Use of a prediction model for high-order multiple implantation after ovarian stimulation with gonadotropins

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Objective: To determine prospectively the effectiveness in clinical practice of a prediction model for high-order multiple pregnancies (HOMP) (triplets or more).
Design: Prospective study.
Setting: University teaching hospital.
Patient(s): Eight hundred forty-nine consecutive infertile patients undergoing a total of 1,542 treatment cycles.
Intervention(s): Gonadotropin ovarian stimulation or induction of ovulation without IVF
Main Outcome Measure(s): Observed and predicted overall pregnancy rates and the incidence of HOMP.
Result(s): The use of the prediction model (implying cancellation of all cycles at high risk for HOMP) would result in an 8% (95% confidence interval, 6.8%–9.2%) reduction of overall pregnancy rate but also in a 285% (95% CI, 279%–291%) reduction of HOMP.
Conclusion(s): By using our prediction model, it was possible to maintain a low risk of HOMP with a good pregnancy rate in patients receiving gonadotropin ovarian stimulation or induction of ovulation without IVF. (Fertil Steril® 2005;83:116–21. ©2005 by American Society for Reproductive Medicine.)

Key Words: Gonadotropins, high-order multiple gestation, multiple pregnancy, ovulation induction

Multiple pregnancies reached epidemic proportions in the late 1990s and the consequences of some multiple pregnancies for the children, the parents, and the community remain significant (1, 2). Whereas ovulation induction accounts for approximately 40% of the problem of high-order multiple pregnancies (HOMP), it accounts for almost 100% of the problem of very HOMP (2). In both medical and social terms, such pregnancies can have highly negative consequences (2). According to some studies, it appears that an individual infertile couple is at significantly greater risk of a HOMP from ovulation induction alone or associated with intrauterine insemination (IUI) than they are from IVF (3, 4).

The above notwithstanding and as recently stressed, no official or unofficial body has offered any regulations or guidelines to avoid HOMP caused by ovulation induction treatments (5, 6). Indeed, it has been pointed out that data to achieve this simply do not exist (6). A recent study by Gleicher et al. (4) was cited to support the idea that specific ultrasonographic and estradiol parameters do not prevent HOMP. In fact, that study concluded that current criteria result in an unacceptably high incidence of HOMP after the induction of ovulation with gonadotropins, and the authors suggested that better criteria cannot easily be developed without negatively affecting overall pregnancy rates (4).

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However, more recent work by us (7) and others (8) has suggested that certain factors are associated with HOMP (triplets or more) after gonadotropin stimulation and if relatively conservative limits for follicular development and E_2 serum levels are rigorously applied, the number of HOMP that result from ovulation induction with exogenous gonadotropins might be significantly reduced. It has been very recently stressed that those studies suggest parameters that are clearly worthy of prospective trials to determine their actual effectiveness in practice (9).

In our previous study (7) we retrospectively analyzed a large series of 1,878 consecutive pregnancies obtained in cycles stimulated with gonadotropins. Employing univariate, multivariate, and receiver-operating characteristic analysis, we developed a three-variable model to identify patients at high risk for HOMP in ovulation induction cycles. We found that the risk of high-order multiple implantation correlated significantly with increasing total number of follicles and was significantly increased in women with a serum E_2 level >862 pg/mL and aged ≥ 32 years (7). The present study was undertaken to determine prospectively the effectiveness in clinical practice of such a prediction model.

MATERIALS AND METHODS

Between June 2001 and December 2002, there were 849 consecutive patients receiving gonadotropin ovarian stimulation or induction of ovulation without IVF for a total of 1,542 treatment cycles at the Reproductive Medicine Ser-

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TABLE 1

Observed numbers of cycles with low-order and high-order pregnancy and predicted probability of high-order pregnancy according to multivariate ordinal logistic regression analysis.[a]

Total no. of follicles >10 mm on hCG day	Peak serum E_2 ≤862 pg/mL		Peak serum E_2 >862 pg/mL	
	Age >32 y	Age ≤32 y	Age >32 y	Age ≤32 y
1 to 3 follicles				
Low-order pregnancy (n)	319	266	22	35
High-order pregnancy (n)	10	8	4	7
Probability	0.033	0.054	0.082	0.117
4 to 5 follicles				
Low-order pregnancy (n)	87	85	29	35
High-order pregnancy (n)	4	9	4	3
Probability	0.043	0.066	0.084	0.130
>5 follicles				
Low-order pregnancy (n)	66	92	67	132
High-order pregnancy (n)	2	5	7	29
Probability	0.052	0.087	0.126	0.189

[a]From Tur et al. (7).

