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MATERNAL UNTREATED SYPHILIS INFECTION AND PREGNANCY OUTCOME – AN OBSERVATIONAL STUDY

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Abstract: **Background.** *More than 1 million newborns are infected yearly worldwide making from congenital syphilis a global concern. In 2009 in Romania were reported rates of global seroprevalence of 15 per 100.000 population representing the highest rate in Europe.* ***Study design.*** *A retrospective observational study was carried out, starting from January 2011 to December 2012, on syphilis infection in pregnant women who delivered at Clinical Hospital of Obstetrics and Gynecology Brasov. The study included 98 cases with positive serological screening test for syphilis at delivery.* ***Main outcome.*** *To evaluate the impact of maternal seropositivity for syphilis on pregnancy outcome in terms of maternal-fetal transmission, intrauterine fetal death, birth weight (preterm birth and intrauterine growth restriction), fetal status at birth and correlate this complications with maternal VDRL titers.* ***Results.*** *We discovered 98 new cases of syphilis in women at delivery, in the last two years. 59 new syphilis cases were identified in 2011 from a total of 4325 births (1,36%) and 39 cases in 2012 from 4055 births (0,96%). %) We found significant statistical differences in terms of stillbirth in the VDRL high titer group vs. VDRL low titer group (5,01% vs. 1,02%, p=0,005). In contrast, we did not find a significant association between the VDRL titer and gestational age at birth or birth weight (p=0,34 vs 0,79). Conversely, obstetrical hemorrhages had occurred more frequently in the VDRL high titer group (p=0,03). We also found a significant association between Apgar scores ≤ 7 and maternal VDRL titer (p=0,01). The transmission rate of syphilis infection from mother to fetus was 61,24% higher in the high VDRL titer group.* ***Conclusions****. The transmission rate of infection from mother to fetuses in cases of untreated maternal syphilis was 61,24% in close relationship with higher VDRL maternal titers. Stillbirth rate is significant higher in VDRL high titer group (≤ 1/8) than in the VDRL low titer group (5,01% vs. 1,02%, p=0,005). Lower Apgar scores also occurred more frequently in the VDRL high titer group (p=0,03). Our results showed an expected higher incidence of fetal low birth weight in seropositive pregnant women (27,55%) and an extremely high incidence of preterm birth (41,84%) but, in contrast with the literature data, we didn't find a significant association between the VDRL titer and gestational age at birth or birth weight (p=0,34 vs 0,79). However, our results may be affected by the relatively small number of cases included in the study.*

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Key words: *congenital syphilis, stillbirth, low birth weight, preterm birth.*

1. Background

Congenital syphilis is the direct consequence of inappropriate antenatal care and control of sexually transmitted infections. It can be prevented if infected women are identified before pregnancy or early in the first trimester and properly treatment readily applied [1],[2],[3]. More than 1 million newborns are infected yearly making congenital syphilis a global concern [4].

In addition, maternal syphilis can also lead to other serious adverse outcomes of pregnancy such as spontaneous abortion or stillbirth, low birth-weight fetuses, fetal non-imune hydrops, or serious infections that are associated with an increased risk of perinatal death.

The highest prevalence of syphilis seropositivity is found among pregnant women in the Sub-Saharan Africa, 2,5-17% [5]. In western countries seroprevalence during pregnancy ranges from 0,02% in Europe to 4,5% in some US regions [6].

According a 2008 estimates from WHO, about 1.9 million pregnant women had active syphilis [7].

Despite its huge spread worldwide, few of these infections lead to congenital syphilis. In US, the rate of congenital syphilis in 2008 was 8.5 cases per 100.000 live births [8].

In 2009, in Romania, were reported rates of global seroprevalence of 15 per 100.000 population representing the highest rate in Europe [9].

Because of low costs of syphilis tests, screening all pregnant women is feasible, even in low-resource countries. Those pregnant women considered at risk should be retested in the last trimester.

Nontreponemal tests such as VDRL test (Venereal Disease Research Laboratory) or RPR (Rapid Plasma Reagin test) are used for syphilis screening. Because of high incidence of false positive results mainly during pregnancy, a confirmation test is compulsory. Confirmation of infection is made by treponemal tests such as Treponema pallidum hemagglutination assay (TPHA), FTA – ABS (Fluorescent Treponemal Antibody – Absorbtion) and EIA (enzyme immuno assay) wich are diagnostic and remain positive even after treatment [10], [11].

Treponema pallidum is vertical transmitted from infected women to their babies either by transplacental route or direct contact with infectious inferior genital tract lesions. The transplacental transmission is possible at the end of the first trimester, but congenital syphilis occurs after 18 weeks when the fetus becomes immunocompetent [12].

The risk of transmission is evaluated at 70% to 100% in women with untreated primary or secondary syphilis and 40% in those with untreated early latent syphilis [13], [14]. An untreated woman has about 70% of chance of fetal infection during the first 4 years of disease and, overall, the risk of perinatal death is up to 40% in the untreated cases [15 –17].

