European Journal of Obstetrics & Gynecology and Reproductive Biology 210 (2017) 217–224

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Review article

Prevention of spontaneous preterm birth: Guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF)

Loïc Sentilhes[a,*], Marie-Victoire Sénat[b], Pierre-Yves Ancel[c], Elie Azria[d], Guillaume Benoist[e], Julie Blanc[f], Gilles Brabant[g], Florence Bretelle[f], Stéphanie Brun[a], Muriel Doret[h], Chantal Ducroux-Schouwey[i], Anne Evrard[i], Gilles Kayem[j], Emeline Maisonneuve[k], Louis Marcellin[l], Stéphane Marret[m], Nicolas Mottet[n], Sabine Paysant[o], Didier Riethmuller[n], Patrick Rozenberg[p], Thomas Schmitz[q], Héloïse Torchin[c], Bruno Langer[r]

[a] *Service de Gynécologie-Obstétrique, CHU Bordeaux, Université de Bordeaux, France*
[b] *Service de Gynécologie-Obstétrique, Hôpital Bicêtre, AP-HP, Le Kremlin-Bicêtre, France*
[c] *Equipe de Recherche en Epidémiologie Obstétricale, Périnatale et Pédiatrique, Centre de Recherche Epidémiologie et Statistique Sorbonne Paris Cité, Inserm U1153, Bâtiment Port-Royal, 53 avenue de l'Observatoire, 75014 Paris, Université Paris Descartes, France*
[d] *Maternité Notre Dame de Bon Secours, Groupe Hospitalier Paris Saint Joseph, DHU Risque et Grossesse, Université Paris Descartes, Paris, France*
[e] *Service de gynécologie obstétrique et médecine de la reproduction, CHU de Caen, Caen, France*
[f] *AP-HM, Hôpital Nord, Service de Gynécologie-Obstétrique, Gynépôle, Aix-Marseille Université Marseille, France*
[g] *Hôpital Saint Vincent de Paul, GHICL, FLMM, Lille, France*
[h] *Hospices Civils de Lyon, Hôpital Femme Mère Enfant, Service de Gynécologie Obstétrique, 59 Boulevard Pinel, 69677 Bron Cedex, France*
[i] *Collectif interassociatif autour de la naissance (CIANE), France*
[j] *Service de Gynécologie-Obstétrique, Hôpital Trousseau, APHP, Paris, France*
[k] *Service de Médecine fœtale, Hôpital Trousseau, APHP, Paris, France*
[l] *Université Paris Descartes, Sorbonne Paris Cité, Faculté de Médecine, Assistance Publique–Hôpitaux de Paris (AP–HP), Hôpital Universitaire Paris Centre, Centre Hospitalier Universitaire (CHU) Cochin, Paris, France*
[m] *Service de Pédiatrie néonatale et Réanimation, Neuropédiatrie, Centre de Référence des Troubles des Apprentissages de l'Enfant, CAMSP, Hôpital Charles Nicolle, CHU de Rouen, France*
[n] *Service de Gynécologie-Obstétrique, CHU Hôpital Jean Minjoz, 25030 Besançon Cedex, France*
[o] *Collège National des Sages-Femmes de France, France*
[p] *Département d'Obstétrique et Gynécologie, Hôpital Poissy-Saint Germain, Université Versailles, St Quentin, France*
[q] *AP-HP, Hôpital Robert Debré, Service de Gynécologie Obstétrique, Université Paris Diderot, Paris, France*
[r] *Pôle de Gynécologie-Obstétrique, Hôpital de Hautepierre, Avenue Molière, 67098 Strasbourg, Université de Strasbourg, France*

ARTICLE INFO

Article history:
Received 5 November 2016
Accepted 29 December 2016

Keywords:
Preterm birth without preterm premature rupture of membranes
Progesterone
Cerclage
Cervical pessary
Ultrasound cervical length
Fetal fibronectin
Tocolysis
Corticosteroid
Magnesium sulfate

ABSTRACT

In France, 60,000 neonates are born preterm every year (7.4%), half of them after the spontaneous onset of labor. Among preventable risk factors of spontaneous prematurity, only cessation of smoking is associated with decreased prematurity (level of evidence [LE]1). It is therefore recommended (Grade A).

Routine screening and treatment of vaginal bacteriosis is not recommended in the general population (Grade A). The only population for which vaginal progesterone is recommended is that comprising asymptomatic women with singleton pregnancies, no history of preterm delivery, and a short cervix at 16–24 weeks of gestation (Grade B). A history-indicated cerclage is not recommended for women with only a history of conization (Grade C), uterine malformation (professional consensus), isolated history of preterm delivery (Grade B), or twin pregnancies for primary (Grade B) or secondary (Grade C) prevention of preterm birth. A history-indicated cerclage is recommended for a singleton pregnancy with a history of at least 3 late miscarriages or preterm deliveries (Grade A). Ultrasound cervical length screening is recommended between 16 and 22 weeks for women with a singleton previously delivered before 34 weeks gestation, so that cerclage can be offered if cervical length <25 mm before 24 weeks (Grade C). A

* Corresponding author at: Service de Gynécologie–Obstétrique, Centre Hospitalier Universitaire de Bordeaux, Place Amélie Raba-Léon, 33000 Bordeaux, France.
E-mail address: loicsentilhes@hotmail.com (L. Sentilhes).

http://dx.doi.org/10.1016/j.ejogrb.2016.12.035
0301-2115/

cervical pessary is not recommended for the prevention of preterm birth in a general population of asymptomatic women with twin pregnancies (Grade A) or in populations of asymptomatic women with a short cervix (professional consensus). Although the implementation of universal screening by transvaginal ultrasound for cervical length at 18–24 weeks of gestation in women with a singleton gestation and no history of preterm birth can be considered by individual practitioners, this screening cannot be universally recommended. In cases of preterm labor, (i) it is not possible to recommend any one of the several methods (ultrasound of the cervical length, vaginal examination, or fetal fibronectin assay) over any other to predict preterm birth (Grade B); (ii) routine antibiotic therapy is not recommended (Grade A); (iii) prolonged hospitalization (Grade B) and bed rest (Grade C) are not recommended.

