Original Article

Pregnancy Predictors after Intrauterine Insemination: Analysis of 3012 Cycles in 1201 Couples

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Abstract

Background: Intrauterine insemination (IUI) is the first therapeutic step in assisted reproductive techniques and many factors, including male and female infertility and technique-dependent factors, have been reported to influence pregnancy rates after IUI.

Methods: We carried out this retrospective study on 1201 couples undergoing 3012 intrauterine insemination cycles during 2002 to 2009. Pregnancy rate per cycle in terms of female infertility factors, male infertility factors, and technique-dependent factors were evaluated. The χ^2, t-test, Kaplan-meier method, and multiple logistics regression model, were used for data analysis. The $p<0.05$ was considered statistically significant.

Results: The highest pregnancy rates were obtained in cases whose infertility duration was shorter ($p<0.05$), Body Mass Index (BMI) was ≥25 ($p<0.05$), FSH<9 *IU/L* ($p<0.05$), anovulation due to polycystic ovary syndrome ($p<0.05$), donor sperm was used due to azoospermia ($p<0.01$), three IUI cycles ($p<0.01$), at least two follicles were recruited through controlled ovarian hyperstimulation ($p<0.01$), and where higher total doses of FSH were administered as necessary ($p<0.05$).

Conclusion: This study characterizes predictors of pregnancy following IUI, for cases with shorter periods of infertility, BMI of 25 or more, FSH value below 9 *IU/L*, anovulation, donor sperm and performance of three intrauterine insemination cycles.

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Introduction

Intrauterine insemination (IUI) is the first therapeutic step in assisted reproductive techniques, and is especially appropriate for cases with mild male factor infertility, anovulation, endometriosis with at least one patent tube, and unexplained infertility (1). Among the assisted reproductive techniques, IUI is considered a first-line procedure due to its simplicity, easy management, low cost, and absence of potentially serious complications. Although the literature reports several factors affecting the likelihood of pregnancy after IUI, among them, age, body mass index (BMI), female etiology, and semen quality, there is little consensus regarding the extent to which these factors affect the likelihood of pregnancy (2–4).

Epidemiological studies report varying rates of infertility in developed countries, ranging between 8% and 32% of couples of reproductive age (5–10). Recent data for Spain indicate that approximately 15% of couples of childbearing age have problems conceiving (11).

The objective of this study was to identify factors that predict pregnancy in terms of 3 categories: female infertility factors (duration of infertility, age, weight, hormones on the 3rd day of the cycle, and etiology), male infertility factors (semen analysis according to the strict morphology criteria), and technique-dependent factors (type of insemination, number of cycles, number of inseminations per cycle, follicle development, type of stimulation received, and total dose administered).

Methods

This is a retrospective study performed between 2002 and 2009 on 1201 couples with infertility problems, who consulted the reproduction department of Virgen de la Arrixaca University Hospital in Murcia, Spain. Overall, we analyzed 3012 IUI cycles. A basic infertility study was performed before starting controlled ovarian hyperstimulation (COH). The study consisted of medical history, physical examination, transvaginal ultrasonography, hormone study, hysterosalpingogram, and semen analysis. The hormones studied were follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), and estradiol on the third day and estradiol, progesterone, and PRL on the 22nd day of menstrual cycle. PRL was analyzed twice in the same cycle, since the value of this hormone can be affected by punction stress.

The swim-up technique was used to prepare the semen and the total motile spermatozoa (TMS) count was done by multiplying the total sperm count by the prewash percentage of motile sperm. Based on semen analysis, oligo/astheno/ teratospermia (OAT) were classified: mild OAT (TMS >5 million); moderate OAT (TMS 3–5 million); and severe OAT (<3 million sperm). Sperm morphology was rated according to Kruger criteria (teratospermia<5% normal sperm shapes).

All IUI cycles were stimulated by gonadotropins. Treatment was started between the second and fifth day of the cycle, using pure urinary FSH (pFSH; Fostipur), recombinant FSH (rFSH; Gonal-F or Puregon), or human menopausal gonadotropin (hMG; Menopur). The most frequent starting dose of gonadotropins was 75–150 *IU*/24 *hr*. Hormone administration was adjusted according to each patient's characteristics, especially age, hormones on the third day of the cycle, and BMI. The first ultrasound scan to assess the number and size of follicles and endometrial thickness was performed five days after starting the treatment, and subsequent scans were performed on individual patients depending on ovarian response. Ovulation was induced by 250 μg of subcutaneously administered recombinant human chorionic gonadotropin (hCG; Ovitrelle), and insemination was performed 36 *hr* later. The criterion used to trigger ovulation was to obtain at least a single 18 *mm* follicle.