Approximately 66% of infected infants from congenital syphilis are asymptomatic at the time of birth and are identified only by routine prenatal screening. Clinical signs appear in approximately 2/3 of affected infants from 3rd to 8th week of life and in most cases by three months of age [18]. Congenital syphilis have an early

form when the clinical manifestations occur before the age of two years and a late one when symptoms occur after hat.

Some complications of congenital syphilis could have an ultrasound associated feature and could be generally detectable after the 24th week of gestation [19], [20]. The most common signs are hepatoplenomegaly, placentomegaly, fetal growth restriction, intrahepatic calcifications, ascites, fetal hydrops or fetal death [19–21].

In spite of generally excellent response of syphilis infection to penicillin G antibiotherapy, it is known that treatment may be frequently ineffective, when is applied in the third trimester of pregnancy. For a consistent reduction in the rates of congenital syphilis, thorough prenatal follow-up of pregnant women is mandatory, with serial serological tests, ultrasound examinations and epidemiological survey of these cases [19–21].

2. Study design

A retrospective observational study was carried out, starting from January 2011 to December 2012, on syphilis infection in pregnant women who delivered at Clinical Hospital of Obstetrics and Gynecology Brasov. The study included 98 cases with positive serological screening test for syphilis at delivery. Positive VDRL tests were confirmed with TPHA tests.

The study group was identified and selected from delivery registries and epidemiological reports using the inclusion/exclusion criteria.

Inclusion criteria

- Documented syphilis infection
- New case identified at delivery
- Singleton pregnancies

Exclusion criteria

- Another simultaneous infection present (HIV, HBV,etc)
- Multiple pregnancies
- Other pathological conditions that may affect the pregnancy outcome such as placenta praevia, diabetes, severe hypertension, etc.

3. Main outcome

To evaluate the impact of maternal seropositivity for syphilis on pregnancy outcome in terms of maternal-fetal transmission of the infection, intrauterine fetal death, low birth weight (preterm birth, intrauterine growth restriction) and hemorrhagic complications and correlate them with the maternal VDRL titers.

Statistical analysis was performed using SPSS for Windows version 9.1. P values were calculated using chi-square test or Fisher's exact test, for pregnancy outcomes in the study groups. Results were expressed in number, percentage, mean and standard deviation.

4. Results

We discovered 98 new cases of syphilis in women at delivery, in the last two years. 59 new syphilis cases were identified in 2011 from a total of 4325 births (1,36%) and 39 cases in 2012 from 4055 births (0,96%). The rate is lower in 2012 (1,36% vs. 0,98%). Because these women had been diagnosed with syphilis at delivery, treatment with Penicillin G was started after birth for both mother and child, according to national guidelines.

In the study group, the mean age of the women involved was 27,97 ± 6,29 (14 - 41 years); most of them had delivered more than two children and had had no antenatal screening.

Maternal and children parameters Table 1

Parameter	Value
Age	27,97 ± 6,29 14 – 41 years
Primiparous	27,6% (27 cases)
Multiparous	72,4% (71 cases)
Stillbirths	9,2%
Gestational age at birth	36,86 ± 3,16 24 - 42 weeks of gestations
Gestational age ≤ 37 weeks	41,84%
Birth weight	2797,04 ± 663,74 820 - 4000 g
Birth weight ≤ 2500 g	27,55%
Apgar Score	8,19 ± 2,19
Apgar Score ≤ 7	10,2%

Results are expressed in number (%), mean and standard deviation (SD).

We found significant statistical differences in terms of stillbirth in the VDRL high titer group vs. VDRL low titer group (5,01% vs. 1,02%, p=0,005), results that are in concordance with data reported in the scientific literature.

In contrast, we did not find a significant association between the VDRL titer and gestational age at birth or birth weight (p=0,34 vs 0,79), although there are many reports that suggested that. We cannot strongly sustain, however, our results because of relatively small number of cases included in our study. Conversely, obstetrical hemorrhages had occurred more frequently in the VDRL high titer group (p=0,03).

Pregnancy outcome related to maternal VDRL titer ≤1/8 and VDRL>1/8 Table 2

Parameter	Value (VDRL ≤ 1/8) n=24	Value (VDRL > 1/8) n=74	P value
Stillbirth	5,10%	1,02%	0,005
G ≤ 2500 g	6,12%	20,41%	0,79
GA ≤ 37 weeks	10,20%	31,63%	0,34
Apgar Score ≤ 7	7,14%	3,06%	0,01

Results are expressed in number (%), mean and standard deviation (SD)

Our findings indicate a significant association between Apgar scores ≤ 7 and maternal VDRL titer (p=0,01).

The transmission rate of syphilis infection from mother to fetus was 61,24% in close relationship with higher VDRL titer. Only 37 newborns had not been diagnosed with congenital syphilis.

