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Antibiotic Therapy in the Management of Couple Infertility outside Assisted Reproductive Technology in a Low-Income Setting

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Abstract

Background Antibiotic therapy in infertility management is one of the most frequent and useful practices in sub-Saharan setting. Infertility of tubal origin and secondary to infections are the most prevalent. The current study aimed to take stock of antibiotic therapy in infertility management without *in Vitro* Fertilization (IVF). **Material and Methods** A cross-sectional analytical study undertaken in University Clinics of Kinshasa and the Edith Medical Center, from January 2001 to December 2021. It involved 3754 patients who sought care for infertility and received antibiotics during the treatment. **Results** The mean age of the patients was 33.3 ± 5.7 years and ranged from 16 to 49 years. Most of them were nulliparous with secondary infertility. The average duration of infertility was 4.5 ± 3.6 years and ranged from 1 to 20 years. Most had a history of unsafe abortion and tubal obstruction. The pelvic infections were the main diagnosis. After antibiotic therapy, especially made of Doxycycline alone or in association 442 (8.8%) patients conceived. **Conclusion** In the low-income sub-Saharan setting, infection remained the common cause of infertility and doxycycline was found to be the most used and efficient antibiotics.

Keywords

Antibiotic Therapy, Infertility Management, Sub-Saharan Region, Conception, Doxycycline in Infertility

1. Introduction

Antibiotics therapy is the use of antibiotics to treat or to prevent infectious diseases and a most frequent and useful practice in infertility management in sub-Saharan area, where infertility is the most of tubal origin due to infection and its consequences [1].

In fact, couple infertility, defined by the WHO as the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse, is a public health problem [2]. Its prevalence varies from 12.6% to 17.5% worldwide and can climb to 30% in certain sub-Saharan regions [3] [4]. On the other hand, this region is known to be one of the most pronatalists. Infertility is a dramatic situation and huge burden for the couple and her family. Therefore, many social complications such as stigmatization, divorce, and polygamy are more prevalent [5].

As above-mentioned, infertility is mostly of infectious origin. Because of relaxation of morals and sexual promiscuity in developing countries, the sexually transmitted microorganisms (e.g. Chlamydia trachomatis and Neisseria gonorrhea) spread among young people provoking the sexually transmitted disease. Ericksen *et al.* considered the urban setting as the reservoir of infection [6]. And the low prevalence of contraceptives favors the occurring of unintended pregnancies that often finish by unsafe abortions, complicated by post arboretum infections [7]. On the other hand, owing to the lack of relevant medical facilities, most deliveries happened in non-recommended conditions, providing post-partum infection. All of those conditions make the infection; the paramount cause of infertility in our setting [8]. To prevent infertility, the strategies including efficient national health policy by organizing the sexual education, contraceptives program and facilities for safe deliveries need to be developed. For medical care providers, Antibiotic therapy constitutes one of the most efficient methods for preventing or treating couple infertility. In Democratic Republic of Congo, a previous study undertaken in 2019 by our team [9] found that antibiotic therapy was the means most associated with the success in terms of clinical pregnancy outside of IVF. The aim of the current research is to make stock of the use of antibiotic therapy in our area by finding out the most frequent and efficient families of antibiotics in our practice.

2. Material and Methods

This was a cross-sectional analytical study undertaken from January 2001 to December 2021 at the Kinshasa University Clinic and the Edith Medical Center. Period corresponding with the better recording of patients' data in the two institutions. A total of 7290 patients seeking care for infertility were recorded in the database during this period. Among them, 3754 patients who received antibiotics during the first three medical visits and whose files contained the majority of variables of interest were included. The above-mentioned variables of interest were: sociodemographic (patient and her partner age, gynecological-obstetrical history and type of marriage), clinical (duration of infertility, history of unsafe abortion (USA), diagnosis made and conception), paraclinical (hysterosalpingography and endometrial biopsy

findings), therapeutic (antibiotics) and the success of the treatment in terms of clinical pregnancy. Among the diagnosis made, the functional diseases were made up of hyperprolactinemia and polycystic ovary. For antibiotics, the families were considered, and others represent especially aminoglycosides. And Doxycycline was the main of tetracyclines family. Those variables were extracted from the two institutions databases and the patients' files if necessary; and then they were recorded in a Microsoft Access 13 and analyzed by Stata IC 18 program. Quantitative variables were summarized as mean and standard deviation, and qualitative variables as proportion. The Pearson Chi-square test was used for the comparison of proportions, the student t-test for the means comparison, the strength of association between the variables by logistic regression. The difference was statistically significant for a p-value less than 0.05. The study received validation from the council of the Department of Gynecology and Obstetrics of the Kinshasa University Clinics and the national ethic committee. There is no conflict of interest.

