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## REDUCING THE RISK OF HIGH-ORDER MULTIPLE PREGNANCY AFTER OVARIAN STIMULATION WITH GONADOTROPINS

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### ABSTRACT

**Background** The incidence of multiple gestation after therapy for infertility is especially high among women in whom ovulation is induced with gonadotropins. Whether the number of high-order multiple pregnancies (those with three or more fetuses) can be reduced is not known.

**Methods** We analyzed data on 3347 consecutive treatment cycles in 1494 infertile women, 441 of which resulted in pregnancy. The data collected included the peak serum estradiol concentration, the number of follicles 16 mm or larger in diameter, and the total number of follicles on the day of induction of ovulation with human chorionic gonadotropin. Receiver-operating-characteristic curves and ordinal logistic-regression analyses were used to identify values that predicted multiple conceptions.

**Results** Among the 441 pregnancies, 314 resulted from the conception of singletons, 88 of twins, 22 of triplets, 10 of quadruplets, 5 of quintuplets, and 2 of sextuplets. Neither the number of follicles 16 mm or larger nor peak serum estradiol concentrations greater than 2000 or 2500 pg per milliliter (7342 or 9178 pmol per liter) (the cutoff values currently in wide use) were significantly associated with the incidence of high-order multiple pregnancy. However, increasing total numbers of follicles and increasing peak serum estradiol concentrations correlated significantly with an increasing risk of high-order multiple pregnancy ( $P < 0.001$ ), as did younger age ( $P = 0.008$ ). The risk of high-order multiple pregnancy was significantly increased in women with a peak serum estradiol concentration of 1385 pg per milliliter (5084 pmol per liter) or higher (multivariate odds ratio, 1.9; 95 percent confidence interval, 1.3 to 2.8) or with seven or more follicles (multivariate odds ratio, 2.1; 95 percent confidence interval, 1.2 to 3.9) on the day of induction of ovulation.

**Conclusions** Gonadotropin stimulation that is less intensive than is currently customary may reduce the incidence of high-order multiple pregnancy in infertile women, though only to a limited extent and at the expense of overall pregnancy rates. (N Engl J Med 2000;343:2-7.)

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THE incidence of high-order multiple gestation, defined as a pregnancy involving three or more fetuses, has been rapidly increasing, because of the growing use of infertility treatment, especially induction of ovulation with gonadotropins and in vitro fertilization.<sup>1-3</sup> In the case of in vitro fertilization, this risk can be considerably reduced by transferring only two embryos, with minimal effect on overall pregnancy rates.<sup>4</sup> The American Society for Reproductive Medicine currently recommends the transfer of a maximum of three to five embryos that have been fertilized in vitro.<sup>5</sup> Furthermore, the ability to culture embryos to the blastocyst stage<sup>6</sup> now permits the transfer of fewer but more highly viable embryos.<sup>7,8</sup> The transfer of only two such embryos to the uterus can be expected to result in a clinical pregnancy in up to 60 percent of women.<sup>7,8</sup> High-order multiple pregnancies thus do not occur except in rare instances of monozygotic splitting.

In contrast, there is no way to reduce the risk of multiple births after induction of ovulation alone without reducing the rate of conception.<sup>9</sup> As a consequence, multiple pregnancies after induction of ovulation have come to constitute the majority of all multiple pregnancies related to infertility treatment,<sup>3</sup> and this proportion will increase as in vitro fertilization results in fewer such pregnancies. The recent increase in the incidence of multiple births after ovulation induction suggests that this treatment may now be in clinical use on a broader scale. The considerable human and financial costs of high-order multiple

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births<sup>10,11</sup> therefore necessitate a reevaluation of controlled gonadotropin-stimulated induction of ovulation. We conducted this study to assess the risk factors associated with high-order multiple pregnancies after induction of ovulation and to determine whether the incidence of such pregnancies could be reduced without adversely affecting the overall rate of pregnancy.

