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Maternal, Fetal, and Neonatal Outcomes Associated With Measles During Pregnancy: Namibia, 2009–2010

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Abstract

Background.—Previous studies of maternal, fetal, and neonatal complications of measles during pregnancy suggest the possibility of increased risk for morbidity and mortality. In 2009–2011, a nationwide laboratory-confirmed measles outbreak occurred in Namibia, with 38% of reported cases among adults. This outbreak provided an opportunity to describe clinical features of measles in pregnant women and assess the relative risk for adverse maternal, fetal, and neonatal outcomes.

Methods.—A cohort of pregnant women with clinical measles was identified retrospectively from 6 district hospitals and clinics over a 12-month period. Each pregnant woman with measles was matched with 3 pregnant women without measles, randomly selected from antenatal clinic registers at the same hospital during the same time interval. We reviewed hospital and clinic records and conducted in-person interviews to collect demographic and clinical information on the pregnant women and their infants.

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Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official positions of WHO or the CDC. The authors assume full responsibility for the study design, data collection, data analysis, data interpretation, content of the report, and the decision to submit for publication. Six of the authors were employees of one of the study sponsors but were not involved in the decision to fund the study.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Results.—Of 55 pregnant women with measles, 53 (96%) were hospitalized; measles-related complications included diarrhea (60%), pneumonia (40%), and encephalitis (5%). Among pregnant women with known human immunodeficiency virus (HIV) status, 15% of those without measles and 19% of those with measles were HIV positive. Of 42 measles-related pregnancies with known outcomes, 25 (60%) had ≥1 adverse maternal, fetal, or neonatal outcome and 5 women (12%) died. Compared with 172 pregnancies without measles, after adjusting for age, pregnancies with measles carried significantly increased risks for neonatal low birth weight (adjusted relative risk [aRR] = 3.5; 95% confidence interval [CI], 1.5–8.2), spontaneous abortion (aRR = 5.9; 95% CI, 1.8–19.7), intrauterine fetal death (aRR = 9.0; 95% CI, 1.2–65.5), and maternal death (aRR = 9.6; 95% CI, 1.3–70.0).

Conclusions.—Our findings suggest that measles virus infection during pregnancy confers a high risk of adverse maternal, fetal, and neonatal outcomes, including maternal death. Maximizing measles immunity among women of childbearing age would decrease the incidence of gestational measles and the attendant maternal, fetal, and neonatal morbidity and mortality.

Keywords

measles; pregnancy; maternal morbidity; neonatal outcome; fetal outcome

In the prevaccine era, nearly all children were infected with measles virus by age 10 years and measles during pregnancy was unusual, estimated to occur in 4–6 per 100 000 pregnancies [1–3]. Following the widespread use of a safe, effective, and inexpensive measles vaccine available since 1963, reported measles incidence and deaths have declined globally [4]. However, in settings with persistent suboptimal measles vaccination coverage, measles virus infection has shifted to older ages and measles outbreaks are increasingly affecting adults, including women of childbearing age [5]. In the World Health Organization (WHO) African Region during 2002–2009, approximately one-third of measles cases occurred among adults [6, 7]. One particularly large outbreak occurred in Namibia during 2 August 2009–2 February 2011, in which 4605 measles cases were reported, including 3256 (71%) cases confirmed by either laboratory testing or an epidemiological link to a confirmed case. A high proportion of cases (38%) in this outbreak occurred among adults, [8] which provided an opportunity to describe the potential complications of measles during pregnancy in a resource-limited setting.

Physiological adaptations in the immune system during pregnancy can increase a woman's susceptibility to infections or adversely alter the clinical course of infection [9]. Previous studies have provided evidence that measles during pregnancy can lead to poor clinical outcomes, including fetal loss and preterm delivery [2, 3, 10–18]. However, these studies were primarily descriptive analyses in developed countries, with relatively small numbers of cases, and only 3 studies included a comparison group [2, 10, 17, 18]. To provide a better understanding of the complications associated with measles during pregnancy, we conducted a retrospective cohort study in the aftermath of the large laboratory-confirmed measles outbreak in Namibia. Our study compared maternal, fetal, and neonatal outcomes among women with measles during pregnancy to those outcomes among women without measles during pregnancy.