3. Results

3.1. General Characteristics

The average age of the patients was 33.3 ± 5.7 years and it ranged from 16 to 49 years. Most of them (73.3%) were over 35 years old. Most patients were nulliparous (62.2%), followed by primiparous (23.8%) and more than two-thirds (68.5%) had secondary infertility. Forty-two percent of patients had a history of at least one unsafe abortion. A large majority (89.9%) were in a monogamous marriage. The partners' age ranged from 24 to 74 years, with an average of 40.51 ± 6.60 years and the majority of them (70.41%) were aged between 36 and 50 years old. The average duration of infertility was 4.5 ± 3.6 years and ranged from 1 to 20 years. More than a third of patients (35.7%) had a duration of more than 5 years. Fifty-two percent had pelvic infections as the diagnosis, followed by uterine myomas (28.2%), and almost two-thirds (60%) had an abnormal hysterosalpingography: the majority (53%) had a tubal obstruction. On endometrial biopsy, seventy-two patients (5%) had endometritis with 1.3% chronic endometritis and 3.7% acute. More than a third (38.5%) of patients were treated with doxycycline alone or in combination, followed by quinolones in 35.2%. During that period less than 10% of patients got pregnant (8.8%).

3.2. Relations between Characteristics

According to the Table 1: the diagnosis after three first visits, 781 patients had a pelvic infection, among them seventy-four percent were less than 36 years old. On the other hand, 422 patients had uterine myoma, fifty-six percent were over 35 years. Antibiotics therapies were more used in the group of patients less than 36 ($p = 0.03$). For infections, the most used antibiotics were Doxycycline alone or in combination (60.6%) and Quinolones associated with Metronidazole (53.5%) ($p = 0.000$). In relation with the parity, the nulliparous were the more affected with Infections: pelvic (60.3%) and vaginal (70.6%) and with myomas (70.6%) ($p <$

0.001). The pelvic infections were treated specially by Cyclins alone or in association (60.6%) (p > 0.001). In regard of the history of unsafe abortion, Antibiotics seemed to be used (p = 0.089) the most in the non-USA group. For all the families of antibiotics, almost seventy percent (69.4%) of them were used by the male partners, aged between 36 and 50 (p < 0.001).

Table 1. Diagnosis and treatment according to age of patients.

	Effective (%)	Age	(%)	
Diagnosis		≤35 y	>35 y	p = 0.000
Pelvic infections	781 (51.6)	74.14	25.86	
Vaginal infections	35 (2.3)	77.14	22.86	
Myomas	422 (28.2)	44.4	55.69	
Functional pathologies	267 (17.9)	64.04	35.96	
Total	1505 (100)	64.05	35.95	
Antibiotics		<35	>35	p = 0.031
Quinolone	983 (35.2)	62.05	37.95	
Macrolides	41 (1.5)	65.85	34.15	
Beta-lactams	247 (8.9)	64.78	35.2	
Doxycycline + others	1078 (38.5)	69.67	30.33	
Quinolone + Metronidazole	449 (15.9)	62.58	37.42	
Total	2798 (100)	65.37	34.63	

Legend: y = years.

