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Unexplained infertility: live-birth's prognostic factors to determine the ART management

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ABSTRACT

BACKGROUND: The purpose of this retrospective observational study was to identify prognostic factors that lead to a live birth (LB) in couples with unexplained infertility in order to define the best assisted-reproductive technique (ART) strategy.

METHODS: Prognostic factors of couples with unexplained infertility managed initially with gonadotropin intrauterine inseminations (IUI) at a single university fertility center were analyzed. Infertility was not considered "unexplained" in case of mild male infertility and suspicion of diminished ovarian reserve (FSH>10 IU/L). ART management consisted to start with IUI cycles and then, if failure, to propose *in vitro* fertilization (IVF). Couples were compared according to the results of IUI cycles in terms of LB.

RESULTS: Between January 2011 and July 2015, 133 couples with unexplained infertility were included (320 IUI cycles). The average age of women was 31.6±4.6 years and the average number of IUI per couple was 2.4±1.2. The IUI live birth rate (LBR) was 37.6%, with an average of 2 cycles to obtain a pregnancy. For 63 couples, no pregnancy occurred after IUI cycles. The prognostic factors of the two groups "LB after IUI" *vs.* "no LB after IUI" were not statistically different. The remaining 20 couples had a spontaneous pregnancy with a LB. Cumulative LBR, including spontaneous and ART pregnancies, was 65.7 %. Of the 63 couples with no LB after IUI, 33.3% dropped-out from infertility treatments before starting IVF.

CONCLUSIONS: To avoid couple's drop-out, we advise to start infertility treatment for unexplained infertility with two IUI before undergoing IVF if IUI failure.

Key words: Infertility - Fertilization in vitro - Reproductive techniques, assisted - Pregnancy.

About 48.5 million couples worldwide would be infertile in the word.[1] In France, 1 in 5 couple consults for infertility.[2] In 10% to 30% of couples with infertility, no etiology is identifiable, that is usually called unexplained infertility.[3-7] However, the diagnosis of unexplained infertility requires all the necessary diagnostic tests to exclude an etiology, after ensuring the existence and regularity of unprotected sexual intercourse. Depending on the country, recommended tests may be different. Nevertheless, all the societies of reproductive medicine agree with semen analysis, assessment of the integrity of the female genital tract and the absence of ovulation disorder. The assessment of ovarian reserve by day 3 serum

follicle-stimulating hormone (FSH) level, serum anti-Müllerian hormone (AMH) level and antral follicular count (AFC) remains controversial.[7-10] Laparoscopy should be performed in case of suspicion of tubal or pelvic pathology.[7-9] *Chlamydiae trachomatis* serology is not systematically recommended; in case of seropositivity, tubal abnormalities are suspected and a laparoscopy should be performed.[9]

Several management of unexplained infertility are proposed: expectant management, intrauterine insemination (IUI) with ovarian stimulation and then, if unsuccessful, *in vitro* fertilization (IVF), or starting the treatment with IVF.[4, 6, 11-27] There is no international consensus on the best strategy for the management of unexplained infertility. For example, the Guidelines of the National Institute for Health and Care Excellence on infertility advise couples to try to conceive for a total of 2 years, including up to one year before their infertility investigations, before considering IVF.[7] In France, the choice between IUI or IVF remains to the physician, depending on prognostic factors such as age and infertility duration, without clear cutoffs.[9] However, these ART options are greatly different in terms of cost, hardship and risk for the woman. Thus, the aim of our study was to identify live birth's (LB) prognostic factors of couples with unexplained infertility in order to define the best infertility treatment.

Materials and methods

The study protocol was approved by the French Committee of Ethics for Research in Obstetrics and Gynecology in January 2016 (CEROG 2015-GYN-1204). Informed consent was obtained from all participants.

Patients

We conducted a retrospective observational study in a single university fertility center in France. The data were collected from the medical records of couples. We included all the couples managed for unexplained infertility and who underwent their first IUI between January 2011 and June 2015.

