UK National Screening Committee

Screening for syphilis in pregnancy

External review against programme appraisal criteria for the UK National Screening Committee (UK NSC)

Version: 1

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On behalf of the UK National Screening Committee

14/05/2013

The UK NSC advises Ministers and the NHS in all four UK countries about all aspects of screening policy. Its policies are reviewed on a 3 yearly cycle. Current policies can be found in the policy database at http://www.screening.nhs.uk/policies and the policy review process is described in detail at http://www.screening.nhs.uk/policyreview

Template v1.2, June 2010

Introduction

Syphilis is an infectious disease caused by *Treponema pallidum* subspecies *pallidum*. This spirochete bacterium is transmitted through sexual contact and from mother to fetus during pregnancy or at birth.

Universal screening for syphilis in pregnancy has been reviewed in the past. In 1998, the National Screening Committee (NSC) recommended the continuation of universal antenatal screening for syphilis based on the report, produced by the Public Health Laboratory Service and the PHLS Syphilis Working Group: "Antenatal syphilis screening in the UK: a systematic review and national options appraisal with recommendations" (July 1998). This report assessed the question raised by cost-effectiveness analyses that due to the low prevalence of syphilis in the UK, universal screening might no longer be necessary. The review directly addressed the issue of whether screening should continue. However, the authors concluded that due to the important and devastating consequences of syphilis in pregnancy, concerns about the potential for increases in the incidence of syphilis highlighted by **an outbreak in Bristol and increased immigration** and limited resource savings from withdrawal of the programmethe benefits of continuing screening outweighed the cost of such a programme. In 2007 the results of a literature search were considered at a UKNSC / HPA stakeholder workshop and it was agreed that no publications suggested the need to withdraw the programme.

The current IDPS Programme recommends screening for syphilis so that those with a positive test can be clinically assessed and a diagnosis made to determine whether treatment and follow up is required. Infants born to infected mothers who have received adequate penicillin treatment during pregnancy are at minimal risk for congenital syphilis. This document was developed as part of the UKNSC's cycle of evidence reviews and summarises the results of an external review on syphilis screening in pregnancy, using evidence published since 2007. A particular focus of the review was to establish whether any of publications suggested a need to revisit the question of the discontinuation of screening which was addressed by the PHLS in 1998.

Appraisal against UK NSC Criteria

These criteria are available online at http://www.screening.nhs.uk/criteria.

1. The condition should be an important health problem

The association of maternal syphilis with poor pregnancy outcomes, including congenital syphilis, has been well recognised, although its full characterization was not possible until Wasserman's development of a serologic test in 1906[2]. Our ability to study the impact of treatment, now that highly effective treatment is available, is limited by the ethical requirement to treat those diagnosed, making existing historical sources of information particularly valuable. In 1917, William Osler observed that syphilis accounted for 20% of all stillbirths and 18 to 22% of infant deaths in the United States[3]. Similar neonatal mortality rates were observed in the U.K. in that era[4]. In a recent systematic review and meta-analysis of historical observational studies, an increase of 21% foetal losses and stillbirths, of almost 10% neonatal deaths (before 29 days of life), and of 6% among infants born prematurely or with a low birth weight, were estimated in syphilitic pregnancies compared to non-syphilitic pregnancies in the absence of treatment[5]. An additional 15% of infants will present with signs and symptoms of syphilis infection. In total, 66.5% of pregnancies affected by syphilis resulted in adverse outcomes, compared to 14.3% of

non-syphilitic pregnancies, in the absence of treatment[5]. In other words, untreated active syphilis in a pregnant woman increases the incidence of adverse outcomes of pregnancy almost five-fold.

2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage

In the UK, surveillance data are available on sexually transmitted diseases since 1917. Since 2001, such infections are reported to the Health Protection Agency (HPA), through an enhanced surveillance system [6].

