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ARTICLE

# Evaluating congenital syphilis in a reverse sequence testing environment

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## Abstract

**Objectives** To examine the effect of maternal reverse-sequence (RS) syphilis screening on management of infants at risk for congenital syphilis (CS) using a standardized approach.

**Study design** A retrospective study from 2011 to 2014 at an academic medical center using RS testing, involving chemiluminescent immunoassay (CIA), rapid plasma reagin (RPR), and fluorescent treponemal antibody-absorption (FTA-ABS) assays for syphilis. Clinical management and outcomes of infants born to mothers with discordant (CIA+/RPR−/FTA+) serology were compared with national or internal guidelines.

**Results** Sixty-three infants were classified as discordant ($n = 21$), presumed false positive (CIA+/RPR−/FTA−; $n = 16$), or true positive (CIA+/RPR+; $n = 26$) based on maternal serology. Only 24% of cases in the discordant group underwent recommended full evaluation. None of the evaluated infants in the discordant group ($n = 8$) were diagnosed with CS.

**Conclusions** Management of infants with discordant maternal RS serology remained reliant on clinical judgment. In our high-risk population, RS testing did not identify additional cases of CS.

## Introduction

Syphilis, an infection caused by the spirochete *Treponema pallidum*, remains a public health concern, particularly during pregnancy. Globally, an estimated 1.36 million pregnant women have probable active syphilis [1]. According to the Centers for Disease Control and Prevention (CDC), congenital syphilis (CS) cases have been increasing annually in the United States since 2012 [2]. The recent estimate of 23.3 cases per 100,000 live births within the United States in 2017 represents a 43.8% increase from the prior year and an overall 153.3% increase relative to 2013 [2].

The epidemiology of CS in the state of Maryland creates a unique population for evaluation of syphilis testing. In contrast to the declining rates of CS across the country from the late 1990s to 2012, Maryland faced a rising syphilis epidemic, including the Baltimore City outbreak in 1996–1997 [3]. By 2009, Maryland had the highest number

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of CS cases with an annual rate of 41.3 CS cases per 100,000 persons (compared with the national average of 10.4 per 100,000 persons) [2–4]. Since then, Maryland continues to rank among the top ten states with the highest rates of CS, mirroring the national trend of steadily rising CS rates since 2012 [2].

Clinical manifestations of CS can include a maculopapular rash, jaundice, hepatosplenomegaly, and rhinitis ("snuffles") [2, 5]. However, these findings are absent in more than half of infected infants at birth [5–7]. Therefore, the evaluation of infants for CS usually is driven by abnormal antenatal maternal screening serology. Per CDC recommendations, all pregnant women should be screened for syphilis at the initial prenatal visit [8], and women at high risk for syphilis infection or living in areas of high syphilis burden should undergo additional screening in the third trimester and again at delivery [6, 8]. In Maryland, this screening is legally mandated [9]. Traditional syphilis screening, as recommended by the CDC, starts with a non-treponemal assay (e.g., rapid plasma reagin [RPR]) followed by a confirmatory treponemal-specific test (e.g., fluorescent treponemal antibody-absorption test [FTA-ABS] or *T. pallidum* particle agglutination test [TP-PA]) if the RPR is positive [8, 10].

With development of high-throughput automated treponemal-specific immunoassays, many laboratories have adopted a "reverse sequence" (RS) paradigm for syphilis screening [11, 12]. RS testing starts with a treponemal-specific assay (e.g., chemiluminescent immunoassay [CIA] or enzyme immunoassay [EIA]), followed by the non-treponemal RPR assay when the CIA or EIA is positive. In cases of conflicting results (e.g., CIA positive [CIA+]/RPR negative [RPR−]), the CDC recommends performing a different confirmatory treponemal-specific antibody test (e.g., [TP-PA]) [13]. If the subsequent treponemal assay is negative, the initial CIA + result can represent early syphilis [6, 14], though more commonly it is presumed to be a false-positive result. However, if the second treponemal test is positive, this discordant result may represent a prior treated syphilis infection, a prior untreated infection (with a natural diminution of the RPR titer over time), or an early untreated infection. Each of these clinical outcomes in a pregnant woman represents a difference in the risk of vertical syphilis transmission and impacts the evaluation or management of the neonate possibly exposed to syphilis in utero [15, 16].