In the image below it is showed the association between birth weight and maternal VDRL titer. We can note the higher rate of low birth weight in maternal high VDRL titer group, but no significant association was found (p=0,79). (Chart no.1)

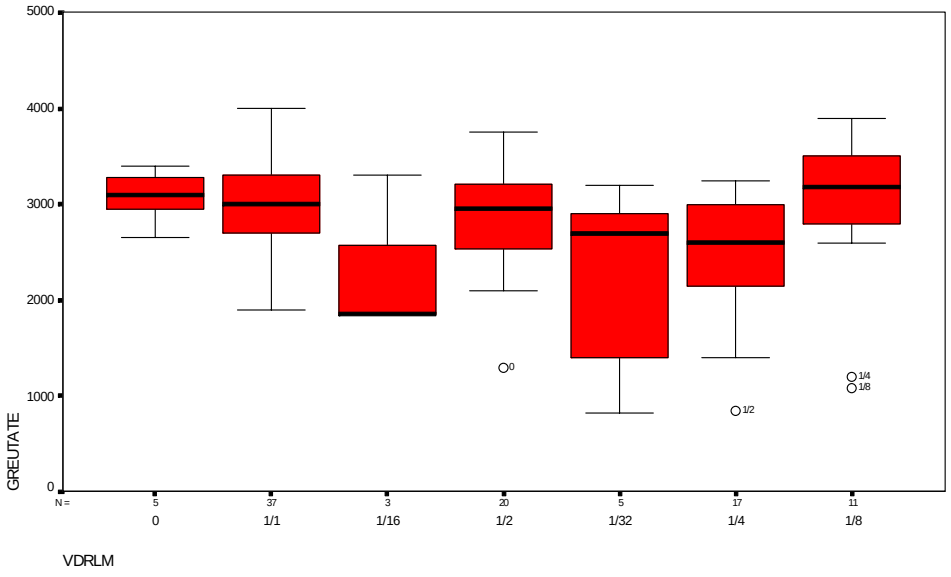

Chart no.1.

In regard of delivery mode, 86,5% of women delivered vaginally and 13,5% by caesarean section with no significant association between delivery mode and VDRL titer of newborns (p=0,83).

5. Discussion

Prevention of congenital syphilis is inefficient mainly because of lack of prenatal care. Rigorous prenatal surveillance is dependent on age, socioeconomic and marital status, rural or urban residence and level of education. The most beneficial action to reduce congenital syphilis is prenatal screening [22].

The pathological syphilis consequences are villitis and obliterative arteritis, which are severe lesions in the placenta leading to the perinatal complications associated with maternal infection [6].

10-35% of cases of congenital syphilis are stillbirths, this infectious condition being one of the leading causes of intrauterine fetal demise [23], [24].

Our findings are consistent with this, even the overall percent of stillbirths in our study is lower than it is generally agreed in literature (9,2 %). The risk of intrauterine death is strongly correlate with the higher VDRL titers (5,01% in titer > 8 group vs. 1,02% in titer < 8 group).

Although most infants with congenital syphilis (about two thirds) [25] are asymptomatic at birth there remains one third who presents suggestive organs impairments that could explain the high percentage of lower Apgar scores (<7) recorded in our statistics particularly in the group with higher VDRL titers (7,14%).

Many recent studies affirm the role of maternal syphilis in the pathogenesis of preterm birth and intrauterine growth retardation. Carles et al. (2008) studied the adverse obstetric outcomes in 85 seropositive women and found 18,8% preterm deliveries and 28,2% low birth weight [26]. Accordingly, Gravett et al. (2010) asserts that syphilis is a risk factor for both stillbirth and preterm birth [27] and Zhang RL et al. (2007) correlates high maternal RPR titers (< 1/8) with higher neonatal mortality, preterm birth rate and low birth rate in the newborns [28]. A study carried out in 2002 by Watson-Jones et al. emphasized that women with high-titer active syphilis had a six-fold increased risk of preterm birth and a three-fold greater risk for low birth weight infants compared with seronegative women [5].

Our results showed an expected higher incidence of fetal low birth weight in seropositive pregnant women (27,55%) and an extremely high incidence of preterm birth (41,84%), but no significant association was demonstrated with higher maternal serum VDRL titers (p=0,79). These findings could be influenced by the relatively small number of cases included in our study.

Studies report that high VDRL titres (a measure of disease activity) are significantly associated with delivery of a congenitally infected infant [29], [30]. Accordingly this, our study results indicate a 61,24% transmission rate in close association with high VDRL titers.

6. Conclusions

The incidence of syphilis rate in our hospital decreased from 1,39% in 2011 to 0,96% in 2012. The transmission rate of infection from mother to fetuses in cases of untreated maternal syphilis was 61,24% in close relationship with higher VDRL maternal titers. Stillbirth rate is significant higher in VDRL high titer group (≤ 1/8) vs. VDRL low titer group (5,01% vs. 1,02%, p=0,005). Lower Apgar scores occurred more frequently in the VDRL high titer group (p=0,03). Our results showed an expected higher incidence of

fetal low birth weight in seropositive pregnant women (27,55%) and an extremely high incidence of preterm birth (41,84%) but, in contrast with the literature data, we didn't find a significant association between the VDRL titer and gestational age at birth or birth weight (p=0,34 vs 0,79). However, our results may be affected by the relatively small number of cases included in the study.

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