Compared with placebo, tocolytics are not associated with a reduction in neonatal mortality or morbidity (LE2) and maternal severe adverse effects may occur with all tocolytics (LE4). Atosiban and nifedipine (Grade B), unlike beta-agonists (Grade C), can be used for tocolysis in spontaneous preterm labor without preterm premature rupture of membranes. Maintenance tocolysis is not recommended (Grade B). Antenatal corticosteroid administration is recommended for all women at risk of preterm delivery before 34 weeks of gestation (Grade A). After 34 weeks, the evidence is insufficiently consistent to justify recommending systematic antenatal corticosteroid treatment (Grade B), but a course of this treatment might be indicated in clinical situations associated with high risk of severe respiratory distress syndrome, mainly in case of planned cesarean delivery (Grade C). Repeated courses of antenatal corticosteroids are not recommended (Grade A). Rescue courses are not recommended (Professional consensus). Magnesium sulfate administration is recommended for women at high risk of imminent preterm birth before 32 weeks (Grade A).

Cesareans are not recommended for fetuses in vertex presentation (professional consensus). Both planned vaginal and elective cesarean delivery are possible for breech presentations (professional consensus). Delayed cord clamping may be considered if the neonatal or maternal state allows (professional consensus).

Contents

Introduction

The sponsor (the French College of Gynecologists and Obstetricians, CNGOF) appointed a steering committee (Appendix A) to define the exact questions to be put to the experts, to choose them, follow their work, and draft the synthesis of recommendations resulting from their work [1]. The experts analyzed the scientific literature on the subject to answer the questions raised. A literature review identified the relevant articles through mid-2016 by searching the MEDLINE database and the Cochrane Library. The search was restricted to articles published in English and French [2,3]. Priority was given to articles reporting results of original research, although review articles and commentaries were also consulted. Guidelines published by organizations or institutions such as the American College of Obstetricians and Gynecologists (ACOG), the Royal College of Obstetricians and Gynaecologists (RCOG), the Canadian Society of Gynecology and Obstetrics (SOGC), the National Institute for Health and Clinical Excellence (NICE) as well as previous guidelines published by the CNGOF were reviewed, and additional studies were located by reviewing bibliographies of identified articles. For each question, each overview of validated scientific data was assigned a level of evidence based on the quality of its data, in accordance with the framework defined by the HAS (French Health Authority) [3], summarized below.

Quality of evidence assessment

LE1: very powerful randomized comparative trials, meta-analysis of randomized comparative trials;

LE2: not very powerful randomized trial, well-run non-randomized comparative studies, cohort studies;

LE3: case-control studies;

LE4: non-randomized comparative studies with large biases, retrospective studies, cross-sectional studies, and case series.

A synthesis of recommendations was drafted by the organizing committee based on the replies given by the expert authors. Each recommendation for practice was allocated a grade, defined by the HAS as follows:

Classification of recommendations

Grade A: Recommendations are based on good and consistent scientific evidence

Grade B: Recommendations are based on limited or inconsistent scientific evidence

Grade C: Recommendations are based primarily on consensus and expert opinion

Professional consensus: In the absence of any conclusive scientific evidence, some practices have nevertheless been recommended on the basis of agreement between the members of the working group (professional consensus).

All texts were reviewed by persons not involved in the work, i.e., practitioners in the various specialties concerned, working in various situations (public, private, university or non-university establishments) (Appendix A). Once the review was completed, changes were made, if appropriate, considering the assessment of the quality of the evidence.

The original long texts in French are cited [4–17], but their individual references are not included here in view of the enormous space they would occupy in this article intended to summarize the guidelines.

Epidemiology and risk factors of preterm birth [4]

Worldwide, around 15 million children were born before 37 weeks of gestation in 2010, that is, around 11% of live births. Around 85% of the children born before 37 weeks of gestation can be considered to be moderately or late preterm births (32–36 weeks), 10% very preterm (28–31 weeks), and 5% extremely preterm (<28 weeks). In France, 60,000 (7.4%) children each year are born before 37 weeks, including 12,000 before 32 weeks; half of these births are due to spontaneous preterm delivery (spontaneous preterm labor or premature rupture of the membranes) and half to induced preterm birth. Numerous factors that can be identified during the periconceptional period are associated with the risk of preterm delivery. Most are maternal factors (social and demographic, obstetric, psychological, and genetic), but some are paternal or environmental. Gestational age at birth strongly affects mortality, severe neonatal morbidity, and child development. Diseases of pregnancy and the context of birth also play a role in determining the child's outcome into adulthood.

Lifestyle recommendations for prevention of spontaneous preterm birth in asymptomatic pregnant women [5]

Among working mothers, the risk of preterm delivery rises slightly in those who work more than 40 h a week or have physically strenuous working conditions, measured by a score that assesses arduousness at work (LE3). With a workweek of 35 h, sick leave before maternity leave is not routinely recommended (Grade B).

Regular sports and exercise during pregnancy do not increase the risk of delivery before 37 weeks (LE2) and are recommended for women with normal pregnancies (Grade A). Sexual relations during pregnancy do not increase the risk of preterm delivery (LE2), even in women with a history of preterm delivery (LE3).

A diet rich in fruit, vegetables, and whole grains may be associated with a reduced risk of spontaneous preterm delivery (LE3), but vitamin D and omega-3 supplements have no effect on term of delivery (LE1). It is thus recommended to advise women to eat a diet rich in fruit, vegetables, and whole grains (Grade C).

Smoking is associated with an increase in spontaneous preterm delivery (LE2). Although smoking cessation interventions result in effective cessation during pregnancy in only 6% of cases, they are associated with a 14% reduction in preterm delivery (LE1). Nicotine substitutes alone, such as patches, have no effect on either smoking cessation or preterm delivery (LE1). Smoking cessation is therefore recommended for pregnant women at any stage of pregnancy (Grade A).

