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Differences in clinical practice regarding screening and treatment of infections associated with spontaneous preterm birth: An international survey

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ABSTRACT

Objective: An association between infections in pregnancy and increased risk of preterm birth (PTB) is described in the literature. We anticipated that differences may exist in screening and treatment approaches for infections associated with PTB, within and between European countries. The aim of this study was to examine and analyse these differences in clinical practice in greater detail.

Study Design: We created a descriptive survey examining the screening and treatment of infections in pregnancy. The survey was sent to European representatives of the International Spontaneous Preterm Birth Young Investigators (I-SPY) group in Europe, who sent it to their network. Finally, we had 50 respondents from ten European countries.

Results: We found substantial differences in screening for bacterial vaginosis and asymptomatic bacteriuria, administration of antibiotics to women with preterm prelabour rupture of membranes (PPROM), and timing of induction of labour after PPROM. These differences in clinical practice were present both within, and between countries.

Conclusions: Approaches for screening and treatment of infections associated with PTB differ between European countries. There is a lack of robust evidence, which is reflected in a lack of uniformity in international guidelines. International collaboration is paramount to enlarge sample sizes in obstetric studies and to facilitate the process of developing, updating, and implementing consistent guidelines across Europe and beyond.

Introduction

Preterm birth (PTB) causes the death of 1.1 million neonates worldwide each year [1] and long-term neurological and developmental disabilities in infants.[2] PTB is a syndrome, resulting from different etiological pathways, such as overdistention of the uterus, infections and cervical insufficiency.[3]

Previous studies have demonstrated an association between PTB and infections, such as urinary tract infections and bacterial vaginosis (BV).[4–6] It has been suggested that infections may trigger an inflammatory response, thereby producing prostaglandins, which promote uterine contractility, leading to PTB.[3,7] However, the evidence underpinning the efficacy of screening and treatment for such infections in pregnancy is not clear-cut, leading to disparities in guidelines and clinical practice between countries. For example, the NICE-guideline states 'The results of clinical trials investigating the value of screening for and treating BV in preg-

Abbreviations: PTB, Preterm birth; BV, Bacterial vaginosis; I-SPY, International Spontaneous Preterm Birth Young investigators; PPROM, Preterm prelabour rupture of membranes; UK, United Kingdom; GBS, *Group B Streptococcus*.

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nancy have been conflicting. It is therefore difficult to make firm recommendations'.[8]

The International Spontaneous Preterm Birth Young investigators (I-SPY) group is a collaborative group of young researchers from 16 countries working towards identifying gaps for future research in PTB and fostering international collaboration. Previous research topics focused on tocolytic therapy, the prognostic accuracy of commercially available biomarkers and cervical length measurements.[9,10]

Based on I-SPY group discussions, we identified substantial differences in clinical practice within and between European countries regarding screening and treatment of infections associated with PTB.

Using an online survey, we aimed to analyse these differences in greater detail.

Material and methods

We created an online survey to assess current practice for screening, diagnosis and treatment of infections associated with PTB between countries.

Study population

The survey was created by two researchers (DW, BK). Subsequently, a panel from I-SPY with a focus on PTB critically revised and tested the questionnaire (six members of I-SPY: ID, LG, JH, EL, LB, FH). The survey was sent via email to representatives of I-SPY.[11]

The representatives were asked to voluntarily fill out the online questionnaire and forward it to colleagues. Reminders were sent, where necessary, after three weeks and after another three weeks. All questionnaires were filled out without guidance and collected between 29-11-2019 and 13–3-2020.

The survey was designed in Survio®[12] and included 29 questions addressing the following topics:

- Screening and treatment of infections in the first trimester of pregnancy;
- Screening and treatment in women with threatened PTB, without preterm prelabour rupture of membranes (PPROM);
- Screening and treatment in women with threatened PTB with PPROM.

The first part consisted of general baseline questions regarding the respondent. The second part consisted of four multiple choice questions regarding screening. The third part consisted of nine multiple choice questions and one closed question regarding threatened PTB with intact membranes. The last part consisted of seven multiple choice questions and three open questions regarding PPROM.

We asked participants to answer questions based on daily practice in the hospital/clinic where they were currently working. The full questionnaire can be found in appendix A. Data were collected anonymously.

