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The role of VDRL Testing in routine screening of antenatal women in the present decade.

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Abstract : Background - Prevalence of syphilis is decreasing in India, but it has been a part of routine antenatal screening. With the increasing number of laboratories varied recommendations and reverse screening algorithm , we undertook this study to determine the present prevalence of syphilis in the antenatal women, cost effectiveness of routine screening with VDRL test and to identify the best method of screening for syphilis. Methods - Retrospective review of charts from January 2006 to June 2011. Results - Prevalence of syphilis was 0.1 among the antenatal women. Since syphilis is a preventable cause perinatal mortality and morbidity, routine screening was identified as the defence against these problems. The present CDC recommendation of screening with VDRL followed by TPPA on VDRL reactive cases was found to be the best method of screening. Conclusion - Though the seroprevalence of syphilis is low and showing a downward trend in our population, still screening for syphilis is cost effective. The best method of screening is with VDRL and confirmation of reactive cases with TPPA. We need further studies before we could implement TPPA as screening test for antenatal women.

Key-word : Syphilis ,Antenatal ,prevalence ,screening ,VDRL ,TPPA .

AIMS AND OBJECTIVES

1. To determine the cost effectiveness of Venereal Diseases Research Laboratories (VDRL) investigation as a routine serological screening for syphilis among pregnant women who receive antenatal care at the Christian Medical College and Hospital Vellore.
2To find out the prevalence of syphilis in antenatal women in a tertiary care centre in South India.
3. To find out if routine screening for syphilis is necessary for all antenatal women.
4. To find out if the present screening by routine testing of VDRL followed by TPHA/TPPA on VDRL positive cases are cost effective.
5. To find out the best mode of screening for syphilis in antenatal women.

Introduction

Syphilis is a systemic infection caused by the spirochete Treponema pallidum. It has a very high risk of transplacental spread to the fetus causing adverse perinatal outcomes,(1) Untreated maternal syphilis is responsible for approximate annual 360,000 foetal and perinatal deaths worldwide and 270,000 cases of congenital syphilis with serious permanent defects.(2) WHO in 2004 estimated a 1 million pregnancies were affected by syphilis worldwide.(3) . Studies have shown varied prevalence of syphilis among pregnant women in developing countries with published studies from India showing a prevalence range of 2.5% to 3.4%. Study conducted by Sunil et al in Chandigarh (North India) in 2006 showed a seroprevalence of 1.8% with decreasing trends.(4)(5).Mathai et al in the audit of management of pregnant women with positive VDRL in Christian Medical College, Vellore in 2001 found the prevalence of syphilis to be 0.98%.(6). Syphilis has 4 stages namely primary, secondary, tertiary and latent syphilis. (1)The vertical transmission rate in untreated women is 70 to 100% in primary syphilis, 40% in early latent syphilis, and 10% in late latent disease. The longer the interval between infection and pregnancy the less severe is the disease (7). US Centres for Disease Control (CDC) and Prevention and many other global and national organisations recommend that all antenatal women should be screened for syphilis and treated appropriately in order to eliminate or eradicate complications. The major drawback in following this recommendation is unwanted anxiety of a false positive test.(1)(7) Various modes of screening strategy that have been proposed are Non treponemal test alone (VDRL).

Treponemal test alone.(TPHA/TPPA, FTA - ABS). Non treponemal test screening followed by confirmation with the treponemal test.(8) The advantage of doing a non treponemal test alone is that, it does not detect treated cases. But disadvantage is that it may yield false positive results especially when there are associated diseases of connective tissue disorder .(9) and also the tests are nonreactive in 30% of patients with early syphilis in their initial visit with lack of sensitivity in the late stage of syphilis .(8) On the other hand advantage of a TPHA test for screening is that it can detect all stages of syphilis beyond the primary stage. In primary syphilis, TPHA test is less sensitive than the nontreponemal test. It cannot be used to follow up cases of treated syphilis as TPHA test remains positive after treatment

