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ABSTRACT BOOK

INTERNATIONAL SOCIETY FOR ISIDOG INFECTIOUS DISEASES IN OBSTETRICS AND GYNECOLOGY

F.1 Mixed vaginitis in third trimester of pregnancy are associated with adverse pregnancy outcomes a cross-sectional study

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Introduction/Aim: To clarify the epidemiological characteristics, risk factors, clinical symptoms and signs, laboratory features, and pregnancy outcomes of women with mixed vaginitis during late pregnancy.

Methods/Patients: The population consisted of 1103 women in late pregnancy who attended the Tianjin Medical University General Hospital from November 2019 to September 2020. Standardized questionnaires, vaginal discharge laboratory examinations and follow-up pregnancy outcomes were performed on this population. Chi-square test and logistic regression analysis were used to analyze this information. $P<0.05$ is considered statistically significant.

Results: A total of 1103 women were enrolled in the study, and 1075 women were finally enrolled according to the completeness of delivery outcome. The incidence rate of vaginitis during late pregnancy was 19.3% (207/1075). The incidence rate of mixed vaginitis during late pregnancy was 4.1% (44/1075). The independent risk factors for women with mixed vaginitis in late pregnancy were a positive glucose tolerance test during pregnancy (OR = 2.697, 95% CI 1.293-5.625) and a history of vaginitis during this pregnancy (OR = 2.276, 95% CI 1.030-5.032). Mixed vaginitis has complex symptoms and signs, which was difficult to distinguish from the corresponding single vaginitis. Compared with women without vaginitis, women with mixed vaginitis have an increased incidence of puerperal infections (6.8% vs. 1%; $P<0.05$).

Discussion: Mixed vaginitis in late pregnancy leaded to an increased incidence of puerperal infections. Positive glucose tolerance test during pregnancy and a history of vaginitis during this pregnancy are the independent risk factor for mixed vaginitis in the third trimester. Patients with mixed vaginitis had complex genital symptoms and signs, which will delay the diagnosis and treatment of mixed vaginitis when it's confused with single vaginitis. Early intervention and differential diagnosis is very important to prevent mixed vaginitis in late pregnancy and adverse pregnancy outcomes.

F.2 Do pregnant women with obstetric medical history have a vaginal microbiome associated with higher recurrence risk of preterm birth

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Introduction: Every year 14.9 million babies are born preterm worldwide (before 37 weeks of gestation), this is 11% of all live births and the incidence still increases. Previous cohort studies identified AVF (abnormal vaginal flora) and an increase in vaginal pH as important risk factors. During normal pregnancy lactobacillus spp. dominate the vaginal microbiome. More diversity in microbiome and a less stable microbiome with reduced or absent lactobacilli seems to be associated with higher risk of preterm birth, mainly in early pregnancy.

Aim: The investigation of a difference in vaginal microbiome in the first trimester of pregnancy in women with and without obstetric medical history.

Methods/Patients: 360 pregnant women were included in the ProPreB trial (a double blind double dummy Placebo controlled multicenter prospective trial using Prophylactic Treatment with Vaginal and Oral Exogeneous Probiotic lactobacilli in Women with Abnormal Vaginal Flora tot Prevent Preterm Birth), in 2 Flemish centers. Vaginal smears were sampled at the first visit in the first pregnancy trimester (AD 6w+1d and 13w+6d). This study (nested case control study) compares the vaginal microbiome of pregnant women with and without obstetric medical history Odds ratio's were calculated and interpreted with a 95% confidence interval. The vaginal microbiome was analysed by microscopy and culture. A DNA extraction is ongoing at the Institute of General and Molecular Pathology, Antwerp University.

Results: A total of 360 women were included in this study, 244 without obstetric medical history and 116 (32%) with obstetric medical history (miscarriage (early/late, premature birth). Compared to women without obstetric medical history, significantly more aërobic flora was found in women with obstetric medical history in the first trimester smear analysis (OR 1.89, 95% CI 1.058-3.402, p 0.015). In addition candida is less present in the vaginal microbiome of women with obstetric medical history compared to those without obstetric medical history (OR 0.33, 95% CI 0.122-0.873, p 0,013).

Discussion: However most data in literature show a link between bacterial vaginosis and miscarriage/ preterm birth, we found that abnormal aerobic microflora (aërobic vaginitis) is linked to miscarriage and preterm birth, and not bacterial vaginosis. As far as we know, this is the first report which proves that a obstetric medical history is linked to Aërobic vaginitis in early pregnancy, and thus increases the risk of recurrent preterm birth.

F.3 In vitro study of polybacterial infection of chorioamniotic membranes: modulation of immune response at maternal-fetal interface

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Introduction/Aim: Preterm labor (PTL) is considered one of the main obstetric clinic problems that occurs in almost 10% of all pregnancies in the world. Polybacterial invasion and inflammation of the amniotic cavity is a common scenario in PTL that results in host inflammatory response(1). Among this bacteria diversity, the most frequently detected bacteria in the amniotic fluid of cases of PTL are Mycoplasma hominis and Ureaplasma. spp. We aimed to evaluate the production and kinetics of inflammatory mediators in in vitro models of fetal membrane coinfection with mycoplasmas and other bacteria species.

Methods/Patients: Fetal membranes collected from healthy pregnancies by c-section were stimulated with heat-killed genital micoplasmas (Mycoplasma hominis, Ureaplasma parvum), Streptococcus agalactiae and Fusobacterium nucleatum, alone or in combination. Culture supernatants were collected at five different time-points: 0h, 6h, 12h, 18h, and 24h. Interleukin (IL) -1, IL-6, IL-8, IL-10 and Factor Necrosis Tumoral alpha (TNF-α) were measured in the culture medium by immunoenzymatic assay (ELISA).

Results: Stimulation by genital mycoplasmas, alone or in combination, increased the levels of proinflammatory cytokines in relation to control group, whereas F. nucleatum and S. agalactiae did not produce significant differences. The TNF-α production was detected six hours after bacterial stimulation. Mycoplasmas, alone or in combination (Mh+Up), induced increased levels of this cytokine after 6 and 12 hours of incubation ($p<0.05$). Furthermore, IL-6 was significant increased after 18 hours in mycoplasmas groups, alone or in combination, and after 24 hours in the groups with mycoplasmas and F. nucleatum and S. agalactiae. A significant increase in IL-10 concentration was seen after 18 hours of stimulation among mycoplasmas groups, either alone or combined [669.50 (56.67-924.60) pg/mL] ($p<0.05$). Stimulation of M. hominis alone showed a peak of concentration in the moment 24 hours, but when combined with U. parvum the highest production occurred at moment 18h.

Discussion: Different combinations of opportunistic pathogens were evaluated at various time points after stimulation, showing the cytokines kinetics, including the anti-inflammatory profile by IL-10 concentration. As in previous studies (2), we found that host inflammatory response varies based on the species and the combination of bacteria. M. hominis and U. parvum sustain a proinflammatory response in

the fetal membranes in vitro alone or in combination. In our study, TNF-α was detected from 6h-culture in all groups, which was in agreement with other study that its concentration was reported to be increased in the amniotic fluid in cases of intra-amniotic infection (3). Considering S. agalactiae and F. nucleatum, these species did not have the same response in isolated groups, but in combination with Mycoplasmas may result in a proinflammatory pattern with a balance of anti-inflammatory response.

