

Review

Antibiotics' Influence on Fertility: A Narrative Review

Mihai Nechifor ¹, Cristina Gales ^{2,*}, Gabriela Rusu-Zota ¹, Carmen Lacramioara Zamfir ² and Daniel Costel Gales ³

¹ Department of Pharmacology, “Grigore T. Popa” University of Medicine and Pharmacy, 700115 Iasi, Romania; mihainechif@yahoo.com (M.N.); rusu.i.gabriela@umfiasi.ro (G.R.-Z.)

² Department of Histology, “Grigore T. Popa” University of Medicine and Pharmacy, 700115 Iasi, Romania; carmen.zamfir@umfiasi.ro

³ Department of Pedotechnics, University of Life Sciences “Ion Ionescu de la Brad”, 700115 Iasi, Romania; daniel.gales@iuls.ro

* Correspondence: cgales81@yahoo.com or cristina.gales@umfiasi.ro; Tel.: +40-758565007

Abstract

The purpose of this review is to highlight the complex influence of antibiotics on human fertility and the need for them not to be underestimated. In creating this review article, data and information from the following international databases were used: PubMed, Scopus and Clarivate Analytics. Only full text articles were used. Antibacterial antibiotics are a group of drugs essential in fighting infections, having multiple mechanisms of action at the level of the bacterial cell; but at the same time they also act on human cells. One of the important actions of antibiotics is on fertility. There are both experimental and clinical data showing the influence of some antibiotics on fertility. There are both positive and negative influences of these drugs on fertility. Some of the most important actions with a positive impact on fertility are: therapy of pelvic infections in women, treatment of endometritis, reduction in post-abortion infections, treatment of infections of the male genital tract—infections that reduce fertility. The most important negative implications of some antibiotics are the direct effects of reducing the production of gametes, decreasing the activity or quality of the gametes, reducing the synthesis of sexual hormones and negative influences on the evolution of pregnancy, including spontaneous abortion in some cases. Other negative influences are produced by the direct action of some antibiotics on the embryo. Some antibiotics such as azithromycin and nitrofurantoin increase the risk of miscarriage. Although only a limited number of antibiotics are known to have an influence on fertility, this influence should not be underestimated in clinical practice.

Keywords: antibacterial antibiotics; fertility; sperm quality; abortion

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1. Introduction

Human fertility has several definitions, but in general it is considered to be the ability of a couple to have children through normal sexual activity. Subfertility and infertility are important public health problems. Over the past few decades fertility has declined in most countries and globally [1]. The increase in the mean age at initiation of first pregnancy, the effect of many toxic agents, stress, ignoring genital infections and other factors are among the important causes of infertility [2,3]. In the first two decades of the 21st century, infertility affected more than 183 million people globally [4]. Infertility is defined (by the World Health Organization) as the absence of conception of a child after one year of normal regular unprotected sexual intercourse in a couple [5,6].

The average prevalence of infertility in the world is currently around 10% [7]. The World Health Organization shows that worldwide about 9% of couples have fertility problems [8]. The contribution of male infertility to total infertility is 30–50% [9].

Other studies state that infertility affects about 15% of all couples in the world [10]. Worldwide, it is estimated that at least 50 million couples are affected by infertility [11]. Various statistics indicate important differences between different regions of the world and between urban and rural areas [12].

Fertility is affected by many factors, including some medicines. Antibacterial antibiotics are some of the most used drugs. Currently, a number of 100–110 antibacterial antibiotics are used in the world. Their implications for human fertility and interactions with factors that regulate fertility are only partially known. Antibacterial antibiotics influence fertility both through their actions on bacteria and through their interactions with the cells and systems of the human body [13–18]. Quite frequently the interactions of antibacterial antibiotics with human and animal body cells are underestimated and they are sometimes not taken into account in clinical practice.

The influence of antibiotics on fertility occurs both through their action in the bodies of men and in the bodies of women. Antibiotics have both positive and negative effects on human fertility. The aim of this review is to highlight the influence of some antibacterial antibiotics on fertility. The data used were taken from the following databases: Pubmed and Google Scholar. Only full text articles were used. The main keywords used were: human infertility, antibiotics, male infertility, antibiotic treatment of genital infections of women and men. The aim of this review is to show the influences that antibiotics have on fertility.

1.1. Positive Action of Antibiotics on Fertility

The benefits of their use are huge. The positive effect of the use of antibiotics on fertility is produced by treating bacterial infections that reduce fertility.

The most important practical uses of antibiotics in this direction are:

Therapy of pelvic infections in women.

Preventing infection during embryo transfer and increasing pregnancy rates.

Treatment of all kinds of infections of the male genital tract [19].

Treatment of postpartum uterine infections which induce ovarian dysfunctions [20]

Prevention of infective sequelae of abortion [21] and management of post-abortion complications.

Broad-spectrum antibiotics are necessary to treat or prevent infections in the case of surgical complications of cesarean section and also in some cases of hysterectomy [22]. Administering antibiotics before cesarean section for all patients is a controversial issue [23]. However, for some women there are indications for use. Penicillins are the most recommended antibiotics in the management of preterm premature rupture of membranes and the reduction in the incidence of chorioamnionitis [24].

Urinary tract infections reduce fertility [25]. Treatment with antibiotics is beneficial for increasing fertility. Multiple antibiotics are used in the treatment of urinary tract infections. A high proportion of pathogenic bacteria have developed resistance to co-trimoxazole [26]. Extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae are frequent and pose therapeutic problems. Carbapenems and nitrofurantoin are commonly used in these cases [27]. Fosfomycin, an old drug, has been reintroduced into the treatment of infections related to ESBL-producing *E. coli* spp [28]. Nitrofurantoin and pivmecillinam are also used in the treatment of urinary tract infections [29].

There are a few situations where some antibiotics have a direct positive effect on gametes or gamete production.