. Furthermore it has a decreased positive predictive value in a population with low prevalence .(8). TPPA test is a modification of TPHA in which sensitized gelatin particles are used as carrier instead of erythrocytes cells. TPPA offers greater sensitivity and specificity compared with TPHA with a sensitivity of 96% in primary syphilis.(10). Fluorescence treponema pallidum antibody absorbtion test(FTA–ABS) is the test with maximum sensitivity for primary syphilis.(8) A combination of VDRL followed by TPHA can detect more cases of primary syphilis. It provides a better sensitivity and specificity in screening the various stages of syphilis. But all these test cannot be automated and is labour intensive with subjective interpretation(8) The usual testing algorithm is to screen with a nontreponemal test such as the VDRL; a reactive specimen is then confirmed as a true positive with a treponemal test such as TPHA. (1) WHO also recommends VDRL and TPHA test in parallel for diagnosis of syphilis. A study done by Errico et al on blood donors comparing VDRL or RPR test with VDRL and TPHA test in parallel found that there was a significant increase in sensitivity from 47% to 98% with good specificity when the two tests were done in parallel than one nontreponemal test alone.(11) Similarly a study done by Young et al on TPHA as screening test showed that TPHA alone had a sensitivity of 96.1% and VDRL had sensitivity of 74.2 % .TPHA detected 56 patients more than VDRL, but of these 45 were treated cases while only 8 were new cases. On the other hand VDRL had detected 6 new cases which were missed by TPHA test , but both test together detected all the
256 positive cases.Thus it can be concluded that TPHA is more sensitive and specific than VDRL in detecting late andlatent syphilis while VDRL is more sensitive than TPHA in detecting early syphilis.
Both tests togetherare complementary and they can identify all cases of syphilis.(12)On the other hand Viroj et al in his study on blood donors concluded that VDRL is the most costeffective and that the cost of TPHA testing needs to be reduced to one-third to reach the same cost-utility as VDRL .(13).There are multiple options available for screening but each option has its own advantages anddisadvantages.Therefore we decided to carry out this retrospective study with the above mentioned objectives.

Methodology

Retrospective data review of the VDRL results of the pregnant women attending the antenatal clinic in the Obstetrics and Gynaecology Department of Christian Medical college Vellore from 2006 January to 2011 June, was carried out. All data were collected from the records of the Microbiology Department after taking permission from the five Obstetrics and Gynaecology units and Department of Microbiology.The study was approved by the Institutional Review Board of Christian Medical College,Vellore. The total number of VDRL tests done over these years were calculated and the total number of women with reactive VDRL test were identified separately. The VDRL reactive cases had a confirmatory treponemal test (TPPA) done on them.Total number of cases who were TPPA positive among those with reactive VDRL was calculated. Biological false positives were then calculated by subtracting the number of cases who are TPPA positive from the total VDRL positive. The prevalence of syphilis in the routine antenatal population was then determined by these results. The cost analysis was done by calculating the cost involved for VDRL test done alone and VDRL and TPPA test done in parallel and comparing the treatment cost of the mother and the baby in both groups.

Results

All antenatal women who were booked or had their delivery in CMCH, had VDRL test done. During the study period, the total number of VDRL tests done were 57,625 tests. Of these , 765 (1.32%) were reported as positive. All these women were requested to have a confirmatory test (TPPA). But only 551 (0.95 %) had a TPPA confirmatory test done , which left 214 (0.37%) women without a confirmatory report for various reasons. Out of the 551 women who had TPPA carried out, 42 (7.62 %) were confirmed positive.

Total tested for VDRL = 57.625
Number positive = 765 (1.32%)
TPPA test Done = 551(0.95%)
(a) Positive 42 (7.62%); (True positive)
(b) Negative 509 (92.37%); (False positive)

TPPA test Not done 214(0.37%) Therefore the VDRL biological false positives in those who had the confirmatory tests were 509 (
92.37 %) out of 551women.Conversely, the number of VDRL true positives in those who had the confirmatory TPPA test was 42(7.62 %) out of 551women. If one presumes that the same number of true positives i.e. 8% were present in the women who did not have their confirmatory TPPA test, then it would work out as 17 women, in addition to the 42 true positives in whom TPPA was done . This accounts for a total of 59 (7.71%) out of the total 765 VDRL reactive cases of syphilis, and 59 (0.098% approx 0.1%) out of a total of 57,625 screened for syphilis with the VDRL test. Thus the prevalence of syphilis in our antenatal population screened was found to be 1 in 1000. (0.098% approx 0.1%).

