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2 **Retrospective study on** the association of
3 maternal macronutrient intake with urogenital
4 infections during pregnancy **in a Swiss cohort**

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ABSTRACT

Aims: Urogenital infections in pregnancy have been linked to adverse pregnancy outcomes. The objective of this study was to test the hypothesis that macronutrient intake and the relative macronutrient contribution to diet is related to the risk of developing urogenital infections during pregnancy.

Study design: The study is a retrospective single-center cohort study.

Place and Duration of Study: Outpatient Clinic of Obstetrics at the University Hospital Zurich, Switzerland, between January 2009 and December 2010.

Methodology: We included 774 pregnant women with ages ranging from 16 to 47 years with data on urogenital infections and diet history. A diet history based on the food intake of the last seven days of pregnant women was collected in a nutritional counselling program. Diet information was matched with vaginal/urinary/cervical specimens collected within 90 days (range) prior to the nutrition assessment in the same women. The pathogens analysed were: Gram-negative rods, Gram-positive rods, Gram-positive cocci (including group B *Streptococcus*), *Gardnerella vaginalis*, *Chlamydia trachomatis* and *Candida spp.* The covariates were maternal age, BMI, origin and parity. Crude and adjusted OR were determined by logistic regression.

Results: Out of 774 pregnant women 47.7% had any kind of infection. High fat intake was positively associated with *Gardnerella vaginalis* (adjusted OR = 3.6, 95% CI = 1.3 – 10, p = 0.01). No association was seen between macronutrients or their distribution and other pathogens. However, significant associations were found between infections and the covariates.

Conclusions: The findings suggest that increased dietary fat intake is associated with vaginal infections, thereby predisposing women to adverse pregnancy outcomes, thus signifying the importance of appropriate diet during pregnancy.

Keywords: vaginal infection, macronutrients, *Gardnerella vaginalis*, bacterial vaginosis, pregnancy

1. INTRODUCTION

During pregnancy, an imbalance in the vaginal flora favors the colonization of the urogenital system by pathogenic microorganisms. The microbiota dominating a normal vagina, also in pregnancy, are lactobacilli [1-2]. Lactobacilli, which are the characteristic flora of the urogenital tract have been shown to prevent pathogenic bacteria from causing infections. The properties of lactobacilli that help in this protective effect are the production of hydrogen peroxide, bacteriocins and lactic acid [3-5]. The lactic acid decreases the pH of the vaginal environment thereby preventing the colonization of harmful pathogens [5]. Some in vitro studies have also demonstrated the ability of lactobacilli to block adherence of pathogenic bacteria such as *Gardnerella vaginalis* to the vaginal epithelial cells by co-aggregating with them [6].

The vaginal microbiota of women with bacterial vaginosis (BV) consists of higher numbers of *Gardnerella vaginalis*, *Mycoplasma hominis*, *Prevotella*, *Peptostreptococcus*, *Mobiluncus* or *Bacteroides spp.* and lower numbers of lactobacilli [7]. Pregnant women are also susceptible to *Candida spp.*, a fungus type which are known to interact with the other members of vaginal microbiota thereby decreasing the commensal lactobacilli [8]. Urinary tract infections during pregnancy have been reported to be associated with low birth weight and preeclampsia [9]. BV in pregnancy has been associated with endometritis, pelvic inflammatory disease, amniotic fluid infection, preterm delivery, preterm labor and premature rupture of the membranes [10,11]. *Group B Streptococcus* has been implicated in chorioamnionitis, premature rupture of membranes and preterm labor [12]. *Chlamydia trachomatis* has long been associated with adverse pregnancy outcomes such as conjunctivitis and pneumonia in the infant [13].

Studies have shown the association between maternal diet and urogenital infections: In terms of micronutrients, inadequate pre-conceptional iron supplies [14], and maternal vitamin D deficiency [15] are known to be associated with genital tract infections, vaginosis like microflora and BV. With regards to macronutrients, high dietary fat intake has been shown to be associated with increased risk of BV [16].