Psychological disorders such as depression, anxiety, and maternal stress are significantly associated with overall preterm delivery (LE1). Screening for depression during pregnancy, whether or not followed by cognitive-behavioral therapy, is associated with a diminution of depression (LE1), but data about its effect on the reduction of preterm delivery are unavailable.

Although the treatment of periodontal disease does not reduce the risk of preterm delivery (LE1), its treatment should not be delayed on account of pregnancy (Grade B).

An interval of less than 18 months between 2 pregnancies is associated with a risk of preterm delivery (LE3). It is advisable to inform women of the risks inherent in closely spaced pregnancies (professional consensus). These risks must nonetheless be discussed according to maternal age, because of the increase in obstetric complications and decrease in fertility above the age of 35 years and in light of the number of children desired (professional consensus).

In asymptomatic women with a shortened cervix, bed rest is not associated with a reduction in preterm deliveries (LE3) and is therefore not routinely recommended (Grade C). Preventive hospitalization with bed rest is not recommended for women with asymptomatic multiple pregnancies, (Grade A), especially as bed rest during pregnancy is associated with a higher risk of thromboembolic complications (LE3).

Bacterial vaginosis and preterm birth [6]

Bacterial vaginosis is a dysbiosis expressed as an imbalance of the vaginal flora favoring the multiplication of anaerobic bacteria and the simultaneous disappearance of the lactobacilli considered to be protective. Its diagnosis is based on Amsel's clinical criteria and/or Gram staining with the determination of a Nugent score. Its prevalence varies according to ethnic and/or geographic origin (4–58%); in France it is close to 7% in the first trimester of pregnancy (LE2). The association between bacterial vaginosis and spontaneous preterm delivery is low, with odds ratios ranging from 1.5 to 2 in the most recent studies (LE3). Metronidazole and clindamycin are effective in treating this vaginosis (LE3). One of these antibiotics should be prescribed for pregnant women with symptomatic bacterial vaginosis (professional consensus).

In the general population, screening for bacterial vaginosis combined with treatment for the cases identified has not been shown to reduce the risk of spontaneous preterm delivery (LE2). Studies have found no benefits to screening for and treating bacterial vaginosis to prevent the risk of spontaneous preterm delivery in either the asymptomatic population at low risk (defined by the absence of a history of preterm delivery) (LE1) or in the population at high risk (defined by a history of preterm delivery) (LE3); accordingly this strategy is not recommended in either of these situations (respectively, Grade A and Grade C). Nonetheless, in the subpopulation of women with a history of preterm delivery and maternal-fetal bacterial infection, early and systematic screening and treatment of all lower genital infections, especially bacterial vaginosis, may be beneficial (professional consensus).

Tools for predicting preterm birth in asymptomatic high-risk pregnancies [7]

Careful questioning of the patient and consideration of her obstetric history, in particular her history of spontaneous preterm delivery, make it possible to identify a population at risk of preterm delivery of their current pregnancy (LE3). This risk is correlated with the number of previous preterm deliveries and is highest for the earliest events and those during the most recent pregnancy (LE3).

Data from the literature do not justify the recommendation of routine digital cervical examination at each prenatal visit in asymptomatic patients at high risk (multiple pregnancy, uterine malformation, history of preterm delivery, cervical treatment, at least two previous elective abortions) (professional consensus).

In an asymptomatic high-risk population, neither the regular recording of uterine activity nor home visits allow the prediction or reduction of the risk of preterm delivery (LE2); neither is recommended (Grade B).

Within this asymptomatic population at high risk, however, the detection of fetal fibronectin (LE3) and ultrasound measurement of cervical length (LE2) make it possible to estimate the risk of preterm delivery. The shorter the cervix at an early stage, the greater the risk of preterm delivery (LE3).

Nonetheless, routine fetal fibronectin assays in this population are not recommended (Grade C). Data in the literature are insufficient to justify recommending the routine or repeated measurement of cervical length by transvaginal ultrasound except in women with a history of preterm delivery (professional consensus). Repeated studies have failed to show that such measurements prevent preterm delivery or reduce neonatal morbidity or mortality.

Progestational agents for the prevention of spontaneous preterm birth [8]

17-hydroxyprogesterone caproate (17OHPC) is not recommended for the primary prevention of preterm delivery in a population of women with singleton pregnancies and no history of preterm delivery (Grade C). Although transvaginal ultrasound screening of women with a shortened cervix is not routinely recommended (professional consensus), the prescription of natural micronized progesterone administered vaginally daily for up to 36 weeks is recommended for asymptomatic women with a singleton pregnancy, no history of preterm delivery, and a cervical length less than 20 mm at 16–24 weeks (Grade B).

One trial has associated 17OHPC with a reduction in the risk of delivery before 34 weeks (LE2) and with a reduction in neonatal morbidity (LE3) in singleton pregnancies among women with a history of at least one delivery before 34 weeks. We cannot recommend the routine administration of 17OHPC to women with a history of preterm delivery to reduce their risk on the basis of this single randomized trial, especially in view of its limited external validity (professional consensus).

Vaginal progesterone for asymptomatic women with a history of preterm delivery does not appear to be associated with a reduced risk of delivery before 34 weeks (LE3), improved neonatal status (LE3), or a better cognitive score at age 2 (LE3). The vaginal administration of progesterone to reduce the risk of preterm delivery in women with a history of preterm delivery is not recommended (professional consensus).

Treatment with 17OHPC has not shown any benefits in women with a singleton pregnancy, a history of preterm delivery, and a cervical length less than 25 mm during the second trimester (LE2). Accordingly the use of 17OHPC in this situation is not recommended (Grade B). In the same population, vaginal progesterone might reduce the risk of preterm delivery, but further studies are needed before its use can be recommended (professional consensus).

Progesterone is not recommended as a tocolytic, either initially (professional consensus) or for maintenance (Grade A).

