately, in pregnant women was ∼12% (103 women with HIV and 101 with malaria). Only one-fifth of HIV-infected women knew their HIV status before pregnancy. A significantly higher proportion of women with HIV attended four or more antenatal care visits than women without HIV. Caesarean section was less frequent in HIV patients, and peripartum urinary infection was more frequent than in seronegative women (13/103 [12.6%] vs. 34/716 [4.7%]). HIV/malaria co-infection were 17/819 (2%) and was significantly associated with the development of pre-eclampsia when HIV-infected patients received anti-retroviral treatment, and with an increase in urinary tract infections around delivery. With respect to the newborn, co-infection increased the frequency of early neonatal death, as well as neonatal asphyxia and jaundice.

Conclusions: In Mozambique, the prevalence of malaria and HIV infection in women of childbearing age continues to be high and contributes additively to complications during pregnancy and childbirth, and in the newborn. Therefore, integrating HIV, malaria and reproductive health services is essential if maternal and foetal outcomes are to improve.

KEYWORDS
Africa, HIV, malaria, Mozambique, pregnancy

INTRODUCTION

Malaria and HIV remain a major public health threat in sub-Saharan Africa. During pregnancy, both infections can have a significant impact on both the mother and the newborn. Maternal and child health, malaria and HIV infection are priority aspects of Sustainable Development Goal 3, which aims to reduce maternal mortality and the eradicate malaria by 2030 [1].

Malaria, a protozoan parasitic disease, accounted for 241 million cases and 627, 000 deaths in 2020, with ∼95% of cases and deaths occurring in sub-Saharan Africa. Four African countries accounted for just over half of all malaria deaths worldwide: Nigeria (31.9%), the Democratic Republic

Sustainable Development Goal: Good Health and Wellbeing.

of the Congo (13.2%), the United Republic of Tanzania (4.1%) and Mozambique (3.8%) [2], whereas HIV, which is a viral disease, accounted for 37.7 million cases and about 1 million deaths in 2020 [3]. This region of the world has the highest proportion of HIV-positive pregnant women, with 85% of the global burden [4]. Both diseases affect the poorest segment of the population and particularly pregnant women.

Malaria is a major cause of morbidity and mortality among HIV-infected pregnant women in endemic regions of sub-Saharan Africa, where at least 1 million malaria co-infections occur annually among pregnant women [5].

The World Malaria Report estimated that 11.6 million pregnant women in sub-Saharan Africa (35% of pregnancies in that region) in 2020 were infected with *Plasmodium* spp. In East Africa and Southern Africa, the prevalence of malaria exposure during pregnancy was 22% [6].

Focusing on Mozambique, malaria transmission occurs throughout the country, ranging from low, seasonal transmission in the south, to holoendemic in the centre and north of the country [7, 8]. Malaria is the fourth leading cause of mortality in pregnant women (10.1%) [9]. Mozambique is one of the sub-Saharan African countries most affected by the HIV/AIDS epidemic [10], where the two infections coexist, with 2.2 million infected people and an overall prevalence of 12.6% in adults between 15 and 49 years of age, with a clear predominance in women (60%) [11].

Interactions between pregnancy, HIV infection and malaria are multiple. HIV infection has been associated with a number of complications during pregnancy and delivery [12, 13, 14, 15], including: (i) increased incidence of anaemia, especially severe anaemia in pregnancy; (ii) increased antepartum bleeding; (iii) increased prevalence of hypertensive disorders of pregnancy; (iv) increased puerperal sepsis and endometritis; (v) pre-term delivery; (vi) low birth weight (LBW); and (vii) stillbirth. However, the results of several individual studies and meta-analyses are inconsistent and even contradictory, depending, among other factors, on the study site or the use of anti-retroviral treatment. At the same time, malaria also has multiple negative consequences in pregnancy, such as maternal anaemia, LBW, foetal growth retardation, preterm delivery, spontaneous abortion, stillbirth, neonatal and maternal death [16]. Finally, a number of interactions between HIV infection and malaria have been described, so that the coexistence of both infections 'increases the frequency of clinical parasitemia and severe malaria, with increased viral and parasite load and impaired immunity to malaria' [17, 18].

The role of HIV/malaria co-infection in pregnancy, childbirth and the newborn has been less well evaluated [19, 20, 21]. The main objective of this study was to analyse the obstetric and perinatal consequences of both malaria, HIV infection and HIV/malaria co-infection among women giving birth in the maternity unit of a tertiary hospital in Tete Province, Mozambique.

POPULATION AND METHODS

Study site

The study was conducted in the Maternity Services Unit of Tete Provincial Hospital (HPT). The province of Tete is located in the central region of Mozambique, bordering on Zambia to the north and Zimbabwe to the east (Figure 1); Mozambique is one of the least developed countries in the world [22]. The province has an area of 100,724 km^2 and average temperatures range between 23.4°C and 32.9°C. Tete province is the third most populated province in the country and has a population of 2,829,594 inhabitants, 1,442,880 of whom are women [23]. In recent years, Tete has experienced a boom in mineral resources, which has led to major socioeconomic changes and considerable population growth due to national and international immigration. Despite this, the local economy is still based primarily on subsistence agriculture, and levels of poverty and inequality are high. Literacy levels are low, especially among women, and access to safe water and sanitation or improved housing is scarce [22]. The average fertility rate is 4.7 births per woman [24]. It has a limited health system with a shortage of trained health personnel, especially in rural areas. The number of physicians is ~0.1 physicians per 1000 inhabitants [25]. The specific data of the hospital are shown in Table 1.

Study population

Between 1 March and 31 October 2016, the women in the study were recruited during labour and/or the immediate postpartum period. For sample selection, the primary criterion was to recruit women only when investigators were present at the time of delivery.

During the study period, 2906 deliveries were recorded. Investigators were present at the time of delivery in 1162 (40%) cases. In total, 215 women refused to participate for different reasons resulting in a sample of 947 (33%) women. Data were only completed in 819 (28%) cases, this being the final number of women included in the study. The flow chart of selection is shown in Figure 2.

Procedures

A cross-sectional study was conducted by completing a structured questionnaire that included demographic data and information about the current pregnancy, delivery and the newborn. The interviews were conducted by the researchers with the help of medical students from Zambeze University who were in the Maternity Services and acted as translators. Each interview lasted between 10 and 15 min. In addition, to complete the questionnaire data, the pregnancy record of the National Health Service of the Republic of Mozambique and the clinical history of childbirth of all women in the study were reviewed.

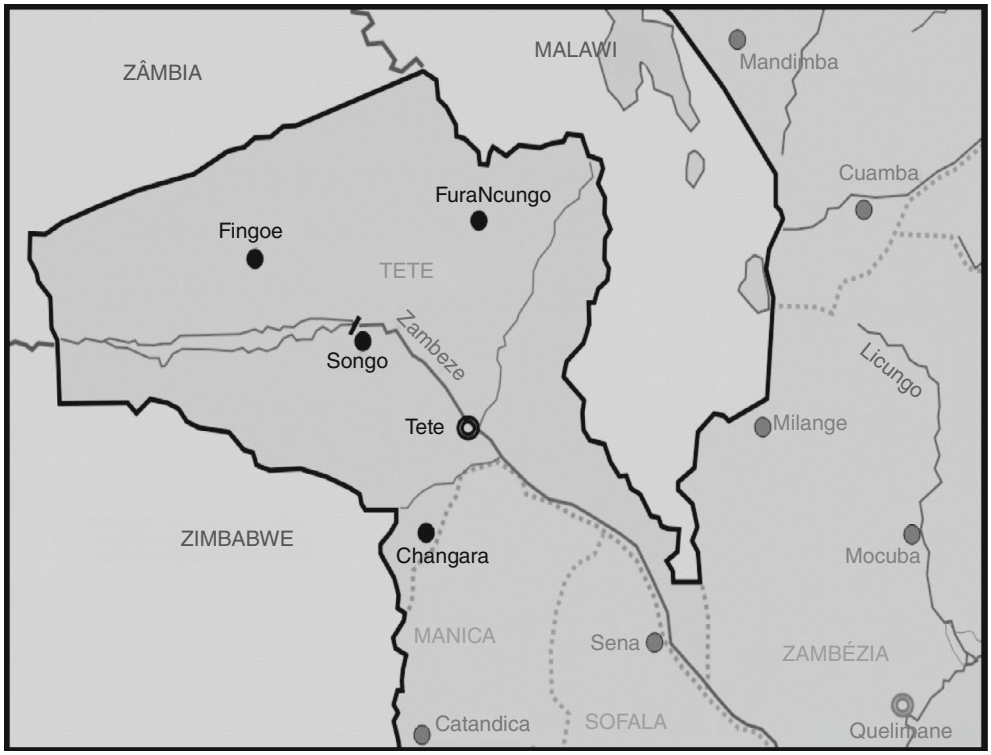

FIGURE 1 Political map of Tete (Mozambique).

HIV serostatus was assessed using a rapid test (Determine, Abbot Laboratories, USA) and positive results were confirmed using the Uni-gold rapid test (TM HIV, Trinity Biotech, Ireland). Test were performed during pregnancy control visits and/or delivery. The diagnosis of malaria was made from peripheral blood samples using the SD BIOLINE Malaria Ag P.f/Pan test (Abbott®). In suspected cases, malaria was also diagnosed using Giemsa-stained thick blood films for microscopic observation of plasmodium parasites. Proteins in urine were measured with the Multistix® 10 SG reagent strip.

