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Chapter 2

Unexplained Female Infertility Alert Over Overt and Hidden Genital Infections

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Abstract

Female genital tract infections represents a real challenge for the gynecologists. The exact role of these infections in infertility induction is not clear. The impact of uterine infections on implantation is not clearly defined. This chapter will discuss the implication of overt as well as hidden genital tract infection among women with unexplained infertility. Whether these infections cause infertility or induced by infertility diagnostic as well as therapeutic procedures will be addressed. In short, this chapter will attract attention of gynecologists to put the possibility of genital tract infections in every case of infertility particularly cases with unexplained infertility.

Keywords: Unexplained infertility, hidden infections, manifest infections, hysteroscopy, laparoscopy

1. Introduction

1.1. What's unexplained infertility (UI)?

Current definitions of infertility lack uniformity, rendering comparisons in prevalence between countries or over time difficult and inconclusive. The absence of an agreed definitions compromises clinical management and undermines the impact of research findings [1]. Idiopathic or unexplained infertility (UI) term is used whenever the cause remains unclear even after basic infertility work-up which usually includes semen analysis, detection of ovulation and fallopian tubal patency testing. The current diagnostic tools for intrauterine causes of infertility include transvaginal ultrasonograogy, hysterosalpingography (HSG) or saline infusion sonography (SIS) [2]. The levels of investigations to explain infertility are insufficient and require more intensive evaluation. In a previous open access free book chapter published by InTech [3], many explanations of UI utilizing endoscopic evaluation that were missed by many organizations were demonstrated.

2. Position of genital tract infections in infertility work-up

International societies didn't include infections as a definite cause of infertility. Practically, local gynecologic examination should be an essential routine step in infertility evaluation. Both speculum and bimanual examinations can detect or suspect a wide variety of lower or upper genital tract infections. With the extensive routine use of transvaginal ultrasonography (TVS) in all gynecologic clinics, unfortunately many gynecologists miss the five basic steps of gynecologic examination which can detect definite infertility causes (inspection of the external genitalia, palpation of the external genitalia, palpation of the vaginal walls and fornices, bimanual examination and vaginal speculum examination). Moreover, many women don't prefer local gynecologic examination due to fear or inconvenience. Gynecologic examination is a cheap valuable basic step that should not be ignored. Moreover, local examination can detect many vaginal and cervical disorders. For instance, some congenital anomalies like transverse or longitudinal vaginal septae, Gartner's cyst in one of the fornices which occludes the external os or congenital vaginal atresia. Practically and literally, genital tract infection detected by speculum examination can be a direct cause of female subfertility.

3. Manifest (overt) genital tract infections

Overt uterine causes of infertility would include clinically symptomatizing cervical and uterine infections, intrauterine adhesions, polypi or uterine cavity malformations. Gynecologists usually pay little care towards manifest lower and upper genital tract infections among infertile women and rely mainly on ultrasonography and hormonal profile.

4. Increasing rate of lower genital tract infections

Cervicitis as well as vaginitis has been one of the common diseases influencing the health of female genital system. The happening rate of female vaginal and cervical inflammation is increasing rapidly in modern world which may be organism mutations, immunological changes, and poor hygiene in underdeveloped world or liberal sexual behaviors particularly in western countries. Fortunately enough, with the increased medical knowledge, health education, improved diagnosis and aggressive lines of therapy, prompt eradication of these infections is possible.

5. Impact of lower genital tract infection on fertility

In general, cervicitis has a negative impact on pregnancy. When a woman is diagnosed with cervicitis, especially for those who have severe cervicitis, the possibility of infertility is high. When cervicitis occurs, the cervix secretes more discharge with large amount of WBCs and pathogens thus hindering normal vaginal environment. This changes the PH of the vagina and

kills semen as if pyospermia exists. The activity of sperms will be limited and their living time will be shortened. Furthermore, WBCs can swallow the sperms. Moreover, because of the thick and purulent discharge, it is more difficult for semen to swim-up into the uterine cavity. Of clinical importance, long standing endocervicitis is usually associated with mucosal proliferation with narrowing of the cervical canal and even inflammatory polyp formation preventing smooth ascend of sperms. In addition, severe untreated longstanding cervicitis can cause infertility by affecting nearby organs. It may cause endometritis, cervical endometriosis, acute or chronic PID, tubal blockage, hydrosalpinx and even more deeper infections like urinary diseases. In such cases, treatment becomes more sophisticated and requires more aggressive lines of management. Lastly, local genital medications would affect sperm quality and adds another fertility obstacle.