Progestational agents, whether administered vaginally or by injection as 17OHPC, are not associated with a reduced risk of preterm delivery, with neonatal risk (LE1) after preterm labor, with perinatal benefits, or with the prolongation of pregnancy for asymptomatic twin pregnancies with normal or unknown cervical length measurements (LE2). They are therefore not recommended in these two twin-pregnancy situations (respectively Grade A and Grade B).

Among women with twin pregnancies and a cervix less than 25 mm, the preventive administration of 17OHPC has shown no benefits for prolonging pregnancy or reducing perinatal risk (LE1). It is thus not recommended in this context (Grade A). Moreover, the daily administration of vaginal progesterone is not associated with a reduction in perinatal risk (LE3) and is also not recommended in this situation (Grade C).

Because no benefits from 17OHPC administration have been demonstrated for triplet pregnancies (LE2), its administration in this case is not recommended (Grade B).

Accordingly, the only population for which progestational treatment is recommended is asymptomatic pregnant women with singleton pregnancies and no history of preterm delivery who have a cervical length less than 20 mm between 16 and 24 weeks.

Prevention of preterm birth by cervical cerclage [9]

Cervical incompetence (insufficiency) is a pathophysiologic concept for which there is not currently any consensual definition: it is diagnosed clinically and suggested retrospectively for women with a history of late miscarriages or spontaneous preterm delivery with asymptomatic cervical dilation (professional consensus). The risk of preterm delivery is higher among women with a history of cervical conization with a bistoury compared with loop diathermy (LE3); laser vaporization has a negligible impact (LE3).

An investigation for a uterine malformation is recommended for women with a history of late miscarriage or preterm delivery (Grade C). No paraclinical examinations for cervical incompetence can be recommended (professional consensus). A cerclage because of obstetric history is not recommended solely due to a history of conization (Grade C), uterine malformation (professional consensus), isolated' previous preterm delivery (Grade B) or for twin pregnancies, for primary (Grade B) or secondary (Grade C) prevention.

Cerclage is recommended for women with a singleton pregnancy and a history of at least 3 late miscarriages or preterm deliveries (Grade A). Likewise, an ultrasound-indicated cerclage for women with a shortened cervix in the second trimester of a singleton pregnancy is not recommended for those with no relevant obstetric or gynecologic history (Grade B). For women with a history of late miscarriage or spontaneous preterm delivery before 34 weeks of a singleton pregnancy, ultrasound monitoring of cervical length between 16 and 22 weeks is recommended so that cerclage can be proposed if the cervix shortens to less than 25 mm before 24 weeks (Grade C). It is also recommended that ultrasound-indicated cerclage not be performed in women with a shortened cervix and a multiple pregnancy (Grade C).

An emergency cerclage according to McDonald's technique is recommended during the second trimester in cases of major clinical modifications of the cervix, with or without protrusion of the amniotic sac, in singleton pregnancies without preterm rupture of the membranes or chorioamnionitis (Grade C). Use of tocolysis and antibiotic therapy before and after the procedure

should be discussed on a case-by-case basis (professional consensus). There is no evidence to support recommending a delay for watchful waiting before considering emergency cerclage (professional consensus). No upper term limit can be recommended (professional consensus).

Cervicoisthmic cerclage can be considered should a McDonald cerclage fail (professional consensus). Laparoscopy is an acceptable alternative to laparotomy and a vaginal approach to cervicoisthmic cerclage appears to be the least invasive (professional consensus).

Insufficient scientific data exist to determine whether a vaginal sample should be recommended before cerclage (professional consensus). Use of a double cervical cerclage does not improve the perinatal prognosis of pregnancies with cerclage (LE3) and is not recommended (Grade C). There is not enough scientific evidence to recommend one type of thread over another (Grade C). The data in the literature do not show that the Shirodkar cerclage is superior for cerclage indicated either because of obstetric history or ultrasound findings. Because it is technically easier to perform and less risky, the McDonald cerclage is recommended as the first-line method (Grade C).

Complications of cerclage are rare but potentially serious. The complication rate does not differ for history-based or ultrasound-indicated cerclage (LE4). Measurement of the height of the cerclage after either type does not predict the onset of preterm delivery (LE3) and is not recommended (Grade C). The practice of a second cerclage if the cervix is subsequently modified is not recommended (professional consensus). There is no scientific evidence that bed rest or adjuvant treatment (indometacin or antibiotics) are beneficial at the moment of a cerclage indicated because of history or ultrasound findings (professional consensus).

Overall, the level of evidence of the data in the literature about cerclage is low.

Cervical pessary and spontaneous preterm birth [10]

At this point, the data about for the effectiveness of the pessary in preventing preterm delivery remain contradictory, in asymptomatic populations of women with singleton pregnancies and a cervical length $\leq$25 mm between 20 and 24 weeks + 6 days and of women carrying twins and at high risk of preterm delivery, defined by a shortened cervix. Other studies are necessary to determine whether its use should be recommended for these indications (professional consensus). A cervical pessary placed before 22 weeks does not reduce the risk of preterm delivery in the general population of asymptomatic women carrying twins (LE1). It is therefore not recommended in this population (Grade A).

Other randomized studies are needed to determine the best strategy (expectant, progesterone, pessary, or cerclage) for preventing preterm delivery (professional consensus).

Is universal screening for cervical length justified among singleton pregnancies with no history of preterm birth? [11]

Transvaginal ultrasound measurement of cervical length is useful for estimating the risk of spontaneous preterm delivery in the general population. The shorter the ultrasound-measured cervical length between 18 and 24 weeks, the greater the risk of spontaneous preterm delivery (LE1). When the cervical length is $\leq$15 mm at approximately 23 weeks, the risk of spontaneous preterm delivery $\leq$32 weeks is approximately 50%, and neonatal morbidity before then is substantial (LE2). Accordingly, transvaginal ultrasound measurement of cervical length with a threshold of 15 mm is currently the best method for identifying the group of asymptomatic women at risk of spontaneous preterm delivery in the general population, and especially among the asymptomatic women with a singleton pregnancy and no relevant history, that is, the population at low risk (Grade B).