The advent of RS testing has resulted in an increase in discordant syphilis serology results. For example, an assessment of automated treponemal syphilis screening in five laboratories over a 5-year period demonstrated a greater than 50% rate of discordant serology with initial screening, roughly a third of which were likely false positives (based on subsequent negative treponemal [TP-PA or FTA-ABS] test results) [13]. Rates of discordant sera were nearly three times higher in populations with low syphilis prevalence and were more common in patients previously treated for syphilis or currently HIV positive [6, 13]. In addition, a 3-year cohort reviewing RS testing results among pregnant women demonstrated that up to 20% of patients had discordant syphilis serology of unclear clinical significance [6]. As a consequence, with limited established guidelines for the evaluation of CS in these settings, clinicians are often unsure about the management of infants born to mothers with discordant RS serology.

To date, there are no articles examining the impact of reverse-sequence testing on neonatal evaluation for CS. In June 2011, the Immunology Laboratory at the Johns Hopkins Hospital adopted RS syphilis screening across all clinical areas. Anecdotal reports immediately after implementation suggested inconsistencies in the clinical evaluation of neonates admitted to the Newborn Nursery or Neonatal Intensive Care Unit (NICU) and born to mothers with discordant RS serology. In response to this feedback, we developed and implemented, in December 2011, an internal standardized clinical algorithm to assist in the evaluation of neonates born to mothers undergoing RS testing, especially those born to mothers with discordant serology (CIA positive, RPR negative). Here, we report on the effect of RS testing on newborn management in a population with high syphilis prevalence.

## Methods

### Study design and population

We performed a retrospective analysis from December 1, 2011 to May 31, 2014 of neonates with suspected, probable, or confirmed CS based on maternal syphilis testing. Using the administrative databases from the Department of Gynecology and Obstetrics and the Immunology Laboratory at the Johns Hopkins Hospital, we identified all women with positive CIA serology who delivered live or stillborn infants and created linked maternal–infant dyad data. In addition, we included any newborn admitted to the hospital for suspected CS not identified by our maternal screening process. Women with negative CIA serology (and their infants) were also excluded. This study was approved by the Institutional Review Board of the Johns Hopkins University School of Medicine (IRB NA_00091544).

### Syphilis testing

All sera samples evaluated in this study were assayed initially using the LIAISON automated chemiluminescence immunoassay (DiaSorin, Inc., Stillwater, MN). Non-treponemal serologies were determined by the RPR card quantitative non-treponemal serologic test (Becton

Dickinson, Franklin Lakes, NJ). Confirmatory treponemal testing was performed via the FTA-ABS assay (ZEUS Scientific, Inc., Branchburg, NJ).

## RS algorithm

The RS algorithm (Fig. 1) was created as a multidisciplinary effort among the Divisions of Neonatology, Pediatric and Adult Infectious Diseases, Gynecology and Obstetrics, and Immunopathology. This algorithm targeted management of neonates born to mothers with discordant RS results. All pregnant women with a positive CIA had a reflexive RPR test and a final confirmatory FTA-ABS if the RPR was negative. The algorithm recommended infant testing to allow for comparison with maternal test results. Given the high endemic rates of CS within Baltimore City, the algorithm further recommended conservative management of any infant born to a mother with confirmed discordant results (CIA+, RPR−, and FTA positive [FTA+]), including laboratory and radiographic evaluation and treatment with penicillin based on the results of infant evaluation.

This standardized algorithm was available to providers in the NICU, Newborn Nursery, Labor and Delivery suite, and Pediatric Emergency Department (through the Johns Hopkins Hospital internal online database for pediatric inpatient policies) and as posters in provider workrooms.

## Data collection

Maternal–infant dyads were divided into three groups based on maternal syphilis serology: discordant (CIA+/RPR−/FTA+), presumed false positive (CIA+/RPR−/FTA−), or true positive (CIA+/RPR+).

We obtained demographic, medical, and socioeconomic data from medical records. Maternal data included age at delivery, race, marital status, education level, prenatal visits in the current pregnancy, prior history of sexually transmitted infections (STIs) other than syphilis, illicit drug use during this pregnancy, and high-risk sexual activity (including commercial sex work, multiple [>1] concurrent sex partners in pregnancy, or sex with intravenous drug users or HIV infected patients). We also documented the history of maternal syphilis infection and treatment. All available follow-up maternal syphilis screening results in the discordant and false-positive groups (for up to 3 years after the study period) were obtained from the Baltimore City Health Department (BCHD) to identify seroconversion and/or treatment after delivery.

