IFFS-GIERAF WEBINAR: "IFFS-GIERAF Webinar: The Management of Infertility in Lower- and Middle-Income Countries" 17 September 2020
*Please excuse any errors in translation*

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Moderated by:
Dominique De Ziegler, IFFS (France)
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Moise Fiadjoe, GIERAF (Togo)

**5:30 pm** **Adjourn**

**Introduction – Mark Hamilton**

Good day, and welcome to the first of two webinars organized jointly by IFFS with GIERAF.

My name is Mark Hamilton, and I am Director of Workshops for Education Board of the IFFS. I have so enjoyed working with our colleagues at GIERAF in putting together what I hope you will find to be a useful and relevant program for you.

We were of course looking forward to partnering with GIERAF in person in Lomé, Togo in June, but we were alas prevented by COVID. Many of you will be grappling with the challenges posed by the virus and IFFS is well aware of how difficult times have been for many of you. Clinical life has certainly changed, but the foundations of medical need remain.

This is at the heart of the work of the IFFS, and our education strategy continues throughout reproductive health. A virtual educational event is part of a larger educational program to which IFFS is committed. Our first webinar will focus on the organization of services and clinical management of infertility without IVF. The second, in November, will focus on IVF. We have a busy schedule that has posed challenges for us, including the need to support two languages. So here's the plan…

Each presentation has been pre-recorded and will be given in the speaker's preferred language. A translation will be available simultaneously in French or English as needed. The link to the corresponding PDF file will be made available to you according to your needs. Five of the talks will be in French and three in English.

There will be two twenty minute open discussion sessions, firstly halfway through the webinar and again at the end. You are welcome to ask questions to and register comments with the speakers via the onscreen chat feature. The speakers will be available to respond live and this part of the meeting will be conducted in French and English.

We have over two hundred and fifty participants, which is fantastic. So let's go!

To kick us off, we are delighted that Mr. Moustafa Mijiyawa, Minister of Health of the Republic of Togo has agreed to record a message for the meeting. M the Minister….

**STATEMENT FROM TOGO MINISTER OF HEALTH - MOUSTAFA MIJIYAWA**

Ladies and gentlemen experts, dear colleagues and dear friends, after Nigeria and Ghana, Togo is proud and happy to welcome the experts that you are, and this, although virtually, to this important symposium organized jointly by the Group. inter-African fertility research and application studies and the International Federation of Fertility Societies. What could be more normal than to extend a cordial welcome to you on behalf of the Togolese government, thus responding to a concern written in African DNA.

This concern is all the more marked since the symposium, the subject of your meeting, has been centered on one of the constant concerns of humanity since the dawn of time. Fertility, and the reproduction which results from it, constitute the only palliative opposable to our inevitable end, which death symbolizes.

This, as random as it is indeterminate, torments our thought and brings our pride to its knees. Numerous approaches have been opposed and magnified to the uncertainties that characterize it, aimed at galvanizing fertility and therefore fighting its opposite, infertility, always experienced as a tragedy, all the more marked as life expectancy is low.

The palliative role of fertility in the face of death has long made it the sole purpose of the sexual act, then the primary object of marriage. It is easy to understand that reproductive health revolves around fertility, the absence of which, more than a question of public health, is a drama, on the [Inaudible] of the lived, the perceived and the imagined.

We also understand why reproductive health constitutes an entire part of the health policy of our African countries, where infertility has consequences as damaging as they are sprawling. And although suffered by almost all families, infertility remains a taboo subject, loaded with stigma, bearing in the African context, an accusing finger on the woman, which hinders its management.

The data attest to the importance of the topic. Africa is the continent most affected by infertility, with reproductive difficulties affecting 15 to 30% of couples. Only 1% of the 5 million children born through in vitro fertilization are African. Medically assisted procreation, of which we must salute the first promoters in Africa, almost all present here, is inaccessible to the vast majority of couples for various and varied reasons.

The health policy in force in Togo, inspired by the Head of State, aims to overcome certain factors which, in the long term, make the bed of infertility, fight against ignorance through schooling, in particular of the young girl, fight against early marriage, fight against clandestine abortions, access to contraceptive methods, sexual education of students; access to safe deliveries, fight against sexually transmitted infections, and so on. The Togolese government, through my modest voice, sincerely congratulates you for the holistic approach which permeates the themes to furnish your seminar.

This sprawling approach, taking into account the different facets of infertility in Africa, on the diagnostic, sociological, financial, anthropological, cultural and medical levels, bodes well for the fruitfulness of your exchanges and your work to which I wish the greatest success, and which I declare open.

I sincerely thank you for your kind attention.

**WHO PRIORITIES IN INFERTILITY - GITAU MBURU**

Thank you very much ladies and gentlemen for the invitation to participate in this important webinar. My name is Gitau Mburu. I am with the Department of Sexual and Reproductive Health and Research at WHO in Geneva. The talk that I'm going to give today is titled WHO priorities in infertility. I hope to be able to cover this within the next 10 minutes.

Infertility is a cause of significant social and public health impacts across the world. We define it as a disease of the reproductive system characterized by the failure to achieve a clinical pregnancy after 12 or more months of regular unprotected sexual intercourse. An initial 2004 DHS comparative report reported that there were 186 million married women of reproductive age in developing countries who were attempting to conceive and failing. Much more recently, we have had other estimates showing that there are between 48 and 72 million couples who have infertility.

We shall be coming back to this point of estimate. But at this point it is, of course, important to bear in mind that infertility is a significant problem that is causing heavy social and public health impacts for many individuals, women, couples, and families across the world. Given the significant burden that is caused by infertility across the world, WHO has put in place a program of work to respond to infertility that consists of a combination of normative research, policy, and technical assistance activities which should be the focus of my presentation today.

In terms of normative guidelines, WHO's guideline on the prevention, diagnosis, and management of infertility is currently underway. The scope of these guidelines is that they are looking at female, male, and unexplained infertility. The guidelines will be looking at the continuum from prevention, investigation, and first, second, and third line treatment of infertility.

The process itself started in 2019 with a systematic review of 35 PICO questions. These PICO questions were including primary clinical outcomes as well as a number of secondary outcomes related to acceptability, visibility, equity, and cost. This systematic review process has now been completed.

The guideline development group is currently assessing the strength of the evidence that has come out from the systematic reviews, and using this evidence, will be making recommendations for the guidelines. This process is expected to be completed by the end of the year. From next year, WHO will be working with countries to support country level adaptation of the guidelines and thereafter to support both implementation and monitoring of the ways in which the recommendations included in these guidelines are taken up by different countries.

The second key priority in terms of norms and guidelines is the semen manual. The manual on the laboratory examination and processing of human semen is an important WHO product. It is currently in its fifth edition. It is not really a guideline but a laboratory standards manual. We are currently updating it to include a number of procedures on human semen examination, which may include computer-assisted semen analysis. Reference values for different semen parameters will also be published separately. We are hoping to be able to launch the sixth edition of the manual at the end of this year.

In terms of epidemiology and statistics, previous estimates of infertility prevalence suggested that between 48 million couples and 186 million individuals have infertility. There is a lot of uncertainty in these estimates because of the fact that the primary studies that have gathered data on prevalence of infertility generally use very varying methods of methodologies and also they use different definitions of clinical, population, primary, and secondary infertility, which conflates the figures that we have currently.

However, accurate data is really needed to identify the need that exists in different countries and to be able to monitor access to services in those countries. WHO has embarked on a program of work to generate updated estimates of infertility and these will be available next year.

Another key area that I would like to mention is the economic aspects of infertility which WHO is looking at. This is particularly important because public financing of infertility in many low and middle income countries is neglected. In those countries, it is only accessible to a small middle income group of citizens and even those couples are often forced to really spend quite a significant amount of their household wealth to achieve and obtain fertility services leading these households to poverty.

The actual data on the extent of economic costs on families in many countries is not available even at the global level. And on top of that, we do feel that there is need for data on the economic return on ART to be able to inform investments by governments into this area. For this reason, we are working in the three key areas. One is a systematic review on economic costs of infertility in low and middle income countries, which will provide information on direct and indirect costs of infertility. This data will be useful to inform social protection, insurance, and advocacy for universal health coverage.

