Maternal age and body mass index as risk factors for rectovaginal colonization with group B streptococci

Khalil, Mohammad Rohi El; Hartvigsen, Camilla Mirian; Bak Thorsen, Poul; Møller, Jens Kjølseth; Uldbjerg, Niels

Published in:
International Journal of Gynecology & Obstetrics

DOI:
10.1002/ijgo.14449

Publication date:
2023

Document version:
Final published version

Received: 9 June 2022 | Revised: 19 August 2022 | Accepted: 2 September 2022

DOI: 10.1002/ijgo.14449

CLINICAL ARTICLE

Obstetrics

Maternal age and body mass index as risk factors for rectovaginal colonization with group B streptococci

Mohammed R. Khalil[1] | Camilla M. Hartvigsen[2] | Poul B. Thorsen[3] | Jens K. Møller[4] | Niels Uldbjerg[5,6]

[1]Department of Obstetrics and Gynecology, Lillebaelt Hospital, Kolding, Denmark

[2]Department of Obstetrics and Gynecology, Aabenraa Hospital, Aabenraa, Denmark

[3]Department of Obstetrics and Gynecology, Odense University Hospital, Odense, Denmark

[4]Department of Clinical Microbiology, Lillebaelt Hospital, Vejle, Denmark

[5]Department of Obstetrics and Gynecology, Aarhus University Hospital, Denmark

[6]Institute of Clinical Medicine, Aarhus University, Aarhus, Denmark

Correspondence
Mohammed R. Khalil, Department of Obstetrics and Gynecology, Lillebaelt Hospital, Kolding, Denmark.
Email: mohammed.khalil@rsyd.dk

Funding information
Johs. M. Klein og Hustrus Mindelegat

Abstract

Objective: To examine the effect of including maternal age and body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) as additional risk factors in the traditional risk-based strategy at term pregnancies consisting of previous early-onset group B streptococcus (GBS) disease, GBS bacteriuria during pregnancy, maternal temperature of 38.0°C or more intrapartum, and rupture of membranes of 18 h or longer.

Methods: A secondary analysis of a Danish cohort including 902 pregnant women. Exposures were maternal age and pre-pregnancy BMI. Outcome was rectovaginal GBS colonization at the time of labor. The logistic regression analysis adjusted for parity, gestational age, vaginal delivery, and smoking.

Results: The GBS prevalence was 17% in the entire population, 35% among participants older than 40 years, and 23% among those with a BMI of 25 or greater. Including maternal "age > 40" as an additional risk factor increased the sensitivity of the risk-based strategy from 21% to 26% and decreased the specificity from 90% to 87%. Inclusion of "BMI ≥ 25" increased the sensitivity from 21% to 57% and decreased the specificity from 90% to 59%.

Conclusions: Maternal age and BMI might be included as additional risk factors in risk-based programs for identification of GBS-positive laboring women to receive intrapartum antibiotics prophylaxis.

KEYWORDS
body mass index, colonization, group B streptococci, maternal age, risk factors

1 | INTRODUCTION

Globally, four main strategies are in use for identifying laboring women who should be offered intrapartum antibiotics prophylaxis to prevent neonatal early-onset group B streptococcus disease (EOGBS): (1) a risk-based strategy, (2) an antepartum culture-based strategy, (3) an intrapartum GBS polymerase chain reaction (PCR) strategy, and finally (4) GBS-PCR for those deemed at risk of EOGBS. These strategies differ concerning performance, economy, and implementability (logistics). Canada, the UK, and other European countries use the risk-based strategy including previous EOGBS, GBS bacteriuria during the actual pregnancy, maternal temperature of 38.0°C or more intrapartum, and rupture of membranes for more than 18 hours.[1–4] However, it is of concern that about 70% of these

women at risk are GBS-negative, and up to 50% of EOGBS cases develop in neonates born to mothers colonized with GBS without any of these risk factors.[5–7]

In addition to the five traditional risk factors, maternal age[8–13] and maternal obesity might be associated with both rectovaginal GBS colonization[14–18] and neonatal EOGBS disease.[19] The pathophysiologic pathway for these associations may be related to alterations of the gut microbiota, as obesity is associated with a 50% reduction in the division *Bacteroidetes* (Gram-negative) and a proportional division-wide increase in Firmicutes (Gram-positive).[20] Research is needed to elucidate the hormonal, immunomodulatory, and metabolic mechanisms underlying microbe-microbe and microbiota-host interactions.