Infertility was defined by the lack of pregnancy after one year of regular unprotected intercourse. To define the unexplained infertility, no etiology must be found after infertility investigations: for the man, at least two normal semen analyses, according to World Health Organization criteria.[28] If one semen parameter (sperm concentration, motility, morphology) was out of the reference range, the couple was not included in the study. For the woman, the assessment of the tubal patency and uterine cavity was made by hysterosalpingogram (HSG) and pelvic ultrasound. The ovarian reserve was assessed by antral follicle count (AFC), serum AMH level (ng/mL, Kit Beckman-Coulter, Immunotech) and day 3 serum FSH level (IU/L). In case of suspected diminished ovarian reserve (DOR, FSH>10 IU/L), the couple was not included. In case of suspected tubal pathology, a laparoscopy was proposed to women.

The management of unexplained infertility consisted to start with gonadotropin IUI and then, if unsuccessful, to propose IVF. The maximum number of IUI before undergoing IVF was determined in the center depending on the woman age: up to 4 IUI up to 38-years-old, up to 2 after 38-years-old.

Prognostic factors

The prognostic factors that we aimed to study were: age, Body Mass Index (BMI) and smoking status for both man and woman, infertility duration, type of infertility (primary or secondary), AFC, day 3 serum FSH level (UI/L), serum AMH level (Beckman-Coulter kit, ng/mL), woman *Chlamydiae trachomatis* serology, a diagnostic laparoscopy in the initial workup for infertility. We also assessed the number of IUI cycles, pregnancy outcomes (with IUI or IVF), and spontaneous pregnancies with the time to conceive.

Statistical analysis

The main analysis compared prognostic factors between two groups of couples: the couples with a LB after IUI, and the couples

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who should undergo IVF after IUI failure. A secondary analysis compared two groups of couples: couples with a spontaneous pregnancy and LB, and the childless couples despite time trying to conceive spontaneously associated to ART management (IUI±IVF).

IBM SPSS Statistics version 20.0 (Inc., IL., USA) software was used for data analysis. Statistical significance was defined as $P<0.05$. Quantitative data were expressed as mean±standard deviation (SD) or as medians with range (minimum, maximum), qualitative data were expressed as numbers and percentages. Qualitative data were compared using the Pearson's χ^2 Test or Fisher's Exact Test when available. The relationship between a dichotomous variable and a quantitative variable was assessed using the Student *t* test or the nonparametric Mann-Whitney Test. If the qualitative variable had more than two categories, the F Test ANOVA was used.

Results

Between January 2011 and July 2015, 133 couples with unexplained infertility were included, corresponding to 320 gonadotropin IUI cycles. The average number of IUI by couple was 2.4±1.2. At the first cycle, the mean age was 31.6±4.6 years for women, 34.9±6.2 years for men. Primary infertility was observed on 67% of couples. The mean infertility duration at first cycle was 3.1±1.6 years. Current smoking was observed on 32% of women and 40% of men. Mean BMI was 24.7±5.6 kg/m² for women, 24.4±3.4 kg/m² for men. Mean AFC was 17.6±8.5. Mean value of women's basal FSH level was 6.5±1.7 IU/L, mean serum level of AMH was 4.0±2.7 ng/mL. *Chlamydiae trachomatis* antibody was tested in 52 women (39%), and 6 women were seropositive. Ten women (7.5%) had a diagnostic laparoscopy, and no pelvic pathology was found.

Among the 133 couples included, 50 couples had a LB after IUI, most of the time after the second IUI cycle. Twenty couples had a spontaneous pregnancy leading to a LB. Mean time to spontaneous pregnancy was 3.7±1.6 years. For the remaining 63 couples, IVF was decided after several failed IUI. Of these 63 couples, 21 dropped-out from infertility treatments, before starting IVF. Seventeen couples had a pregnancy after IVF (fresh and frozen-thawed embryo transfer) with LB. It was the first IVF attempt for two thirds of couples. Prognostic factors of the 50 couples with a pregnancy after IUI were compared with those of the 63 couples who should have started IVF, without any difference (Table I).

Moreover, the 20 couples who finally had a spontaneous pregnancy were compared with the childless couples despite IUI and IVF, without any prognostic factor being highlighted (Table II). Finally, cumulative LB rate (LBR), including spontaneous and ART pregnancies, for couples who were managed for unexplained infertility was 65.7% (N.=87).