The second key area is that we are gathering data, empirical data, on actions that women take when they fail to conceive. These data include costs that are associated with those actions. We are collecting these data in two large studies conducted in India and China, which will be involving about 2,500 women of reproductive age.

Another key area which I would like to highlight to participants is that we have developed a fiscal model of returns on investment on ART. Basically, this is showing the benefits to governments should they invest in ART because if a person is born from IVF procedures, they will live a productive life. They might provide returns in terms of future taxes. This economic model is important because it helps us to give an additional argument to government as to why they should be investing in ART.

These models are being used in Scandinavian countries with a good amount of success for informing the numbers of cycles that governments should be paying for or subsidizing in those countries. In South Africa, we employed this model. We found that the government of South Africa may expect to get up to four times return on investment for any amount of money that they put into ART. And therefore, we think it's a good model to try in a number of other countries and use for advocacy.

Another key area is our work on policy analysis and technical assistance. And here I just want to highlight the policy portal. The sexual reproductive health and rights policy portal contains data on policies from 155 countries on six thematic areas which includes cervical cancer, family planning, infertility, sexual health, STIs, and prevention of violence against women. And in particular, in regard to infertility, it contains data on the kinds of policies and registrations that are existing in countries in relation to infertility, which includes data on policies and legislation on access to and provision of public subsidy for ART, general regulation of infertility services, regulation on fetal reduction practices, and so on and so forth.

I would invite you to come and have a look at this portal later on when it's completed. This is something that we're working on now. We hope to launch in the last quarter of this year. In addition, WHO basically is working towards facilitating attention and visibility to infertility by national governments. One of the key areas we are really focusing on is supporting governments to make sure that infertility is included as part of the sexual reproductive health strategies and plans in different countries. We have had some success in this regard.

For example, Thailand included infertility for the first time within a second national reproductive health strategy just last year. And we think there is a lot that can be learnt and replicated from what Thailand has been able to do

successfully. Finally, I just want to highlight the issue of human rights aspects of infertility, which is an important priority in WHO in relation to infertility.

The context here as I mentioned in the previous slide is that infertility is regarded by WHO as an essential component of sexual and reproductive health and rights. But the way that this is interpreted or operationalized in different countries can actually hinder access to infertility by some populations. So we conducted a jurisprudential survey of infertility in human rights last year to really examine ways in which the national laws and policies see and interpret the human rights aspects of infertility services.

What we found is that instead of a human rights focus, many of national laws adopted policies that either completely discriminated against a number of individuals based on their sex, sexual orientation, gender, disability, or HIV status, and many of them are actually disadvantaged people from low income categories or failed to appropriately identify and remedy some of the health and treatment gaps that lead people to seeking infertility services in the first place. In some cases they privileged conservative religious interpretations over contemporary and scientific advances in the area of infertility.

So clearly, the communication and the message we are giving out from the survey is that we do need to do more to make sure that laws and policies in countries are better responding to rights based approaches and the rights of people with infertility. Thank you very much indeed for your attention. That's all I have time for. I invite you to visit our website for more information. Thank you very much indeed ladies and gentlemen.

**INITIAL ASSESSMENT OF THE INFERTILE - MOISE FIADJOE**

Hello dear friends, dear colleagues.

It is with great pleasure that I participate in this webinar and I would first of all like to thank the organizers of the IFFS and GIERAF who kindly entrusted me with speaking about the couple's initial infertility assessment.

I must say that I have no conflict of interest on this subject.

And I am going to talk to you about this subject in seven points, after a brief introduction, generalities, questioning, clinical examination, additional examinations, summary and end with a conclusion.

The first consultation is very important in the assessment of the infertility of the couple because each partner has a fertility potential that must be determined.

A couple is infertile because the sum of male and female fertility is insufficient to achieve pregnancy.

It is therefore imperative to see the two partners in consultation, listen to them, carry out an exhaustive clinical examination, supplement if necessary, by paraclinical examinations.

WHO defines infertility as the absence of pregnancy after more than twelve months of regular intercourse without contraception.

Fertility is the ability to procreate.

Infertility is the inability to procreate without medical intervention.

Infertility is not irreversible.

The term sterility is used if the infertility is permanent, such as menopause in women or bilateral castration in men.

In an infertile couple, infertility can be of male origin in 30% of cases, of female origin in 30 % of cases, of mixed origin in 30 % of cases and of unexplained origin in 10 % of cases.

We can see that in the couple, both men and women are concerned.

The exploration of an infertile couple must therefore be carried out in parallel in both partners.

When to see a case of infertility for the first time?

It is considered that in the general population, 70 % of the desired pregnancies are obtained after six months and 90 % of these pregnancies are obtained after one year.

We therefore advise the couple to consult after one year if the woman is under 35 years old, or after six months the woman is over 35 years old, or even rather, if one of the members of the couple has a particular history, gender, testicular ectopia or primary amenorrhea .

What are the necessary conditions to achieve a natural pregnancy?

To have a pregnancy, the couple must have regular sexual intercourse, the husband must have good sperm, the ovaries are functioning normally with very regular ovulations, and the tubes are normal, permeable and functioning without any obstacle to the pregnancy, collection of oocytes, and finally, that the cavity is normal.

Thus, the initial assessment must seek to see if all these conditions have been met.

We start with the interrogation for the couple which will focus on the date of their cohabitation.

How long have they been together?

With or without contraception?

Is sexual intercourse regular, physiological, scheduled in the pre- ovulatory period or not?

Is the frequency of intercourse regular or episodic?

The review of previous or current treatments and explorations that had been done previously.

The questioning of women will focus on finding the real age of the woman.

The age of the woman is an essential element of the prognosis.

We will also look for the age of puberty for the first period.

We will look for the regular or irregular nature of the menstrual cycles.

The second essential element is the age of the infertility.

Is it primary or secondary?

Is there a notion of previous pregnancy or not?

With the same partner or another partner?

Look for notions of infection or curettage, look for genital infections, salpingitis, sexually transmitted diseases or post-partum or post-abortion uterine curettages, history of surgery on the cervix, small pelvis, abdomen, appendectomy, peritonitis, myomectomy, torsion of adnexa or ectopic pregnancy.

Pelvic pain during menstruation or during sex.

Finally, the questioning must look for the living conditions: stress, taking medication in progress or in the past.

In humans, we will seek to find the antecedents of testicular pathology: cryptorchidism or testicular trauma.

History of inguinal hernia surgery or bladder neck surgery.

Medical history: old diabetes, a sexually transmitted disease and especially mumps orchitis or repeated sinusitis or bronchitis, and finally taking toxic products, occupational exposure to heat, organic solvents or pesticides, and finally, past or current treatments.

The clinical examination must be done in women and will focus on the search for weight, size, hairiness, appearance of the skin, examination of the breasts for provoked galactorrhea or mammary dystrophy.

For the speculum examination, we will assess the vaginal trophicity, the presence and quality of cervical mucus in the pre-ovulatory period, the apparent state of the cervix, the existence or not of leucorrhoea and the vaginal examination will assess the presence of pelvic mass and will appreciate the uterine sensitivity to mobilization or pressure of the uterus.

In humans, we will look for in addition to the BMI (Body Mass Index), the hair, the appearance of gynoid or android, we will look for a gynecomastia or we will look for the scars of surgical procedures at the level of the inguinal folds or in the scrotal level.

And when examining the external genital organs, we will look for the existence of a varicocele or not, will assess the state of the vas deferens and the epididymis and above all will assess the testicular volume which is a capital element of the initial assessment.

The testicular volume will be appreciated using the Prader orchidometer or measured with a tape measure.

We will look for firmness, symmetry of the testicles and testicular sensitivity.

What are the additional first-line examinations that can be requested after this clinical examination?

In women, by looking for the exploration of the menstrual cycle by the menothermal curve which must be carried out over at least two cycles: taking the temperature on the head in the morning when getting up, it will make it possible to visualize the regularity of the cycles, the thermal shift which will be a witness of ovulation and the duration of the post-ovulatory plateau.

You should know that any abnormality in the curve will require a hormonal assessment.

This thermal curve may seem tedious and outdated but will be very rich in information.