Statistical analyses

Completed questionnaires were extracted from Survio® and tables were created with Excel.

Answers were stratified by country. Data was presented as absolute values and percentages.

For this research no funding was available.

Approval was requested from the Medical Ethics Review Committee of the Academic Medical Centre; an official approval of this study by the committee was not required (METC review number W21_032).

Results

Initially, the survey was sent to 23 clinicians (from 13 countries) who forwarded the survey to colleagues. Between 29 November 2019 and 13 March 2020, we had 50 respondents from ten European countries: 11 from the United Kingdom (UK), 11 from Belgium, eight from Spain, six from the Netherlands, four from France, three from Denmark, three from Sweden, two from Italy, one from Czech Republic and one from Finland. There were no responses that were completely similar, we therefore assumed that there were no duplicate responses. The majority of respondents were female (68%) and working in a university hospital (84%). Most respondents were specialist clinicians in Obstetrics and Gynaecology (76%), the remaining respondents were still in training (Table S1 and S2).

First trimester screening tests

Bacterial vaginosis

Most respondents (40 respondents in ten countries) reported that they did not routinely screen for BV. The remaining ten respondents (in four countries) reported screening only in high-risk women (Table 1). Treatment for BV (clindamycin or metronidazole) was consistent across countries.

Asymptomatic bacteriuria

Screening for asymptomatic bacteriuria is performed in all respondent countries, but not consistently at all hospitals. Seven respondents in four countries reported screening only in high-risk pregnancies, whereas 32 respondents in seven countries reported routine screening (Table 1).

Screening and treatment in women with threatened PTB and intact membranes

GBS and threatened PTB

Group B Streptococcus (GBS) screening is performed in women with threatened PTB and intact membranes in all countries, but is not universal practice across all hospitals. In five countries (33 respondents) GBS screening differs between hospitals. In four counties (six respondents) screening only takes place in certain cases (shortened cervix, abnormal vaginal discharge, etcetera) (Table 2). Criteria for initiating GBS treatment also differ between countries and hospitals. GBS treatment is usually initiated at the onset of labour in women with unknown GBS status (32 respondents from nine countries). However, in six countries (18 respondents) treatment is only initiated in GBS-positive women, whereas in two countries (four respondents) treatment is initiated irrespective of GBS status in threatened PTB.

Other screening tests in women with threatened PTB

Respondents perform several tests in women with threatened PTB and intact membranes. The majority of respondents perform a urine culture (43 respondents from ten countries). Blood leukocytes and CRP are routinely tested in six and seven countries, respectively, and tests for Candida species and Chlamydia trachomatis are performed in respectively seven and five countries (Table 3).

Table 1
Screening at first trimester.

Country (number of respondents)	Screening for bacterial vaginosis		Screening for asymptomatic bacteriuria	
	Yes	No	Yes	No
Belgium (11)	3*/11	**8/11**	**10/11**	1/11
Czech Republic (1)	0/1	**1/1**	0/1	**1/1**
Denmark (3)	0/3	**3/3**	**3/3**	0/3
Finland (1)	0/1	**1/1**	**1*/1**	0/1
France (4)	1*/4	**3/4**	1/4	**3/4**
Italy (2)	0/2	**2/2**	**2/2**	0/2
Spain (8)	0/8	**8/8**	**8/8**	0/8
Sweden (3)	0/3	**3/3**	**2*/3**	1/3
the Netherlands (6)	1*/6	**5/6**	1/6	**5/6**
United Kingdom (11)	5*/11	**6/11**	**8/11**3*/11	0/11

*In high risk pregnancies/women with previous PTB
Bold denotes the most frequent answer

Table 2
Screening for GBS.

Country (number of respondents)	Screening for GBS in women with threatened preterm birth and intact membranes			Screening for GBS in women with PPROM		
	Yes	No	Under certain conditions	Yes	No	Under certain conditions
Belgium (11)	**9/11**	0/11	2/11[#]	**11/11**	0/11	0/11
Czech Republic (1)	**1/1**	0/1	0/1	**1/1**	0/1	0/1
Denmark (3)	**3/3**	0/3	0/3	**3/3**	0/3	0/3
Finland (1)	0/1	0/1	**1/1**[#]	**1/1**	0/1	0/1
France (4)	**4/4**	0/4	0/4	**4/4**	0/4	0/4
Italy (2)	**1/2**	**1/2**	0/2	**2/2**	0/2	0/2
Spain (8)	**8/8**	0/8	0/8	**8/8**	0/8	0/8
Sweden (3)	1/3	**2/3**	0/3	1/3	**2/3**	0/3
the Netherlands (6)	**4/6**	1/6	1/6[#]	**5/6**	1/6	0/6
United Kingdom (11)	4/11	**5/11**	2/11[#]	**7/11**	3/11	1/11[*]

