



Year: 2018

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Abstract: Aims: Urogenital infections during pregnancy have been linked to adverse pregnancy outcomes. The objective of this study was to test the hypothesis that macronutrient intake and relative macronutrient contribution to diet is related to the risk of developing urogenital infections during pregnancy. Study Design: This 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 of ages ranging from 16 to 47 years with data on urogenital infections and diet history. A diet history of these pregnant women based on food intake during the last seven days was collected in a nutritional counselling program. Diet information of these same women was matched with vaginal/urinary/cervical specimens collected within 90 days (range) prior to the nutrition assessment. The pathogens analyzed included 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, body mass index (BMI), origin, and parity. Crude and adjusted odds ratios (ORs) were determined by logistic regression. Results: Among the 774 pregnant women, 47.7% had some kind of infection. High fat intake was positively associated with Gardnerella vaginalis (adjusted OR=3.6; 95% confidence interval (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 covariates. Conclusions: Findings suggested that increased dietary fat intake is associated with vaginal infections, thereby predisposing women to adverse pregnancy outcomes. This signified the importance of appropriate diet during pregnancy.

DOI: <https://doi.org/10.9734/ejnfs/2018/42904>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-168814>

Journal Article

Published Version



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Originally published at:

Snophan, Agusta Viola; Quack Lötscher, Katharina C (2018). Retrospective Study on the Association between Maternal Macronutrient Intake and Urogenital Infections during Pregnancy in a Swiss Cohort. European Journal of Nutrition, 8(4):225-232.

DOI: <https://doi.org/10.9734/ejfnfs/2018/42904>



Retrospective Study on the Association between Maternal Macronutrient Intake and Urogenital Infections during Pregnancy in a Swiss Cohort

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Authors' contributions

This work was carried out in collaboration between both authors. Authors AVS and KCQL designed the study and performed the analyses. Author AVS prepared the first manuscript. Both authors approved the final manuscript.

Article Information

DOI: 10.9734/EJNFS/2018/42904

Original Research Article

Received 24th June 2018
Accepted 23rd August 2018
Published 5th September 2018

ABSTRACT

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

Study Design: This 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 of ages ranging from 16 to 47 years with data on urogenital infections and diet history. A diet history of these pregnant women based on food intake during the last seven days was collected in a nutritional counselling program. Diet information of these same women was matched with vaginal/urinary/cervical specimens collected within 90 days (range) prior to the nutrition assessment. The pathogens analyzed included 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, body mass index (BMI), origin, and parity. Crude and adjusted odds ratios (ORs) were determined by logistic regression.

Results: Among the 774 pregnant women, 47.7% had some kind of infection. High fat intake was positively associated with *Gardnerella vaginalis* (adjusted OR=3.6; 95% confidence interval (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 covariates.

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Conclusions: Findings suggested that increased dietary fat intake is associated with vaginal infections, thereby predisposing women to adverse pregnancy outcomes. This signified the importance of appropriate diet during pregnancy.

Keywords: Vaginal infection; macronutrients; *Gardnerella vaginalis*; bacterial vaginosis; pregnancy.

1. INTRODUCTION

During pregnancy, an imbalance in vaginal flora favors colonization of the urogenital system by pathogenic microorganisms. The microbiota dominating a normal vagina (during pregnancy as well) are lactobacilli [1,2]. It has been shown that lactobacilli, the characteristic flora of the urogenital tract, can 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]. 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 the adherence of pathogenic bacteria such as *Gardnerella vaginalis* to 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 type of fungus known to interact with 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 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 preconceptional iron supplies [14] and maternal vitamin D deficiency [15] are known to be associated with genital tract infections, vaginosis like microflora

and BV. With regard to macronutrients, high dietary fat intake has been shown to be associated with increased risk of BV [16].