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Distribution of Gardnerella species in pregnant women with and without bacterial vaginosis from Bukavu, Democratic Republic of Congo

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Introduction/Aim: Bacterial vaginosis (BV) is a dysbiosis of the healthy vaginal microbiome (VMB) causing symptoms such as vaginal discharge, itching, burning and malodor. BV is the most common gynecological condition among women of reproductive age worldwide and is associated with important adverse pregnancy outcomes. Gardnerella vaginalis has been identified as a key pathogen in BV, although it is also frequently isolated from women without vaginal dysbiosis. We recently clarified the taxonomy of Gardnerella with the identification of at least 13 (genomo)species [1]. We published three of these as new species (G. leopoldii, G. piotii, G. swidsinskii) and emended the description of G. vaginalis. Here, we aimed to document the prevalence of the different Gardnerella species in pregnant women with and without BV and identify correlates of the different Gardnerella species with clinical signs and symptoms of BV.

Methods/Patients: In Bukavu, Democratic Republic of Congo, 533 pregnant women were recruited between 16 and 20 weeks of gestation. Nugent scoring was used for diagnosing BV and cervicovaginal lavages were analyzed from 331 participants for G. leopoldii, G. piotii, G. swidsinskii and G. vaginalis with in-house developed qPCR assays. Additionally, Lactobacillus crispatus, L. iners and Atopobium vaginae were also analyzed to study the VMB as a whole. Clusters of women with a distinct pattern of species distribution were defined after hierarchical clustering.

Results: In this study population, G. vaginalis was the most prevalent Gardnerella species (33.8%), followed by G. piotii (23.0%), G. swidsinskii (18.4%) and G. leopoldii (14.5%). Not one of the four Gardnerella species was significantly associated with the most important clinical signs and symptoms of BV. Four

clusters of BV-positive women were defined. All four contained G. vaginalis and A. vaginae, in addition to G. swidsinskii (cluster 1), G. swidsinskii and G. piotii (cluster 2), G. piotii (cluster 3) or G. leopoldii (cluster 4). In the clusters with women without BV, only two Gardnerella species were detected: G. vaginalis and G. piotii. Two clusters were significantly associated with clinical symptoms of BV, i.e. cluster 1 with vaginal discharge ($p = 0.044$) and cluster 4 with burning sensation after sexual intercourse ($p = 0.019$).

Discussion: Here, the distribution of G. leopoldii, G. piotii, G. swidsinskii and G. vaginalis among pregnant women was described for the first time. All Gardnerella species appear to be involved in (asymptomatic) BV. In healthy women, only G. leopoldii and G. swidsinskii were not observed, which might suggest they are not commensals. Further studies of clusters of women with distinct distribution patterns of species are needed to help clarify the role of the different Gardnerella species in the pathogenesis of BV.

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Torquetenovirus in the vagina of pregnant women: a biomarker for microbiome composition and cervical length

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Introduction/Aim: Torquetenovirus (TTV) is an endogenous DNA virus present in biological fluids in a majority of healthy individuals. While non-pathogenic, its titer is a sensitive measure of immune status. The higher the TTV titer the greater is the level of immune suppression. In pregnant women, the dominance of L. iners, G. vaginalis or other non-Lactobacillius species is associated with altered immunity, decreased cervical length and increased susceptibility to preterm birth, while L. crispatus dominance is associated with immune quiescence, an adequate cervical length and normal pregnancy outcome. We measured the TTV titer in vaginal secretions from pregnant women and assessed its relation to vaginal microbiome composition, vaginal compound composition and cervical length.

Methods/Patients: TTV titers in vaginal secretions from 462 mid-trimester pregnant Brazilian women were determined by quantitative gene amplification analysis. Composition of the vaginal microbiome was assessed by analysis of the V1-V3 regions of 16S rRNA genes. Concentrations of D- and L-lactic acid, tissue inhibitor of matrix metalloproteinase (TIMP-1), matrix metalloproteinase (MMP)-8 and MMP-9 were quantified by ELISA. Cervical length was determined by transvaginal ultrasonography.

Results: TTV was detected in 60.4% of the vaginal samples. The TTV titer was lower when Lactobacillus crispatus was dominant as compared to when L. iners ($p = 0.0094$) or Gardnerella vaginalis ($p = 0.0043$) dominated. The TTV titer was inversely proportional to L. crispatus abundance ($p<0.0001$) and directly proportional to levels of G. vaginalis ($p = 0.0008$), L. iners ($p = 0.0271$) and Atopobium vaginae ($p = 0.0165$). The TTV titer was highest in women with a cervical length <25mm ($p=0.0268$), proportional to TIMP-1, MMP-8 and MMP-9 ($p<0.001$) levels and inversely proportional to the level of D-lactic acid ($p = 0.0086$). Women with a short cervix were treated with progesterone and so there was no association between TTV and pregnancy outcome.

Discussion: The TTV titer in vaginal secretions reflects the immune status in the lower genital tract in pregnant women and is a predictor of microbiome composition and cervical length.

Mycoplasma genitalium in women in Germany

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First isolated in 1981, much is still unknown regarding its natural history in untreated infection. It is recognized as a sexually transmitted pathogen causing acute and chronic non-gonococcal urethritis, with a growing body of evidence to suggest it also causes cervicitis and pelvic inflammatory disease in women. Asymptomatic infections are common.

Guidelines recommend azithromycin 1,5 g and a test of cure after a minimum of 3 weeks. Our own data in the center of sexual health Bochum showed 11,2% positive tests (men included), a treatment control was done in 78,8% with a 90,4% cure rate. About 1/3 of infections of women were symptomatic. Multiple side Infections were common. We therefore always offer oral, vaginal and anal swabs (pooling possible). Other than in men (especially MSM) we saw no azithromycin resistance in women.

F.4 Aerobic Vaginitis Diagnosis Criteria Combining Gram Stain with Clinical Features: An Establishment and Prospective Validation Study

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Introduction/Aim: Wet-mount microscopy AV diagnostic criteria fails to take clinical features into consideration, and wet-mount smears cannot be long-term preserved and retrospectively reviewed. This study aimed to develop an AV diagnostic criteria that combined Gram staining with clinical features.

Methods/Patients: From 2014.12 to 2019.09, 325 AV patients and 325 controls were enrolled as study population to establish new criteria. Subsequently, 500 participants were prospective enrolled from 2020.01 to 2020.08 as validation group.

For the study population, AV-related microscopic findings on Gram-stained and wet-mount smears were compared. Based on vaginal bacterial 16S rRNA V4 sequencing, the accuracy of bacterial indicators (LBG, background flora) evaluation by the two methods were compared. Key AV clinical features were screened by Logistic regression, combined with Gram staining to establish new diagnostic criteria. In the validation group, the accuracy and reliability of new criteria were calculated.

