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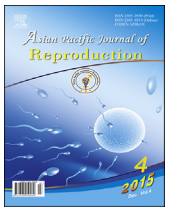

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# Is abnormal vaginal microflora a risk factor for intrauterine fetal growth restriction?

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ABSTRACT

**Objective:** To conduct a literature review in search of possible preventable causes for fetal growth restriction.
**Methods:** We performed a systematic literature search regarding abnormal vaginal microflora and fetal growth encompassing the last 27-year (starting from 1986) in PubMed, Embase, and Cochrane Central to study the evidence that abnormal vaginal microflora is may be related to diminished fetal growth or small for date birth.
**Results:** Most of the 14 studies suggested a significant role of vaginal organisms in impaired fetal growth, unrelated to preterm birth. The neonatal outcome has shown to be largely linked to the preventable or foreseeable fetal factors, such as genetic abnormalities, but also ascending intrauterine infections. Our previous work suggested a role of vaginal organisms in adverse pregnancy outcome, not only preterm birth, but also impaired fetal growth.
**Conclusions:** There is a need for cohort studies designed to unravel this link between abnormal microflora and FGR, in order to enable preventive actions to protect these small babies from severe damage and death by early screening and treatment.

## 1. Introduction

Fetal growth restriction (FGR) is defined as the inability of a fetus to maintain its expected growth [1]. In spite of the advanced and sophisticated diagnostic technologies, it remains a major challenge for obstetricians to understand its pathogenicity in order to adjust treatment or preventive actions. Indeed, FGR is associated with significant perinatal morbidity and mortality [2], an increased risk of neurological impairment in childhood [3,4] and cardiovascular and metabolic diseases in adults [5]. These complications are mostly related to the newborns with a birth weight below the 3rd percentile [6]. Known contributing factors to the ethiology of FGR are substance abuse, fetal chromosomal anomalies, hypertension and severe chronic maternal diseases [7–9]. Also infections with cytomegalovirus, *Toxoplasma gondii (T. gondii)*, herpes virus and rubella have been shown to cause detrimental effects on fetal growth [10–12]. However, the role of other infectious agents and genital infections remain controversial and perhaps underestimated.

According to several follow-up studies, there is a strong link between infectious conditions of the lower genital tract, such as bacterial vaginosis (BV), aerobic vaginitis (AV) and trichomoniasis (TV) and preterm deliveries [13–18]. Among bacterial infections, *Ureaplasma urealyticum (U. urealyticum)*, *Mycoplasma hominis (M. hominis)* and bacterial vaginosis associated organisms have been linked to an increased risk of miscarriage, as they are thought to interfere with trophoblast formation [19,20]. At the same time, little attention is paid to the possible effect of abnormal genital flora on fetal growth.

## 2. Materials and methods

We performed a systematic review of the literature about the correlation between bacterial vaginosis and FGR in order to provide evidence for the hypothesis that the presence of abnormal vaginal flora can be responsible for intrauterine growth restriction.

We performed a literature search encompassing the last 27-year (starting from 1986) in PubMed, Embase, and Cochrane Central. Keywords and MeSH terms were combined to generate lists of studies: bacterial vaginosis, abnormal microflora, vaginitis,

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mycoplasmata, *U. urealyticum*, *M. hominis*, fetal growth restriction, and birth weight. Papers containing original data were included without language restriction. The outcome measures were diminished fetal growth or small for date birth weight.

## 3. Results

The literature search identified 14 eligible studies (Table 1). Investigators of the John Hopkins study found colonization with *Chlamydia trachomatis* (*C. trachomatis*) (*OR* 2.4, 90% *CI* 1.32–4.18). And *Candida albicans* (*C. albicans)* were significantly associated with FGR (*OR* 1.9, 90% *CI* 1.2–3.14) [21]. The odds ratio for *M. hominis* and FGR did not demonstrate a significant association (*OR* 0.96, 90% *CI* 0.59–1.56) after adjustment to confounding factors like smoking, alcohol intake. In the study of Gravett neonates born to women with BV had lower mean birth weight than did neonates born to women without BV, but the difference was not statistically significant [22]. Analyzing the cohort of 13,914 pregnant women, Germain *et al.* [23] found that vaginal presence of *M. hominis, U. urealyticum*, and the

**Table 1**
Characteristics of studies documenting the influence of abnormal vaginal microflora on fetal weight and fetal growth.

