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Editorial

Antibiotics Use in Infertile Couples and During ART Procedures: A Review

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Introduction

In the context of Assisted Reproductive Technology (ART) in particular and Reproductive Medicine (RM) in general, antibiotics are administered in a wide spectrum of conditions. The aim of this manuscript is to analyze the pros and cons for using antibiotics in ART and RM from both a qualitative and a quantitative point of view and whether the utilization of these drugs is already optimal or needs an improvement taking into consideration the present literature and the WHO and the National Institute for Health and Clinical Excellence (NICE) guidelines.

The prescription of antibiotics in RM and during ART therapies can be summarized into five main categories:

i. For the improvement of female-related infertility/subfertility;

ii. For the improvement of male-related infertility/subfertility;

iii. During the diagnostic and interventional surgeries for the work up of infertility;

iv. At the time of oocyte retrieval;

v. In preparation for embryo transfer.

The very first two points deal with female and male infertility. Globally the prevalence rates of infertility/subfertility are difficult to determine, but according to WHO data from a study analyzing couples in 190 countries over the 1990-2010 time period, 48.5 million couples are unable to conceive (mettere reference). About 30-40% of these cases are due to problems in both the female and the male components of the couple; 50% are due to a female problem only. The etiology of the female problem has to be dealt from a geographical and cultural point of view. In the Developing World, women are secondarily infertile mostly because of sequelae from sexually transmitted infectious diseases (STD), while in the Developed World, the causes of infertility are linked to ovulatory dysfunction (40%), tubal-pelvic pathologies (40%), unexplained causes (10%), while STD's are responsible for less than 10% of all the cases. Since our work deals with women belonging to the Developed World the impact that antibiotics may have on the prevention or on the resolution of infertility problems associated with infections is evidently small. In this 10%, the main causes are cervico-vaginal infections [1], bacterial vaginosis, endometritis [2-4] and pelvic inflammatory disease (PID)., The pathogens most commonly responsible for infections are *Chlamydia trachomatis* (CT), *Neisseria gonorrhea* (NG), *Trichomonas vaginalis* (TV), *Ureaplasma urealyticum* (UU) and Anaerobes as shown with cervico-vaginal swab and cultures. For all these conditions, the literature supports the use of antibiotics for an effective resolution of the acute disease and for the prevention of any potential impairment of fertility. Chlamydia infections are the likely pathogens for STD's in women under 25 years of age, while infrequent in older women. The anatomical damage caused by CT can be quite serious and it can occur even in cases completely asymptomatic. As a consequence, it is very common to diagnose tubal disease infertility in young women referred to ART programs because of a poorly or untreated past Chlamydia infection having caused tubal damage and with a completely negative culture panel. In these instances is debatable whether pursuing a diagnosis through the research of IgGs would still be useful, since it is too late for the antibiotic therapy to reverse the anatomical damage, or if it is only a pure diagnostic curiosity [5,6]. We support the second point of view: CT screening should be performed only when suspecting an acute infection enabling the choice of the best antibiotic therapy, while routine screening has limited validity since there is no specific treatment for the sequelae of a past Chlamydia infection. It should also be kept in mind that an excessive use of antibiotics may alter the "normal" female tract flora thus disrupting the optimal environment for conception and implantation [3,7].

For what concerns male fertility problems, it has been showed by the current literature that prolonged use of antimicrobials is in itself one of the main causes of male infertility; in fact when used in the treatment of systemic infections, antibiotics are significantly associated with a worsening in semen quality and quantity [8]. However, it is still unclear whether the effect of antibiotics on the male fertility potential is compounding the impairment due to the underlying infectious and inflammatory process [9].

In the presence of confirmed infections of the male genital tract, antibiotics play an important therapeutic role. Although routine seminal culture screening is not performed because of the high number of false positives, it is considered useful only in the presence of symptoms and signs (including ultrasound findings) of infection with no response to previous antibiotic therapy. The clinical signs and symptoms of infection could be related to urinary tract infections, painful and swollen epididymis, transrectal US showing signs of prostatitis or inflammation of the seminal vesicles, and whenever the partner has a positive and confirmed history of STD [10-12].