Results: Gram staining had better ability to differentiate bacterial morphology based on sequencing results. The new diagnostic criteria for AV included LBG and background flora (Gram stain, 1000×), leucocyte count and PBC proportion (Gram stain, 400×), and clinical features (vaginal pH>4.5, vaginal hyperaemia, and yellow discharge). The total score ranged from 0-10, with each item allocated score 0-2, and a composite score above 4 was diagnosed as AV. According to validation results, the new criteria had a sensitivity and specificity of 86.79% and 95.97% for simple AV diagnosis, and a higher inter-observer agreement than wet mount (Kendall's W=0.899 vs. 0.811).

Discussion: The new diagnostic criteria of AV based on Gram staining and clinical features have satisfied accuracy and reliability, which is suitable for clinical application and artificial intelligence diagnosis in the future.

F.5 Vaginal microbial profiles of Aerobic Vaginitis: A case-control study

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Introduction/Aim: Aerobic vaginitis (AV) draws increasing attention for its threat to women's reproductive health and pregnancy. However, little is known about the overall structure of vaginal microbial communities in AV.

Methods/Patients: The diversity of vaginal microbiota was evaluated by amplicon sequencing targeting the 16S rRNA V4 region. Routine laboratory examination including cultivation was used.

Results: Firmicutes (mainly Lactobacillus crispatus and L.iners) dominated in healthy women (n=160), while Actinobacteria and Bacteroidetes were strongly associated with AV (n=80). The onset of AV was marked by a striking decline in L. crispatus, and an increasing in multiple aerobes including Streptococcus agalactiae, S.anginosus, etc. The overall drug resistance level of Gram-positive bacteria was high against erythromycin and clindamycin; the overall drug resistance level of Gram-negative bacteria was high against ampicillin.

Discussion: Multiple aerobes and facultative anaerobes involve in vaginal dysbiosis with L.crispatus decreasing. Probiotics containing L.crispatus may be a potential choice of supplementary agents.

F.6 Characteristics & diagnostic ability of vaginal microflora in patients with Aerobic Vaginitis: A comparative study with 16S-RNA sequencing

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Introduction/Aim: To investigate the characteristics and the composition of vaginal microbiota of Aerobic vaginitis (AV) in patients with AV, and to explore the diagnostic ability and potential pathogenic mechanisms.

Methods/Patients: A total of 42 patients with AV and 55 candidates as normal control were included. The vaginal discharge from the upper third of the vagina was collected. The samples were examined for vaginal microecology evalution, and high-throughput 16 ribosomal RNA (16S-rRNA) sequencing with Illumina Miseq PE300. After splicing and filtering, the original data were constructed to analyze the information of bacterial community composition. KEGG was used as a reference database for functional prediction analysis of bacterial function.

Results: Compared with the normal control, the diversity of vaginal flora in patients with AV was significantly higher. Streptococcus agalactiae and Streptococcus agalactiae were the characteristic dominant bacteria of AV. Particularly in patients with severe AV Streptococcus Anginosus Streptococcus agalactiae, Atopobium vaginae, Prevotella Bivia and Aerococcus Christensenii were significantly higher than the normal population, while Lactobacilla was significantly lower than the normal population. Arginine biosynthesis, phenylalanine, tryptophan and tyrosine biosynthesis were significantly increased in vaginal microflora of patients with AV, while DNA repair was significantly decreased. These pathways may be associated with acid-tolerant growth of bacteria and avoidance of host clearance, which may be the pathogenic mechanism of AV disease.

Discussion: The increased colonization of Streptococcus agalactiae and Streptococcus angina and the absence of lactobacillus could be used as diagnostic markers of AV.

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F.7 Cervicovaginal load of Gardnerella spp. is increased in immunocompetent women with persistent high-risk HPV Infection

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Introduction/Aim: Two genotypes of high-risk human papillomavirus (hrHPV), HPV16 and HPV18, are responsible for the majority of the cases of cervical cancer worldwide. Bacterial vaginosis contributes for hrHPV persistence, although its mechanistic basis has not been elucidated. Gardnerella spp. is present in nearly all cases of bacterial vaginosis and is the major source of bacterial sialidases in the cervicovaginal environment. Although it was recently shown that NanH1 is not the actual sialidase-encoding gene in Gardnerella it is present in virtually all sialidase-producing strains. Thus, NanH1 has been has been considered as a potencial marker for hrHPV persistence. Therefore, the aim of our study was to compare the cervicovaginal loads of Gardnerella spp. and the frequency of NanH1 gene between women with persistent HPV16 and/or HPV18 infection with those who cleared the infection after 11 months.

Methods/Patients: From 1614 HPV-screened women by genotyping, we identified 104 cases of HPV16/HPV18 positive women. Based on women´s HPV16+HPV18 status at enrollment and follow up, they were assigned to in 'persistence' or 'clearance' groups. We used cervicovaginal fluid samples obtained upon enrollment for quantification of 23s rRNA gene of Gardnerella spp. and detection of NanH1 using real-time polymerase chain reaction (PCR). We compared Gardnerella spp. loads and NanH1-positivity between the groups using, respectively, Mann-Whitney and chi-squared tests, with p-value <0.05 considered as significant.

Results: Of the 104 participants, 31 (29.8%) cleared HPV16 and/or HPV18 detected at enrollment, while 73 (70.2%) persisted with at least one of them. 'Persistence' group showed significantly higher loads of Gardnerella spp. [9.4E+02 (0 – 3.0E+05) copies/uL] in relation to 'clearance' group [4.4E+01 (0–7.7E+04) copies/uL] (p-value=0.03). Frequency of NanH1 at baseline was higher in ´persistence´ (n=46, 63.0%) than in ´clearance´ (n=14, 45.2%) group, althought not statistically significant (p-value=0.09).

Discussion: Gardnerella spp. has been strongly associated with bacterial vaginosis, then we aimed to determine whether its higher loads are associated with persistence of hrHPV. Our hypothesis was confirmed since we found that women with persistent HPV16+HPV18 infection have increased baseline loads Gardnerella spp.. These findings reinforce the negative effect of vaginal microbiota for the clearance of hrHPV. On the other hand, our findings did not show any evidence that NanH1 could be used as a marker for hrHPV persistence, what could be explained that other sialidase genes are mandatory for sialidase producing. Presence of the newly described sialidase-encoding genes of Gardnerella spp., NanH2 and NanH3, should be investigated by further studies.

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F.8 Association of vaginal microecology and Cervical Intraepithelial Neoplasia among reproductive women with high-risk HPV Infection

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Introduction/Aim: The purpose of this study is to evaluate the association between vaginal microecology and Cervical Intraepithelial Neoplasia (CIN).

Methods/Patients: A retrospective study was performed among 423 high-risk HPV(HR-HPV) infected women at the General Hospital of Tianjin Medical University from December 2014 to August 2017. Ninety-eight women diagnosed of cervical high-grade squamous intraepithelial lesion (HSIL) with histological results verified by colposcopy-directed cervical biopsy were assigned as the HSIL group, while 325 women diagnosed of low-grade squamous intraepithelial lesions (LSIL) or no dysplasia were assigned as the control group. The vaginal discharge samples were processed for Gram staining and wet mount to evaluate vaginitis and vaginal microeclogical indicators.