	Positive	Negative
TPPA	59	706
VDRL	765	56860

In order to find out the cost effectiveness of this screening procedure, the total cost of the screening test (VDRL)and the confirmatory test TPPA were first totalled.
Cost of a VDRL test in CMCH = INR 120.00 Cost of a TPPA test in CMCH = INR 185.00 Total cost spend on VDRL by antenatal women – INR 120 x 57625 = INR 69,15000 Total cost spend on TPPA by these women – INR 185 x 551 = INR 1,01935
This was calculated to be INR 70,16,935.00.

	Cost x Total number of antenatal women who underwent test.	Cost spend on antenatal women in INR
VDRL	120 x 57625	69,15,000
TPPA	185 x 551	1,01,935
TOTAL		70,16,935.

Neonate with syphilis needs injectable antibiotics and hospitalisation for 14 day. If however CSF is positive for syphilis then treatment is instituted for 21 days. In addition investigations including VDRL, CBC, lumbar puncture and CSF analysis is done. Charge of drugs (approximately) = INR 20.00 per day Investigation charges = INR 750.00 Bed and professional charges (approximately) = INR 750.00 per day Therefore cost of treatment (antibiotics + investigations + bed and professional charges) approximately for 14 and 21 days respectively amounts to (INR 20 x 14) + INR 750 + (INR 750 x 14) = 11.530 and (INR 20 x 21) + INR 750 + (INR 750 x 21) = INR 16,920.

	Cost per day	Cost for 14 days	Cost for 21 days
Drugs	20.00	280.00	420.00

Investigations	750.00	750.00	750.00
Bed and Prof	750.00	10,500 .00	15,750.00
Total	1520.00	11,530.00	16,920.00

With the prevalence of 1 in 1000, if 1000 antenatal women were not screened with VDRL test, only 1 child would be missed. The amount recovered by not doing the VDRL test would be INR 120 X 1000=1,20,000.The cost of treating 1 child with syphilis would be approximately around INR 12,000 to INR 17,000. Additional cost would be added to treatment if this child is encountered with the long term defects of congenital syphilis. Furthermore the emotional, and social effects and associated cost also has to be accounted for, which is beyond our calculation In order to identify the best screening test, the cost involved in treatment and monitoring of these women who were diagnosed as syphilis and the amount saved from not doing additional test were calculated. Women with syphilis are treated with Benzathine penicillin G, 2.4 million units intramuscularly weekly for 3 doses Post treatment patients are followed up with antibody titres after 1 month, 3 months, 6 months, 12 months and 24 months with the same treponemal test that was initially used for diagnosis. The titres should decrease fourfold by six months of post treatment and should be nonreactive by 12 to 24 months. Cost of 3 doses of Benzathine Penicillin = INR 75.00 Cost of follow up with VDRL test at least twice = INR 240.00 Total cost of treatment = INR 315.00.

Cost analysis of VDRL alone as screening test

If VDRL alone was used for screening, 765 women would have been reactive. The cost for treating and follow up of these women would have been INR 315 X 765 = INR 2,40,975. Cost of TPPA on 765 cases - 765 x INR 185 = INR 1,41,525 The amount recovered by not doing TPPA was INR 185 X 765 = INR 1,41,525. Therefore the expenditure over the income incurred by not doing TPPA test INR 2,40,975 .00 – INR 1,41,525.00 = INR 99,450.00

VDRL alone as Screening

	VDRL +ve cases with treatment cost	VDRL +ve cases with TPPA cost	Total
Expenditure	765 x 315	-	2,40,975.00
Income incurred by not doing TPPA	-	765 x 185	1,41,525.00
Expenditure over Income	-	-	99,450.00

Cost analysis of additional TPPA confirming test

On the other hand if TPPA was used as an additional confirming test for the VDRL reactive cases then only 59 cases would have been diagnosed with syphilis. The cost involved in treating these patients would be INR 315 X 59 = INR 18,585 Additional cost of TPPA on 765 reactive patients INR 185 x 765 = INR 1,41,525. This totals to INR 1,60,110. The amount recovered by not treating the false positive cases was INR 315 X 706 = INR 2,22,390. Therefore the income incurred over expenditure by doing TPPA as an additional screening test will amount to INR 2,22,390.00 – INR 1,60,110.00 = INR 62,280.00