Neither cerclage (LE2) nor 17OHPC (LE2) is effective in reducing the risk of preterm delivery among asymptomatic women with a shortened cervix on ultrasound during the second trimester of pregnancy. On the other hand, two large randomized trials have shown that vaginal progesterone is effective in reducing the risk of preterm delivery (LE1) and possibly the composite morbidity and perinatal mortality associated with it (LE2) among asymptomatic women with a shortened cervix in the general population, selected by second-trimester cervical ultrasound.

Three convergent medical economics analyses show that universal screening of cervical length followed by vaginal progesterone appears cost-effective compared with no screening (LE3).

Nonetheless, there remain several reasons that it is too early to conclude definitively that this universal screening is justified:

-A large number of women must be screened to prevent a relatively small number of preterm deliveries. Thus, while the number needed to treat (NNT) is low (7–13) (LE2), the number needed to screen is very high: from 400 to 588 (LE2). Moreover, the epidemiology of preterm delivery indicates that in the general population the use of progesterone among asymptomatic women with a shortened cervix screened by a cervical ultrasound during the second trimester does not notably reduce the prevalence of preterm deliveries (LE2).

-The available trials have assessed the effectiveness of progesterone among women with a shortened cervix identified by transvaginal ultrasound. No data compare the effectiveness of universal ultrasound screening followed by vaginal progesterone treatment in women with a shortened cervix to that of no universal screening, associated with progesterone treatment of a fortuitously discovered shortened cervix.

-Universal ultrasound screening cannot produce the same results in practice as those observed in the various published randomized trials, because of differences in populations, slippage in the eligibility criteria, or the “stretching” the threshold defining a shortened cervix. Moreover, the use of unevaluated or unrecommended treatments, such as bed rest, tocolytics, 17OHPC, or cerclage, can lead to unintended harmful consequences and reduce its cost-effectiveness ratio.

-The cost-effectiveness analyses assessing universal screening of cervical length involve uncertainties for critical variables including, especially, the prevalence of a shortened cervix and the effectiveness of progesterone. Supplementary data are necessary before the adoption of such a policy in France (professional consensus).

In conclusion, all the indicators discussed above must be taken into consideration before deciding on the appropriateness of modifying prenatal care for millions of women by instituting universal ultrasound screening of cervical length between 18 and 24 weeks for women with singleton pregnancies but no history of preterm delivery. Although the implementation of such a screening strategy might be considered by physicians individually, this screening cannot be universally mandated (professional consensus).

Prediction of preterm birth in case of preterm labor [12]

Threatened preterm delivery (TPD) is a clinical situation that occurs between 22 and 36 weeks + 6 days, in which cervical modifications and uterine contractions are observed, whether or not they evolve spontaneously toward preterm delivery (professional consensus). These uterine contractions can be detected by tocodynamometry and by the patient herself. Neither their frequency nor the existence of associated symptoms allow the

reliable prediction of preterm delivery (LE3). Cervical modifications can be assessed by the ultrasound measurement of cervical length and by a digital cervical examination (Bishop score). Cervical length is significantly correlated with the risk of spontaneous preterm delivery (LE1). The thresholds of 15 mm and 25 mm are the most relevant for, respectively, predicting and ruling out the risk of spontaneous preterm delivery at 48 h and at 7 days (professional consensus).

Among symptomatic patients, routine ultrasound measurement of cervical length at admission is not associated with a significant reduction in the preterm delivery rate (LE3). Clinical evaluation of the cervix (Bishop score) by digital cervical examination is also an effective indicator for predicting preterm delivery (LE2). The higher the Bishop score, the greater the risk of preterm delivery (LE3). It is not possible to recommend the use of one tool rather than another (cervical ultrasound or digital cervical examination) in TPD (Grade B). Nonetheless, because of the excellent negative predictive value of ultrasound cervical measurement and its lower interobserver variability, it is useful to measure cervical length by ultrasound before deciding to transfer the mother to a more specialized hospital (known in France as in utero transfer) for TPD (professional consensus).

Fetal fibronectin assays in women with TPD also have an excellent negative predictive value for predicting the absence of preterm delivery within 48 h and 7 days (LP2). Nonetheless, because the detection of fetal fibronectin in women with TPD does not allow the clinician to define a strategy to reduce the spontaneous preterm delivery rate (LE2), it is therefore not recommended (professional consensus).

Management of preterm labor [13]

Both hyperleukocytosis, identified by a complete blood count, and a high level of C reactive protein (CRP), are associated with similar risks of preterm delivery and maternal-fetal infection (LE3), but their routine joint prescription in cases of TPD (professional consensus) is not recommended in view of their low sensitivity for predicting these events. In view of the additional information provided by a complete blood count, this test is recommended at admission for TPD to screen for inflammatory syndrome (professional consensus).

Antibiotics should not be routinely administered to women with TPD and intact membranes (Grade A). Nonetheless, urinalysis to screen for urinary infections must be routine and antibiotic treatment for a period of 4–7 days is necessary for women with bacterial colonization or urinary infection (Grade A). A vaginal sample is useful to screen for streptococcus B; if positive, antibiotic treatment should be prescribed during labor (Grade A). Cardiotocography (ECTG) and fetal ultrasound are recommended when the mother is admitted for TPD (professional consensus). There are no available data about the utility of repeating ECTG in cases of hospitalization and no evidence to support repeating it in the absence of a clinical indication (professional consensus). Repeating a cervical ultrasound within the first 48 h after admission in the absence of an intercurrent event is not recommended (Grade C). Prolonged hospitalization does not reduce the risk of preterm delivery (LE3) and is not recommended (grade B). Strict bed rest does not reduce the risk of preterm delivery (LE3) but does increase the thromboembolic risk (LE3); it is therefore not recommended (Grade C). There is no published literature about the methods of and indications for transfer between maternity units and therefore no evidence base for recommendations. Hospitals must reach agreements that take local specificities and perinatal network policies into account (professional consensus).