Results: HPV type 16 was identified most frequently, followed by types 52, 58, 18 and 51. Under univariate analysis, age older than 35 years (p=0.001), aerobic vaginitis (AV) (p=0.036), vaginal mixed infection (p=0.011), vaginal pH value greater than 5 (p=0.014), and leukocyte count >10 per high-power field (hpf) (p=0.015) were correlated with HSIL. Results of multivariate analysis further revealed that women with age older than 35 years [OR 2.09 (95% CI: 1.31–3.36)], leukocyte count >10/hpf [OR 2.00 (95% CI: 1.13–3.53)] had increased risk of HSIL.

Discussion: The association of vaginal microecology and cervical preneoplasia is still an unsettled issue. Several factors may be involved in the progression to CIN in HR-HPV infected women. We observed significant changes in the vaginal microecological indicators in women with HSIL. The depletion of lactobacillus, pH value greater than 5, WBC count greater than 10/hpf, AV and mixed vaginal infection were more common in women with HSIL. Among them, age older than 35 and WBC count greater than 10/hpf were two independent risk factors for developing HSIL. The effect of older age on HR-HPV persistence may be owing to high viral load, high proportion of viral integration caused by physiological and immunological disorders. Women with age older than 35 years have more work pressure, more family responsibilities, and chronic sleep deprivation, thus their immune state is worse than that of younger women, which may weaken their resistance to the HPV, leading to persistent infection. In general, older age was associated with high-grade CIN. Intriguingly, we found WBC count greater than 10/hpf were associated with HSIL rather than AV and other vaginal infections after multivariate analysis. It can be hypothesized that vaginal inflammatory status maybe disrupt mucosa epithelial barrier, which lead to the HPV persistence and CIN progression.

Clinical recommendations on mixed vaginitis

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Introduction/Aim: Mixed vaginitis is caused by the simultaneous presence of at least two vaginal pathogens, contributing to an abnormal vaginal milieu and leading to the development of vaginal symptoms and signs. Nevertheless, simply identifying the presence of at least two vaginal pathogens in situ does not establish a cause-effect relationship with clinical symptoms and signs. Therefore, mixed vaginitis is an inflammatory condition that remains understudied and underrecognized. This review summarizes the available and relevant clinical data to improve clinical knowledge about mixed vaginitis.

Methods/Patients: The MEDLINE database was searched, and only articles written in English were considered. Additional references were identified by hand searching the bibliographies of the included articles.

Results: (1) We List a table to summarize the representative epidemiology data of mixed infection in the last 10 years, which was associated with some factors. (2) Mixed vaginitis generally involves the formation of mixed biofilms. The main courses are illustrated with one schematic diagrams. (3) The key points in diagnosing mixed vaginitis are as follows: the simultaneous presence of at least two vaginal pathogens; an abnormal vaginal milieu due to the pathogens and, hence, symptoms and signs of vaginitis; and the requirement of specific therapies for both pathogens. (4) We enumerates the treatment strategies of various mixed vaginitis.

Discussion: (1) The frequency with which mixed infections occur depends upon definition. one challenge is that studies have failed to correlate symptoms with microbe types. Therefore, most reports do not distinguish between mixed vaginitis and coinfection. (2) Polymicrobial influence each other in diverse ways via synergistic or antagonistic interactions. These interactions are highly complex, and the type of interaction that occurs often depends on a range of environmental, pathogenic and host factors. (3) At present, although two pathogens may be identified, a potential pathogen may be present but may not be the cause of existing vaginal symptoms. Therefore, the accuracy of diagnosis remains understudied and underrecognized. (4) Many countries have banned the availability of combination antimicrobial products for use in vaginitis. However, the demand for polytherapy comprising multiple antimicrobials will increase with the development of laboratory-based diagnostics. As noted above, how to identify at-polytherapy subpopulations requires further consideration.

Aerobic Vaginitis/Desquamative Inflammatory Vaginitis: arguments for an immunological disease

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Introduction/Aim: DIV was described by Gardner (1) as an inflammatory vaginitis. Donders et al. (2) defined Aerobic Vaginitis (AV) in contrast to Bacterial Vaginosis (BV) as an inflammation of the vagina with predominantly aerobic bacteria. He discussed DIV as the „tip of the iceberg" of more severe forms of AV.

Methods/Patients: The clinical data of all 53 patients with the diagnosis AV/DIV of our Centre between 2013 and 2022 were retrospectively analysed.

Results: N = 53, caucasian, mean age 44.3 (19 – 73) years, purulent discharge and vaginitis since up to 7 years. From 24 of 53 patients was no other disease documented, but 29 of 53 (54.7%) with mostly stronger vaginal inflammation suffered from at least one autoimmune disease (AID): atopic dermatitis, rheumatoide arthritis, follicular lymphoma, Morbus (M.) Hodgkin, alopecia, anti-NMDA-receptor-encephalitis, Hashimoto-thyreoiditis, M. Basedow, psoriasis, M. Behcet, autoimmune retinitis, - hepatitis, - gastritis, - colitis, M. Crohn, colitis ulcerosa, neuromyelitis optica, urticaria, lichen sclerosus.

The vaginal pH value with AID was higher than without AID, but not significant 5.68 (4.3 – 7) vs. 5.34 (4.5 – 6.4) (p = 0.091).

Biopsies showed in cases with AID light unspecific (pH 7!) to floride granulomatous or lymphocytic-granulocytic vaginitis, in the case of anti-NMDA-rec.-encephalitis malformation of lymph- and blood vessels, but also in one case without AID and pH 5.5 lymphocytic vaginitis with plasmacells.

The patients received Clobetasole 0.05% vaginal cream 2 – 3 g 3x/week for 4 weeks, some clindamycin cream once/day for 2 weeks. All patients responded more or less well. They suppressed recurrences with one vaginal dose every 1 - 4 weeks. Only 5 of 28 controlled patients after 2 to 6 months seemed to be cured, 3 with and 2 without AID.

Discussion: Non-culture based methods indicated a reduced bacterial abundance with dominance of Lactobacilli, Prevotella, Streptococcus and Gardnerella, low microbiome differences between AV and BV, but lower activation of Toll-Like Receptor 2 – 6 in AV patients with lower anti-inflammatory activity (3), which hints to an immunological origin of AV/DIV. Our clinical data, to our knowledge never reported before, are strong arguments for the immunological origin of AV/DIV.

AV and DIV are no bacterial infections, but immunological disorders (4) and at least DIV closely connected with AID. Antiinflammatory therapy suppresses only the symptoms.

The best name for AV/DIV should therefore be „Inflammatory Vaginitis".

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F.10 Advances in vaginal microecology theory in the application of vulvovaginal candidiasis

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Introduction/Aim: Vulvovaginal candidiasis is the most common vulvovaginal infection. Some patients show recurrent symptoms, which are difficult to cure and seriously affect their physical and mental health. The newly proposed vaginal microecology has provided a new direction for the diagnosis and treatment of vulvovaginal candidiasis. This article reviews the application of vaginal microecology theory in the pathogenesis of vulvovaginal candidiasis, which was aimed at comprehensively understanding and managing vulvovaginal candidiasis.

Methods/Patients: Data was extracted through extensive searches in the Pubmed from January 1980 to January 2021, using the keywords: "Vulvovaginal candidiasis", "Vaginal Microbiota", "Lactobacilli", "Candida albicans".