Following 48–72 *hr* of abstinence, semen was collected three hours before insemination for laboratory processing. After determining motility (TMS), sperm were washed free of seminal fluid and prepared for insemination. A soft catheter (Laboratoire CCD, Paris, France) was used for insemination. The proximal end of the catheter was located in the center of the uterine cavity, and 0.5 *ml* of sperm preparation was slowly injected over about 15 *s*. A hard catheter (Laboratoire CCD) was used if it was not possible to pass the soft catheter through the cervix. Luteal phase support was provided by 200 *mg*/24 *hr* of natural micronized progesterone (Utrogestan), administered vaginally starting on the night of insemination and continuing until the pregnancy test; if pregnancy occurred, administration continued until the 12th week of gestation.

Statistical analysis was carried out using SPSS version 15. Results were expressed as means. Categorical variables were compared using the chi-square test (χ^2) and quantitative variables were analyzed using the Student's t-test. A value of $p<0.05$ was considered statistically significant. The Kaplan-Meier method was used to measure the time elapsing until pregnancy as a function of baseline FSH levels. Multivariate logistic regression analysis was performed to identify correlations between the study variables and pregnancy. Only statistically significant co-variables were selected.

Results

We studied a total of 3012 IUI cycles corresponding to 1201 couples between 2002 and 2009, for which the outcome was 306 pregnancies (10.2% per cycle), representing a pregnancy rate per couple of 25.5%. Infertility was primary and secondary in 87.8% and 12.2% of the cases, respectively. Female and male infertility factors were detected in 21.9% and 26.3% of the cases, respectively. Infertility was due to combined

factors in 35.3% of the cases, and was unexplained in the remaining 16.5%. The mean duration of infertility was 3.04 years (range, 1 to 10). The pregnancy rate decreased significantly ($p< 0.05$), in line with years of infertility: 1 year (12.3%), 2 years (10.3%), 3 years (9.8%), and 4 or more years (8.9%).

Female infertility factors: The mean age of the participants was 32.2 years (range, 23 to 41 years), and mean BMI was 26 (range, 18 to 38). Age was not a strong predictor of success: the pregnancy rates per cycle for age brackets below 30 years, 30 to 35 years, and 35 to 40 years, were 11.4%, 10.6%, and 9.6%, respectively. Women older than 40 years only underwent 20 cycles, and none became pregnant. The participant's weight, however, did affect the pregnancy rate. The proportion of pregnancies increased with BMI, with a significant difference between a BMI (kg/m^2) under 25 (18.5 to <25), and a BMI of 25 or more (≥25 to 35.0) (8.9% *vs*. 12.1%; $p<0.05$).

Ovarian function was calculated in terms of serum concentrations of FSH and estradiol before cycle commencement. A strongly significant relationship was observed between the FSH value on the third day of the cycle and the probability of pregnancy ($p<0.01$), (Table 1).

In terms of baseline FSH, we observed that the probability of pregnancy during IUI cycles fell significantly for baseline FSH values of 9 *IU/L* or more ($p<0.05$) (Figure 1).

The estradiol value on the third day of the cycle (over 80 *pg/ml*) was not a relevant pregnancy predictor.

Table 1. Results for female- and male-dependent factors

Pregnancy predictors	Rate/Cycle (%)
Female factors	
Irregular ovulation	8.9
Occult ovarian failure	7.7
Anovulation (PCOS)	13.3
Tuboperitoneal	7.7
Endometriosis	
I-II	7.0
III-IV	6.4
Male factors	
Asthenospermia	8.1
OAT	
Mild	9.4
Moderate	8.5
Severe	6.4
Teratospermia	10.8
Azoospermia	16.7

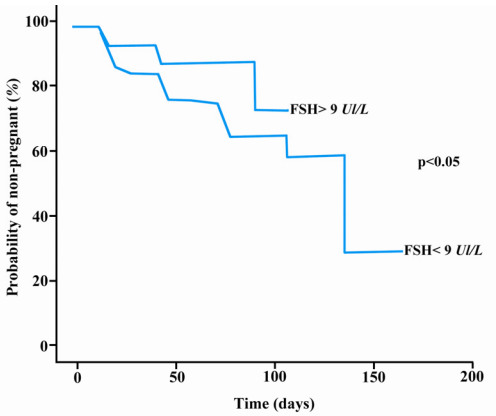

Figure 1. Accumulated probability over time of no pregnancy (Kaplan-Meier test) for participants with baseline FSH≥9 *IU/L* and <9 *IU/L*

Female infertility factors were classified as follows, in order of frequency: irregular ovulation due to short or unsuitable luteal phases (41.2%); tuboperitoneal factors (16.5%); anovulation associated with polycystic ovary syndrome (PCOS) (10.4%); occult ovarian failure (10.2%); stage I-II endometriosis (7.8%); stage III-IV endometriosis (2.8%); uterine factors (2.6%); cervical factors (1.7%); and other causes (6.8%).

