Low Multiple Pregnancy Rates and Reduced Frequency of Cancellation After Ovulation Induction with Gonadotropins, If Eventual Supernumerary Follicles Are Aspirated to Prevent Polyovulation

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Purpose: Our purpose was to demonstrate the feasibility of the routine aspiration of supernumerary follicles in infertile patients with imminent polyovulation after ovulation induction with gonadotropins and to examine its effect on the frequency of cycle cancellation and on the (multiple) pregnancy rate.

Methods: The data on 796 treatment cycles, performed between 1989 and 1996 on 410 infertile couples, were analyzed retrospectively. From October 1992, whenever necessary, supernumerary ovarian follicles were selectively aspirated transvaginally under ultrasound guidance to prevent the ovulation of more than three follicles. Thereafter, intrauterine insemination was performed.

Results: After the adoption of transvaginal ultrasound-guided aspiration of supernumerary follicles into the treatment protocol in October 1992, the number of canceled cycles ($P < 0.0001$) and the multiple pregnancy rate ($P < 0.01$) were significantly reduced compared to those previously. The overall pregnancy rate remained stable. No ovarian hyperstimulation syndrome requiring hospitalization was noted, and no complications resulting from the follicle aspiration were registered.

Conclusions: Transvaginal ultrasound-guided aspiration of supernumerary ovarian follicles increases both the efficacy and the safety of ovulation induction with gonadotropins. Because of the limited equipment required, this method represents an alternative for conversion of overstimulated cycles to more costly alternatives such as in vitro fertilization.

KEY WORDS: intrauterine insemination; ovulation induction; ultrasound-guided follicle puncture; ovarian stimulation; multiple pregnancy.

INTRODUCTION

Since the beginning of the 1980s several countries have experienced an abrupt increase in the number of deliveries of multiples (1–3). Multiple pregnancies are associated with a significantly higher fetal morbidity and mortality, an increased cost, and much more strain on neonatal care facilities (3). Furthermore, the parenthood of triplets and other high-grade multiples leads to depression and social isolation (4). The recent increase in multiple births is caused by the rapid development of modern reproductive medicine, which relies heavily on concomitant stimulation of ovarian function. Modern reproductive medicine appears to have reversed a demographic trend, characterized by previously slowly declining rates of dizygotic twinning (5). Although in vitro fertilization (IVF) has been blamed for most of the excess multiple pregnancies occurring nowadays, it has been demonstrated that not assisted reproduction technology (ART), but rather simple ovulation induction without ART, contributes to the majority of high-order multiple pregnancies (33.3 to 50%)(1–3). In ART the frequency of high-order multiple pregnancies can be limited effectively by reducing the number of replaced oocytes and embryos without compromising the overall pregnancy rates (6–9). However, ovarian stimulation with clomiphene citrate or with gonadotropins is used outside the centers specializing in ART on a much larger scale and the degree of multiple ovulation is only moderately controlled by additional monitoring with ultrasound and serial estradiol determinations (10).

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Ultrasound-guided selective aspiration of supernumerary follicles prior to ovulation has been used in the past to prevent high-grade multiple pregnancies in patients suffering from polycystic ovaries (11–13). The successful prevention of high-grade multiple pregnancies by transvaginal ultrasound-guided aspiration of supernumerary ovarian follicles was studied in a prospective setting in patients with various causes of infertility (14). The feasibility of the routine use of the preovulatory aspiration of supernumerary follicles in a large patient collective and its effect on the cancellation and the multiple pregnancy rates are demonstrated in the present study.

MATERIALS AND METHODS

The results of 796 treatment cycles performed between 1989 and 1996 in 410 couples were reviewed. At initial treatment the women's median age was 32 years, ranging between 23 and 44 years. The husband's median age was 35 years, ranging between 24 and 73 years. The median duration of infertility was 5 years, ranging between 1 and 18 years. Male infertility was the main cause of infertility in 294 couples (71.7%), incipient ovarian failure [third cycle day serum follicle stimulating hormone (FSH) concentration >12 U/L] in 11 couples (2.7%), polycystic ovarian disease (PCOD) in 52 couples (12.7%), hypogonadotropic hypogonadism in 8 women (2.0%), and unexplained infertility in 45 couples (11.0%).