After hospitalization for TPD, regular home visits by a healthcare provider can be useful for women in precarious social or economic situations or psychologically vulnerable (professional consensus). No benefits have been shown from repeated external tocography after hospitalization for TPD (LE3). Accordingly, it is not routinely recommended for home surveillance after TPD (Grade C).

Tocolysis for preterm labor without premature preterm rupture of membranes [14]

No placebo-controlled studies have found tocolytic agents to be associated with a reduction in neonatal mortality and morbidity (LE2). Compared with beta-agonists, nifedipine is associated with a significant reduction in the risks of necrotizing enterocolitis, intraventricular hemorrhage, and acute respiratory distress syndrome (LE2). Neonatal prognosis does not differ between nifedipine and atosiban, except that nifedipine is associated with a modest reduction in transfers to neonatology (LE2). Beta-agonists, atosiban, and nifedipine show equivalent effectiveness in prolonging pregnancy beyond 48 h (LE2). Compared with beta-agonists, nifedipine reduces the rate of deliveries before 34 weeks (LE2) and is associated with a greater prolongation of pregnancy (LE2). Atosiban is equivalent to nifedipine for prolonging pregnancy more than 7 days (LE2), but, in the case of TPD without premature rupture of the membranes, nifedipine reduces the risk of delivery before 37 weeks and is associated with a greater prolongation of pregnancy, although without any demonstrated neonatal benefits (LE2).

All these tocolytics can induce serious adverse effects (LE4). The adverse maternal cardiopulmonary effects described with beta-agonists frequently cause treatment to be interrupted (LE2) and are sometimes serious (maternal death) (LE4).

Maternal tolerance is better for atosiban and nifedipine than for beta-agonists (LE2). Adverse cardiovascular effects occur moderately more often with nifedipine than with atosiban (LE2), but their treatment interruption rates are similar (LE2).

In view of their benefits for prolonging pregnancy and good maternal tolerance, atosiban and nifedipine can be used for tocolysis for both singleton (Grade B) and multiple (professional consensus) pregnancies. Nifedipine's advantages include its oral administration and low cost (professional consensus). It is recommended that nicardipine not be used (professional consensus) and that beta-agonists no longer be prescribed for tocolysis (Grade C). Maintenance treatment after the conclusion of 48 h of initial tocolysis is no longer recommended (Grade A).

If the first-line tocolytic agent fails, one of the substances not recommended as first-line treatment can be tried (professional consensus). Combining tocolytic agents is not recommended (Grade C). In the absence of scientific data, no recommendation can be made about the relevance of a second tocolysis at some time after the first in a woman whose symptoms have recurred and who has completed a corticosteroid treatment (professional consensus). There is no evidence for recommending tocolysis at an advanced dilatation (Grade C) nor for prescribing tocolysis after 34 weeks (professional consensus). There are no data that make it possible to define a gestational age after which tocolysis can be performed (professional consensus).

Prevention of preterm birth complications by antenatal corticosteroid administration [15]

Administration of a single course of prenatal corticosteroid treatment before 34 weeks is associated with a significant reduction during the neonatal period of hyaline membrane disease, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and death (LE1), and possibly with a long-term reduction in cerebral palsy and an increase in psychomotor development scores and in survival without sequelae (LE3). The

administration of a course of antenatal corticosteroids after 34 weeks is associated, albeit with a high "number needed to treat", with a reduction in severe respiratory distress (LE2) but not in digestive (LE2) or neurological (LE2) morbidity. Nonetheless, this treatment is associated with modifications in response to the hypothalomo-pituitary gland-adrenal axis persisting for the first 8 weeks of life (LE2) and possibly with increased insulin resistance in adulthood (LE3). Because of the very favorable benefit-to-risk ratio, antenatal administration of a course of corticosteroids is recommended for all women at risk of preterm delivery before 34 weeks (Grade A). The gestational age from which this treatment begins depends on the thresholds chosen for active care in the NICUs in maternity units and perinatal networks (professional consensus). There is not sufficient evidence to recommend the routine administration of prenatal corticosteroids after 34 weeks (Grade B), but treatment can nonetheless be discussed in situations at high risk of severe respiratory distress, in particular for planned cesareans (Grade C). It is recommended that a second betamethasone injection not be performed early when delivery appears imminent (grade C), because this practice may be associated with an increase in the rate of NEC (LE3).

In the neonatal period, the only benefits of repeated treatment with antenatal corticosteroids are respiratory (LE1); because this treatment is also associated with a dose-dependent reduction in birth weight (LE1) and, in the long term, with potentially harmful neurological effects (LE2), the repetition of this treatment is not recommended (Grade A). The benefits associated with rescue treatment concern only the neonatal period and are only respiratory (LE2). In view of both the possible harmful effect associated with this strategy when birth takes place in the 24 h after the first injection (LE2) and the fears raised by the repetition of treatment, this rescue treatment cannot be recommended (professional consensus).

The data from the literature do not allow us to recommend either betamethasone or dexamethasone as the preferable corticosteroid (professional consensus). The team must be aware of the modifications of the fetal heart rate and active fetal movements that are induced by prenatal corticosteroids in women at risk of preterm delivery to prevent any unjustified decisions of induced delivery (professional consensus). Neither gestational nor prepregnancy diabetes is a contraindication to the administration of an antenatal course of corticosteroids (professional consensus). Nonetheless, its use must be carefully weighed in women with poorly controlled type 1 diabetes (professional consensus). The fear of inducing maternal or fetal infection must not delay the administration of prenatal corticosteroids (Grade A).