Chronic and acute endometritis have negative effects on fertility [30]. Chronic endometritis plays an important role in female infertility. Postpartum endometritis is frequently a polymicrobial condition. It occurs more frequently after cesarean sections than normal vaginal delivery [31]. This disease is present in 19.5% of infertile women compared to 7.7% in the control group [32]. Chronic endometritis is a common cause of failure of in vitro fertilization procedures. These diseases were identified in 30.3% of patients with repeated implantation failure [33]. Antibiotic treatment has significantly reduced the rate of pregnancy loss and significantly increased the rate of successful pregnancies [33].

Postpartum endometritis is also relatively common after cesarean section. Among its consequences, it causes an important reduction in fertility. And in this situation, antibiotic treatment can restore normal fertility [34].

The prophylactic administration of antibiotics reduces the incidence of post-abortion infectious complications and limits the cases of post-abortion infertility [35]. Pelvic bacterial infections are common in women during the fertile period and they reduce fertility [36]. Pelvic inflammatory disease is diagnosed in 4% to 12% of women of reproductive age. In the case of women aged between 18 and 49 years with pelvic inflammatory disease, infertility is associated in 13.8% of cases, a significantly higher percentage than in the case of women without this disease [37]. Treatment with antibacterial antibiotics had a positive effect both on the evolution of the disease and on fertility [38]. Prophylaxis with antibiotics increases the effectiveness of in vitro fertilization and implicitly fertility [39].

Bacterial infections of the male genital tract also reduce fertility. Infertility is attributable to male genital tract infection in 15% of cases. Infections are considered the third cause of male infertility after idiopathic infertility (28.4%) [40] and varicocele (18.1%) [41]. The prevalence of female genital tuberculosis in infertile women ranges from 7% to 15% in developing countries. Female genital tuberculosis affects the fallopian tubes (90%), endometrium (50–80%) and ovaries (20–30%) [42,43].

Treatment with anti-tuberculosis antibiotics for six months significantly reduces the incidence of infertility in these women.

Bacterial infections affect sperm quality, can cause DNA fragmentation in spermatozoa, and increase oxidative stress and apoptosis in male gametes. Toxins produced by some bacteria can negatively affect sperm quality. In some cases, bacteria can attach to the sperm membrane [26]. Antibiotic treatment prevents or suppresses these negative effects. Prostate infections negatively affect the prostatic epithelium and also the prostatic fluid. Male fertility is closely related to the quality of the prostate gland and is significantly reduced by these infections [44]. Some bacterial infections of the male genital tract produce acrosome impairment [45].

The administration of minocycline at 200 mg/day for 7–14 days to infertile men caused an increase in the number of spermatozoa and their motility [46]. Chronic administration of minocycline at 25 mg/kg/day enhanced the number of germ cells in testis but testosterone production and Leydig and Sertoli count were not changed in rats [47]. Minocycline at both 50 and 100 mg/kg/day for 5 days reduced male germ cell apoptosis in rats [48].

Doxycycline increases the plasma level of FSH and increases ovulation. In female mice, doxycycline doubled the number of ovulations and increased the number of embryos by 30% [49]. In the case of experimental models of polycystic ovary syndrome (PCOS), minocycline produced an increase in the number of ovarian follicles and corpus luteum [50].

1.2. Negative Effect of Antibiotics on Fertility

However, some antibiotics also have negative influences on human fertility.

There are more and more frequent cases of infertility in contemporary society. Antibiotics influence fertility by acting on both sexes. In the case of male infertility, idiopathic sperm abnormalities occur in about 30% of cases. We consider that in some of these cases the abnormalities could be determined by some antibiotics [8]. Some studies show a decline in sperm concentration worldwide. The causes of this are multiple, but it is wrong to underestimate the possibility that sometimes this decrease in sperm concentration may be due to some antibiotics [51].

The mechanisms by which antibiotics effect a negative influence on fertility are as follows:

- I. Action on gametes and gamete production:
 - a. Direct action;
 - b. Indirect action.
- II. Preconception effects of antibiotics.
- III. Effects on the subsequent evolution of a pregnancy.

2. Action on Gametes and Gamete Production

2.1. Direct Action

2.1.1. Fluoroquinolones

Regarding the direct action of some antibiotics on gametes, the ability of these drugs to reach effective concentrations in the gonads and at the sperm level is very important. Some groups of antibiotics such as the fluoroquinolones have a good penetrability both in the sperm and in the prostatic fluid [52,53]. For some fluoroquinolones, such as gatifloxacin and lomefloxacin, concentrations in the seminal fluid are approximately equal to those in the blood plasma, but for other antibiotics in this group, the concentrations in the seminal plasma are higher than those in the blood plasma [54].

Ofloxacin at 2×200 mg/day for a period of 20 days administered to adult men determined significant morphological changes in the spermatozoa but reduced their motility compared to the motility before the administration of the antibiotic. The motility of the spermatozoa slowly recovered to the level measured before treatment with ofloxacin after finishing the treatment [55]. Experimental animal studies have shown that doses of oxytetracycline and enrofloxacin similar to those used in the human clinic administered for 7 days decreased sperm density, sperm motility and testosterone levels, and prompted an increase in sperm DNA damage in comparison with a control group that did not receive any drug. These effects were more intense in the case of enrofloxacin [56]. There were no statistically significant changes in sperm volume in the animals that received the two antibiotics. In the case of pubescent mice, the experimental administration of enrofloxacin determined the inhibition of mouse Leydig and Sertoli cell proliferation. This antibiotic reduced the expression of some genes (17 β -HSD, cyp11a1, 3 β -HSD) in the Leydig cells and also altered the gene expression in Sertoli cells [56]. Testicular weight was reduced compared to animals that did not receive this antibiotic. Ciprofloxacin induced injury of spermatogonial tissue and reduced the sperm weight [57]. Oral ciprofloxacin (150 mg/kg/day) for 10 days reduced the testicular volume and sperm concentration in rats [58].

Total sperm count, viability, and motility reductions were observed in the case of the administration of these doses of levofloxacin. The most important morphological lesions observed were the presence of spermatid giant cells, cystic dilatation of seminiferous tubules, a few spermatogenic cells lining the seminiferous tubules and interstitial edema. It

is important that even at lower doses (0.06–0.08 mg/kg/day) levofloxacin induces testicular lesions and negatively affects sperm quality and spermatogenesis [59].