In all treatments the ovaries were stimulated with human urinary gonadotropins (Pergonal; Serono, Unterschleißheim, Germany; and Ferring HP; Serono), followed by ovulation induction with human chorionic gonadotropin (hCG; 10,000 IU; Choragon; Ferring, Kiel, Germany) and by intrauterine insemination (IUI) with sperm prepared following the swim-up protocol (15). The use of IUI even in the presence of normal semen quality was based on our therapeutic principle, in which infertility is treated with medical means only and any intentional interference with the private and sexual relationship of the couple is avoided. All couples were informed about the rationale of the treatment and the risk of multiple pregnancies, and written consent was obtained prior to treatment.

The patients treated because of male and unexplained infertility and because of incipient hypergonadotropaemic ovarian failure were given human urinary gonadotropins combined with a gonadotropin releasing hormone (GnRH) analogue (decapeptyl, 0.5 mg; Ferring) following the ultrashort protocol described elsewhere (16). The stimulatory dosage of the urinary

gonadotropin preparation applied during the initial 4 days of follicular development consisted of 1 or of 2 ampoules daily. Thereafter, the daily dosage was increased stepwise according to the individual patient's needs as assessed with ultrasound and based on serum estradiol concentration. In patients with PCOD ovaries ovarian stimulation was performed exclusively following the low-dose FSH protocol described elsewhere (17). Follicular development was monitored by frequent measurements of estradiol concentrations in the serum and by repeated vaginal ultrasound examinations. A first IUI with swim-up sperm was performed 36 hr after ovulation induction and a second IUI 40 hr after ovulation induction. A disposable catheter (modified Shepard Catheter; Cook, Mönchengladbach, Germany) equipped with a sterile tuberculin syringe was used for each intrauterine transfer of 0.2 ml of the sperm dissolved in culture medium (modified Ham's F10 medium). Semen analysis was performed following WHO guidelines (18). The luteal phase was supported with repeated injections of human chorionic gonadotropin (hCG). Pregnancy was diagnosed by repeated measurements of the hCG concentration in the serum and by vaginal ultrasound examinations.

The procedure of selective aspiration of supernumerary follicles has been described in detail elsewhere (14). Briefly, if on the day of ovulation induction with hCG, more than three ovarian follicles with a mean diameter of at least 14 mm were revealed by ultrasound (mean of two measurements of each visible follicle), the couple was informed about the risk of a high-grade multiple pregnancy and ultrasound-guided transvaginal aspiration of the supernumerary ovarian follicles was performed on the day of IUI as an outpatient procedure. Follicles were punctured freehandedly with a disposable monoluminal needle (Swemed Lab, Frölunda, Sweden). The three largest follicles were left intact. We attempted to leave one large follicle in each ovary and to aspirate only the smaller follicles. The number of aspirated cumulus-oocyte complexes was counted under a stereomicroscope and they were immediately discarded.

Statistical analysis was performed using the Kruskal-Wallis test, Mann-Whitney *U* test, and chi-square analysis as appropriate. Statistical significance was set at the 5% level.

RESULTS

In the present retrospective study the data of 796 treatment cycles performed from 1989 to 1996 in 410

infertile couples were analyzed retrospectively. The mean number of treatment cycles per couple was 1.94, ranging between 1 and 5 cycles. The mean sperm concentration in the semen sample was 60 million/ml, ranging between 0.3 and 392 million/ml. The median progressive motility of sperm in the seminal plasma was 49%, ranging between 0 and 79%. The median rate of normally formed sperm in the semen was 24%, ranging between 2 and 70%. Pregnancy was defined by the measurement of rising hCG concentrations in the serum. The combined use of ovulation induction with gonadotropins and IUI resulted in 163 pregnancies (pregnancy rate per couple: 39.8%). The pregnancy rate per treatment cycle was 20.5%. Among these pregnancies 39 miscarriages (23.9%), 7 tubal pregnancies (4.3%), and 20 multiple pregnancies (12.3%) were diagnosed. Fifteen pregnancies were twins (9.2%), and five pregnancies were triplets (3.1%). Originally, in two pregnancies a quadruplet and a quintuplet pregnancy were diagnosed, each necessitating selective fetal reduction to triplets. Thereafter, each patient later delivered healthy triplets. During the course of the present retrospective analysis no ovarian hyperstimulation syndrome requiring hospitalization was noted.

Motivated by the experience of several uncontrolled polyovulations leading to high-grade multiple pregnancies in two patients, the ultrasound-guided selective aspiration of one or more supernumerary ovarian follicles was first introduced in October 1992 to prevent the ovulation of more than three follicles. Since October 1992, 257 ultrasound-guided aspirations of supernumerary ovarian follicles were performed to prevent the ovulation of more than three follicles, corresponding to 45.0% of all treatment cycles within this period.