Results: Candida albicans(C. albicans) is a member of the endogenous human microbiota, which can cause vulvovaginal candidiasis (VVC) in healthy women. Clinical signs of VVC include pruritus, burning, soreness and redness of the vulva and vaginal mucosa, often accompanied by abnormal vaginal discharge. An estimated 75% of women will have at least one episode of VVC. Other species, such as C. parapsilosis, C. glabrata, C. tropicalis, and C. krusei, can also cause VVC. Disruption of the vaginal microbiota may facilitate increased virulence and high burden of Candida. The most represented species of Lactobacilli occurring in the vaginal environment of healthy women are L. crispatus, L. gasseri, L. jensenii and L. iners. L. crispatus has been mainly associated with a healthy microbiota, but L. iners has been found to be ubiquitous even during dysbiosis. In VVC patients, the diversity of vaginal flora decreased, and the dominant Lactobacilli was L. iners, while the content of L. crispatus decreased significantly. Most studies suggest that local vaginal mucosal immunity plays an important role in the mechanism of host resistance to Candida. Th1 cells are the main immune cells of the host against Candida candida, and the occurrence of recurrent vulvovaginal candidiasis (RVVC) is related to the immune deficiency of the host, especially the immune deficiency of Th1 cells. Th17 cells also play an important role in mucosal immunity against Candidiasis. Currently, the treatment of VVC is mainly oral or topical antifungal drugs. Probiotic therapy, where Lactobacilli can be orally administered or directly applied to the vagina, has been successful in helping patients with vaginitis or vaginosis with an excellent overall safety record, when associated with conventional antimicrobial and antifungal therapies. The immunotherapeutic vaccine (NDV-3A) containing a recombinant C. albicans adhesin/invasin protein for RVVC was safe and highly immunogenic and reduced the frequency of symptomatic episodes of vulvovaginal candidiasis.

Discussion: VVC patients are characterized by dysregulation of vaginal microflora, changes of pathogenic bacteria species, and imbalance of lactobacilli species in the vagina. Meanwhile, local vaginal mucosal immune changes can also affect the occurrence and development of VVC. The application of probiotic therapy to the recovery of human vaginal microecology has shown great application prospects. More studies are needed to reveal the pathogenesis of VVC, as well as effective treatment of VVC.

F.11 Candida biofilms in vulvovaginal candidiasis

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Introduction/Aim: The ability of Candida spp. to form biofilms is crucial for its pathogenicity, and thus, it should be considered an important virulence factor in vulvovaginal candidiasis (VVC) and recurrent VVC (RVVC). Its ability to generate biofilms is multifactorial and is generally believed to depend on the site of infection, species and strain involved, and the microenvironment in which the infection develops.

Therefore, both cell surface proteins, such as Hwp1, Als1, and Als2, and the cell wall-related protein, Sun41, play a critical role in the adhesion and virulence of the biofilm.

Immunological and pharmacological approaches have identified the NLRP3 inflammasome as a crucial molecular factor contributing to host immunopathology. In this context, we have earlier shown that Candida albicans associated with hyphae-secreted aspartyl proteinases (specifically SAP4-6) contribute to the immunopathology of the disease.

Methods: Transcriptome profiling has revealed that non-coding transcripts regulate protein synthesis post-transcriptionally, which is important for the growth of Candida spp. Other studies have employed RNA sequencing to identify differences in the 1,245 Candida genes involved in surface and invasive cellular metabolism regulation.

Results: In vitro systems allow the simultaneous processing of a large number of samples, making them an ideal screening technique for estimating various physicochemical parameters, testing the activity of antimicrobial agents, and analysing genes involved in biofilm formation and regulation (in situ) in specific strains.

Murine VVC models are used to study C. albicans infection, especially in trials of novel treatments and to understand the cause(s) for resistance to conventional therapeutics. This review on the clinical relevance of Candida biofilms in VVC focuses on important advances in its genomics, transcriptomics, and proteomics.

Discussion and Conclusion: Moreover, recent experiments on the influence of biofilm formation on VVC or RVVC pathogenesis in laboratory animals have been discussed.

A clear elucidation of one of the pathogenesis mechanisms employed by Candida biofilms in vulvovaginal candidiasis and its applications in clinical practice represents the most significant contribution of this manuscript.

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F.12 Three phase 3, randomized, double-blind, placebo-controlled studies to evaluate the efficacy and safety of Oteseconazole (Vt-1161) oral capsules in subjects with recurrent vulvovaginal candidiasis.

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Introduction/Aim: RVVC affects nearly 138 million women globally each year. Three Phase 3 studies were conducted to evaluate the efficacy and safety of oteseconazole in treatment of women with RVVC.

Methods/Patients: In two global Phase 3 studies (Violet), 656 subjects with a history of RVVC (≥ 3 acute episodes within previous 12 months) were enrolled at 181 centers in 11 countries. Subjects were required to present with a vulvovaginal signs and symptoms score of ≥ 3 and a positive KOH. Subjects with resolved signs and symptoms on Day 14 following the treatment of the presenting acute infection with fluconazole (3 sequential 150 mg oral doses, every 72 hours), were randomized to receive either 1) 150 mg oteseconazole once-daily for 7 days, then 150 mg once-weekly for 11 weeks or 2) matching placebo for 12 weeks. Subjects were followed for 48 weeks.

The third Phase 3 study (ultraViolet) enrolled 219 RVVC subjects at 51 US centers. The study consisted of two phases. An Induction Phase, where subjects who presented with signs and symptoms score of ≥ 3 and a positive KOH were randomized to receive either 1) 600 mg oteseconazole (4x150 mg capsules) on Day 1 and 450 mg oteseconazole (3x150 mg capsules) on Day 2 and matching placebo; or group 2) 3 sequential 150 mg oral doses (every 72 hours) of over encapsulated fluconazole together with matching placebo.

Subjects with resolved acute VVC infections (clinical signs and symptoms score of < 3) on Day 14 and initially randomized to receive oteseconazole entered the Maintenance Phase and received 150 mg oteseconazole weekly for 11 weeks or otherwise received placebo weekly for 11 Weeks. The subjects were then followed for an additional 37 weeks.

Results: All Phase 3 studies achieved the primary efficacy endpoint, demonstrating significant differences

between oteseconazole and placebo for the proportion of subjects with ≥ 1 culture-verified acute VVC episode through the 48-week or 50-week study period in the ITT populations. In Violet, over 90% of subjects randomized to receive oteseconazole did not experience a recurrence during the 48-week maintenance phase compared to approximately 40% in the control group (P < 0.001).

In ultraViolet, the Oteseconazole recurrence rate at week 50 was 5.1%, whereas the recurrence rate in subjects who received fluconazole followed by placebo was 42.2% (P-value < 0.001).

Oteseconazole was non-inferior to fluconazole for treatment of acute VVC in RVVC subjects.

Subject compliance was high in all three studies with no notable differences between the groups. Treatment-emergent adverse events (TEAE) were mild or moderately severe, and rates were similar across all treatment groups. There were no drug-related SAEs and no evidence of adverse effects on the limited number of pregnancies occurring while on study. There were also no trends or abnormal clinically relevant laboratory tests including liver function or QT intervals.