The mechanisms of the harmful action of some antibiotics at the level of the testicle are not completely known, but increased oxidative stress is certainly one of the most important.

Levofloxacin at 40 mg/kg/day in rats causes a decrease in sperm quality simultaneous with an increase in oxidative stress at the testicular level. The administration of zinc oxide resveratrol nanoparticles (a compound with antioxidant action) reduced the harmful effect of levofloxacin on the testicle and sperm. These data show that increased oxidative stress is an important mechanism of the damaging action of fluoroquinolones at the testicular and spermatogenic levels [60]. Ofloxacin administered at a dose of 400 mg/day in healthy volunteers reaches a concentration in the spermatogenic fluid of 2.4–2.5 mg/L. At this concentration, the antibiotic does not change sperm motility [61]. Experimental data show that enrofloxacin at its usual doses causes a significant reduction in the number of growing follicles and atresia of granulosa at the ovarian level. These negative effects were observed two months after the end of antibiotic administration, which implies that enrofloxacin primarily affects early-growing follicles [62]. It should be noted that there are few data regarding the late adverse effects (after stopping the treatment) of antibiotics. It is possible that some of them occur in the reproductive area.

Moxifloxacin at 30 mg/kg/day daily for 7 days significantly reduced the percentage of mobile sperms compared to a control group [63].

2.1.2. Aminoglycosides

Streptomycin, neomycin and gentamicin significantly decrease the number and concentration of spermatozoa in human sperm [64]. The major mechanism by which aminoglycosides produce negative effects on spermatozoa is the increase in oxidative stress and the decrease in the activity of antioxidant systems [65,66].

In mice testis, the administration of gentamicin significantly decreased the level of reduced glutathione (GSH) and affected the activity of superoxide dismutase (SOD). Spermatogenesis was decreased compared to animals that did not receive antibiotics. In experimental studies in adult rats, gentamicin 80 mg/kg increased oxidative stress at the testicular level. At the same time, apoptosis increased significantly. Streptomycin produced a significant increase in sperm head defects in rats. The addition of amikacin to stallion sperm did not affect sperm quality, sperm mobility or fertility [67].

2.1.3. Anti-Tuberculosis Drugs

The administration of widely used anti-tuberculosis drugs (rifampicin, isoniazid, pyrazinamide, streptomycin and ethambutol intraperitoneally, for 4 weeks) to mice during the prepubertal period causes a reduction in the number of oocytes produced by the ovaries in females, as well as an increase in the incidence of degenerated oocytes or those with various anomalies. Regarding male animals, anti-tuberculosis drugs do not reduce the number or motility of spermatozoa, but they decrease their quality and increase the number of DNA anomalies and the frequency of mitochondrial lesions [68]. Therapeutic doses of ethambutol administered to rats produced a significant reduction in sperm count and fertility index [69].

Isoniazid, another anti-tuberculosis drug, did not adversely affect sperm quality [70]. This fact has clinical importance because many patients with tuberculosis have received or have been receiving this drug for a long time, usually associated with other anti-tuberculosis drugs.

2.1.4. Tetracyclines

Tetracycline at a dose of 28.6 mg/kg body-weight daily 14 days in adult rats for two weeks significantly affected sperm quality, reduced sperm motility and the amount of sperm produced and increased the amount of sperm with different morphological defects.

This antibiotic also significantly reduced testicular weight and seminal vesicle weight in rats, as well as motility in the epididymal sperm motility and sperm count. These effects of tetracycline are partially diminished by the simultaneous administration of vitamin C or N-acetylcysteine (NAC) with the antibiotic [71]. Administration of antioxidants reduced but did not suppress these negative effects of tetracycline on sperm.

2.1.5. Chloramphenicol

Experimental studies showed that therapeutic doses of chloramphenicol (28 mg/kg body-weight) for ten days produced a decrease in epididymal sperm number, a reduction in sperm motility and a decrease in the live/dead ratio for sperm. Thiamphenicol has also shown in experimental studies a degree of toxicity at the level of male gonads and spermatozoa [72].

2.1.6. Beta-Lactams

α . Penicillins

Amoxicillin increased the rate of malformed human sperm [73]. In the case of animals such as bulls, the percentage of mobile spermatozoa decreases if the concentration of dicloxacillin in the incubation medium is higher than 200 microg/mL.

β . Cephalosporines

Cefpodoxime administered to male rats at 20 mg/kg bid for 7 days determined a significant reduction in live sperm count and the number of intact acrosomes [74,75]. This effect was not observed for other third-generation cephalosporins.

In rats, cefuroxime at 30, 60 or 120 mg/kg administered daily for 7 days decreased sperm quality and reduced the weight of the testicles and epididymis as well as testosterone secretion [76]. In these cases, the decrease in testosterone secretion is probably the consequence of the direct action of the antibiotic on the testis.

Cefotaxime at 0.5 mg/kg/day administered for five days to non-pregnant adult rats reduced the number of ovarian follicles [77]. In our experimental studies using adult rats, cefepime at 100 mg/kg/day daily for 10 days reduced the sperm motility (tested in vitro 3 h after the last dose of cefepime) by 56% compared to the sperm motility of a group of rats that received no drug [63].

γ . Imipenem/Cilastatin

Imipenem/cilastatin administration (30 mg/kg, 50 mg/kg and 80 mg/kg daily) for 7 days in rats also decreased testis, seminal vesicle and prostate weights as well as the plasma testosterone level. The main reason for this effect is the increase in the testicular level of lipid peroxidation. Severe lesions of the seminiferous tubules were observed after the administration of this antibiotic, alongside a significant decrease in the activity level of superoxide dismutase [76].

In male rats, imipenem (15, 50 or 100 mg/kg) increased oxidative stress and increased the expression of B-cell lymphoma 2 (Bcl-2) and interleukin-1 beta (IL-1 beta) at the testicular level. It also resulted in a stronger expression of Bax, which is a regulatory factor in apoptosis [78].