We hypothesized that maternal age and body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) constitute potential risk factors, which may increase the performance of the risk-based strategy. Therefore, the aim of this study was to investigate the association between maternal age and pre-pregnancy BMI and intrapartum rectovaginal GBS colonization in a cohort of pregnant Danish women.

2 | MATERIALS AND METHODS

The study is a secondary analysis of a previously reported cohort study of 902 pregnant Danish women attending the prenatal clinic at Lillebaelt Hospital, Kolding, Denmark, between April 1, 2013 and June 30, 2014, and giving birth at term.[3,4] In all, 2343 pregnant women attending the Prenatal Clinic at Lillebaelt Hospital, Kolding were invited to participate. Exclusion criteria were: women who delivered preterm (<37 weeks of pregnancy), women who received antibiotics after 35 weeks of pregnancy, women with communication restrictions, and women under 18 years of age. Among the invited women, 1091 rejected the invitation, and a further 350 were not included for various reasons, e.g. sampling missed during delivery.

The participants were categorized according to their maternal age (<25, 25–34, 35–40, and ≥40 years); and their pre-pregnancy BMI: underweight (<18.5), normal weight (18.5–24.9), overweight (25.0–29.9), and obesity (≥30.0). The included confounders were parity, gestational age, vaginal delivery, and smoking. The outcome variable was defined as a GBS-positive intrapartum rectovaginal culture obtained during labor from all participants as previously described.[21]

All participants had given written and verbal informed consent before inclusion in the cohort study.[3,4] The Regional Scientific Ethical Committees for Southern Denmark (case number S-20130089) and the Danish Data Protection Agency (case number 2008-58-0035) approved the study.

The statistical analyses included comparisons between groups presented as dichotomous and categorical variables (maternal age, four categories) and (BMI, four categories) using univariate logistic regression reported as odds ratios (ORs) with 95% confidence interval (CI). Covariates were chosen based on differences identified in baseline characteristics between two cohorts (GBS-positives and GBS-negatives) and were assessed by unpaired Student *t* test for continuous variables and χ^2 or Fisher exact test for categorical variables, as appropriate ($P < 0.05$). According to predefined variables in well-established clinical studies, a multivariable regression analysis was adjusted for parity, gestational age, vaginal delivery, and smoking (adjusted odds ratios [aOR] with 95% CI). Sensitivity, specificity, positive predictive values, negative predictive values, and 95% CI were calculated. All statistical analyses were conducted using STATA Statistics/Data Analysis software version 14 (StataCorp LP, College Station, TX, USA).

3 | RESULTS

Within the cohort of 902 pregnant women, the overall prevalence of intrapartum rectovaginal GBS colonization was 17.2% (155/902).

This prevalence of intrapartum rectovaginal GBS colonization was significantly associated with maternal age (Table 1). The aOR was 4.2 (95% CI 1.5–12.0) for maternal age 40 years or older compared with younger age (less than 25 years) (Table 1). A dose–response relationship was seen with a GBS-positive fraction of 12%, 16%, 20%, and 35% for age groups less than 25, for BMI 18.5–24.9, 25.0–29.9, and 30, respectively. Among the 10 GBS-positive women aged 40 years or older, only two (20%) had other risk factors (data not shown).

The prevalence of intrapartum rectovaginal GBS colonization was also associated with an increasing pre-pregnancy BMI (Table 1): 5.5% for underweight, 14% for normal weight, 21% for overweight, and 25% for obesity. The aOR was 2.7 for obesity (95% CI 1.2–3.2) as compared with normal weight (Table 1). Among the 76 overweight GBS-positive women, only 19 (25%) had other risk factors (data not shown), and among 30 obese GBS-positive women, only 6 (20%) had other risk factors.