Tur. Predicting high-order multiple pregnancy. Fertil Steril 2005.

vice, Department of Obstetrics and Gynecology, Institut Universitari Dexeus. In patients receiving more than one treatment cycle with gonadotropin, each cycle was considered to be an independent event for the analysis of results. Women were either anovulatory (n = 196 cycles) or were undergoing ovarian stimulation on an empirical basis, usually in conjunction with IUI (n = 1,346 cycles) with husband's (n = 1,138 cycles) or donor frozen-thawed (n = 208 cycles) spermatozoa. The mean (±SD) age of the patients was 33.7 ± 4.1 years. All patients provided informed consent, and the study was approved by the ethics committee of the Institut Universitari Dexeus.

Patients were administered highly purified FSH (Neo-Fertinorm; Serono S.A., Madrid, Spain) or recombinant FSH (Gonal-f; Serono S.A.). The regimen of gonadotropin administration was the chronic low-dose step-up regimen, in which the starting dose was 75 IU/d for most women (it was >85%; 37.5 IU/d in previous high responders and 150/d IU for those women aged ≥40 years or for previous poor responders). The ovarian response was monitored by serial vaginal ultrasonographic follicular measurements and serum E_2 determinations.

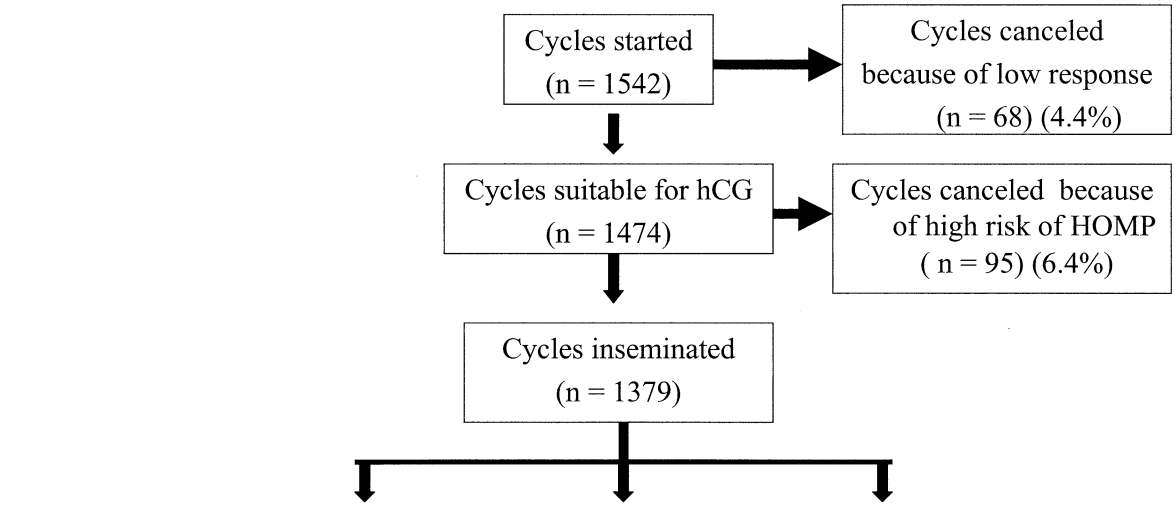
After 5–7 days of gonadotropin treatment, ultrasound scanning and E_2 serum concentration determinations were commenced to monitor stimulation progress and determine subsequent gonadotropin dose and monitoring, the length of stimulation, and the time of intercourse or insemination. Couples were counseled about the risk of multiple pregnancy according to the prediction model established in our study published elsewhere (7) (Table 1). Patients with predicted probability of HOMP >6.6% were considered to be at high risk for high-order multiple gestation and were advised to cancel the cycle (i.e., no hCG administration with a clear instruction of no unprotected intercourse), with the final decision always being the couple's.