For neonates, we recorded demographic data at delivery (gestational age, sex, birth weight, and head circumference). Infant syphilis screening results documented abnormalities on physical examination (i.e., dysmorphic features, skin lesions, hepatosplenomegaly), and clinical evaluation results (including imaging [long-bone X-rays, abdominal sonography], serum chemistries [transaminases], hematologic studies [complete blood count], lumbar puncture (LP) results, and neurosensory testing [ophthalmologic examination, hearing screen]) were collected. Subspecialty consultation data were reviewed and extracted. If the infant was treated with penicillin, the dosing regimen (single or multiple doses) was recorded. When available, infants in the discordant group with follow-up data for up to 6 months after birth within our institution were reviewed to assess for any potential missed CS cases.

## Comparing clinical management with standardized algorithm recommendations

For the true-positive and presumed false-positive groups, 2015 Red Book® guidelines [17] and maternal syphilis history were used to determine the recommended testing and management for neonates with suspected CS. For the discordant group, the internal algorithm (Fig. 1) was used to determine the necessity for and extent of infant evaluation. These recommendations were compared with the clinical evaluation performed and documented in the infants' clinical charts. Infants were considered to have had a "full" evaluation if all clinical tests (LP, CBC, transaminases, long-bone films, abdominal ultrasound, ophthalmologic examination, and hearing screen) were performed and "partial" evaluation if any of the testing was missing.

## Outcomes

The primary outcome was the proportion of infants evaluated for CS, according to the standardized clinical approach, using the 2015 Red Book® [17] and our internal RS algorithm. Secondary outcomes included the number of patients with unnecessary evaluation or testing, number of patients treated with penicillin, and number of possibly missed cases of CS.

## Statistical analysis

Categorical demographic data for mothers and birth data for infants were compared using Pearson's chi-squared ($\chi^2$) tests and Fisher exact tests. Descriptive statistics were used for continuous variables and presented as means and standard deviations, and compared with analysis of variance (ANOVA). Statistical analysis was performed using IBM SPSS Statistics (v24, IBM Corp, Armonk, NY).

# Results

During the study period, 4,872 pregnant women underwent RS syphilis screening at our hospital. Among those, 60