The effect of the aspiration of supernumerary preovulatory follicles on the outcome of ovulation induc-

tion and IUI listed according the various causes of infertility is summarized in Table I. Since the change of the protocol in October 1992 significantly fewer multiple pregnancies were induced in couples treated because of male infertility ($P < 0.02$) and in the overall population ($P < 0.01$). Significantly fewer pregnancies and no multiple pregnancies at all were observed in patients suffering of incipient ovarian failure. Confronted with the alternative of cancellation of the treatment cycle, no patient refused the preovulatory aspiration of supernumerary follicle. In 257 interventions no complications such as intraabdominal bleedings or infections were noted.

The outcome of ovulation induction and IUI before and after the modification of the treatment protocol in October 1992 are summarized in Table II. When the couples' and treatment characteristics before and after October 1992 were compared, the duration of infertility became significantly shorter ($P < 0.001$), but the age of the patients remained similar. The number of ampoules of human urinary gonadotropin administered increased after October 1992 ($P < 0.0001$), and ovarian stimulation lasted significantly longer ($P < 0.0001$).

The routine aspiration of eventual supernumerary follicles prior to IUI, which was introduced into the protocol in October 1992 (Fig. 1), was associated with a significant reduction in the number of canceled treatment cycles ($P < 0.0001$) and with a significant decrease in the number of multiple pregnancies ($P < 0.01$). After October 1992 most cancellations were due to inadequate ovarian reaction to stimulation with gonadotropins (24; 51.1%), 11 due to absence of ovulation (23.4%) and 12 due to an exceedingly exaggerated number of maturing follicles in both ovaries (25.5%). In the patients treated with gonadotropins and IUI after October 1992 and left without aspiration of supernumerary follicles, the multiple pregnancy rate was 3.5%;

Table I. Number of Pregnancies (Rate per Cycle) and Number of Multiples (Rate per Pregnancy) After Ovulation Induction with Gonadotropins and IUI Before and After October 1992, Together with Frequency of Aspiration of Supernumerary Follicles (per Cycle), Listed According to the Main Causes of Infertility (Chi-Square Analysis)

Cause of infertility	Before October 1992			Since October 1992			
	Cycles	Pregnancies	Multiple pregnancies	Cycles	Aspirations	Pregnancies	Multiple pregnancies
Male infertility	161	35 (21.7%)	9 (25.7%)*	420	198 (47.1%)	82 (19.5%)	9 (11.0%)*
Incipient ovarian failure	5	0	0	16	2 (12.5%)	2 (12.5%)	0
Polycystic ovaries	25	8 (32.0%)	0	77	28 (36.4%)	16 (20.8%)	1 (6.3%)
Unexplained infertility	35	3 (8.6%)	0	57	29 (50.9%)	17 (29.8%)	1 (1.8%)
All indications	226	46 (20.4%)	9 (19.6%)**	570	257 (45.1%)	117 (20.5%)	11 (9.4%)**

*Statistically significant difference, $P < 0.02$.

**Statistically significant difference, $P < 0.01$.

Table II. Patients' Characteristics, Ovarian Stimulation Modalities, and Outcome of Ovulation Induction and IUI as Influenced by Ultrasound-Guided Aspiration of Supernumerary Follicles Since October 1992 (Mean with 95% Confidence Interval)

	Before October 1992	After October 1992	Significance
Couples treated	124	316	
Treatment cycles	225	571	
Aspirations	0	257 (45.0%)	
Duration of infertility (yr)	6.3 (± 0.2)	5.3 (± 0.1)	$P < 0.001^a$
Patient's age (yr)	32.9 (± 0.3)	32.7 (± 0.2)	n.s. ^a
Husband's age (yr)	35.7 (± 4.2)	38.6 (± 2.6)	n.s. ^a
Ampoules administered	20.0 (± 1.1)	26.7 (± 0.7)	$P < 0.0001^a$
Stimulated days	12.0 (± 0.2)	13.0 (± 0.1)	$P < 0.0001^a$
Max. estradiol conc. (nM)	2.6 (± 0.1)	2.8 (± 0.1)	n.s. ^a
Canceled cycles	76 (20.9%)	47 (8.2%)	$P < 0.0001^b$
Pregnancies (rate per cycle)	45 (20.0%)	118 (20.7%)	n.s. ^b
Miscarriages (/pregnancy)	16 (35.6%)	21 (17.8%)	$P < 0.001^b$
Ectopic rate (/pregnancy)	2 (4.4%)	6 (5.1%)	n.s. ^c
Twin pregnancies (/pregnancy)	6 (13.3%)	9 (7.6%)	$P < 0.01^c$
Triplet pregnancies (/pregnancy)	1 (2.2%)	2 (1.7%)	n.s. ^c
High-order multiple pregnancies (/pregnancy)	2 (4.4%)	0	n.s. ^c
Multiple pregnancies (/pregnancy)	9 (4.0%)	11 (1.9%)	$P < 0.01^c$

