ANTENATAL PREVENTION OF THE RISK OF EARLY NEONATAL BACTERIAL INFECTION

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Clinical Practice Guidelines

Guidelines Department

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GUIDELINES

INTRODUCTION

The control of maternal and foetal infection is a major public health challenge given the consequences for the neonate, in particular neurological and pulmonary complications.

These clinical practice guidelines on "Antenatal Prevention of the risk of early neonatal bacterial infection" were produced at the request of the Paediatric Infectious Disease group of the French Paediatrics Society (*Société Française de Pédiatrie*). They are intended for gynaecologists and obstetricians, midwives, microbiologists, general practitioners, paediatricians, neonatologists and paediatric intensive care specialists.

Proposals are graded A, B or C according to the following system:
- a grade A guideline is based on scientific evidence established by trials of a high level of evidence, for example randomised controlled trials of high power and free of major bias, and/or meta-analyses of randomised controlled trials or decision analyses based on properly conducted studies;
- a grade B guideline is based on presumption of a scientific foundation derived from studies of an intermediate level of evidence, for example randomised controlled trials of low power, well-conducted non-randomised controlled trials or cohort studies;
- a grade C guideline is based on studies of a lower level of evidence, for example case-control studies or case series.

In the absence of scientific evidence, the proposed guidelines are based on agreement among professionals.

I. WHEN SHOULD PREGNANT WOMEN BE TESTED FOR CERVICOVAGINAL INFECTION?

Routine vaginal samples should not be taken at the start of pregnancy except in women with a history of premature labour (grade A).

A vaginal sample should be taken:
- when there are clinical signs of vulvitis or vaginitis in the pregnant woman, i.e. vulval itching, cervicovaginal burning sensation, coloured or offensive-smelling leucorrhoea (grade B);
- if there is a threat of premature labour or premature rupture of the membranes (PROM), or if chorioamnionitis is suspected (grade B);
- routinely at the beginning of pregnancy to test for bacterial vaginosis if there is a history of premature labour, because treating asymptomatic bacterial vaginosis in this at-risk group reduces the rates of PROM and premature labour (grade A).

Cervicovaginal infection is asymptomatic in more than half of all cases (grade B).

An endocervical smear should be taken:
- if there are clinical signs of cervicitis in a pregnant woman, i.e. presence of seropurulent cervical discharge (rare in France) or inflammation of the cervix or contact bleeding (grade B);
- if there are signs of urinary tract infection or leukocyturia with negative urine microscopy and culture;
- in patients with any sexually transmitted disease or patients with multiple partners;
- in a patient whose partner has a genitourinary infection.

Infections identified by endocervical smear are *Chlamydia trachomatis*- and *Neisseria gonorrhoeae*-induced cervicitis. If there are urinary symptoms, a first catch urine sample improves detection of these infectious agents.

Given its relatively low prevalence in France, routine screening for *Chlamydia trachomatis* by endocervical smear is not justified at the start of pregnancy, or in cases of PROM or threatened premature labour. There are no trials which have assessed the benefit of such screening in women with a history of premature labour.

II. SAMPLES TO BE TAKEN FROM A PREGNANT WOMAN TO DETECT CERVICOVAGINAL BACTERIAL INFECTION, AND INTERPRETATION OF RESULTS (NORMAL AND ABNORMAL FLORA)

II.1. Diagnosis of bacterial vaginosis

The best way of diagnosing bacterial vaginosis is direct examination of vaginal secretions by Gram staining. The results should be interpreted according to the criteria of Spiegel, Nugent or Thomasson (grade A).

Specific culture testing for *Gardnerella vaginalis* and for mycoplasma co-involved with anaerobic bacteria in bacterial vaginosis is not justified during pregnancy (grade A).

II.2. Isolation of *Streptococcus agalactiae* (group B Streptococcus), *Escherichia coli K1*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Streptococcus pneumoniae* or other bacteria of intestinal or oropharyngeal origin.

If these bacteria, with or without *Lactobacillus acidophilus*, are found on monomicrobial culture in a vaginal sample from a pregnant woman, this is more likely to indicate carrier status than actual local infection causing vaginitis. Nevertheless, if there are symptoms of vulvovaginitis, a pure culture of one of these bacteria, with no or much reduced normal vaginal flora and no vaginosis flora, may explain the inflammation observed and suggest specific treatment.