Ovulation was triggered with the injection of hCG (5,000 IU; Profasi IM; Serono S.A.) when at least one leading follicle measuring >17 mm in diameter was detected in association with a consistent rise in serum E_2 concentration. The mean (±SD) number of follicles >10 mm observed on ultrasonography and the mean (±SD) E_2 serum levels that were reached on the day that criteria for hCG injection were fulfilled were 4.7 ± 2.2 and 410 ± 272 mg/mL, respectively. Ovulatory hCG injection was followed by timed intercourse or by IUI, as appropriate. The luteal phase was supported with two additional doses of 2,500 IU hCG (administered 4 and 7 days after the hCG ovulatory injection, respectively) or intravaginal micronized P (300 mg/d until menses occurred or until pregnancy was diagnosed), according to the ovarian response.

Pregnancy was diagnosed by positive urine and/or blood tests and by the subsequent demonstration of at least one intrauterine gestational sac by transvaginal ultrasonography at 6 weeks' gestation. Treatment cycles leading to biochemical pregnancies or ectopic gestations were excluded. The order of the multiple pregnancy was classified according to the highest number of gestational sacs observed by ultrasound imaging, including pregnancy sacs that did not contain an embryonic pole, and is referred to in the text as a multiple conception. The subsequent outcome of pregnancy was not considered for the specific purpose of this study.

FIGURE 1

Observed HOMPs in 1,542 ovulation induction cycles.



Risk of HOMP	Low risk	High risk	Low + high risk
n (%)	1067 (77.4%)	312 (22.6%)	1379
Clinical pregnancy n (%)	149 (14.0 %)	58 (18.6 %)	207 (15.0%)
T riplet pregnancies n (%)	1 (0.7%)	4 (6.9%)	5 (2.4%)

Tur. Predicting high-order multiple pregnancy. Fertil Steril 2005.

Estradiol serum concentrations were determined by RIA (Orion Diagnostica, Espoo, Finland). The interassay and intra-assay coefficients of variation were 10.2% and 9.7%, respectively. Pelvic ultrasound was performed with a 6-mHz vaginal transducer attached to a Sonolayer SSA-270A (Toshiba Co., Tokyo, Japan). Follicular sizes are the average of two dimensions, measured from the outer wall of one side of the follicle to the inner wall of the other, and corresponding to the maximum diameters of the follicle measured in both longitudinal and transverse scan planes.

For statistical analysis, the χ^2 test was used.

RESULTS

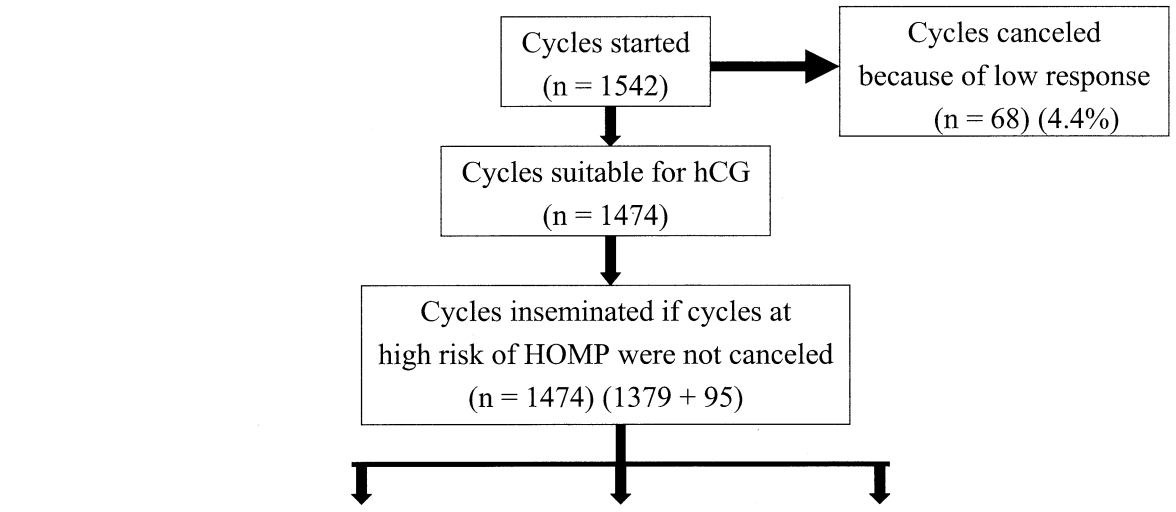
Results are summarized in Figures 1 and 2 and in Table 2. Among 1,542 started ovulation induction cycles, 68 (4.4%) were canceled because of low response to ovarian stimulation with gonadotropins (Fig. 1). Of the remaining 1,474 (95.6%) cycles suitable for hCG injection and insemination, 95 (6.4%) were canceled because couples did not accept the high risk of HOMP; thus, there was a total of 1,379 (93.6%) cycles with hCG injection and insemination. Of them, 1,067 (77.4%) cycles had low risk for HOMP according to the prediction model, and 312 (22.6%) cycles were inseminated despite the high risk of HOMP.