Female etiology was a powerful predictor of success in achieving pregnancy. Couples treated for anovulation associated with PCOS had the highest pregnancy rate per cycle (13.3%; $p<0.05$). The lowest pregnancy rates were obtained for moderate to severe cases of endometriosis (6.4%), (Table 1).

Male infertility factors: Based on semen analysis, male infertility factors were classified as follows, in order of frequency: asthenospermia (29.4%); mild oligo/astheno/teratospermia (OAT) (24%); moderate OAT (18.9%); severe OAT (6%); oligospermia (0.7%); teratospermia (4.1%); azoospermia (12.5%); and causes unrelated to semen quality, such as erectile dysfunction, positive serology results, etc (4.4%).

Male factor etiology was a powerful predictor of success in achieving pregnancy when donor sperm was used due to azoospermia in the partner. Couples treated for azoospermia had the highest pregnancy rates per cycle (16.7%; $p<0.01$), (Table 1).

Multivariate analysis was used to determine whether there was an association between pregnancy and the predictors that were found to be

Table 2. Factors associated with the probability of pregnancy (Multivariate analysis)

Factors	Odds Ratio	95% Confidence Interval	p-value
Anovulation (due to PCOS)	1.47	0.93-2.31	0.09
Infertility duration (less than 4 years)	0.56	0.26-1.18	0.13
BMI (25 and over)	0.82	0.54-1.25	0.35
FSH (below 9 *IU/L*)	3.17	1.36-7.41	0.008

significant. The results are shown in table 2.

Women with a baseline FSH below 9 *IU/L* were 3.17 times more likely to become pregnant than women with a baseline FSH of 9 *IU/L* or more (95% CI: 1.3–7.4 times).

Technique-dependent factors: The type of semen used (partner or donor) was a strong predictor of success, with a pregnancy rate per cycle of 18.1% for donor sperm ($p<0.01$) Results for the technique-dependent factors are summarized in table 3.

In terms of the number of IUI cycles performed, the couples underwent an average 2.1 cycles each (range, 1 to 6). In 98.2% of the cases, between one to four inseminations were performed. A maintained pregnancy rate was observed until the third cycle, after which the pregnancy rate decreased noticeably ($p<0.01$), (Table 3).

In terms of the number of inseminations per cycle, in 95.6% of the cases a single insemination was performed. The pregnancy rate was not found to increase when two inseminations were performed in the same cycle.

The number of pre-ovulatory follicles recruited was observed to be a significant factor ($p<0.01$). Recruitment of at least two follicles increased the pregnancy rate in cases of COH combined with IUI (Table 3).

Regarding the type of gonadotropin used, rFSH was administered in most cycles (86.3%), followed by hMG (11.5%), and pFSH (2.2%). The type of stimulation used did not affect the probability of pregnancy (Table 3). The mean dose of administered gonadotropin was 600 *IU/L*. The units of

Table 3. Results for technique-dependent factors

		Cycles (*n*)	Pregnancies	Rate/Cycle (%)
Insemination type				
	IUI–Partner	2708	251	9.3
	IUI–Donor	304	55	18.1
Cycle				
	1st	1202	129	10.7
	2nd	884	94	10.6
	3rd	571	59	10.3
	4th	300	22	7.3
	≥5th	55	2	3.6
Follicles (*n*)				
	1	1535	124	8.1
	≥2	1477	182	12.3
Stimulation				
	rFSH	2549	259	10.2
	hMG	347	33	9.5
	pFSH	67	7	10.4
Total dose				
	<300 *IU/L*	152	14	9.2
	300-499 *IU/L*	1139	104	9.1
	500-699 *IU/L*	1294	121	9.4
	700-899 *IU/L*	320	53	12.6
	900-1100 *IU/L*	107	14	13.1

FSH used for COH were a marker of success ($p< 0.05$).