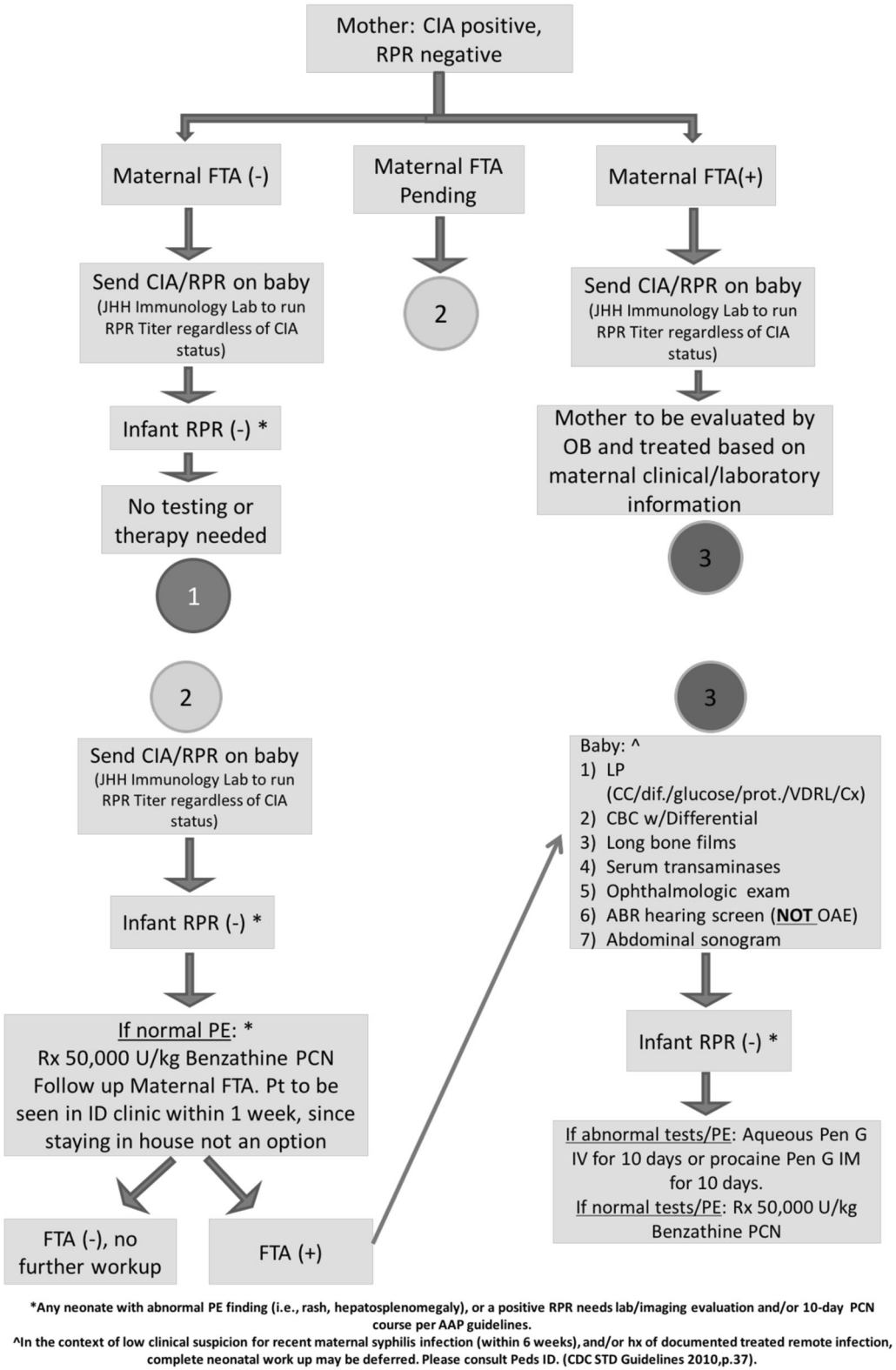


**Fig. 1** Expert-driven multidisciplinary syphilis reverse-sequence testing algorithm

women had positive CIA results; 19 women (32%) had discordant test results (CIA+/RPR−/FTA+), 16 (26%) had presumed false-positive results (CIA+/RPR−/FTA−), and 25 (42%) had true-positive results (CIA+/RPR+) (Fig. 2a). Based on data from the BCHD, only one of the mothers in the discordant or false-positive group received treatment for

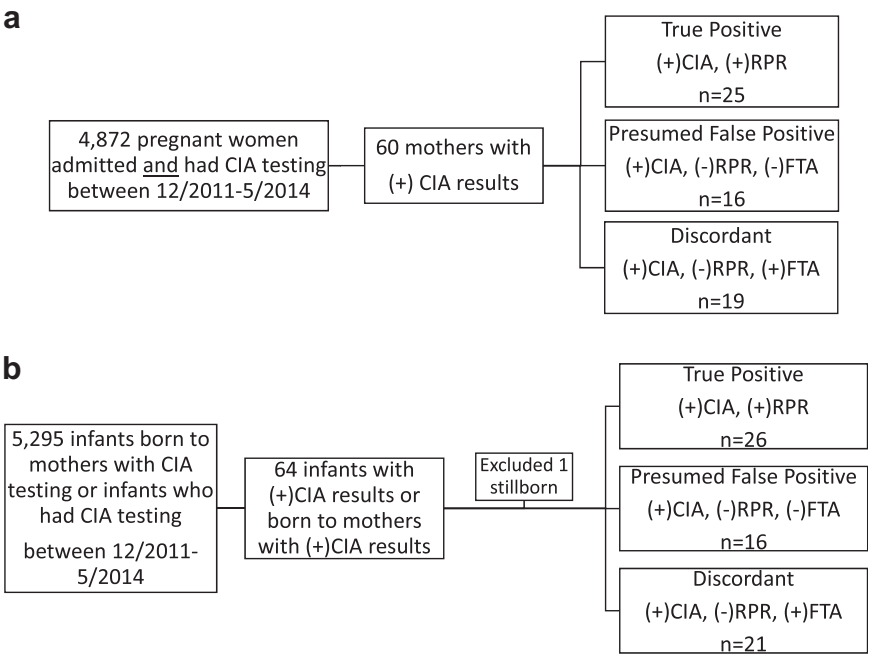


**Fig. 2** Maternal (**a**) and infant (**b**) flow diagram with stratification by maternal syphilis screening status. Specifically, infants were classified based on maternal RS serology results into three groups—true positive, presumed false positive, and discordant