METHODS

Laboratory-confirmed measles cases were defined as patients having a measles-specific immunoglobulin M (IgM) antibody–positive test result and not receiving a measles vaccination during the 30 days prior to rash onset. Testing for measles-specific IgM antibody was performed at the Namibia National Institute of Pathology using a standard enzyme-linked immunosorbent assay (Enzygnost for IgM, Dade Behring, Marburg, Germany).

Study Sites and Data Collection

The Namibian districts of Windhoek, Swakopmund/Walvis Bay, Engela, Opuwo, Outapi, and Rundu were selected for the study. The rationales for selecting these districts were to include both rural and urban settings and to reflect the high number of confirmed measles cases in each of these districts. Trained study teams of healthcare workers reviewed district hospital outpatient and inpatient registers to identify women with a chief complaint of measles or rash/fever illness during 1 September 2009–31 August 2010. For each pregnant woman identified, available inpatient and outpatient medical charts were reviewed by the study teams to determine if the illness met the WHO measles case definition of fever and maculopapular rash, and cough, coryza, or conjunctivitis [19]. Pregnancy was confirmed by documentation of laboratory testing results for the detection of human chorionic gonadotropin in a urine or blood specimen, abdominal ultrasound scan, or clinical assessment of gravidity based on physical examination and date of last menstrual period. During the measles outbreak, the Namibia Ministry of Health and Social Services (MOHSS) established a standard protocol to hospitalize all pregnant women with measles irrespective of illness severity.

At the antenatal clinic of the same health facility where each pregnant woman with measles was identified, 4 pregnant women without measles were systematically randomly selected from the register of all pregnant women seen during the study period. The identified pregnant women with and without measles were traced by the study teams to complete an in-person interview until 3 pregnant women without measles were interviewed for each pregnant woman with measles. If the study participant was deceased or unavailable after 3 visits to the household, her closest relative was interviewed as a proxy.

Medical records reviewed for pregnant women with and without measles and their infants included all available outpatient clinic and hospital inpatient charts, antenatal clinic records, the woman’s health passport, and the infant’s health passport and well-baby clinic card. In Namibia, health passports are the personal health information records under the custody of each individual patient, and contain physician and health worker records of illnesses and treatments during all clinic visits. Data collected from available medical records included sociodemographic information; date of clinic visit or hospital admission; human immunodeficiency virus (HIV) infection status; gestational age at study pregnancy termination; maternal, fetal, and neonatal outcomes; and presence of congenital anomalies. For pregnant women with measles, additional data were collected on the history of the measles illness, including clinical symptoms, measles-associated complications, date of measles rash onset, gestational age at measles rash onset, the number of days from rash onset to study pregnancy termination, and presence of congenital measles.

The study protocol was reviewed and approved by the Namibia Ministry of Health and Social Services Institutional Review Board prior to data collection. All study participants provided informed consent prior to in-person interviews.

Variable Definitions

Maternal death was defined using the WHO case definition of any death of a woman while pregnant or ≤42 days of pregnancy termination, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes [20]. Gravidity was defined as the total number of times a woman had been pregnant, including the study pregnancy. Fetal gestational age in weeks at the time of measles rash onset in the pregnant woman was as documented in the medical chart. The first, second, and third trimesters were defined as 1–12, 13–27, and ≥28 weeks' gestational age, respectively. A preterm and a full-term delivery were defined as live childbirth occurring during 24–37 weeks and ≥38 weeks of gestation, respectively. Neonatal low birth weight was defined as <2500 g at the time of live birth. Spontaneous abortion included any unintended fetal expulsion of a nonviable fetus <24 weeks' gestational age or any diagnosis of spontaneous abortion as recorded in the medical chart. An intra-uterine fetal death (IUFD) was defined as any delivery of a lifeless fetus ≥24 weeks of gestation [21]. Neonatal mortality included all-cause deaths in a live-born infant ≤28 days postpartum. Congenital measles was defined as an illness meeting the WHO measles case definition in an infant ≤10 days of age.