Discussion

IUI is frequently offered to couples with problems conceiving, provided the woman has at least one patent ovarian tube and her partner has only mildly altered semen quality. An important factor to assess as a predictor of pregnancy in response to IUI is the duration of infertility. A number of studies have reported higher pregnancy rates corresponding to shorter periods of infertility (12,13) but our study revealed significant differences ($p<0.05$) in this regard. Nuojua-Huttunen et al. (14), unlike Goverde et al. (15), reported significant differences that depended on whether the infertility period was more or less than six years (14.2% *vs.* 6.1%). We observed that pregnancy rate fell as the duration of infertility increased, suggesting that other more complex assisted reproduction techniques should be used after four years of infertility.

Female infertility factors: In our study, the woman's age did not significantly affect the pregnancy rate. Nuojua-Huttunen et al. (14) reported a pregnancy rate of 13.7% per cycle for a total of 811 IUI cycles in women up to the age of 40, and a rate of 4.1% thereafter. Like Brzechffa et al. (15), we found that, after COH, age did not affect the pregnancy rate provided the woman was under 40 years. Other researchers, however, such as Goverde et al. (16), and Bronte et al. (17) consider age to be an important factor in achieving pregnancy.

Souter et al. (10) described the impact of BMI on IUI cycles. In our analysis, BMI significantly affected the pregnancy rate; however, women with a BMI of 25 or more achieved a higher pregnancy rate (12.1% per cycle) than women with a BMI below 25 (8.9%). Our results would indicate that in women with overweight that undergo treatment for anovulation, the likelihood of achieving pregnancy increases significantly. Dodson and Legros (18) found no differences for weight, although they did observe that higher gonadotropin doses were necessary for ovarian stimulation in obese women. Another study (19) pointed to the impact of lifestyle factors such as excess weight on the time elapsing before becoming pregnant; the annual probability of pregnancy for couples not exposed to risk factors was 83%, compared to 38% when they were present. Undoubtedly, lifestyle changes, exercise and weight loss are key factors in successfully treating infertility in such patients (20, 21).

A hormone analysis (estradiol and FSH) on the third day of the cycle is the main method for evaluating ovarian reserve. In our study we found a significant difference in pregnancy rates according to FSH levels, with values above 9 *IU/L* reducing the probability of pregnancy. In contrast, there was no clear difference regarding estradiol concentrations. A number of authors agree that higher FSH concentrations reduce the overall number of follicles produced, affect oocyte quality, and indicate a less favorable prognosis for treatment (22,23), even though the cycle may appear to be regular (24). However, Mullin et al. (25), who evaluated threshold FSH and estradiol values of 15 *IU/L* and 80 *pg/ml*, respectively, found no significant differences in the pregnancy rate per couple. We agree with the opinion that women for whom ovulation induction prior to IUI is likely to be effective–that is, those with functioning ovaries–should be selected for this procedure (26).

In our study, the pregnancy rate per cycle for patients with anovulation due to PCOS was 13.3%, confirming the significant relationship between this etiology and IUI outcomes. It seems clear that COH corrects ovulation and, therefore, results in a high IUI success rate. Endometriosis, on the other hand, which is among the disorders that are the most difficult to treat (27), decreased the IUI success rate in our study to 7% per cycle for mild cases and to 6.4% for severe ones. Similar results were obtained by Vlahos et al. (28), who reported a pregnancy rate per cycle of 19.1% for cases with anovulation, compared to 9.1% for cases with endometriosis, and by Dickey et al. (29), who also reported better results for cases with anovulation. Toma and Hammond (30) reported a pregnancy rate of 6.5% per IUI cycle for donor sperm in women with stage I-II endometriosis compared to 14% in the control group. Some other authors (14) reported similar results.

Male infertility factors: Dorjpurev et al. (31) described the influence of semen characteristics on the pregnancy rate following IUI. In our case, using donor sperm for cases of azoospermia resulted in a pregnancy rate per cycle of 16.7%. When only mobility and altered morphology were considered, our study showed no significant differences; however, when OAT was included, the

pregnancy rate decreased in line with severity (9.4%, 8.5%, and 6.4% for mild, moderate, and severe OAT, respectively). Sakhel et al. (32) reported a direct relationship between sperm count and poor sperm mobility with the pregnancy rate.

Unexplained infertility: We were unable to determine the cause of infertility in 16.5% of the couples. In these cases, the pregnancy rate per couple was 10.5%. Hughes (33) achieved a pregnancy rate of 15% for this indication after stimulition by gonadotropins. This author strongly recommends IUI as a first-line treatment for such couples, provided the woman's age and the duration of infertility are acceptably low. Aboulghar et al. (34) proposed performing three cycles of IUI, and if pregnancy did not result, using a more complex assisted reproduction technique.