Bold denotes the most frequent answer
[#] In case of shortened cervix, if the woman is in labour, only when there is a history of abnormal vaginal discharge or seen on examination.
[*] Don't know.

Table 3
Tests performed in case of threatened preterm birth with intact membranes.

	Leucocytes	CRP	Urine sediment	Urine culture	GBS swab	Candidiasis swab	Chlamydia swab
Belgium	**8/11**	**8/11**	**10/11**	**10/11**	**9/11**	**7/11**	**6/11**
Czech Republic	**1/1**	**1/1**	**1/1**	**1/1**	**1/1**	**1/1**	**1/1**
Denmark	**2/3**	**2/3**	0/3	**3/3**	**3/3**	0/3	0/3
Finland	0/1	0/1	0/1	**1/1**	**1/1**	**1/1**	**1/1**
France	**4/4**	**3/4**	1/4	**4/4**	1/4	1/4	0/4
Italy	0/2	1/2	0/2	**2/2**	1/2	0/2	0/2
Spain	**8/8**	**8/8**	**6/8**	**7/8**	**8/8**	**5/8**	4/8
Sweden	0/3	0/6	0/3	**3/3**	0/3	0/3	0/3
the Netherlands	0/6	0/6	**6/6**	2/6	**5/6**	1/6	0/6
United Kingdom	**8/11**	**10/11**	1/11	**10/11**	2/11	3/11	1/11

Majority screens
Half of respondents screen
Majority does not screen

Screening and treatment in women with PPROM

Antibiotics in women with PPROM

Respondents reported a large variety of approaches to antibiotic treatment for PPROM in the absence of signs of infection (Table 4). Twenty five respondents in six countries reported always giving antibiotics to women with PPROM (other than those routinely used for GBS prophylaxis). In four other countries (18 respondents) treatment approaches were different per respondent. In one country (six respondents) antibiotics are not given. In PPROM with signs

Table 4
PPROM without signs of infection.

Country (number of respondents)	Antibiotics, GBS prophylaxis excluded, for PPROM		Type of antibiotic for PPROM without signs of infection (GBS prophylaxis excluded) not in labour (one reported treatment regimen per line)	Timing of induction
	Yes	No		
Belgium (11)	**11/11**	0/11	Azithromycin + amoxicillin Erythromycin	36–37 weeks
Czech Republic (1)	**1/1**	0/1	Penicillin	35 weeks
Denmark (3)	**3/3**	0/3	Cefuroxime + metronidazole + pivmecillinam Pondocillin + metronidazole	34 weeks
Finland (1)	**1/1**	0/1	Cefuroxime (+azithromycin if less than 35 weeks' gestation)	34–37 weeks
France (4)	**2/4**	**2/4**	Amoxicillin Cefotaxim Cephalosporin	37 weeks or above
Italy (2)	**2/2**	0/2	Ampicillin + azithromycin Ampicillin + azithromycin + amoxicillin	36–37 weeks
Spain (8)	**8/8**	0/8	Ampicillin + ceftriaxone + clarithromycin Ampicillin + erythromycin Ampicillin + gentamycin Ampicillin + gentamycin + azithromycin	34–36 weeks
Sweden (3)	**1/3** **1/3***	**1/3**	Erythromycin	34 or 37 weeks
the Netherlands (6)	0/6	**6/6**	Amoxicillin	37 weeks
United Kingdom (11)	**10/11**	1/11	Erythromycin	34–37 weeks or above

*<34 weeks.
Bold most given answer.

of infection, the majority of respondents reported switching to another type of antibiotic. Overall, the type of antibiotics used differs widely between countries (Table S3).

