Title

Prevention of congenital syphilis within antenatal PrEP services in South Africa: missed opportunities

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Prevention of congenital syphilis within antenatal PrEP services in South Africa: missed opportunities

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Syphilis is a major global cause of fetal loss, stillbirth, neonatal death, and symptomatic disease in neonates and infants.[1,2] In 2020, the global incidence of congenital syphilis was 425 cases per 100 000 livebirths, 8·5 times higher than elimination target of 50 cases per 100 000 livebirths set by WHO. Syphilis in pregnancy and congenital syphilis are increasing globally, especially in locations with poor access to antenatal testing and due to global shortages of benzathine penicillin.[3,4] In South Africa, the National Institute for Communicable Diseases (NICD) reported a steady increase in clinical notifications of congenital syphilis cases and rapid plasma reagin-positive results in infants and children aged younger than 2 years between 2017 and 2020.[5,6] Pregnant women are at increased risk of HIV acquisition and syphilis, and are a key population for HIV prevention through pre-exposure prophylaxis (PrEP) services.[7,8] There is growing concern around congenital syphilis globally; however, little data are available regarding the burden of syphilis in pregnant women using PrEP and their infants in Africa.

We evaluated syphilis positivity and congenital syphilis incidence in a cohort of HIV-negative pregnant women (aged ≥16 years) using oral PrEP and their infants in Cape Town, South Africa, between March 10, 2022, and Dec 20, 2023 (records were reviewed between Nov 15, 2023, and Jan 31, 2024). Per local standard of care, women were tested with an onsite rapid treponemal test to guide treatment, followed by laboratory testing (*Treponema pallidum* antibody test [TPHA] with rapid plasma reagin testing). Maternal and infant data were extracted from antenatal care files, neonatal clinical records, and National Health Laboratory Systems data. We identified congenital syphilis cases per South African NICD guidelines, defined as an infant rapid plasma reagin titres at least four times higher than maternal rapid plasma reagin at the time of delivery.[9] Considering this conservative definition, we are likely to have underestimated the true number of congenital infections. We defined adequate maternal treatment as receipt of 3-weekly doses of 2·4 million units of benzathine penicillin G administered