6. Prevalence of local genital tract infections among infertile women

Since a long time, many studies clearly demonstrated that genital tract infections would decrease fertility of women. For instance, in a previous study [4], 92 infertile women were compared with 86 pregnant controls regarding rates of isolation of Neisseria gonorrhoeae, Candida albicans, Trichomonas vaginalis and other facultative organisms. They found that the rate of isolation of Neisseria gonorrheae was 17.4% among infertile women compared with 10.5% in the group of pregnant women ($p > 0.05$). There was no significant difference between the groups in the rate of isolation of Candida albicans, Trichomonas vaginalis and other facultative organisms. High rates of isolation of microorganisms were observed in both groups. However, women with secondary infertility had higher rate of carriage of Neisseria gonorrheae, Candida albicans and Staphylococcus aureus as compared with women with primary infertility. Nearly 15% of infertile women had previous episodes of pelvic inflammatory disease and 26% had had induced abortions. A positive history of vaginal discharge was a poor predictor of vagina and endocervical carriage of microorganisms. They concluded that high rates of pathogenic organisms exist in the lower genital tract of infertile women and controls. Women with secondary infertility are more likely to have pathogenic organisms than women with primary infertility and recommended routine screening for this group of infertile women.

7. Vaginal microbiome and female infertility

Vaginal microbiome is a new era under continuous evaluation and research. It is well established that the vagina is colonized by bacteria that serve important roles in homeostasis. Imbalances in the proportion of bacteria may lead to a predisposition to infection or reproductive complications. Molecular-based approaches found high variations within and between women than previously reported. Moreover, the vaginal microbiome may increase or decrease according to the health status, menstrual cycle or menopause with ethnic variations. Dysbiosis and the transmission of sexually transmitted infections are affected by the

composition of the microbiome. An understanding of the diversity of the vaginal microbial environment during states of health is essential for the identification of risk factors for disease and the development of appropriate treatment [5]

The effect of known pathogens such as Mycoplasma, tuberculosis, Chlamydia trachomatis, and Neisseria gonorrhoeae is clear, causing subclinical changes thought to be risk factors in subfertility. Colonizing the transfer-catheter tip with Lactobacillus crispatus at the time of embryo transfer may increase the rates of implantation and live birth rate while decreasing the rate of infection [6]. On the other hand, the presence of vaginal–cervical microbial contamination at the time of embryo transfer is associated with significantly decreased pregnancy rates [7]. Nevertheless, the exact implication of microbiome in infertility requires more studies.

8. Role of cervical-vaginal swab in overt lower genital tract infections

8.1. The vaginitis wet mount test

It is the simplest and cheapest test to detect vaginal infection by taking a high vaginal swab to be examined by wet mount microscopy. It may detect vaginal yeast infection, trichomoniasis and bacterial vaginosis. Vaginal bleeding may alter the results. The patient should be instructed to avoid condoms or tampon use or vaginal sex 24 hours before the test. Moreover, vaginal pessaries, creams or douches should not be used during the 2 to 3 days before the test.

The test is very easy where a speculum is inserted inside the vagina while the patient is in the lithotomy position to get a sample fluid from the upper vagina. The sample is then smeared on a glass slide mixed with few drops of saline and examined by wet mount microscopy. Normally, no yeast, trichomonas or clue cells are found on the slide.