3.3. Getting Pregnant in Relation with Other Characteristics

Table 2 shows that, in univariate analysis, compared to nulliparous, the chance to conceive was reduced by 40% (OR 0.604 [0.393 - 0.927] p = 0.021) for pauciparous; it dropped with the duration of infertility and the partners' age. Indeed, the chance to conceive decreased by 60% for the partners aged between 36 to 50 and by 87% for those between 51 to 74 years, compared with the youngest (24 - 35 years). For patients with myomas, chance to conceive was reduced by 65% and 43% for those with offset endometrium and by 40% for the patients who received quinolones. In multivariate analysis, patients who received Cyclin alone or in combination had four times more chance to conceive (OR 4.45 95% CI [1.448 - 13.727], p = 0.009) than those who received Beta-lactams. The chance to conceive for partners between 36 to 50 years was reduced by 45% (OR 0.545 [0.300 - 0.992] p = 0.047) compared to those between 24 to 35 years and by 56% for patients with uterine myomas (OR 0.442 [0.186 - 1.048] p = 0.064).

Table 2. Association between conception and characteristics.

VARIABLES	Uni variable analysis			Multivariable analysis		
	OR	95% IC	p	OR	95% IC	p
Age (years)						
≤35	1			1		
>35	0.492	0.390 - 0.621	0.000	753050.9	0	0.991

Continued

Parity						
Nulliparous	1			1		
Primiparous	1.018	0.778 - 1.331	0.894	1.202	0.636 - 2.270	0.570
Pauciparous	0.604	0.393 - 0.927	0.021	1.208	0.392 - 3.721	0.741
Multiparous	0.244	0.059 - 1.001	0.050			
Type of infertility						
Iary infertility	1					
IIary infertility	0.946	0.738 - 1.212	0.661			
USA						
No	1					
1	0.867	0.629 - 1.195	0.384			
2	0.816	0.542 - 1.227	0.329			
>2	0.561	0.306 - 1.029	0.062			
Duration of infertility (years)						
1	1			1		
2	0.666	0.468 - 0.948	**0.024**	0.961	0.450 - 2.053	0.919
3	0.639	0.432 - 0.946	**0.026**	1.467	0.625 - 3.444	0.378
4	0.453	0.274 - 0.747	**0.002**	0.865	0.338 - 2.170	0.744
>4	0.259	0.179 - 0.376	**0.000**	0.728	0.327 - 1.619	0.437
Partner's age (years)						
24 - 35	1			1		
36 - 50	0.402	0.311 - 0.519	**0.000**	0.545	0.300 - 0.992	0.047
51 - 74	0.139	0.056 - 0.347	**0.000**			
Diagnostic						
Functional pathologies	1			1		
Pelvic infections	0.754	0.496 - 1.118	0.156	0.872	0.473 - 1.607	0.661
Vaginal infections	0.770	0.257 - 2.304	0.641	1.613	0.147 - 17.675	0.695
Myomas	0.354	0.207 - 0.603	**0.000**	0.442	0.186 - 1.048	0.064
Endometrial biopsy						
Compatible endometrium	1					
Offset endometrium	0.578	0.384 - 0.870	**0.009**			
Proliferative endometrium	0.841	0.400 - 1.768	0.650			
Acute endometritis	0.991	0.416 - 2.357	0.984			
Chronic endometritis	0.778	0.172 - 3.519	0.745			
Bone splinters	2.076	0.210 - 20.474	0.531			

Continued

Antibiotics						
Bêta-lactam	1			1		
Quinolone	0.6001	0.371 - 0.968	0.036	0.968	0.306 - 3.056	0.956
Macrolide	0.919	0.303 - 2.781	0.881	1.644	0.230 - 11.724	0.620
Cyclin + others	1.174	0.752 - 1.833	0.479	4.459	1.449 - 13.727	**0.009**
Quinolone + Imidazole	0.579	0.331 - 1.011	0.055	0.433	0.107 - 1.745	0.239

Legends: USA = Unsafe Abortion; NO = no history of unsafe abortion.

4. Discussion

4.1. General Characteristics of the Patients

The average age of patients was 33 ± 5.69 years, ranging from 16 to 49 years with the majority being above 35 years. This finding is comparable with the ones of our team in 2011 (33.7± 5.2 ys) in the same environment [10] and of Fatima B *et al.*, in 2018 (33.2 ± 5.6 ys) in Pakistan [11]. Indeed, the age of patients seeking care for infertility is increasing worldwide and in sub-Saharan areas [12]-[14]. The majority of patients were nulliparous (62.3%), married (89.9%) and had secondary infertility (68.5%), known of the infectious origin in Saharan. That explains the usefulness of antibiotic therapy in this setting.

