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CLINICAL ARTICLE
Obstetrics

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

Mohammed R. Khalil | Camilla M. Hartvigsen | Poul B. Thorsen | Jens K. Møller | Niels Uldbjerg

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. 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 age8–13 and maternal obesity might be associated with both rectovaginal GBS colonization14–18 and neonatal EOGBS disease.19 The pathophysiology pathway for these associations may be related to alterations of the gut microbiota, as obesity is associated with a 50% reduction in the division Bacteroides (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 χ² 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

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

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.
aData are presented as percentage.
bFever 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

<table>
<thead>
<tr>
<th>Variableb</th>
<th>Established risk factors</th>
<th>Established risk factors + BMI ≥25</th>
<th>Established risk factors + BMI ≥30</th>
<th>Established risk factors + age ≥40 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>21% (32/155)</td>
<td>57% (89/155)</td>
<td>36% (56/155)</td>
<td>26% (40/155)</td>
</tr>
<tr>
<td>Specificity</td>
<td>90% (671/747)</td>
<td>87–92</td>
<td>80% (595/747)</td>
<td>87% (653/747)</td>
</tr>
<tr>
<td>PPV</td>
<td>30% (32/108)</td>
<td>22–38</td>
<td>27% (56/208)</td>
<td>30% (40/134)</td>
</tr>
<tr>
<td>NPV</td>
<td>85% (671/794)</td>
<td>83–86</td>
<td>86% (595/694)</td>
<td>85% (653/768)</td>
</tr>
</tbody>
</table>

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.
aData are presented as percentage (number/total number) unless otherwise stated.
bUsing the rectovaginal intrapartum culture as the reference standard.
Realizing that rectovaginal GBS colonization\textsuperscript{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\textsuperscript{19} and that the mothers of neonates with EOGBS tend to have BMI of 25 or more.\textsuperscript{23} Furthermore, newborns of obese mothers\textsuperscript{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),\textsuperscript{25,26} and placetas with increased interleukin-1β and interleukin-8 expression.\textsuperscript{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 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%.\textsuperscript{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.\textsuperscript{29,30}

### REFERENCES


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