Group B streptococcus and pregnancy : towards an optimal prevention strategy for neonatal Group B Streptococcal Disease

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Chapter 5

Association between colonization with Group B Streptococcus and preterm delivery:

A systematic review of the literature

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ABSTRACT

Background Up to 36% of pregnant women is colonized with GBS, most often without having symptoms. Preterm delivery in GBS colonized mothers is a recognized risk factor for early onset neonatal GBS disease (GBS-EOD), but whether maternal GBS genital colonization is related to preterm delivery is unclear.

Objective The objective of this review was to determine the relationship between maternal colonization with Group B Streptococcus and preterm delivery.

Study Design Pubmed searches and reference lists of all selected publications were used to find studies reporting on the relationship between maternal GBS colonization and preterm delivery. Study characteristics were abstracted, and validity scores were performed. To assess the relationship between GBS colonization and pregnancy outcome, four-fold prognostic tables were constructed for each study.

Results Out of more than 60 full-text articles, 16 follow-up studies and four case control studies were included in this review. Follow-up studies were divided into 'cohort studies', in which cultures were taken early in pregnancy and which reported on pregnancy outcome, and 'cross-sectional studies', in which cultures were collected during delivery. Studies differed widely in methods, validity score and GBS prevalence. The combined estimate from a random effect meta-analysis of the eleven cohort studies was 1.06 (95%CI 0.95-1.19) and for the five cross-sectional studies 1.75 (95%CI 1.43-2.14). For the case control studies the pooled odds ratio was 1.59 (95% CI 1.03-2.44).

Conclusions This systematic review did not show an association between maternal GBS colonization during pregnancy and preterm delivery. However, in case of preterm delivery, there is an increased risk of subsequent maternal GBS colonization.

INTRODUCTION

Despite major advances in perinatal care, preterm delivery is still the predominant cause of perinatal mortality and a major cause of neurological morbidity in surviving infants. Although the determinants of preterm delivery are uncertain, evidence suggests maternal genital tract colonization with specific organisms can play a role in preterm rupture of membranes and preterm delivery. Bacterial products such as phospholipases A_2 and C, endotoxin, and induction of the cytokine cascade can stimulate the prostaglandin pathway and initiate labour. (1;2) Reproductive tract infections or colonization associated with preterm delivery include Chlamydia trachomatis (3) and bacterial vaginosis. (4-6)

Up to 36% of pregnant women is colonized with GBS, most often without having symptoms.(7-10) Preterm delivery in GBS colonized mothers is a recognized risk factor for early onset neonatal GBS disease (GBS-EOD)(11), but whether maternal GBS genital colonization is related to preterm delivery is unclear.

The objective of this study was to critically review the literature to find any association between maternal GBS colonization and preterm delivery.

METHODS

The review process of our study, including methods of reporting outcomes was based on recommendations of Stroup et al.(12)

Search for studies

The selection process for studies reporting on GBS colonization and the outcome of pregnancy involved several steps following the guidelines provided by the book *Systematic Reviews in Health Care*.(13) Pubmed was searched for potentially relevant articles on the predictive value of positive GBS-cultures for preterm delivery published from 1966 to December 2008.

The search strategy included the terms Streptococcus *agalactiae*, streptococcus group B, premature, preterm, labor, labour, delivery, birth, pregnancy outcome, infant, and combinations of all these search terms.

Selection process, selected studies and validity

All possibly relevant articles were selected on the basis of title and abstract by two researchers (AV, AS) and were retrieved for more detailed examination. The selected articles had to meet met the following inclusion criteria:

1. They were published in English, French, Italian, Spanish or German.
2. They reported pregnancy outcome in GBS carriers and non-GBS carriers.
3. They reported patient population did not receive antibiotics during pregnancy.