Neuroprotection for preterm infants with antenatal magnesium sulfate [16]

Antenatal administration of intravenous magnesium sulfate ($MgSO_4$) before 32 weeks reduces cerebral palsy and motor development disorders in children born preterm (LE1). These benefits are independent of gestational age, number of fetuses, and cause of the preterm delivery (LE2). Its administration is therefore recommended in both singleton and multiple pregnancies, regardless of the cause of preterm delivery in cases of imminent delivery, spontaneous or scheduled, before 32 weeks (Grade A) (LP2). The doses proposed in randomized trials of neuroprotection have no severe maternal side effects and no short- or intermediate-term adverse effects in the newborn (LE1). The moderate maternal side effects (flushes and tachycardia) are not eliminated by administration of a loading dose for a period longer than 60 min compared with the standard 20 min (LE1). The antenatal administration of $MgSO_4$ for neuroprotection was not associated with either harmful effects or significant benefits at school age (LE4). Administration is recommended by a loading dose of 4 g (professional consensus) followed by maintenance doses of 1 g/h until delivery for a maximum period of 12 h (professional consensus).

Mode of delivery in spontaneous preterm births [17]

No study justifies the affirmation that cesarean delivery improves neonatal prognosis during spontaneous preterm labor for infants in cephalic presentation. Moreover, cesarean delivery appears to be associated with worse maternal morbidity than is vaginal delivery (LE4). Accordingly, routine cesarean for preterm delivery alone is not recommended in spontaneous preterm labor (professional consensus). The current data do not allow us to recommend one type of delivery rather than another for preterm delivery of children in breech presentation (professional consensus). Continuous monitoring of fetal heart rate is recommended during preterm labor (professional consensus). The available data are insufficient to justify suggesting the use of pH or scalp lactates before 34 weeks as a means of second-line monitoring (professional consensus).

Routine instrumental delivery is not recommended for very preterm births (professional consensus). The choice of instrument depends on the operator's experience. Vacuum extraction is possible when bone formation is judged satisfactory, most often after 34 weeks (professional consensus). No study has analyzed routine episiotomy for preterm delivery alone. Similarly, a routine episiotomy is not recommended for the delivery of preterm newborns (professional consensus). If neonatal or maternal condition so permit, delayed clamping can be envisioned (professional consensus). The data available in the literature are insufficient to justify its routine recommendation during the birth of preterm children (professional consensus).

Conflicts of interest

LS was a board member and carried out consultancy work and lectured for Ferring. The other authors had no conflicts of interest

Appendix A.

A.1 Steering committee

B. Langer, president (gynaecologist/obstetrician, CHU, Strasbourg, France), L. Sentilhes, co-coordinator and methodologist (gynaecologist/obstetrician, CHU, Bordeaux, France), MV. Senat, co-coordinator and methodologist (gynaecologist/obstetrician, CHU, Le Kremlin-Bicêtre, France), S. Paysant (midwife, Collège National des Sages-Femmes de France), C. Ducroux-Schouwey (Collectif interassociatif autour de la naissance), A. Evrard (Collectif interassociatif autour de la naissance)

A.2 Working group

PY. Ancel (health public researcher, Inserm, France), E. Azria (gynaecologist/obstetrician, ESPIC, Paris, France), G. Benoist (gynaecologist/obstetrician, CHU, Caen, France), J. Blanc (gynaecologist/obstetrician, CHU, Marseille, France), G. Brabant (gynaecologist/obstetrician, ESPIC, Lille, France), F. Bretelle (gynaecologist/obstetrician, CHU, Marseille, France), S. Brun (gynaecologist/obstetrician, CHU Bordeaux, France), M. Doret (gynaecologist/obstetrician, CHU, Lyon), G. Kayem (gynaecologist/obstetrician, CHU, Paris, France), E. Maisonneuve (gynaecologist/obstetrician, CHU, Paris, France), L. Marcellin (gynaecologist/obstetrician, CHU, Paris, France), S. Marret (pediatrician, CHU,

Rouen, France), N. Mottet (gynaecologist/obstetrician, CHU, Besançon, France), D. Riethmuller (gynaecologist/obstetrician, CHU, Besançon, France), P. Rozenberg (gynaecologist/obstetrician, CHI, Poissy, France), T. Schmitz (gynaecologist/obstetrician, CHU, Paris, France), H. Torchin (pediatrician, Inserm, France)