Marriage and the motherhood are delayed worldwide [14]. Because of the relaxation of the morals and the lower prevalence of contraceptive methods, patients are exposed to sexually transmitted infections and unintended pregnancies, leading to unsafe abortions [15]. As reported by Leke *et al.*, in the world, it is estimated that every minute, 380 women become pregnant, among them 190 pregnancies are unwanted and unplanned, leading to 40 voluntary induced abortions in risky conditions [8]. In the current study, antibiotics were more widely used in patients under 36 years of age than those over 35 years. This is in concordance with the literature which stated that in sub-Saharan areas, patients are younger than in developed countries with secondary and tubal infertility. That means that they get infected earlier and in their thirties, the consequences in terms tubal infertility become apparent [15]. And also, one of the factors favoring infertility among young women remains sexual contact with relatively older partners who are often sexually promiscuous. In the current study, the majority of male partners (70.4%) were aged between 36 and 50 years. This finding is consistent with Bouya *et al.*, [16] in 2015 in Brazzaville, Dia *et al.*, [12] in Côte d'Ivoire in 2016 and Fatima and *al*, [11] in 2018 in Pakistan. The patients in our study had a high rate of unsafe abortions (41.9%). More than a third of patients (35.7%) consulted after a duration of infertility of more than 5 years; period devoted to medical wandering from a care provider to another [10]. Among them, traditional healers, whose practices are at risk of infectious consequences [17]. Almost two-thirds (60%) of patients had any anomalies in hysterosalpingography findings: the majority (53%) had tu-

bal obstruction among them 33.5% bilateral obstruction. On endometrial biopsy, seventy-two patients (5%) had endometritis, including 1.3% chronic and 3.7% acute. Pelvic infections were diagnosed in 51.6% of patients. Our findings are consistent with those of Fatima *et al.*, [11] in Pakistan and Cesar *et al.*, [18] in Pointe Noire. and Kadima *et al.*, [19] in 2023, in DRC. Pelvic infections and their direct and indirect consequences are the main causes of infertility in the sub-Saharan environment [20]-[22].

In most cases, Doxycycline (tetracycline family) was used. Several authors have also reported a wide use of Cyclins alone or combined with other molecules in their studies: McQueen *et al.*, [22], Cicinelli *et al.*, [23] and Stewart J [24] suggest that Doxycyclin can be more efficient against Sexually Transmitted microorganism; namely Chlamydia trachomatis. On the other hand, a previous study undertaken in our setting [25] showed that the high titer of antichlamydia antibodies is associated with the tubo-peritoneal lesions (tubal occlusion and tubo-peritoneal adhesions). Confirming the paramount role of Chlamydia trachomatis, known to be more sensitive to tetracycline. According to the WHO, in 2020, there were an estimated 128.5 million new Chlamydia trachomatis infections worldwide among adults aged 15 - 49 years [24].

4.2. Conception after Antibiotic Therapy

Of the 3714 patients who received antibiotics, the rate of conception was 8.8% in our series. A study conducted in our environment by our team [9] in 2019 reported that 9% of women seeking care for infertility conceived. Most conceptions were associated with antibiotics therapy (73%). Similarly in Pakistan, Fatima *et al.*, [19] in 2018 reported a rate of 9% (*i.e.* 294 women out of 2913) of conception after treatment with antibiotics. Cicinelli *et al.*, [23] in 2015; in Italy and Kitaya *et al.*, [20] in 2017 in Japan; who conducted their works on infertile patients with chronic endometritis, recorded a rate of 28% and 32.5% conception respectively. Infections remain one of the most common causes of infertility in sub-Saharan areas and elsewhere; antibiotic therapy, used correctly, remains one of the efficient treatments.

The present study had limitations, its retrospective design and the lack of data related to germ isolation and antibiogram. As a strength, it is the first undertaken in our environment, with a large sample.

5. Conclusion

Most of patients were older, nulliparous with secondary type infertility, with a history of unsafe abortion and an elderly partner. Pelvic infections and its consequences constitute the essential diagnosis. Doxycycline alone or associated with other antibiotics is the more used and efficient.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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