Diagnoses of infectious syphilis declined during the 1980s following the primary prevention prevention response to the arrival of the HIV/AIDS epidemic. A relatively low level of reported diagnoses was maintained in the 1990s throughout the UK. The first recent outbreak of infectious syphilis affecting women occurred in Bristol in 1997. This was followed by outbreaks in the cities of Manchester, Brighton, Peterborough, London, Newcastle upon Tyne, Glasgow, Edinburgh, Walsall and the regions of south Wales and Northern Ireland[7]. More recently, in 2011, there have been several new outbreaks reported across the UK [8-13], mainly among young heterosexuals.

Figure 1: Diagnosis of infections syphilis made in genito-urinary clinics, United Kingdom, 2002 - 2011.

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Male	1315	1688	2183	2683	2683	2783	2508	2502	2349	2622
Female	245	317	443	503	433	424	366	349	293	291
Total	1560	2005	2626	3186	3116	3207	2874	2851	2650	2915

Note: HPA STI Report 2002 – 2011
(http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1215589015024)[7]

The table shows minor fluctuations in annual reported cases in women and the HPA report an increase in the cases of congenital infection[14]. The number of cases of syphilis in pregnancy requiring treatment and congenital syphilis is currently being investigated by the Surveillance of Antenatal Syphilis Screening (SASS) study and a British Paediatric Surveillance Unit (BPSU) study.

Congenital syphilis is the result of transplacental transmission of spirochetes. The risk of vertical transmission depends primarily on the stage of maternal syphilis and, if the woman is newly infected while pregnant, on the stage of the pregnancy. Syphilis infection in the adult evolves over time through three symptomatic stages[15]: 1) primary syphilis follows an incubation period of one to four weeks. The typical primary chancre is a single papule. Both men and women may ignore a visible lesion, because it is painless and heals completely in three to six weeks; 2) secondary and latent syphilis is a systemic, multi-organ disease that begins six to twelve weeks after infection. Mucocutaneous lesions are common and even without treatment, complete

resolution of secondary syphilis occurs after three to twelve weeks. The disease then enters a latent phase which may last for many years; 3) tertiary syphilis is marked by destructive lesions. The manifestations are divided into three main subgroups: neurosyphilis, cardiovascular syphilis, and late benign syphilis (gummas).

Mother-to-child transmission is higher (60% to 90%) in untreated maternal primary or secondary syphilis, decreasing to 40% in early latent syphilis, and to <10% in late latent syphilis[15].

3. All the cost-effective primary prevention interventions should have been implemented as far as practicable

Primary prevention of congenital syphilis relies on prevention strategies to avoid sexual transmission of syphilis among adults of reproductive age. There are no primary prevention programmes for syphilis in isolation from other sexually transmitted infections. Preventing sexual transmission of syphilis relies on general primary prevention programmes for sexually transmitted infections, including HIV. These interventions were successful in the 1990s but, as shown by the re-emergence of syphilis in the general population, they have had mixed results more recently. As such, relying on primary prevention programmes alone is currently inadequate to prevent transmission occurring in pregnancy.

4. If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

Not applicable.

5. There should be a simple, safe, precise and validated screening test

Currently, antenatal screening for syphilis is a well established component of the Infectious Diseases in Pregnancy Screening Programme, where pregnant women are offered tests for hepatitis B, HIV, syphilis and rubella susceptibility[16].

The most commonly used method to diagnose syphilis is serology. Serologic tests include treponemal and nontreponemal tests. Nontreponemal tests (e.g. RPR or VDRL) detect antibodies present from 4 to 8 weeks after infection onwards. These tests can be quantified by serial serum dilution and changes in titres can help indicate successful treatment. Treponemal tests (e.g. FTA-ABS, MHA-TP, and TPPA) are reactive slightly earlier than nontreponemal tests and patients remain seroreactive for life, even if successfully treated. False-positive treponemal tests can be seen in various conditions, especially spirochetal infections, including Lyme disease (in which the nontreponemal test shows negative results)[15].