Discussion: Oteseconazole was shown to be effective and well tolerated in treatment and prevention of RVVC including the acute episodes of RVVC in women.

F.13 Efficacy and safety of oral Ibrexafungerp in subjects with vulvovaginal candidiasis: Pooled data analysis from two phase 3, randomized, blinded, studies vs. placebo (VANISH-303 and VANISH-306)

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Introduction/Aim: Vulvovaginal candidiasis (VVC) is the most prevalent candidal infection that affects 75 million women at least once in their lifetime (1). Historically, there are a limited number of well-controlled treatment studies in the literature comparing an active control to placebo for VVC. The current approved therapies for treatment of VVC are all azoles which are fungistatic. Here, we introduce oral ibrexafungerp (IBX), a novel triterpenoid antifungal, with fungicidal activity against a broad range of Candida species for treatment of VVC, that was recently approved for use in adults and post-menarchal females with VVC. The purpose of this research is to examine efficacy and safety; and subpopulation outcomes from two phase 3 clinical trials of oral IBX versus Placebo (PLC) in patients with vulvovaginal candidiasis (VVC) in a pooled analysis.

Methods/Patients: Two randomized, double-blind, placebo-controlled clinical trials of IBX were conducted in patients with VVC, (VANISH 303 and 306). VANISH 303 enrolled patients in the United States (US) and VANISH 306 in the US and Bulgaria. Inclusion criteria were: females with vaginal sign and symptoms (VSS) ≥4 at baseline, age ≥12 years, potassium hydroxide (KOH)-positive microscopy. Patients were randomized 2:1 to receive IBX 300 mg BID for one day for a total treatment dosage of 600 mg or matching PLC. The primary endpoint was the percentage of patients with clinical cure (complete resolution of VSS=0) at the test-of-cure (TOC) (day 11±3) visit. Data from both studies were pooled, and key subgroups of interest analyzed.

Results: Pooled MITT group in VANISH studies included 376 subjects (188 in V-303, 188 in V-306) in the IBX arm and 182 subjects (98 in V-303, 84 in V-306) in the PLC arm. Primarily women with VVC at baseline VSS ≥ 7, 94% on IBX and 92% on PLC were enrolled. The Clinical Cure at TOC for IBX was 56.9%, significantly superior (p=0.001) to PLC, 35.7%. The secondary endpoint of clinical improvement for IBX and PLC (VSS ≤1) at TOC was 72.9% vs. 52.2%, respectively (p<0.001) and mycological eradication at TOC was 54.0% and 24.2%, respectively (p<0.001). Clinical cure at TOC in sub-populations for IBX were as follows: in patients aged <65, 57.0% (n=374), in Black patients, 52.3% (n=107), in Hispanic or Latino patients, 54.7% (n=75), in patients with BMI >35, 46.2% (n=65). IBX was generally well-tolerated, with Treatment-Emergent Adverse Events (TEAEs) reported in ≥5% of IBX-treated patients including diarrhea (16.7%), nausea (11.9%), and abdominal pain (8.3%), the majority were mild to moderate in nature, lasting 1 day.

Discussion: This analysis shows the efficacy and safety of IBX, a fungicidal anti-fungal in the treatment of VVC, and in relevant sub-populations. Oral IBX was approved in the US by the FDA in June 2021 and provides the first new non-azole treatment option for clinicians to prescribe to their patients suffering from VVC.

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F.14 Dyspareunia in women: is it always vulvodynia?

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Introduction: Dyspareunia are complaints of persistent or recurrent pain before, during or after sexual intercourse and are an important and underreported problem in women (1). Approximately, with prevalence of 54,5%, 46% and 45%, 1 on 2 women experience dyspareunia (2, 3). A lack of knowledge and skills about diagnostic and treatment issues could probably lead to more undiagnosed and untreated dyspareunia (1-3). Multiple factors, from vulvodynia to atrophy and infections, can cause dyspareunia (3). Also the age of first sexual contact has already been identified as a provocative factor (4). Because the treatment of dyspareunia has to be depended on the specific cause, there is a high need for a better understanding and knowledge about this problem in clinical practice.

Aim: This study aimed to describe the kind of pain and causes of women who experienced dyspareunia to gain a better understanding of this problem.

Methods: All women who consulted their gynecologist (Prof. Dr. Donders) between October 2019 and November 2020 where asked if their data may be used for medical research whereafter the physician completed a questionnaire with demographic data, medical history, kind and severeness of dyspareunia, diagnose and treatment for these women. Data was descriptive analyzed using Microsoft Excel.

Results: 210 participants with a mean age of 37,2±14,2 years old were included. The mean coïtarche age was 17,8±2,8 years. 68,1% experienced secondary dyspareunia. Women experienced the most pain during penetration (89,3%), rubbing (59,7%) and after sexual intercourse (68,9%). 19,5% and 14,3% experienced severe lateral pain on 5h and 11h, with a VAS score of 7 or above. 65,2% reported central and distention pain while only 8,1% and 10,0% reported central pain or distention pain only. Causes of dyspareunia where widely diverse such as Increased muscle tone (37,6%), lateral vulvodynia (30,0%), infection such as bacterial vaginosis, aerobic vaginitis, and/or candida (25,2%), vulvovaginal atrophy (18,6%), dermatosis (9,5%), scar problem (4,3%) or other less frequently complaints such as rectocele and vaginal septum (1,4%). Only ¼ women suffered from 1 disease that led to dyspareunia, 70% suffered from more than 1 problem and only within 5% of the women no cause could be found to clarify their dyspareunia complaints.

Discussion: Our study results showed the widely variety of possible causes of dyspareunia. Physicians has to be aware of this widely variety of factors that cause dyspareunia complaints and that there has a compressive clinical examination of the patient before starting a treatment.

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Access to STI and HIV testing during the COVID-19 restrictions

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Introduction/Aim: The COVID-19 pandemic has resulted in decreasing the provision of medical care in cases without emergency. At the same time, restricting availability of testing can have an impact on spread of HIV and other STIs. Latvia is among countries with the highest number of new HIV cases in EU. Barriers in accessing testing may have significant long-term impact on public health. The aim of the study was to evaluate the availability of HIV and STI testing in EU countries during the early stages of COVID-19 pandemic and compare the data between the countries.

Methods/Patients: An online survey was conducted during the first wave of COVID-19 as part of an international multi-country study: I-SHARE (International Sexual and Reproductive Health Survey in the time of COVID-19). In Latvia this survey was carried out as a part of the state research program "Impact of COVID-19 on health care system and public health in Latvia; ways in preparing health sector for future epidemics" (VPP-COVID-2020/1-0011). Data were summarized and analyzed using MS Excel and IBM SPSS 26.0. In this study we included the data from I-SHARE European countries with more than 1000 participants.

Results: The responders who wanted to perform a test to rule out HIV infection or other STI during COVID-19 distancing measures (%; N): Latvia - male 7.4 (15/189), female 5.2 (50/919); Portugal - male 8.7 (54/564), female 6.1 (166/2536); France – male 5.8 (16/261), female 3.3 (43/1271); Check Republic – male 2.4 (14/573), female 2.1 (13/599); Denmark – male 2.8 (13/446), female 2.2 (12/530); Sweden – male 19.8 (130/527), female 12.3 (79/657).