8.2. Additional vaginal discharge tests

In a previous study [8], we performed more evaluation of vaginal discharge as a screening for bacterial vaginosis. Sterile cotton tipped swab was inserted in the posterior vaginal fornix, then two swabs were taken. The first swab was rolled on a clean slide, and then a drop of isotonic saline was added and the slide was examined microscopically (¥400) for the presence of clue cells;7 0.1 mL methylene blue was also added to the wet preparation, so that the blue stained bacteria on clue cells could be easily seen. A second swab of secretions was applied to a clean glass slide and allowed to dry in air. This sample was later fixed by flame and Gram staining was performed to visualize clue cells. The slide was examined under oil immersion microscopy (¥1000). After examination of vaginal discharge, the diagnosis of BV was made if three of the four criteria of Amsel and Thomson's criteria were fulfilled: these include thin homogenous vaginal discharge, vaginal pH 4.5, characteristic amine or fishy odor when alkali (10% KOH) is added to the specimen of vaginal secretions, and the presence of clue cells on wet mount examination of vaginal fluid. Clue cells are described as a vaginal epithelial cell with an ill-defined outline that appeared to be granular because of the large number of bacillary *G.*

vaginalis (and other bacteria) attached to their surface. To be significantly indicative of BV, more than 20% of the epithelial cells on the slide should be clue cells.

8.3. Screening for Chlamydial Infection [9]

The primary focus of chlamydia screening efforts should be to detect chlamydia infection, prevent complications and test and treat their partners. Several sequelae can result from *C. trachomatis* infection in women including PID, ectopic pregnancy, and infertility. *C. trachomatis* urogenital infection can be diagnosed in women by testing first-catch urine or collecting swab specimens from the endocervix or vagina. Nucleic acid amplification tests (NAATs) are the most sensitive tests for these specimens and therefore are recommended for detecting *C. trachomatis* infection [10]. NAATs that are FDA-cleared for use with vaginal swab specimens can be collected by a provider or self-collected in a clinical setting. Self-collected vaginal swab specimens are equivalent in sensitivity and specificity to those collected by a clinician using NAATs, and women find this screening strategy highly acceptable [11]. Previous evidence [12] suggests that the liquid-based cytology specimens collected for Pap smears might be acceptable specimens for NAAT testing, although test sensitivity using these specimens might be lower than that associated with use of cervical or vaginal swab specimens; regardless, certain NAATs have been FDA-cleared for use on liquid-based cytology specimens.

8.4. Cervical screening opportunity

Perfect diagnosis utilizing a simple bivalve vaginal speculum is the key of success for proper diagnosis and subsequent treatment of local genital tract infections. Don't ignore to screen for premalignant cervical lesions even if your patient is young. Premalignant cervical lesions usually precede invasive cervical cancer by about 17-25 years. So, your patient's health should have the priority before treating infertility. Screening starts by meticulous naked eye examination of the cervix. It is a very important costless step. In a previous study [13], we tested the reliability of unaided Naked-Eye Examination (UNEE) of the cervix as a sole screening test for cervical premalignant and malignant lesions as compared to the standard cervical cytology. A total of 3,500 non pregnant women aged between 25 and 55 years were included. An unlubricated bivalve speculum was inserted into the vagina under good light to visualize the cervix. A thorough UNEE of the cervix was done to detect any apparent lesions. Cervical smears were obtained using the long tip of Ayre's spatula. An additional endocevical sample was obtained by cytobrush. Woman with abnormal Pap smear or visible cervical lesions by UNEE were scheduled for colposcopic examination. A biopsy was taken in every abnormal colposcopic examination. Preinvasive cervical lesions (CIN 1-3) diagnosed by various diagnostic tools used in the study and confirmed by histopathological examination were 9 / 3500 cases (2.57 %). Invasive cervical lesions were diagnosed in 6 /3500 cases (1.71 %). The sensitivity of UNEE was much more better than Pap smear (80 % vs 60 %) but less than colposcopy (86.7 %). However, specificity of UNEE was lower than Pap smear (91.16 %) vs. 100 %) and better than colposcopy (83.12 %). UNEE had poor positive predictive value (3.75 %) when compared to Pap smear (100 %) and to colposcopy (20 %). The negative predictive values of the three tests were nearly comparable. Whenever access to Pap smear is limited, UNEE performed by

general gynecologists and a well-trained nurse is an acceptable alternative for detection of cervical premalignant or malignant lesions especially in low resource settings. Optimally, a Pap smear should be taken routinely from every patient. Any suspicion of premalignant or malignant lesions deserves a colposcopically-guided biopsy.