The primary objective of this study was to test the hypothesis that during pregnancy the nutrient composition of diet is related to the risk of developing vaginal and/or urinary tract infections. It also aimed to show the correlation of a particular macronutrient (protein, carbohydrate, and fat) with the occurrence of vaginal and/or urinary tract infections 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

This is a retrospective single center cohort study. We collected data from pregnant women who participated in 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 database (Ernährungsanamnese®). In a previous master's 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 as per morning, midday, and evening. Snacks were added to the most appropriate time of day. To reduce recall bias, a photo book of foods and portion sizes was used for the assessment. Foods were grouped as follows: milk and yoghurt, cheese, meat and poultry, sausages and cold meat, fish, eggs, tofu and

quorn, bread, potatoes, pasta and rice, cereals, pulses, vegetables, fruits, oils and butter, sweets, and drinks (sweetened and unsweetened separately). The portions were then multiplied with macronutrient content (in grams) given by the Swiss Food Composition Database [18]. The macronutrient intake variable was categorised as low for protein (<58 grams/day) and high for fat (>80 grams/day) and carbohydrate (>330 grams/day). In our analysis, we included 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) in order to calculate the total energy intake in kcal. Thereafter, we calculated the percentage of each macronutrient for each woman. Similar categorization was then applied to the distribution of each macronutrient in the diet (normal distribution: for protein $\geq 20\%$; for fat $\leq 40\%$; and for carbohydrate $\leq 55\%$). 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 (IMM), University of Zurich for information on vaginal swabs and/or urinary bacterial cultures collected within 90 days (range) prior to the dietary assessment of these pregnant women. Ethical approval was given by the local ethics committee (KEK No. 2015-0520).

Vaginal and cervical smears were collected using swabs and specimen collection kits (eSwab™), and midstream specimens of urine were collected in tubes with boric acid. The specimens were sent on the same day to IMM at room temperature for instant laboratory analyses.

Standard laboratory procedures involve selective and non-selective culture methods, and subsequent identification of selected colonies based on their phenotypic (morphology and metabolism), biochemical (proteins, fatty acids, and antigens), and genotypic characteristics [20]. Gram-stained preparation of direct smears from the cervical specimens was used to identify Gram-positive rods, Gram-negative rods and Gram-positive cocci. Pathogens from vaginal smears and urine samples were identified by culture methods based on colony morphology or other appropriate techniques used in routine analysis. *Candida sp.* was identified by culture-based methods, MALDI-TOF, and ID 32C systems. The techniques used in pathogen identification are discussed in detail elsewhere [21–24].

Pathogens were classified based on laboratory reports and Gram-staining properties.

Enterobacter aerogenes, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Escherichia coli* were classified as Gram-negative rods. *Corynebacterium sp.* was classified as a Gram-positive rod. *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 a 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 analyzed 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 $\leq 25 \text{ kg/m}^2$ and $> 25 \text{ kg/m}^2$. The parity categories included ≤ 3 and > 3 deliveries [25]. Maternal age was categorized as < 30 and ≥ 30 years. Finally, the origin variable was categorised as Swiss and non-Swiss.

Chi-square test was used to analyze differences in the distribution of variables. A *P* value of ≤ 0.05 was considered statistically significant. The measure of association reported in this study is OR. Unadjusted and adjusted models were analyzed. Multivariable models were adjusted for BMI, age, origin, and parity; these are potential confounders known to be significantly associated with vaginal or urinary tract infections. Strength of association was calculated as OR in a multivariable analysis with 95% CI and *P* values of < 0.05 . Multivariable analysis was performed using a stepwise logistic regression model with Stata (Version 14.1, StataCorp LP, Texas, USA).

3. RESULTS AND DISCUSSION

3.1 Results

Nutrition assessment data were available from 884 pregnant subjects. Among 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. In this group, 47.7% had some kind of infection and more than two thirds (68.9%) were of 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 years (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 |
| Protein intake in grams (mean, standard deviation) | 67.5 (20.8) |
| Fat intake in grams (mean, standard deviation) | 42.5 (17.1) |
| Carbohydrate intake in grams (mean, standard deviation) | 177.4 (49.9) |

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 group 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) |

Table 2 lists the distribution of pathogens, and high or low macronutrient intake.