Table 2 illustrates how the performance of the risk-based strategy was affected if BMI 25 or higher, BMI 30 or higher, and age 40 years or older were added to the standard risk factors (previous infant with EOGBS, GBS bacteriuria during the current pregnancy, temperature > 38.0°C, and rupture of membranes >18 h). The highest sensitivity was achieved with conventional risk factors supplemented with the risk factor BMI 25 or above.

4 | DISCUSSION

This study showed that the risk of intrapartum rectovaginal GBS colonization in women giving birth at term increases with increasing maternal age and with increasing pre-pregnancy BMI. Furthermore, including maternal age and BMI as additional risk factors in the traditional risk-based strategy at term pregnancies increases the performance of the strategy. The variables we adjusted for were parity, vaginal delivery, and smoking. These associations did not change when adjusting for other variables.

TABLE 1 Prevalence of GBS colonization and ORs in a multivariable logistic regression analysis stratified by maternal age and BMI categories and other study covariates

GBS colonization	GBS+ (%)[a]	GBS−(%)[a]	Crude OR	95% CI	Adjusted OR	95% CI	*P* value
Number	155 (17.2)	747 (82.8)					
BMI							
<18.5	2 (1.3)	34 (4.6)	0.35	0.08–1.48	0.26	0.06–1.11	0.07
18.5–24.9	77 (49.7)	456 (61.0)	Ref		Ref		
25.0–29.9	46 (29.7)	169 (22.6)	1.62	1.07–2.42	1.62	1.10–2.38	0.01
≥30	30 (19.4)	88 (11.8)	2.02	1.25–3.26	2.68	1.26–2.72	0.01
Maternal age, year							
<25	10 (6.5)	77 (10.3)	Ref		Ref		
25–34	101 (65.2)	513 (68.7)	1.52	0.76–3.03	1.39	0.70–2.83	0.35
35–40	34 (21.9)	138 (18.5)	1.90	0.89–4.05	1.68	0.76–3.69	0.19
>40	10 (6.5)	19 (2.5)	4.05	1.48–11.13	4.17	1.45–11.95	0.008
Parity							
Para 0	58 (37.2)	349 (46.7)	Ref		Ref		
Para ≥1	97 (62.6)	398 (53.3)	1.47	1.03–2.09	1.50	1.03–2.19	0.03
Gestational age, week							
<40	66 (42.6)	293 (39.2)	Ref		Ref		
≥40	89 (57.4)	454 (60.8)	0.87	0.61–1.24	0.97	0.67–1.40	0.85
Tobacco use							
Non-smoker	140 (90.3)	687 (92.0)	Ref		Ref		
Smoker	15 (9.7)	60 (8.0)	1.23	0.68–2.22	1.46	0.79–2.72	0.23
Risk factors							
GBS in urine	9 (13.6)	21 (1.2)	12.85	5.76–28.66	12.52	5.47–28.62	0.000
Fever[b] ≥38.0°C	1 (0.7)	8 (1.1)	0.60	0.07–4.83	0.62	0.08–5.51	0.71
ROM ≥18 h	10 (6.5)	58 (7.8)	0.82	0.41–1.64	0.94	0.46–1.91	0.86
EOGBS earlier	0 (0.0)	1 (0.1)	0.21	0.17–0.25	1	–	–

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters), was categorized as underweight (<18.5), normal weight (18.5–24.9), overweight (25.0–29.9), and obese (≥30.0); CI, confidence interval; EOGBS, early-onset GBS disease; GBS, group B streptococcus; GBS+, GBS positive; GBS−, GBS negative; OR, odds ratio; ROM, rupture of membranes.

[a]Data are presented as percentage.

[b]Fever defined as maternal temperature ≥38.0°C intrapartum.