**METHODS**

Between January 1, 1997, and November 30, 1998, the Center for Human Reproduction–Illinois scheduled 4035 cycles of ovarian stimulation in 1661 women. Of these 4035 cycles, 688 (17.1 percent) were canceled before stimulation with gonadotropins was started, and 210 of the remaining cycles (6.3 percent) were canceled during stimulation, before the administration of human chorionic gonadotropin, leaving 3137 completed cycles for analysis (Table 1).

These completed cycles of stimulation were performed in 1494 women; their mean (±SD) age was 34±5 years. These women either were anovulatory or were undergoing ovarian stimulation on an empirical basis,<sup>12</sup> usually in conjunction with intrauterine insemination, as previously described.<sup>13</sup>

Among the 3137 completed cycles, 441 (14.1 percent) resulted in a clinical intrauterine pregnancy, defined as a sonographically confirmed pregnancy with fetal heart activity, and were analyzed in this study. In addition, there were 11 ectopic pregnancies (0.4 percent of completed cycles) and 44 pregnancies manifested only by an elevated serum chorionic gonadotropin concentration (1.4 percent of completed cycles); neither of these types of pregnancy was considered in this study. Of the 441 intrauterine pregnancies, 76 (17.2 percent, or 2.4 percent of completed cycles) ended in loss during the first trimester, and 12 (2.7 percent, or 0.4 percent of completed cycles) ended in loss during the second trimester.

Data on all treatment cycles were entered into an electronic data base and analyzed monthly. A coordinator generated monthly reports on outcomes and extracted the data to be analyzed in this study. Ovarian cycles were stimulated by administration of gonadotropins and monitored as previously described.<sup>13</sup> Serum estradiol was measured and ovarian ultrasonography was performed serially from day 4 of stimulation until peak serum estradiol concentrations were reached, at which time human chorionic gonadotropin was administered to induce ovulation. Similarly, the number of preovulatory follicles with a diameter of 16 mm or more and the total number of follicles were counted serially beginning on day 4.

The cycles of ovarian stimulation were managed by physicians according to general guidelines.<sup>14</sup> They were given a choice of various gonadotropin products, but during the latter half of 1997 and most of 1998, more than half the women were given a generic preparation of human menopausal gonadotropins (Ferring Pharmaceuticals, Tarrytown, N.Y.), described elsewhere in detail.<sup>15</sup> Institutional guidelines strongly recommended the cancellation of cycles of stimulation if serum estradiol concentrations were greater than 2500 pg per milliliter (9178 pmol per liter) or if there were six or more preovulatory follicles 16 mm or larger in diameter on the day of human chorionic gonadotropin administration; cancellation was suggested if serum estradiol concentrations were greater than 2000 pg per milliliter (7342 pmol per liter) or if there were four or five follicles 16 mm or larger in diameter.

Serum estradiol was measured with a competitive immunoassay that uses direct chemiluminescence (Automated Chemiluminescence System 180 Estradiol-6 Assay, Bayer/Chiron Diagnostics, Norwood, Mass.). The lower limit of detection of this assay is 10 pg per milliliter (37 pmol per liter).

Comparisons among the women with intrauterine pregnancies according to the number of gestations were made by one-way analysis of variance. Candidate variables for multivariate analysis were examined with use of receiver-operating-characteristic curves

**TABLE 1.** CHARACTERISTICS AND OUTCOMES OF THE CYCLES OF OVARIAN STIMULATION IN INFERTILE WOMEN.

VARIABLE	NUMBER	PERCENT OF COMPLETED CYCLES
Cycles		
Scheduled	4035	
Canceled before gonadotropin stimulation	688	
Started	3347	
Canceled during gonadotropin stimulation	210	
Completed	3137	
Clinical pregnancy	441	14.1
Loss of pregnancy		
During first trimester	76	2.4
During second trimester	12	0.4
Ectopic pregnancy	11	0.4
Pregnancy manifested only by an elevated serum chorionic gonadotropin concentration	44	1.4

and Pearson's correlations. Quintiles of the group of women defined according to the number of follicles and according to the peak serum estradiol concentration were examined with respect to the outcome of pregnancy with use of receiver-operating-characteristic curves that were constructed with SPSS software (SPSS, Chicago),<sup>16</sup> with high-order multiple pregnancy as the test state.