| Study (first author) | Type of study; enrolment into the study | N of pregnant women | BV *n* (%) | Mycoplasma – | Dg method | Birthweight |
|---|---|---|---|---|---|---|
| 1. Gravett *et al.*, 1986 [22] | Prospective | 534 | 102 (19%) | – | Gas-liquid chromatographic identification of microbial organic acid metabolite | 2960 ± 847 g *vs.* 3184 ± 758 g (ns) |
| 2.The John Hopkins Study of Cervicitis and Adverse Pregnancy Outcome, 1986 [21] | Prospective, 22–30 weeks | 801 | 291 (36.3%) | UU 290 (39.8%) MH 205 (25.7%) | Culture from the vagina and cervix | FGR in 35 (9%) ns *OR* 0.96 (95% *CI* 0.59–1.56) |
| 3. Carey *et al.*, 1991 [24] | Multicenter, From 23 to 26 weeks of gestational age | 4,934 | | Vaginal colonization with *U. urealyticum* | Gram stain, Culture from the vagina and cervix | $P > 0.2$ |
| 4. Germain *et al.*, 1994 [23] | Multicenter, From 23 to 26 weeks of gestational age | 13,914 | *Bacteroides, Prevotella*, and *Porphyromonas* sp.p | *M. hominis*, *U. urealyticum* | Speciment from the vagina and cervix | 1.79 95% *CI* 1.27–2.52 |
| 5. Zhou *et al*, 1999 [31] | Prospective, case -control | 100 | | *U. urealyticum* | PCR in samples of cervical secretions | ns |
| 6. Rizvi *et al.*, 2003 [32] | Prospective, at the time of labour | 149 | 95 (65.9%) | | Gram stain, Culture from the vagina and cervix | ns |
| 7. Thorsen *et al.*, 2006 [25] | Population-based prospective, before 24 weeks | 2,927 | 468 (13.7%) | | speciment from the vagina Amsel's clinical criteria | *OR* 1.6 95% *CI* 0.7–3.1 |
| 8. Vogel *et al.*, 2006 [26] | Population-based, prospective cohort at 17 weeks | 2,662 | | | speciment from the vagina Amsel's criteria and culture | 1.with BV only *OR* 1.3 95% *CI* 0.6–2.9 2. with UU only *OR* 1.7 95% *CI* 1.1–2.5 3. with UU + BV *OR* 2.3 95% *CI* 1.3–4.0 |
| 9. Svare *et al.*, 2006 [27] | from 20 weeks | 3,262 | 583 (17%) | | speciment from the vagina, Schmidt and Hansen | 3408 vs. 3511 g, $P < 0.01$; *OR* 1.95, 95% *CI* 1.3–2.9 |
| 10. Kalinka *et al.*, 2006 [34] | 8–16 weeks | 179 | 55 (28.1%) | 20/29.5 | speciment from the vagina, Spiegel's criteria; culture | Birthweight 2864 g with BV vs. 3224 g with N microflora $P = 0.02$ |
| 11. Donders *et al.*, 2008 [16] | Prospective, until 14 weeks | 173 | 18 (10.4%) | | speciment from the vagina culture | BV to birthweight:ns abnormal microflora (VECO score IV) to birthweight: $P < 0.01$ |
| 12. Hemalatha *et al.*, 2008 [30] | Prospective, Case-control at delivery | 148 | 25 (13.8%) | | Gram stain-Nugent score | ns (*P* value not stated) |
| 13.Vedmedovska *et al.*, 2010 [28] | Prospective, Case-control | 156 | 9 (5.8%) | | speciment from the vagina Amsel's criteria | $P = 0.02$ |
| 14. Lata *et al.*, 2010 [33] | Prospective double blind cohort study; at 10 weeks | 200 | 41 (20.5%) | | speciment from the vagina Amsel's criteria | ns (*P* value not stated) |

group *Bacteroides, Prevotella*, and *Porphyromonas* spp., were associated with a significant increased risk for FGR (*OR* 1.79, 95% *CI* 1.27–2.52). Carey *et al*. analyzed cultures from the vagina and cervix of 4934 pregnant women and found that birthweight of newborns from mothers colonized with *U. urealyticum* was significantly lower than those who were not (3 276 g *vs.* 3 325 g, $P < 0.01$) [24]. But after adjustment for ethnicity, parity, smoking and age this difference in the mean birth weight was no longer significant. Also Donders *et al*. [16] found the correlation between abnormal vaginal microflora and reduced fetal head circumference together with diminished birth weight in the study group ($P < 0.0001$), but in his study, specific BV microflora alone was not associated with FGR. In 2006 three studies were published simultaneously regarding abnormalities of vaginal microflora and newborn weight. Thorsen *et al*. [25] followed women from 24 weeks of gestation until delivery in a population-based prospective study and found that BV was associated with small for gestational age (SGA) babies in nulliparous, but not multiparous women. In a study of 3 262 singleton pregnancies included before 20 weeks of gestation Svare *et al.* [27] found that mean birthweight was significantly lower in infants of women with BV than in infants of women without BV (3 408 g *vs.* 3 511 g, $P < 0.01$), where BV was only marginally associated with preterm delivery (*OR* 1.5, 95% *CI* 1.0–2.1). Also after multivariate analyses adjusting for previous miscarriage, smoking, gestational diabetes and fetal death showed this association between BV and low birthweight remained significant (*OR* 2.7, 95% *CI* 1.4–5.1). According to Vogel *et al*. [26] pregnant women with BV had a twofold increased risk of SGA newborns when they were colonized with *U. urealyticum*, leading to the suggestion that *U. urealyticum* may intensify the risk of lower birthweight in women with BV. Kalinka *et al*. [34] studying Chlamydia in pregnancy, demonstrated significant differences in neonatal weight between groups with and without BV. BV was diagnosed in 28.1%, grade II microflora in 71 (36.2%) of the women. As lactobacilli grade II flora [16] often harbours non BV flora like *Escherichia coli* (*E. coli*) and enterococci, the possibility of ascending infection should be considered in some cases. An animal study demonstrated that the fetal and placental weight were significantly lower in *E. coli* infected rats than in the noninfected controls [41].