Technique-dependent factors: Most studies are based on artificial insemination using partner sperm. When we compared our study with studies that also included donor sperm insemination, we found that the proportion of cycles in which donor sperm was used were similar (35,36). The fact that donor sperm is of higher quality explains why the percentage of pregnancies per cycle was significantly higher (18.1%) than when partner sperm was used (9.3%).

In our study, the mean number of IUIs per couple was 2.1. Over 90% of pregnancies occurred in the initial three cycles, with the pregnancy rate dropping noticeably from the fourth cycle ($p<0.01$). Plosker and Amato (37) advise considering *in vitro* fertilization after three failed inseminations. For 811 cycles, Nuoja-Huttunen et al. (14) observed that the highest pregnancy rate occurred in the first cycle, and that 97% of all pregnancies occurred within four cycles.

The number of inseminations per cycle did not affect the pregnancy rate. In a prospective study of 226 cycles in 169 patients, Ransom et al. (38) found no difference in results for one or two inseminations per cycle. In contrast, for 449 cycles in 273 patients, Ragni et al. (39) concluded that results improved in response to two inseminations per cycle. From the literature, we could not conclude which approach was more appropriate. With ultrasound-controlled ovulation, a single insemination per cycle is probably sufficient and is certainly less costly (40).

In our study, the number of pre-ovulatory follicles recruited was a significant predictor of pregnancy ($p<0.01$). Plosker and Amato (37) showed that recruitment of at least two follicles increased success rates in COH in combination with IUI-by 2% for one follicle, and by 15% for two or more follicles ($p<0.01$). In their study of 9963 cycles, Bronte et al. (17) reported similar results, with pregnancy rates of 7.6% for one follicle, 10.1% for two follicles, 8.6% for three follicles, and 14% for four follicles ($p<0.01$). Similar analyses by some other authors (14) confirm these results.

It is not clear which of the drugs available on the market is preferably used for COH (41–45). It seems that higher pregnancy rates result when gonadotropins are primarily used (46, 47). Several studies have compared different types of gonadotropins (48–50), with some authors pointing to the greater potency of rFSH (51, 52). However, recent studies have reported higher pregnancy rates for the 'older' hMG, rather than the more recent FSH and rFSH products (53, 54). In our hospital we mainly use rFSH, as it has been reported to reduce the possibility of developing ovarian cysts associated with LH contamination, and also to increase the probability of a more consistent, effective, and efficient response (51,52). In our study, no differences in pregnancy rates were found for the different protocols used.

The probability of success increases with higher total gonadotropin doses. This occurs in cases of PCOS, where ovarian stimulation represents a real challenge, first, because of the range of endocrine factors to consider, including chronic anovulation and obesity, and second, because of the variability in ovarian response (55, 56). To obtain a single mature follicle, FSH should reach but not exceed the threshold FSH, as otherwise the response will be multifollicular, resulting in a higher rate of cycle cancellation, an increased risk of multiple pregnancy, and ovarian hyperstimulation (57). In our setting, we applied a protocol based on low doses administered over time, sometimes over 10 to 15 days. This induction protocol, although lengthy and expensive for the amount of gonadotropin administered, aimed to avoid excessive recruitment of follicles.

Conclusion

In this study aimed at identifying factors that predict pregnancy following IUI, we found that the probability was greatest for couples composed as follows: men with mildly altered semen quality, and women aged less than 40 years, with a BMI of 25 or more, with an infertility duration of less than four years, with an FSH value on day three of the cycle below 9 *IU/L*, who undergo COH, and in

whom anovulation due to PCOS can be corrected. According to our results, the 'ideal' stimulation is to administer the amount of gonadotropin necessary to induce ovarian response and recruit at least two follicles in a maximum of three cycles.

Conflict of Interest

Authors declare no conflict of interest.

