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Influence of mother VDRL titers on the outcome of newborns with congenital syphilis

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Abstract. Congenital syphilis still represents a significant public health problem worldwide, and particularly in developing countries. Despite years of research on different clinical and immunological features, many physiopathological aspects still lacks of knowledge, one of them the role of immune response against *Treponema pallidum* by infected mothers on the birth outcomes, e.g. birthweight. In this study we analyzed if the mother VDRL titers were significantly associated with the birthweight of newborns with congenital syphilis. We observed a highly significant association between both variables, finding at the linear regression that with higher mother VDRL titers, the newborn birthweight was lower (p=0.0345). We identified that higher VDRL titers are associated with lower birth weights, although the physiopathological reasons to explain this still remains unclear.

INTRODUCTION

Syphilis remains an important sexually transmitted disease and the threat of congenital disease continues to be an important problem in many countries of Africa (Gichangi *et al.*, 2004), Asia (Lim *et al.*, 1995) and Latin America (Valderrama *et al.*, 2004), including Venezuela (Sangtawesin *et al.*, 2005; Vasquez-Manzanilla *et al.*, 2007). In this country the burden of disease is not well known, as most published studies date back many decades (Oropeza *et al.*, 1950). Among other population groups, Venezuelan studies have found, for example, in pregnant women anti-*Treponema pallidum* seroprevalences of 0.65 to 1.5% (Schmidmajer, 1981), 1.07% in blood donors (Schmunis *et al.*, 1998) and 2.4% in sex workers (Camejo *et al.*, 2003). In the case of congenital syphilis, only case reports have been recently published from Venezuela (Quintero *et al.*, 1999), however, an interest in the topic has been raised from those cases (Sales *et al.*, 1999).

Even the clinical efficiency of penicillin in the treatment of pregnant patients with syphilis, infants with congenital syphilis are still encountered in a varied rate range across different surveys and studies as is reflected in the reviewed literature (Valderrama *et al.*, 2004). Congenital syphilis poses significant challenges for the clinician because infants may be asymptomatic at birth or present with a highly variable clinical picture (Vasquez-Manzanilla *et al.*, 2007).

Despite years of research on the effects of *T. pallidum* infection during pregnancy, knowledge on many physiopathological aspects are still lacking. Recently, it has been suggested that low pregnancy weight gain and intrauterine growth retardation (IUGR),

followed by low birth weight (LBW), with its associated greater risks of infection and higher perinatal mortality rates, are significantly evidenced on fetal syphilis. This has been reported in many studies (Sangtawesin *et al.*, 2005), although a causal link remains to be completely proven (Lucas *et al.*, 1991; Gichangi *et al.*, 2004; Carles *et al.*, 2007; Simms & Broutet, 2008). The frequency of this outcome has been measured in those studies, but none of them has addressed if the values of mother VDRL titers influence the newborns outcome in terms of their birth weight. For these reasons in this study we analyzed if these variables were significantly associated.

MATERIALS AND METHODS

Central Hospital of Valera (CHV), Valera, Trujillo state, western Venezuela, is a 400-bed, general hospital of the Trujillo state (the main), was opened in 1958 (with two initial departments, Gynecology and Obstetrics, and Pediatrics). Currently there are seven departments in the hospital: pediatrics, gynecology & obstetrics, surgery, internal medicine, emergency, anesthesiology and radiology & laboratory. Pediatrics service includes pediatric ward, surgical pediatric ward and neonatology.

All mothers in antenatal control were evaluated for routine tests at the Obstetrics & Gynecology Service at the CHV, including HIV-1 and -2 ELISA and VDRL and FTA-ABS, among other serological studies (e.g., for CMV, HBV, HCV), between 2001 and 2006.

Statistical analysis

Statistical evaluation was performed by chi squared (χ^2) test for categorical variable comparisons, unpaired t test with Welch's correction (t_{Welch}) was used for comparison of means of newborn birth weights, and linear regressions between mother VDRL titers and newborn birth weights were also carried out. Statistical significance was defined as $p < 0.05$. Statistical analyses were performed on GraphPad Prism v.4.0 ®.

RESULTS

In the study period no HIV cases were diagnosed, but 44 syphilis cases were observed in mothers, with 38 cases in their newborns (86%). Most cases of congenital syphilis were seen in 2005 (47%), according to the trend in the last 6 years, we are observing an increase in the incidence of this disease (r^2=0.2045) ($p>0.05$). As regard to the sex, 73% were males and 27% females (χ^2=6.53; $p<0.01$).

Mean birth weight (BW) of newborns was 3,073±640 g (±SD) (range 1,500 – 4,800) (11.5% were low birth weight newborns), whilst their mean birth height was 50±4 cms (range 42 – 56). With regards to newborn VDRL titers, the median titer was 1:6 dilutions. In their mothers this figure was also a median of 1:6 dilutions, although these last were significantly higher in terms of variance (F=18.20; $p<0.0001$). In the matching of tests we observed that 27% of cases VDRL titers of newborns were higher than their mothers, but in 53% were equal or lower.