There was a total of 207 clinical pregnancies among 1,379 cycles inseminated, for an overall pregnancy rate of 15%. Of them, 5 (2.4%) were triplets. Pregnancy rate in cycles inseminated at low risk for HOMP was 14% (149 gestations among 1,067 treatment cycles, including 20 [13.4%] pairs of twins), and there was only one set of triplets (0.7%). In contrast, 58 (18.6%) clinical pregnancies (including 13 [22.4%] pairs of twins) were obtained in the group of 312 patients given hCG and inseminated despite high risk for HOMP, but there were four sets of triplets (6.9%). However, considering that the present study was a nonrandomized intervention trial rather than a prospective cohort, the data may be analyzed in an intention-to-treat fashion. This would change the overall pregnancy rate to 207/1,474 (14%) and the pregnancy rate in the high-risk group to 58/407 (14.2%). The HOMP rate would still be 4/58 (6.9%) in the high-risk group and 5/207 (2.4%) overall.

The predicted pregnancy rate and incidence of HOMP in the 1,474 ovulation induction cycles suitable for hCG injection and insemination when the prediction model is not applied is shown in Fig. 2. The total number of cycles inseminated would be 1,474, and of them, 407 (312 plus 95; 27.6%) would be at high risk for HOMP. Clinical pregnancies obtained in the 1,067 cycles inseminated with low risk

FIGURE 2

Predicted HOMPs with cancellation of cycles at high risk of HOMP.



Risk of HOMP	Low risk	High risk	LOW+ HIGH RISK
n (%)	1067 (72.4%)	407 (27.6%)	1474
Clinical pregnancy n (%)	149 (14.0 %)	76 (18.6 %)	225 (15.2%)
Triplet pregnancies n(%)	1 (0.7%)	5 (6.9%)	6 (2.7%)

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of HOMP would be 149 (14%), whereas 76 clinical gestations (18.6% of 407) would be obtained among patients inseminated, despite their being at high risk for HOMP. Thus, a total of 225 clinical pregnancies would result for an overall pregnancy rate of 15.2%. The number of HOMP obtained among patients being at low and high risk would be 1 (0.7%) and 5 (6.9% of 76), respectively, for a total HOMP rate of 2.7% (6 HOMP among 225 clinical gestations). The sensitivity and specificity of the prediction model were 99.3% and 80.0%, respectively. Analyzing these data as if all high-risk individuals were canceled, and using the entire population, such an analysis would yield a 407/1,474 (27.6%) cancellation rate, resulting in a 149/1,474 (10.1%) overall pregnancy rate with a 1/149 (0.7%) HOMP rate.

Table 2 summarizes pregnancy rates and the incidence of HOMP according to the use or not of the prediction model for HOMP. The use of the prediction model (implying cancellation of all cycles at high risk for HOMP) would result in an 8% (15.2 divided by 14 = 1.08; 95% confidence interval, 6.8%–9.2%) reduction of overall pregnancy rate but also in a 285% (2.7 divided by 0.7 = 3.85; 95% confidence interval, 279%–291%) reduction of HOMP. Thus, the use of the prediction model is associated with a significant reduction in HOMP but not in total pregnancy rate (Table 2).

TABLE 2

Pregnancy rates and incidence of HOMP according to the use or not of a prediction model for HOMP.