Second element, it is the ultrasound which must be performed, preferably performed by the endovaginal route, which will specify the size and appearance of the ovaries.

At the start of the cycle, it will assess the count of the antral follicles.

In the middle of the cycle, it will allow tracking of follicle growth.

Ultrasound will also allow the thickness of the uterine mucosa to be measured and the presence of any intracavitary pathologies to be detected.

The study of the tubes and the uterus by hysterosalpingography which will delimit the uterine cavity in morphology, dimensions, contours, evaluate the tubal lumen by appreciating the filling, the tubes, the mucous folds, the tubal wall, pa sage and peritoneal diffusion.

Or if we have the possibility, to perform hydrosonography or hysterosonography which is a vaginal ultrasound with injection of a contrast product in 2D or 3D which is an invasive method, which assesses the state of the endometrium, the cavity, the existence or not of synechiae, septum, intracavitary polyp and which will also appreciate the permeability of the tubes.

Other factors to look for are the male factors.

We can start with a post coital test or Huhner's test which will explore the interaction between cervical mucus and sperm deposited in the vagina during intercourse.

C ow this test is done?

It is carried out during the supposed ovulatory period and it first involves the examination of the cervical mucus which will be assessed by the Insler Score from the four parameters: the opening of the cervix, the abundance of mucus, the fill ance, crystallization.

And then, post coital test will assess the motility of the sperm in the cervical mucus.

And the results ...

To say that the post-coital test is positive, you must have at least five to ten spermatozoa
with progressive mobility per field in a field at magnification 400, but it must be said that a positive post-coital test does not dispense with the need for 'a spermogram.

Finally, the spermogram, the spermogram holds the first place in the assessment of male infertility, but it should be known that there is an extreme variability of the parameters both inter and intra individual.

A spermogram does not mean anything since there is this variation between two ejaculates.

The conditions of collection must be carefully controlled.

The semen must be emitted in the laboratory by masturbation after three days of abstinence.

Three essential parameters must be sought: count, mobility and morphology.

According to the WHO, here are the normal parameters: mobility greater than 40%, morphology greater than 15, the count between 15 and 200 million and the volume between 1.5 ml and 6 ml.

The synthesis, after this interrogation, the clinical examination and the additional examinations, it is necessary to make the synthesis.

In women, is it anovulation or dysovulation?

Is it a OPK or an Early Ovarian Failure?

Are there any mechanical obstacles, either at the level of the cervix, insufficient cervical mucus, for example?

Is there a uterine obstacle: uterine malformation, synechiae, polyps, fibroids?

Or is there an obstruction at the tube level which is a major cause which could be due to an unnoticed infection or surgical trauma or endometriosis.

Endometriosis, we do not do in particular, the diagnosis is evoked on the clinical signs, especially the tumors and the echographic and hysterographic signs, but the diagnosis is confirmed by the laparoscopy which will specify the stage of the endometrios e.

In men, is it simply Oligo-Astheno-Teratozoospermia which is one of the most frequent causes of male infertility?

Or simply a symptom whose causes are varied and which must be sought?

Or is it azoospermia, either secretory or non-obstructive azoospermia or excretory or obstructive azoospermia?

Or is it an unexplained infertility that is primary or secondary infertility with normal male and female medical check- ups.

No cause has been clearly identified in the various fertility tests, nothing allows, a priori, to understand the blockage of pregnancy.

Here are the stages of infertility therefore of a couple.

After an interrogation of clinical examinations, there is no orientation, one does not complete the complementary examinations.

And if nothing is found, we complete it with a laparoscopy and a hysteroscopy, or there is an orientation and we hope to continue the explorations in the same order in order to find an appropriate treatment.

What to say to conclude?

First, say that the initial assessment is of great importance for the couple.

The first consultation must be methodical and complete.

The initial assessment is the starting point of the architecture and the basis of the care and will help orient the additional assessments and avoid therapeutic wanderings.

The second essential element is the complementarity of the couple: a child is made together.

The hyper-fertility of one can compensate for the hypo-fertility of the other.

The couple is infertile because the fertility of both spouses is insufficient to achieve a heavy pregnancy.

The third essential element is accessibility.

This initial assessment must be able to be done everywhere and at all levels of the health pyramid, whether you are a doctor, gynecologist, fertility specialist or general practitioner, or whether you are a midwife or nurse or medical assistant.

And behind the element is time.

A woman's time must count.

The time of infertility exposure should also count.

Time is the best doctor and time sorts out hypo fertile couples.

I will not end by saying that the time is for infertility, what the wind and for the fire.

It stirs up the greatest, that is to say the most fertile, and extinguishes the weakest, that is to say the less fertile.

Thank you.

**MALE INFERTILITY: NON-IVF SOLUTIONS - ANTTI PERHEENTUPA**

Hello. This is Dr. Perheentupa, from the Turku University Hospital, and the University of Turku here in Finland. I have the pleasure of presenting my talk to you today on the topic of male infertility non-IVF solutions. I have no disclosures on this topic, and I will be talking on the following content.

I will first briefly go through the hormonal regulation of the testicular function. I will then say a few words about the use of intrauterine insemination. I will go through some of the specifics in the treatment of hypogonadotrophic hypogonadism. Say a few words about an interesting new concept of treating the idiopathic male infertility with FSH. Compare the possibility of using an aromatase inhibitor for the same function. And then come to my conclusions

Now, it will be clear for most of the audience how the testicular function is regulated. Obviously, the hypothalamus secretes the GnRH, which drives the pituitary function. So that LH acts on the Leydig cells, which will produce testosterone from cholesterol through the steps of steroidogenesis.

FSH, in turn acts on the sertoli cells, and this together with the high concentration of testosterone intertesticularly will form the optimal milieu for spermatogenesis. Now, there is the classical feedback loop, where testosterone feeds back to the hypothalamus, and to the pituitary. And there's obviously also the inhibitors, and the activates.

Now, when we think about perhaps the most classical treatment for mild and moderate male factor infertility, intrauterine insemination is obviously the one you would be thinking first. It's fairly hard to clearly define where this treatment may be useful. Ombelet and colleagues have looked at 36 retrospective analyses, 14 prospective observations, and five meta-analyses in their paper from a few years back. And they observed from these studies that perhaps the inseminated mobile count of the sperm, and maybe the most, has the best prognostic value.

Some of the studies set the limit at 1 million motile sperm. Another four studies set the limit at between 1 and 2 million motile sperm in the insemination. Morphology has also been suggested for this purpose. It is, however, clear that these parameters have a poor sensitivity for predicting which one of our patients will conceive. However, they do give a high specificity for predicting the failure of the treatment.

As in many of the evaluation of the male fertility treatments, there is a lot of other parameters, particular the female age, that will make the evaluation of these studies very hard. In this talk I will not go into the effects of lifestyle changes, but it is worth mentioning that as the DNA fragmentation has become a fairly popular analysis, the time from the previous ejaculation should be kept to only a few days prior to the treatment, which is in contrast to the WHO semen analysis manual instructions.

If we then move on to the induction of spermatogenesis in the adult onset hypogonadotropic hypogonadism, the treatment scheme is fairly straightforward. The idea is to improve the testicular sperm production, and that is done by hCG, which obviously has the LH action on the Leydig cells. In theory, you could use a GnRH pump, but this is rarely used in practice.

Typically the dose for the hCG will be 2,500 to 5,000 units, which will be given twice a week. But it is important to check for this testosterone response, which you can already see after two or three weeks of treatment. The semen analysis can be done after several months of treatment. Typically, after about half a year.

If azoospermia, is still the finding, then FSH, can be included in the treatment, and typically the dose would be 150 units two to three times a week. And the semen analysis will be repeated after another four to six months. It's important to both understand for the doctor, as well as the patient, that the response may take quite a while. A year is not a very long time to wait for the response. However, most hypo-hypo men will present with sperm although normospermia is not always reached.

It is important to understand that it is the number of sertoli cells that is the limiting factor for the spermatogenic capacity of the testes. So a single sertoli cells can only support a certain number of spermatogenic cells. Now, these immature sertoli cells will divide, proliferate during mini puberty, and finally in early puberty. And this differentiation will end, and is linked to, the increased expression of the androgen receptor, as well as the intra testicular testosterone.