2.1.7. Sulfonamides

Some sulfonamides, such as sulfasalazine, cause oligospermia, reduction in sperm motility and morphological changes [79]. Treatment with sulfamethoxazole decreased sperm quality in humans [80].

2.1.8. Macrolides

The administration of erythromycin in men with asthenospermia did not significantly increase either the number or the motility of sperm compared to a group of patients with the same disease who received a placebo [81]. In human studies, clarithromycin induced an increase in the sperm concentration and the rate of malformed sperm [73]. Clinical studies have shown that erythromycin reduces sperm motility and testosterone production [82]. In male mice, clarithromycin (2–10 mg/kg/day) reduced epididymal weight and seminal vesicle weight after seven to ten days of treatment [83]. Clarithromycin acts as a mixed inhibitor, binding to both active and inactive sites of CYP3A4 [84].

2.1.9. Vancomycin

Vancomycin administered at high doses to rats for seven weeks has a toxic action at the testicular level. The number of spermatozoa and the plasma concentration of testosterone were significantly reduced. Administration of resveratrol simultaneously with vancomycin reduces the effect of vancomycin. The increased oxidative stress is involved in the toxic effect of vancomycin at the testicular level [85].

2.1.10. Metronidazol

Low and medium doses of metronidazole administered for 2–4 weeks to adult male rats slightly affected spermatogenesis without changing testicular or epididymal weight. However, fragmentation of spermatozoa or spermatids occurred sporadically. Higher doses or longer treatments (6–8 weeks) determined the inhibition of spermatogenesis and the appearance of areas of atrophy of the seminiferous tubules [86]. Metronidazole at 165 mg/kg/day for 16 days in mice reduced spermatozoon tail length and sperm count as well as the number of spermatozoa [87]. A significant reduction in the weights of the testis and epididymis was also observed [88]. Ornidazole decreased sperm motility in rats. Experimental studies in female mice showed that this drug, when administered for 28 days, significantly reduced the fertility index [88].

Apart from increasing oxidative stress, no other mechanisms have been identified for the negative effects of some antibiotics on fertility. We believe that some antibiotics produce these negative effects through other mechanisms. Fluoroquinolones penetrate the human cell membrane [89]. This is an important advantage in the treatment of intracellular bacterial infections, but is also the route through which some adverse effects, including those related to fertility, can occur. Fluoroquinolones (norfloxacin, ciprofloxacin, and enrofloxacin) are strong ion chelators. These antibiotics inhibit histone demethylases and collagen prolyl 4-hydroxylases. This fact causes an increase in the amount of methylated histones and disrupts collagen metabolism [90]. Ciprofloxacin reduces cell proliferation and produces G2/M cell cycle arrest [91]. Fluoroquinolones, not only the older ones (ciprofloxacin, levofloxacin) but also the newer ones (moxifloxacin and gatifloxacin) decrease membrane integrity and increase paracellular permeability [92]. Not only fluoroquinolones have good penetrability into the human cell. Azithromycin penetrates the cells of the human body and accumulates there. Azithromycin decreases tropomyosin-related kinase A signaling and reduces protein kinase B activity [93]. Direct negative influences of some antibiotics on sperm and sperm production are indicated in Figure 1.