II.3. Cervicitis caused by *Chlamydia trachomatis*

The best way of identifying *Chlamydia trachomatis* in an endocervical smear is by using gene amplification techniques of nucleic acid sequences specific to this species (grade A).

II.4. Cervicitis caused by *Neisseria gonorrhoeae*

In view of the need to test for antibiotic sensitivities, testing for *N. gonorrhoeae* is performed by culture on two enriched heated blood agars, one selective and the other non-selective. If there is a strong suspicion of gonococci, incubation in a humid CO_2-enriched atmosphere should be extended to five days (grade B).

III. WHAT TO DO IN THE EVENT OF CERVICOVAGINAL BACTERIAL INFECTION DURING A NORMAL OR PROBLEM PREGNANCY

III.1. Bacterial vaginosis

All bacterial vaginosis should be treated during pregnancy. Treatment is oral metronidazole (1 g/day for 7 days or 2 g as a single dose). This is effective in obtaining negative bacteriological samples and has no teratogenic action (grade A). There is no proof that treatment with pessaries is effective in pregnant woman.

Because of the frequency of recurrence after treatment, a control sample should be taken every trimester from treated women, and treatment should be repeated if necessary.

III.2. Isolation of *Streptococcus agalactiae* (group B Streptococcus), *Escherichia coli K1*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Streptococcus pneumoniae* or other bacteria of intestinal or oropharyngeal origin

In the absence of a risk of imminent labour (PROM, premature labour, suspected chorioamnionitis), treatment of asymptomatic carriers of these vaginal bacteria is not recommended.

In the event of suspected chorioamnionitis or if there is a risk of premature labour, antibiotic therapy - guided by the antibiotic sensitivity results - seems justified. What to do in the event of PROM is explained in Section VII.

Pregnant women who are asymptomatic carriers of group B Streptococcus should not be treated ahead of labour because treatment does not reduce the level of organisms carried during labour (grade A).

III.3. Isolation of mycoplasma in the vagina

No specific treatment is recommended to reduce vaginal colonisation by mycoplasma.

III.4. Cervicitis caused by *Neisseria gonorrhoeae*

A number of different treatments – 3g amoxicillin orally combined with 1g probenicide orally, 2 g spectinomycin intramuscularly, 250 mg ceftriaxone intramuscularly or 400 mg cefixime orally – are equally effective in treating gonococcal cervicitis during pregnancy (grade A). The partner must be treated.

III.5. Cervicitis caused by *Chlamydia trachomatis*

Symptomatic cervicitis caused by *Chlamydia trachomatis* should be treated with azithromycin (single 1 g dose) or erythromycin (500 mg 4 times a day for 7 days).

Erythromycin is less well tolerated and leads to lower compliance. The partner must be treated. Amoxicillin (500 mg 3 times a day for 7 days) is a possible alternative.

IV. IS THERE ANY BENEFIT IN ROUTINELY SCREENING FOR GROUP B STREPTOCOCCUS CARRIERS DURING PREGNANCY AND LABOUR? IF SO, WHAT METHOD SHOULD BE USED, WHEN AND HOW?

Routine screening for carriers of *Streptococcus agalactiae* or group B Streptococcus (GBS) (ordered as such) is recommended at the end of pregnancy, ideally between 34 and 38 weeks after the last period, for the following reasons:

- the percentage of the population who are carriers in France: 10%, i.e. at least 75 000 pregnant women a year (grade A);
- the prevalence of consequences during labour at term, i.e. chorioamnionitis, infection in neonates weighing over 2,500 g, postpartum endometritis (grade A), which makes it a public health problem;
- the efficacy of intrapartum antibiotic prophylaxis guided by screening outcome, i.e. reduction of the risk of neonatal infection (grade A) and of postpartum maternal infection (grade B) by more than 75%;
- the cost of screening for GBS and of antibiotic prophylaxis is offset by the savings made from avoiding complications and rationalising prescriptions (grade C);
- the lack of efficacy after 37 weeks of approaches which do not include screening for GBS (grade A);
- the availability of a non-traumatic screening test for GBS which is reliable and cheap, namely a simple culture test for GBS on blood agar, without selective enrichment in liquid medium (grade B60; NABM[1] Code: 0214). The vaginal sample is taken with a swab from the whole of the vaginal cavity and must include cells from the walls of the lower half of the vagina as far as the vestibule of the vagina and vulva (grade B). The response is expressed semi-quantitatively (1+, 2+, 3+, 4+) in relation to the number of quadrants in which there is growth of GBS. This means that the risk can be quantified as low (1+) to high (4+).