Latvian participants statistically significantly more often wanted to perform tests compared to Denmark

(M p=0.008 and F p=0.006) and the Czech Republic (M p=0.001 and F p=0.003), as well as significantly less often compared to Sweden (M and F p<0.001).

According to the survey results, the availability of testing was considerably limited in Portugal [(M – 59% (27/54), F – 38.6% (64/166)] and in Sweden [M – 59.2% (77/130) and F – 48.1% (38/79)] accordingly. The most common reasons for not having access to testing in all countries were long waiting times in clinics or their closure, and restrictions on public transport services.

Discussion: It is essential to define essential sexual and reproductive health services, which should be available during all crises. Self-assessment of HIV and STIs requires further promotion and extended availability.

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Prevalence of HIV, four non-viral STIs and BV among attendees of sex-parties in Moscow, Russia

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Introduction/Aim: At the moment heterosexual sex-parties gain their popularity in Moscow, Russia, despite anti-COVID restrictions. Parties vary in format and number of participants, but still attract people looking for various sex practices with multiple partners that can be realized during the party. At the same time curators of the parties focus on sex education among participants, performing lectures on STIs, condom use, etc. The objective of the study was to estimate the prevalence of HIV, Chlamydia trachomatis (CT), Neisseria gonorrhoeae (GC), Mycoplasma genitalium (MG), Trichomonas vaginalis (TV) and bacterial vaginosis (BV) among attendees of sex-parties in Moscow, Russia.

Methods/Patients: A cross-sectional study was implemented in 2020 during 3 sex-parties. A total of 173 participants were tested, 161 filled in a questionnaire, 163 participants underwent HIV testing (OraQuick RAPID test), 96 females were tested for STIs [1] and BV [2] (AmpliPrime PCR kits, Moscow, Russia) using self-collected vaginal swabs.

Results: A total of 171 participants provided gender information (55 males (32,2%) and 116 females (67,8%)). Median age was 28 [18-46] and 27.5 [19-45] years, respectively. Median age of sexual debut was 17 [12-30] years. Five or less sexual partners in previous 6 months were reported by 119/157 (75.8%) participants, whereas 8/157 (5.1%) reported more than 20 partners. 57/156 (36.5%) respondents (8.8% men, 52.5% women) practiced bisexual contacts Regular practices with three types of sex (vaginal, oral and anal) were reported by 86/151 (56.9%) participants. Non-parenteral drug use during sex was reported by 44/156 (28.2%) responders. Consistent condom use was reported by 57/157 (36.3%) attendees only. Oral HIV rapid test revealed 2/151 positive cases (prevalence 1.3% (95% CI: 0.36%-4.6%)). Among females 1 GC, 1 CT and 1 MG -positive cases were detected (prevalence 1.05% ((95% CI: 0.19%-5.7%) for each). BV prevalence was 18.9% (95% CI% 12.3%-28%).

Discussion: These results show that prevalence of HIV and other STIs among attendees of sex-parties in Moscow, Russia, correspond to the prevalence of those infections in the general population [3]. This might be due to the effort of organizers of the parties to educate participants and provide condoms. At the same time increased testing coverage will provide more accurate information on HIV and STI prevalence as 1) few positive cases were detected; 2) only females were tested for STIs; 3)only vaginal samples were tested, although extragenital infection is common as well.

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Metronidazole resistance and ineffectiveness of Clindamycin on biofilms hamper the therapy of bacterial vaginosis, and may be overcome with the Gardnerella specific endolysin PM-477

Lorenzo Corsini (IT)

Objectives: Currently, antibiotics are the mainstay of therapy for bacterial vaginosis (BV). However, the rate of treatment failure in patients with recurrent BV is about 50 %. It has been disputed whether Metronidazole (MDZ) resistance might be a crucial factor for therapy failure in BV, particularly in patients with recurrent BV. Herein, we investigated how easily the keystone pathogen of BV, Gardnerella, can develop MDZ resistance in comparison to the recently described endolysin PM-477, a novel Gardnerella biofilm disrupting agent with a low probability to induce resistance.

Methods: We determined the minimum inhibitory concentration (MIC) of metronidazole (MDZ), Clindamycin (CLI), and PM-477 on a panel of 22 Gardnerella strains. Initially susceptible isolates were passaged with sub-inhibitory concentrations of MDZ, the more potent hydroxy MDZ metabolite, or PM-477, respectively, for up to 25 rounds. The MIC was determined after each round of passaging. Subsequently, non-passaged and passaged Gardnerella strains were grown in biofilms, treated with MDZ, CLI or PM-477, and the minimum biofilm eradication concentration (MBEC) was assessed. The effect of PM-477 on clinically occurring biofilms in a vaginal swab of a patient with recurrent BV was analyzed by fluorescence in situ hybridization.

Results: 60 % of Gardnerella strains of four different species were found to be initially resistant to MDZ, while all strains were highly susceptible to CLI, and the endolysin PM-477. Six out of six strains that were initially susceptible to MDZ and passaged for 10 days with MDZ hydroxy metabolite generated full resistance with MIC > 512 µg/mL within 5-10 passages. In contrast, no intrinsic nor induced resistance formation over the 25 rounds of passaging was found for PM-477. There was also no cross-resistance formation, as those Gardnerella strains in suspension and in pre-formed biofilms, which were fully resistant to MDZ, remained highly susceptible to PM-477. Strains that were resistant to MDZ were also tolerant to MDZ at >2048 µg/mL when growing as biofilm. All strains were susceptible to PM-477 at MBECs in the range 1-4 µg/mL when growing as biofilm. Surprizingly, the MBEC of CLI was >512 µg/mL for 4 out of 6 tested Gardnerella strains, all of which were susceptible when growing planktonic. PM-477 was also able to eradicate clinically occurring biofilms in a vaginal swab of a patient with recurrent BV who was repeatedly treated with MDZ without success.

Conclusion: Gardnerella spp. can quickly develop resistance against MDZ in vitro, which may also happen

in vivo. CLI is largely ineffective on Gardnerella grown as biofilm, which might be caused by its mechanism of action as a protein biosynthesis inhibitor. The failures of MDZ and CLI due to resistance formation and ineffectiveness on biofilm, respectively, could be one explanation for the frequent treatment failures in uncomplicated or recurrent BV. Therefore, the high effectiveness of PM-477 in eliminating Gardnerella in in vitro biofilms as well as in polymicrobial biofilms derived from BV patients, makes PM-477 a promising alternative for the treatment of bacterial vaginosis, especially in patients with frequent recurrence.

COVID and sperm

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Introduction : COVID-19 has been a worldwide pandemic problem since March 2020. This disease caused by the SARS-CoV-2 virus infect the human cells due binding of the receptor binding domain of the spike proteins to angiotensin-converting-enzyme (ACE-2) receptors. ACE-2 receptors are widely represented in the male reproductive system (i.e., Leydig cells, Sertoli cells...)(1, 2). Due this, it is not inconceivable that SARS-CoV-2 can cross the blood-testis barrier like previous RNA viruses (i.e., ZIKA, EBOLA, MARBUGA)(3-5). Also, previous studies showed seminiferous tubular injury, reduced Leydig cells and local inflammation in died COVID-19 patients(6).