For the FTA-ABS, although it was performed in the mothers in antenatal control, the results were available just in less than 50% of them.

When we linked the mothers VDRL titers with the birth weight of newborns we observed a highly significant association between both variables, finding at the linear regression that with higher mother VDRL titers, the newborn BW was lower (r^2=0.2252; F=5.232; p=0.0345) (or if mother VDRL titers were lower, newborn BW was higher) (Figure 1). This association was also assessed as the comparison between mean BW of newborns according to their mother VDRL titers, finding that the mean BW was significantly lower in the group of newborns with mothers with higher VDRL titers (≥16 dilutions) (2,758 ± 181.9 g) than those with mothers with lower VDRL titers (<16 dilutions) (3,263±128.1; t_{Welch}=2.266; p=0.0368) (Figure 2). These associations were not observed between mother VDRL titers and the birth height (r^2=0.002; F=0.04;

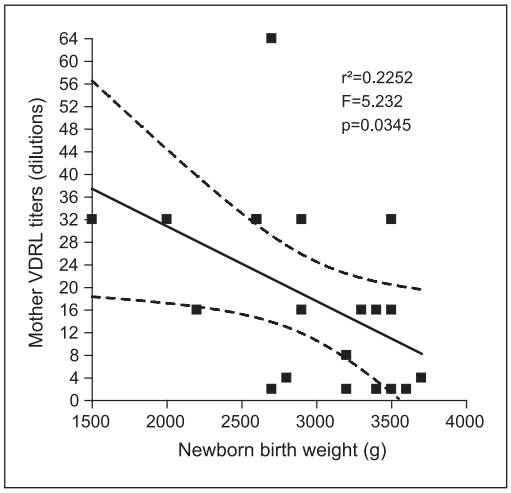

Figure 1. Linear regression between mothers VDRL titers and birth weight of newborns with congenital syphilis.

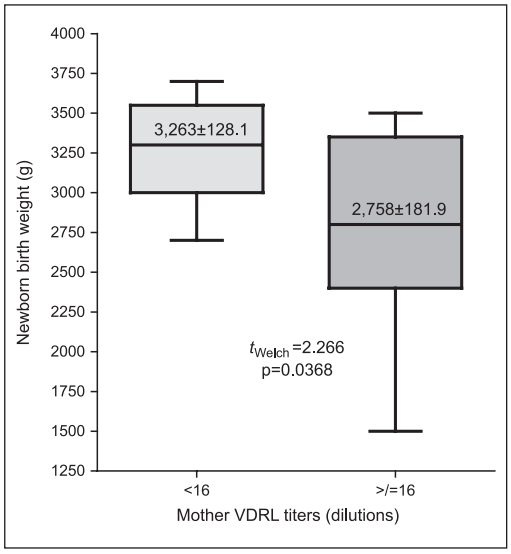

Figure 2. Comparison of birth weights of newborns with congenital syphilis according the mother VDRL titers.

p=0.8276), neither between mother age, gestation numbers, gestational age, and the birth weight or birth height (p>0.05).

DISCUSSION

Syphilis is common in the developing world with localized prevalence in pregnant women varying widely from 2.5% in Burkina Faso to 17.4% in Cameroon (Chakraborty & Luck, 2008), in Latin America ranges from 1.0% in Peru, 2.0% in Colombia, 3.0% in Honduras, 4.0% in Brazil, up to 6.21% in Paraguay (Valderrama *et al.*, 2004). In Venezuela these figures ranges from 0.65 to 1.5% for year 1981 (Schmidmajer, 1981). In the case of congenital syphilis, its incidence ranges from 1.4 cases per 1,000 live born in El Salvador, 2.0 cases per 1,000 live born in Peru, 4.0 cases per 1,000 live born in Paraguay, up to 12 cases per 1,000 live born in Honduras (Valderrama *et al.*, 2004), being in Venezuela ranging from 0.88 to 4.31 cases per 1,000 live born (Vasquez-Manzanilla, 2008).

In pregnant women untreated or inadequately treated syphilis has been associated with prematurity, LBW, non immune hydrops and intrauterine death (Chakraborty & Luck, 2008). It has been estimated that at least two thirds of all fetuses of mothers with infectious syphilis are in some way affected (Walker & Walker, 2002; Walker & Walker, 2004). The World Health Organization (WHO) estimates that 1 million pregnancies are affected by syphilis worldwide. Of these 460,000 will result in abortion or perinatal death, 270,000 infants will be born prematurely or with low birth weight (Walker & Walker, 2004), and 270,000 will be born with stigmata of congenital syphilis (Chakraborty & Luck, 2008). Although this, most studies just report the frequency of LBW among congenital syphilis infected newborns in their series; estimates of 50% have been recently reported (Simms & Broutet, 2008); in Tanzania during 1998-1999 LBW was described in 33% newborns with congenital syphilis (Terris-Prestholt *et al.*, 2003), whilst in French Guyana among 85 seropositive pregnant women the incidence of LBW among their children was 28.2% (Carles *et al.*, 2007), in Russia this figure was 24.6% (Southwick *et al.*, 2007) in one study and 18.3% in another (Salakhov *et al.*, 2004), but was stratified finding in the first that women with adequately treated current syphilis and no antenatal care were more likely to deliver a LBW newborn (odds ratio [OR] 3.8; 95% confidence interval [CI]