What can be done to optimize the spermatogenic capacity of the hypo-hypo prepubertal boy before the actual puberty induction, is the pretreatment with FSH, which will improve the number of sertoli cells. Typically, a dose between 75 to 225 units, given two to three times a week, is used for at least six months prior to the induction of puberty, which can be done either with exogenous testosterone if fertility is not the direct target, or later when fertility is desired, you would combine that as I previously showed with HCG treatment.

How about FSH for the treatment of idiopathic male infertility? The idiophatic male infertility means that no etiology can be found for the decreased fertility observed in the male partner. Manuela Simmons group, have looked at a number of studies in their review from 2015. They had 15 studies which included 614 men who were treated with FSH and 660 controls. 11 of the studies evaluated the semen quality, and overall saw an improvement of 2.7 million per mil.

The improvement for the concentration of progressively motile sperm did not reach significance. Three studies looked at the testicular volume, and a non-significant increase was observed. But obviously, the important parameters, be it the spontaneous pregnancy or the increase in ART pregnancy rates, were looked at. And in the nine studies that looked at the spontaneous pregnancy, an odds ratio of 4.5 was observed, meaning that the number needed to treat was 10 men to reach an additional pregnancy.

For the ART pregnancies, The odds ratio was 1.6, meaning that 18 men would need to be treated for one additional pregnancy. As there are currently several FSH preparations, these were evaluated separately, but no difference was observed between the different FSH preparations. Now, this only shows the same finding that the improvement in pregnancy rates in spontaneous pregnancies, is far greater than what you see in the ART pregnancies.

Now, an interesting study was carried out with the idiopathic oligospermic men who were treated by FSH with different doses. 50, 100, 200, and 300 units on alternate days, meaning every other day. The analysis was done after 2, 3, 4, and 5 months. And it was clear that the number of sperm increased using 200, and 300 units, the morphology and motility were increased after five months. And using the 300 units of recombinant human FSH, the spontaneous pregnancy rates were also improved.

Now, the findings were similar in the men whether or not their inhibin levels where low or normal. And here you see, in the table analysis, here are the different doses. And with the 200 units and 300 units, after a treatment of three months, you see an improvement in the sperm counts as well as the sperm concentration. You will also see that there's the increase in the spontaneous pregnancy rates with the 300 units, as well as an increase in the ART pregnancy rates, with the 200 and 300 units.

It's important to notice that with time, the results improve from 3 to 4 and again until 5 months. And of interest is the fact that even after three months of the end of the therapy, the values are still very, very good. So it appears that there is a group of men within the idiopathic infertile men, who would benefit from FSH treatment. However, it's also clear that the dose needs to be high enough to reach this positive response and the improved fertility. We do need some more work to find the optimal target population, and it is important to understand that the cost of this treatment is fairly significant.

Could we then substitute FSH with aromatase inhibitor? Now, the aromatase inhibitor will improve the secretion of the endogenous FSH and LH. And in this study where the testosterone-oestradiol ratio was normal in these men, they

were given 2.5 milligrams of letrozole for four months. 15 men with the sperm count below 5 million per mil were included. A very clear improvement in their sperm concentration was observed 5.5 fold. The testosterone concentration improved. Obviously the oestradiol concentrations were decreased.

And we see about a two-fold increase in the control levels. This is of importance as only about 10% is the testosterone-oesradiol ratio below 10. This is some of our own patients selected randomly from the ones that I have treated, and you see that with the same dose of 2.5 milligrams, you'll see a doubling of the FSH concentration irrespective of the level they had to start from. Sometimes the testosterone response is very high, and you may have to decrease the dose.

So from this we can say that letrozole appears to be very able to increase the FSH levels, similarly to the LH levels. The question is, is there a difference between the endogenous FSH and the exogenous FSH? There are some side effects to the treatment. Typically loss of libido, headache, fatigue. And we do see the improvement in semen parameters, but how about the pregnancies?

What is quite obvious is that this is an inexpensive treatment, and it's easy to administer. So for the conclusions, it's clear that intrauterine insemination has a place in the treatment of mild and moderate male infertility. And obviously, this has a lot to do with the available resources, be it the equipment and the other medications. FSH has a clearly defined role in the induction of spermatogenesis in adult hypo-hypo men.

It's also become apparent that the pre-treatment with FSH prior to puberty induction improves the spermatogenic capacity of the testes. This may also be true in adults, if their testes has never had a high concentration of testosterone. The interesting finding of improving the fertility in idiopathic male sub fertility with FSH needs more research to get the details right. It's also very likely that a lot of these same benefits could be reached by using aromatase inhibitor.

But we do need to find the optimal target population in order to target these treatments correctly. Thank you. And I remind you of the IFFS Congress that we have planned for 2022, in Athens. Thank you.

**MANAGING AN ANDROLOGY LABORATORY - VIRGINIA BOLTON**

Hello. I'm Virginia Bolton. And I'm going to be talking about managing an andrology laboratory. I have no financial interests to declare, and I would like to acknowledge the co-producers of this webinar.

In this talk, I will describe how to design and build the andrology laboratory from scratch. For those of you who already have a lab up and running, there may be things I describe here that you may wish to consider incorporating into your existing lab to optimize performance.

When designing the lab, remember that it does not function in isolation. It is an integral part of the clinical service. So it's essential to consider how the lab space interacts with patients and clinicians, as well as the laboratory staff. So we need to consider proximity to clinical and patient areas, with special consideration given to where the male patients will produce their semen samples, how the samples will be delivered to the lab, bearing in mind the need for sensitivity and patient confidentiality.

Regarding access to the lab itself, It needs to be restricted so that only authorized staff are able to enter. And where is the space for storing consumables? Is there adequate space? How will clinical waste be disposed of?

In terms of lab layout, each item of equipment should be interspersed with work surfaces, providing adequate space for staff to write and keep records, in an arrangement that optimizes smooth and efficient workflow.

There must be a system for regulating laboratory temperature, so that it's a comfortable work environment. And as for air quality ideally the lab should have positive air pressure, with a HEPA air filtration system to remove particle contaminants and activated carbon filters to reduce levels of toxic VOCs.

If the lab is providing a semen cryopreservation service, it's absolutely essential that the cryostore for tanks of liquid nitrogen is constructed with adequate ventilation. Failure to ensure this could have fatal consequences.

When it comes to construction, certain details must be addressed in terms of their potential for damaging sperm cells, including any glues or paint used, they must be nontoxic. Sealants containing silicon should not be used, and lights should have filters to exclude UV and harmful radiation.

If the lab has incubators needing a gas supply, such as CO2, then for purposes of cleanliness, the gas cylinders must be situated outside the lab with associated pipework constructed along with some form of automated gas changeover, or a system alerting staff when cylinders are empty and need changing.

Now we come to the consideration of safety in the lab. Risk assessments should be carried out for all lab processes and procedures and should be reviewed at prescribed intervals. Risk assessments should consider all aspects of risk, including risks to staff, to patients, and to samples.

In terms of safety it is a golden rule that Class II hoods should always be used when handling any body fluids, and this includes semen. This is because the Class ll hood provides protection from any possible contamination for both the operator and the sample. When a Class ll hood is used, there is no need for any additional PPE other than gloves, although it goes without saying that the lab staff will be wearing appropriate clothing, such as scrubs and caps.

Regarding the cryostore, there are particular safety concerns that must be addressed, considering the potentially fatal consequences of neglecting to do so. First of all, the liquid nitrogen tanks, or dewars, must be stored in a separate location from the main andrology lab, and access to the cryostore must be strictly controlled. Although separated from the lab, the cryostore must be near to and easily accessible from the andrology lab for authorized staff. And obviously, it must be easily accessible from the outside to receive deliveries of liquid nitrogen.

Appropriate PPE consisting of cryogloves, goggles, apron, and shoes should be available, and staff must be trained in their use. As I said earlier, the cryostore must be well ventilated. And it is mandatory that low level oxygen monitors and alarms are installed, functioning, and tested regularly, and that staff are trained in how to respond appropriately when an alarm is triggered. Lives depend on it.