According to results of Vedmedovska *et al*. genital infections including BV during the current pregnancy were more frequent in the FGR group than in the control group [28]. Furthermore, women with genital infections had four times more frequently Doppler flow abnormalities of the uterine and fetal vessels than control women as a possible explanation for the FGR ($P = 0.02$) [29].

In 4 of 14 papers the authors did not find significant differences of the neonatal birth weight in women with or without BV [30–33].

Recently, a group of Latvian researches studying the effect of Vitamin C on vaginal microflora and the outcome of pregnancy, demonstrated lower birth weights in women with AV (3 497 g *vs.* 3 576 g, $P = 0.045$) and in the group harbouring mixed BV and AV (3 430 g *vs.* 3 576 g, $P = 0.02$) compared to the normal vaginal microflora group.

## 4. Discussion

Although previous reports demonstrate that about 5%–10 % of the cases with FGR may be attributable to viral or protozoan infections in utero, its possible relation to reproductive tract infections was not mentioned [7]. According to results of our literature search, there is also evidence that abnormal vaginal microflora may be involved in the causation of FGR. Ascending genital infections can install low grade intrauterine infection and inflammation, selectively damage the invasive trophoblast cells, disturb placental invasion and result in later placental dysfunction, thereby affecting intrauterine fetal growth potential [35]. The damage of trophoblast cells may be mediated through elevated levels of the proinflammatory cytokine IL-1β and the inhibition of other chemokines. Marconi *et al*. found that the presence of *C. trachomatis* endocervicitis is associated with increased cervicovaginal IL-1b, IL-6 and IL-8 levels in women with concomitant BV, but not in those with normal flora [36]. She and others have found that IL-1b is increased in BV, but not IL-6 and IL-8, and typically, no leukocytosis or other signs of inflammatory response are seen in the vaginal fluid of women with BV [36–39]. Of note, also in women with AV, IL1b is produced in large quantities [36,37].

As altered chemokine production by the trophoblast prevents migration of macrophages into the maternal-fetal interface [35], this altered innate immune responses may have an impact on trophoblast function later in pregnancy and contribute to the pathology, such as first trimester miscarriages [40] and deprived fetal growth. It seems plausible that BV and abnormal vaginal flora have similar effects on the innate immunity of trophoblast in the first trimester and subsequent alterations of spiral artery remodeling during ongoing pregnancy.

Furthermore the association of reproductive tract infections with abnormal Doppler flow pattern types, may predispose the patient to placental abruption, a major cause of the increased perinatal mortality in FGR pregnancies.

Besides above discussed alterations of trophoblast proliferation, a possible explanation of infection related FGR may also be transplacental transfer of virulent bacteria, such as *E. coli* [41], or specific BV associated bacteria directly to the developing fetus, causing low grade congenital bacterial infection in fetal organs. The FGR may also be the result of infection-induced placental changes, such as thrombosis, necrosis and destruction of placental villi [29,42].

Firm conclusions from our literature review are hampered by the heterogeneous gestational age at entry of most studies, different definitions of main outcome, and varying diagnostic methods to define altered microflora. Furthermore, the majority of previous trials were designed to evaluate the effect of BV on premature delivery, missing potentially important association with fetal growth deficiencies. Hence we would advocate that further studies of abnormal vaginal flora in pregnancy would aim to resolve the impact of vaginal and cervical flora alterations on fetal growth potential, using standardized and well defined criteria for both diagnosis of AVF (abnormal vaginal flora) and outcome (SGA newborns).

## Conflict of interest statement

The authors claim that none of them has a potential financial or other interest in the publication of this paper.

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