Testing for GBS antigens by rapid diagnosis tests is not recommended as a routine practice at the start of labour. It does not fit in with the way staff duties are organised in most maternity wards, and it is too costly and no more effective than culture at the end of pregnancy (grade B). If available, the technique may be used in pregnant women who were not screened at the end of pregnancy and who have been admitted to hospital with PROM.

There is no point in taking an anorectal sample for screening for GBS. This second sample has not been shown to improve efficacy in terms of maternal and infant infection avoided (grade B). Moreover, it increases screening costs.

There is no point in routine screening for GBS in women with a history of maternal or foetal infection caused by GBS or who have presented GBS-positive bacteriuria during pregnancy, as they will be given routine intrapartum antibiotic prophylaxis (see Section V).

[1] *Nomenclature des Actes de Biologie Médicale* (Nomenclature for Medical Laboratory tests)

The current data do not justify routine screening at the end of pregnancy for bacteria other than GBS that are likely to cause infection in the mother or foetus. Testing for these bacteria is justified if there are risk factors for infection (premature opening of the cervix, PROM, fever in the mother).

V. INTRAPARTUM ANTIBIOTIC PROPHYLAXIS OF NEONATAL INFECTION CAUSED BY GROUP B STREPTOCOCCI

Intrapartum antibiotic prophylaxis of GBS infection is recommended:

- when the mother is diagnosed as a carrier of GBS during pregnancy, whether near labour or not (grade B);
- in the event of bacteriuria positive for GBS during pregnancy (grade B);
- in the event of history of neonatal GBS infection (grade B);
- in the absence of a vaginal sample for GBS screening, if one of the following risk factors is present: labour before 37 weeks, membranes ruptured for more than 12 hours or a maternal temperature over 38 °C during labour (grade B).

Intrapartum antibiotic prophylaxis of GBS infection consists of penicillin G at a dose of 5 million IU followed by 2.5 IU million given intravenously every 4 hours until expulsion, or intravenous amoxicillin (2 g followed by 1 g every 4 hours) (grade A).

Treatment should be started as early as possible during labour, as optimum efficacy is only obtained from the second injection (grade B).

In the event of allergy to penicillin, antibiotic sensitivities should be done because certain strains of GBS are resistant to macrolides. The alternatives are erythromycin or a cephalosporin, despite the risk of cross-allergy.

VI. WHAT TESTS SHOULD BE CARRIED OUT IN THE EVENT OF PROM?

No single laboratory test can predict time of labour after PROM, diagnose amniotic infection or indicate pregnancy termination to prevent neonatal infection. Decisions can only be based on an array of clinical and biochemical factors.

VI.1. A vaginal sample is essential during PROM:

- to test for bacteria carrying a high risk of infection to the amniotic cavity, the most common being S. agalactiae (GBS), E. coli K1 and the other enterobacteria, H. influenzae, S. aureus, S. pyogenes, pneumococci and meningococci (grade A). The best pattern for taking a vaginal sample has not been determined. It could be repeated once or twice a week.
- to test for bacterial vaginosis (see diagnosis of vaginosis) as there is a strong correlation between bacterial vaginosis and PROM (grade A).

VI.2. Endocervical smear

In France there is no point in carrying out routine testing by endocervical smear for cervicitis caused by *C. trachomatis* and *N. gonorrhoeae* during PROM (low prevalence)

(grade B). However, this test is justified in women at risk of sexually transmitted diseases (Section I).

An endocervical smear which samples the amniotic fluid in the cervical cavity during PROM may aid diagnosis of colonisation or infection of the amniotic cavity, but its efficacy has not been determined. In this indication, it should be performed after antisepsis of the exocervical area (rinsing with an antiseptic for more than 1 minute) to limit vaginal contamination and be interpretable.