Another critical aspect of safety is witnessing patient samples to confirm and record their origin. Failure to address this adequately can have consequences that you do not want to contemplate. We've all heard of cases where the wrong sperm has been used in a patient's treatment. So obviously witnessing is especially important when samples are to be used in treatment, whether fresh or for cryopreservation and use later.

Some form of witnessing system must be incorporated into the design of the lab. There are two options available, the first of which is manual witnessing. This requires the presence of additional trained staff in the lab, which will incur additional expense in terms of manpower. And it must be borne in mind that with manual witnessing, the potential for human error is never completely eliminated.

The second option is electronic witnessing, such as a bar code system, or a radio frequency RFID system. Unlike manual witnessing, any electronic witnessing system will require specialized equipment, which will entail additional capital expenditure. But it does minimize the risk of human error.

And this brings us neatly to the topic of the quality management system. The QMS is sometimes seen as an unnecessary burden on staff, serving no purpose other than to create a mountain of paperwork. But in fact, not only is the QMS inexpensive, it is also effective in that through its implementation everyone, patients and staff, are assured of the highest standards of service. Through the QMS, problems are identified before they happen, which means that potential problems can be addressed before they affect outcomes.

So the QMS represents a system for continuous improvement in the laboratory. This is achieved through planning, through a documented quality policy which defines the objectives and targets of the service. Doing, with implementation of the quality policy through a defined management structure with defined lines of responsibility, through formalized staff training, through measures addressing safety and risk, and through defined lines of communication between staff at all levels, and with patients. Checking through quality control with regular monitoring, recording, measuring, and auditing defined outcomes. And acting, with regular review of defined outcome measures, and taking preventive or corrective action to address any weaknesses identified, which completes the cycle back to planning.

A part of Quality Control, or QC, is to confirm regularly that everything is operating as it should. For example, even if the LED of a piece of equipment displays the required temperature, this needs to be checked and confirmed independently on a regular basis with the frequency of checking determined by how critical temperature is for the equipment's function.

This slide shows items of equipment in the andrology lab that must have regular QC checks. Indeed, equipment servicing schedules should also be established. And for consumables, records of batches should be maintained.

Staff training and competency assessments should be part of the QMS. The lab should have a formal training program for its staff. Ideally, this would be a national training program. If one is not available, a training scheme should be developed, documented, and recorded through the QMS.

Trainees will need supervision by a designated appropriately qualified supervisor. They should maintain training logs recording each supervised procedure undertaken, signed off by the supervisor when completed to their satisfaction. Training should include structured competency assessments for individual tasks. And all staff should participate in regular Standard Operating Procedure, SOP, reviews, where colleagues audit each other performing tasks alongside

the associated SOP. All staff should have regular competency assessment updates and performance reviews to ensure that everyone continues to develop professionally.

The QMS will include documented SOPs for all laboratory procedures, such as QC checks, as well as those involving processing semen samples. Each SOP should detail exactly who will perform the task, what materials are required, where and when the task will be performed, how it will be executed, and how and where resulting information is recorded.

Now let us turn to the routine clinical procedures carried out in the andrology lab. Every andrology lab should have a copy of the WHO manual for the examining and processing of human semen, currently in its fifth edition. The only major items of equipment that are essential to carry out semen analysis are a Class ll hood, a simple histology microscope-- ideally with a warmed stage, but not essential-- and a counting chamber.

For semen analysis, it is necessary to assess the quality and quantity of sperm present in the semen sample. The WHO threshold parameters for normal semen are, the sperm concentration should be at least 15 million per mL, of which at least 40% should show good forward progression, and of which at least 4% should appear normal.

Although other chambers are available and arguably easier to use, the Neubauer counting chamber and counting immobilized sperm gives the most accurate assessment of sperm concentration. When the Neubaer chamber has been set up correctly, Newton's rings can be seen, and the volume of the chamber is fixed accurately.

And [INAUDIBLE] dilution of semen, diluted in water so the sperm are immotile, is loaded into the chamber by capillary action. The total number of sperm head seen on five squares the grid is counted and gives the sperm concentration in millions per mL of semen. For accuracy two grids, one on each side of the chamber, should be counted. And the average of the two counts is the sperm concentration in millions per mL.

This slide shows images of normal and abnormal sperm. High magnification should be used to assess sperm morphology, and a minimum of 100 sperm should be assessed and recorded as either normal or abnormal to give a percentage of normal forms. While it is possible to assess a wet preparation with motile sperm, it is easier to assess morphology using fixed, stained specimens. However, if the lab is to undertake fixation and staining as part of semen analysis, the toxicity of the reagents used means that a separate laboratory should be used with these steps to avoid any risk to semen samples in the main lab that are intended for use in treatment.

For quality assurance, the lab staff should undertake regular comparisons of semen assessments, both internally between each other, and externally between themselves and other andrologists working in different laboratories. Results should be compared for assessments of sperm concentration, motility, and morphology. QA exercises such as this confirm the consistency and reproducibility of a lab's performance both within and between laboratories and are essential in ensuring best practice.

It is possible to register with an international QA scheme for semen analysis, such as the UK NEQAS scheme, much of which can be carried out online with four assessments circulated each year.

Finally, we come to the procedures carried out in the andrology lab for the purpose of treatments, such as IUI, or even IVF, and ICSI.

Essentially, there are two methods that can be employed for sperm preparation for use in treatment. Both result in the collection of a concentrated suspension of motile sperm in a relatively small volume of medium. The first method, wash and swim up, requires only a centrifuge, and a warming incubator with or without CO2 together with culture medium buffered appropriately for the gas mixture in the warming incubator.

The second method, density gradient centrifugation, requires only a centrifuge and the reagents for preparation of a density gradient, as well as an appropriately buffered culture medium. Finally, if a semen cryopreservation service is provided, it is essential to define clearly to patients in advance the terms and conditions of storage. And to enshrine these in carefully drafted, signed consent forms.

Consent should stipulate the length of time samples will be stored, for whose treatment they may be used. Consider including the types of treatment that will be permitted, and what should happen to the samples in the event of the man's death or mental incapacitation. It is advisable to ensure that for long term storage, the patients know they are responsible for maintaining contact with the storage center, and to devise and implement a system that ensures this happens.

In terms of storage itself, each sample must be labeled clearly and unambiguously, and storage locations recorded meticulously. Stored samples should be audited regularly. The last thing anyone wants is to accumulate vast numbers of samples over the years and have any confusion over their provenance or their intended fate.

Thank you.

**PCOS & INFERTILITY: KEY ISSUES - DOMINIQUE DE ZIEGLER**

Hello, I'm Dominique de Ziegler. I work at Hopital Foch where I'm a university consultant. I work with Professor Jean Marc Ayoubi who's a chairman And I work particularly with Dr. Pirtea who is a close collaborator in our team. I'm going to talk to you about polycystic ovary disease, or PCOS. It's Diagnostic and Management.

This is one of the most common ovary dysfunctions that exists in humans and we are going to see the details of that. These are my disclosures. I want you to read them. And let's put PCOS in the context of other ovulation disorders, and particularly WHO type I ovulation disorder by which the hypothalamus and the pituitary are misfunctioning. Therefore, the whole system stops and leading to a situation amounting to hypothalamic amenorrhea.

In WHO type III, the ovaries are not functioning. This is what you have in menopause and in premature menopause. But we have to add to this, what is the topic of the discussion today, the WHO type II, which is oligo-anovulation encountered in PCOS. In this case, all the levels of the system function, but they don't function together correctly. And therefore, we have this ovulation problem called PCOS.

These are the learning objectives. We want to talk about the clinical diagnosis, and I want to emphasize the fact that sometimes we can consider PCOS as a variant of normal or other true disease. It is so frequent, actually that it's the most frequent disorder encountered in women of reproductive age. It is present in 12% to 14% of women.

We're going to talk about the clinical management. At the end of this talk, you should be familiar with the clinical management of PCOS. In PCOS, as you will see, there are more follicles. But the question is, for how long? Do we have a prolonged fertility, or is that not the case? We will discuss that. Finally, we will look briefly into lipotoxicity and metabolic syndrome, which often accompanies PCOS.