In the context of RM there are conditions during the diagnostic work-up when the administration of antibiotics is seen as a prophylaxis to prevent complications. These conditions are: a) Sonohysterosalpingography (SHS); b) Hysterosalpingography (HSG); c) diagnostic hysteroscopy (DH); and d) diagnostic laparoscopy (LPS).

LPS is the only one that requires an antibiotic prophylaxis in all patients because of the invasiveness of the exam itself. The WHO guidelines of 2009 on safe surgery state that in this type of procedures an antibiotic prophylaxis administered in the 60 minutes preceding the intervention is enough for the patient safety [13]. For all the other diagnostic procedures, instead, no antibiotic coverage seems to be needed considered the low invasiveness of the intervention; the

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ACOG clearly excludes sonohysterography, hysterosalpingography and diagnostic hysteroscopy from the list of exams requiring routine prophylaxis in the general population [14].

For what concerns operative hysteroscopy, antibiotic prophylaxis is not recommended by international guidelines [13] in healthy women, given the risks of causing antibiotic resistance by administering antibiotic prophylaxis to all the patients and the low risk of developing PID by prescribing prophylaxis only in those patients carrying particular risk factors [15] as those with:

-Endometriomas;

-Hydrosalpinx;

-Complications after previous surgeries;

-Previous major abdominal interventions.

Guidelines introduced by NICE in 2013, support the use of antibiotic prophylaxis only for surgeries that are:

-Clean surgery involving the placement of prosthesis or an implant;

-Clean-contaminated surgery;

-Contaminated surgery;

-Surgery on a dirty or infected wound (which requires specific antibiotic treatment in addition to prophylaxis).

NICE also does not recommend antibiotic prophylaxis routinely for clean non-prosthetic uncomplicated surgery because of the risk of adverse events, *Clostridium difficile*-associated disease, resistance and drug hypersensitivity [16].

Whether patients undergoing oocyte-retrieval require antibiotic coverage is still a matter of debate. Prophylaxis is clearly recommended for patients carrying the same risk factors considered also for operative hysteroscopy [17]. On the other hand, antibiotic prophylaxis has not been demonstrated beneficial in the general population, since women with positive tests for CT, NG, Bacterial Vaginosis, TV are generally treated with antibiotic therapy well before the oocyte pick-up. At the time of oocyte retrieval the vaginal preparation is commonly accomplished either with povidone-iodine douching together with normal saline irrigations or by sterile warm water and the cases of oocyte pick-up-associated pelvic inflammation (OPU PI) are very rare [18]. Our own data, collected over the period 01/2000-10/2015, showed an OPU PI percentage of 0.028% over 21,233 cases and supports the indication of the official literature prescribing antibiotic prophylaxis only in few selected cases.

The very last aspect of this discussion is the role of antibiotics in the setting of embryo transfer (ET). At present, the literature and our own data do not support the routine use of antibiotics for the ET. By keeping to the good clinical practice of screening for the most common endocervical and vaginal pathogens followed by an aggressive treatment of both partners in the event of positive screening tests well before the initiation of the ART therapy, there is no need of further antibiotic therapy prior to ET [19]. Recent findings that using broad-spectrum antibiotics for prophylaxis may decrease the colonies of dominant H2O2-producing Lactobacillus species in the reproductive tract (which yields the most successful implantation outcome), has led further to the choice not to cover the patients with a prophylactic therapy for ET [7].

Conclusions

In conclusion, despite a robust literature suggesting conditions that deserve the use of antibiotics in ART and RM, there are still instances where the administration of antibiotic relies not on evidence based data but on physician's personal choices. Further studies are still needed to establish the optimal quantitative and qualitative use of these drugs.

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