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Pregnancy outcomes in Liberian women who conceived after recovery from Ebola virus disease

Although sporadic outbreaks continue to arise in west Africa, the recent Ebola virus disease (EVD) epidemic, which resulted in nearly 28 650 cases, has been contained. In Liberia specifically, the epidemic began in June, 2014, with the latest outbreak ending in January, 2016. Over 10 670 probable, suspected, and confirmed cases have been documented to date in the country.[1] Individuals who survived EVD now face significant health challenges.[2] Post-Ebola syndrome has been associated with uveitis, headache and other neurological symptoms, musculoskeletal pain, and insomnia, at least some of which are suspected to involve viral sequestration in body tissues and fluids.[3] The medical issues of EVD survivors are often compounded by social stigmatisation due to fears of viral reactivation and potential transmission. Although pregnancy during acute EVD has been almost invariably associated with fetal loss,[4,5] little is understood as to the antenatal courses and pregnancy outcomes in female EVD survivors who conceived after recovery.

We collated demographic and treatment history data on women who recovered from EVD and sought health care for pregnancy between October, 2014, and April, 2016, at designated referral facilities (JFK Hospital, ELWA Hospital, Redemption Hospital, or Duport Road Health Center in Montserrado County; Dolo Town Health Center, Hindi Clinic, Worhn Clinic or C H Rennie in Margibi County). Approval for data collection was via the Ministry of Health (MOH) Incident Management System for overseeing the Liberian response to Ebola. History of confirmed EVD was verified using the official MOH database. Maternal age, number of months between discharge from an Ebola treatment unit and conception, frequency of antenatal care, and pregnancy outcomes were analysed. There were no exclusion criteria.

70 EVD pregnant survivors from Montserrado (n=54) and Margibi (n=16) counties were evaluated as of April 28, 2016. Of these, 15 women miscarried (six in Montserrado, nine in Margibi); four neonates were stillborn (defined as fetal death ≥28 weeks' gestation; three in in Montserrado, one in Margibi); and two EVD survivors elected to terminate their pregnancies (both in Montserrado). Mean age and number of antenatal care visits per month of pregnancy were not significantly different between the group of 49 whose pregnancies resulted in normal births and the 19 women who experienced stillbirth or miscarriage (26·4 years [SD 5·7] *vs* 28·8 years [6·8], and 0·78 visits [0·24] *vs* 0·72 visits [0·40], respectively). In seven cases, the mothers' partners were also EVD survivors; six of the seven had apparently normal infants and one had a miscarriage.

Notably, of six pregnancies that occurred within 2 months of discharge from the Ebola treatment unit, three resulted in stillbirths (figure 1). One additional stillbirth occurred in a pregnancy conceived 6 months after recovery. In contrast, all 15 miscarriages occurred in women who became pregnant 4 months or longer after discharge (figure 1). The mean interval in months between recovery from acute EVD and conception was significantly shorter in women who had stillbirths than in those who had miscarriages (mean 2·5 months [SD 2·4] *vs* 9·9 months [3·0]; p=0·0011).

The overall miscarriage rate in clinically identified pregnancies for this cohort of Ebola survivors (15/68; 22·1%) was slightly higher than the ranges expected for healthy women in developed countries (10–15%)[6] and women in west Africa (11–13%),[7] although published data on miscarriages are sparse. Taken together, the rate of adverse pregnancy outcomes in the present cohort (19/68; 27·9%) suggests the possibility that EVD engendered reproductive health risks after clinical

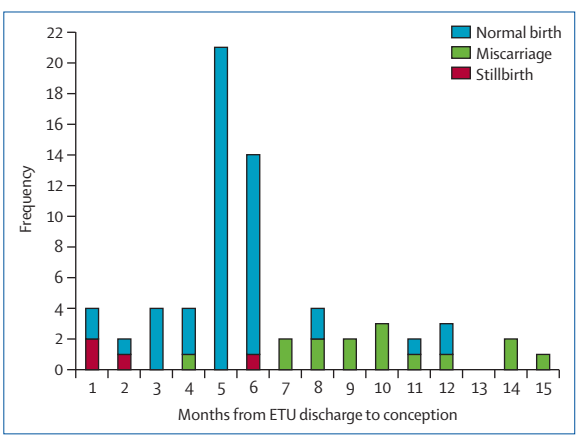

Figure 1: **Frequency of adverse pregnancy outcomes relative to the interval (months) between discharge from the Ebola treatment unit (ETU) and conception**

disease resolved, especially when pregnancy occurred within 2 months of recovery. Prospective evaluation of additional pregnancy outcomes in EVD survivors compared to age-matched controls from west Africa will be helpful to further quantify the relative risks of adverse pregnancy outcomes.

We disclose a number of caveats to the interpretation of these findings. Liberia-specific miscarriage rates among uninfected women before, during, or after the acute epidemic were not available. EVD survivors who noted or suspected problems with their pregnancy may have been more likely to seek medical attention than those who did not. Indeed, the vast difference in miscarriage frequencies between Margibi (9/16; 56·3%) and Montserrado (6/52; 11·5%) counties suggests a possible case-finding artifact; we are unaware of a biologically plausible explanation. Conversely, it is conceivable that our findings underestimate the number of stillbirths and miscarriages among EVD survivors; for example, under-reporting may have occurred due to fear of stigmatisation or because of disrupted health services in the aftermath of the Ebola outbreak.

It has been postulated that Ebola virus persistence in immune-privileged sites such as brain and retina may pose risks to the developing fetus of the gravid EVD survivor.[8] Male survivors have been shown to shed Ebola virus RNA in semen for at least 18 months after onset of EVD.[9] There has been one report of Ebola virus relapse in the central nervous system of a 39-year-old female EVD survivor.[10] Evidence of Ebola virus persistence in other female survivors of childbearing age would heighten the concerns raised here. If confirmed, potential mechanistic questions include whether the reduced immune response during pregnancy and the immunological functions of the placenta, which allow fetus and mother to co-exist, may increase risk of reactivation, and whether genetic risk factors play a role.

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