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RESEARCH ARTICLE

NON-IN VITRO FERTILIZATION INDUCTION OF OVULATION EXPERIENCE.

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Abstract

Infertility has always been a preoccupation in a couple's life. To tackle this infertility, a therapeutic arsenal is available but can be expensive. In Morocco, the lack of coverage by infertility health insurances can lead to a late care for the couples who need it.
The objective of this work is to present a non-in vitro fertilization (non-IVF) stimulation method, which is more affordable. However, this technique is only possible when sperm parameters, the biological check-up and the tubular permeability allow it.
This is a retrospective study on infertile couples gathered into two Assisted Human Reproduction private practices, from January 2007 to January 2017. The protocol we have been using includes clomiphene citrate and FSH.
998 couples analyses have been compiled. 2674 cycles of non-IVF induction of ovulation were undergone. The presence of one or several follicles was noticed in 2450 cycles. This has led to 598 pregnancies, 18 of which are twin pregnancies.
Our results, which stay stable, reassure us into keeping up the use of this protocol.

Introduction:-

Infertility has always been a preoccupation in a couple's life. Ovulation disorders represent at least 20% of infertility causes [1].

It is essentially the context on which the ovarian stimulation is undertaken that determines the ovarian response. Thus, it should be examined with care in order to select the right stimulation protocol [2].

The objective of this work is to present the results of a non-in vitro fertilization (non-IVF) stimulation technique undertaken into two medically assisted procreation units.

The published recommendations advocate a quality approach that includes in particular an appropriate organization of care structures, to undertake medical tests similar to IVF tests and the compliance of indications[3].

Patients and methods:-

This was a retrospective study on infertile couples among two liberal medically assisted procreation facilities, from

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January 2007 to January 2017.

Couples to whom are proposed a non-IVF stimulation technique are couples who were facing a primary or secondary infertility with at least one of the tubes permeable in hysterosalpingography.

The exclusion criteria for women were impermeable tubes, fibroma and uterin polyps in hysterosalpingography, and polycystic ovary syndrome or an alteration of the ovarian reserve. Concerning men, the detection of azoospermia or severe oligoasthenospermia was an exclusion parameter in the study.

An ultrasound between the second and the fifth day of the cycle completes the test, so that the uterus and the ovaries can be successively observed.

Our protocol:
We have adapted and developed our protocol according to the age of the patient.

1/ Women aged less than 30 years old with a normal hormonal examination

The used protocol is as follows:
Starting at the first day of the cycle, it is prescribed 100mg of lysine acetylsalicylate per day and 800 mg of naftidrofuryl per day to help forming a sufficiently developed endometrium.

2^{nd} day of the cycle: Clomiphene citrate is prescribed at 50 mg in the morning and evening for five days.

The 6^{th} day of the cycle, we start the treatment with FSH at the dose of 75 UI every other day: one injection the 6^{th} day of the cycle, one the 8^{th} day of the cycle, and one the 10^{th} day of the cycle.

Ultrasound monitoring of follicles sizes, and of thickness and aspect of the endometrium is handled every other day. An estradiol dosage is made when a follicle has reached 16 mm.

We keep up with injections of FSH 75 UI at the same pace until one of the three follicles reaches a minimum of 18mm, and when a classic-looking endometrium in triple band is at least 8 mm of thickness and from 150 to 250 pg of estradiol, per follicle.

Afterwards, we set off an injection of human chorionic gonadodostimulin (HCG) at a rate of 10,000 IU or recombinant HCG.

If spermogram constants are normal and if the Hühner test is positive, we recommend to keep up sexual intercourse several times a day during 4-5 days as from the induction day.

If the Hühner test is negative, the injection of HCG 10,000 UI or recombinant HCG will be done between 11pm and midnight and the intrauterine insemination of spermatozoa will be performed the day after next morning after sperm preparation in the laboratory by the swim-up technique or upward migration.

On the insemination day, we administer sublingual phloroglucinol to release the cervix.