9. How to manage local cervical inflammatory lesions in women with UI?

If you see an inflammatory cervical polyp, it should be excised in the office utilizing a sterile ring forceps. It should be sent for histopathologic assessment. Any bleeding from its pedicle can be controlled by simple gauze compression or rarely cauterization. Other lesions like ectopy, ectropion or chronic non-specific cervicitis can be treated by an ablative therapy. In a prospective study [14], we tested the efficacy, tolerability and safety of 70% trichloroacetic acid (TCA) painting versus monopolar spray coagulation of the cervix for treating persistent benign cervical lesions that failed to respond to local medications. We included a total of 246 cases with objective evidence of benign cervical lesions that were divided into 2 groups according to the line of management. Group A comprised 126 cases subjected to spray monopolar coagulation while group B comprised 120 cases subjected to trichloroacetic acid application. Cervical smearing and colposcopy with or without cervical biopsy to exclude underling malignant lesions was done. TCA painting or spray monopolar coagulation of the benign cervical lesion(s). Follow-up was performed to assess relief of symptoms and cervical morphology for one month. Main outcome measures include success of management tool, relief of symptoms and normal cervical morphology after one month of therapy. We achieved a statistically significant cure rate of cervical lesions after treatment in both groups without significant difference between both groups. Failure rate was reported more in group B than group A mainly due to hypertrophied ectopy and cervical polyp. Patient in group A reported low satisfaction (26.9%) and poor tolerability rate (44.5%) as compared to patients in group B, who reported high satisfaction (77.5%), and good tolerability rate (77.5%), this difference was statistically significant. We concluded that both topical application of 70% TCA and monopolar spray coagulation offer considerable efficacy, acceptable success rates and minimal complications. Spray coagulation is significantly superior in terms of less persistent or incompletely healed lesions. Nevertheless, topical application of 70% TCA has the advantages of simplicity, higher patient tolerability and safety that can be widely used by gynecologists who have limited experience with surgical procedures. It is highly recommended if the cervical lesion is ectopy or non-specific cervicitis but not hypertrophic lesion like hypertrophic ectopy or polyp.

9.1. Hidden genital tract infections in UI

Hidden uterine factors of infertility may include thin endometrium, poor endometrial receptivity, and immunological incompatibility which have received good interest in modern practice [15]. Literally, little attention has been directed towards asymptomatic hidden intrauterine infections like Mycoplasma, Ureaplasma, Klebsiella and Chlamydia trachomatis particularly among infertile women [16].

9.2. Prevalence of hidden intrauterine infections (IUI) in UI

In an unpublished study, we tried to find out if women with UI have high prevalence of hidden intrauterine infections (IUI). We included 100 women allocated into two groups. A study group included 50 women with UI and control group included 50 fertile women who came for contraceptive advice. Sample size calculation was carried out using Epi Info software version 7 (CDC, 2012). A calculated sample of 82 (41 cases and 41 controls) was needed to detect an effect size of 0.1 between the two groups unexplained infertility and control group, with a p value < 0.05 and 80% power. Inclusion criteria for UI were criteria according to The Practice Committee of the American Society for Reproductive Medicine (ASRM) [17] which includes normal semen analysis at least twice, patent fallopian tubes as seen by hystrosalpingography (HSG) and positive ovulation utilizing ultrasound or serum progesterone in the second half of the cycle.