Multivariate ordinal logistic regression with the proportional-odds model, performed with SAS-NT software (version 6.12, SAS Institute, Cary, N.C.), was used to determine the extent to which the peak serum estradiol concentration, the total number of follicles, and the age of the woman were associated with the number of gestations. From the ordinal logistic-regression model, proportional odds for cumulative probabilities were generated. Quintiles of peak serum estradiol concentration and quintiles of the total number of follicles were transformed into four dummy variables each with the lowest level serving as the reference value. The ages of the women were entered as a continuous variable.

The C statistic, calculated with the SAS Proc Logist procedure,<sup>17</sup> was used to evaluate the predictive ability of the examined models in the form of a rank correlation. The ordered form of the dependent variable, coded as 1 (to indicate no pregnancy in a cycle), 2 (to indicate one or two gestations), or 3 (to indicate three or more gestations), yielded the highest C statistic (0.64), representing the area under the curve, and hence had the greatest predictive value. This form of the model was used to derive predicted probabilities, with all the terms simultaneously entered into the model. The statistical tests were two-sided.

**RESULTS**

Of the 441 clinical intrauterine pregnancies, 314 (71.2 percent) resulted from the conception of singletons, 88 (20.0 percent) of twins, 22 (5.0 percent) of triplets, 10 (2.3 percent) of quadruplets, 5 (1.1 percent) of quintuplets, and 2 (0.5 percent) of sextuplets. Low-order pregnancies (singletons and twins) thus made up 402 (91.2 percent) of the pregnancies, and high-order pregnancies (three or more embryos) 39 (8.8 percent) of them.

**TABLE 2. RESULTS OF UNIVARIATE ANALYSIS OF THE CORRELATION BETWEEN THE WOMAN'S AGE AND TYPE OF PREGNANCY.\***

VARIABLE	WOMAN'S AGE
	yr
Type of pregnancy	
Singleton	33±4
Twins	32±4
Triplets	32±3
Quadruplets	32±4
Quintuplets	33±4
Sextuplets	28±1
P for trend	0.008
Pregnancy order†	
Low	33±4
High	32±4
P value	0.12

\*Plus-minus values are means ±SD.

†A low-order pregnancy was defined as one involving the gestation of a singleton or twins, and a high-order pregnancy as one involving triplets, quadruplets, quintuplets, or sextuplets.

The age of the women correlated significantly with the risk of multiple pregnancy ( $P=0.008$ ), with younger women at higher risk (Table 2). The peak serum estradiol concentration and the total number of follicles, but not the number of large follicles (those  $\geq 16$  mm in diameter), also varied significantly according to the number of gestations (Table 3). Receiver-operating-characteristic curves were calculated for quintiles of the number of follicles 16 mm or more in diameter ( $\leq 6$ , 7 to 9, 10 to 14, 15 to 21, and  $\geq 22$  follicles) and quintiles of the peak serum estradiol concentrations ( $\leq 404$ , 405 to 660, 661 to 934, 935 to 1384, and  $\geq 1385$  pg per milliliter [ $\leq 1486$ , 1487 to 2426, 2427 to 3431, 3432 to 5083, and  $\geq 5084$  pmol per liter]). Only the quintiles of the peak serum estradiol concentration and the total number of follicles yielded areas under the curve that indicated that their respective increasing values were predictive of high-order multiple pregnancies.

A correlation matrix revealed that the peak serum estradiol concentration and the total number of follicles were directly correlated with the incidence of high-order multiple pregnancy (for peak serum estradiol concentration:  $r=0.24$ ,  $P<0.001$ ; for total number of follicles:  $r=0.26$ ,  $P<0.001$ ). Age was inversely correlated with the incidence of high-order multiple pregnancy ( $r=-0.14$ ,  $P=0.008$ ). There was no correlation between the number of follicles 16 mm or more in diameter and the incidence of high-order multiple pregnancies.