Definitions

Several types of data were evaluated:

i. *Demographic* data, including age and residence (urban: Ciudad de Tete and Moatize), semiurban (Changara) and rural (Chifunde, Chiuta, Maravia, Mutarara, Zumbu, Macanga, Angonia, Cahora-Bassa and Tsangano),
ii. *Pregnancy data*, including pregnancy number (first, second or later); previous abortion history, defined as the expulsion of the conceptus before 28 weeks of gestation, or before the foetus weighs 500 g; expected date of delivery as calculated by midwives by adding 9 months and 7 days to the last menstrual period; symphysis fundal height (SFH) measured taking as a reference that the umbilical scar is normally reached at 20 weeks; pregnancy follow-up assessments based on completing at least four or more antenatal care (ANC) visits (≥4); complications during pregnancy. Complications evaluated were antepartum haemorrhage (including placenta previa and placental abruption) and hypertensive disorders induced by pregnancy (pre-eclampsia and eclampsia). For the diagnosis of preeclampsia, current criteria [26, 27] were used, which included (a) the presence of arterial hypertension (systolic blood pressure equal to or over 140 mm Hg and/or diastolic blood pressure equal to or over 90 mm Hg), determined on two occasions at least 4 h apart; (b) onset after the 20th week of pregnancy; and (c) proteinuria>300 mg/24 h and/or adverse conditions that increase the risk of severe complications and/or severe complications that warrant delivery. A diagnosis of eclampsia was made if seizures developed in patients with criteria for pre-eclampsia,
iii. *Infection data*, including HIV and malaria status. HIV patients were subdivided into two groups, according to whether or not they were on HAART (highly active anti-retroviral therapy) during pregnancy. Patients diagnosed with malaria were also subdivided into two groups, depending on whether the infection was diagnosed during pregnancy or at delivery (malaria in pregnancy [MiP] and no malaria in pregnancy [no MiP]).
iv. *Delivery data*, included type of delivery (vaginal or caesarean section), use of episiotomy, complications, such as urinary tract infection, maternal fever and uterine rupture. When available, haemocytometer parameters were recorded.
v. *Neonatal characteristics*, including: gestational age (*pre-term* was defined as occurring before week

TABLE 1 Tete provincial hospital structure

	Tete provincial hospital
12 immediate puerperium beds	6 beds and also
12 immediate puerperium beds	2 for intermediate care
12 immediate puerperium beds	4 beds for complicated pregnancies
12 immediate puerperium beds	12 immediate puerperium beds
Childbirths	4350 deliveries in 2016
Staffing rates	Gynaecology and obstetrics service
	5 gynaecologists
	3 senior nurses and 6 nurses during normal hours
	Maternity Service: 8 nurses on duty rotation and 2 morning nurses
Services available	3 operating rooms (general, gynaecology and obstetrics and emergencies), Neonatology Service (6 beds and 6 for neonatal ICU)
	Gynaecology and Obstetrics Service Internal Medicine
	Paediatric
	Legal Medicine
	Traumatology
	Surgery
	Emergency
	Radiology
	Urology

37, *at-term* as between weeks 37 and 42, and *post-term* from 42 weeks of gestation), anthropometric measurements (sex, weight [kg]) and complications: stillbirth, LBW, Apgar score <7 at 1 min [28], respiratory distress (> 60/min), neonatal fever (T > 38.0°C) and neonatal jaundice (clinical assessment of conjunctiva/sclera). Stillbirth was defined as occurring after 28 complete weeks of gestation, and LBW as weighing <2500 g at birth.

Specifically, the variables that were collected from medical or antenatal records were pregnancy number, previous abortion history, SFH, ANC, HIV infection diagnosed before delivery, HAART before delivery and malaria during pregnancy. The rest of the variables were collected through the questionnaire carried out by the researchers.

Statistical analysis

Categorical variables are summarised as frequencies and percentages, and continuous variables as means and standard deviation (SD). Categorical data were analysed for associations using the Chi-square test or Fisher's exact test. Means of continuous variables were compared using Student's *t*-test (2 groups) or ANOVA (>2 groups) when the data followed a normal distribution, and the Mann–Whitney *U* test (2 groups) or Kruskal–Wallis (>2 groups) for non-normally distributed data. Multivariate analyses were performed on adverse maternal and neonatal outcomes found in univariate analysis to be associated with gestational malaria and/or HIV. Logistic regressions were performed for binary outcomes (i.e., peripartum urinary tract infection, intrapartum maternal fever, neonatal death, respiratory distress, and neonatal jaundice) and linear regression for continuous outcomes (i.e., neonatal weight). The multivariate models controlled for maternal age, number of previous pregnancies, and gestational age at delivery. For each model, odds ratios and p-values are shown. Statistical significance was set at $p < 0.05$. Data were analysed using Stata version 15 (StataCorp®).

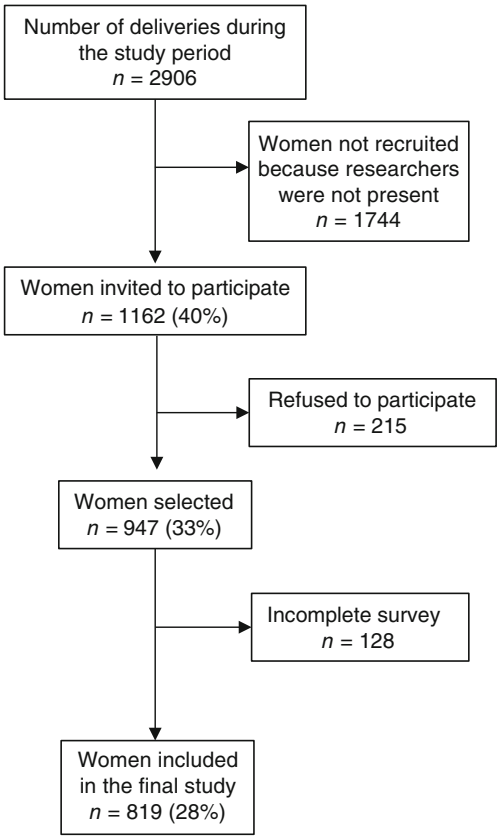

FIGURE 2 Flowchart for selecting the women in the study.

Ethics approval and consent to participate

Study protocols and informed consent forms for trials were reviewed and approved by the National Ethics Review Committee in Mozambique 432/CNBS/16. The study was conducted under the provisions of the Declaration of Helsinki and in accordance with Good Clinical Practice guidelines set up by the WHO and the International Conference on Harmonisation. Participation in the

study was completely voluntary. All the study participants were informed about the purpose of the study and written informed consent was obtained from each study participant. The consent was signed by parent/guardian if the participant was under 18 years of age. Illiterate women were read and explained the consent and the information sheet for the patient and those who verbally agreed to participate in the study signed the consent form with their finger.

RESULTS

In total, 81.5% (947/1162) of the 40% (1162/2906) of eligible women agreed to participate (Figure 2). A total of 819 women (13–45 years) were recruited during delivery and/or in the immediate postpartum period. 103/819 (12.6%) women had HIV infection. Infection was diagnosed during gestation in 67/103 (65.0%) cases, at delivery in 15/103 (14.6%) and before gestation in 21/103 (20.3%). 96/103 (93.2%) of HIV-positive pregnant women were in Stage I of the disease (asymptomatic, one case had persistent lymphadenopathy), 6/103 (5.9%) in Stage II (recurrent infections) and 1/103 (0.9%) in Stage III (weight loss >10%). A total of 86/103 (83.4%) women received anti-retroviral treatment during pregnancy, and the most commonly used regimen was tenofovir disoproxil, lamivudine and efavirenz in 65/86 (75.5%) of cases.

In our study, the frequency of malaria during pregnancy and/or delivery was 101/819 (12.4%): 93 (11.5%) during pregnancy, and 8 (0.9%) at delivery. Malaria and HIV co-infection was found in 17/819 (2%) of pregnant women. 17/103 (16.7%) of women with HIV had an episode of malaria during pregnancy, higher than the incidence of 84/716 (11.7%) in pregnant women without HIV, although with no significant differences ($p = 0.158$) between the two groups.

No significant differences were observed when different obstetric complications (previous abortions, antepartum haemorrhage and pre-eclampsia/eclampsia) were compared (Table 2). However, mean age was significantly higher in HIV-negative women without malaria and lower in HIV-uninfected women with gestational malaria (Table 2). Significant differences were also found when comparing the number of pregnancies, being higher in multiparous HIV-infected women without malaria and in HIV-uninfected women with gestational malaria (Table 2). A larger proportion of HIV-infected women had ≥4 ANC visits than HIV-uninfected women.

When the characteristics of delivery were compared in the different groups and subgroups, significant differences were observed between HIV-infected and non-HIV-infected women, with fewer Caesarean births in infected patients (Table 3). Significant differences were also observed in delivery complications, with urinary tract infection being more frequent in HIV-infected patients, and intrapartum fever in HIV-uninfected women with gestational malaria (Table 3). Regarding newborn characteristics, birth weight was lower in the presence of gestational malaria (both in HIV-infected and uninfected women; Table 4). It was statistically significantly ($p = 0.020$) more likely that newborns would have some of these complications if during pregnancy the mother was co-infected with HIV and malaria (Table 4).

HIV/malaria co-infection was significantly associated with a higher number of stillbirths ($p = 0.02$), asphyxia

TABLE 2 Demographic and obstetric characteristics of pregnant women.