Table 1 Characteristics and results of original studies Ordered by study design and validity score

Source	Primary Location	No. of Patients	Study Design	Gestational Age at time of culture	Definition Adverse Outcome	Prevalence adverse outcome	Prevalence GBS colonization	Validity Score	OR	RR	CI	Conclusion per Study
McDonald 1992	Adelaide, Australia	786	Cohort	Between 22-28 weeks	Preterm birth <37 weeks	6.2%	10.8%	7		0.95	0.58-1.58	NR
Regan 1996	Several States, USA	10385^	Cohort	23-26 weeks	Delivery < 37 weeks	11.4%	21.1%	5		1.04	0.91-1.20	NR
Feikin@ 2001	Aarhus and Odense, Denmark	2846	Cohort	24 weeks GA	Preterm Delivery < 37 weeks GA	3.1%	8%	5		0.97	0.47-1.98	NR
Mc Kenzie 1994	Dundee, UK	1971	Cohort	1. Booking	Preterm delivery <37 weeks	6.8%	4.3%	5		0.49	0.16-1.52	NR
Minkoff 1984	Brooklyn, USA	218	Cohort	13.8 +/- 3.6 weeks	Preterm labour Contractions < 37 weeks with changes in the cervix length	16%	9.9%	4		1.84	0.86-3.94	NR
Baker 1975	Houston, USA	183*	Cohort	Second trimester (20-28 weeks GA)	Premature Onset of Labour < 37 weeks	7.1%	14.8%	2		1.73	0.51-5.89	NR
Gerards 1982	Utrecht, The Netherlands	161	Cohort	Before GA 20 weeks, selection recultured week 28 and 34	Premature Delivery >28 weeks < 37 weeks	12%	13.9%	3		0.62	0.26-1.50	NR
Hastings 1986	London, UK	1059	Cohort	Booking 28 weeks 36 weeks	Prematurity <37 weeks	6.4 %	28%	3		1.01	0.60-1.68	NR
Chua 1995	Singapore	279	Cohort	1. < 12 weeks GA 2. 13-28 weeks 3. 29-32 weeks	Preterm labour <36 weeks	8.6%	16.3% 13.5% 14.7%	2		0.54#	0.13-2.22	NR
Moller 1984	Aalborg, Denmark	2745	Cohort	Between GA 12 and 38 weeks	Delivery < 37 weeks gestation	8.4%	2%	0		2.52	1.55-4.08	R
White 1984	Liverpool, UK	8083	Cohort	Antenatally	Premature <37 weeks	4.9%	1.7%	0		1.49	0.81-2.73	NR

Source	Primary Location	No. of Patients	Study Design	Gestational Age at time of culture	Definition Adverse Outcome	Prevalence adverse outcome	Prevalence GBS colonization	Validity Score	OR	RR	CI	Conclusion per Study
Hakansson 2008	Sweden	1507	Cross sectional	Time of Delivery	Gestational age at birth < 37 weeks	6.0%	25.4%	4		0.63	0.37-1.07	NR
Dawodu 1983	Nigeria	225	Cross sectional	Labour	Premature onset of labour <37 weeks	12.4%	19.5%	2		1.12	0.48-2.60	NR
Joshi 1987	Saskatoon, Canada	3078	Cross sectional	Time of Delivery	1. Preterm Delivery <37 weeks	9.6%	2.3%	1		2.59	1.69-3.98	R
Regan 1981	New York, USA	6706	Cross sectional	Time of Delivery	Preterm Delivery <32 weeks	1.8%	13.4%	1		4.11	2.88-5.87	R
Citernesi 1996	Toscane, Italia	4672	Cross sectional	Time of Delivery	Preterm Delivery <37 weeks	5.2%	6.6%	1		1.35	0.84-2.16	NR
Lamont 1986	London, UK	98	Case Control	Time of Delivery between GA 26 and 33 weeks	Preterm labour >26 weeks <33 weeks	ND	4%	3/6	3.48		0.18-66.92	NR
Martius 1988	Seattle, USA	212	Case Control	Between AD 20-36 weeks	Premature labour contractions < 37 weeks	ND	ND	3/6	1.41		0.73-2.73	NR
Feikin@ 2001	Aarhus and Odense, Denmark	384	Case Control@	24 weeks GA	Preterm Delivery < 37 weeks GA	3.1%	8%	2/6	2.11		1.0-4.46	NR
Persson 1986	Malmö,Sweden	366¢	Case Control	Time of Delivery	Preterm Delivery < 37 weeks	ND	22%	2/6	1.24		0.5-3.06	NR

