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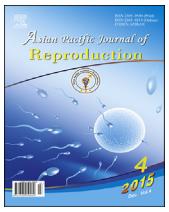

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Is abnormal vaginal microflora a risk factor for intrauterine fetal growth restriction?

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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)