Table 4 summarizes the number of cycles with no

**TABLE 3. SERUM ESTRADIOL CONCENTRATIONS, NUMBERS OF LARGE FOLLICLES, AND TOTAL NUMBERS OF FOLLICLES IN THE WOMEN WITH CLINICAL INTRAUTERINE PREGNANCIES.\***

VARIABLE	PEAK SERUM ESTRADIOL pg/ml	NO. OF FOLLICLES	
		LARGE ( $\geq 16$ mm)	TOTAL
Outcome of pregnancy			
Singleton	978±671	3.0±1.9	17.2±10.1
Twins	1458±922	4.0±2.0	20.6±9.0
Triplets	1534±367	2.9±1.6	24.2±10.0
Quadruplets	1506±921	3.0±1.6	24.8±15.2
Quintuplets	1168±511	2.6±0.9	29.4±9.3
Sextuplets	1573±921	2.0±1.4	30.0±14.1
P for trend	<0.001	0.78	<0.001
Pregnancy order†			
Low	1057±716	3.2±2.0	17.8±10.0
High	1482±583	2.8±1.5	25.3±11.3
P value	<0.001	0.31	<0.001

\*Plus-minus values are means ±SD. Numbers of follicles are the numbers on the day of administration of human chorionic gonadotropin. To convert the values for serum estradiol to picomoles per liter, multiply by 3.671.

†A low-order pregnancy was defined as one resulting in a singleton or twins, and a high-order pregnancy as one resulting in triplets, quadruplets, quintuplets, or sextuplets.

pregnancy, low-order pregnancy (singleton or twins), or high-order multiple pregnancy and the respective predicted probability of pregnancy, after adjustment for age, according to multivariate ordinal logistic regression. Table 5 presents an ordinal logistic-regression model of increasing incidence of multiple pregnancy according to the total number of follicles at the time of administration of human chorionic gonadotropin, the peak serum estradiol concentration, and age of the woman. For example, a peak serum estradiol concentration of 1385 pg per milliliter or higher was associated with a significantly increased risk of a high-order multiple pregnancy (adjusted odds ratio, 1.9;  $P=0.002$ ), as was the presence of seven to nine follicles (adjusted odds ratio, 2.1;  $P=0.01$ ). In fact, adjustment for all the terms in this model suggested that for the peak serum estradiol concentration and the total number of follicles, these are the respective threshold values that indicate an increased risk of high-order multiple pregnancy. The data also demonstrate that this risk increases further with increasing serum estradiol concentrations and increasing total numbers of follicles (and with younger age).

Table 4 also permits assessment of the effect of terminating or continuing cycles characterized by certain combinations of serum estradiol concentrations and total numbers of follicles. For example, when the number of follicles exceeds nine and the highest quintile for the peak serum estradiol concentration ( $\geq 1385$  pg per milliliter) is reached, the probability of pregnancy starts to exceed that of no pregnancy.

**TABLE 4.** OBSERVED NUMBERS OF CYCLES WITH PREGNANCY AND PREDICTED PROBABILITY OF PREGNANCY, ACCORDING TO MULTIVARIATE ORDINAL LOGISTIC-REGRESSION ANALYSIS.\*

TOTAL NO. OF FOLLICLES	≤404 pg/ml		405–660 pg/ml		661–934 pg/ml		935–1384 pg/ml		≥1385 pg/ml	
	no.	probability	no.	probability	no.	probability	no.	probability	no.	probability
≤6 Follicles										
No pregnancy	173	0.82	100	0.79	58	0.78	23	0.77	6	0.70
Low-order	7	0.16	5	0.19	3	0.20	0	0.20	0	0.26
High-order	0	0.02	0	0.02	0	0.02	0	0.03	0	0.04
7–9 Follicles										
No pregnancy	128	0.67	160	0.64	99	0.62	55	0.61	12	0.52
Low-order	8	0.28	21	0.30	8	0.32	5	0.33	3	0.40
High-order	0	0.05	0	0.06	0	0.06	0	0.06	0	0.08
10–14 Follicles										
No pregnancy	125	0.63	142	0.59	193	0.57	172	0.56	58	0.47
Low-order	16	0.32	13	0.35	27	0.36	15	0.37	16	0.43
High-order	0	0.05	1	0.06	0	0.07	4	0.07	2	0.10
15–21 Follicles										
No pregnancy	66	0.56	87	0.58	110	0.56	151	0.55	153	0.46
Low-order	11	0.38	12	0.36	15	0.37	24	0.38	20	0.44
High-order	0	0.06	0	0.06	3	0.07	5	0.07	3	0.10
≥22 Follicles										
No pregnancy	55	0.60	53	0.55	69	0.54	119	0.53	257	0.44
Low-order	6	0.34	6	0.38	10	0.39	20	0.40	50	0.45
High-order	0	0.06	0	0.07	1	0.07	3	0.07	17	0.11