VI.3. Amniocentesis

There are no microbiological reasons for recommending amniocentesis as a routine practice.

Direct examination is not very sensitive, but does detect high-risk major colonisation. Culture helps identify the colonising or infecting organisms (grade A). There are no absolute bacteriological criteria to differentiate between "normal" colonisation, "abnormal" contamination, and infection. The presence in the amniotic fluid of *L. monocytogenes*, *S. agalactiae*, *E. coli* and other enterobacteria, *S. aureus*, *S. pyogenes*, *H. influenzae*, pneumococci and meningococci is extremely serious (grade B), since it indicates a high risk of bacteraemia in the mother and newborn.

An increase in the level of interleukin-6 (IL-6) in the amniotic fluid, taken by amniocentesis or from the endocervix, appears to be a good early marker of inflammation (grade B). The real impact of these results on decision-making has not been determined.

VI.4. Blood culture

Blood culture is recommended (1 or 2 series) in all pregnant women with fever who undergo PROM (suspicion of chorioamnionitis). If positive, it indicates a complication of bacteraemia in the mother and is therefore a sign of serious disease for the mother and newborn (grade B).

VI.5. Serum determination of markers of inflammation

- Maternal hyperleucocytosis and elevated C-reactive protein are normally tested for in France in the initial battery of tests for PROM, then once or twice a week. They are low-performance, late markers of inflammation (grade B).
- Elevated serum concentration of IL-6 is earlier and more powerful in differentiating between infected and non-infected subjects. It correlates better than other markers available with the time to start of labour, development of chorioamnionitis and risk to the newborn (grade B). The fact that the cost of this test is still high limits its use and therefore its assessment in everyday practice.

VII. PROCEDURE IN THE EVENT OF INFECTION DURING PROM

VII.1. PROM after 37 weeks

In the event of PROM after 37 weeks, labour should be induced by oxytocin with or without prior cervical maturation using prostaglandins (grade A). In this case one observes an infection rate that is significantly reduced in the mother and that tends to be reduced in the

newborn, when compared with watchful waiting without antibiotics. This approach does not increase the Caesarean section rate (grade A).

In cases of unfavourable cervix, prostaglandins by the vaginal route reduce the Caesarean section rate compared with oxytocin induction, without increasing maternal or neonatal infection rates (grade A).

It is not recommended that antibiotics be given routinely in the event of rupture of the membranes at term except to women who are known carriers of pathogens. A routine vaginal sample for bacteriological tests is recommended to help the paediatrician decide on management.

VII.2. PROM between 34 and 37 weeks

Experts recommend that a vaginal sample be taken at the start of labour, followed either by induction of labour or by watchful waiting with antibiotic cover. At present there is no evidence to suggest that either of these two strategies is better than the other. The choice should be made according to the situation and the stage of pregnancy when the membranes rupture.

VII.3. PROM before 34 SA

In the event of PROM before 34 weeks, antibiotic therapy should be prescribed routinely to reduce morbidity from infection in the newborn, prolong pregnancy, and reduce the incidence of intraventricular haemorrhage and of chorioamnionitis (grade A). In addition, such therapy tends to reduce perinatal mortality and the incidence of endometritis.

Amoxicillin should be used as first choice drug (grade A). The addition of a beta-lactamase inhibitor does not reduce infection rate and increases the incidence of necrotising enterocolitis (grade A).

In the event of allergy to penicillin, a cephalosporin appears to be preferable to a macrolide. There is no point in prolonging antibiotic therapy if cultures are negative and if there are no clinical signs of maternal or foetal infection.

In the event of PROM before 34 weeks, antibiotics should be combined with corticosteroids which reduce the level of respiratory distress syndrome and perinatal mortality (grade A). Corticosteroid therapy does not increase the incidence of neonatal infection or chorioamnionitis, but could increase the incidence of endometritis.

Although its efficacy has not been demonstrated, tocolysis appears to be justified for a short time in the event of PROM before 34 weeks, long enough to allow for corticosteroid therapy.

In the event of cerclage of the cervix, the stitch or tape should be removed and tested for bacteria when rupture of the membranes occurs.