Discussion

In the management of unexplained infertility, the choice between IUI and IVF is still

Table I.—*Prognostic factors of live birth after IUI.*

	Live birth after IUI, N.=50	IUI failure, N.=63	P value
Women's age (y), mean (SD)	30.8±4.4	32.1 ±4.7	0.1
Men's age (y), mean (SD)	34.6 ±6.1	34.5±5.9	0.9
Women's BMI (kg/m²), mean (SD)	25.7±5.9	24.3±5.8	0.2
Men's BMI (kg/m²), mean (SD)	24.3±3.6	24.5±3.7	0.8
Female smokers, (N.)%	18 (36)	20 (31.7)	0.7
Male smokers, (N.)%	18 (36)	28 (44.4)	0.4
Primary infertility, (N.)%	31 (62)	45 (71.4)	0.3
Infertility duration (y), mean (SD)	3.2±1.7	3.1±1.5	0.9
FSH (UI/L), mean (SD)	6.2±1.9	6.8±1.6	0.05
AMH (ng/mL), mean (SD)	4.2±3.0	4.1±2.5	0.9
AFC, mean (SD)	18.2±9.5	17.1±7.8	0.6

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Table II.—*Prognostic factors of LBR after spontaneous pregnancy.*

	Spontaneous pregnancy and live birth, N.=20	Childless after IUI±IVF, N.=46	P value
Women's age (y), mean (SD)	32.1±4.5	32.1±5.1	1
Men's age (y), mean (SD)	36.8±7.3	35.1±6.2	0.3
Women's BMI (kg/m²), mean (SD)	23.3±3.7	24.2±5.8	0.5
Men's BMI (kg/m²), mean (SD)	24.5±2.0	24.5±4.0	1
Female smokers, (N.) %	4 (20)	16 (34.8)	0.2
Male smokers, (N.) %	6 (30)	22 (47.8)	0.2
Primary infertility, (N.) %	13 (65)	35 (76.1)	0.4
Infertility duration (y), mean (SD)	2.6±1.2	3.1±1.5	0.3
FSH (UI/L), mean (SD)	6.4±1.4	6.8±1.7	0.4
CFA, mean (SD)	18.2±9.6	17.0±8.6	0.7
AMH (ng/mL), mean (SD)	3.4±2.2	3.8±2.0	0.6

debated. Our study wanted to assay LB's prognostic factors in these infertile couples in order to counsel them the best as possible: IUI prior IVF or starting immediately with IVF? Our study did not show any predictive factor of LB after IUI in these couples. LBR after IUI was 38%. Most of the time, 2 IUI cycles were required to be pregnant.

In 2014, Kaser *et al.* published a secondary analysis of 2 trials, FASTT and FORT-T, including 603 infertile women aged 21 to 42 years, randomized to conventional or accelerated treatment with IUI and/or IVF (2717 total cycles). Women were stratified in 4 groups according to basal FSH and estradiol. Women with FSH of 10-15 IU/L and estradiol ≥40 pg/mL on day 3 testing were unlikely to achieve LB after IUI.[29] However, FSH of 10 IU/L is highly suggestive of DOR, and could explain the "unexplained" infertility. In our study, we excluded women with hormone profile suggesting a DOR. The difficulty of analyzing the literature is due to differences in the definition of "unexplained" infertility and the paraclinic exams that have led to this diagnosis. Ideally, we should use "unexplained infertility" only with a normal complete workup including pelvic ultrasound, HSG, hormone profile, assessment of ovarian reserve, a *Chlamydia trachomatis* serology and for male a normal semen analysis.[30] In addition, diagnostic laparoscopy is not routinely performed for these women. Devranoglu *et al.* published a cross-sectional study including couples with unexplained infertility, with women at the age ≤36 years with at least unilateral tubal patency at HSG: 105 women with a day 3 FSH≥10 IU/L (170 IUI cycles) were compared to 95 women with a normal FSH (170 IUI cycles too). hCG positivity, clinical and ongoing pregnancy rates did not differ between women with normal and elevated FSH levels (P=0.2, 0.3 and 0.4, respectively). Thus, according to this study, in women under 36 years, basal serum FSH was not a prognostic factor for pregnancy after IUI.[31] Hansen *et al.* published a secondary analysis of a prospective, randomized, multicenter clinical trial including 900 couples with unexplained infertility who underwent IUI treatment, up to 4 cycles. Ovarian stimulation was performed with clomiphene citrate, letrozole, or gonadotropins. Woman's age, infertility duration, level of income and prior pregnancy loss were significant predictors of LB. In this study, the FSH level was not studied in contrast to AMH that was not correlated with the LBR, confirming the data from our study.[32] Tjon-Kon-Fat *et al.* published a secondary analysis of a randomized controlled trial including 116 couples with unexplained or mild male subfertility. The couples were randomized to one cycle of IVF with elective single embryo transfer with subsequent frozen-thawed embryo transfers or 3 cycles of IUI. Female age and infertility duration were not associated with better ongoing pregnancy chances after IVF compared to IUI. Only when prewash total motile count was lower than 110 (x10^6 spermatozoa/mL), the probability of ongoing pregnancy was higher in women al-