	HIV-infected ($n = 103$)			Non-HIV infected patients ($n = 716$)			Overall	
Variable, by class	A MiP ($n = 17$)	B No MiP ($n = 86$)	p	C MiP ($n = 84$)	D No MiP ($n = 632$)	p	p^*	p^{**}
Age, median years (range)	24.4 (5.0)	26.6 (6.4)	0.186	22.4 (5.6)	23.3 (6.2)	0.237	**<0.001**	**<0.001**
Residence, n (%)			0.497			**0.047**	0.091	0.091
Urban	15/15 (100)	74/81 (91.3)		61/75 (81.3)	516/576 (89.6)			
Semi-urban	0	5/81 (6.2)		7/75 (9.3)	21/576 (3.6)			
Rural	0	2/81 (2.5)		7/75 (9.3)	39/576 (6.8)			
Number of pregnancies, n (%)			0.239			**0.053**	**<0.001**	**<0.001**
1	5/17 (29.4)	11/83 (13.3)		42/81 (51.8)	232/613 (37.8)			
2	5/17 (29.4)	26/83 (31.3)		17/81 (21)	164/613 (26.8)			
≥3	7/17 (41.1)	46/83 (55.4)		22/81 (27.2)	217/613 (35.4)			
Antenatal care visits, n (%)	6/10 (60)	43/62 (69.3)	0.556	27/58 (46.5)	268/478 (56.0)	0.169	0.086	**0.036**
Previous abortions, n (%)	4/17 (23.5)	20/86 (23.3)	0.981	8/84 (9.5)	103/631 (16.3)	0.106	0.724	1.000
Antepartum haemorrhage, n (%)	1/17 (5.9)	3/86 (3.5)	0.641	2/84 (2.4)	28/632 (4.5)	0.368	0.207	0.657
Pre-eclampsia/eclampsia, n (%)	5/17 (29.4)	12/86 (13.9)	0.117	16/84 (19)	89/632 (14.1)	0.227	0.199	0.733

Note: Percentages expressed data of the column. Bold indicates statistically significant value.
Abbreviations: MiP, malaria in pregnancy; No MiP, no malaria in pregnancy.
*All groups (A, B, C, D).
**HIV infected (A + B) versus Non-HIV infected (C + D).

TABLE 3 Delivery characteristics. Clinical complications

Variable, by class	HIV-infected ($n = 103$)			Non-HIV infected patients ($n = 716$)			Overall	
	A MiP ($n = 17$)	B No MiP ($n = 86$)	p	C MiP ($n = 84$)	D No MiP ($n = 632$)	p	p^*	p^{**}
Type of delivery, n (%)			0.790			0.666	0.215	**0.045**
Vaginal	14/17 (82.3)	66/83 (79.2)		57/84 (67.8)	442/630 (70.1)			
Caesarean	3/17 (17.6)	17/83 (20.5)		27/84 (32.1)	188/630 (29.9)			
Clinical complications, n (%)								
Peripartum urinary infection	3/17 (17.6)	11/86 (12.8)	0.593	6/84 (7.1)	28/632 (4.4)	0.223	**0.003**	**0.001**
Intrapartum maternal fever	1/17 (5.8)	3/86 (3.5)	0.641	13/84 (15.5)	16/632 (2.5)	**<0.001**	**<0.001**	1.000

Note: Percentages expressed data of the column. Bold indicates statistically significant value.
Abbreviations: MiP, malaria in pregnancy; No MiP, no malaria in pregnancy.
*All groups (A, B, C, D).
**HIV infected (A + B) versus Non-HIV infected (C + D).

TABLE 4 Neonatal characteristics

Variable, by class	HIV infected ($n = 103$)			Non-HIV-infected patients ($n = 716$)			Overall	
	A MiP ($n = 17$)	B No MiP ($n = 86$)	p	C MiP ($n = 84$)	D No MiP ($n = 631$)	p	p^*	p^{**}
Gestational age, n (%)			0.588			0.931	0.724	0.498
Term delivery	14/17 (82.3)	75/86 (87.2)		71/84 (84.5)	543/621 (86.0)			
Pre-term	3/17 (17.6)	9/86 (10.5)		12/84 (14.3)	81/621 (13.0)			
Post-term	0/17 (0)	2/86 (2.3)		1/84 (1.2)	6/621 (1)			
Neonatal sex, n (%)			0.487			0.256	0.628	0.902
Male	5 (55.5)	29/67 (43.3)		30/59 (50.8)	188/437 (43.0)			
Female	4 (44.4)	38/67 (56.7)		29/59 (49.1)	249/437 (57.0)			
Anthropometrics measures, n (%)								
Neonatal weight (g)	2803.1 (757.7)	3096.6 (483.2)	**0.047**	2806.8 (638.1)	2952.4 (558.2)	**0.032**	**0.008**	**0.063**
Neonatal complications	9/17 (53)	18/86 (20.1)	**0.006**	32/84 (38.1)	231/632 (33.7)	0.425	**0.020**	0.107
Stillbirth	3/17 (17.6)	3/86 (3.5)	**0.023**	6/84 (7.1)	47/632 (7.4)	0.923	0.185	0.563
Apgar <7	5/17 (29.4)	9/84 (10.7)	**0.042**	16/77 (20.8)	114/611 (18.7)	0.654	0.171	0.221
Neonatal jaundice	1/14 (7.1%)	0/84 (0.0%)	0.014	2/84 (2.4%)	4/571 (0.7%)	0.113	**0.025**	0.893

Note: Percentages expressed data of the column; Neonatal complications include stillbirth, low birth weight, Apgar <7, respiratory distress, neonatal fever and neonatal jaundice. Bold indicates statistically significant value.
Abbreviations: MiP, malaria in pregnancy; No MiP, no malaria in pregnancy.
*All groups (A, B, C, D).
**HIV infected (A + B) versus Non-HIV infected (C + D).

($p = 0.042$) and jaundice ($p = 0.02$) (Table 4). Antiretroviral treatment did not influence obstetric morbidity except in women who also had malaria, in whom an increased risk of hypertensive disorder was observed (Table 5).

In multivariate analyses on adverse maternal and neonatal outcomes found in the univariate analyses associated with gestational malaria and/or HIV, we found results very similar to those shown by the univariate analysis. However, with regard to neonatal asphyxia and jaundice as well as HIV infection in women undergoing treatment for pre-eclampsia, statistical significance disappeared. HIV increased the risk of urinary tract infection, while malaria increased the risk of intrapartum maternal fever and was associated with lower neonatal weight, and HIV / malaria co-infection increased the risk of early neonatal death.

DISCUSSION

In low-income and middle-income countries, malaria and HIV are the main causes of indirect maternal mortality [29]. In our series, the overall prevalence of each infection considered separately was ~12% in pregnant women. These figures are lower than those published for *Plasmodium falciparum* infection (24%) in Mozambique [30] and similar to those reported for HIV infection [14]. In our study, it was also observed that pregnant women with malaria were younger and usually primiparous, unlike those infected with HIV, as already described in the literature [14, 16].

In general, *HIV infection* is asymptomatic, and its diagnosis depends on women agreeing to undergo offered and recommended screening tests during pregnancy and delivery. Between 60% and 70% of HIV-infected women in our series had adequate pregnancy control, which was

TABLE 5 The impact HIV, malaria and HIV/malaria co-infection on maternal and neonatal morbidity and neonatal mortality

	Multivariate[a]		
	OR	**95% CI**	***p*-value**
Peripartum urinary infection			
HIV	**3.31**	**1.49–7.33**	**0.003**
Malaria	1.60	0.64–4.03	0.317
HIV/Malaria	0.91	0.17–4.93	0.911
Intrapartum maternal fever			
HIV	1.67	0.45–6.11	0.441
Malaria	**5.83**	**2.47–13.76**	**0.000**
HIV/Malaria	0.29	0.24–3.55	0.335
Neonatal death			
HIV	0.31	0.72–1.31	0.111
Malaria	0.75	0.25–2.17	0.595
HIV/Malaria	**11.62**	**1.33–101.24**	**0.026**
Neonatal respiratory distress			
HIV	0.50	0.12–2.17	0.358
Malaria	1.81	0.83–3.96	0.137
HIV/Malaria	3.13	0.34–28.47	0.312
Neonatal jaundice			
HIV	_		0.999
Malaria	3.50	0.61–19.98	0.159
HIV/Malaria	_		0.998
	Marginal effect	95% CI	p-value
Neonatal weight (g)			
HIV	94.10	−30.67 to 218.81	0.139
Malaria	−150.14	**−275.44 to − 24.85**	**0.019**
HIV/Malaria	−81.89	−389.10 to 225.29	0.601

Note: Bold indicates statistically significant value.
[a]Models control for mother's age, number of previous pregnancies and gestational age at delivery.

significantly more than in HIV-uninfected pregnant women. Furthermore, approximately two-thirds of HIV infections were diagnosed during a gestational check-up or at the time of delivery, and only 20% before pregnancy. These data are similar to those reported in some studies conducted in Mozambique, which indicated that 72.5% of HIV infection cases were diagnosed during pregnancy [31] and that 7% of women attending ANC were HIV-infected [32]. However, other publications have observed that only 52% of HIV-positive women of childbearing age are aware of the presence of the infection [33]. In this context, the data suggest on the one hand that HIV screening offered to pregnant women is widely accepted, and on the other hand, that screening for HIV infection increases gestational control. In our study, 84% of HIV-infected pregnant women received anti-retroviral treatment, being the regimen of choice recommended by WHO in 2016 (tenofovir, lamivudine and efavirenz) [34], but they recently switched from efavirenz to dolutegravir [35] although in another series of pregnant women studied in Mozambique, the percentage of HIV-positive pregnant women on treatment was markedly lower, ranging between 56% [31] and 61% [32]. Another important aspect, which however was not evaluated in our study, is low adherence to anti-retroviral treatment; in some series, only 37% have an undetectable viral load [33]. Consequently, it cannot be automatically assumed that a prescription for treatment indicates adherence.

In our series, HIV infection in pregnant women was not globally associated with maternal morbidity, according to the presence and number of previous abortions, antepartum haemorrhage or pre-eclampsia/eclampsia, although there was a trend towards a higher frequency of previous abortions in patients with HIV infection ($p = 0.064$). The design of our study did not allow us to evaluate other causes of maternal morbidity, such as severe anaemia or urinary tract infection, which in some studies are more frequent in HIV-infected pregnant women [12–16, 36].

With regard to *delivery*, we observed two significant differences between HIV-infected and HIV-uninfected pregnant women. First, caesarean sections were less frequent in infected patients. In some situations, this procedure is recommended for prevention of mother-to- child transmission of HIV [36], both in Mozambique and in neighbouring countries. Due to the high cost of caesarean section, required infrastructure, and health care workers' concerns about the risk of occupational transmission of HIV and the possible complications of the procedure, caesarean section was not indicated, as has been pointed out in other studies [13, 37]. Secondly, pregnant women with HIV infection more frequently presented peripartum urinary tract infection than seronegative women (12.6% vs. 4.5%), as reported in other publications [38, 39]. Considering that the prevalence of asymptomatic bacteriuria is similar in women with or without HIV infection [40], it is likely that the smaller number of Caesarean sections plays a role in the higher incidence of peripartum urinary tract infections. In our series, HIV infection did not appear to influence newborn morbidity and mortality, also reflected in another study [31].