Let's talk first about PCOS diagnosis. Are we dealing with a variant of normal, or are we dealing with a disease? The Rotterdam consensus actually allows to have a common definition of PCOS.

This is a diagram showing ovarian follicles. To the left, you have the primordial follicles, which is actually the number of follicles that a woman has at any given age. And from this number of primordial follicles, there is a constant growth of follicle that leaves the total number of primordial to become primary, secondary, and antral follicles. Antral follicles imply that there is an antrum, and they are visible on ultrasound, and therefore you can count them on ultrasound.

From this cohort of antral follicles, which in normal women is anywhere from 10 to 20 total and more numerous in PCCOS, there is the follicular growth taking place during the follicular phase of the menstrual cycle. This is the gonadotropin-dependent phase of the follicular growth, with one follicle acquiring dominance and the other follicles undergoing atresia.

The primordial follicles are all the follicles that a woman has at a given time, as said before. But we cannot count them, because it needs a biopsy to do that, which is not possible. However, we can count the antral follicles by ultrasound. They are visible, and they can be counted. As we will see, there number defines the criteria of PCOS.

And then we have a way to measure, indirectly, the amount of pre-antral and small antral follicles. Because they produce AMH, and AMH can be assessed in the blood. At a given time, there is anywhere from 100 to 200 pre-antral follicle-producing AMH.

An important factor is that the loss of follicles occurs at a constant percent of the total number, so that actually the level of AMH and the count of antral follicles gives a reflection-- indirect, but a reflection-- of the number of primordial follicles remaining at a given time.

And this is what we have in PCOS. In PCOS there is an excess number of antral follicles that are in the cortex of the ovary. And you can see here that we have more than 20 follicles. Clearly, as I said, the criteria for polycistic ovary disease is ≥12 follicles per side, and here you have about 20. So, this image is characteristic polycystic ovaries, which is one of the three criteria of the Rotterdam consensus convention. These require that you have polycystic ovaries,

hyperandrogenism – either clinical or chemical-- and only oligo-anovulation. Two of these three criteria suffice for making the diagnosis of PCOS, according to Rotterdam.

The clinical management of PCOS depends upon the particular interests of women. If the woman is interested in inducing ovulation, if she is infertile and wants to ovulate, you will provide-- the first line of treatment, which is clomiphene citrate, or more often today, letrozole, an aromatase inhibitor, administered from day 2 to 3 of spontaneous or induced menses, induced by progesterone or dydrogesterone. Clomiphene citrate is commonly used in a dose of 100 milligram – two 50 milligram tablets per day for five days.

Letrozole (Femara®), which is the most commonly used aromatase inhibitor, is administered at the dose of 25 to 50 milligram, one to two tablets per day for five days as well. Ultrasound are commonly performed around day six to eight. When follicles reach the size of about 18 millimeters, ovulation can be induced by hCG. But in case of clomiphene citrate or letrozole, you can also let ovulation occur by itself.

When this doesn't work, you have to induce ovulation with FSH or hMG. It typically does not work in about 20 to 30 percent of the cases. FSH and hMG has been used in very different ways, but today there is a consensus for preferring the 'step-up' regimen, whereby from day 2 to 3 of spontaneous or induced menses, you use FSH or hMG, commonly at a dose of 50 units per day. You monitor the response on the sixth day of the treatment. In this case, when one or two follicles are larger than 12 millimeters, you wait until you have a follicle reaching 17 millimeters, then you trigger ovulation with hCG. In this case, hCG is mandatory, because ovulation will not occur naturally and it would not work, so you have to give hCG and time intercourse or possibly intrauterine insemination accordingly.

Timed-intercourse is set on the day of ovulation and the day after. Intrauterine insemination does not add any value over timed intercourse, except in case of sexual problems, but for male factors, it is not helpful. Luteal phase support is not mandatory but may be used with vaginal progesterone for 14 days.

When induction of ovulation fails, you can have access to ovarian drilling for restoring natural ovulation. And for this we require that AMH is more than 5 nanogram per mil. And if this doesn't work, or if this is not desired because the sperm is not normal, you have access to ART. In this case you have to be careful, because PCOS women have a higher risk of ovarian hyperstimulation syndrome (OHSS). Hence, you need to give an antagonist protocol, and most often trigger ovulation with GnRH agonist, and process with a deferred embryo transfer to avoid ovarian hyperstimulation.

If women were not trying to become pregnant, then you just provide them with estrogen and progesterone. The best way to do that, actually, is to prescribe it in the contraceptive pill. But this is not really the topic of today.

One other question is, PCOS women have more follicles, but for how long? Actually, we are showing data that looked at this from a recent publication. There's been a long belief-- actually wrong-- that ovarian polycystic women have a longer reproductive life and longer fertility, but this is not true. It has long been assumed that women affected by PCOS tended to reproduce later in life. Not true. It was believed, but not true.

This belief stems from the fact that PCOS women have higher ovarian reserve parameters and their ovulation disorder often normalizes in the late reproductive years. It is indeed a lingering die-hard belief that women with PCOS enjoy an extended window of fertility as compared to their regularly ovulating counterparts, just because they have better ovarian reserve parameters. However, actual facts-- they are not very numerous, for the reason explained below-- speak differently, and this is actually not the case.

Judging AMH levels according to age, you see that woman with PCOS have higher AMH, and it declines with time as it does in normal women but starting from a higher level. It is such that at the age of 40, PCOS women tend to have the same AMH level as normal women with regular ovulation at the age of 20. Yet, it is a wrong assessment to believe that a 40-years-old PCOS woman is actually like a 20-year-old woman ovarian reserve wise.

Women with ovarian polycystic syndrome get regular menstrual cycles when they age. This is clearly established, so that actually, when you look at, for example, the Rotterdam criteria, women escape from the radar and do not meet the PCOS criteria. They are not visible anymore, because they ovulate regularly and therefore, they are not accounted for.

In order to actually assess a PCOS patient, you need to do longitudinal studies, taking young women who are PCOS and follow them over time, based on the principle that once a woman is PCOS, she will always remain PCOS, even if she doesn’t meet the PCOS criteria because her cycles have normalized. These studies were conducted in the long-term follow-up of patients with polycystic ovarian syndrome. We see the reproductive outcome and ovarian reserve has been studied.

In PCOS, the number of parous women compared to controls of the same age is a little over 1. This is the low reproduction level that you have in Europe. And the duration of infertility is less than a year. And this is not different from control. So actually, PCOS women do conceive with similar results as controls. They often consult for infertility when clearly do conceive as well as controls.

FSH levels in PCOS are lower, and AMH levels remains higher. But in spite of that, as you will see, the fertility window is not extended in PCOS women. the extension of the fertility window in PCOS has been questioned.

In SART data, which is the US ART reproductive registry, people have looked at the impact of reproductive aging on live-birth rate in PCOS and control. And this is really what you have, if you look at IVF. If you look at implantation rates, these are slightly higher in PCOS in young women. The miscarriage rate is the same, and the clinical pregnancy rate is slightly higher in PCOS young patients.

However, when you look at the subgroup of women who are above the age of 40, from 40 to 44, you see that in controls and in PCOS you have a difference in number of oocytes. You have more oocytes in PCOS because ovarian reserve parameters are higher. However, when you look at actual pregnancy rates in controls and in PCOS, the drop is fairly similar, and the chances of becoming pregnant in IVF at the age of 41, 42, 43 in controls and PCOS is actually the same, in spite of the fact that they have higher ovarian reserve parameters.

If you look at the conclusion, we talk about diagnosis, we talk about clinical management, and more follicles, but for how long? They have more follicles, but the quality of the follicles according to the oocytes declines just as rapidly as it does in normal women.

And for just one last slide for talking to you about the metabolic syndrome, which is often associated with PCOS. And this is important, clinically. There is obesity and an alternation of fat distribution in 50 to 60 percent of women with PCOS who are obese, with PCOS women preferentially accumulating abdominal fat.

Metabolic syndrome includes an increased abdominal fat, high blood pressure, hyper triglycedemia, low HDL, increased insulin resistance and impaired insulin receptor signaling, and decreased insulin-mediated glucose uptake. Hyperinsulinemia acts synergistically with elevated LH and IGF-1 to actually promote ovarian androgen production and perpetuate the metabolic syndrome.