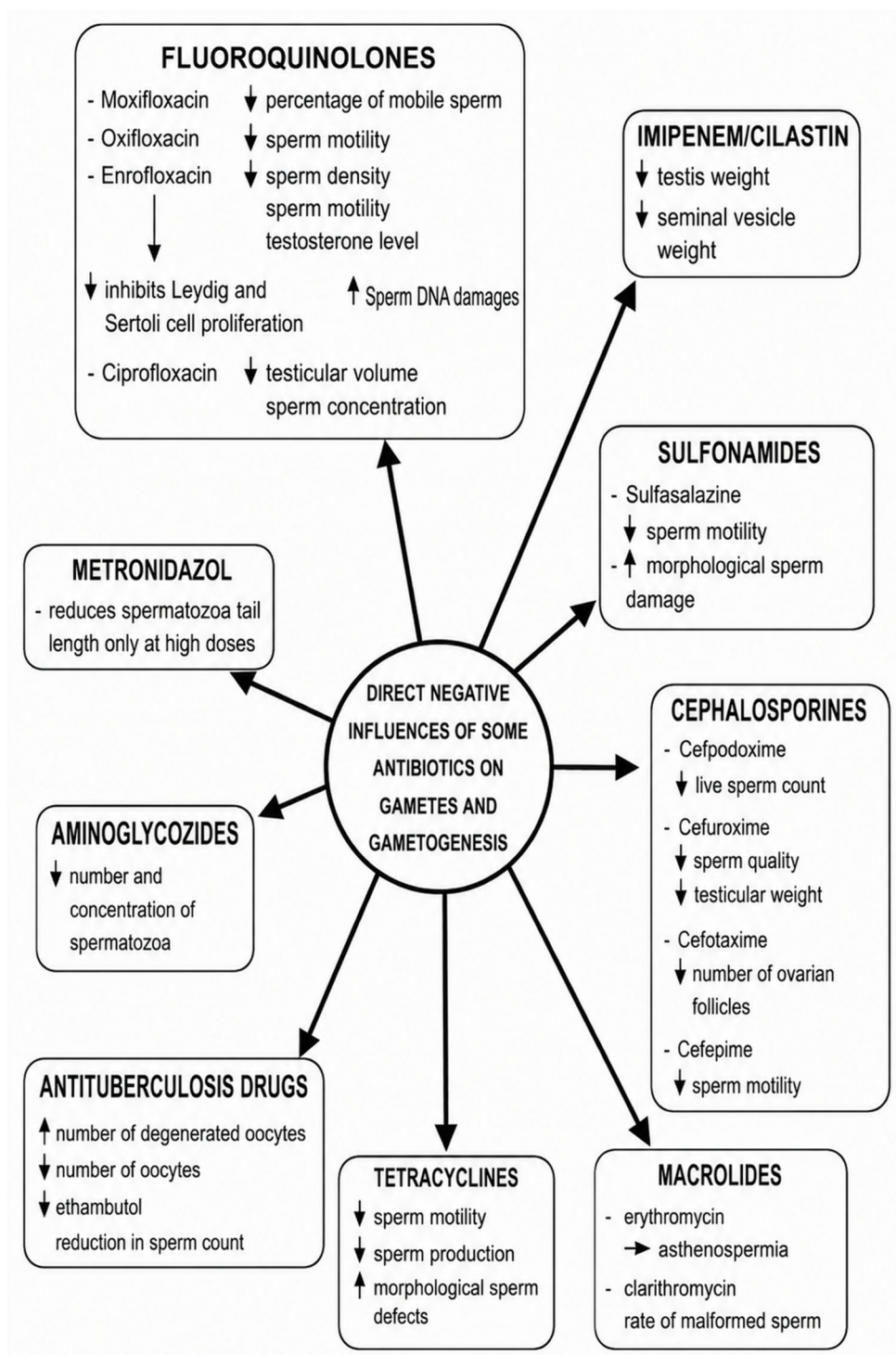


Figure 1. Negative influences of some antibiotics on sperm and sperm production.

2.2. Indirect Action

The main indirect mechanism through which some antibiotics can influence the production of gametes and their quality is their action on the secretion of pituitary and gonadal hormones in both sexes. In the case of some antibiotics, different morphological lesions and functional changes in the gametes are produced both by direct action and by a significant reduction in the secretion of gonadotropins and sex hormones.

2.2.1. Anti-Tuberculosis Drugs

Anti-tuberculosis drugs (ATDs) used in DOTS (directly observed treatment short course) have a complex effect on ovarian activity. They reduce the level of progesterone in plasma and the number of ovulated oocytes, but increase the number of morphological changes in the ovarian follicles. The levels of LH and FSH are also reduced after taking these drugs [94].

2.2.2. Fluoroquinolones

Experimental research on animals has shown that norfloxacin acts on male gonad and gamete production both directly and indirectly by reducing testosterone secretion and by altering androgen receptor gene expression in the testes [95]. Levofloxacin at 40 mg/kg/day administered orally every day for 2 months decreased the plasma level of testosterone in adult rats (6.89 ± 0.5 ng/mL in animals from the control group vs. 3.77 ± 0.5 ng/mL that received this antibiotic). Significant statistical decreases also occurred in the case of FSH (0.97 ± 0.18 mU/mL in the control group vs. 0.41 ± 0.08 mU/mL in the group treated with levofloxacin), and also in the case of LH [60].

Ciprofloxacin and enrofloxacin experimentally administered to adult male animals reduced their sperm concentration and significantly decreased the plasma levels of LH and FSH. Some authors [57] consider that the mechanism of action mediated by this reduction in gonadotropin secretion is the main mechanism of action of these antibiotics in the male gonads.

Ciprofloxacin at 135 mg/kg/day administered to adult male rats negatively influenced the hypothalamic–pituitary–gonadal axis, reduced FSH and LH secretion and affected sperm quality and fertility [96]. In male zebrafish, ciprofloxacin significantly decreased the secretion of FSH, LH and testosterone [57].

At the gonadal level, at least in some species of animals, the action of enrofloxacin is complex. It increases the conversion of estradiol to estriol but inhibits the conversion of testosterone to estradiol [97]. Norfloxacin at 20 mg/kg/day for 14 days can reduce fertility through another mechanism. In some animals, such as male quail, this antibiotic reduced androgen receptor (AR) gene expression and also sperm concentration and serum testosterone.

2.2.3. Other Antibacterial Drugs

Rifampin at 600 mg daily administered for 2 weeks in adult women (median age was 28.2 years) caused a significant increase in serum estradiol concentration [98].

Experimental research has shown that relatively high concentrations of sulfathiazole reduce aromatase activity and the synthesis of sexual hormones. Through this effect, fertility is negatively influenced.

Metronidazole administered to rats in doses close to the clinical practice (15 mg/kg) does not change the levels of testosterone or serum FSH and does not change the count or the mobility of sperm. At high doses (200 mg/kg/day) the serum levels of the two hormones and sperm motility are reduced [99]. Daily administration of metronidazole for 6 weeks to prepubertal rats produced a significant decrease in serum concentrations of testosterone, FSH and LH [100]. More studies are needed to clarify whether age plays a role in this effect of metronidazole. Existing experimental data on the negative influences of some antibiotics on fertility are presented in Table 1.

Table 1. Experimental data on the negative influence of antibiotics on fertility.

Antibiotic Actions	Antibiotics
I. Action on gametes and gamete production	
a. Direct action	
Fluoroquinolones	- Enrofloxacin and Ofloxacin decrease sperm density, sperm motility and testosterone levels, and increase sperm DNA damage [56]. - In pubescent mice, the experimental administration of enrofloxacin determined the inhibition of mouse Leydig and Sertoli cell proliferation, reduced the expression of some genes (17β-HSD, cyp11a1, 3β-HSD,) in the Leydig cells, and also altered gene expression in Sertoli cells [56]. - Ciprofloxacin induced injury of spermatogonial tissue and reduced sperm weight [57]. - Oral ciprofloxacin (150 mg/kg/day) for 10 days reduced testicular volume and sperm concentration in rats [58]. - Levofloxacin reduced total sperm count, viability, and motility. - At lower doses (0.06–0.08 mg/kg/day) levofloxacin induces testicular lesions and negatively affects sperm quality and spermatogenesis [71]. - Levofloxacin at 40 mg/kg/day in rats causes a decrease in sperm quality simultaneous with an increase in oxidative stress at the testicular level. - In the common marmoset, enrofloxacin at usual doses causes a significant reduction in the number of growing follicles and atresia of granulosa at the ovarian level [62]. - Moxifloxacin at 30 mg/kg/day daily for 7 days significantly reduced the percentage of mobile sperm compared to a control group [63].
Aminoglycosides	-In mice testes, the administration of gentamicin significantly decreased the level of reduced glutathione (GSH) and affected the activity of superoxide dismutase (SOD), decreasing spermatogenesis. - In adult rats, gentamicin at 80 mg/kg increased oxidative stress at the testicular level. Apoptosis increased significantly. - Streptomycin produced a significant increase in sperm head defects in rats.
Anti-tuberculosis drugs	- Anti-tuberculosis drugs (rifampicin, isoniazid, pyrazinamide, streptomycin and ethambutol intraperitoneally) administered for 4 weeks to mice during the prepubertal period cause a reduction in the number of oocytes produced by the ovaries in females, as well as an increase in the incidence of degenerated oocytes and those with various anomalies [68]. - Anti-tuberculosis drugs do not reduce the number or motility of spermatozoa, but they decrease their quality and increase the number of DNA anomalies and the frequency of mitochondrial lesions [68]. - Therapeutic doses of ethambutol administered to rats produced a significant reduction in sperm count and fertility index [69].