Globally, it has been estimated that 1 million pregnant women per year suffer from *malaria and HIV* [14, 18] in sub-Saharan Africa. In our series, this co-infection accounted for 2% of pregnant women, similar to the proportion described in East Africa (0.94% in Ethiopia) and much less than in West Africa (37% in Nigeria) [18].

With regard to pregnancy, co-infection was not observed to increase complications, although HIV/malaria co-infection was significantly associated with the development of preeclampsia when HIV-infected patients receiving anti-retroviral treatment were evaluated separately. However, this association is not found in multivariate analysis. The effect between HIV infection on treatment and an increased risk of the onset of preeclampsia has been widely reported in the literature [12, 15, 41]. The data are controversial, and malaria infection has the potential to be an important factor for hypertensive disorders, but it has not been confirmed as such as the studies on this has poor design and marked biases [42, 43].

However, HIV/malaria co-infection was significantly associated with an increase in urinary tract infections around delivery compared with the rest of the groups in our series. This observation is similar to that published in the literature, where the authors also showed a greater variety of bacterial species and a higher prevalence of resistant strains [38].

Finally, with respect to the newborn, HIV/malaria co-infection in our series significantly increased the frequency of stillbirths. In this sense, the results are similar to those described in the literature [44, 45] and can be explained as placental involvement in both infections.

Limitations

This study has several limitations, such as: (i) the omission of including women from rural areas where deliveries are carried out in health centres or at home, as this study was performed in the main urban hospital in the province; (ii) limited documentation in the patient's medical records because record-keeping is poor during ANC and, less so, during admissions; (iii) underestimation of malaria diagnosis, since diagnostic tests were only performed in the presence of clinical manifestations; (iv) difficulty in accessing information on pregnancy in women without malaria or HIV infection, (v) lack of diagnostic resources in the hospital, which prevented the collection of laboratory values (blood count, CD4 and HIV viral load) in a significant number of pregnant women as well as urine culture in women with suspected urinary tract infection for confirmation and (vi) lack of human resources to offer the survey to all women who gave birth during the study period.

CONCLUSIONS

In summary, in HPT, Mozambique, the prevalence of malaria and HIV infection among women of childbearing age remains high and further contributes to complications during pregnancy, childbirth and increases the frequency of stillbirths. HIV screening should be a priority among women of reproductive age, as only one-fifth of HIV-infected women know their HIV status before pregnancy. An improved approach to quality of care has the potential to find significant benefits for all mothers and newborns at Tete Provincial Hospital.

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DATA AVAILABILITY STATEMENT

All relevant data related to the study were included in the article. The data will not be publicly shared to protect the anonymity of participants. Anonymised data used for analysis are available from the corresponding author on reasonable request.

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4.3 Artículo Tercero

Título: Aumento de la mortalidad neonatal asociada con la malaria materna subclínica en Mozambique.

Objetivo: Estudiar la prevalencia de la malaria subclínica en la mujer embarazada y su impacto en el recién nacido.

Metodología: Se realizó un estudio transversal entre marzo de 2017 y mayo de 2019. Se utilizó la reacción en cadena de la polimerasa multiplex semianidada para evaluar la presencia de *Plasmodium falciparum* en sangre placentaria y periférica de 232 mujeres embarazadas parturientas en el Hospital Provincial de Tete, Mozambique.

Principales resultados: En total, el 17,2% (n=40) de las mujeres estudiadas tuvieron la PCR positiva para *P. falciparum* (7 en sangre placentaria solamente, 3 en sangre periférica solamente). Se observó preeclampsia en 40,5% (n=94) de las mujeres y eclampsia en 15,5% (n=36). La infección por VIH estuvo presente en el 15,5% (n=36). Se encontró una asociación positiva entre la infección por *P. falciparum* y la adolescencia (p=0,028) y negativa entre la infección por *P. falciparum* y la presencia de preeclampsia (p=028). Finalmente, se observó un aumento del riesgo de mortalidad neonatal asociado con malaria subclínica [odds ratio ajustada: 3,54 (1,12-11,19)], así como con la eclampsia [odds ratio ajustada: 4,83 (1,31-17,85) y la infección por VIH [odds ratio ajustada 3,79 (1.04-13.77)].

Conclusiones: Este estudio demostró el grave efecto sobre los recién nacidos de la malaria subclínica en mujeres embarazadas. Por lo tanto, se necesitan métodos moleculares que detecten densidades de parásitos extremadamente bajas para reducir su impacto en la mortalidad neonatal y su contribución a la transmisión sostenida del parásito en países endémicos.

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Increased peripartum mortality associated with maternal subclinical malaria in Mozambique

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Abstract

Background *Plasmodium falciparum* infection in pregnant women in sub-Saharan Africa is often asymptomatic. As these forms of malaria are often submicroscopic and difficult to diagnose by conventional methods (microscopy and/or rapid diagnostic test), diagnosis requires the use of molecular techniques such as polymerase chain reaction (PCR). This study analyses the prevalence of subclinical malaria and its association with adverse maternal and neonatal outcomes, a topic that has been scarcely evaluated in the literature.

Methods A cross-sectional study was conducted using semi-nested multiplex PCR to assess the presence of *P. falciparum* in placental and peripheral blood of 232 parturient pregnant women at the Hospital Provincial de Tete, Mozambique between March 2017 and May 2019. Multivariate regressions were performed to assess the associations of maternal subclinical malaria with several maternal and neonatal outcomes after controlling for the presence of preeclampsia/eclampsia (PE/E) and HIV infection, as well as for other maternal and pregnancy characteristics.

Results In total, 17.2% (n = 40) of the women studied had positive PCR for *P. falciparum* (7 in placental blood only, 3 in peripheral blood only). We found a significant association between subclinical malaria and a higher peripartum mortality risk, which persisted after controlling for maternal comorbidity and maternal and pregnancy characteristics (adjusted odds ratio: 3.50 [1.11–10.97]). In addition, PE/E and HIV infections were also significantly associated with several adverse maternal and neonatal outcomes.

Conclusion This study demonstrated the association of subclinical malaria, as well as of PE/E and HIV, in pregnant women with adverse maternal and neonatal outcomes. Therefore, molecular methods may be sensitive tools to identify asymptomatic infections that can reduce the impact on peripartum mortality and their contribution to sustained transmission of the parasite in endemic countries.

Keywords Subclinical malaria, Pregnancy, Preeclampsia/eclampsia, HIV, Mozambique

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Background

According to the latest World Health Organization report on malaria [1], the incidence of malaria was estimated at 241 million cases worldwide in 2020, approximately 95% of which were in Africa. Indeed, six African countries accounted for 55% of all cases worldwide, with Mozambique ranked fourth after Nigeria, the Democratic Republic of Congo and Uganda.

Approximately 12 million pregnant women in 33 African countries have been exposed to *Plasmodium* spp. infection during pregnancy [1]. In this population, malaria has some special features. A significant percentage of pregnant women with malaria often remain asymptomatic and may act as reservoirs of *Plasmodium*, especially *Plasmodium falciparum*, favouring transmission to the rest of the population. At the same time, these infections are often submicroscopic and have low parasite loads, making them difficult to diagnose by conventional tests (microscopy and/or rapid diagnostic test). Hence, molecular diagnosis by polymerase chain reaction (PCR) is of particular importance for the diagnosis of subclinical infection [2–5].

In sub-Saharan Africa, the main causes of maternal and neonatal morbidity and mortality, are malaria, preeclampsia/eclampsia (PE/E) and HIV infection [6–8]. There are multiple interactions between these three diseases, well described by other authors [9, 10]. However, there is little information on the relationship between subclinical malaria in pregnant women [11–13]. In addition, the potential consequences of subclinical malaria on maternal and neonatal outcomes have not been extensively studied to date.

The two main objectives of this study therefore were to determine the prevalence of asymptomatic *P. falciparum* infection in pregnant women and the associations of asymptomatic *P. falciparum* with adverse maternal and neonatal outcomes. A secondary objective includes the assessment of the associations of PE/E and HIV infection with maternal and neonatal outcomes.

Methods

Study site

The study was conducted in the Maternity Services Unit of Tete Provincial Hospital (HPT). The province of Tete, with an area of 100,724 km^2, is located in central Mozambique and is bound by Zambia to the north and Zimbabwe to the west (Fig. 1). The average temperature ranges between 23.4° and 32.9°. It is the third most populated province in the country and has a population of 2,829,594 inhabitants, 1,442,880 (50,1%) of whom are women [14].

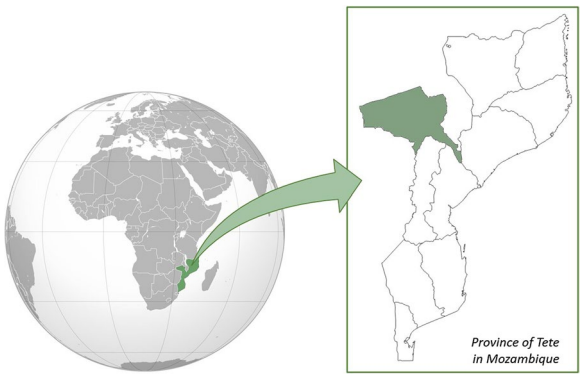

Fig. 1 Political map of Tete (Mozambique)

Study population and procedures

Between 1 March 2017 and 30 May 2019, 232 women were recruited during delivery. For the selection, the criterion was only to recruit women when the researchers were present at the delivery. Women who refused to participate in the study or when the data could not be completed in the questionnaire were excluded. A cross-sectional study was carried out involving completion of a structured questionnaire that included demographic data and information about the current pregnancy, delivery, and the newborn. Each interview lasted between 10 and 15 min. The data collection instruments were the pregnancy cards of the National Health Service of the Republic of Mozambique and the clinical delivery records.