TABLE 2 Performance characteristics of risk-based screening of the cohort ($N = 902$) using BMI ≥25 and BMI ≥30 and maternal age ≥40 years as an additional risk factor[a]

	Established risk factors		Established risk factors + BMI ≥25		Established risk factors + BMI ≥30		Established risk factors + age ≥40 year	
Variable[b]		95% CI		95% CI		95% CI		95% CI
Sensitivity	21% (32/155)	15–18	57% (89/155)	49–65	36% (56/155)	29–44	26% (40/155)	19–33
Specificity	90% (671/747)	87–92	59% (442/747)	56–63	80% (595/747)	77–83	87% (653/747)	85–90
PPV	30% (32/108)	22–38	23% (89/394)	20–26	27% (56/208)	22–32	30% (40/134)	23–37
NPV	85% (671/794)	83–86	88% (442/508)	85–89	86% (595/694)	84–87	85% (653/768)	84–86

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CI, confidence interval; GBS, group B streptococci; NPV, negative predictive value. PPV, positive predictive value.

[a]Data are presented as percentage (number/total number) unless otherwise stated.

[b]Using the rectovaginal intrapartum culture as the reference standard.

Realizing that rectovaginal GBS colonization[14–18] is only a proxy variable for EOGBS, our data support previous publications finding that the risk of EOGBS increased by 80% in obese women[19] and that the mothers of neonates with EOGBS tend to have BMI of 25 or more.[23] Furthermore, newborns of obese mothers[24] may be more prone to developing EOGBS as they have increased levels of inflammatory markers in the cord blood (C-reactive protein, interleukin-6 and tumor necrosis factor α),[25,26] and placentas with increased interleukin-1β and interleukin-8 expression.[27,28] The relationship between the increased inflammatory mediators in obese mothers and in their newborns may stem from a chronic low-grade inflammatory condition in the obese mother by way of an increased secretion of pro-inflammatory adipokines and cytokines. If so, the clinical significance of including "BMI ≥25" as a risk factor may be even more important than our findings suggest.

Nevertheless, the risk-based strategy for identification of laboring women to be offered intrapartum antibiotics prophylaxis is still problematic, as the performance of the strategy is very low. Hence, the GBS-positive prevalence increases from an overall 17% in the entire cohort (Table 1) to merely 21% in the group of pregnant women with standard risk factors (Table 2).

The inclusion of pre-pregnancy BMI of 25 or above or 30 or above increased the sensitivity to 57% and 36%, respectively, but led to markedly decreased specificities of 59% and 80%, respectively (Table 2). The same pattern will apply when adding both "age ≥40 years" and "BMI ≥25" as extra variables; the performance of the conventional risk-based strategy with these additions will change sensitivity from 21% to 60% at the expense of decreased specificity from 90% to 56% and a positive predictive value of 22%. This means that using an extended risk-based screening strategy, a substantial increase in the number of women (419/902) needing an intrapartum GBS PCR test to find the 93 of 155 GBS PCR-positive cases in our cohort. The dose–response associations between increasing age, pre-pregnancy BMI and rectovaginal GBS colonization strengthen the reliability of the demonstrated risk factor associations (Table 1).

A strength of the study is that it was performed on pregnant women who did not receive antibiotics the month before inclusion in the study at 35 weeks of pregnancy. It might be considered a limitation of the study that direct culture of rectovaginal swab material on Granada plates had been used without prior broth enrichment; however, the expected difference in the detection rates of GBS is only 4%.[22]

For programs that continue to rely on the risk-based strategy, maternal age and BMI of 25 or above might be included as additional risk factors in risk-based programs for identification of laboring women to be examined for GBS carriage and intrapartum antibiotics prophylaxis. However, the increased sensitivity of the extended risk-based screening strategy comes at the price of more women to be GBS PCR tested intrapartum compared with our present strategy using the conventional risk-based screening of pregnant women with a risk of EOGBS in the newborn. It is also a concern that the extended risk-based screening strategy leads to an increased number of women who may receive unnecessary intrapartum antibiotics prophylaxis during their childbirth with potential negative consequences for the microbiome of their newborns.[29,30]

AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design of the study, the collection, analysis and interpretation of data. All authors approved the final published version of the article. MRK, CMH, PBT, JKM, and NU contributed to writing and revising the manuscript.