syphilis within 3 years after the study period. The baseline maternal characteristics were similar among groups, with the exception of race ($P < 0.001$), marital status ($P < 0.001$), education level ($P < 0.001$), and prior history of STI ($P < 0.05$) (Table 1).

In the study period, 5,295 infants underwent syphilis testing or were born to mothers undergoing syphilis screening. Of those, 64 infants were identified as CIA positive or born to mothers with CIA-positive results. One stillborn infant without postnatal syphilis testing or evaluation was excluded from the final analysis. The remaining 63 infants were stratified based on maternal screening results, with 21 infants (33%) in the discordant group, 16 (25%) in the presumed false-positive group, and 26 (41%) in the true-positive group (Fig. 2b). There were no differences in sex, gestational age, birth weight, or head circumference between groups (Table 2). Nineteen infants in the discordant group also had syphilis tests obtained, with 15 having matched maternal discordant results (CIA+/RPR−/FTA+).

In the true-positive and presumed false-positive infant groups, clinical evaluation for CS corresponded well with the algorithm, which reflected the Red Book® guidelines [10] in 85–94% of the cases, respectively. In contrast, only 38.1% of infants in the discordant group were evaluated for congenital syphilis (23.8% [$n = 5$] fully evaluated and 14.3% [$n = 3$] partially evaluated, Table 3), despite recommendation for a complete evaluation in all these infants based on our algorithm. Six of these infants were born to mothers with a documented prior-treated infection, but had additional high-risk behaviors during pregnancy that increased the likelihood of reinfection and necessitated an evaluation. For the remaining two infants, full evaluations were performed because of inadequate maternal treatment of prior syphilis infection. All eight of these infants received penicillin treatment (either a single dose of benzathine penicillin or multiple doses of aqueous penicillin G). However, none of them had clinical findings at birth consistent with CS.

Of the 13 remaining infants in the discordant maternal group not evaluated for CS, two (a set of twins) were born to a mother with a prior yaws infection, two were born to mothers who received intravenous immunoglobulin therapy during pregnancy (known to cause false-positive treponemal testing in pregnant women [18, 19]), and nine (seven singletons and a set of twins) were born to women with documented prior syphilis treatment.

We subsequently reviewed all available clinical data from infants of discordant mothers attending our hospital-based pediatric primary care clinic to assess for possible delayed onset of CS. A 6-month follow-up was available for 12 of these 21 infants (57%); none of them had documented clinical evidence of syphilis. Furthermore, we noted that in this cohort, 6 of these 12 infants neither underwent evaluation nor received penicillin treatment during their newborn hospitalization.

**Table 1** Baseline maternal characteristics of women with positive chemiluminescence immunoassay (CIA) results for syphilis

| Maternal characteristics | True-positive CIA+, RPR+ ($n = 25$) | Presumed false-positive CIA+, RPR−, and FTA-ABS− ($n = 16$) | Discordant CIA+, RPR−, and FTA-ABS+ ($n = 19$) |
|---|---|---|---|
| Age, mean (SD), years | 29.7 (7.2) | 31.1 (4.2) | 31.5 (4.8) |
| Race, no. (%)*** | | | |
| White | 0 | 8 (50%) | 4 (21.1%) |
| African American | 22 (88%) | 3 (18.8%) | 15 (78.9%) |
| Other | 3 (12%) | 5 (31.2%) | 0 |
| Marital status, no. (%)*** | | | |
| Married | 3 (12%) | 13 (81.2%) | 4 (21.1%) |
| Single | 22 (88%) | 3 (18.8%) | 15 (78.9%) |
| Education level, no. (%)*** | | | |
| Less than high school | 10 (40%) | 1 (6.3%) | 6 (31.6%) |
| High school graduate or GED | 12 (48%) | 1 (6.3%) | 7 (36.8%) |
| More than high school | 2 (8%) | 14 (87.5%) | 6 (31.6%) |
| Unknown | 1 (4%) | 0 | 0 |
| Prenatal OB visits, no. (%) | | | |
| Yes | 24 (96%) | 16 (100%) | 16 (84.2%) |
| No | 1 (4%) | 0 | 3 (15.8%) |
| Prior history of STI (not including syphilis), no. (%)** | | | |
| Yes | 18 (72%) | 5 (31.2%) | 11 (57.9%) |
| No | 7 (28%) | 11 (68.8%) | 8 (42.1%) |
| Illicit drug use, no. (%) | | | |
| Yes | 10 (40%) | 3 (18.8%) | 8 (42.1%) |
| No | 15 (60%) | 13 (81.2%) | 11 (57.9%) |
| High-risk sexual activity, no. (%) | | | |
| Yes | 3 (12%) | 2 (12.5%) | 6 (31.6%) |
| No | 22 (88%) | 14 (87.5%) | 12 (63.2%) |
| Unknown | 0 | 0 | 1 (5.3%) |