- ND= not described , NR= no relation between GBS colonization and reported outcome, R=relation between GBS colonization and reported outcome
- * Baker 1974: Only patients with second trimester cultures were analyzed in this review.
- $ Mc Kenzie 1994: Only patients with midstream urine cultures at booking were analyzed in this review
- # Chua 1995: Results in different trimester cultures were analyzed as total group in relation with preterm labour
- ^ Regan 1996: Only patients with no effective antibiotics against GBS were analyzed in this review
- @ Feikin 2001: Article presents a case control study and a cohort study, both analysed separately in this review
- ¢ Persson 1986: In total 858 women were screened for GBS. Analysis was done in all GBS positive women (183) and in 183 non-colonized women matched for age

4. It was possible to formulate a fourfold table with well defined outcome numbers.

The bibliographies of all relevant articles were searched for additional references. All the retrieved articles were screened by the two researchers to ensure that the articles described original research and met the inclusion criteria mentioned above. In case of disagreement, the articles or abstracts were re-examined and discussed until consensus was achieved. Duplicate reporting from a single institution was excluded.

A validity score was calculated according to the criteria described by the Evidence-Based Medicine Working Group.(14) To determine the validity of selected studies, each study was graded on the basis of 7 criteria for prospective studies (range 0-11) or 4 criteria for case control studies (range 0-6). The following criteria of validity were used: adequate description of study population, well defined moment of antenatal cultures, use of selective broth medium and chosen culture-site(s), completeness of follow-up and/or clear description of dropouts and adjustment for prognostic factors.

Data extraction and statistical analysis

From each report, two researchers (AV, AS) extracted information about the study location and design, study population, number of patients, inclusion and exclusion criteria, study objectives, methods for GBS screening, timing of cultures, culture-site, completeness of follow-up, frequency of GBS colonization, and frequency of preterm delivery. A selection form based on the above criteria was constructed and filled in independently by both researchers. Both filled in a fourfold prognostic table based on the available data. In cases of disagreement, articles were re-examined and discussed until consensus was achieved.

We used Review Manager (Update Software, Oxford) to calculate relative risks and 95% confidence intervals, which were graphically displayed in Forest Plots.

RESULTS

Selection of articles

After screening more than 150 citations, 60 full-text articles were retrieved. Nineteen articles describing 20 studies were included in this review. Four of the studies were case control studies(15-18) and 16 were follow-up studies (15;19-33) (see Table 1). One of the 19 articles described both a case control study and a cohort study, which we analyzed separately.(15) Follow up studies were divided into 'cohort studies,' in which cultures were taken at a well defined moment in pregnancy and reported on pregnancy outcome (n=11)(15;19-28) and 'cross-sectional studies,' in which patients were only cultured at time of delivery, preterm or term (n= 5).(29-33) Case control studies matched patients with preterm delivery with patients with the same gestational age but not in labour. From three studies, only the results of well described subgroups were included in this review.(20;22;23)

Review articles and articles which did not represent original research were excluded.(34-45) Articles were also excluded if they did not deal with our research question or did not report outcomes according to our definition(4;6;46-60), if they reported patients received antibiotics at any time during pregnancy (5;61-65), if they overlapped with another publication included in our review(66;67), if the reported outcome numbers were inconsistent(68), or if the study population was unclear.(69)

Description of selected studies

The 20 studies included 45,888 patients living in ten different countries. Results of data-extraction are listed in Table 1. The overall prevalence of GBS colonization varied from 1.7%-28% (mean 12.2%, median 10.8%). In only nine studies GBS was cultured on a selective broth medium, which is reported to be an important factor for adequate detection of GBS. In twelve studies either vaginal or rectal or cervical cultures were taken, and in four studies vaginal cultures were combined with rectal cultures. In three other studies, urine specimens were cultured, and in one study (18) samples were taken from both urine, rectum and urethra, but the study did not specify which sample was positive in patients with preterm delivery. The reported prevalence of adverse outcome varied from 1.8%-16% (mean 7.6%, median 6.8%). However, the studies did not define adverse outcome consistently. Outcome measures included so-called preterm delivery (n=7), preterm labour (n=3), premature onset of labour (n=2), delivery < 37 weeks (n=3), preterm birth (n=1), premature delivery (n=1) prematurity (n=1), premature labour (n=1) and 'premature' (n=1). The studies also do not always give a clear definition of outcome; not all studies indicate whether deliveries were spontaneous or elective, what gestational age was defined as 'term,' and whether membranes were intact or not.