GBS in women with PPROM

In seven countries (30 respondents) all respondents screen for GBS in women with PPROM. In the remaining three countries, it differs per respondent (20 respondents, Table 2). In seven countries (22 respondents) GBS treatment in women with unknown GBS status is initiated at the onset of labour. In eight countries (15 respondents) treatment is initiated immediately after rupture of membranes. In four countries (eight respondents) treatment is not initiated in women with unknown GBS status. The main antibiotic used for GBS treatment (37 respondents, eight countries) is (benzyl)penicillin.

Induction of labour in women with PPROM

The timing of induction of labour after PPROM in women without infections or other complications, varies per country, with a gestational age at induction of 34 weeks or above (Table 4).

Other screening tests in women with PPROM

In the majority of countries, blood leukocytes (nine countries) and CRP (ten countries) in blood, and urine culture (eight countries) are performed in women with PPROM. Seven countries (20 respondents) perform a vaginal swab to screen for candidiasis, however, this differs between countries. Half of the countries (13 respondents in five countries) perform tests for Chlamydia trachomatis with a cervical or vaginal swab (Table 5).

Discussion

Main findings

In this manuscript, we report substantial differences in clinical practice from respondents between European countries regarding screening and treatment approaches for infections associated with PTB. Our findings are based on feedback from 50 respondents from ten European countries. There is great practice variation on all topics investigated, both within and between countries.

Strengths and limitations

A strength of this study is the broad variety and number of countries represented (20% of all European countries) and the fact that there were respondents from different hospitals within one country. Furthermore, as far as we know, no evaluation of differences in clinical practice between European countries regarding screening and treatment of infections associated with PTB has been published.

However, due to the limited number of respondents, we were unable to gain deeper insight into the screening and treatment approaches for infections associated with PTB between countries. We consider that the variety of daily practice may be even wider than indicated by this survey.

Interpretation

In most countries, BV screening is not routinely performed or is performed only for high-risk pregnancies. A recent review concluded that BV treatment has no benefit in low-risk pregnancies for women with a previous PTB the data is inconclusive.[13] The guidelines of the four countries with the most respondents are consistent with this recent data. The Dutch guideline advises BV screening and treatment in women with previous PTB.[14] Spanish guidelines advise screening in women with symptoms.[15] UK and Belgium guidelines do not recommend screening.[16,17]

The majority of countries screen for asymptomatic bacteriuria, but this is not universal practice in every hospital. The latest Cochrane review concludes that antibiotics for asymptomatic bacteriuria may reduce PTB risk, but the level of evidence is low.[18] The Netherlands, Spain and the UK have partially incorporated into their guidelines different versions (2007, 2015, 2019) of the Cochrane review 'Antibiotics for asymptomatic bacteriuria in pregnancy'.[18–21]

Table 5
Tests performed in women with PPROM.

	Leucocytes	CRP	Urine sediment	Urine culture	GBS swab	Candidiasis swab	Chlamydia swab
Belgium	**11/11**	**11/11**	**11/11**	**10/11**	**11/11**	**9/11**	**7/11**
Czech Republic	**1/1**	**1/1**	0/1	0/1	**1/1**	**1/1**	0/1
Denmark	**2/3**	**2/3**	0/3	**2/3**	**2/3**	0/3	0/3
Finland	**1/1**	**1/1**	0/1	0/1	**1/1**	0/1	0/1
France	**4/4**	**4/4**	1/4	**4/4**	2/4	1/4	0/4
Italy	**2/2**	**2/2**	0/2	**2/2**	**2/2**	1/2	1/2
Spain	**7/8**	**7/8**	**5/8**	**5/8**	**6/8**	3/8	2/8
Sweden	0/3	**2/3**	0/3	**3/3**	1/3	0/3	1/3
the Netherlands	**5/6**	**5/6**	**5/6**	3/6	**5/6**	2/6	0/6
United Kingdom	**9/11**	**9/11**	1/11	**7/11**	4/11	3/11	1/11

Majority screens
Half of respondents screen
Majority does not screen

Screening and treatment for GBS in threatened PTB differs depending on whether the membranes are ruptured or intact and whether labour is established. Most countries screen for GBS in women with threatened PTB. The timing for initiating treatment, however, varies widely.