*FTA-ABS* fluorescent treponemal antibody-absorption test, *GED* general education diploma, *RPR* rapid plasma reagin, *SD* standard deviation

**$P < 0.05$ (between groups), ***$P < 0.001$ (between groups)

## Discussion

To date, there are no published studies describing the impact of RS testing on infants at risk for CS, and until recently, no guidelines existed for the management of infants born to mothers with discordant syphilis RS serology. The high prevalence of syphilis in Baltimore City provided us an excellent opportunity to study the impact of implementing RS testing and the utility of clinical tools to aid in the management of patients with discordant RS results. In our retrospective analysis, despite the presence of our standardized algorithm to assist with management of infants in a RS testing environment, evaluation of infants born to mothers with discordant syphilis serology was still based predominately on clinical judgment, often influenced by maternal risk factors and prior history of syphilis treatment.

Automation and reproducibility of RS testing may be beneficial in the adult population [20] and is expected to be more cost-effective and provides earlier detection of seroconversion among recently infected patients. However, when used for screening in pregnant women, RS may lead to additional, unnecessary neonatal testing [7]. In this study, as a consequence of maternal RS testing, eight infants in the discordant group who would not have been identified as being at risk for CS under the traditional CDC algorithm (based on an initial negative maternal RPR) underwent full or partial evaluation. Importantly, none of them had laboratory or radiographic evidence of CS in the newborn period. These results suggest that maternal RS testing may result in overevaluation of neonates and increased hospital costs without clinical benefit.

Another concern about RS testing is the inability to discriminate between women with newly acquired syphilis and those with past syphilis infections (treated or untreated). As a result, our standardized algorithm for a high-risk population was notably more conservative than national guidelines and recommended full evaluation for syphilis in every infant with discordant maternal testing. However, the majority of infants in the discordant group were not evaluated according to the algorithm, likely due to available documentation of maternal pre-pregnancy syphilis treatment and low risk for syphilis reacquisition in pregnancy among the mothers. In addition, an available 6-month follow-up data for over 50% of these babies did not identify any missed cases of CS. Therefore, proper assessment of maternal syphilis treatment and risk stratification of mothers for syphilis reinfection must be coupled with any RS testing algorithm or strategy to identify infants at risk for CS acquisition.

Since the completion of this study, updated CS recommendations in the 2018 AAP Red Book® [10] now include a provision for health-care institutions that employ reverse-sequence testing. The new guidelines take a similar approach to our internal algorithm, treating all discordant infants along the same pathway as RPR+ mothers. The results of our study, albeit with a small sample size, demonstrate the potential for excess testing using a conservative approach in a high-risk environment and may inform policymakers regarding future iterations of CS testing guidelines.