Validity

Table 2A shows total validity scores for the follow-up studies (maximum validity score: 11), and Table 2A shows them for the case control studies (maximum validity score: 6). All studies were found to have methodological limitations, with a validity score from 0-7.

Table 2A Characteristics and results of original studies according to the validity in prospective studies

Source	Study population	Gest.age	Methods		Follow-up		Adjustment	Validity
	Population defined (Demografic Data Described) *Yes=1* *No=0*	*Spread of antenatal cultures* *<6 wks=2* *>6 wks=0*	*Swabs; number of sites* *Urine=0* *R/V/C=1* *RV=2*	*Used selective broth medium* *Yes=1* *No=0* *ND*	*Complete Follow-up (100%)* *Yes=2* *No=0*	*Description of follow-up* *Yes=1* *No=0*	*Adjustment for Prognostic Factors* *Yes=2* *No=0*	***Score*** ***Min 0*** ***Max 11***
Baker 1975	1	0	1	ND	ND	0	0	**2**
Regan 1981	0	0	1	ND	NA	0	0	**1**
Dawodu 1983	0	0	1	1	NA	NA	0	**2**
Gerards 1982	0	0	2	1	0	0	0	**3**
Minkoff 1984	0	2	1	0	0	1	0	**4**
Moller 1984	0	0	0	0	0	0	0	**0**
White 1984	0	0	0	0	ND	0	0	**0**
Joshi 1987	0	0	1	0	NA	NA	0	**1**
Hastings 1986	0	0	2	1	0	0	0	**3**
McDonald 1992	1	2	1	1	ND	0	2	**7**
Mc Kenzie 1994	1	2	0	0	0	0	2	**5**
Chua 1995	0	0	1	0	0	1	0	**2**
Citernesi 1996	0	0	1	0	NA	NA	0	**1**
Regan 1996	0	2	1	1	0	1	0	**5**
Feikin 2001	1	0	1	0	0	1	2	**5**
Hakansson 2008	1	0	2	1	NA	NA	0	**4**

NA= Not applicable ND= Not described

Table 2B Characteristics and results of original studies according to the validity in Case Control studies

Source	Study population	Methods		Adjustment	Validity
	Population defined (Demografic Data Described)	*Swabs; number of sites*	*Used selective broth medium*	*Adjustment for Prognostic Factors*	***Score***
	Yes=1 No=0	*Urine=0 R/V/C=1 RV=2*	*Yes=1 No=0*	*Yes=2 No=0*	***Min 0 Max 6***
Lamont 1986	*0*	*2*	*1*	*0*	***3***
Martius 1988	*1*	*1*	*1*	*0*	***3***
Feikin 2001	*1*	*1*	*0*	*0*	***2***
Persson 1986	*0*	*1**	*1*	*0*	***2***

* Persson 1986: Rectal, urethral and urine specimens were cultured, from the text it is not clear which sample was positive in women with preterm delivery

Relation between GBS colonization and preterm delivery

Relative risks for preterm delivery in women colonized with GBS are shown graphically in Forest Plots. Figure 1 presents all cohort studies and Figure 2 all cross-sectional studies. Figure 3 shows all case control studies with odds ratios.

For cohort and cross-sectional studies, the combined estimates from a random effect meta-analysis were 1.06 (95%CI 0.95-1.19) and 1.75 (95%CI 1.43-2.14), respectively. The pooled odds ratio of case control studies for colonization given preterm delivery was 1.59 (95% CI 1.03-2.44).

Pooling cross-sectional studies and case control studies revealed odds of 1.76 (95%CI 1.44- 2.15) (not shown in table).

Interpretation of results

The search strategy yielded studies with different study designs and different study periods, from countries with different prevalence of GBS colonization and preterm delivery. Preterm delivery seems positively associated with GBS colonization at the time of delivery, but colonization during pregnancy does not seem to be associated with preterm delivery.