The tests used to define seroreactivity vary across settings and over time, from the Wasserman and Kahn tests (for which sensitivity and specificity data are not available) in early studies to the Venereal Disease Research Laboratory or rapid plasma reagin tests (sensitivity, 71–100%; specificity, 98%), the fluorescent treponemal antibody absorption test (sensitivity, 84–100%; specificity, 97%) and the microhaemagglutination assay for T. pallidum (sensitivity, 76–100%; specificity, 99%) in more recent studies.[47]

The UK-recommended screening procedure for syphilis includes a highly sensitive test to detect antibodies (Enzyme immunoassay, EIA), followed by a highly sensitive and specific confirmatory treponemal test (*Treponema pallidum* particle agglutination (TPPA) or *Treponema pallidum* haemagglutination (TPHA))[17]. The use of EIAs in the UK has been reported to have the advantage of producing objective results since there is linkage of EIA plate readings directly to laboratory computer systems[18]. The reported sensitivity and specificity of treponemal EIAs is high, ranging from 85 – 99.5% and 98.3 – 100%.[48]

Similar recommendations are found in the United States, where two tests are used in sequence: one to screen and the other one to confirm infection. However, in the United States the initial screening includes the non-treponemal tests such as Venereal Disease Research Laboratory (VDRL) and the Rapid plasma regain (RPR); followed by confirmatory treponemal tests (fluorescent treponemal antibody absorbed (FTA-ABS) and the *Treponema pallidum* particle agglutination (TPPA))[19].

Recently, newer treponemal-based EIAs and chemoluminiscence immunoassays have been released. The following tests are being evaluated and are not currently recommended within the UK screening programme:

The LIAISON Treponema Screen, Enzygnost Syphilis, and the ARCHITECT Syphilis TP have demonstrated sensitivity and specificity when evaluated as a confirmatory test and as a screening test for syphilis among various patient populations. However, the use of a confirmatory test, such as TPHA, remains prudent in order to avoid false-positive results[20-24].

Although IMMULITE 2000 syphilis screen uses a single p17 antigen, it was found to be more sensitive than the Bioelisa SYPHILIS 3.0 which uses three recombinant antigens (p15, p17 and p47). IMMULITE 200 Syphilis Screen was found to be a specific and sensitive method of syphilis screening and could be considered as alternative to other ELISA tests[25]. It was shown to be comparable to the TPPA, with the advantage of being a fully automated system[26].

Captia Select-Syph-G ELISA was evaluated focusing on discrepancies between the results of IgG ELISA and the TPHA tests. The authors found it to be a reliable tool for syphilis testing in high-risk population and recommended its use as a confirmatory test in at-risk patients.[27]

6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed

Screening tests, confirmatory tests and guidelines for the reporting of results are available in the Infectious Diseases in Pregnancy Screening programme – handbook for laboratories[17].

In 2009 1,142 screen positive test results were reported to the HPA National Antenatal Infections Screening Monitoring Programme (reference IDPS Annual Report 2010 – 11). However these reports do not distinguish between new diagnoses, false positives, other infections and previously treated infections. This issue is currently being explored within the Surveillance of Antenatal Syphilis Screening (SASS). Emerging data suggests that 24% may be new diagnoses and 43% previously treated infections (personal communication, SASS study). This will be more fully reported following completion of the study and analysis of the data.

7. The test should be acceptable to the population

Current practice guidelines recommend that all pregnant women are offered screening for syphilis early in pregnancy alongside the other antenatal booking blood tests as part of the Infectious Diseases in Pregnancy Screening Programme[16]. The work of this programme and reported uptake rates of over 95%[28 29] implies that the syphilis screening tests are acceptable to pregnant women.

8. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals

Guidelines for the assessment and management of syphilis in pregnancy and infancy have recently been developed by British Association for Sexual Health and HIV (BASHH) and these represent best management practice[30]. In these guidelines, it is recommended that all pregnant women are offered screening for syphilis at the initial antenatal visit. All women with positive syphilis screening test results should be offered testing for other Sexually Transmitted Infections including HIV. With regards to treatment recommended, briefly, a single dose of benzathine penicillin G 2.4MU is effective in most cases of syphilis during pregnancy although failures have been reported, mainly in those at increased risk of transmission (higher RPR/VDRL titre, early stage maternal disease and last trimester treatment). When maternal treatment is initiated in the third trimester a second dose of benzathine penicillin is recommended 1 week after the first, with careful assessment. Retreatment in those with a previous diagnosis of syphilis should be considered when there is uncertainty of efficacious past treatment. Non-penicillin alternatives include ceftriaxone and erythromycin or azithromycin. Desensitization to penicillin in those reporting allergies should be considered. Multidisciplinary management is recommended, with a close liaison with obstetric, midwifery and paediatric colleagues. Referral to fetal medicine for ultrasound to evaluate fetal involvement and fetal monitoring for fetal distress in the early stages of therapy is recommended after 26 weeks gestation.

9. If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out

Not applicable. [313233]

10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment

Observational studies show a lower prevalence of any adverse outcome among pregnant women who received an intervention (to include screening and treatment for syphilis) in the first and second trimesters compared to those women who did not receive screening and treatment until the third trimester[31-35]. For example, Zhu et al, Watson-Jones et al and Carles et al reported a higher prevalence of adverse outcomes when women were treated or tested in the third trimester compared to earlier in pregnancy (19 vs 27.8, 13.4 vs 21.1, and 13.2 vs 68.8 respectively)[313233].

11. There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered

Guidelines for the assessment and management of syphilis in pregnancy and infancy have recently been developed by BASHH and these represent best management practice[30]

12. Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme

This criterion is not directly applicable as there is an ongoing screening programme. The IDPS Programme standards and BASHH guideline emphasise the need for quick laboratory turnaround times and prompt referral of women with screen positive results and robust communication between GUM and the referring maternity unit. A number of issues relating to these points are worth noting.

For example a recent national audit of laboratory diagnostic methods for syphilis showed that 24% of positive antenatal syphilis screening results were not returned to antenatal clinics within 2 weeks, and some respondents reported turnaround times in excess of 3 weeks.[44] The declining number of health professionals with knowledge of syphilis and its management has also been noted.[45, 46]

An audit from one UK GUM clinic recently noted that 'the average time between a positive test and review in AN clinic was 25 days and that between positive test and review in GUM was 35 days.' The report also found that communication between GUM and maternity services was an area requiring further exploration and protocol development.[28] Similarly, emerging information from the Surveillance of Antenatal Syphilis Screening study suggests that some units are unable to provide information on diagnosis and treatment of women who screened positive for syphilis in pregnancy, even after the women have delivered. This appears to relate to a lack of communication between the maternity units and the GUM clinics to which the women were referred, with issues around confidentiality sometimes cited. This issue will be more fully explored when the study is complete and the data analysed. (personal communication, SASS study)

13. There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (eg. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened

A recent review of syphilis screening interventions confirmed that syphilis screening programmes coupled with appropriate, prompt penicillin treatment for women testing positive are efficacious in reducing adverse pregnancy outcomes, particularly rates of stillbirth and perinatal death[36]. This review did not identify randomised controlled trials of screening because

syphilis screening programmes are well established and it would be considered unethical to do such a trial.

A Cochrane review updated in 2010 aimed to identify the most effective antibiotic treatment regimen of syphilis in pregnancy[37]. The authors found no randomised controlled trials to review. However, from the observational studies identified, they concluded that both duration and dosage were important considerations, re-treatment rates were lowest for primary infections and highest for patients with second-stage infection, and that long-acting preparations were probably as effective as regimens using multiple injections of aqueous crystalline or procaine penicillin G.

14. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public

The work of the Infectious Diseases in Pregnancy Screening Programme[16],the guidelines for the assessment and management of syphilis in pregnancy and infancy by BASHH representing best management practice[30] and the high uptake of screening implies that the syphilis screening tests, the diagnosis procedures and the treatment are acceptable to both pregnant women and the health care professions.