Tetracyclines

- Tetracycline significantly affected sperm quality, reduced sperm motility and the number of sperm produced and increased the number of sperm with different morphological defects [71].
- Tetracycline significantly reduced testicular weight and seminal vesicle weight in rats, as well as motility in the epididymal sperm motility and sperm count [71].

Chloramphenicol

- Therapeutic doses of chloramphenicol (28 mg/kg body-weight) for ten days produced a decrease in epididymal sperm number.
- Thiamphenicol has shown, in experimental studies, a degree of toxicity at the level of male gonads and spermatozoa [72].

Beta-lactams

- Amoxicillin increased the rate of malformed human sperm [73]. The percentage of mobile spermatozoa decreased.
- Cefpodoxime administered to male rats at 20 mg/kg bid for 7 days caused a significant reduction in live sperm count and the number of intact acrosomes [74,75].
- In rats, cefuroxime at 30, 60 or 120 mg/kg administered for 7 days daily decreased sperm quality and reduced the weight of the testicles and epididymis as well as testosterone secretion [64].
- Cefotaxime at 0.5 mg/kg/day administered for five days to non-pregnant adult rats reduced the number of ovarian follicles [66].
- Cefepime at 100 mg/kg/day daily 10 days reduced sperm motility (tested in vitro 3 h after the last dose of cefepime) by 56% compared to the sperm motility of a group of rats that received no drug [65].

Imipenem/cilastatin

- Imipenem/cilastatin (30 mg/kg, 50 mg/kg and 80 mg/kg daily) administered for 7 days in rats decreased testis, seminal vesicle and prostate weights as well as plasma testosterone level. Severe lesions of the seminiferous tubules were observed [76].
- In male rats, imipenem (15, 50 or 100 mg/kg) increased oxidative stress and increased the expression of B-cell lymphoma 2 (Bcl-2) and interleukin-1 beta (IL-1 beta) at the testicular level. It also resulted in a stronger expression of Bax, which is a regulatory factor in apoptosis [78].
- Some sulfonamides, such as sulfasalazine, cause oligospermia, reductions in sperm motility and morphological changes [79].

Macrolides

- In male mice, clarithromycin (2–10 mg/kg/day) reduced epididymal weight and seminal vesicle weight after seven to ten days of treatment [83].
- Clarithromycin binds to both active and inactive sites of CYP3A4 [84].

Vancomycin

- Vancomycin administered at high doses to rats for seven weeks has a toxic action at the testicular level [85].

Metronidazole

- Higher metronidazole doses or longer treatments (6–8 weeks) caused the inhibition of spermatogenesis and the appearance of areas of atrophy of the seminiferous tubules [86].

b. Indirect action

Fluoroquinolones

- Metronidazole at 165 mg/kg/day for 16 days in mice reduced spermatozoon tail length and sperm count as well as the number of spermatozoa [87].
- A significant reduction in the weights of the testis and epididymis was observed after metronidazol administration in mice [87].
- Ornidazole decreased sperm motility in rats [88].
- In female mice, ornidazol administered for 28 days significantly reduced the fertility index [88].

- Norfloxacin acts on the male gonad and gamete production both directly and indirectly by reducing testosterone secretion and by altering androgen receptor gene expression in the testes [95].
- Levofloxacin at 40 mg/kg/day administered orally every day for 2 months decreases the plasma level of testosterone in adult rats (6.89 $\pm$ 0.5 ng/mL in animals from the control group vs. 3.77 $\pm$ 0.5 ng/mL in those that received this antibiotic) [60].
- Levofloxacin also decreases FSH level (0.97 $\pm$ 0.18 mU/mL in the control group vs. 0.41 $\pm$ 0.08 mU/mL in the group treated with levofloxacin) and LH concentration [60].
- Ciprofloxacin and enrofloxacin experimentally administered to adult male animals reduced the sperm concentration and significantly decreased the plasma levels of LH and FSH [57].
- Ciprofloxacin at 135 mg/kg/day administered to adult male rats negatively influenced the hypothalamic–pituitary–gonadal axis, reduced FSH and LH secretion and affected sperm quality and fertility [92].
- In male zebrafish, ciprofloxacin significantly decreased the secretion of FSH, LH and testosterone [57].
- Enrofloxacin increases the conversion of estradiol to estriol but inhibits the conversion of testosterone to estradiol [97].
- In some animals, norfloxacin reduced androgen receptor (AR) gene expression and also sperm concentration and serum testosterone.
- Sulfathiazole reduces aromatase activity and the synthesis of sexual hormones.
- Metronidazole administered daily for 6 weeks to prepubertal rats produced a significant decrease in serum concentrations of testosterone, FSH and LH [100].

II. Effects on evolution of pregnancy

a. Direct action on embryo

b. Action on uterine contractility

- Tetracycline produced major disturbances in the development of *Cyprinus carpio* embryos and teratogenic effects. The concentrations at which these effects (145.3 μ g–500/L) occur can be reached in the human body [101].
- In an organ bath containing uteri from pregnant rats, it was shown that pretreatment of the animals for 7 days with amoxicillin increases the sensitivity of the uterus to oxytocin. Administering fosfomycin before testing achieves the same thing [102].
- Enrofloxacin (10^{-4} M in the organ bath) also increases the contractile response of the non-pregnant uterus to oxytocin [103].