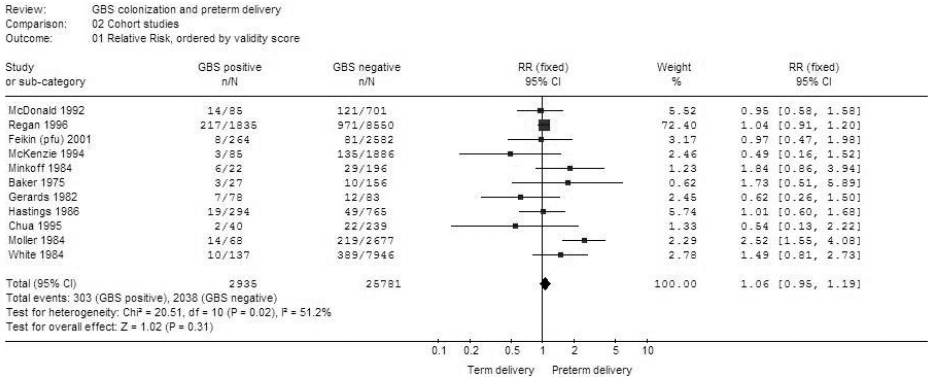

Figure 1 GBS colonization and preterm delivery in cohort studies

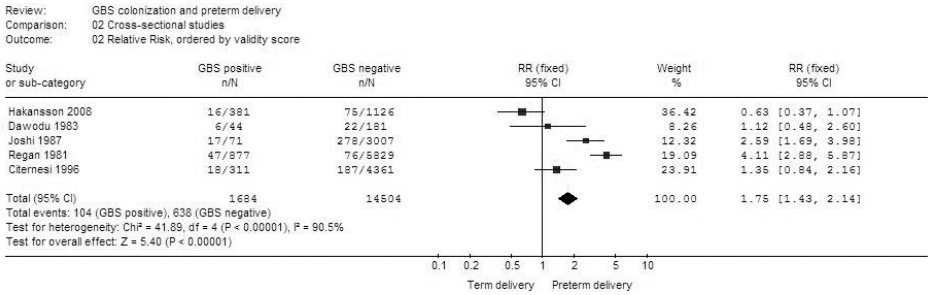

Figure 2 GBS colonization and preterm delivery in cross-sectional studies

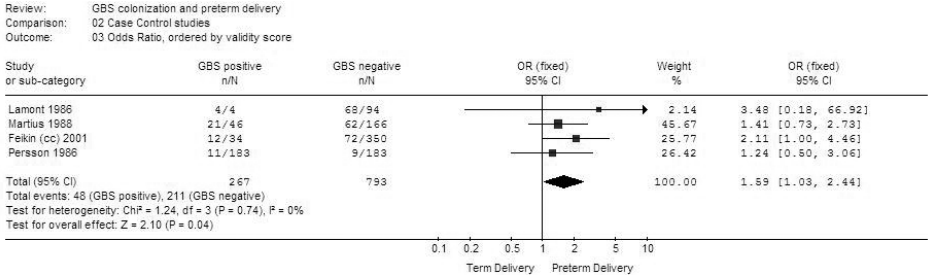

Figure 3 GBS colonization and preterm delivery in case control studies

DISCUSSION

To the best of our knowledge, this is the first systematic review on this topic containing studies from different parts of the world. This review analysed 19 publications covering 20 studies that dealt with the association between maternal GBS colonization and preterm delivery. In only one follow-up study was an association between GBS colonization during pregnancy and preterm delivery described.(27) Moller et al. found a higher risk of preterm delivery in women who had GBS in their urine, but their study had a low validity score. Cross-sectional studies during delivery and case control studies showed positive GBS cultures more frequently in patients with preterm delivery.

The results of the present study are in concordance with those of Romero et al.(39) They reviewed seven studies on genital colonization and three on asymptomatic bacteriuria with GBS in relation to preterm delivery. Genital colonization was examined in one cross-sectional study (tested at the time of admission), two case control studies, and four cohort studies. Romero et al. concluded that there was no evidence of an association between GBS colonization of the maternal genital tract and preterm delivery. The studies which examined asymptomatic GBS bacteriuria indicated that GBS bacteriuria in early pregnancy seems to be a risk factor for premature delivery. However, a major problem in literature is inconsistency of definition of asymptomatic bacteriuria.

Romero suggested that asymptomatic bacteriuria may be a marker of the most severe form of GBS genitourinary tract colonization. The incidence of GBS in quantities $>10^5$ colony forming units (cfu) /ml urine in pregnant women has been reported to be between 0.4 and 5%.(70;71) It has been shown that only 60% of bladder punctured pregnant women whose urine specimens contained $>10^5$ cfu/ml urine harboured GBS in the bladder.(18) Thus, a high quantity of GBS in urine is assumed to reflect heavy colonization of urethra, vulva and vagina. It remains unclear whether heavy GBS colonization by itself influences pregnancy outcome or whether the urinary tract infection is responsible.