The Dutch guideline, which was published in April 2017 and has not been updated since, is based on the NICE guideline 'Prevention of Early-onset Neonatal Group B Streptococcal Disease'. In the UK, the updated version of this guideline (September 2017) is used. In the light of emerging evidence from a UK national surveillance study which reports a higher mortality rate in preterm born babies due to GBS, the UK national guidance now advocates a more active approach of treating all woman in preterm labour with intravenous antibiotic prophylaxis for GBS.[22,23]

We found substantial differences in the use of antibiotics in women with PPROM. About half of the countries routinely administer antibiotics. Dutch and British guidelines base their recommendations for antibiotic prophylaxis in women with PPROM on two studies from Kenyon et al.: the ORACLE I trial and follow-up study.[24,25] However, recommendations differ in both guidelines: the Dutch guideline advises not to give antibiotics, as long term follow up suggests that no beneficial effect of treatment is demonstrated.[24,26] In contrast, the guideline of the UK advises to treat with antibiotics due to the short term evidence demonstrating delay of birth and reduced neonatal infection when antibiotic prophylaxis is used.[19,25] The Spanish guideline recommends to treat with antibiotics based on the most recent Cochrane review (2013).[27,28] The Cochrane review concludes that the use of antibiotics in women with PPROM reduces the risk of chorioamnionitis, neonatal infections, use of surfactant, oxygen therapy and abnormal cerebral ultrasound scan prior to discharge.[27] Based on the short-term advantages, they would recommend the use of antibiotics in women with PPROM.[27]

The timing of induction of labour after PPROM varies between countries, between 34 weeks and above 37 weeks. The latest Cochrane review (2017) shows more infant and maternal complications with an early delivery approach compared to an expectant management approach. With early delivery, respiratory distress syndrome (RR 1.45, 95%CI 1.10–1.90) and chorioamnionitis (RR 0.26, 95%CI 0.12–0.57) are more prevalent, whereas endometritis (RR 0.26, 95%CI 0.12–0.57) is less prevalent.[29] The RCOG guideline is based on the latest Cochrane review and advises expectant management until 37 weeks with timing of delivery tailored to the woman.[30] The Dutch guideline is based on two studies published in the nineties, the guideline itself dates from 2002 and advises induction at 37 weeks.[31,32] The Spanish guideline advises to induce at 34 weeks due to the potential risk of chorioamnionitis and the perceived low risk of neonatal morbidity at this gestational age.[28] Belgian guidelines do not address this topic.

Interestingly, when comparing answers to this survey with the respective national guidelines, adherence to guidelines was relatively high in Spain and considerably lower in the UK and the Netherlands. A systematic review shows that guideline non-adherence is common, within a range of 8.2–65.3%.[33] The lack of clear evidence in these clinical questions may also result in lower guideline adherence. We also should be aware of bias due to the number of respondents per country.

Conclusions

In conclusion, different strategies for screening and treating infections associated with PTB are currently common practice across European countries. We have highlighted the differences between and even within countries and identified knowledge gaps. Differences in clinical practice and guidelines may be due to 1. lack of robust evidence (e.g. low quality research, limited numbers of studies), 2. slow incorporation of new evidence into guidelines, 3. implementation barriers once guidelines are drafted (e.g. lack of resources, unawareness, fatigue regarding (new) guidelines), and 4. different interpretations of research (e.g. individual clinicians do not agree with the evidence, different patient populations at a local level). Future research should focus on these issues in order to ensure the best evidence-based care for pregnant women.

Although we treat women with threatened PTB on a daily basis, there are still gaps in sound evidence. Countries should work together on clinical trials to gather more evidence and include more women in clinical trials. Finally, the process of updating and implementing guidelines at an international level must be facilitated. The fact that international collaborations can be useful is underlined by the fact that recently a collaboration between four countries (Belgian, Germany, the Netherlands and the UK) started

the 'European Collaborative Obstetrics and Gynaecology Guidelines' in order to create guidelines together.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Contribution to Authorship

DEW: development of questionnaire, data analysing, writing manuscript; ID: critically revising questionnaire, critically revising manuscript; LG: critically revising questionnaire, critically revising manuscript; MVB: critically revising manuscript; BK development of questionnaire, data analysing, critically revising manuscript.

Details of Ethics Approval

Approval by the Ethics Review Board was applied for at the Medical Ethics Review Committee of the Academic Medical Centre. An official approval of this study by the committee was not required (METC review number W21_032).

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Appendix A. Supplementary data

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