Statistical Analysis

Questionnaire data were double-entered into an Access database (Microsoft, Redmond, Washington) and exported into SAS software version 9.3 (SAS Institute, Cary, North Carolina) for data cleaning and statistical analyses. A descriptive analysis of pregnant women with measles was completed. We compared demographic as well as clinical characteristics between pregnant women with measles and pregnant women without measles to assess sources of confounding. To evaluate the relative contribution of measles during pregnancy on clinical outcomes, we compared maternal, fetal, and neonatal complications in pregnant women with measles with complications in pregnant women without measles. The Fisher exact test was used to assess the association. A P value <.05 was considered to be significant. The magnitude of the association was estimated with a crude and age-adjusted relative risk (aRR) and asymptotic 95% confidence interval (CI).

RESULTS

In the 6 study districts, 55 pregnant women with measles and 172 pregnant women without measles were included in the study. Of the 55 pregnant women with measles, medical records data abstraction was completed for all; 30 (55%) were also traced for an in-person interview. Of the 30 interviews, 4 (13%) were completed by proxy with the closest relative of the pregnant women with measles, including 3 who had died and 1 who was unavailable. Of the 172 pregnant women without measles, medical records data abstraction was completed for all and 123 (72%) were also traced and interviewed. Of

the 123 completed in-person interviews, 2 (2%) were conducted with the closest relative, including for 1 study participant who had died and 1 who was unavailable.

Among the 55 pregnant women with measles, the median age was 26 years (range, 16–43 years). Measles rash onset occurred during the first trimester for 7 (13%), the second trimester for 21 (38%), and the third trimester for 20 (36%) of the women. Two of the pregnant women with measles were managed as outpatients and 53 (96%) were hospitalized. Measles-related complications occurred in 39 of the 55 (71%) pregnant women with measles, including 33 (60%) with diarrhea, 22 (40%) with pneumonia, and 3 (5%) with encephalitis (1 of whom died) (Table 1).

A higher proportion of pregnant women with measles were less educated, and of Ovahimba ethnicity when compared with pregnant women without measles (Table 2). No differences were found between pregnant women with measles and pregnant women without measles with regard to age, gravidity, and urban or rural residence. Similarly, the source of participant identification was distributed evenly across the 2 groups per study design. Due to the small number of pregnant women with non-HIV-related comorbid conditions, we could not statistically compare the proportions with these conditions. However, there was no apparent difference between the pregnant women with measles and the pregnant women without measles with regard to the presence of non-HIV comorbid conditions. HIV infection status was unknown for 35% of pregnant women with measles and for 5% of pregnant women without measles. Measles vaccination status was unknown or missing for 67% of pregnant women with measles and 50% of the pregnant women without measles.

Among the 55 pregnant women with measles, 42 (76%) had known fetal or neonatal outcome status. Of these, 25 (60%) had ≥1 adverse fetal or neonatal outcome, including 7 (17%) with a spontaneous abortion, 4 (10%) with an IUFD, and 9 (21%) with a premature delivery (Table 3). Twelve (29%) pregnant women had multiple adverse outcomes (2 with 4 adverse outcomes, 3 with 3 adverse outcomes, and 7 with 2 adverse outcomes; Supplementary Table). Of the 25 pregnant women with at least 1 adverse outcome, 6 (24%) were HIV positive, 13 (52%) were HIV negative, and 6 (24%) had unknown HIV status. Of the 9 premature deliveries, 2 infants had a normal birth weight, 4 had low birth weight, and 3 had missing data on birth weight. Among the 4 premature infants with low birth weight, 2 were hospitalized in the neonatal intensive care unit and 1 died during the neonatal period.

Of the 55 pregnant women with measles, both the date of measles rash onset and the date of the end of pregnancy were available for 30 (55%); of these, 9 (30%) ended at ≤7 days, 13 (43%) ended at ≤14 days, 15 (50%) ended at ≤21 days, and 17 (57%) ended at ≤42 days of rash onset.