Gibbs et al.(72) found no relationship between maternal genital tract GBS colonization and preterm delivery. However, in three of the four studies they described, there was a significant association between maternal genital group B streptococci colonization and premature rupture of membranes.

Recently, Colbourn and Gilbert(73) described the natural history of GBS-EOD in the UK. In a meta-analysis of eleven studies, three of which were case control studies, the pooled odds ratio for preterm delivery in mothers with GBS colonization during delivery was 1.53 (95% CI 1.14-2.05).

The vaginal microbial ecosystem in pregnant women has been shown to be an equilibrium of antagonistic and synergistic organisms.(74;75) Disruption of the normal vaginal flora, dominated by lactobacilli, may allow pathogenic bacteria to colonize and infect the

amniotic fluid, initiating preterm labour. It is generally accepted that amniotic fluid infection caused by microorganisms is associated with preterm delivery.

In a review of the association between maternal GBS colonization and preterm delivery, Kubota et al.(45) postulated that GBS was a marker of a lactobacilli-reduced vaginal environment, which would increase the risk of bacterial vaginosis. However, so far no empirical evidence of an association between GBS colonization and lactobacilli-reduced flora has been found.(76)

Intra-amniotic bacterial colonization or progression to infection depends on the effectiveness of the amniotic fluid antibacterial mechanisms and the number and pathogenicity of the colonizing bacteria. (77) It is conceivable that maternal genetic variation in response to these infections also plays a role in the risk of intra-uterine infection. Romero et al. speculated that it is not the presence of the organism itself, but the response of the host that is the critical step in this chain of events. When the host defence system is inadequate, bacterial growth may become excessive and lead to an infection ascending into the uterus. As part of its uncontrolled proliferation, the organism may penetrate the urinary tract and be detected as asymptomatic GBS bacteriuria.(39)

A review such as this one is hampered by the wide variation in the published reports, with different methods, incomplete information on follow-up, regional differences in GBS prevalence, adjustment for other risk factors, and different definitions of preterm delivery. The validity of the studies also varied widely, from 0-7 points out of 11, and the control studies in particular considered only very small groups of patients.

Approximately 6-36% of pregnant women carry GBS in the rectovaginal compartment. (9;10;78;79) The detected prevalence depends on the culture technique used, the locations tested, the culture media, the number of body sites cultured, and on the population studied. (80) Using selective broth media and sampling several culture sites (i.e., vagina and rectum) improves recovery of GBS up to 50%(81), but only seven of the studies did both. Few studies performed urine cultures to detect GBS.

Epidemiological studies on preterm delivery should adjust for known risk factors. Race, Social Economic Status (SES), age at beginning of pregnancy, duration of pregnancy, and multifetal gestation have been reported to influence GBS colonization. (9;81-84) Therefore, differences in reported prevalence of GBS can be a reflection of different risk profiles, which could also include different risk profiles for preterm delivery.

Risk factors for preterm delivery have been described, such as history of preterm delivery (RR 2,6: 95%-BI 2,0-3,4), ethnicity, age < 16 years (OR 1,7; 95%-BI 1,1-2,8)(85), cigarette smoking(86), use of cocaine(87), uterine malformation, cervical conization(88), DES exposition in utero, and multifetal gestation. Only three of the studies considered in this review described adjustments for prognostic risk factors for preterm delivery.

Finally, when we want to solve a problem, we should clearly distinguish cause and consequences. Although all the studies considered in this review described patients admitted to hospital because of contractions before 37 weeks of gestational age, most studies did not make it clear whether deliveries were spontaneous, whether membranes were intact or not, and whether preterm contractions led to preterm delivery or not. In addition, it is not known whether researchers were aware of the results of cultures. All of this might influence how follow-up studies are interpreted.

CONCLUSION

In this review we did not find a causal relationship between maternal GBS colonization and preterm delivery. However, in cases of preterm delivery, there is a significantly increased prevalence of GBS colonization. To understand the effect of GBS on pregnancy, large observational studies are needed, with clearly defined outcomes, and with prognostic risk factors for preterm delivery taken into account.

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