The insemination is undertaken with a Frydman cannula.

We prescribe a natural micronized progesterone at a rate of 200 mg in the morning and 400 mg in the evening within the vagina, starting the night of the insemination or 48 hours after the injection of human chorionic gonadodostimulin (HCG) or recombinant HCG in case of a positive Hühner test (case of no intrauterine spermatozoa insemination).

The progesterone will be kept up until 12 weeks in case of pregnancy.

Bêta-HCG serum level will be asked 14 days after the insemination or 16 days after the injection of human chorionic gonadodostimulin (HCG) or recombinant HCG in case of a positive Hühner test.

The first ultrasound is undertaken one week after the bêta-HCG serum level dosage.

In case of failure after 3 cycles of treatment or when the first cycle does not give a sufficient response, we proceed with a more aggressive treatment, the one we propose to patients aged more than 30 years old with a normal hormonal examination or to patients with an FSH serum level from 8 to 12 mUI/ml, or to patients with a low AMH (Anti-Mullerian Hormone) and antral follicle count inferior to 8.

2/ Women aged more than 30 years old with a normal hormonal examination or patients with an FSH serum level from 8 to 12, or patients with a low AMH (Anti-Mullerian Hormone) and antral follicle count inferior to 8

In relation to the above-mentioned protocol, clomiphene citrate is prescribed in double dose.

The 6^{th} day of the cycle, we start the treatment with FSH in double dose (150 UI every other day). The rest of the protocol is identical to the one prescribed above.

At the end of the stimulation, we undertake the support of the luteal phase with an intra-vaginal progesterone supplement at a rate of 3 pills per day (1 in the morning, 2 in the evening).

Result of the treatment
The studied population is summarized in the table 1:

Table 1:-Patient characteristics

	Number	Percentage
Number of couples	998	
Women less than 30 years old	244	24,45
Abnomalities in men Varicocele	252	25,25
Mild to moderate oligoasthenospermia	280	28
Positive Hühner test	180	18,04

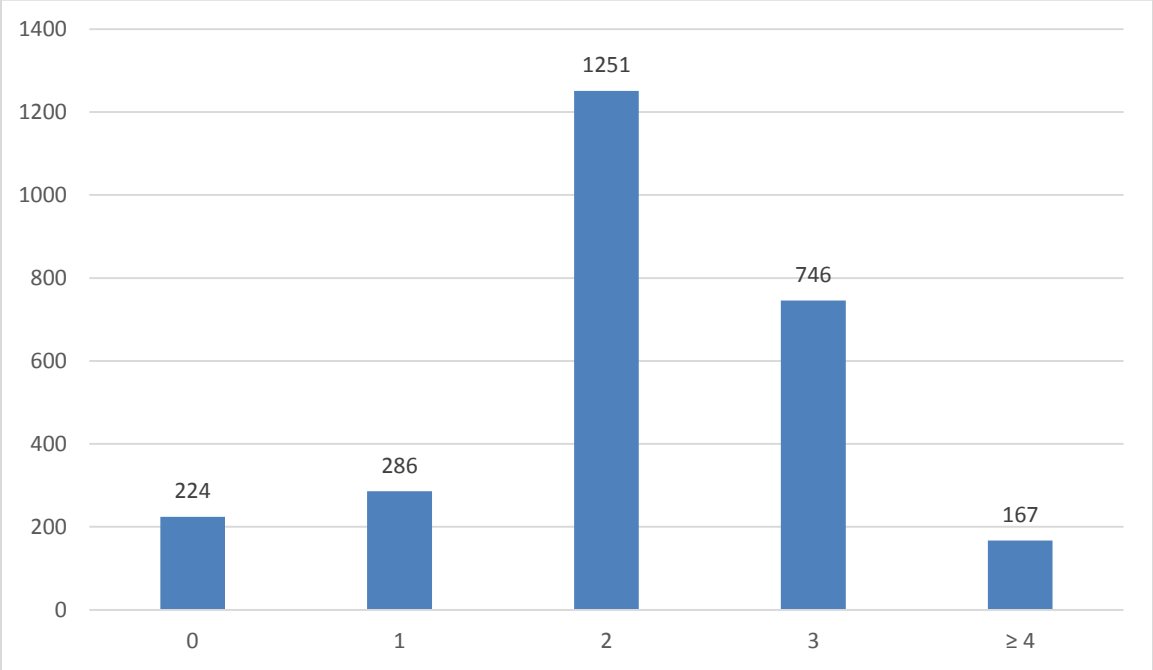
Out of the 2674 cycles of non-IVF induction of ovulation treatment, we had to interrupt 224 of them because of absence of response or because of follicles that do not evolve beyond 15 mm of diameter and with a low remaining estradiol rate, that being 8,38% of the cycles.