This is so important, actually, that if you do have women who are under the age of 35, the proper measure is to actually propose lifestyle changes to reduce weight, because the ultimate outcome is better. Unfortunately, in women who are above the age of 35, you can't actually do that, because you have no time, and the benefit from losing weight is lost by the decrease in fertility with increasing age.

With this, I would like to thank you very much and again show the participants in my group, putting the emphasis on Professor Jean Marc Ayoubi, chair of the department, and Dr. Paul Pirtea, who has been working with me very closely. And I'd like to thank you very much, all.

**ASSESSMENT OF THE PELVIS - ANA TOURE-ECRA**

Good morning all.

First of all, I would like to express my joy and gratitude to the organizers of this webinar, namely: IFFS, GIERAF and WHO, for giving me the opportunity to participate in this scientific meeting.

The subject that was entrusted to me is the evaluation of the pelvis under the general theme which is “Infertility management in middle income countries”.

Infertility is a public health problem in Africa, both because of the pathologies that underlie it and because of the pro-natalist atavism of our countries.

Indeed, infertility within the couple gives rise to ostracism, social exclusion and domestic violence.

The first baby born by in vitro fertilization in 1978 in England revolutionized the care of infertile couples and gave hope to all these couples.

In Africa, in vitro fertilization did not come until two decades later.

And despite this gap, it remains a luxury for our populations for two essential reasons: the insufficiency of the technical platform and the prohibitive costs of these methods.

I have no conflict of interest to declare.

In the introduction, it must be said that the evaluation of the basin in the care of infertile couples in a developing country is essential for two essential reasons: First of all, not everyone will have access to the methods of medically assisted procreation (MAP).

The first phase of ART with us must really remain with natural procreation.

Then, a failure in the attempts to take charge, in particular in AMP, often sign the definitive stop of all procedures, because the first test is often the test of the last chance.

Indeed, it is either all the savings of a lifetime that are used, or it is a bank loan.

No one has the right to fail, let alone in our countries.

In vitro fertilization was originally designed to bypass the tubal barrier.

The essential element here being the implantation in the uterus.

This intrauterine transfer is the last step that can ruin all the painstaking work of a team in an instant if the transfer is laborious.

This ultimately amounts to saying that in natural as well as assisted procreation, the evaluation of the pelvis is an essential step.

What are the anatomical bases of this pelvic assessment?

The assessment of the pelvis involves three entities: the cervix which determines cervical infertility, the uterus which determines uterine infertility, the tubes and the peritoneum which determine turbo peritoneal infertility.

What will be the role of these three stages in the two types of procreation?

In natural procreation, the cervix must be permeable, it must be able to synthesize mucus.

In assisted procreation, it must be waterproof, of course, but it must not be too sinuous to avoid having a traumatic transfer.

The uterus in natural procreation as in assisted procreation must not be deformed there must be no large polyps, no adenomyosis, no intracavitary myoma and no synechiae.

Regarding the tubes and the peritoneum, the tubes must be permeable, there must be no peritoneal adhesion in assisted reproduction.

At the level of the tubes that we are going to bypass in spite of everything, there must be no hydrosalpinx.

At the level of first of the cervical floor, the essential pathology is the synechia which is a cicatricial adhesion on the level of the two faces of the neck.

The clinical signs will be: algomenorrhea, oligomenorrhea.

And the questioning here will be very important because it will highlight an anteriority of the rules which were normal with the notion of symptomatology occurring in the months which followed the maneuver, in general, in the first year.

It is most often a voluntary termination of pregnancy, but other endo-uterine maneuvers can be the cause of synechia.

The diagnosis will be made in front of a hysterometry or a hysterosalpingography difficult to carry out, because one could not cross the cervix, or even, a transfer test which will be laborious, even impossible.

Often, hysterosalpingography is not possible.

This is why the hysteroscopy will allow the diagnosis to be made with certainty.

In a study that we carried out at the Yopougon University Hospital where we received many patients with infertility, many couples because we were a referral center, 25 % of these couples had cervical infertility.

Voluntary terminations of pregnancy are more indicative of a low contraceptive prevalence in us than of the high rate of clandestine abortions.

We see in these photos the flanges connecting the two sides of the collar.

At the level of the uterine floor, we will describe several pathologies.

First of all, fibroids.

Fibroids, it must be said that in Africa, 40% to 45% of women over 30 have a fibroid, this is what a study, already carried out in 2006, found.

And the fibroid problem is twofold, because first it will lead to infertility, although there the relationship is not always proven, is it.

We know that it is the submucosal or intra-cavitary fibroids that deform the cavity, which have had an impact on fertility.

Also a size of 6 cm, if it is interstitial, can affect infertility.

The ones really that aren't blamed at all are strict subserous fibroids.

So there is this problem with the relationship between fibroids and infertility, which is why we say to do a myomectomy only if we have nothing else to blame for infertility.

The fibroid problem, as I said, is twofold because the surgical treatment is also a problem, because it is very adhesive.

You can have a m yomectomy and end up infertile because there have been too many adhesions.

In our same study at the CHU, we found that 42% of patients nevertheless had infertility of uterine origin.

And the signs of fibroma in general are menorrhagia, whatever the location, metrorrhagia if the fibroma is intracavitary.

At hysterography, for the fibroid, we have subtraction or double-tone images.

And on ultrasound, myomas are hypoechoic.

On the left, we see a myo me embedded in the myometrium, and on the right, on the MRI, the endometrium which is molded around the myoma.

So, on hysterosonography, we can clearly see these submucosal myomas, and on the right, on hysteroscopy, the myoma that we can clearly see protruding into the cavity.

And the polyps, for their part, will be well seen on hysterosonography because we will use the contrast of the water to make the polyp appear.

And if we make this diagnosis of polyps on ultrasound, it is better to do it in the first phase, because there, the hypoechogenicity of the endometrium will serve as a contrast.

Another pathology is uterine synechiae which will manifest as oligomenorrhea, or even amenorrhea.

The context is the same as that of cervical synechia.

On the left, we have subtraction images going up to the pass.

On the left, on the hysterosalpingography, we see subtraction images going up to the cervix and on the right during hysteroscopy, we will see the same fibrous bridges.

Then we have adenomyosis.

On the left, a myometrium which is thickened with this characteristic aspect of the spoke of a wheel.

On the right, there is a localized, non-systematized thickening, with blurred and ill-defined outlines, unlike the fibroid, which is hypoechoic and has well-defined outlines.

On the left, the image is very characteristic, in the head of a bull linked to the erection of the tubes, tuba erecta, it is the hysterosalpingographic aspect.

And on the right, we notice the spiculated aspect of the right edge of the uterus.

At hysteroscopy, this raspberry-red appearance is sometimes petechial and truly characteristic of adenomyosis.

And on the right, this aspect of crypt in the mucous membrane, also characteristic of adenomyosis.

Finally, on MRI, the goal of MRI is not so much the diagnosis of adenomyosis, that it is necessary to measure only the junctional zone, that is to say the zone which will separate the endometrium from the myometrium.

And this junctional zone must be less than 8 mm, or if this zone is not regular, the addition of the anterior / posterior junction zone at the level of the fundus must be less than 12 mm, because when the zone of The implantation is thick, the implantation rates of the embryo decrease.

So, we can clearly see here the plane, which is the endometrium, the black which is the internal myometrium called the junctional zone, and the gray which is the external myometrium.

So, we see that in many pathologies, hysteroscopy is called.

So the question still arises: "Should the hysteroscopy be systematic?" Multiple studies have been done, with different conclusions.

It is known that even myomectomies can lead to adhesions, even when they are interstitial.

And with us, nearly 50% of patients consulting for infertility have a history of myomectomy.

And the same goes for the history of voluntary termination of pregnancy.

So, there are many asymptomatic intrauterine pathologies which were discovered after failure of IVF in our establishment, that is to say in Bingerville, which means that at the beginning, the hysteroscopia , which does not was not mandatory, we have now made it mandatory for precisely this chance discovery of submucosal pathologies.

With regard to the tubal stage, it should be noted that the frequency of tubal pathologies is high, and as a consequence, salpingitis under diagnosed or poorly treated.