The primary objective of this study is to test the hypothesis that during pregnancy the nutrient composition of the diet is related to risk of developing vaginal and/or urinary tract infection. It also aims to show a correlation of a particular macronutrient (protein, carbohydrate and fat) with the occurrence of vaginal and/or urinary tract infection caused by common pathogenic microbes such as *Gardnerella vaginalis*, *Candida albicans*, *Chlamydia trachomatis*, Gram-negative

rods, Gram-positive rods and Gram-positive cocci, including *group B Streptococcus*; and to show the correlation of macronutrient contribution to total energy (macronutrient distribution) with the occurrence of vaginal and/or urinary tract infections caused by the aforementioned pathological microbes.

2. MATERIALS AND METHODS

The study is a retrospective single-centre cohort study. We collected data from pregnant women who had a dietary assessment between January 2009 and December 2010 in the outpatient department of the Outpatient Clinic of Obstetrics at the University Hospital Zurich. Inclusion criteria were being pregnant and participating in the nutrition assessment. Exclusion criteria were any chronic infections and communication problems (not German or English speaking). During the dietary assessment (diet history), all information on macronutrients was recorded in a specific data base (Ernährungsanamnese®). In a previous master thesis, the amount (in grams) of macronutrient intake was calculated for each woman [17]. In summary, a trained dietician asked the patient what she ate over the last seven days and recorded the number of standard portions of food items by morning, midday and evening. Snacks were added to the most appropriate daytime. To reduce recall bias a photo book of foods and portion sizes was used for the assessment. The foods were grouped as follows: Milk and yoghurt, cheese, meat and poultry, sausages and cold meat, fish, egg, tofu and quorn, bread, potatoes, pasta and rice, cereals, pulse, vegetables, fruits, oils and butter, sweets and drinks (sweetened and unsweetened separate). The portions were then multiplied with macronutrient content (in gram) given by the Swiss Food Composition Database [18]. Macronutrient intake variable was categorised as low for protein (< 58 grams/day); high for fat (> 80 grams/day) as well as high for carbohydrate (> 330 grams/day). We included in our analysis the average of macronutrients in grams per food group and multiplied each macronutrient by its energy equivalent (fat 9.3, protein and carbohydrate 4.1) to calculate the total energy intake in kcal. Thereafter we calculated the percentage for each macronutrient for each woman. Similar categorisation was applied then to the distribution of each macronutrient in the diet; for protein $\geq 20\%$, for fat $\leq 40\%$ and for carbohydrate $\leq 55\%$ as normal distributions. The intake and distribution limits were set based on DACH 2012 reference values [19]. The patient ID was then matched with data from the Institute of Medical Microbiology, University of Zurich, for information on vaginal swabs and/or urinary bacterial cultures, collected within 90 days (range) prior to dietary assessment of these pregnant women. Ethical approval was given by the local ethical committee (KEK No. 2015-0520).

Vaginal and cervical smears were collected using swabs and specimen collection kits. Midstream specimens of urine were collected in tubes with boric acid. The specimens were then sent to the Institute of Medical Microbiology in the University of Zurich for laboratory analysis.

The standard laboratory procedures involve selective and non-selective culture methods and subsequent identification of selected colonies based on their phenotypic (morphology, metabolism), biochemical (proteins, fatty acids and antigens) and genotypic characteristics. Bacteria were identified and classified based on their Gram staining properties. Gram-positive bacteria retain the initial crystal violet stain and Gram-negative bacteria get discoloured and stain red with carbol fuchsin or safranin. Gram-variable bacteria lyse during staining due to their sensitivity to the Gram stain [20]. Gram stained preparation of direct smear from the cervical specimens was used to identify Gram-positive rods, Gram-negative rods and Gram-positive cocci. Pathogens from the vaginal smear and urine samples were identified by culture methods based on colony morphology. *Chlamydia trachomatis* was identified using polymerase chain reaction (PCR), a simple and rapid method for the identification of a wide spectrum of bacteria by amplification of selected sections of DNA. *Candida sp.* were identified by culture based methods, MALDI-TOF and ID 32C systems. The techniques used in pathogen identification are discussed in detail elsewhere [21-24].