Exclusion criteria included current or recent use of systemic or local antibiotics, vaginal douches or creams in the preceding month. Inclusion criteria of the control group included new clients attending the family planning outpatient clinic asking for a contraceptive method and not complaining of recent or recurrent abnormal vaginal discharge. In both groups, patients were subjected to a detailed history taking stressing on possible use of vaginal creams or vaginal douches in the preceding month followed by thorough and meticulous vaginal and general examinations. Patients with evidence of overt upper or lower genital tract infection on routine clinical examination were also excluded from this study. In both groups, in lithotomy position, an un-lubricated bivalve vaginal speculum was inserted intravaginally then an endouterine swab was taken utilizing a soft 3 mm pipette. After injection of few milliliters of 0.9% saline, the aspirate was immediately sent to bacteriology department for assessment. The endouterine swab was incubated on Amies transport medium (Himedia), pleuropneumonia-like organism broth (PPLO) (Himedia – Cat. No. M266), and brain heart infusion (BHI) (Himedia – Cat. No. M210), to isolate Mycoplasma hominis. The plates were kept under microaerophilic conditions at 37 °C. Liquid media were examined daily for 10 days for the color change indicating growth. Other media like columbia Agar base (Himedia – Cat. No. M144) and MacConkey Agar (Himedia – Cat. No. MM081), were used to identify other organisms by conventional methods. Vaginalis Agar (Himedia – Cat. No. M1057) medium was used to detect Gardnerella vaginalis. Part of the fluid was fixed on slides, frozen in acetone, and subjected to a direct immunofluorescence assay (IFA) with fluorescence isothiocyanate conjugated anti-chlamydia trachomatis monoclonal antibodies (Imagen TM Chlamydia, Dako Cytomation, UK). Detection of group B streptococci (GBS) was done by specific antiserum on the isolated colonies (HiStrep – Latex test kit – Himedia LK06-50NO). The isolated organisms were confirmed biochemically using API system (20A Biomerrieux RES 20300). All women with unexplained infertility (group A) were subjected to diagnostic laparoscopy using standard double puncture technique. Laparoscopic findings were correlated with bacteriologic findings.

There was a statistically insignificant difference between both groups regarding the age and residence (p value >0.05) and it was highly significant regarding parity (p value <0.001). Hidden IUI were diagnosed by culture and biochemical confirmation in 42 cases (84%) and 10 cases

(20%) in both groups respectively with a high statistically significant difference (P=0.001). The most common organisms detected in the study group were Mycoplasma (24%), klebsiella (20%), Chlamydia (18%) and Proteus (10%). In group A, positive laparoscopic findings were reported in 33 patients (66 %). There was a significant correlation between the positive cases of hidden IUI and the pathological lesions diagnosed by laparoscopy (P Value= 0.0001). The most common laparoscopic abnormalities were hyperemic uterus, peritubal adhesions and chronic salpingitis which were reported in 10 (20%), 6 (12%) and 4 (8%) cases respectively, which demonstrate a highly significant correlation between confirmed hidden IUI and abnormal laparoscopic findings in UI. Laparoscopy revealed upper genital tract pathology in 30 cases (71.4%) of positive cases of hidden infections (42 cases) and it was negative in 3 cases (37.5%) of negative cases of hidden intrauterine infections (P Value= 0.0001). Cases with abnormal laparoscopic findings (33 cases) could be explained by positive culture of hidden intrauterine infection in UI group except 7 cases of endometriosis and 3 cases were culture-free. Abnormal laparoscopic findings were found more in positive cases with Mycoplasma (10 cases), Chlamydia (8 cases), Klebsiella (3 cases) and Proteus (2 cases) respectively.

9.3. Discussion on prevalence of hidden IUI

Hidden IUI may be a possible cause of UI [18]. This can be achieved by alterations in the intraperitoneal environment that may lead to an inflammatory process in the absence of visible abnormalities [19]. In our work, high prevalence of hidden IUI (84%) proved by culture of endouterine discharge in women with UI raise the recommendation that before starting a lengthy and costly list of sophisticated level II investigations of both partners, attention to hidden IUI is a mandatory basic step in UI. It has been found that women with tubal factor were two to three times more likely to have genital tract infections than women with other types of infertility [20]. We think that culture would be accepted as a basic screening tool for hidden IUI due to availability and feasibility in many hospitals. Screening test should not be expensive, time consuming or complicated before being extended to all hospitals particularly in low resource countries with limited resources.