The amount of obtained follicles is reported in the graph 1. We obtained from 1 to 2 follicles in 62,73% of the cases that had responded to the treatment.

In one case, we obtained 15 follicles in a 28 years old patient. The cycle had been dropped. It has been recommended to the patient the absence of sexual intercourse until the occurrence of menstruations in order to avoid a multiple pregnancy. A second attempt has been made the next month with a lesser dose of FSH (50 UI per injection) and we obtained 3 follicles then a singleton pregnancy.

We had just one case of hyperstimulation that needed a hospitalization with treatment with human albumin and anticoagulants.

Graph 1:-Number of follicles obtained during the stimulation



The thickness of the endometrium has been measured in each ultrasound monitoring of the induction of ovulation treatment. We have found in our patients classic-looking endometria in triple band and a thickness that varies from 7 to 14 mm.

Two weeks after the attempt, we obtained 1070 positive bêta-HCG serum levels (40,01%) but we have seen an intrauterine sac one week later, only in 899 cases (33,6%).

We have seen a pregnancy during the ultrasound in 84,02% of the chemical pregnancies.

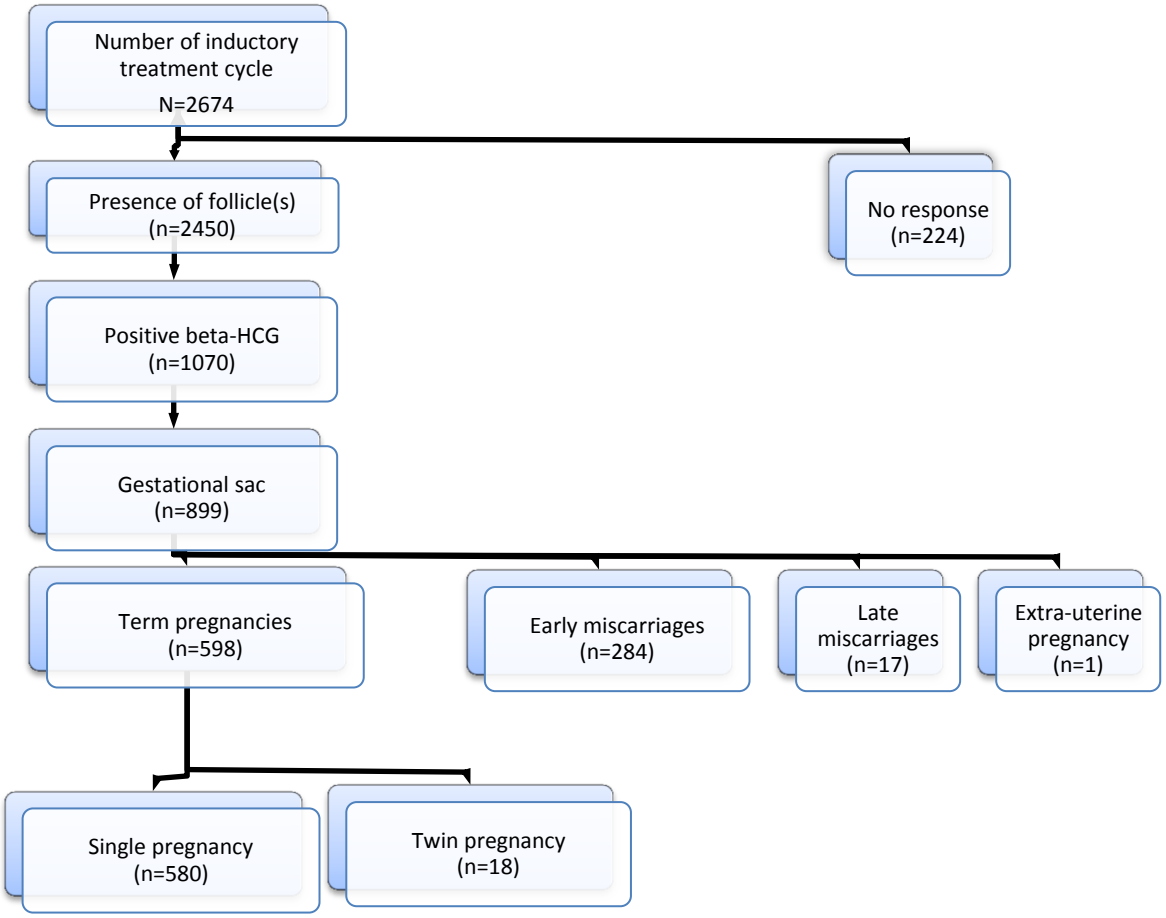
The rate of early miscarriages was 284 cases, that being 10,62% of all attempts; 26,54% of the cases when the bêta-HCG was positive and 31,59% of the cases when an intrauterine gestational sac was objectified despite the prescription of the progesterone treatment (natural micronized progesterone).