Based on the laboratory reports and Gram staining properties the pathogens were classified. *Enterobacter aerogenes*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Escherichia coli* were classified as Gram-negative rods. *Corynebacterium sp.* were classified as Gram-positive rods. *Enterococcus sp.*, viridans streptococci, *Staphylococcus aureus* and coagulase-negative *Staphylococcus* species were grouped as Gram-positive cocci. Group B *Streptococcus* was examined as a separate group. *Gardnerella vaginalis* was considered as Gram-variable rod.

Not all women were tested for all pathogens. The pathogen groups along with *group B Streptococcus*, *Chlamydia trachomatis* and *Candida sp.* were categorized into dichotomous variables based on the presence or absence of the pathogen and each pathogen group was analysed separately. Additionally, all women who had any infection with one or

more of the mentioned pathogens were summarized in a group called 'any infection'. The BMI categories included ≤ 25 kg/m² and >25 kg/m². The parity categories included ≤ 3 and >3 deliveries [25]. The age was categorised as < 30 and ≥ 30 years and finally the origin variable was categorised as Swiss and non-Swiss.

3. RESULTS AND DISCUSSION

3.1 Results

Data from nutrition assessment were available from 884 pregnant subjects. Out of them, 774 subjects with data on vaginal and/or urinary tract infections collected within 90 days prior to dietary assessment were included in the study. Of this group 47.7% had any infection and more than two thirds (68.9%) had a non-Swiss nationality. Characteristics of the study participants are displayed in Table 1.

Table 1 Characteristics of study cohort (N=774)

BMI (mean, standard deviation)	23.19 (4.61)
BMI > 25 kg/m ² (N, %)	179 (23.1)
Age (mean, standard deviation)	30.71 (5.55)
Age > 30 y (N, %)	446 (57.6)
Parity 1 (first child), (N, %)	538 (69.5)
Parity > 3 (N, %)	22 (2.8)
Swiss nationality (N, %)	241 (31.1)
Weeks of gestation at nutrition assessment (range)	6 to 37

In table 2 the distribution of the pathogens and of high or low macronutrient intake are listed.

Table 2 Distribution of pathogens and macronutrient intake

Macronutrient	Intake N (%)	Distribution N (%)
Low Protein	261 (33.7)	412 (53.2)
High Fat	26 (3.4)	25 (3.2)
High Carbohydrate	5 (0.7)	271 (35)
Pathogens	Tested N (%)	Tested Positive N (%)
Any Infection	774 (100)	369 (47.7)
<i>Streptococcus B</i>	571 (73.8)	101 (17.7)
<i>Chlamydia</i>	325 (42)	9 (2.8)
<i>Candida</i>	536 (69.2)	131 (24.4)
<i>Gardnerella vaginalis</i>	502 (64.8)	97 (19.3)
Gram-negative rods	496 (64.1)	91 (18.3)
Gram-positive rods	449 (58)	44 (9.8)
Gram-positive cocci	518 (67)	113 (21.8)

When analysing the OR for any infection, we did not find a significant association between any pathogen and macronutrient intake or macronutrient distribution (P value: 0.36 – 1.0). We found a significantly higher risk for infection for younger women (≤ 30) compared to women older than 30 years ($P=0.02$), as well as higher risk for women with a BMI > 25 ($P = 0.01$). A trend for higher risk in Non-Swiss women was detected ($P = 0.07$).

The 571 pregnant women tested for *group B Streptococcus* were aged 30.6 ± 5.5 y with BMI 23.2 ± 4.5 kg/m². We did not find a significant relationship between *group B Streptococcus* and macronutrient intake or macronutrient distribution (P : 0.14 – 1.0).