ACKNOWLEDGMENTS

The study was supported by Forskningsraadet Lillebaelt Hospital, Udviklingsraadet Lillebaelt Hospital, Johs. M. Klein og Hustrus Mindelegat, Region of Southern Denmark, and Farusa Emballage A/S.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ORCID

Mohammed R. Khalil https://orcid.org/0000-0002-5102-9976

REFERENCES

1. Boyer K, Gotoff SP. Prevention of early-onset neonatal group B streptococcal disease with selective intrapartum chemoprophylaxis. *N Engl J Med*. 1986;314:1665-1669.
2. Schrag S, Verani JR. Intrapartum antibiotic prophylaxis for the prevention of perinatal group B streptococcal disease: experience in the United States and implications for a potential group B streptococcal vaccine. *Vaccine*. 2013;31:D20-D26.
3. Khalil MR, Uldbjerg N, Thorsen PB, Henriksen B, Møller JK. Risk-based screening combined with a PCR-based test for group B streptococci diminishes the use of antibiotics in laboring women. *Eur J Obstet Gynecol Reprod Biol*. 2017;215:188-192.
4. Khalil MR, Uldbjerg N, Thorsen PB, Henriksen B, Møller JK. Corrigendum to "Risk-based screening combined with a PCR-based test for group B streptococci diminishes the use of antibiotics in laboring women" [Eur J Obstet Gynecol Reprod Biol 215 (August) (2017) 188–192]. *Eur J Obstet Gynecol Reprod Biol*. 2018;221:208.
5. Flidel-Rimon O, Galstyan S, Juster-Reicher A, Rozin I, Shinwell ES. Limitations of the risk factor based approach in early neonatal sepsis evaluations. *Acta Paediatr*. 2012;101(12):e540-e544.
6. Heath PT, Balfour G, Weisner AM, et al. Group B streptococcal disease in UK and Irish infants younger than 90 days. *Lancet*. 2004;363(9405):292-294.
7. Hakansson S et al. Real-time PCR-assay in the delivery suite for determination of group B streptococcal colonization in a setting with risk-based antibiotic prophylaxis. *J Matern Fetal Neonatal Med*. 2014;27(4):328-332.
8. El-Kersh TA, Al-Nuaim LA, Kharfy TA, Al-Shammary FJ, Al-Saleh SS, Al-Zamel FA. Detection of genital colonization of group B streptococci during late pregnancy. *Saudi Med J*. 2002;23:56-61.
9. Khan MA, Faiz A, Ashshi AM. Maternal colonization of group B streptococcus: prevalence, associated factors and antimicrobial resistance. *Ann Saudi Med*. 2015;35(6):423-427. doi:10.5144/0256-4947.2015.423