In the study we carried out at the Yopougon University Hospital, 66% of affected patients had tubal pathologies.

So, we have the example of hydrosalpinx.

We know that those which are deleterious are the bulky hydrosalpinx visible on ultrasound.

The reflux of fluid is accused of having inflammatory effects on the endometrium, which decreases implantation rates.

The hysterosalpingography will show the stagnation of the product in the distal portion with no passage.

And on the right, the endoscopy will allow the diagnosis with certainty by showing a tube distended by liquid which will turn blue during the blue test.

Regarding tubal obstruction, it is important to distinguish two forms.

There is the form where really the obstruction is from the start with no interstitial opacification, and there, we know that it can be a spasm.

And on the right, a permanent obstruction which leads to an organic lesion.

The endoscopy will still allow us to make the diagnosis with certainty of certain lesions, including peritoneal infertility on the left, and on the right, endometriosis with the bluish dots, you see the adhesions that are really solid and everything.

What emerges from this analysis is the endoscopy which will allow the diagnosis with certainty of most pathologies.

The double advantage of this endoscopy is that it allows for a curative phase just after the diagnostic time.

However, in our countries, endoscopy remains the prerogative of private medicine, because very few public establishments do not have this technical platform.

And when they do exist, they lead to endless queues.

In conclusion, we will say that the occurrence of pregnancy requires the proper functioning of various stages of the reproductive system.

This same requirement will be found in medically assisted procreation, and the real assessment of the different stages is essential.

Indeed, the good results cannot be freed from the quality of a good evaluation of the basin.

The effective management of infertility in developing countries is still reserved for a privileged section of infertile couples.

Thank you for your attention.

I would like to add on the first slide synechiae, after that of synechial polyps at uterine level, I would just like to add this sentence, after talking about the signs which are oligomenorrhea and amenorrhea.

It should, please, be translated after the context, of course, so after the signs which are gomenorrhea oli and the context which is the same as cervical synechia.

I would like to add just a word of description to say that here, the synechia is materialized by the interruption, you see, of the continuity of the endometrium that we can clearly see on the c liché.

Thank you.

**SURGERY IN INFERTILITY: KEY ISSUES - JUSTIN MBOLOKO**

Ladies and gentlemen, good afternoon. On behalf of GIERAF, I would like to thank our colleagues of IFFS and WHO for all they have done for this webinar.

I was asked to talk about surgery in infertility in the lower- and middle-income countries. Among them, we have Sub-Saharan countries.

My talk was planned like that. After environment and its consequences, in terms of diseases, we'll say something about surgery in infertility, and also surgery by different organs, and draw some conclusions. Ladies and gentlemen, Sub-Saharan population are pronatalist. They like having baby and having many babies. So contraceptive methods, mainly barrier methods, are less used. That leading to the high risk of sexually transmitted infection and also non-desired pregnancy, leading to unsafe abortion.

[INAUDIBLE]Let mentioned that in many of our countries, voluntary induced abortion is prohibited by the law. It's common to have delivery in bad conditions, as we'll see in the next slide, with the risk of postpartum infections.

Sexually transmitted infection, post abortion infection, and postpartum infection, the three can explain the high frequency of secondary infertility in this region. Secondary infertility of tubal origin due to tubal blockade and peritubo ovarian and pelvic adhesions.

African are among the people most susceptible to develop myoma. And finally, shifting to Western diet, European or American diet and behavior, we see rising metabolic and endocrinologic pathology like obesity and the polycystic ovarian syndrome.

As illustration, iIn our area, it isn't rare to find some kind of delivery room like that. Infection with its consequences: the pelviperitonitis, tubal blockage, peritubo ovarian adhesions, myoma, and obesity.

Most of those problems are treated by ART or surgery. Some center practicing assisted reproductive technology are available in our area, but average people have difficulties to attend these centers because of the lack of money. And also the main problem is that in many countries in our setting, medical insurance coverage is not organized.

It is well known that endoscopic surgery provides better outcomes than open surgery. Because open surgery has many drawbacks, mainly the post-operative adhesions, as we see.

Endoscopic surgery offers many advantages, like panoramic view of pelvic and abdominal organs, allowing many treatments in one operation. And also, we have a shorter hospital stay and quick recovery after the procedure.

But endoscopic surgery has some problems, mainly the problem of the training of the personnel and also the equipment. Most of the pioneers of endoscopic surgery were trained in the UNFPA program of planning family by laparoscopic tubal ligation in USA, in Morocco, and Tunisia. You can see the group of 1998 in Tunisia, they are from different countries.

After that, Professors Bruhat and Kasia organized the training for a group of doctors in Cameroon. Nowadays, some countries continue to organize the training. But in spite of this training sessions, many areas are not provided with endoscopy surgery. For example, the Democratic Republic of Congo, we have only 12 centers able to provide endoscopic surgery.

Another problem is the evolution of new equipment. Endoscopy is one of the fast-moving fields in terms of the evolution of the technology. This device was used in the UNFPA program, and in 2003 we are changing with this column. That equipment worked with reusable instruments.

But nowadays, we have more complex equipment with a single-use instruments. That rise the problem of getting the spare parts when the device is broken down, and another problem, the disposal instruments, they need to spend a lot of money to have your surgery made.

Ladies and gentlemen, what's the most surgery practiced in our area? Myomectomy, adhesiolysis, and the tubulal surgery, fimbrioplasty and neosalpingostomy, are the most practiced in our area.

Myoma is the most common gynecologic tumor in our area and worldwide. In our setting, patients of more than 35 years, almost half of them have myoma.

According to the Donnez publication, in Afro-American and African, the prevalence climbed to 60% and 80%. According to the recommendation, class 0, 1, and 2, and the other classes that can distort uterine cavity had an impact on the fertility and have to be removed. Is it the same for our area? I don't think so. We have some particularities.

Myoma arise very early, here is a 22 years patient with big myoma. A 45 woman with a very big myoma and here numerous myoma. For them, the management needs to be made by open surgery with its drawback I said.

For some cases, laparoscopy is also possible. But for many cases, if you want to go by laporoscopy, it needs to be treated before by medical treatment made of GnRH analogue and selective progesterone receptor modulator (SPRM): ulipristal acetate. In our city, it is known as Esmya as tradename.

Those treatments, at the beginning, arrived with many hopes it was the solution for our problem. Mainly when Donnez published his finding that after four courses of three months of ulipristal acetate we can reduce the size of the myoma down to 67%.

But as they noticed, for some patients liver function impairment. Some medical authorities decided to stop the use of ulipristal acetate until we have the result of the trial made in with Esmya. Today, the result of this trial, and mainly the recent publication of IWONA, 2020 of recommend the use of Esmya, but in the short time (3 months), and also checking the function of liver by the hepatic tests.

Endometriosis is also one of the problems we faced in our practice. According with the last meta-analysis, laparoscopy and the GnRH analog are best for increasing the pregnancy rate, and also, it's better to reduce pain and to delay the recurrence of endometriosis.

For uterine cavity, synechiae is one of the problems. I said previously that induced abortion in our area are made in bad condition for most of them. One of the complications is synechiae. But another kind of synechiae is the one related to herbal potion.

Some traditional healers use herbalist potion to induce abortion or to treat some case of fertility. But those kind of synechiae are more severe, and the treatment available failed to resolve (Unpublished data).

Tubal disease in our region, for most of them, they are due to chlamydia trachomatis infection. Laparoscopic treatments provide good results in terms of increasing pregnancy rates after treatment like tubal cannulation and the salpingolysis and also salpingectomy.

So that Courtney, in its more recent publication advocate for resorting to tubal surgery first before to go to ART treatment in moderate and mild lesions.

laparoscopy ovarian drilling, LOD.

More and the more we have some cases of Letrozole and Clomid resistance that need to be treated by LOD. But the problem is, how to set your energy in order to avoid premature ovarian failure and the periovarian adhesions, its main complications.

In conclusion, the key problems of surgery in our area are about myoma, tubul blockade, and adhesions. Endoscopic surgery is the best but less available. For myoma, medical treatment before surgery is the good strategy. For mild and minimal lesions we need tubal surgery before to go to ART.

Thank you for attention.