Women tested for *Chlamydia trachomatis* (n=325) were aged 30 ± 5.5 years with BMI 23.6 ± 4.8 kg/m². We did not find a significant association between *Chlamydia trachomatis* and macronutrient intake or macronutrient distribution (P : 0.49 - 1.0). For younger women below 30 years there was again an increased risk for *Chlamydia infection* (P = 0.01).

The number of pregnant women tested for *Candida sp.* was 536. These women were aged 30.8 ± 5.6 y with BMI 23.1 ± 4.5 kg/m². There was no significant association between *Candida sp.* and macronutrient intake or macronutrient distribution (P value: 0.25 – 1.57). For women of BMI>25 (P = 0.009) and age less than 30 y (P = 0.01), there was an increased risk of *Candida sp.* infection. Women with more than three children were shown to have a higher risk of infection (P = 0.008) in a multivariate logistic regression.

The 502 pregnant women tested for *Gardnerella vaginalis* were aged 31 ± 5.4 y with BMI 23.2 ± 4.4 kg/m². We found a significant association between high fat intake and *Gardnerella vaginalis* (P = 0.05). Higher risk was also detected in women with more than 3 children (P = 0.01), BMI > 25 (P = 0.002) and age < 30 (P = 0.01). The results for the logistic regression are listed in table 3.

Table 3 The association of the study variables and the covariates with *Gardnerella vaginalis* by multivariate logistic regression model

Variables/Covariates	OR	95% CI	P value
Fat intake	3.6	1.3 - 10	0.01
Parity	4.7	1.4 -15.9	0.01
BMI	2.0	1.2 -3.4	0.004
Age	0.4	0.3 -0.7	0.003
Origin	1.2	0.7 -1.9	0.4

The number pregnant women tested for Gram-negative rods was 496 with median age of 31.2 ± 5.5 y and BMI 23.1 ± 4.5 kg/m². No significant association was seen between Gram- negative rods and macronutrient intake or macronutrient distribution (P : 0.21 – 0.72). We revealed a significantly higher risk of infection for women with a BMI > 25 kg/m² (P = 0.01) and for non-Swiss women (P = 0.04).

The 449 pregnant women tested for Gram-positive rods were aged 31.2 ± 5.4 y with BMI 22.9 ± 4.4 kg/m². We did not find a significant association between Gram-positive rods and macronutrient intake or macronutrient distribution (P : .25 – 1.0).

The number of pregnant women tested for Gram-positive cocci was 518. The women were aged 31.2 ± 5.5 y with BMI 22.9 ± 4.2 kg/m². There was no significant association between Gram-positive cocci and macronutrient intake or macronutrient distribution (p value: 0.35 – 1.0). A higher risk was shown in the non-Swiss women (P = .04).

3.2 Discussion

In this study, the association of maternal macronutrient intake and the relative macronutrient distribution in maternal diet with vaginal/urinary tract infections in pregnancy was examined. The microorganisms that are known to be part of the polymicrobial community involved in vaginal and urinary tract infections, were studied as separate entities. Significant association was found between excessive fat intake and infection with *Gardnerella vaginalis*. The mechanism behind this association could be based on the findings which suggest that fatty acids modulate immune function and inflammatory

status. The mucosal immune system is regulated by the gut-associated lymphoid tissue [26]. The innate immune cells are known to sense lipopolysaccharide (LPS), a pathogen associated molecular pattern, by activation of Toll like receptor (TLR4) resulting in a series of signaling events, stimulating the production of inflammatory mediators [27]. Dietary fatty acids may influence the mucosal immune system by mimicking the LPS inflammatory response [28]. Specific polymorphisms in genes encoding for the cytokines and TLR4 have been associated with hyporesponsiveness to mucosal stimulation resulting in increased risk of inflammatory diseases. It has been shown that few of these polymorphisms are associated with BV in pregnancy [29]. Therefore, with genetic variation the role of fatty acids in the modulation of immune function may be altered. It is also shown that blood levels of LPS increased after consumption of a meal rich in saturated fatty acids but decreased following a meal rich in n-3 polyunsaturated fatty acids [30] implying that the type of fatty acids may influence the production of inflammatory mediators. The amount of dietary fat along with the type of fat is also shown to influence immune response [31]. The influence of dietary fat on the alteration of vaginal pH could also increase the risk of vaginal infections. Reports have suggested that diet rich in saturated or unsaturated fatty acids can alter serum steroid concentration which in turn may influence vaginal pH [32]. A significant association has been reported between dietary fat intake and vaginal pH in pregnant women suggesting that a high fat intake may alter the vaginal pH thereby increasing the risk of BV during pregnancy [16].