Aims: The SPERM-COVID study aimed to study the presence of SARS-CoV-2 RNA in semen, the effect of COVID-19 on semen quality (sperm concentration, motility, morphology and DNA damage) and the SARS-CoV-2 antisperm antibodies and serum antibodies to investigate the immunological response after COVID-19.

Methods: We conducted an observational, cross-sectional study as a part of a prospective cohort study.

Males who recovered from a proven COVID-19 infection where included till 31st December 2020. This infection had to be documented by nasopharyngeal PCR test OR positive SARS-CoV-2 IgG serum antibodies 1 week till 6 months after a symptomatic COVID-19 infection. Participants completed a questionnaire, inquiring epidemiological characters and the severity of their COVID-19 episode. Sperm and blood samples were collected and transported to a specialized lab as soon as possible. Sperm was obtained by self-masturbation. In case of semen deviated, participants were asked to complete 1-3 follow-up visits.

Sperm was tested with a validated PCR test and with a classic fertility test including DNA fragmentation, DNA high density and the presence of antisperm antibodies. Blood was tested for IgG antibodies against spike-1, receptor binding domain and nucleotide antigen against the SARS-CoV-2 virus. Subject were divided into 3 time-lapse groups from moment of COVID-19 infection till inclusion (short (0-31 days after COVID), Medium-long (32-62 days) and long (63+ days post infection) for analysis using SPSS.

Results: 120 males were included of which 118 males where tested for sperm quality due to a previous vasectomy.

In none of the semen samples, SARS-CoV-2 RNA could be detected. Motility and sperm concentration reduced shortly after their COVID-19 infection (p=0,001).

The severity of the disease did not correlate with the reduced semen parameters. Increased Sperm count and concentration encountered more frequently in men 1 month after COVID-19 compared in men tested after 2 months (37% vs. 6,3%; P=0,003). Also, progressive motility was reduced in 60%, 37% and 28% of men tested <1 month, 1-2 months or >2 months after COVID-19, respectively (p=0,02). Only 24,6% (29/118 males) tested fully normal on semen quality (concentration, motility and morphology).

Also, Serum titers IgG antibodies against the spike protein (S-1) and the receptor binding domain (RBD) correlated very strong with semen concentration and motility.

In 61% of semen samples, IgA antisperm antibodies (ASA) were detected. In 1 subject this percentage was above 40% which indicates immunologic infertility. In 14 subject (13,2%) IgA ASA percentage was between 10-40% which indicates reduced fertility. IgG ASA was less frequently detected (p<0,0001).

Time lapse after Covid-Characteristics	**Short 0-31 days**	**Medium-long 32-62 days**	**Long 63(+) days**	**Total 0-181 days**	**P**
Participants, n	35	51	32*	118*	
Sperm concentration <15 million/ml	**13 (37,1%)**	**15(29,4%)**	**2(6,3%)**	30(25,4%)	0,003
Total number of sperm/ ejaculate**	82,8±109,0	98,4±113,6	131,4±90,1	101,6±80,0	
Progressively motility <32%***	**21 (60%)**	**16/43(37,2%)**	**8/29 (27,6%)**	45/107(42,1%)	0,02
Total motile count <40% ***	**18 (51,4%)**	**11/43(25,6%)**	**6/29 (20,7%)**	35/107(32,7%)	0,01
Morphology ideal shape <4%	27 (77,1%)	38 (74,5%)	25 (78,1%)	90 (76,3%)	
MAR IgG >10%	1/33(3,0%)	3/50 (6,0%)	0/31 (0,0%)	4/114(3,5%)	
MAR IgA >10%	3/30 (10,0%)	5/45 (11,1%)	7/31 (22,6%)	15/106(14,2%)	
DFI % >25%	**10 (28,6%)**	**6 (11%)**	**5 (15,6%)**	-17,80%	0,049
SARS-CoV-2 RNA in semen	0 (0,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)	

Table I: semen parameters after COVID-19

** Analyzed on males who could fully collect their semen sample

***Analyzed on samples which were analyzed in lab within 4 hours after collection

Discussion: One week or later after an active COVID-19 infection semen is not infectious with SARS-CoV-2 virus. This indicates that COVID-19 cannot be sexually transmitted by semen one week or later after recovery of the disease. However, during the acute infection a breach of the virus due the blood-testis barrier with direct infection of the semen cannot be ruled out. COVID-19 can increase sperm quality that causes temporally reduced infertility. In some cases, this infertility can be immunological and permanently. Further follow-up studies should prove these understanding of which our cohort study with follow-up of the participants will further assist this.

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Reduced Incidence of Early Preterm Birth in Association with a Screening Program for Genital Infection Based on Intravaginal (i.vag.) pH-Self-Monitoring

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Introduction/Aim: The government of the State of Thuringia, Germany, in cooperation with the professional organization of OB/GYN physicians established and promoted in 2016 a self-care screening program based on i.vag. measurement of pH in order to reduce the incidence of preterm birth by early diagnosis and immediate therapy of genital infection.

Methods/Patients:

- Screening for pH > 4.5 i.vag. at > 14 to 32 gestational weeks, recommendation of self-examination twice a week
- Diagnosis of bacterial vaginosis, abnormal vaginal flora, vaginitis, cervicitis, sexually transmitted infection, others
- Therapy preferrably < 24 weeks, e.g. Clindamycin, Metronidazole, lactobacilli
- Objective prolongation of pregnancy > 32 weeks as well as cure
- Monitoring of results annually by the national department for medical quality control.

Results: More than 200 local OB/GYN specialists in the state were in charge of diagnosis and therapy. Starting at zero in 2016, > 80% of pregnant women in the state had their vaginal pH measured at the end of 2020, about 20 % of them by self-measurement. The incidence of preterm birth < 32 + 0 weeks has declined in 2017 from 1.46 % to 1.31 % (n = 17.387), 1.26 % in 2018 (n = 17.180) 1.18 % in 2019 (n = 16.080) and 1.1 % in 2020 (n = 15 156) as of newborns < 1500 g from 1.48 % to 1.22 %, 1.15 %, 1.13 % and 1.1 % respectively.

Discussion: These data are in contrast to an almost unchanged higher incidence of early preterm birth in neighbouring states with a similar socio-economic structure in 2019 as well as the whole of Germany in 2017. The 4th millennium goal missed worldwide in 2015 as well as the newly declared 3rd objective of the UN could come closer using the simple and cheap i.vag. pH-self-screening regime in prevention of preterm birth, an approach partly turning the woman from being object of medical care to being the subject in self-control of her pregnancy.

Reference: This regime is a well perceived change in paradigm from the perspective of females as well as physicians and also a new quality in prevention. It is effective as well as uncomplicated and should

have the potential to be used by everyone everywhere. Another hypothetical aspect, reduced incidence of post-partum maternal death due to pre-partum screening, diagnosis and treatment of genital infection, also deserves further investigation.

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