However the communication issues discussed in criterion 12 may suggest that the practical requirements of an antenatal screening programme are ethically challenging to some professionals.

15. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment)

Potential harms may include false-positive results that require clinical evaluation (unnecessary utilisation of resources), unnecessary anxiety to the patient in case of false-positive result, and unnecessary use of antibiotics. There is also evidence of the women experiencing fear of gender-based violence from a partner following the disclosure of sexually transmitted infection status[38].

Strategies to overcome such potential harms include: use of highly sensitive and specific diagnostic testing; and identifying women at potential increased risk of violence from an intimate partner when giving them a positive diagnosis. Such women have been shown to prefer provider-initiated referral mechanisms (rather than patient-initiated), and may need additional counselling and support strategies to be implemented[39].

16. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (ie. value for money). Assessment against this criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource

Syphilis testing coupled with appropriate, prompt penicillin treatment for women testing positive has been recognized to be highly cost-effective even in moderate and low prevalence settings[40] - in agreement with the conclusion of the Public Health Laboratory Service and the PHLS Syphilis Working Group: "Antenatal syphilis screening in the UK: a systematic review and national options appraisal with recommendations" (July 1998) supporting their recommendation to continue universal screening of syphilis in pregnancy in the UK.

No UK studies of cost effectiveness studies were retrieved by the literature search for this review.

17. All other options for managing the condition should have been considered (eg. improving treatment, providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available

Several strategic alternatives to universal antenatal screening for syphilis have been assessed in the past. These included the targeting of the screening programme to pregnant women in high risk groups and discontinuing the screening programme entirely. It was concluded that antenatal screening of syphilis should continue in the UK[41].

No publications, retrieved by the literature search, revisited this question.

18. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards

Governance of the syphilis screening component is part of the overall governance of the Infectious Disease in Pregnancy Screening programme. Across the English National Screening Programmes, Key Performance Indicators (KPIs) are now collected to monitor local performance of the Infectious Diseases in Pregnancy Screening programme[42]. However, there is no KPI related to syphilis screening. The only two KPIs available to date are: 1) HIV coverage (first return 31/12/2011), and 2) Timely referral of hepatitis B positive women for specialist assessment (first return 30/06/2011).

19. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme

Not directly assessed.

20. Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice

As specified in the National Infectious Diseases in Pregnancy Screening Programme standards[16]: Informed consent for screening must be given before a specimen is taken and tests requested. The midwife should ensure that the woman has seen the written information, "Screening tests for you and your baby", or has access to it in a format appropriate to their requirements.

21. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public

n/a

22. If screening is for a mutation the programme should be acceptable to people identified as carriers and to other family members

n/a

Conclusions

Syphilis continues to occur in women of reproductive age and, as such, there is a continuing risk of congenital infection.

No publications, retrieved by the literature search, suggested that there should be a change in the current screening policy.

Syphilis screening during pregnancy is a cost-effective intervention for which the benefits currently outweigh the harms.

Implications for policy

A change to the UK NSC's policy position is not supported by the literature covered in this review.

Implications for research

Syphilis screening in pregnancy is well-established and seems to be acceptable to both pregnant women and to health care providers. Although we do not recommend any change to the current UK NSC policy position (to screen all pregnant women), consideration could be given to the following issues:

1. Evaluation of single platform HIV/syphilis screening tests – these are currently under development. Their use as point of care diagnostics may help improve efficiency of testing procedures.
2. Studies and audits of issues relating to the interaction between GUM and maternity services
3. Studies and audits of issues relating to and affecting laboratory turnaround times

Methodology

Search strategy

<Details to be entered by UK NSC>

Quality

All abstract were reviewed. Abstracts were then classified by relevance to UK context. The quality of the evidence was assessed for each publication included by study design and quality. Comparisons were made across studies for consistency in results and potential differences in populations.

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