Bacterial vaginosis in pregnancy has been shown to be a risk factor for spontaneous pregnancy loss and preterm delivery [33]. Although bacterial vaginosis is known to be polymicrobial in nature, the likelihood of *Gardnerella vaginalis* being the initiating organism has been shown [34]. Increasing evidence suggests that *Gardnerella vaginalis* is capable of greater adherence to vaginal epithelial cells and biofilm formation, aiding the adherence and growth of intermediate BV associated anaerobes, eventually establishing a symbiotic relationship with them [35].

In our study, a significant association was seen between the covariates and the pathogens. It was shown that older age group (>30 y) is associated with decreased risk of *Chlamydia sp.*, *Candida sp.* and *Gardnerella vaginalis*; higher BMI (> 25 kg/m²) with increased risk of *Candida sp.*, *Gardnerella vaginalis* and Gram-negative rods; multiparity (>3) with increased risk of *Candida sp.* and *Gardnerella vaginalis*. Participants of non-Swiss origin were seen to be associated with increased risk of infections with Gram-negative rods and Gram-positive cocci. Other studies have also shown the association of age, parity, BMI and origin with vaginal flora imbalances and urogenital infections [36-38].

The strengths of the study include a large sample size and the control for known confounders/covariates that may influence the vaginal microbiome namely age, parity, BMI and origin. The results showing the association of the covariates with infections are consistent with studies involving the same covariates, indicating a proper sample. As the screening for these infections is a standard procedure performed for every pregnant subject there is minimal chances of missing data and the analysis of pathogens was done as separate entities.

The limitations of the study include the possibility of change in dietary behavior during the time interval between the sample collection and dietary assessment; NVP (nausea and vomiting of pregnancy) being a common experience altering dietary behavior mainly in the first trimester of pregnancy. The diet history program used for the dietary assessment has not been validated and information about probiotics intake, which have been correlated with lower risks of BV was missing [39]. Several potential confounders that were not available for the study such as smoking, douching, sexual behaviour and personal hygiene practices which could have interfered with the results. The generalization of the findings needs to be addressed with caution as only 3.6% of the subjects tested for *Gardnerella vaginalis* had high fat intake.

4. CONCLUSION

High fat intake might influence the composition of the vaginal flora. Further investigations on the potential relationship between maternal fat intake and *Gardnerella vaginalis* should focus on the type of fat. The findings of this study could be replicated with sample collection and dietary assessment done on the same day and include other potential confounders. Future research also needs to examine the protective dietary factors that could ward off vaginal and urinary tract infections during pregnancy.

In summary, the findings of this study are consistent with a prior study by Neggers et al [16] and suggest that dietary fat intake may be associated with *Gardnerella vaginalis*, which has been shown to play a pivotal role in the pathogenesis of BV. The findings emphasize on the significance of optimal nutrition during pregnancy and could be used to improve clinical counselling for pregnant women to avoid vaginal and urinary tract infections.

ACKNOWLEDGEMENTS

We thank Dr. Vera Bruderer of Institute of Microbiology, University of Zurich, for her support on techniques in bacterial sampling.

COMPETING INTERESTS

The authors declare that they have no conflict of interest.

AUTHORS' CONTRIBUTIONS

AVS und KQL designed the study and performed the analyses. AVS prepared the first manuscript. All authors have approved the final manuscript

ETHICAL APPROVAL

Ethical approval was given by the local ethical committee (KEK No. 2015-0520).

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