The Sysmex® autoanalyzer and Cellpack® reagents were used to provide hemoglobin values. Due to the cost of the study, haematometry was only performed when indicated by the obstetrician. HIV serostatus was assessed using a rapid test (Determine, Abbot Laboratories, USA) and positive results were confirmed using the Uni-gold rapid test (TM HIV, Trinity Biotech, Ireland). The Multistix® 10 SG reagent strip was used to measure protein in urine.

In parallel to data collection, samples of peripheral blood and placenta were collected at delivery for the detection of *P. falciparum* by multiplex PCR. Within 30 min of delivery, attending staff collected placental blood via the incision method and prepared filter paper samples [15]. In brief, staff made a shallow incision into the maternal side of the placenta using sterile scissors and collected the accumulated blood in the intervillous space with the help of a syringe. Peripheral blood was also collected by venipuncture and stored on filter papers. Filter paper samples were collected on

FTA™ Classic Card (GE Healthcare UK Limited, UK) and stored in individual sterile plastic envelopes with desiccant.

DNA extraction and multiplex PCR development

Parasite DNA was isolated from the blood samples on filter paper with Chelex, as previously described [16], and samples were tested in duplicate by species-specific nested PCR for *P. falciparum* [17]. Amplifications were performed in 25 µl reactions containing 1 µl of template DNA, 0.4 µg of each primer, 2.5 U of Taq DNA polymerase (Promega, Madison, Wis.), and each deoxynucleotide triphosphate at a concentration of 0.2 mM. All amplifications were performed in a conventional thermocycler (Applied Biosystems™), the template DNA was denatured at 94 °C for 7 min, followed by 40 cycles of amplification (melt at 94°C for 20 s, anneal/extend at 62 °C for 20 s, and 72 °C for 30 s) and final extension at 72 °C for 10 min. For the second round of amplification, 1 µl of the PCR product from the initial amplification was used as the template in 25 µl final volume**.** Amplified DNA was run on 2.5% agarose gels containing ethidium bromide and analyzed under UV light. A positive PCR of placental blood was defined as the presence of a species-specific band of amplified DNA.

Definitions

Subclinical malaria: characterized by low levels of parasitemia and absence of symptoms. The adolescent population includes individuals in the 10–19 years group.

The following variables were analysed:

- Maternal and pregnancy characteristics: age (in years and = 1 if women were under 20-year-old), weight (in kilograms); pregnancy number (primigravida versus multigravida); pregnancy type (single versus multiple); malaria prophylactic treatment [defined as intermittent preventive treatment with sulfadoxine-pyrimethamine (IPTp)]; and pregnancy follow-up [assessed on the basis of completion of at least four or more antenatal care visits (ANC)].
- Maternal comorbidity: the presence of hypertensive disorders induced by pregnancy (preeclampsia and eclampsia) and HIV infection. For the diagnosis of preeclampsia, current criteria were used [18, 19], which included (a) the presence of arterial hypertension (systolic blood pressure (SBP) ≥ 140 mm Hg and/or diastolic blood pressure (DBP) ≥ 90 mm Hg, determined on two occasions at least 4 h apart; (b) onset after the 20th week of pregnancy and (c) associated with proteinuria > 300 mg/24 h and/or adverse conditions that increase the risk of severe complications and/or severe complications that warrant delivery. The diagnosis of eclampsia was made if seizures appeared in patients with preeclampsia criteria.

Maternal and neonatal outcomes (dependent variables in multivariate models): delivery type (vaginal versus caesarean); the haemoglobin level (g/dL); gestational age at delivery (defined as preterm when occurring before week 37), newborn weight (in kilograms) and as low birth weight (LBW) = 1 if weight was less than 2500 g at birth; Apgar score < 7 at 1 and 5 min after birth [17]; neonatal resuscitation (defined as cardiopulmonary resuscitation maneuvers); and stillbirth (defined as fetal death occurring after 28 complete weeks of gestation).

Statistical analysis

Categorical variables are summarized as absolute numbers and percentages, and continuous variables as means and 95% confidence intervals. In univariate analyses, categorical data were analysed for associations with subclinical *P. falciparum* infection using the Chi-square test, while means of continuous variables were compared using Student's t-tests. Multivariate analyses were performed to assess associations between subclinical *P. falciparum* infection and each maternal and neonatal outcome, after controlling for maternal comorbidity (presence of E, PE and HIV) and maternal and pregnancy characteristics available for most women (i.e., mother's age, pregnancy number and pregnancy type). Logistic regressions were performed for binary outcomes (i.e., cesarean delivery, pre-term birth, LBW, Apgar < 7 at 1 and 5 min, neonatal resuscitation, and still birth) and linear regressions for continuous outcomes (i.e., hemoglobin level and neonatal weight). For each model, odds ratios and 95% confidence intervals are presented. Statistical significance was set at p-value < 0.05. Data were analysed with Stata version 15 (StataCorp®).

Results

A total of 232 pregnant women between 14 and 43 years of age were evaluated, with a mean age of 23 years (interquartile range 18–28). Among them, 137 (59.3%) had attended at least 4 antenatal care visits.

Subclinical *P. falciparum* infection was detected in 40 women (17.2%) (7 exclusively in placental blood, 3 only in peripheral blood and 30 in both). Among the infected

Table 1 Distribution of maternal and pregnancy characteristics, maternal comorbidity and maternal and neonatal outcomes according to the presence of subclinical *P. falciparum* infection

	No Pf n = 192	**Yes Pf n = 40**	**Total 232**	**p-value**
Maternal and pregnancy characteristics				
Age (years) N = 231	23.6 [22.7–24.6]	21.8 [19.7–23.9]	23.31 [22.5–24.2]	0.109
Adolescent (< 20 year-old) N = 231	65/191 (34.03%)	21/40 (52.5%)	86/231 (37.23%)	0.028
Weight (Kg) N = 134	67.05 [64.7–69.4]	68.66 [58.3–79.0]	67.25 [64.9–69.6]	0.661
ANC ≥ 4 N = 231	116/191 (60.7%)	21/40 (52.5%)	137/231 (59.3%)	0.335
Number of pregnancies N = 232				0.087
Primigravida	82/192 (42.7%)	23/40 (57.5%)	105/232 (45.3%)	
Multigravida	110/192 (57.3%)	17/40 (42.5%)	127/232 (54.7%)	
Type of pregnancy N = 232				0.855
Single	181/192 (94.2%)	38/40 (95.0%)	219/232 (94.4%)	
Multiple	11/192 (5.7%)	2/40 (5.0%)	13/232 (5.6%)	
Profilaxis (IPTp) ≥ 3 N = 203	136/165 (82.4%)	30/38 (79.0%)	166/203 (81.8%)	0.617
Maternal comorbidity				
PE N = 232	84/192 (43.8%)	10/40 (25.0%)	94/232 (40.5%)	0.028
E N = 232	29/192 (15.1%)	7/40 (17.5%)	36/232 (15.5%)	0.703
PE/E N = 232	113/192 (58.9%)	17/40 (42.5%)	130/232 (56.0%)	0.058
HIV-positive N = 228	33/188 (17.5%)	3/40 (7.5%)	36/228 (15.5%)	0.113
Maternal and neonatal outcomes				
Cesarean-section N = 224	55/187 (29.4%)	13/37 (35.1%)	68/224 (30.4%)	0.489
Hemoglobin (g/dL) N = 167	10.9 [10.7–11.2]	11.4 [10.7–12.0]	11.0 [10.8–11.3]	0.229
Pre-term birth N = 228	24/188 (12.8%)	7/40 (17.5%)	31/228 (13.6%)	0.428
Neonatal weight, (g) N = 226	2800.5 [2710–2891]	2679.5 [2480–2879]	2779.6 [2698–2862]	0.272
LBW N = 226	44/187 (23.5%)	10/39 (25.6%)	54/226 (23.9%)	0.778
Apgar < 7 (1 m) N = 232	47/192 (24.5%)	10/40 (25.0%)	57/232 (24.6%)	0.945
Apgar < 7 (5 m) N = 232	25/192 (13.5%)	6/40 (15.0%)	31/232 (13.4%)	0.738
Neonatal resuscitation N = 223	34/185 (18.4%)	8/38 (21.1%)	42/223 (18.8%)	0.701
Stillbirth N = 227	14/187 (7.5%)	7/40 (17.5%)	21/227 (9.3%)	0.047

The data have been expressed as means [95% CI] for continuous data and absolute numbers (%) for categorical data

Pf: *Plasmodium falciparum*; Kg: kilograms, ANC: antenatal care visits, IPTp: Intermitent Preventive Treatment of malaria for pregnant women, mmHg: milimetres of mercury, PE: preeclampsia, E: eclampsia, PE/E: preeclampsia/eclampsia, HIV: Human Immunodeficiency Virus, Pre-term birth: pre-term delivery (< 37 weeks), LBW: low birth weight, g: gram. dl: decilitre, m: minute

cases, 30 (79%) stated that they received IPTp at least 3 doses against *Plasmodium* sp. (Table 1).

Of the total number of pregnant women, 94 (40.5%) had preeclampsia and 36 (15.5%) had eclampsia. 36 (15.5%) of the pregnant women were infected with HIV. Univariate analyses show a negative and significant association of subclinical *P. falciparum* infection and being under 20-year-old and with the presence of eclampsia, and a positive and significant association of subclinical *P. falciparum* infection with peripartum neonatal death.