We had to perform a laparoscopic surgery with tubal conservation on only one extrauterine pregnancy.

17 patients suffered a late miscarriage beyond 12 weeks, among them 3 cases of late abortions beyond 27 weeks.
598 pregnancies led to labour, that being 22,36% of all attempts.

18 pregnancies were twin pregnancies, that being 3,01% of all pregnancies that led to labour for patients to whom we had obtained more than 2 male follicles (913 cases: 37,26% of the cases that responded to the treatment). We had not obtained any triple gestation. (Table 2)

Table 2:-Induction results



Discussion:-

In countries like Morocco where the social care of the disease is not sufficient, the cost of new techniques don't allow many couples to achieve their desire of pregnancy. During the period of this study, no law was supervising the induction of ovulation. As a point of comparison, in France, no law supervises the practice of non-monitored IVF inductions of ovulation or the practice of intrauterine insemination, contrary to the IVF and the intrauterine inseminations ruled by the bioethics laws of July 1994. However, given the recommendations of the French health and safety agency for health products, doctors specialized in infertility unanimously agree that the handling of inducers of ovulation requires a specific medical training and a professional experience in the therapeutic field [3].

The aim of the induction of ovulation treatment is to obtain an evolutive pregnancy with the ultimate goal the birth of a living child. It is then indispensable to evaluate the factors of infertility inside the couple. The ovarian stimulation should aim at increasing the number of follicles, at improving the growth and the maturation of the follicles and at boosting the proliferation of the endometrium.

Whatever the indication, we have to straightaway remind that no stimulation of the ovulation should be initiated without having first checked the condition of the tubes and evaluated the quality of the ovulation and the sperm of the spouse.