There were 31 (56%) live births among the 55 pregnant women with measles; of these, 22 (71%) were full term, 9 (29%) were preterm, and 6 (19%) were hospitalized in a neonatal intensive care unit. Three (50%) of the 6 hospitalized neonates died on or before 28 days of birth, resulting in a neonatal mortality of 10% among the 31 live births in pregnant women with measles. Birth weight data were missing for 13 of the 31 live births among pregnant women with measles. Among the 18 (58%) neonates with known birth weight, 7 (39%) had

low birth weight. One (3%) of the neonates had rash onset on day zero of life, consistent with congenital measles; this infant was born prematurely at 32 weeks' gestation, 6 days following measles rash onset in the 25-year-old, HIV-negative mother; had a birth weight of 1850 g; and died on day 15 as a result of measles-associated respiratory failure.

No congenital anomalies were reported among the infants born to pregnant women with measles. Of the 134 infants born to the pregnant women without measles, 10 (8%) were reported to have had a birth defect (ventricular septal defect [n = 1], hydrocephalus [n = 1], bilateral clubbed feet [n = 1], congenital hepatomegaly [n = 1], left eye squints [n = 1], not otherwise specified [n = 5]).

Five (9%) deaths occurred among the 55 pregnant women with measles compared with 1 (1%) death among the 172 pregnant women without measles (Table 3). Of the 5 pregnant women with measles who died, 2 died in the second trimester (gestational weeks 21 and 22) and 3 died in the third trimester (gestational weeks 32, 33, and 36). Among the 5 measles-related maternal deaths, the fetal outcomes included 2 IUFDs, 1 spontaneous abortion, and 2 premature live births; 1 of the neonates had low birth weight (1800 g). In 4 of the measles maternal deaths, the date of rash onset and the date of death were known; of these 4, the number of days between measles rash onset and maternal death were 7, 8, 11, and 12 days, respectively. Of the 5 measles maternal deaths, 3 were in HIV-positive women and 2 in women with unknown HIV status. The causes of measles maternal deaths were recorded as measles in pregnancy, pneumonia, and retroviral disease; *Klebsiella pneumoniae*; measles in pregnancy; complicated measles in pregnancy, gastroenteritis, and complete abortion; and unknown. The pregnant woman without measles who died was HIV negative, with cause of death recorded as anemia and incomplete abortion.

Compared with pregnant women without measles, and after adjusting for age, pregnant women with measles had significantly increased risks for having a neonate with low birth weight (aRR = 3.5; 95% CI, 1.5–8.2), spontaneous abortion (aRR = 5.9; 95% CI, 1.8–19.7), IUFD (aRR = 9.0; 95% CI, 1.2–65.5), and maternal death (aRR = 9.6; 95% CI, 1.3–70.0).

DISCUSSION

In this retrospective cohort analysis, we found that pregnant women with measles had significantly higher risks of adverse maternal, fetal, and neonatal outcomes when compared with pregnant women without measles. Over the last century, previous studies of maternal, fetal, and neonatal complications of measles during pregnancy in other settings suggest the possibility of increased risk for morbidity and mortality [2,3,10–16,22, 23]. More recent studies in developed countries have found a lower incidence of maternal, fetal, and neonatal complications, which has been attributed to improved medical management of the mother and prophylactic use of immunoglobulin for the infant [3, 11, 12]. However, in many settings, including Africa, prophylactic immunoglobulin is not routinely offered to measles-exposed infants, and the clinical management of pregnancy-related complications is suboptimal. Thus, the higher rates of complications found in our study were not unexpected, and were comparable to findings from a 1997 Saudi Arabian study that reported 15% of

spontaneous abortions, 5% stillbirths, 25% premature births, and 7.5% neonatal mortality among pregnant women with measles [10].

Unlike the Saudi Arabian study that reported no maternal deaths, we found a significantly increased risk of maternal mortality associated with measles during pregnancy. In Namibia, estimated HIV prevalence among pregnant women was 18.8% in 2010 [24]; the severity of illness we found was likely a result of the combined effects of measles and HIV infection, consistent with a previous study among Zambian children which reported that HIV infection more than doubled the odds of death in hospitalized children with measles [25]. To our knowledge, our study is the first to document outcomes in pregnant women with measles in Africa, and calls for further research to understand the full spectrum of measles-related complications among pregnant women, especially in settings with high HIV prevalence. This information is critical to help formulate recommendations for appropriate gestational measles case management in such vulnerable populations.