3. Preconception Effects of Antibiotics

The data regarding the influence on fertility of administration of antibiotics in the days immediately preceding conception are few and sometimes contradictory. In some studies the use of antibiotics such as nitrofurantoin, penicillins and cephalosporins in the last 4 weeks before conception did not change fecundity in women aged between 21 and 45 years. In other studies, at therapeutic concentrations in the human body, cefuroxime axetil and nitrofurantoin monohydrate significantly decreased the motility of human spermatozoa after two days of treatment.

In a recent study of 9462 women with an average age of 29 who were enrolled in the study for 12 months or until conception, a significant reduction in fecundability was shown in women who received macrolides or sulfonamides compared to women who did not receive antibiotics [104]. Lincosamides produced a slight increase in fecundability [105].

On the other hand, in some cases, the long-term use of antibiotics causes disturbances in the vaginal microbial flora. This can influence the vaginal pH and the movement of spermatozoa [106]. In some cases, disturbances in the vaginal flora can cause the ascent of some bacteria in the female genital tract with negative influences on fecundability [107].

Minocycline significantly decreases the number of motile spermatozoa at all concentrations that exceed 100 microg/mL. Administration of doxycycline for the treatment of chronic endometritis in women undergoing assisted reproduction procedures had no effect on pregnancy outcomes [108].

In other studies, it was shown that ciprofloxacin and doxycycline, both in low doses and in high doses, increase the fragmentation of sperm DNA [109]. The previously mentioned authors contraindicated the use of ciprofloxacin for the preservation of human sperm.

If the fertilizing capacity is preserved but a partial DNA fragmentation occurs in the spermatozoa, then we consider that there would be a possibility of an increase in the incidence of spontaneous abortions and even some congenital malformations, but there is no data in this direction [110,111].

Oxytetracycline added to cryopreserved human sperm significantly affected sperm quality.

The total motility, the progressive motility and the speed of movement of the spermatozoa significantly decreased. Administration of this drug for six days in men also decreased all the previously mentioned sperm kinetic parameters [112].

Ciprofloxacin at 200 mg/kg/day for 45 days reduced the rate of fertilization in mice and significantly increased DNA damage [113]. Although these doses are higher than those used in the human clinic, the obtained results indicate possible adverse effects of ciprofloxacin in the fertilization process in humans.

4. Effects on the Evolution of Pregnancy

4.1. Direct Action on the Embryo

The use of antibiotics by pregnant women is common. Approximately 20–40% of women receive antibiotic treatment during pregnancy for various reasons. Regarding the evolution of pregnancy, there are both positive and negative effects of antibiotics.

Administration of antibiotics in the first weeks of pregnancy causes increases of 17% in the risk of preterm birth (<37 gestation weeks) and 11% in low birth weight risk.

Administration of some antibiotics in late pregnancy also increased the risk of preterm birth [114]. Both premature birth and low birth weight cause increased mortality in the first year of the child's life. The problem is complex because untreated urinary and genital infections in pregnant women are also associated with an increase in the frequency

of premature birth and low birth weight. Since not all antibiotics have the same effect on the duration of pregnancy and on the weight of the newborn, more studies are needed in this direction [115,116].

4.1.1. Quinolones

Regarding fluoroquinolones, some studies have shown that their use in the first trimester of pregnancy did not increase the risk of premature birth [117]. However, other studies show that fluoroquinolones increase the risk of bone malformations [118]. There are some suspicions that moxifloxacin could increase the incidence of spontaneous abortion.

In experimental studies, ciprofloxacin induced morphological alterations in the embryos (growth slowing and craniofacial malformations) and in some cases even the death of embryos [119]. Fluoroquinolones should be avoided as much as possible in the first trimester of pregnancy [120].

4.1.2. Other Antibiotics

Administration of metronidazol, azithromycin and clarithromycin increased the incidence of spontaneous abortion [121]. Azithromycin use during pregnancy was associated with an increased risk of abortions [122]. Regarding the use of clarithromycin in women in the first trimester of pregnancy and the risk of spontaneous abortion, the results of clinical studies are controversial. Some studies say that this risk increases and others say that it remains unchanged [123].

There are clinical data that show an increased incidence of spontaneous abortion of 8% in the case of the administration of nitrofurantoin [122].

Tetracycline produced major disturbances in the development of *Cyprinus carpio* embryos and teratogenic effects. The concentrations at which these effects (145.3 µg–500/L) occur can be reached in the human body [101].

4.1.3. Sulfonamides

Studies done on a large number of pregnant women show that sulfonamides administered in the first weeks of pregnancy induce congenital malformations in several cases and increase the risk of spontaneous abortion [124]. Studies conducted on a large number of women show that trimethoprim/sulfamethoxazole significantly increases the risk of premature birth and low birth weight of the child [125].

The use of trimethoprim–sulfamethoxazole in the first weeks of pregnancy significantly increases the risk of spontaneous abortion [126]. Inhibition of folic acid synthesis is probably the main mechanism behind these effects by sulfonamides. Clinical studies show that the use of trimethoprim in the first trimester of pregnancy doubles the risk of spontaneous abortion separate from the effect of sulfonamides. The exact mechanism of this effect is not known, but it is possible that the action of this drug as an antagonist of folic acid is involved [127]. Existing clinical data on the negative influences of some antibiotics on fertility are presented in Table 2.

Table 2. Clinical data on the negative influence of antibiotics on fertility.