Clomiphene citrate is the most important ovarian stimulation strategy. It is similar to a steroid close to diethylstilbestrol, weakly estrogenic, highly anti-estrogenic and with a dose dependent effect. Indeed, clomiphene citrate will be able to be effective on the phenomenon of negative feedback on pituitary gland as well as inter cyclic

peak of FSH. Its anti-estrogenic effect at the hypothalamic level consists of an acceleration of the GnRH pulse frequency and which boosts the secretion of FSH. Therefore, the aim of a short sequence of clomiphene citrate in the early cycle is to artificially reproduce the inter-cyclical rise of FSH. Secretions of the corpus luteum, mainly inhibin A and estradiol lead, during the luteal phase, to an inhibition of the FSH secretion, estradiol probably being the most important inhibitory agent. We will reproduce with the clomiphene citrate the state of estrogen deficiency normally induced by luteolysis. This very precise in time state of estrogenic deficiency is necessary to obtain a "release" of the FSH. Secondarily, inhibin B will intervene as an ovarian component of response to the FSH, expected to come close the FSH window in a physiological way and avoid exceeding the hyperstimulation threshold [1].

It is recommended not to exceed 12 cycles of stimulation due to the theoretical risk of ovarian cancer. In general, the treatment shouldn't pass 6 months unless the case is well selected and that other causes of infertility have been eliminated [1].

Gonadotropins available in Morocco are Metropine, Follitropin alfa and Follitropin beta.

They allow to directly stimulate the ovary by an exogenous FSH before the induction with human HCG or recombinant HCG.

Gonadotropins can be used alone or in combination with clomiphene citrate. The objective is to increase in a limited way the number of growing follicles. The treatment by FSH is indicated in case of failure with stimulation by clomiphene citrate or in case of resistance, when there is no conception despite ovulatory cycles and when there is an absence of ovulation despite normal dosages [4].

The ultrasound monitoring and biological monitoring allow to adapt dosages and to monitor the number of growing follicles, the thickness and aspect of the endometrium.
They enable to decrease the risk of a multiple pregnancy by possibly canceling a cycle where the number of obtained follicles is high [5].

The follicles quality is also determined by the estradiol dosage [6].

We have found in our patients classic-looking endometria in triple band and a thickness that varies from 7 to 14 mm, which anticipated an optimal possibility of developing an embryo in case of fertilization.

Results regarding term pregnancies can vary depending on the used protocol and depending on the studies.

Antoine has obtained 7,9% of pregnancies, among them 0% of multiple pregnancies during strict mono follicular stimulations. He has obtained 10,7% of pregnancies, among them 9,4% of multiple pregnancies in case of minimal stimulation (from 1 to 2 follicles) [3].

Hamilton and al published a pregnancy rate of 10,4% that can go up to 26% when there is a micronized progesterone stimulation [7].

Blumenenfeld and Nahhas published a pregnancy rate of 11,5% that can go up to 27% thanks to the administration of 2500 units of hCG at D.3 and D.9 after injection of 10,000 units of HCG to lead to induction of ovulation [8].

However, in 1991, James and al. didn't find again this effect, the pregnancy rates in their study were only at 7,5% with supplementation, and 15,6% without supplementation [9].

Finally, Messinis and al only demonstrated the effect of hCG supplementation in the group of women with type I anovulation [10].

And most importantly, none of these studies has reported a hyperstimulation rate in the supplemented groups.

Because of the risk of ovulation hyperstimulation and of multiple pregnancies related to the multiplicity of HCG injections, the majority of the teams only administer one supplementation per micronized progesterone.

The rate of term pregnancies in our study is 22,36% out of all attempts, 55,89% out of the positive beta-HCG, 66,52% out of the gestational sacs observed.

Our twin pregnancy rate stays low: 0,67% out of all attempts and 3,01% of term pregnancies. We only had one case of extra-uterine pregnancy and only one case of hyperstimulation that needed a hospitalization with treatment with human albumin and anticoagulants. Our results which remain steady reinforce our will to keep up the use of the protocol that we have successfully been using for many years.

Conclusion:-

Non-IVF ovarian stimulation results are mainly based on obtained pregnancy rates and the percentage of multiple pregnancies.

The treatment and the context in which the stimulation is undertaken are the main parameters that determine the ovarian response. It has to be analyzed with care and choose the stimulation protocol. This protocol has to be financially affordable for the couples so that they accept it and aspire to procreate.

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