The results of this study should be considered in light of its limitations. First, the majority of the pregnant women with measles were identified from inpatient registers; as such, it is possible that they had more serious disease and would not represent the typical clinical course of measles in pregnancy. However, during the measles outbreak, the MOHSS provided guidance to all physicians to hospitalize all pregnant women with measles; this guidance likely resulted in the hospitalization of less-severe measles cases as well as complicated cases, and may have widened the overall clinical spectrum of hospitalized cases in this study. Similarly, because case identification took place at the health facility, cases may have been missed if the clinical presentation of measles was too mild (not severe enough to warrant presenting for clinical care), too severe (eg, early pregnancy termination or maternal death), or too early in pregnancy (and thus the woman was not recognized as being pregnant). The potential impact of these variations of case ascertainment bias on the magnitude of the effect estimates is unknown. Second, measles cases included in our study were not laboratory confirmed; therefore, misclassification of other rash illnesses, including rubella, was possible. However, study enrollment took place during a large nationwide laboratory-confirmed measles outbreak affecting all selected study districts (range of confirmed measles attack rates in study districts during the outbreak, 52–1643 per 100 000 population) and all study cases met the WHO measles-specific clinical case definition. Moreover, rubella-containing vaccine is not used in Namibia, and rubella epidemiology in Africa includes only 5% of cases among adults [26], further minimizing the likelihood of misclassification in our study. Third, missing data on demographic and clinical factors (eg, race/ethnicity, educational level, and comorbid conditions) made it difficult to fully assess for confounding in comparisons between pregnant women with measles and pregnant women without measles. Similarly, missing data on outcomes could result in either over- or underestimation of the true risk of measles in pregnancy. Finally, because of incomplete data on HIV status for pregnant women with (35%) and without measles (5%), it was not possible to fully assess the relative contributions of HIV and measles infection to the increased risk of maternal death. Understanding the combined effects of HIV infection and measles-related complications will require future prospective studies of measles and pregnancy in countries with high HIV prevalence.

Maximizing measles immunity in women of childbearing age would decrease the incidence of gestational measles and the attendant maternal, fetal, and neonatal morbidity and mortality. With a measles elimination goal by 2020 set in 2011 for the WHO African Region [27], interventions that address the special circumstances of this vulnerable population are needed to reduce the morbidity and mortality from this deadly infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Clinical Features of Pregnant Women With Measles (N = 55), Namibia, 2009–2010

Feature	No. of Women
Measles signs and symptoms	
Rash and fever	55 (100%)
Cough	50 (91%)
Conjunctivitis	45 (82%)
Coryza	33 (60%)
Measles complications	
Diarrhea	33 (60%)
Pneumonia	22 (40%)
Encephalitis	3 (5%)
Gestational age at time of rash onset	
≤12 wk (first trimester)	7 (13%)
13–27 wk (second trimester)	21 (38%)
≥28 wk (third trimester)	20 (36%)
Unknown	7 (13%)
Measles-related hospital admission	
Yes	53 (96%)
No	2 (4%)
Length of stay in hospital, d	
≤1	3 (5%)
2–7	29 (53%)
8–14	16 (29%)
>14	5 (9%)
Not admitted	2 (4%)

Table 2.

Comparison of Demographic and Clinical Characteristics of Pregnant Women With Measles and Pregnant Women Without Measles, Namibia, 2009–2010