\*Values for the probability of various outcomes have been adjusted for age. To convert the values for serum estradiol to picomoles per liter, multiply by 3.671. Cycles shown are those for which complete data sets were available for analysis.

Consequently, the equations used in the construction of Table 4 predict that, after adjustment for age, a woman with a peak serum estradiol concentration of 1385 pg per milliliter but only seven follicles has an 8 percent risk of a high-order multiple pregnancy, a 40 percent risk of a low-order pregnancy, and a 52 percent chance of not becoming pregnant at all.

**DISCUSSION**

The availability of a large data set, prospectively collected for quality-review purposes, gave us the opportunity to examine the appropriateness of the current guidelines for controlled ovarian stimulation with gonadotropins. Our results confirm long-recognized correlation of a woman’s age, peak serum estradiol concentration, and number of follicles with the risk of multiple pregnancy.<sup>14</sup> The results also suggest that the peak serum estradiol concentration and the total number of follicles are independent predictors of the risk of high-order multiple pregnancy but that the number of follicles with a diameter of 16 mm or more is not. This finding is surprising, since large follicles are believed to contain the most mature oocytes, which have the greatest potential to lead to pregnancy. It is for that reason that the size and number of preovulatory follicles have been considered important in the medical monitoring of women undergoing ovarian stimulation with gonadotropins.<sup>13,14</sup>

These findings suggest that current guidelines may be inadequate for reducing the incidence of high-

**TABLE 5.** INCIDENCE OF AND ODDS RATIOS FOR PREGNANCY ACCORDING TO QUINTILES OF TOTAL NUMBERS OF FOLLICLES AND PEAK SERUM ESTRADIOL CONCENTRATIONS AND THE AGE OF THE WOMAN, ACCORDING TO ORDINAL LOGISTIC-REGRESSION ANALYSIS.\*

VARIABLE	INCIDENCE OF HIGH-ORDER MULTIPLE PREGNANCY (%)	INCIDENCE OF PREGNANCY (%)	ADJUSTED ODDS RATIO (95% CI)
Peak serum estradiol (pg/ml)			
≤404	0.0	1.6	1.0
405–660	0.0	1.9	1.2 (0.8–1.8)
661–934	0.1	2.2	1.3 (0.9–1.9)
935–1384	0.4	2.5	1.3 (0.9–2.0)
≥1385	0.7	3.7	1.9 (1.3–2.8)
Total no. of follicles			
<7	0.0	0.5	1.0
7–9	0.0	1.5	2.1 (1.2–3.4)
10–14	0.2	3.1	2.6 (1.5–4.7)
15–21	0.4	3.1	2.8 (1.5–5.0)
≥22	0.7	3.8	3.0 (1.6–5.4)
Age (yr)	—	—	1.0 (0.9–1.0)

\*In this model, the three variables (serum estradiol concentration, total number of follicles, and age) were considered simultaneously. Odds ratios were modeled as 0 (no pregnancy), 1 (singleton or twins), or 3 (triplets, quadruplets, quintuplets, or sextuplets). CI denotes confidence interval. To convert the values for serum estradiol to picomoles per liter, multiply by 3.671. The ordinal logistic-regression equations used to construct this table are available from the authors.