When analyzing OR for any kind of infection, we did not find any significant association between any pathogen and macronutrient intake or macronutrient distribution (P value: 0.36–1.0). We found a significantly higher risk of infection in younger women (≤ 30) as compared to women older than 30 years ($P=0.02$). We also found a higher risk in women with BMI >25 ($P=0.01$). Moreover, a trend of 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 years with BMI 23.2±4.5 kg/m². We did not find any significant relationship between *group B Streptococcus* and macronutrient intake or macronutrient distribution (P : 0.14–1.0).

The women who were tested for *Chlamydia trachomatis* (n=325) were aged 30±5.5 years with BMI 23.6±4.8 kg/m². We did not find any 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 of *Chlamydia* infection ($P=0.01$).

The number of pregnant women tested for *Candida sp.* was 536. These women were aged 30.8±5.6 years with BMI 23.1±4.5 kg/m². There was no significant association between *Candida sp.* and macronutrient intake or macronutrient distribution (P : 0.25–1.57). For women aged less than 30 years ($P=0.01$) and with BMI >25 ($P=0.009$), 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 years 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 three children ($P=0.01$), BMI >25 ($P=0.002$) and age <30 ($P=0.01$). Results for the logistic regression are listed in Table 3.

Table 3. The association between study variables and covariates for *Gardnerella vaginalis* in a 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 | 0.71.9 | 0.4 |

The number of pregnant women tested for Gram-negative rods was 496 with median age of 31.2±5.5 years 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 in women with 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 years with BMI 22.9±4.4 kg/m². We did not find any significant association between Gram-positive rods and macronutrient intake or macronutrient distribution (*P*: 0.25–1.0).

The number of pregnant women tested for Gram-positive cocci was 518. The women were aged 31.2±5.5 years with BMI 22.9±4.2 kg/m². There was no significant association between Gram-positive cocci and macronutrient intake or macronutrient distribution (*P*: 0.35–1.0). A higher risk was shown in the non-Swiss women (*P*=0.04).

3.2 Discussion

This study examined the association between maternal macronutrient intake and relative macronutrient distribution in maternal diet and vaginal/urinary tract infections during pregnancy. The microorganisms 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 *Gardnerella vaginalis* infection. The mechanism behind this association could be based on findings suggesting that fatty acids modulate immune functions and inflammatory status. The mucosal immune system is regulated by the gut-associated lymphoid tissue [26]. Innate immune cells are known to sense lipopolysaccharides (LPS), a pathogen-associated molecular pattern, by the activation of Toll-like receptor (TLR4),

resulting in a series of signaling events that stimulate 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 cytokines and TLR4 have been associated with hyporesponsiveness to mucosal stimulation resulting in increased risk of inflammatory diseases. It has been shown that a few of these polymorphisms are associated with BV in pregnancy [29]. Therefore, the role of fatty acids in the modulation of immune functions may be altered with genetic variation. It has also been shown that blood levels of LPS increased after the 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 acid may influence the production of inflammatory mediators. The amount of dietary fat along with the type of fat influences 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 a diet rich in saturated or unsaturated fatty acids can alter the 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 and thereby increase the risk of BV during pregnancy [16].

BV during pregnancy is a risk factor for spontaneous pregnancy loss and preterm delivery [33]. Although BV 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 and eventually establishing a symbiotic relationship with them [35].

In our study, a significant association was seen between covariates and pathogens. It was shown that an older age group (>30 years) is associated with decreased risk of *Chlamydia sp.*, *Candida sp.*, and *Gardnerella vaginalis*; higher BMI (>25 kg/m²) is associated with increased risk of *Candida sp.*, *Gardnerella vaginalis*, and Gram-negative rods; and multiparity (>3) is associated 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 between age, parity, BMI, origin and vaginal flora imbalances as well as urogenital infections [36–38].

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

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

4. CONCLUSION

High fat intake may influence the composition of 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 can be

replicated with sample collection and dietary assessment done on the same day and include other potential confounders. Future research also needs to examine protective dietary factors that could ward off vaginal and urinary tract infections during pregnancy.

In summary, findings of this study were consistent with a prior study by Neggers et al. [16] and suggested 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 emphasized the significance of optimal nutrition during pregnancy and can be used to improve clinical counselling for pregnant women to avoid vaginal and urinary tract infections.

ETHICAL APPROVAL

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

ACKNOWLEDGEMENTS

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

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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