A.3 Peer reviewers

A. Benachi (gynaecologist/obstetrician, CHU, Clamart, France), G. Beucher (gynaecologist/obstetrician, CHU, Caen, France), M. Bornes (gynaecologist/obstetrician, CHU, Paris, France), A. Bourtembourg (gynaecologist/obstetrician, CHU, Besançon, France), C. Brochet (midwife, CHU, Paris, France), G. Carles (gynaecologist/obstetrician, CHU, Saint-Laurent-du-Maroni, France), C. Chauleur (gynaecologist/obstetrician, CHU, Saint-Étienne, France), MT. Chevé (gynaecologist/obstetrician, CH, Le Mans, France), A. Chirol (gynaecologist/obstetrician, CH, Le Mans, France), O. Claris (pediatrician, CHU, Lyon, France), E. Clouqueur (gynaecologist/obstetrician, CHRU, Lille, France), F. Coatleven (gynaecologist/obstetrician, CHU, Bordeaux, France), C.d'Ercole (gynécologue-obstétricien, CHU, Marseille, France), T. Debillon (pediatrician, CHU, Grenoble, France), X. Deffieux (gynaecologist/obstetrician, CHU, Clamart, France), P. Deruelle (gynaecologist/obstetrician, CHRU, Lille, France), G. Ducarme (gynaecologist/obstetrician, CH, La Roche-sur-Yon, France), C. Dupont (midwife, CHU, Lyon, France), H. Fernandez (gynaecologist/obstetrician, CHU, Le Kremlin-Bicêtre, France), F. Foix-L'Helias (pediatrician, CHU, Paris, France), N. Fortineau (biologist, CHU, Le Kremlin-Bicêtre, France), F. Fuchs (gynaecologist/obstetrician, CHU, Montpellier, France), R. Gabriel (gynaecologist/obstetrician, CHU, Reims, France), D. Gallot (gynaecologist/obstetrician, CHU, Clermont-Ferrand, France), A. Gaudineau (gynaecologist/obstetrician, CHU, Strasbourg, France), C. Geron (gynaecologist/obstetrician, CH, Cambrai, France), F. Goffinet (gynaecologist/obstetrician, CHU, Paris, France), G. Grangé (gynaecologist/obstetrician, CHU, Paris, France), M. Groussoles (gynaecologist/obstetrician, CHU, Toulouse, France), JB. Haumonté (gynaecologist/obstetrician, ESPIC, Marseille, France), P. Hoffmann (gynaecologist/obstetrician, CHU, Grenoble, France), C. Huissoud (gynaecologist/obstetrician, CHU, Lyon, France), R. Kutnahorsky (gynaecologist/obstetrician, CH, Colmar, France), C. Le Ray (gynaecologist/obstetrician, CHU, Paris, France), J. Lepercq (gynaecologist/obstetrician, CHU, Paris, France), E. Lorthe (midwife, Inserm, Paris, France), H. Madar (gynaecologist/obstetrician, CHU, Bordeaux, France), M.Massoud (gynaecologist/obstetrician, CHU, Lyon, France), D. Mitanchez (pediatrician, CHU, Paris, France), E. Moxhon (gynaecologist/obstetrician, CH, Le Cateau, France), I. Nisand (gynaecologist/obstetrician, CHU, Strasbourg, France), O. Parant (gynaecologist/obstetrician, CHU, Toulouse, France), F. Perrotin (gynaecologist/obstetrician, CHRU, Tours, France), O. Picone (gynaecologist/obstetrician, CHU, Colombes, France), E. Quarello (gynaecologist/obstetrician, ESPIC, Marseille, France), T. Quibel (gynaecologist/obstetrician, CHI, Poissy, France), L. Renesme (pediatrician, CHU, Bordeaux, France), A. Ricbourg (gynaecologist/obstetrician, CH, Neuilly-sur-Seine, France), A. Rousseau (midwife, Université de Versailles St-Quentin-en-Yvelines (UVSQ), Montigny-le-Bretonneux, France), RC. Rudigoz (gynaecologist/obstetrician, CHU, Lyon, France), E. Saliba (pediatrician, CHRU, Tours, France), F. Sergent (gynaecologist/obstetrician, CHU, Amiens, France), O. Sibony (gynaecologist/obstetrician, CHU, Paris, France), E. Simon (gynaecologist/obstetrician, CHRU, Tours, France), D. Subtil (gynaecologist/obstetrician, CHU, Lille, France), C. Thuillier (gynaecologist/obstetrician, CHI, Poissy, France), B. Tosello (pediatrician, CHU, Marseille, France), C. Vayssière (gynaecologist/obstetrician, CHU, Toulouse, France), F. Venditelli (gynaecologist/obstetrician, CHU, Clermont-Ferrand, France), E. Verspyck (gynaecologist/obstetrician, CHU, Rouen, France), N. Winer (gynaecologist/obstetrician, CHU, Nantes, France), V. Zupan Simunek (pediatrician, CHU, Clamart, France).

References

[1] Langer B, Senat MV, Sentilhes L. Guidelines for clinical practice: prevention of spontaneous preterm birth (excluding preterm premature rupture of membranes). Introduction. J Gynecol Obstet Biol Reprod 2016;45:1208–9.

[2] Sentilhes L, Langer B, Senat MV. Prevention of spontaneous preterm birth (excluding preterm premature rupture of membranes): guidelines for clinical practice – method and organization. J Gynecol Obstet Biol Reprod 2016; 45:1210–2.

[3] HAS. Les recommandations pour la pratique clinique. Base méthodologique pour la réalisation en France. Available: http://www.has-sante.fr/portail/jcms/c_431294/les-recommandations-pour-la-pratique-clinique-base-methodologique-pour-leur-realisation-en-france.

[4] Torchin H, Ancel PY. Epidemiology and risk factors of preterm birth. J Gynecol Obstet Biol Reprod 2016;45:1213–30.

[5] Maisonneuve E. Lifestyle recommendations for prevention of spontaneous preterm birth in asymptomatic pregnant women. J Gynecol Obstet Biol Reprod 2016;45:1231–46.

[6] Brabant G. Bacterial vaginosis and preterm birth. J Gynecol Obstet Biol Reprod 2016;45:1247–60 in press.

[7] Blanc J, Bretelle F. Predictive tools of preterm birth in asymptomatic high risk pregnancy. J Gynecol Obstet Biol Reprod 2016;45:1261–79 in press.

[8] Azria E. Progestatives for the prevention of spontaneous preterm birth. J Gynecol Obstet Biol Reprod 2016;45:1280–98 in press.

[9] Marcellin L. Prevention of preterm birth by cervical cerclage. J Gynecol Obstet Biol Reprod 2016;45:1299–323 in press.

[10] Brun S. Cervical pessary and spontaneous preterm birth. J Gynecol Obstet Biol Reprod 2016;45:1324–36 in press.

[11] Rozenberg P. Is universal screening for cervical length among singleton pregnancies with no history of preterm birth justified? J Gynecol Obstet Biol Reprod 2016;45:1037–44 in press.

[12] Benoist G. Prediction of preterm birth in case of preterm labor. J Gynecol Obstet Biol Reprod 2016;45:1045–363 in press.

[13] Kayem G, Doret M. Management of preterm labor. J Gynecol Obstet Biol Reprod 2016;45:1364–73 in press.

[14] Doret M, Kayem G. Tocolysis for preterm labor without premature preterm rupture of membranes. J Gynecol Obstet Biol Reprod 2016;45:1374–98.

[15] Schmitz T. Prevention of preterm birth complications by antenatal corticosteroid administration. J Gynecol Obstet Biol Reprod 2016;45:1399–417 in press.

[16] Marret S, Ancel PY. Neuroprotection for preterm infants with antenatal magnesium sulphate. J Gynecol Obstet Biol Reprod 2016;45:1418–33 in press.

[17] Mottet N, Riethmuller D. Mode of delivery in spontaneous preterm birth. J Gynecol Obstet Biol Reprod 2016;45:1434–45 in press.