order multiple pregnancies. Since the total number of follicles is often difficult to determine by ultrasonography, and since the number of large follicles (those  $\geq 16$  mm in diameter) was found not to be predictive of high-order multiple pregnancy, ultrasonography may not be a valuable tool in reducing the risk of this outcome. Whether information on peak serum estradiol concentrations can be used to reduce this risk also needs to be questioned. Our findings suggest that conservative stimulation, to a maximal serum estradiol concentration of only 1385 pg per milliliter, may reduce the incidence of high-order multiple pregnancy. A 27-year-old woman with as few as seven follicles would, however, still have a 2 percent risk of a high-order multiple pregnancy, which is almost double the risk of high-order multiple pregnancy for all patients in this study, independent of age. (The multivariate ordinal logistic-regression equations used in these calculations are available from the authors.) Such a risk must be considered unacceptably high. A lesser degree of stimulation, resulting in even lower peak serum estradiol concentrations, could further decrease the incidence of high-order multiple pregnancy but would also increase the number of cycle cancellations and therefore diminish rates of pregnancy and raise costs.

Clinicians have been instinctively aware of this fact when administering gonadotropins to raise serum estradiol concentrations to 2000 or even 2500 pg per milliliter.<sup>14</sup> In this study, only one high-order multiple pregnancy occurred in a woman whose peak serum estradiol concentration exceeded 2500 pg per milliliter, and only five high-order multiple pregnancies occurred in women whose peak serum estradiol concentrations were between 2000 and 2500 pg per milliliter. None of these five women had a peak serum estradiol concentration that exceeded 2257 pg per milliliter (8285 pmol per liter). These observations suggest not only that current criteria for clinical monitoring are inadequate to prevent a high incidence of high-order multiple births but also that better criteria cannot easily be established, given the currently available technology.

The principal weakness of this study lies in its retrospective analysis of the data on gonadotropin stimulation. It could be argued that the results of a stimulation protocol with a goal of much lower peak serum estradiol concentrations and possibly also fewer follicles would differ from those of stimulation protocols that aim to achieve the higher peak serum estradiol concentrations and numbers of follicles currently used as cutoff values. In other words, the outcomes of a lesser degree of stimulation, in terms of both rates of pregnancy and rates of high-order multiple pregnancy, may not be comparable to the results of more aggressive stimulation protocols currently in use. Although, in view of past clinical experience, such a possibility appears unlikely, it cannot be complete-

ly dismissed. Especially in younger women with normal ovarian function, in whom the risk of high-order multiple pregnancy is highest, a prospective study comparing reduced with aggressive stimulation may therefore be indicated.

Women with infertility, however, first and foremost demand high rates of pregnancy, which may entail a relatively high risk of low-order multiple pregnancy.<sup>18</sup> The ideal treatment for infertility would eliminate the expectation that high rates of pregnancy automatically lead to high rates of multiple pregnancy, as occurs with controlled ovarian stimulation.<sup>9</sup>

Whether the use of controlled ovarian stimulation with gonadotropins still makes sense in the environment of medical practice today should therefore be questioned. In contrast to ovarian stimulation, in vitro fertilization allows better control over the risk of a high-order multiple pregnancy. In addition, with in vitro fertilization one can achieve higher overall pregnancy rates<sup>7,8</sup> without ignoring the strong desire of many couples to conceive twins.<sup>18</sup> In the short term, in vitro fertilization can increase costs.<sup>19</sup> However, a single very premature delivery, resulting from high-order multiple gestation, can be very costly. Consequently, the prevention of only one such delivery may compensate for the short-term differences in cost between several cycles of ovarian stimulation and in vitro fertilization, without even taking into account the considerable additional expense families incur as a consequence of the lifelong handicaps of many prematurely delivered infants. Therefore, considering the potential human and financial costs of high-order multiple pregnancies,<sup>10,11</sup> we question a treatment algorithm that exposes women to a substantial risk of high-order multiple pregnancy when the alternative of in vitro fertilization is readily available and can potentially eliminate this risk.<sup>7,8</sup>

In conclusion, our results suggest that current criteria result in an unacceptably high incidence of high-order multiple pregnancies after the induction of ovulation with gonadotropins. This study also suggests that better criteria cannot easily be developed without negatively affecting overall pregnancy rates. The findings therefore raise the question whether the induction of ovulation with gonadotropins should not be replaced by in vitro fertilization.

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