Table 2 shows the results of the multivariate analyses of each maternal and neonatal outcome. Each of these models include as covariates: the presence of subclinical *P. falciparum* infection, the presence of PE, E and HIV infection, and maternal and pregnancy characteristics (i.e., mother's age, pregnancy type and pregnancy number). Odd ratios/coefficients of subclinical *P. falciparum* infection, PE, E and HIV infection are reported in Table 2. Subclinical *P. falciparum* infection was significantly associated with peripartum neonatal mortality, even after controlling for maternal comorbidity and maternal and pregnancy characteristics. In addition, eclampsia was significantly associated with all adverse maternal and neonatal outcomes analysed in this study (with the only exception of haemoglobin level), while preeclampsia was significantly associated with having a cesarean delivery and requiring neonatal resuscitation. HIV infection was significantly associated with low neonatal weight, having Apgar < 7 at 5 min and with peripartum neonatal mortality.

Table 2 Multivariate models of maternal and neonatal outcomes on the presence of subclinical *P. falciparum* infection, PE,E and HIV infections

	Logistic models *	
	Odd Ratio	**95% CI**
Cesarean delivery (N = 219)		
Subclinical Malaria	1.69	[0.71; 4.01]
PE	3.69	[1.69; 8.03]
E	15.38	[5.66; 41.83]
HIV	1.63	[0.63; 4.21]
Pre-term birth (N = 223)		
Subclinical Malaria	1.38	[0.50; 3.80]
PE	2.17	[0.78; 5.97]
E	5.64	[1.87; 17.01]
HIV	1.25	[0.36; 4.26]
Low birth weight (N = 221)		
Subclinical Malaria	1.41	[0.56; 3.59]
PE	2.08	[0.91; 4.74]
E	3.13	[1.16; 8.46]
HIV	3.14	[1.19; 8.29]
Apgar < 7 1 m (N = 227)		
Subclinical Malaria	1.26	[0.53; 3.00]
PE	2.01	[0.95; 4.24]
E	4.59	[1.79; 11.79]
HIV	1.68	[0.69; 4.06]
Apgar < 7 5 m (N = 227)		
Subclinical Malaria	1.53	[0.51; 4.59]
PE	2.08	[0.74; 5.85]
E	4.96	[1.55; 15.85]
HIV	4.36	[1.51; 12.57]
Neonatal resuscitation (N = 218) N = 223		
Subclinical Malaria	1.51	[0.60; 3.79]
PE	3.04	[2.19; 7.16]
E	4.68	[1.64; 13.4]
HIV	1.31	[0.48; 3.58]
Stillbirth (N = 222)		
Subclinical Malaria	3.50	[1.11; 10.97]
PE	1.59	[0.46; 5.56]
E	4.80	[1.30; 17.69]
HIV	3.82	[1.05; 13.88]
	OLS models*	
	Coefficient	95% CI
Haemoglobin (N = 167)		
Subclinical Malaria	0.40	[− 0.38; 1.17]
PE	0.13	[− 0.52; 0.77]
E	0.87	[− 0.002; 1.74]
HIV	− 0.13	[− 0.95; 0.68]
Neonatal weight (N = 221)		
Subclinical Malaria	− 147.70	[− 343.46; 48.06]

Discussion

Pregnant women in sub-Saharan Africa suffer subclinical *P. falciparum* infections more frequently than symptomatic infections [4]. These infections can cause placental infection [2, 21] and adverse health effects in mothers and newborns [3, 4].

Conventional diagnostic methods [light microscopy and rapid diagnostic test (RDT)] have limited sensitivity for the diagnosis of subclinical infections. Low-density infections are more likely to be missed [22]. In the last decade, the use of PCR-based molecular methods for the diagnosis of these infections has emerged, especially in pregnant women [3, 4]. After performing semi-nested PCR, the prevalence of subclinical *P. falciparum* infection in this study was 17.2%. These figures are similar to those of other studies conducted in Africa (Benin: 20.5%, Ethiopia 18.1% and the Democratic Republic of Congo 19%) [2, 4, 23].

Table 2 (continued)

	Logistic models *	
	Odd Ratio	**95% CI**
PE	− 141.26	[− 305.31; 22.80]
E	− 354.94	[− 581.43; − 128.44]
HIV	− 255.94	[− 465.18; − 46.69]

* Each model includes additional covariates for adolescence, primigravity and multiple pregnancy

PE: preeclampsia, E: eclampsia, HIV: Human Immunodeficiency Virus, OLS: Ordinary Least Squared

A high incidence of subclinical malaria was observed despite the fact that 79% of women with malaria reported taking preventive treatment of malaria for pregnant women (IPTp). There could be several reasons for this. First, since IPTp with sulfadoxine-pyrimethamine is contraindicated in the first trimester due to its possible teratogenic effects, the pregnant women in this study may not have been protected during this period [5]. Second, a high prevalence of *P. falciparum* resistance to sulfadoxine-pyrimethamine has been reported in most malaria-endemic areas [24, 25]. Finally, it is likely that women with HIV infection took less IPTp because they were on prophylactic treatment with trimethoprim-sulfamethoxazole against *Pneumocystis jirovecii* and IPTp is contraindicated because of the potential additional risk of adverse effects associated with taking two antifolate drugs simultaneously [26, 27].

In general, most studies suggest that, in malaria-endemic regions, women exposed to placental parasites may be at higher risk of preeclampsia compared to those in malaria-free regions [9, 28–31]. In this study, however a negative association was observed. This could be explained by the inclusion of women with subclinical infections and low parasite loads at the end of their pregnancies (end of the 3rd trimester), as it is the first and second trimester that is associated with increased risk of placental malaria and maternal morbidity [4, 21].

A significant and positive association between peripartum newborn mortality was observed in mothers with subclinical malarial infection. This finding persisted even after controlling for maternal comorbidity and other maternal and pregnancy characteristics. This association is novel and has a high impact, highlighting the importance of diagnosing subclinical *P. falciparum* infection in antenatal care. In a study in Ghana, they detected a great number of anaemia-associated malaria infections were observed under microscope to have less than 1000 parasite count per microlitre of blood [32]. Therefore, asymptomatic malaria could be detected with a malaria and anemia screening intervention during early antenatal care visits [33], improving the chances of missing asymptomatic malaria at antenatal care visits as a possibility in cases where molecular methods cannot be used.

In addition, eclampsia was significantly associated with most adverse maternal and neonatal outcomes analysed in this study. Preeclampsia was significantly associated with having a cesarean delivery and requiring neonatal resuscitation, while HIV infection was significantly associated with low neonatal weight, having Apgar < 7 at 5 min and peripartum neonatal mortality. The effects of these diseases in the newborn have been widely described by other authors [34–37].

Among the limitations of the study, the pregnant women were evaluated only at the time of delivery, with no opportunity to assess the impact of subclinical parasitemia during the first and second trimesters, nor to follow up on both maternal and neonatal complications in the post-partum period. In addition, the multivariate models used were conducted to assess the relationship between subclinical *P. falciparum* infection with maternal and neonatal outcomes after controlling for maternal comorbidities and characteristics. However, given the nature and the size of the sample used, it is difficult to establish causal relationships and assess potential interactions between comorbidities. Further research should focus on studying pregnant women from the first trimester and performing postpartum follow-up and continue with future studies to demonstrate the effect of subclinical parasitemia on maternal and neonatal outcomes.

Conclusion

In conclusion, this study demonstrated the significant association between subclinical malaria in pregnant women and peripartum neonatal mortality. In order to reduce the impact on newborn mortality and its role in maintaining parasite transmission in endemic area countries, it could be necessary to apply molecular methods able to detect extremely low parasite densities.

Abbreviations

PCR	Polymerase chain reaction
PE/E	Preeclampsia/eclampsia
HIV	Human Immunodeficiency Virus
HPT	Provincial Hospital of Tete
DNA	Deoxyribonucleic acid
UV	Ultraviolet
SFH	Symphysis fundal height
ANC	Antenatal care visits
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
LBW	Low birth weight
SD	Standard deviation
RDT	Rapid diagnostic test

IPTp	Intermittent preventive treatment of malaria for pregnant women
WHO	World Health Organization
CUCID	Centro Universitario de Cooperación Internacional al Desarrollo
ULPGC	Universidad de Las Palmas de Gran Canaria

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Author contributions
NJS, GGA, LVT, CCR, PGS, JLPA: conceptualization, methodology, software; NJS, GGA, LVT, NM, CCR: data curation, writing—original draft preparation; NJS, GGA, CCR, JLPA: visualization, investigation; GGA, CCR, JLPA: supervision. NJS, CCR, LVT: software, validation; NJS, GGA, CCR, JLPA: writing—reviewing and editing. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Study protocols and informed consent forms for trials were reviewed and approved by the National Ethics Review Committee in Mozambique 432/CNBS/16 and the number of the CEIm of the CHUIMI (Spain) is CEIm-CHUIMI-2016/848. The study was conducted in accordance with the provisions of the Declaration of Helsinki and the Good Clinical Practice guidelines established by the WHO and the International Conference on Harmonization. Participation in the study was completely voluntary. All study participants were informed of the purpose of the study and written informed consent was obtained from each study participant. The consent form was signed by the parent/guardian if the participant was under 18 years of age. Illiterate women had the consent form and patient information sheet read and explained to them, and those who verbally agreed to participate in the study signed the consent form with their finger.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Publisher's Note

4.4. Indicios de calidad y relevancia de las aportaciones

4.4.1. Aportación 1

Jaén-Sánchez, N., González-Azpeitia, G., Santana, P. S., Saavedra-Sanjuán, E., Manguiza, A., Manwere, N., Carranza-Rodríguez, C., Pérez-Arellano, J. L., & Serra-Majem, L. (2020). Adolescent motherhood in Mozambique. Consequences for pregnant women and newborns. PLOS ONE, 15(6), e0233985. https://doi.org/10.1371/journal.pone.0233985

Indicios de calidad

Plos One [ISSN: 1932-6203] es una revista mensual, de acceso abierto y revisión por pares, cuyo primer número apareció en 2006. De publicación exclusivamente online, este formato le permite alcanzar más de dos millones de visitantes a su portal web cada mes y más de un millón de citas durante los últimos cinco años, asegurando un fuerte impacto en las más de 200 materias de investigación a la que se dedica, desde la medicina, las ingenierías, las ciencias sociales o las humanidades, aplicando la licencia Creative Commons (CC BY 4.0) a los trabajos que publican.