Characteristic	Pregnant Women	
	With Measles (n = 55)	Without Measles (n = 172)
Age, y		
Median (1st quartile, 3rd quartile)	26 (23, 30)	25 (21, 30)
15–24	18 (35%)	83 (49%)
25–34	30 (58%)	67 (39%)
≥35	4 (7%)	21 (12%)
Unknown	3	1
Hospital/clinic of identification		
Windhoek (urban)	9 (16%)	28 (16%)
Walvis Bay/Swakopmund (urban)	2 (4%)	8 (5%)
Engela (rural)	7 (13%)	24 (14%)
Opuwo (rural)	21 (38%)	62 (36%)
Outapi (rural)	13 (24%)	38 (22%)
Rundu (rural)	3 (5%)	12 (7%)
Residence		
Urban	11 (20%)	36 (21%)
Rural	44 (80%)	136 (79%)
Race/ethnicity		
Ovambo	12 (40%)	73 (59%)
Ovahimba	15 (50%)	11 (9%)
Other[a]	3 (10%)	39 (32%)
Not recorded	25	49
Educational level		
No formal schooling	21 (70%)	15 (12%)
Primary school	5 (17%)	25 (20%)
Secondary or university	4 (13%)	83 (67%)
Unknown	25	49
Gravidity		
1	14 (33%)	59 (35%)
≥2	28 (65%)	111 (65%)
Unknown	13	2
HIV status		
Positive	7 (19%)	25 (15%)
Negative	29 (81%)	139 (85%)
Unknown/missing	19	8
Non-HIV-related comorbid conditions during pregnancy		
Malaria	2 (4%)	3 (2%)
Anemia	5 (9%)	11 (6%)

	Pregnant Women	
Characteristic	**With Measles (n = 55)**	**Without Measles (n = 172)**
Diabetes	0 (0%)	0 (0%)
Hypertension	3 (5%)	9 (5%)
Preeclampsia	1 (2%)	6 (3%)
Hypertension and preeclampsia	1 (2%)	5 (3%)
Alcohol	7 (13%)	24 (14%)
Cigarette smoking	2 (4%)	7 (4%)
Tuberculosis	2 (4%)	1 (1%)

Data are presented as No. (%) unless otherwise specified.

Abbreviation: HIV, human immunodeficiency virus.

[a]Other includes Herero, Damaras, Kavango, Lozi (Caprivi), Colored, and Nama.

Table 3.

Relative Risk of Maternal, Fetal, and Neonatal Complications in Pregnancy, Namibia Measles Outbreak, 2009–2010[a]

	Pregnant With Measles		Pregnant Without Measles				
Outcome	**No.**	**No.[b]**	**No.**	**No.[b]**	***P* Value[c]**	**Crude RR (95% CI)**	**Adjusted RR[d] (95% CI)**
Fetal outcomes							
Spontaneous abortion	7 (16.7%)	42	4 (2.9%)	139	0.004	5.8 (1.8–18.8)	5.9 (1.8–19.7)
IUFD	4 (9.5%)	42	1 (0.7%)	139	0.011	13.2 (1.5–115.2)	9.0 (1.2–65.5)
Premature delivery	9 (21.4%)	42	24 (17.3%)	139	0.648	1.2 (.6–2.5)	1.3 (.6–2.6)
Neonatal outcomes among live births (n = 31)							
Neonatal ICU admission	6 (19.4%)	31	19 (14.2%)	134	0.578	1.4 (.60–3.1)	1.7 (.7–4.0)
Neonatal mortality (<28 d)	3 (9.7%)	31	3 (2.2%)	134	0.081	4.3 (.9–20.4)	5.0 (.9–29.3)
Low birth weight	7 (38.9%)	18	15 (12.8%)	117	0.012	2.7 (1.2–6.1)	3.5 (1.5–8.2)
Maternal outcomes							
Maternal mortality	5 (9.3%)	54	1 (0.6%)	167	0.004	15.5 (1.9–129.5)	9.6 (1.3–70.0)
Excessive hemorrhage	3 (7.1%)	42	3 (2.2%)	139	0.139	3.3 (.7–15.8)	3.3 (.7–15.7)

Abbreviations: CI, confidence interval; ICU, intensive care unit; IUFD, intrauterine fetal death; RR, relative risk.

[a]The fetal and neonatal outcomes were not known for 13 pregnant women with measles and 33 pregnant women without measles.

[b]The changing denominator is a result of missing data for different variables.

[c]Fisher exact test.

[d]Logit estimates of the common relative risk, adjusted for age group: 15–24 and ≥25 years.