References

1. Katzorke T, Kolodziej FB. [Significance of insemination in the era of IVF and ICSI]. Urologe A. 2010; 49(7):842-6. German.
2. Kamath MS, Bhave P, Aleyamma T, Nair R, Chandy A, Mangalaraj AM, et al. Predictive factors for pregnancy after intrauterine insemination: A prospective study of factors affecting outcome. J Hum Reprod Sci. 2010;3(3):129-34.
3. Souter I, Baltagi LM, Kuleta D, Meeker JD, Petrozza JC. Women, weight, and fertility: the effect of body mass index on the outcome of superovulation/ intrauterine insemination cycles. Fertil Steril. 2011; 95(3):1042-7.
4. Akanji Tijani H, Bhattacharya S. The role of intrauterine insemination in male infertility. Hum Fertil (Camb). 2010;13(4):226-32.
5. Abma JC, Chandra A, Mosher WD, Peterson LS, Piccinino LJ. Fertility, family planning, and women's health: new data from the 1995 National Survey of Family Growth. Vital Health Stat 23. 1997;(19):1-114.
6. World Health Organization. [Recent advances in medically assisted conception]. Geneva: WHO; 1992. 111 p. Report No.: 820:2-7. Spanish.
7. Gray RH. Epidemiology of infertility. Curr Opin Obstet Gynecol. 1990;2(2):154-8.
8. Templeton A, Fraser C, Thompson B. The epidemiology of infertility in Aberdeen. BMJ. 1990;301(67 44):148-52.
9. Vanrell JA. [Sterility, subfertility and infertility: definition, frequency and etiology]. In: Vanrell JA, Calaf J, editors. Human Fertility and sterility. Barcelona: Masson-Salvat; 1992. p. 1-8. Spanish.
10. Stephen EH, Chandra A. Updated projections of infertility in the United States: 1995-2025. Fertil Steril. 1998;70(1):30-4.
11. Matorras R. [Epidemiology of infertility, Updates of the Spanish Society of Fertility]. Spain: Spanish Fertility Society; 2000. p. 7-9. Spanish.
12. Collins JA, Burrows EA, Wilan AR. The prognosis for live birth among untreated infertile couples. Fertil Steril. 1995;64(1):22-8.
13. Snick HK, Snick TS, Evers JL, Collins JA. The spontaneous pregnancy prognosis in untreated subfertile couples: the Walcheren primary care study. Hum Reprod. 1997;12(7):1582-8.
14. Nuojua-Huttunen S, Tomas C, Bloigu R, Tuomivaara L, Martikainen H. Intrauterine insemination treatment in subfertility: an analysis of factors affecting outcome. Hum Reprod. 1999;14(3):698-703.
15. Brzechffa PR, Daneshmand S, Buyalos RP. Sequential clomiphene citrate and human menopausal gonadotrophin with intrauterine insemination: the effect of patient age on clinical outcome. Hum Reprod. 1998;13(8):2110-4.
16. Goverde AJ, McDonnell J, Vermeiden JP, Schats R, Rutten FF, Schoemaker J. Intrauterine insemination or in-vitro fertilisation in idiopathic subfertility and male subfertility: a randomised trial and cost-effectiveness analysis. Lancet. 2000;355 (9197):13-8.
17. Stone BA, Vargyas JM, Ringler GE, Stein AL, Marrs RP. Determinants of the outcome of intrauterine insemination: analysis of outcomes of 9963 consecutive cycles. Am J Obstet Gynecol. 1999; 180(6 Pt 1):1522-34.
18. Dodson WC, Kunselman AR, Legro RS. The effect of obesity on treatment outcomes for infertile ovulatory women undergoing superovulation and intrauterine insemination. Fertil Steril. 2005;84(Supple1):S72-73.
19. Hassan MA, Killick SR. Negative lifestyle is associated with a significant reduction in fecundity. Fertil Steril. 2004;81(2):384-92.
20. Clark AM, Thornley B, Tomlinson L, Galletley C, Norman RJ. Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment. Hum Reprod. 1998; 13(6):1502-5.
21. Pasquali R, Antenucci D, Casimirri F, Venturoli S, Paradisi R, Fabbri R, et al. Clinical and hormonal characteristics of obese amenorrheic hyperandrogenic women before and after weight loss. J Clin Endocrinol Metab. 1989;68(1):173-9.
22. Buyalos RP, Daneshmand S, Brzechffa PR. Basal estradiol and follicle-stimulating hormone predict fecundity in women of advanced reproductive age undergoing ovulation induction therapy. Fertil Steril. 1997;68(2):272-7.
23. Navot D, Bergh PA, Williams MA, Garrisi GJ, Guzman I, Sandler B, et al. Poor oocyte quality rather than implantation failure as a cause of age-related decline in female fertility. Lancet. 1991;337 (8754):1375-7.