Cost analysis of additional TPPA confirming test

	Cost of treatment on false positives	Cost of treatment on true positives and TPPA cost on VDRL +ve cases	Total
Income incurred by not doing the test	315 x 706	-	2,22,390.00
Expenditure	-	315 x 59 = 18,585 + 1,41,525	1,60,110
Incomeover expenditure	-	-	62,280.00

Discussion

Syphilis is a very important disease in the developing countries and a major cause of perinatal morbidity and mortality all over the world. Study conducted by Mathai et al showed a prevalence of syphilis to be around 10 per 1000 antenatal women in our hospital in 2001. In the present study, the prevalence of syphilis among the antenatal women was 1 per 1000 women. This very clearly shows a declining trend of syphilis in South India probably because of better awareness, increasing antenatal care and screening. In Vellore the seroprevalence of syphilis is low, and in areas of low seroprevalence the positive predictive value of VDRL is low, increasing the number of false positives. With this declining trends, and low seroprevalence of syphilis, and the low positive predictive value of VDRL, the question for the need of routine screening of syphilis with VDRL arises. On analysing the cost effectiveness of syphilis we noticed that the amount spent on identifying 1 case of syphilis is huge, but long term disabilities and the emotional, social, and economic burden which syphilis can cause, which this screening can prevent , is beyond cost analysis. Routine screening is the major defence against the long term problems of congenital syphilis. Mehmet et al had correctly stated “, prenatal screening results in insignificant savings to society even when the prevalence of the maternal syphilis is as low as 0.005”.(14) Presently the screening for syphilis is with VDRL (nontreponemal test) followed by confirmation with TPPA (non treponemal test). Is this the best method of screening , or are we wasting our resources by doing an additional TPPA test is the question which arises. When the cost analysis for treating patients diagnosed to have syphilis by VDRL was done, it was noticed that the amount spent was 99,450 rupees more by over treating the patients. VDRL causes cross reactivity with other diseases like Anti phospholipid syndrome. High false positive is the cause of this over diagnosis and thus the extra expenditure. On doing a TPPA test the amount spent would be around 1,41,525 more, but 2,40,975 rupees is saved by not treating unnecessarily . This argument clearly shows that addition of TPPA into routine screening for confirming VDRL reactive cases is cost effective and saves resources. The development of automated treponemal test in high volume laboratories had made these test economical and therefore reversal of the traditional screening sequence has started in various laboratories. We also wanted to identify the number of extra cases we could have got by screening with TPPA test alone. Study by young et al showed that TPHA could identify 22% more cases.(12).

Since TPPA was not done for all antenatal women in our study it could not be analysed. Furthermore CDC in its editorial in 2008 had stated that these test as screening or reversal of traditional screening algorithm did not provide any specific prognostic information for patient evaluation and treatment as treponemal test once reactive is always reactive throughout life. These results would only indicate that the patient has encountered syphilis at some time in his life but could not distinguish between treated and untreated cases. Lack of standardisation of algorithms and lack of evidence to judge the merit of these algorithms have produced more confusions, over - diagnosis and over - treatment.(15) Since these created confusions among the clinicians, CDC carried out another evaluation of discordant results in reverse sequence screening. They recommended that if treponemal test is positive then a nontreponemal test is done. If this test is discordant then another treponemal test should be done for confirmation. It was found that false positives were 2.9 times more in the low prevalence region than in the high prevalence regions. This suggested detailed studies for better understanding of the serological testing for syphilis.(16) Therefore in our hospital where prevalence is low we need to gather more evidence before we can decide on the cost effectiveness of the reverse sequence screening

Conclusion

Though the seroprevalence of syphilis is low and shows a downward trend in our population, screening for syphilis is still cost effective. The best method of screening is with VDRL and confirmation of reactive cases with TPPA. We need further studies before we can implement TPPA as screening test for antenatal women.

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