Antibiotic Actions	Antibiotics
I. Action on gametes and gamete production	
a. Direct action	
Fluoroquinolones	- For gatifloxacin and lomefloxacin, concentrations in the seminal fluid are approximately equal to those in the blood plasma, having good penetrability both in the sperm and in the prostatic fluid [52,53]. - Ofloxacin at 2 × 200 mg/day for a period of 20 days administered to adult men determined significant morphological

	changes in the spermatozoa and reduced their motility. The motility of the spermatozoa slowly recovers after finishing the treatment [55]. - Ofloxacin administered at a dose of 400 mg/day in healthy volunteers reaches a concentration in the spermatic fluid of 2.4–2.5 mg/L. At this concentration, the antibiotic does not change sperm motility [61].
Aminoglycozides	- Streptomycin, neomycin and gentamicin significantly decrease the number and concentration of spermatozoa in human sperm [64].
Anti-tuberculosis drugs	- Isoniazid did not adversely affect sperm quality [70].
Beta-lactams	- Amoxicillin increased the rate of malformed human sperm [73].
Sulfonamides	- Some sulfonamides, such as sulfasalazine, cause oligospermia, reduction in sperm motility and morphological changes [79].
Macrolides	- Erythromycin administration in men with asthenospermia did not significantly increase either the number or the motility of sperm compared to a group of patients with the same disease who received a placebo [81]. - Clarithromycin induced an increase in sperm concentration and the rate of malformed sperm [55].
Anti-tuberculosis drugs	- Anti-tuberculosis drugs (ATDs) used in DOTS reduce the level of plasma progesterone and the number of ovulated oocytes, but increase the number of morphological changes in the ovarian follicles. The levels of LH and FSH are also reduced after taking these drugs [94].
b. Indirect action	- Rifampin at 600 mg daily administered for 2 weeks in adult women (median age was 28.2 years) caused a significant increase in serum estradiol concentration [98].
II. Preconception effects of antibiotics	- In a recent study of 9462 women with an average age of 29 who were enrolled in the study for 12 months or until conception, a significant reduction in fecundability was shown in women who received macrolides or sulfonamides [104]. - Cefuroxime axetil and nitrofurantoin monohydrate significantly decreased the motility of human spermatozoa after two days of treatment. - Sulfonamides and lincosamides produced a slight increase in fecundability, and macrolides caused a moderate decrease in it [105]. - The long-term use of antibiotics causes disturbances in the vaginal microbial flora. This can influence the vaginal pH and the movement of spermatozoa [106]. - Ciprofloxacin and doxycycline both in low doses and in high doses increase the fragmentation of sperm DNA. Ciprofloxacin is contraindicated for the preservation of human sperm [109].

III. Effects on evolution of pregnancy.

a. Direct action on embryo

- **Oxytetracycline** added to cryopreserved human sperm significantly affected sperm quality [110].
- Administration of antibiotics in the first weeks of pregnancy causes increases of 17% in the risk of preterm birth (<37 gestation weeks) and 11% in low birth weight risk.
- Administration of antibiotics in late pregnancy increased the risk of preterm birth [114].
- **Fluoroquinolones** increase the risk of bone malformations [114].
- Ciprofloxacin induced morphological alterations in the embryos (growth slowing and craniofacial malformations) and in some cases even the death of embryos [120].
- Fluoroquinolones should be avoided as much as possible in the first trimester of pregnancy [120].
- **Azithromycin** use during pregnancy was associated with an increased risk of abortions [122].
- Incidence of spontaneous abortion of 8% was observed in the case of the administration of **nitrofurantoin** [122].
- **Sulfonamides** administered in the first weeks of pregnancy induce congenital malformations in a number of cases and increase the risk of spontaneous abortion [124].
- **Trimethoprim/sulfamethoxazole** significantly increases the risk of premature birth and low birth weight of the child [125].

4.2. Direct Action on Uterine Contractility

The influence of antibiotics on uterine contractility is diverse and insufficiently studied. There is data in this direction for a small number of antibiotics.

The possibility that some antibiotics can influence fertility by inducing spontaneous abortion or premature birth would be due to their direct action on uterine contractility. In experimental studies in an organ bath on uteri from pregnant rats, it was shown that pre-treatment of the animals for 7 days with amoxicillin increased the sensitivity of the uterus to oxytocin. Administering fosfomycin before testing achieved the same thing. The mechanism by which this sensitivity changes is a reduction in protein for aquaporin 5 (AQP5) expression [102]. Enrofloxacin (10^{-4} M in the organ bath) also increases the contractile response of the non-pregnant uterus to oxytocin [103]. Other studies have shown that erythromycin inhibits uterine contractions induced by prostaglandin F₂alpha (PGF₂alpha).

4.2.1. Postpartum Antibiotics@Adverse Effects

The adverse effects of some postpartum antibiotics do not affect fertility but may have important effects on the newborn. Some antibiotics pass into breast milk and can have a negative effect on the gut microbiota [128]. In some cases, alterations to the microbiota are implicated in the pathogenesis of necrotic enteritis, a severe complication with high mortality [129].

4.2.2. Future Research Directions

Clinical and experimental research is needed regarding the effect of antibiotic associations on fertility, but also regarding the possible influence that the associations between antibiotics and other drug groups can have on it. For the future, studies are needed to reveal the differences between species in terms of the influence of some antibiotics on fer-

tility. More data are needed in terms of the impact that different doses and different durations of treatment have on the influence of antibiotics on male and female fertility. The effect of off-label use of antibiotics has not been researched and is not known. More studies are needed to correlate the results obtained with the antibiotic doses used in experimental studies with the doses used in therapeutic practice. It is necessary to research the influence of all groups of antibiotics used today on fertility. Existing data regarding the negative effects of antibiotics on fertility are currently mainly obtained through experimental studies but should not be ignored. Existing data refer to a relatively small number of antibiotics used. Any data on post-antibiotic effects on human fertility are lacking. Studies are needed on the action of the newest antibiotics introduced into medical practice on fertility. Data are also needed on the effect of the association between antibiotics and the association of antibiotics with other groups of drugs on fertility.

4.2.3. Conclusions

The complex influence of antibiotic therapy on fertility should not be underestimated. Existing data show that there are both positive and negative influences of antibiotics on fertility. These effects occur in both sexes.

A significant number of existing results are experimental data. Translating experimental data into clinical practice always requires caution. If the positive effects of antibiotics are generally produced by their bactericidal or bacteriostatic action, the mechanisms by which the negative effects are produced are much less known. The favorable effects of antibiotics on fertility are also frequently underestimated in medical practice. On the other hand, in all cases of infertility without a clear cause, a possible negative effect of antibiotics must be considered.

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