1.8-8.1) (Southwick *et al.*, 2007). In Kenya the prevalence of LBW in newborn from infected mothers was 19% (Gichangi *et al.*, 2004; Watson-Jones *et al.*, 2005). At our study it was 11.5% (RR 1.3, for those with titers ≥1:16 dilutions compared to those with <16 dilutions). In Australia a recent study found that LBW and perinatal death were significantly associated with the presence of sexually transmitted infections and syphilis during pregnancy (Panaretto *et al.*, 2006).

In Tanzania, another study find that women with high-titer syphilis (HTS), defined as a VDRL titer >1:8 were at higher risk of LBW (adjusted relative risk [RR] 3.3) (Watson-Jones *et al.*, 2005), but previous reports in this country by the same research group have indicated that there was no increased risk for adverse pregnancy outcome for women treated for high-titer active syphilis (OR, 0.76; 95% CI, 0.4-1.4) or low-titer active syphilis (OR, 0.95; 95% CI, 0.6-1.5) (Watson-Jones *et al.*, 2002a), compared with seronegative women, even more the rates of LBW observed were similar in women treated for high-titer active syphilis and in sero negative women (6.3% and 9.2% respectively) (Genc & Ledger, 2000; Watson-Jones *et al.*, 2002b).

Although this, none of the previous studies (after a careful review of major biomedical data bases) analyzed the specific relation of values of mother VDRL titers as influencing factor on the newborns outcome in terms of their birth weight, beyond their frequency and their relative risk. We clearly identified that higher VDRL titers are associated with lower birth weights, although the physiopathological reasons to explain this still remains unclear. The fundamental histological changes of congenital syphilis are vasculitis and its consequences, necrosis and fibrosis, in all stages (Chakraborty & Luck, 2008). Doppler studies of both the uterine and umbilical arteries showed statistically significant increases in the mean systolic-diastolic ratios in syphilitic mothers compared with healthy controls (Lucas *et al.*, 1991). This indicates an increased resistance to perfusion of the placenta, probably secondary to focal areas of vasculitis and, similarly, placental villitis and obliterative arteritis in pregnancies complicated by syphilis (Lucas *et al.*, 1991; Genc & Ledger, 2000). Then, an intense inflammatory response in the placenta vascular system with a reduced effective irrigation could explain in part the low pregnancy weight gain and IUGR, followed by LBW, which could be reflected clinically by the VDRL titers in the mother. A limitation of our study was that we were unable to assess additionally the relation between FTA-ABS and LBW that would help to confirm the role of placental anti-*T. pallidum* inflammatory processes and their influence in the birthweight outcome, that as we seen with the VDRL, has also not been quantitatively specifically addressed in any published study.

In order to better understand the physiopathology of this disease during pregnancy, we believe that studying the histomorphology of the placental tissue, searching histopathological changes such as villitis, funisitis, chorangiosis, intervillositis, inflammatory infiltrate (counting cell types present in at least 10 high power field, 400X), infarcts, measuring the extension of fibrinoid deposition and localization, arteritis and obliteration lumen amounts; we could improve our approach to the understanding of this pathology. Further studies most include a selected prospective review of cases looking at clinical data, laboratory tests such as VDRL, FTA-ABS, and a detailed correlated anatomo-pathological evaluation that also can include performing special staining and immunohistochemical procedures. Previous studies indicate that placental size, and particularly placentomegaly, is associated with an inverse proportional relation with the birth weight (Hollier *et al.*, 2001). In the future the use of morphometric placental analyses, measuring villi size, comparing with appropriate controls, and documenting the vascular changes in relation to the birth weight; could be indicative of vascular remodeling and its consequences. Today, morphological changes focused on patterns of angiogenesis and a consistent set of morphometrics descriptors can be chosen to attempt understanding the possible origin of

vasculature damage associated to the *T. pallidum* infection during pregnancy. A limitation in these studies is that unfortunately in developing countries only 1% of the placentas are sent to the Pathology services (Cortés & Muñoz, 2007), then such clinico-pathological studies to understand these hypotheses should be properly planned.

Summarizing, the syndromes of congenital syphilis can be classified as either early or late. Early features are similar to the manifestations of secondary syphilis in adults; late onset is defined as symptoms developing in children older than 2 years of age and characterized by gumma formation in tissues including bone, cardiac and the nervous system (Chakraborty & Luck, 2008). In advanced stages have been described that placentomegaly is found in an increasing proportion as the maternal stage and duration of infection increased, and in these cases all fetuses whose mothers had early latent infection had placental enlargement (Hollier *et al.*, 2001).

Finally, in further studies, with large populations, we will calculate a formula to predict the birth weight of newborn in which their mothers have syphilis during gestation according to their VDRL titers.

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