Our work demonstrated a high prevalence of Mycoplasma (24%), klebsiella (20%), Chlamydia (18%) and Proteus (10%) among women with UI. These results of high prevalence compared to fertile women would call for more attention to screening protocols in all infertility units dealing with UI ideally prior to laparoscopic intervention. Due to high prevalence of Chlamydia in infertile women in a previous study, screening for Chlamydia was recommended for cases with all cases with UI [18]. We reported Mycoplasma in about one quarter of positive cases. Likewise, mycoplasma was reported in 32% of infertile cases with a statistically significant difference from fertile group [12]. In this study, proteus infection was reported in 10% of infected cases. This particular organism is commonly noticed in the urinary system infections. Reporting it in the genital tract would requires more studies to define its role in infertility. Unlike others, we reported low prevalence of Ureaplasma in only 4% of cases despite its previous reports of up to 32% infertile cases [18]. This big difference may clarify the variability of frequency of hidden intrauterine infections in different populations and highlights importance of studies on prevalence in each community.

Laparoscopic evaluation of infertility is the cornerstone test for tubal and peritoneal factors of infertility [21]. In this study we documented 33 cases (66%) with abnormal laparoscopic findings among the infertile group. Abnormal laparoscopic findings were reported in about 53 % of infertile women in a previous stud [22]. The most frequent abnormal laparoscopic finding in their study was pelvic adhesions. More frequent abnormal laparoscopic findings in UI up to 87.2% were reported by others [23] who described endometriosis lesions, peritubal adhesions and tubal obstruction. In a previous study, 114 women with UI were examined laparoscopically. Laparoscopy revealed pelvic pathology in 95 patients. Endometriosis, pelvic adhesions and tubal disease were observed and treated in 72, 46 and 24 patients, respectively. They could treat 72 patients of them, and 35 of them conceived using their own tubes. However they concluded that diagnostic laparoscopy should be strongly considered in UI work-up, and tubal efficacy should not be underestimated [24]. In our work, there was a significant correlation between the positive cases of BV and the pathological lesions diagnosed by laparoscopy especially hyperemic uterus, chronic salpingitis and peritubal adhesions (P Value= 0.0001). Subsequently, we recommend meticulous screening of women with these abnormal laparoscopic findings for possibility of hidden intrauterine infections.

Performing laparoscopy for UI is not universally agreed and questionable since it is an invasive procedure with serious morbidities and mortalities. However, in an detailed book chapter, many benefits of performing endoscopic evaluation of cases of UI were well demonstrated [3].

Limitations of this study included small sample size of individual types of hidden intrauterine infections and lake of precise description of a particular abnormal laparoscopic finding for each organism are clear limitations of this study. Due to ethical considerations, both groups were not homogeneous in that the case group had undergone investigations such as ultrasound and HSG, while the controls had not. We could reasonably argue that instrumentation for HSG might cause retrograde infections that were later on detected at laparoscopy. Some of the "positive" laparoscopic findings are questionable and probably too subjective. This study would be a more meaningful study if included the impact of proper treatment on fertility of women with UI.

We concluded that despite being an underestimated cause of female infertility, hidden IUI are frequent and implicated in UI. Laparoscopy is very beneficial in explaining the effect of hidden intrauterine infections on the upper genital tract but it is not a screening tool for IUI. We recommend postoperative screening for hidden IUI in UI cases with abnormal laparoscopic findings. Further studies are required to test the impact of proper treating these infections on subsequent fertility in cases of UI.