	Prediction model for HOMP applied		
Variable	Yes	No	*P*
Pregnancy rate (%)	14	15.2	NS
HOMP (%)	0.7	2.7	<.001

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DISCUSSION

The main objective of any infertility therapy is to achieve a healthy child for each couple. Multiple pregnancies jeopardize that objective and HOMP should be considered as an adverse outcome (1, 2, 10). In the last decade, the significant increase in the incidence of multiple births in most countries is almost entirely the result of the use of gonadotropins for induction of ovulation or assisted conception (1, 10). It is important to note that, according to population-based stud-

ies, as many as two thirds of iatrogenic multiple pregnancies, mainly involving triplets or more, that represent the majority of the risk usually associated with multiple birth (11–13) may be attributable to ovulation-inducing drugs without IVF or related techniques (14–18), a figure that could be even higher considering that compared with IVF programs, no reporting system on the use of ovulation-inducing drugs not associated with IVF is available (5, 6, 19). In fact, there has been greater control of IVF than ovulation stimulation (5, 16). Therefore, identification of reliable predictors of multiple pregnancy during ovulation induction cycles is clearly necessary.

Because there are no specific guidelines for preventing HOMP during ovulation induction, it has been suggested that ovulation induction should be replaced by assisted reproductive technology such as IVF (4). However, recent studies by us (7) and by others (4, 8) clearly indicate that young age and a high response to gonadotropin stimulation, as evidenced by elevated E_2 serum levels and multiple follicular development, are the main risk factors associated with HOMP. Thus, it has been suggested that these variables should form the basis for establishing appropriate guidelines (2).

Clinicians are regularly called on to make predictions of various kinds. They are asked to predict the presence of a disease from existing symptoms and signs, physical findings, and laboratory results—the task of diagnosis; they are asked to predict the occurrence of future disease on the basis of exposure to factors present in the patient and in the outside world—the task of risk assessment; and they are asked to predict the course of illness or the occurrence of a particular outcome event in patients with a known disease by using demographic factors, clinical findings, and treatments—the task of prognosis.

For the most part, clinicians have made predictions informally and nonquantitatively, working from a combination of clinical experience and published evidence; these predictions have generally served well. However, probability models are more powerful tools with which to predict the probability of clinical states. They have not been widely used for making predictions in individual patients, but they can be used in this way (20).

In the present study we tested prospectively a three-variable prediction model that, on the basis of a large series of 1,878 intrauterine pregnancies, we previously reported in a retrospective study that can identify patients who are at high risk for HOMP (7). What is demonstrated by the current study is that by using our prediction model, it is possible to maintain a low risk of HOMP with a good pregnancy rate in patients receiving gonadotropin ovarian stimulation or induction of ovulation without IVF. Thus, in conclusion, recognizing the importance of certain variables (i.e., woman's age, E_2 serum levels, and follicular development) in predicting multiple pregnancies in gonadotropin-stimulated cycles, appropriate guidelines should be established in each individual center. Several facts should be considered in this regard.

First, significantly different values of E_2 may be obtained depending on the analytical method used, the reagent manufacturer and, of importance, even when the same kits are used at different laboratories (21). Second, lack of standardization in reporting follicular measurements and intraobserver and interobserver variability is a confounding factor in ultrasonographic follicular assessment (22). Third, patients undergoing ovulation induction are a heterogeneous population, and their fecundity with therapy varies according to age, presence of other infertility factors, and clinical setting (23).

However, in a recent study by us (7), variables related to patients' clinical characteristics, treatment characteristics, and ovarian response that have been proposed as potential predictive factors of multiple pregnancy and that are readily available to the clinician were used to develop the prediction model of HOMP. Clinical variables included age of the woman, duration of infertility, type of infertility, body mass index, and basal (days 3–5 of a spontaneous or induced menses in the 3 months preceding treatment) FSH and LH concentrations. Treatment characteristics included the following: initial dose of gonadotropins, total dose of gonadotropins administered, number of days of ovarian stimulation, insemination procedure (IUI vs. timed intercourse), number of spermatozoa inseminated in patients undergoing IUI, and type of luteal support. Variables related to ovarian response included serum E_2 concentration and the number and size of follicles detected by ultrasonography on the day of the hCG injection. That study clearly showed that the possibility of HOMP in gonadotropin treatment cycles is dependent on age, serum E_2 concentrations, and the number of growing follicles on the day of hCG injection (7).

Finally, it should be noted that as many as 77.4% of patients in the present study met the low-risk definition, a result that differs significantly from another published series (8) in which treatment resulted in an average of 3.5 to 7.3 follicles sized >12 mm, depending on the woman's age. This may explained by the conservative step-up treatment approach that we used in the current investigation for ovulation induction.

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