24. Ahmed Ebbiary NA, Lenton EA, Salt C, Ward A M, Cooke ID. The significance of elevated basal follicle stimulating hormone in regularly menstruating infertile women. Hum Reprod. 1994;9(2): 245-52.
25. Mullin CM, Trivax B, Baxter M, Virji N, Saketos M, San Roman G. Day 3 follicle stimulating hormone (FSH) and estradiol (E2): could these values be used as markers to predict pregnancy outcomes in women undergoing ovulation induction (OI) therapy with intrauterine insemination (IUI) cycles? Fertil Steril. 2005;84 Suppl1:S162.
26. Scott RT, Toner JP, Muasher SJ, Oehninger S, Robinson S, Rosenwaks Z. Follicle-stimulating hormone levels on cycle day 3 are predictive of in vitro fertilization outcome. Fertil Steril. 1989;51 (4):651-4.
27. Härkki P, Tiitinen A, Ylikorkala O. Endometriosis and assisted reproduction techniques. Ann N Y Acad Sci. 2010;1205:207-13.
28. Vlahos NF, Coker L, Lawler C, Zhao Y, Bankowski B, Wallach EE. Women with ovulatory dysfunction undergoing ovarian stimulation with clomiphene citrate for intrauterine insemination may benefit from administration of human chorionic gonadotropin. Fertil Steril. 2005;83(5):1510-6.
29. Dickey RP, Taylor SN, Lu PY, Sartor BM, Rye P H, Pyrzak R. Effect of diagnosis, age, sperm quality, and number of preovulatory follicles on the outcome of multiple cycles of clomiphene citrate-intrauterine insemination. Fertil Steril. 2002;78(5): 1088-95.
30. Toma SK, Stovall DW, Hammond MG. The effect of laparoscopic ablation or danocrine on pregnancy rates in patients with stage I or II endometriosis undergoing donor insemination. Obstet Gynecol. 1992;80(2):253-6.
31. Dorjpurev U, Kuwahara A, Yano Y, Taniguchi T, Yamamoto Y, Suto A, et al. Effect of semen characteristics on pregnancy rate following intrauterine insemination. J Med Invest. 2011;58(1-2):127-33.
32. Sakhel K, Abozaid T, Schwark S, Ashraf M, Abuzeid M. Semen parameters as determinants of success in 1662 cycles of intrauterine insemination after controlled ovarian hyperstimulation. Fertil Steril. 2005;84 Suppl 1:S248-9.
33. Hughes EG. The effectiveness of ovulation induction and intrauterine insemination in the treatment of persistent infertility: a meta-analysis. Hum Reprod. 1997;12(9):1865-72.
34. Aboulghar M, Mansour R, Serour G, Abdrazek A, Amin Y, Rhodes C. Controlled ovarian hyperstimulation and intrauterine insemination for treatment of unexplained infertility should be limited to a maximum of three trials. Fertil Steril. 2001;75 (1):88-91.
35. Khalil MR, Rasmussen PE, Erb K, Laursen SB, Rex S, Westergaard LG. Intrauterine insemination with donor semen. An evaluation of prognostic factors based on a review of 1131 cycles. Acta Obstet Gynecol Scand. 2001;80(4):342-8.
36. Dickey RP, Olar TT, Taylor SN, Curole DN, Rye PH. Relationship of follicle number and other factors to fecundability and multiple pregnancy in clomiphene citrate-induced intrauterine insemination cycles. Fertil Steril. 1992;57(3):613-9.
37. Plosker SM, Jacobson W, Amato P. Predicting and optimizing success in an intra-uterine insemination programme. Hum Reprod. 1994;9(11):2014-21.
38. Ransom MX, Blotner MB, Bohrer M, Corsan G, Kemmann E. Does increasing frequency of intrauterine insemination improve pregnancy rates significantly during superovulation cycles? Fertil Steril. 1994;61(2):303-7.
39. Ragni G, Maggioni P, Guermandi E, Testa A, Baroni E, Colombo M, et al. Efficacy of double intrauterine insemination in controlled ovarian hyperstimulation cycles. Fertil Steril. 1999;72(4):619-22.
40. Bagis T, Haydardedeoglu B, Kilicdag EB, Cok T, Simsek E, Parlakgumus AH. Single versus double intrauterine insemination in multi-follicular ovarian hyperstimulation cycles: a randomized trial. Hum Reprod. 2010;25(7):1684-90.
41. Cohlen BJ, Vandekerckhove P, te Velde ER, Habbema JD. Timed intercourse versus intra-uterine insemination with or without ovarian hyperstimulation for subfertility in men. Cochrane Database Syst Rev. 2000;(2):CD000360.
42. Bry-Gauillard H, Coulondre S, Cédrin-Durnerin I, Hugues JN. [Benefits and risks of ovarian stimulition before intrauterine insemination]. Gynecol Obstet Fertil. 2000;28(11):820-31. French.
43. Cantineau AE, Cohlen BJ, Heineman MJ. Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine insemination (IUI) in women with subfertility. Cochrane Database Syst Rev. 2007;(2):CD005356.
44. Casadei L, Zamaro V, Calcagni M, Ticconi C, Dorrucci M, Piccione E. Homologous intrauterine insemination in controlled ovarian hyperstimulation cycles: a comparison among three different regimens. Eur J Obstet Gynecol Reprod Biol. 2006;129 (2):155-61.
45. Dankert T, Kremer JA, Cohlen BJ, Hamilton CJ, Pasker-de Jong PC, Straatman H, et al. A randomized clinical trial of clomiphene citrate versus low dose recombinant FSH for ovarian hyperstimula-