10. Similar studies

One hundred seventy infertile women and 45 pregnant women in the third trimester were evaluated in one study for the prevalence of uterine infections [25]. Classical methods and real time PCR were applied to each cervical sample to detect the presence of these sexually transmitted microorganisms; the ELISA method was applied to blood samples to detect C.

trachomatis antibodies (IgA, IgM and IgG). The proportion of C. trachomatis IgG was significantly higher in the infertile group (23.8%) than in the pregnant group (4.4%), $p < 0.05$. For C. trachomatis antigen (Ag) and N. gonorrhoea Ag no differences were observed between the two groups. The prevalence of mycoplasma genital infections was higher in the pregnant group (U. urealyticum - 53.3% and M. hominis - 20%) than in the infertile group (U. urealyticum - 39.7% and M. hominis - 7.3%). Higher rate of co-infection with C. trachomatis and mycoplasma were observed among the infertile women (25.7%) than among the pregnant women (7.7%). This combination could be involved in the appearance of pelvic inflammatory disease (PID) and its sequele, including infertility. C. trachomatis IgG determination still remains the gold standard for the diagnosis of PID and should be used as a screening test for the prediction of tubal damage in infertile women. They concluded that in view of the large number of cases involving the co-existence of genital infections with C. trachomatis, M. hominis and U. urealyticum, it is clearly necessary to perform screening for all three microorganisms among all women of reproductive age but especially those who are infertile.

Another study [26] was constructed to investigate the detection rates of Chlamydia trachomatis, Neisseria gonorrhoeae, Mycoplasma genitalium, Mycoplasma hominis, Ureaplasma urealyticum, Gardnerella vaginalis, Escherichia coli, Streptococcus agalactiae and Enterococcus faecalis, in asymptomatic fertile and infertile women. It encompassed 161 women, including 101 women treated for infertility and 60 fertile women who had already given birth to healthy children. The material for the presence of C. trachomatis, N. gonorrhoeae, M. genitalium, M. hominis and U. urealyticum was collected from the cervical canal and analyzed by PCR. Furthermore, BD Probe Tec ET system was used to detect C. trachomatis infection. Vaginal swabs were collected for classification of bacterial vaginosis and aerobic vaginitis and assessed according to the Nugent score, as well as by traditional culture methods. U. urealyticum was identified in 9% of the infertile women and in 8% of controls. Presence of M. hominis was demonstrated only in the former (4%) and C. trachomatis only in latter (3%). N. gonorrhoeae and M. genitalium were not found in any of the examined women. The frequency of aerobic vaginitis in both groups was estimated at 12%. There were 7% bacterial vaginosis cases in the study group, and none in the control group ($p=0.0096$). They concluded that despite having no symptoms of an ongoing acute inflammation of the reproductive tract, many women may experience permanent or periodic shifts of equilibrium of the vaginal and/or cervical microflora. BV develops more frequently in infertile patients when compared to the fertile women.

11. Infection induced by infertility work-up maneuvers

During the course of infertility work-up, women are subjected to many invasive diagnostic procedures like hysterosalpingography, hysteroscopy, sonohystrography, premenstrual biopsy or laparoscopy. Moreover, some therapeutic procedures are done to treat definite problems like selective salpingography, egg retrieval, operative resectoscopy or hysteroscopy and operative laparoscopy in addition to some minor vaginal maneuvers. All these diagnostic and operative interventions carry the risk of introduction of infection to the genital tract and

disruption of the natural protective mechanisms. The gynecologist should pay attention to the possibility of inducing infection and stick to aseptic strict precautions during every step. Lastly, whenever suspicion of introduction of infection is raised, proper broad spectrum antibiotics should be considered.

12. Keynote points

Infertility specialists should not underestimate overt lower or upper genital tract infections. Vaginal including speculum examination is an important basic step during infertility evaluation. Gynecologists should keep asepsis during all steps of examination or investigation of the infertile female. Use of appropriate antibiotics is recommended whenever prolonged or invasive procedure is performed. Prompt and aggressive treatment of any detected upper or lower genital tract infection is mandatory to prevent short and long-term sequel that would compromise the fertility status of the female. Concomitant treatment of the male partner shouldn't be forgotten to avoid relapse or persistence of female infections. Think hidden infection of the genital tract in all cases of UI before performing sophisticated procedures like ART. Uterine microbiome is a recent entry to our armamentarium, however its relevance and treatment is unknown and requires more research.

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