Actualmente Plos One está indexada en Crossref, Google Scholar, Scopus, Web of Science, PubMed, DOAJ o MEdline y está editada por Public Libray of Science (Plos), organización sin ánimo de lucro.

El artículo ha sido citado 4 veces en la colección principal de la Web of Science (dos en la discusión). Según esta base de datos, recibió su primera cita en 2022 y las tres últimas en 2023.En Scopus ha recibido 5 citas. Según esta base de datos, recibió su primera cita en 2022 y las cuatro últimas en 2023.Según Dimensions, el artículo ha recibido 6 citas, siendo su Field Citation Ratio 2.84 y Relative Citation Ratio 0.41. En Google Académico ha sido citado 10 veces.

La revista está incluida en el Science Citation Index Expanded (SCIE), y, por tanto, en los Journal Citation Reports de Web of Science. En 2020 obtuvo un factor de impacto de 3.240, lo que la sitúa en el segundo cuartil (**Q2**) de la categoría MULTIDISCIPLINARY SCIENCES ocupando el puesto 26 de 72 revistas, con un percentil de 64.58. La revista, también se encuentra indexada en la base de datos internacional Scopus donde alcanza un indicador CiteScore de 5.3 en 2020, dentro del primer cuartil (**Q1**), ocupando el puesto 9 de 110 revistas en la categoría MULTIDISCIPLINARY, con un percentil 92. Además, de acuerdo con el indicador de impacto SJR (0.990), en 2020 ocupa el primer cuartil (**Q1**) de la categoría MULTIDISCIPLINARY.

Desde el 16 de julio de 2020, el artículo se encuentra en Acceso Abierto en el repositorio institucional de la ULPGC, accedaCRIS, (http://hdl.handle.net/ 10553/ 73303). A través del repositorio, este artículo ha tenido 105 visitas, destacando 31 desde América del Norte y 46 desde Europa.

Según la base de datos Web of Science, este artículo ha sido usado 7 veces desde su publicación (2 en los últimos 6 meses). Por otra parte, en Scopus ha sido visualizado 35 veces desde su publicación.

En cuanto a otras almétricas, ha conseguido un Attention Score de 1 en Almetric, destacando los 132 lectores de Mendeley y 1 mención en X.

La plataforma PlumX Metrics recoge que el artículo ha sido citado 7 veces y almacenado por 125 perfiles en Mendeley. Estas almétricas colocan al artículo en un percentil 94 en cuanto a los artículos más leídos en Mendeley. También ha sido mencionado en dos informes del Banco Mundial: Mozambique Gender Assessment: Leveraging Women and Girls' Potential (septiembre 2023) y Mozambique Gender Assessment: Leveraging Women and Girls' Potential (junio de 2023).

4.4.2 Aportación 2

Jaén-Sánchez, N., González-Azpeitia, G., Carranza-Rodríguez, C., Muianganisso, A. J., Torres, L. V., & Pérez-Arellano, J. L. (2023). Effects of HIV infection and/or malaria on maternal and neonatal health in a high-prevalence setting. Tropical Medicine & International Health, 28(2), 98-106. https://doi.org/10.1111/tmi.13848

Indicios de calidad

Tropical Medicine & International Health, tanto en su versión en papel [ISSN: 1360-2276], como online [eISSN: 1365-3156], está sujeta a revisión por pares y acceso abierto a partir de los 12 meses de publicación, excepto las Editoriales y Revisiones, que están disponibles de forma inmediata.

Con su primer número en 1996 y periodicidad mensual, esta revista es publicada por Wiley en nombre de varias de las más prestigiosas instituciones dedicadas a esta temática, como la Foundation Tropical Medicine and International Health Amsterdam, el Swiss Tropical and Public Health Institute, la London School of Hygiene & Tropical Medicine. Asimismo, es la revista oficial de la Federation of European Societies for Tropical Medicine and International Health (FESTMIH).

Está indexada en SAGE, EBSCO, CABI, ProQuest, Biosis, Embase, Medline o Science Citation Index, entre otras bases de datos.

La revista está incluida en el Science Citation Index Expanded (SCIE), y, por tanto, en los Journal Citation Reports de Web of Science. En 2022 obtuvo un factor de impacto de 3.3, lo que la sitúa en el primer cuartil (**Q1**) de la categoría TROPICAL MEDICINE ocupando el puesto 4 de 24 revistas, con un percentil de 85.4. La revista, también se encuentra indexada en la base de datos internacional Scopus donde alcanza un indicador CiteScore de 4.2 en 2022, dentro del segundo cuartil (**Q2**), ocupando el puesto 193 de 577 revistas en la categoría PUBLIC

HEALTH, ENVIRONMENTAL AND OCCUPATIONAL HEALTH, con un percentil 66. Además, de acuerdo con el indicador de impacto SJR (0.793), en 2022 ocupa el segundo cuartil (**Q2**) de la categoría PUBLIC HEALTH, ENVIRONMENTAL AND OCCUPATIONAL HEALTH.

Desde el 24 de enero de 2023, el artículo se encuentra en Acceso Abierto en el repositorio institucional de la ULPGC, accedaCRIS, (*http://hdl.handle.net/10553/120254*). A través del repositorio, este artículo ha tenido 49 visitas, destacando 13 desde América del Norte y 15 desde Europa.

Según la base de datos Web of Science, este artículo ha sido usado 3 veces desde su publicación.

En cuanto a otras almétricas, ha conseguido un Attention Score de 1 en Almetric, destacando los 12 lectores de Mendeley y 2 menciones en X.

Según la plataforma PlumX Metrics, el artículo ha sido almacenado por 11 perfiles de Mendeley, lo que lo sitúa en un percentil 78 en cuanto a los artículos más leídos en Mendeley.

4.4.3. Aportación 3

Jaén-Sánchez, N., González-Azpeitia, G., Carranza-Rodríguez, C., Manwere, N., Garay-Sánchez, P., Vallejo-Torres, L., & Pérez-Arellano, J. (2023). Increased peripartum mortality associated with maternal subclinical malaria in Mozambique. Malaria Journal, 22(1). https://doi.org/10.1186/s12936-023-04613-3

Indicios de calidad

De formato online, acceso abierto y revisión por pares, Malaria Journal [ISSN: 1475-2875] es la única revista que publica trabajos que versan exclusivamente sobre la malaria.

Malaria Journal está incluida en Embase, DOAJ, Global health, Medline, PubMed, Science Citation Index, Scimago, Scopus o Citebase, alcanzado en 2022 un CItation Impact de 3.0 en el factor de impacto a 2 años y 3.2 en el factor de impacto a 5 años. E, igualmente, 1.148 y 1.237 en SNIP y SCJR, respectivamente.

Está editada por BioMed Central (BMC), editorial británica centrada en las principales áreas temáticas de la biología y la medicina y forma parte del grupo Springer Nature.

La revista está incluida en el Science Citation Index Expanded (SCIE), y, por tanto, en los Journal Citation Reports de Web of Science. En 2022 obtuvo un factor de impacto de 3.0, lo que la sitúa en el segundo cuartil (**Q2**) de la categoría PARASITOLOGY ocupando el puesto 11 de 37 revistas, con un percentil de 71.6. La revista, también se encuentra indexada en la base de datos internacional Scopus donde alcanza un indicador CiteScore de 5.0 en 2023, dentro del primer cuartil (**Q1**), ocupando el puesto 17 de 66 revistas en la categoría PARASITOLOGY, con un percentil 75. Además, de acuerdo con el indicador de impacto SJR (1.237), en 2022 ocupa el primer cuartil (**Q1**) de la categoría PARASITOLOGY.

Desde el 19 de junio de 2023, el artículo se encuentra depositado en acceso abierto en accedaCRIS, repositorio institucional de la ULPGC (http://hdl.handle.net/10553/123596).

Según la base de datos Web of Science, este artículo ha sido usado 1 vez desde su publicación y fue en los últimos 6 meses.

En cuanto a otras almétricas, ha conseguido un Attention Score de 1 en Almetric, destacando los 10 lectores de Mendeley y 3 menciones en X, entre ellas la propia página en X de Malaria Journal.

La plataforma PlumX Metrics recoge que el artículo ha sido almacenado por 9 perfiles en Mendeley.

5. Conclusiones

Conclusiones

Primera. En la población de estudio, aproximadamente un tercio de los embarazos tenían lugar en adolescentes. Este hecho se asoció a un mayor número de episiotomías, un mayor número de abortos así como un menor peso, un puntaje de Apgar más bajo y una mayor frecuencia de distrés respiratorio en neonatos. Entre los factores implicados se han identificado índices de masa corporal mas bajos, un control prenatal inadecuado.

Segunda. Aproximadamente dos tercios de las infecciones por VIH fueron diagnosticadas en las visitas del control gestacional o en el momento del parto. Sin embargo, las mujeres infectadas por el VIH tienen mejor control del embarazo, y menos frecuencia de cesárea.

Tercera. La infección por VIH en el embarazo se asoció a un aumento de infecciones urinarias periparto, la malaria clínica en el embarazo a bajo peso al nacer y a fiebre maternal intraparto y la coinfección por ambos microorganismos a muerte neonatal.

Cuarta. La incidencia de preeclampsia/eclampsia es superior a la descrita previamente en Mozambique en los dos periodos de tiempo del estudio. Los datos obtenidos en este estudio no permiten concluir que la malaria y/o la infección por VIH se asocien a preeclampsia/eclampsia.

Quinta. Existe una alta incidencia de paludismo subclínico en el embarazo, detectada mediante PCR, que se asoció a una mayor mortalidad neonatal periparto.