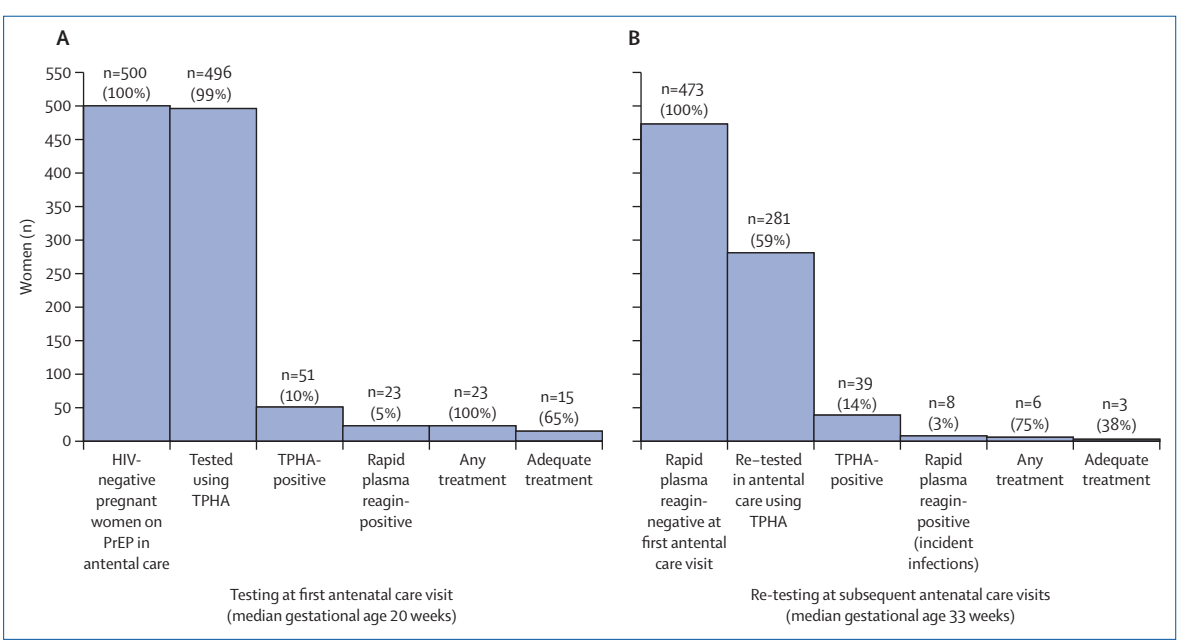

Figure: **Syphilis testing, positivity, and treatment by first antenatal testing (A) versus subsequent testing (B) in Cape Town, South Africa (March 10, 2022 to Dec 20, 2023)**
473 women were eligible for re-testing at the subsequent antenatal visit, of whom 281 were tested. PrEP=pre-exposure prophylaxis. TPHA=*Treponema pallidum* antibody test.

intramuscularly with the first dose received at least 30 days before delivery, as per guidelines of the Western Cape Department of Health and Wellness.[10] We evaluated risk factors of maternal syphilis using logistic regression and adjusted for a-priori confounders (maternal and gestational age at baseline).

Of 500 pregnant women attending routine primary care clinics who started oral tenofovir disoproxil fumarate and emtricitabine PrEP, 496 (99%) were tested for syphilis at least once during antenatal care (median age 25 years [IQR 21–31]; median gestational age 28 weeks [23–35]). At the first antenatal care visit, 413 (83%) of 500 women received a rapid treponemal test; of whom, 26 (6%) tested positive. Of 496 women who underwent laboratory testing at the first antenatal care visit, 51 (10%) were TPHA-positive and of those, 23 were also rapid plasm reagin-positive (overall prevalence of active syphilis 4·6% [95% CI 3·1–6·9]). Overall, 281 women (59% of 473 women who were both TPHA-negative and rapid plasma reagin-negative at their first antenatal care visit) were retested at least once during follow-up antenatal care visits; of these, eight incident syphilis cases were detected (incidence 2·9% [95% CI 1·5–5·5]; figure). Overall, 31 of 496 pregnant women tested were rapid plasma reagin-positive (prevalence 6·3% [95% CI 4·3–8·8]). Among the 31 women who were rapid plasma reagin-positive, 18 (58%) were considered to be adequately treated with three intramuscular benzathine penicillin G injections at least 30 days before delivery, and in 15 (48%) women, rapid plasma reagin titres decreased by four times when compared with baseline. Two congenital syphilis cases were identified (infant rapid plasma reagin titre at least four times higher than maternal rapid plasma reagin titres; 6·4% vertical transmission and 0·4% population prevalence); in both cases maternal diagnosis and treatment was provided less than 30 days before delivery. Risk factors for maternal syphilis were younger age (age 16–24 years *vs* ≥25 years; adjusted odds ratio 2·75 [95% CI 1·30–6·22]), reporting irregular or casual sex partners in the past 3 months (3·07 [0·98–9·22]), experiencing recent intimate partner violence (2·81 [0·99–6·91]), or recent alcohol use in the past 3 months (2·89 [1·35–6·58]).

These novel data demonstrate a high occurrence of syphilis in pregnancy among women enrolled in antenatal PrEP services in South Africa, with almost half not adequately treated in pregnancy. There is a clear and urgent need to integrate syphilis prevention and treatment into antenatal PrEP services. Interventions are needed to improve point-of-care testing, expedited partner treatment, and unify surveillance systems (as done with HIV testing). We identified only one pharmacokinetic study (NCT05309928) evaluating using a high dose amoxicillin in patients who are pregnant, in contrast to ongoing drug trials for HIV. Further funding opportunities to advance research in the field of alternative therapeutics for congenital syphilis are desperately needed. Studies to improve the management of syphilis in pregnant women and prevent congenital syphilis should include treatment offering shorter duration and oral options.

We declare no competing interests.

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