10. Valkenburg-van den Berg AW, Sprij AJ, Oostvogel PM, et al. Prevalence of colonisation with group B streptococci in pregnant women of a multi-ethnic population in The Netherlands. *Eur J Obstet Gynecol Reprod Biol*. 2006;124(2):178-183.
11. Kovavisarach E, Ying WS, Kanjanahareutai S. Risk factors related to group B streptococcal colonization in pregnant women in labor. *J Med Assoc Thai*. 2007;90(7):1287-1292.
12. Marconi C, Rocchetti TT, Rall VL, Carvalho LR, Borges VT, Silva MG. Detection of Streptococcus agalactiae colonization in pregnant women by using combined swab cultures: cross-sectional prevalence study. *Sao Paulo Med J*. 2010;128(2):60-62.
13. Joachim A, Matee MI, Massawe FA, Lyamuya EF. Maternal and neonatal colonisation of group B streptococcus at Muhimbili National Hospital in Dar Es Salaam, Tanzania: prevalence, risk factors and antimicrobial resistance. *BMC Public Health*. 2009;1(9):437. doi:10.1186/1471-2458-9-437
14. Alvareza MD, Subramaniam A, Tang Y, Edwards RK. Obesity as an independent risk factor for group B streptococcal colonization. *J Matern Fetal Neonatal Med*. 2017;30(23):2876-2879.
15. Manzanares S, Zamorano M, Naveiro-Fuentes M, Pineda A, Rodríguez-Granger J, Puertas A. Maternal obesity and the risk of group B streptococcal colonisation in pregnant women. *J Obstet Gynaecol*. 2019;39(5):628-632.
16. Gopal Rao G, Hiles S, Bassett P, Lamagni T. Differential rates of group B streptococcus (GBS) colonisation in pregnant women in a racially diverse area of London, UK: a cross-sectional study. *BJOG*. 2019;126(11):1347-1353.
17. Kleweis S, Cahill AG, Odibo AO, Tuuli MG. Maternal obesity and rectovaginal group B streptococcus colonization at term. *Infect Dis Obstet Gynecol*. 2015;2015:586767.
18. Venkatesh KK, Vladutiu CJ, Strauss RA, et al. Association between maternal obesity and group B streptococcus colonization in a National U.S. Cohort. *J Womens Health (Larchmt)*. 2020;29(12):1507-1512.
19. Håkansson S, Kallen K. High maternal body mass index increases the risk of neonatal early onset group B streptococcal disease. *Acta Paediatr*. 2008;97:1386-1389.10.
20. Musso G, Gambino R, Cassader M. Obesity, diabetes, and gut microbiota: the hygiene hypothesis expanded? *Diabetes Care*. 2010;33:2277-2284.
21. Khalil MR, Uldbjerg N, Thorsen PB, Møller JK. Risk-based approach versus culture-based screening for identification of group B streptococci among women in labor. *Int J Gynaecol Obstet*. 2019;144(2):187-191.
22. El Aila NA, Tency I, Claeys G, et al. Comparison of different sampling techniques and of different culture methods for detection of group B streptococcus carriage in pregnant women. *BMC Infect Dis*. 2010;10:285.
23. Al-Kadri HM, Bamuhair SS, Johani SMA, Al-Buriki NA, Tamim HM. Maternal and neonatal risk factors for early-onset group B streptococcal disease: a case control study. *Int J Women's Health*. 2013;5:729-735.
24. Reilly SM, Saltiel AR. Adapting to obesity with adipose tissue inflammation. *Nat Rev Endocrinol*. 2017;13:633-643.
25. Dosch NC, Guslits EF, Weber MB, et al. Maternal obesity affects inflammatory and iron indices in umbilical cord blood. *J. Pediatr*. 2016;172:20-28.
26. Wilson RM, Marshall NE, Jeske DR, Purnell JQ, Thornburg K, Messaoudi I. Maternal obesity alters immune cell frequencies and responses in umbilical cord blood samples. *Pediatr Allergy Immunol*. 2015;26:344-351.
27. Aye ILMH, Lager S, Ramirez VI, et al. Increasing maternal body mass index is associated with systemic inflammation in the mother and the activation of distinct placental inflammatory pathways. *Biol Reprod*. 2014;90:129.
28. Roberts KA, Riley SC, Reynolds RM, et al. Placental structure and inflammation in pregnancies associated with obesity. *Placenta*. 2011;32:247-254.
29. Keski-Nisula L, Kyynarainen HR, Karkkainen U, Karhukorpi J, Heinonen S, Pekkanen J. Maternal intrapartum antibiotics and decreased vertical transmission of lactobacillus to neonates during birth. *Acta Paediatr*. 2013;102(5):480-485.
30. Khalil MR, Uldbjerg N, Thorsen PB, Møller JK. Intrapartum PCR assay versus antepartum culture for assessment of vaginal carriage of group B streptococci in a Danish cohort at birth. *PLoS ONE*. 2017;12(7):e0180262.

How to cite this article: Khalil MR, Hartvigsen CM, Thorsen PB, Møller JK, Uldbjerg N. Maternal age and body mass index as risk factors for rectovaginal colonization with group B streptococci. *Int J Gynecol Obstet*. 2022;00:1-5. doi: 10.1002/ijgo.14449