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located to IVF. This study included a heterogeneous population, with men with abnormal semen analysis.[33]

A recent retrospective cohort study by Geisler *et al.* included 851 couples with unexplained infertility, mild endometriosis, one patent Fallopian tube, mild male infertility or ovulatory dysfunction, up to 3 cycles IUI. At each attempt, more than 70% couples were couples with unexplained infertility. Independent associates of successful outcome factors were lower age and multiparity, for all the couples and the subgroup of unexplained infertility. The unadjusted cumulative pregnancy rate for LB per cycle started, over three cycles, was 34.9%, which is near from our LBR of 37.6%. In this study, more than 90% of total LBs with IUI is achieved during the first 2 cycles, corroborating our conclusion.[34]

Limitations of the study

The strength of our study was to be very restrictive on the couples' inclusion criteria. We did not include couples with mild male infertility, even with relatively mild sperm abnormalities, neither women with a suspicion of DOR (FSH>10 IU/L).[8] So, we have included a very homogeneous population of couples whose infertility seemed truly unexplained. The very restrictive inclusion criteria, however, lead to include only a small population, even if the data have been studied over many years. The lack of significant results could be correlated with a lack of study power. One can also criticize the retrospective design of the study, the lack of randomization, and the long study period during which management changes could have taken place. *Chlamydiae trachomatis* seropositivity is associated with a lower natural conception rate and a lower likelihood of pregnancy after IUI, even with patent fallopian tubes.[30, 35] In our study, less than half of women (39%) were tested for *Chlamydiae trachomatis*, and we are not able not analyze this factor's reliably. The systematic prescription of the *Chlamydiae trachomatis* serology before IIU in our ART center is the result of recent management changes. Moreover, in our study, only 10 women (7.5%) had a diagnostic laparoscopy, while it may be discussed of the infertility work-up despite normal HSG. Indeed, in unexplained infertility, endometriosis stage 1 or 2, pelvic adhesions or tubal disease are found in 49% to 90.5% of women.[36]

Among the 133 couples included, IUI management failed for 63 couples. A third of these couples stopped infertility treatment after these failures, while an IVF treatment should have been recommended to them. This highlights the high rate of drop-out in infertility treatments, corroborating data from other studies on the subject.[37-40] In our study, the mean infertility duration was 3.1±1.6 years, with a minimum and a maximum of 1 and 8 years respectively, which is relatively long. Added to the time required to perform several IUI and the burnout due to repeated failures, this could contribute to discouraging some couples. So do not let the couples waste their time and let them start directly infertility management by IVF or right after two or three failed IUI cycles.

Conclusions

Prognostic factors for pregnancy in the context of unexplained infertility do not seem to exist.[41] This study suggests the interest to start the treatment with up to 2 gonadotropin IUI attempts for any couple whose infertility is considered unexplained because IUI is less invasive and less expensive than IVF.

Moreover, chance of spontaneous pregnancy in these couples should be considered. Indeed, it has been shown that the diagnosis of infertility and its treatment could lead to sexual dysfunction and less frequent sexual intercourse.[42-48] It is important to track sexual dysfunction and reassure the couple on natural conception.

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