tion in intrauterine insemination cycles for unexplained and male subfertility. Hum Reprod. 2007; 22(3):792-7.

46. Gerli S, Bini V, Di Renzo GC. Cost-effectiveness of recombinant follicle-stimulating hormone (FSH) versus human FSH in intrauterine insemination cycles: a statistical model-derived analysis. Gynecol Endocrinol. 2008;24(1):18-23.
47. Demirol A, Gurgan T. Comparison of different gonadotrophin preparations in intrauterine insemination cycles for the treatment of unexplained infertility: a prospective, randomized study. Hum Reprod. 2007;22(1):97-100.
48. Kocak M, Dilbaz B, Demir B, Taşci Y, Tarcan A, Dede S, et al. Lyophilised hMG versus rFSH in women with unexplained infertility undergoing a controlled ovarian stimulation with intrauterine insemination: a prospective, randomised study. Gynecol Endocrinol. 2010;26(6):429-34.
49. Sagnella F, Moro F, Lanzone A, Tropea A, Martinez D, Capalbo A, et al. A prospective randomized noninferiority study comparing recombinant FSH and highly purified menotropin in intrauterine insemination cycles in couples with unexplained infertility and/or mild-moderate male factor. Fertil Steril. 2011;95(2):689-94.
50. Matorras R, Osuna C, Exposito A, Crisol L, Pijoan JI. Recombinant FSH versus highly purified FSH in intrauterine insemination: systematic review and metaanalysis. Fertil Steril. 2011;95(6):1937-42.
51. Balasch J, Fábregues F, Peñarrubia J, Creus M, Vidal R, Casamitjana R, et al. Follicular development and hormonal levels following highly purified or recombinant follicle-stimulating hormone administration in ovulatory women and WHO group II anovulatory infertile patients. J Assist Reprod Genet. 1998;15(9):552-9.
52. Matorras R, Recio V, Corcóstegui B, Rodríguez-Escudero FJ. Recombinant human FSH versus highly purified urinary FSH: a randomized study in intrauterine insemination with husbands' spermatozoa. Hum Reprod. 2000;15(6):1231-4.
53. Balasch J, Miró F, Burzaco I, Casamitjana R, Civico S, Ballescá JL, et al. The role of luteinizing hormone in human follicle development and oocyte fertility: evidence from in-vitro fertilization in a woman with long-standing hypogonadotrophic hypogonadism and using recombinant human follicle stimulating hormone. Hum Reprod. 1995; 10(7):1678-83.
54. De la Fuente A. [Evaluation of the effectiveness, safety and cost-effectiveness of highly purified human menopausal gonadotropin. Study of use Menopur ® in Intrauterine Artificial Insemination (IAC/IAD)]. Fertil Rev. 2007:24(6):363-7. Spanish.
55. Dickey RP, Taylor SN, Curole DN, Rye PH, Lu P Y, Pyrzak R. Relationship of clomiphene dose and patient weight to successful treatment. Hum Reprod. 1997;12(3):449-53.
56. Mannaerts B, Shoham Z, Schoot D, Bouchard P, Harlin J, Fauser B, et al. Single-dose pharmacokinetics and pharmacodynamics of recombinant human follicle-stimulating hormone (Org 32489*) in gonadotropin-deficient volunteers. Fertil Steril. 1993;59(1):108-14.
57. Chung MT, Chan TF, Loo TC, Tang HH, Lin LY, Tsai YC. Comparison of the effect of two different doses of recombinant gonadotropin for ovarian stimulation on the outcome of intrauterine insemination. Taiwan J Obstet Gynecol. 2011;50(1):58-61.