There are several limitations in our study. First, we performed a retrospective study relying on medical documentation of prior maternal syphilis history and medical management of the neonates. In addition, we had incomplete data on long-term outcomes for all the infants within the study and we did not have confirmatory syphilis serology (3–6 months after birth) on infants within the discordant maternal group. Moreover, the follow-up data were limited to patients within Baltimore City, and patient seroconversions occurring outside of this jurisdiction were not documented. Finally, we did not perform a cost analysis of the additional neonatal testing for infants in the discordant group. However, despite the relatively small sample size,

**Table 2** Baseline characteristics of infants born to mothers with positive chemiluminescence immunoassay (CIA) results for syphilis

| Infant characteristics | True-positive CIA+, RPR+ ($n = 26$) | Presumed false-positive CIA+, RPR−, and FTA-ABS− ($n = 16$) | Discordant CIA+, RPR−, and FTA-ABS+ ($n = 21$) |
|---|---|---|---|
| Sex, no. (%) | | | |
| Male | 13 (50%) | 8 (50%) | 12 (57.1%) |
| Female | 13 (50%) | 8 (50%) | 9 (42.9%) |
| Gestational age at birth, mean (SD), weeks | 36.8 (4.2) | 35.4 (5.0) | 37.5 (3.9) |
| Birth weight, mean (SD), grams | 2720 (797) | 2475 (826) | 2887 (786) |
| Birth weight classification, no. (%) | | | |
| SGA | 4 (15.4%) | 2 (12.5%) | 2 (9.5%) |
| AGA | 22 (84.6%) | 14 (87.5%) | 18 (85.7%) |
| LGA | 0 | 0 | 1 (4.8%) |
| Head circumference classification, no. (%) | | | |
| SGA | 6 (23.1%) | 2 (12.5%) | 4 (19%) |
| AGA | 19 (73.1%) | 12 (75%) | 16 (76.2%) |
| LGA | 1 (3.8%) | 2 (12.5%) | 1 (4.8%) |

*AGA* appropriate for gestational age, *FTA-ABS* fluorescent treponemal antibody-absorption test, *LGA* large for gestational age, *RPR* rapid plasma reagin, *SD* standard deviation, *SGA* small for gestational age

**Table 3** Comparison of clinical practice to algorithm recommendations for management of congenital syphilis, stratified according to maternal syphilis reverse-sequence testing results

| TRUE-POSITIVE MOTHERS (CIA+, RPR+) ($n = 26$) | NO neonatal evaluation per algorithm ($n = 13$) | FULL neonatal evaluation per algorithm ($n = 13$) |
|---|---|---|
| NO evaluation performed | 11 (84.6%) | 0 |
| FULL evaluation performed | 2 (15.4%) | 12 (92.3%) |
| PARTIAL evaluation performed | 0 | 1 (7.7%) |
| PRESUMED FALSE-POSITIVE MOTHERS (CIA+, RPR−, and FTA−) ($n = 16$) | NO neonatal evaluation per algorithm ($n = 16$) | FULL neonatal evaluation per algorithm ($n = 0$) |
| NO evaluation performed | 15 (93.8%) | 0 |
| FULL evaluation performed | 1 (6.2%) | 0 |
| PARTIAL evaluation performed | 0 | 0 |
| DISCORDANT MOTHERS (CIA+, RPR−, and FTA+) ($n = 21$) | NO neonatal evaluation per algorithm ($n = 0$) | FULL neonatal evaluation per algorithm ($n = 21$) |
| NO evaluation performed | 0 | 13 (61.9%) |
| FULL evaluation performed | 0 | 5 (23.8%) |
| PARTIAL evaluation performed | 0 | 3 (14.3%) |

*CIA* chemiluminescence immunoassay, *FTA-ABS* fluorescent treponemal antibody-absorption assay, *RPR* rapid plasma reagin

the notable differences among groups have since been used to improve our standardized algorithm to account for provider judgment, varying clinical scenarios and risk stratification for pregnant women (Supplemental Figure). Larger prospective studies evaluating neonatal outcomes in high- and low-incidence syphilis settings using RS testing are necessary to further standardize management and provide guidelines for clinicians caring for at-risk newborns.

## Conclusion

In this study, despite an established standardized algorithm, the evaluation of infants born to mothers with discordant RS results remained inconsistent. In our high-risk population, maternal RS testing did not identify any additional cases of CS that would not have been identified by the traditional RPR testing method. RS screening is faster and less labor-intensive process but may not be beneficial in identifying infants at risk for CS. The decision to implement RS screening should be based on syphilis seroprevalence in the local population, rates of CS, and the availability of maternal history and a standardized approach to facilitate management of infants born to mothers with discordant syphilis serology. Clinical judgment continues to play a paramount role in the decision to evaluate for infants at risk for CS.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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