6. Anexo metodológico

6.1. Área de Estudio

El estudio se llevó a cabo en la Unidad de Maternidad del Hospital Provincial de Tete (HPT) en la provincia de Tete, ubicada en la región central de Mozambique. La provincia limita con Zambia al norte y Zimbabue al este (**Figura 2**). Con una superficie de 100.724 km^2, la provincia experimenta temperaturas medias que oscilan entre 23,4ºC y 32,9ºC. Tete es la tercera provincia más poblada del país, con una población de 2.829.594 habitantes, de los cuales 1.442.880 son mujeres [**59**]. La tasa de fecundidad media es de 4,7 nacimientos por mujer [**60**]. Sin embargo, el sistema de salud en esta provincia es limitado y sufre de escasez de personal de salud capacitado, especialmente en las áreas rurales. La relación médico-población es de 0,1 médicos por cada 1000 habitantes [**60**].

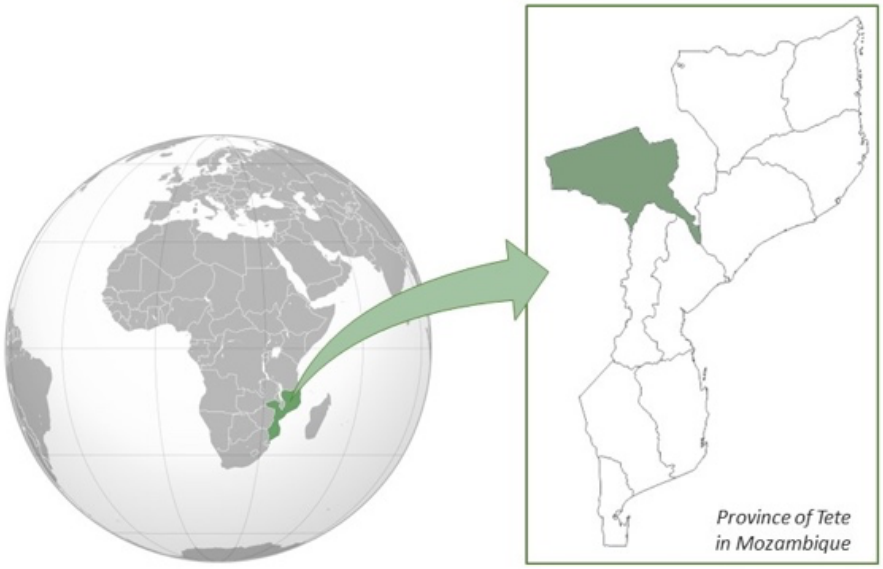

Figura 2: Ubicación de la provincia de Tete, Mozambique

6.2. Población de estudio

La población de estudio consistió en mujeres reclutadas durante el trabajo de parto y/o el período posparto inmediato, en dos periodos diferenciados:

- Entre el 1 de marzo y el 31 de octubre de 2016, se incluyeron un total de 819 pacientes
- Entre el 1 de marzo de 2017 y el 30 de mayo de 2019, se reclutaron 232 mujeres.

Para la selección de participantes, se estableció como criterio que los investigadores estuvieran presentes durante el parto. Aquellas mujeres que se negaron a participar en el estudio fueron excluidas, al igual que aquellas a las que no se pudieron completar los datos en el cuestionario.

6.3. Diseño del estudio

Se realizó un estudio transversal en el que se completó un **cuestionario estructurado** que recopilaba datos demográficos y de información relacionada con el embarazo actual, el parto y el recién nacido, en todas las mujeres incluidas en el estudio.

Las entrevistas fueron realizadas por los investigadores, con la ayuda de estudiantes de medicina de la Universidad de Zambeze, quienes actuaron como traductores en los Servicios de Maternidad. Cada entrevista tuvo una duración aproximada de 10 a 15 min. Para completar los datos del cuestionario, se utilizaron los registros del embarazo del Servicio Nacional de Salud de la República de Mozambique y los registros clínicos de parto. En los siguientes apartados se resumen las variables clínicas y exámenes complementarios:

6.4. Variables

Se analizaron las siguientes variables:

- **Características maternas y del embarazo**: edad, peso, número de embarazo , el tipo embarazo, el tratamiento profiláctico frente a malaria y seguimiento del embarazo.
- **Comorbilidad materna:** la presencia de preeclampsia y eclampsia y la infección por VIH. Los criterios para el diagnóstico de preeclampsia fueron: la aparición posterior a la semana 20 de embarazo de hipertensión arterial (presión arterial sistólica (PAS) igual o superior a 140 mm Hg y/o presión arterial diastólica (PAD) igual o mayor a 90 mm Hg, determinadas en dos ocasiones separadas por un mínimo de 4 horas) asociada a proteinuria > 30 mg en una muestra de orina aislada. Para el diagnóstico de eclampsia se requirió la presencia de convulsiones en pacientes con criterios de preeclampsia.
- **Resultados maternos y neonatales** (variables dependientes en modelos multivariados): tipo de parto, el nivel de hemoglobina, la edad gestacional en el momento del parto, peso del recién nacido, reanimación neonatal y muerte fetal.

6.5. Exámenes complementarios

Para los **datos analíticos**, se utilizó el autoanalizador Sysmex® y los reactivos Cellpack® para proporcionar valores de hemoglobina. Debido a las limitaciones económicas del estudio, se realizó la hematometría únicamente cuando fue indicada por el obstetra. Se utilizó la tira reactiva Multistix® 10 SG para medir la presencia de proteína en la orina.

El **estado serológico del VIH** se evaluó mediante una prueba rápida (Determine, Abbot Laboratories, EE. UU.) y los resultados positivos fueron confirmados mediante la prueba rápida Uni-gold (TM HIV, Trinity Biotech, Irlanda).

Simultáneamente a la recopilación de datos, se obtuvieron **muestras de sangre periférica y de placenta** de las 232 pacientes incluidas en el segundo periodo, en el momento del parto, para la detección de *Plasmodium falciparum* mediante **PCR multiplex**. Dentro de los 30 minutos posteriores al parto, el personal a cargo recogió sangre de la placenta través del método de incisión y fueron preservadas en papel de filtro [61]. En resumen, el personal hizo una incisión poco profunda en el lado materno de la placenta utilizando tijeras estériles, recogiendo la sangre acumulada en el espacio intervelloso con la ayuda de una jeringa. También se extrajo sangre periférica mediante venopunción y se almacenó en papeles de filtro.

Las **muestras en papel de filtro** se recolectaron en tarjeta FTA™ Classic (GE Healthcare UK Limited, Reino Unido) y se almacenaron en sobres de plástico estériles individuales con desecante para la extracción de ADN y desarrollo de la PCR multiplex. El ADN del parásito se aisló de las muestras de sangre en papel de filtro utilizando Chelex, siguiendo el procedimiento descrito anteriormente [62]. Las muestras fueron analizadas por duplicado mediante PCR anidada especie específicas para *Plasmodium* spp [63].

Las **amplificaciones** se llevaron a cabo en reacciones de 25 µl que contenían 1 µl de plantilla de ADN, 0,4 µg de cada cebador, 2,5 U de Taq ADN polimerasa (Promega, Madison, Wis.) y cada desoxinucleótido trifosfato a una concentración de 0,2 mM. Todas las amplificaciones se realizaron en un termociclador convencional (Applied Biosystems™). El ADN molde se desnaturalizó a 94ºC durante 7 minutos, seguido de 40 ciclos de amplificación (desnaturalización a 94ºC por 20 segundos, hibridación a 62ºC durante 20 segundos, y extensión a 72ºC durante 30 segundos), con una extensión final a 72ºC durante 10 minutos. Para la segunda amplificación, se utilizó 1 µl del producto de PCR de la amplificación inicial como plantilla en un volumen final de 25 µl. El ADN amplificado se separó mediante electroforesis en geles de agarosa al 2,5% que contenían bromuro de etidio, y se analizó bajo luz ultravioleta. Se definió como

una PCR positiva de sangre placentaria y periférica que mostrara la presencia de una banda específica de ADN amplificado de la especie.

6.6. Análisis estadístico

Las variables categóricas se expresaron como números absolutos y tantos por ciento, mientras que las variables continuas se presentaron como medias e intervalos de confianza al 95%. En el análisis univariado, se utilizaron pruebas de χ^2-cuadrado para analizar las asociaciones entre los datos categóricos y la infección subclínica por *P. falciparum,* y prueba t de Student para comparar las medias de las variables continuas.

Se realizaron análisis multivariados para evaluar las asociaciones entre la infección subclínica por *P. falciparum* y los resultados neonatales, teniendo en cuenta la presencia de comorbilidades (como preeclampsia, eclampsia e infección por VIH) y las características disponibles para la mayoría de las mujeres (como la edad de la madre, el número de embarazos y el tipo de embarazo). Se llevó a cabo regresiones logísticas para los resultados binarios (como parto por cesárea, parto prematuro, BPN, Apgar < 7 a 1 y 5 min, reanimación neonatal, y mortinatos) y regresiones lineales para los resultados continuos (como nivel de hemoglobina y peso neonatal). Para cada modelo, se presentaron las razones de probabilidad y los intervalos de confianza del 95%. Se consideró significativo un valor de $p < 0,05$. Los datos fueron analizados con Stata versión 15 (StataCorp®).

6.7. Principios éticos

Los protocolos de estudio y los formularios de consentimiento informado fueron revisados y aprobados por el Comité de Revisión de Ética del Consejo Nacional en Mozambique (Número de aprobación: 432/CNBS/16). El estudio se llevó a cabo siguiendo los principios establecidos en la Declaración de Helsinki y de acuerdo con las guías de Buenas Prácticas Clínicas establecidas de la OMS y la Conferencia Internacional de Armonización.

La participación en el estudio fue completamente voluntaria. Todos los participantes del estudio fueron plenamente informados sobre el propósito del estudio. Se obtuvo el consentimiento informado por escrito de cada participante. En el caso de participantes menores de 18 años, el consentimiento fue firmado por el padre o tutor legal.

Para las mujeres analfabetas, se les leyó y explicó el contenido del consentimiento y la información contenida en el formulario para el paciente. Aquellas que accedieron verbalmente a participar en el estudio firmaron el formulario de consentimiento con su huella dactilar.

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