^aMann-Whitney *U* test.^bChi-square test.^cFisher's exact test.

in those treated with ultrasound-guided aspiration, 1.2%. The overall pregnancy rate and the rate of ectopic pregnancies remained unchanged, whereas the miscarriage rate dropped ($P < 0.001$).

DISCUSSION

Although ICSI represents successful treatment of severe forms of male infertility, many couples suffer-

ing from minor abnormalities of seminal quality can still be treated with IUI. The benefits of IUI with washed spermatozoa in patients with male infertility have been demonstrated repeatedly (19–21). Both retrospective (22,23) and prospective (24–26) studies clearly indicated that the efficacy of IUI can be improved considerably by the concomitant stimulation of ovarian function with gonadotropins. The main disadvantage of ovarian stimulation, however, is the risk of multiple pregnancies, which varies between 16 and

Fig. 1. Selective transvaginal ultrasound-guided aspiration of supernumerary ovarian follicles prior to IUI in a 39-year-old patient suffering from male infertility. The sonographic printout represents a stimulated ovary with a large number of preovulatory follicles prior to (A) and after (B) the reduction of supernumerary follicles. Treatment was successful and resulted in an intact singleton pregnancy.

66% (27), involving twins in 23.3% of the cases, triplets in 3.4%, and high-grade multiple pregnancies in 2.2%. Intensive monitoring of the follicular phase with ultrasound and repeated measurements of the serum level of estradiol are necessary to detect the imminent ovulation of more than three ovarian follicles and to prevent high-grade multiple pregnancies. If more than three ovarian follicles are prone to rupture, the treatment may be cancelled and another trial may be started later. Such cancellation of gonadotropin treatment tends to be repeated in the same patients (28), is highly frustrating for both patients and physicians, and causes considerable loss of financial resources.

In several reports the use of selective aspiration of supernumerary follicles shortly before ovulation for the prevention of multiple pregnancies after gonadotropin stimulation was described for patients suffering from polycystic ovaries (11–13). Starting from these initial and limited experiences, the effective prevention of multiple pregnancies in conjunction with a high success rate of ovulation induction and IUI was examined systematically in two prospective studies published recently (14). For obvious ethical reasons preovulatory aspiration of supernumerary follicles could not be compared in a randomized setting with unopposed polyovulation directly. Therefore, the value of the present analysis consists of demonstrating the effect of routine preovulatory aspiration of supernumerary follicles on the outcome of ovulation induction in a large patient population by retrospective comparison with the results of earlier treatments in a patient population in which some polyovulations were certainly unforeseen.

The presentation of the results demonstrated that the duration of infertility became shorter between 1989 and 1996, a trend observed previously by others (29). However, the age of the patients did not change with time and the overall pregnancy rate was maintained. After the modification of the treatment protocol in October 1992, significantly fewer treatment cycles had to be canceled ($P < 0.0001$). The reduced cancellation rate may have permitted the induction of 14 additional pregnancies after October 1992. Some cancellations were still necessary after October 1992, because in the presence of more than 10 follicles in each ovary the option of ultrasound-guided aspiration may not entirely prevent supernumerary ovulations. Furthermore, significantly fewer multiple pregnancies ($P < 0.01$) and no high-grade multiple pregnancies were induced since the introduction of the ultrasound-guided aspiration of supernumerary follicles in October 1992. The number

of aspirations was found to be high throughout the observation period (i.e., 45.0%), but it has been shown previously that the frequency of aspirations can be significantly reduced without compromising the pregnancy rate by lowering the gonadotropin dosage during the recruitment phase of follicular development (14). The use of a low-dose gonadotropin protocol during the recruitment phase in normogonadotropinaemic patients does not reduce the total number of administered ampoules, because the slower follicular growth prolongs the duration of gonadotropin administration. The higher numbers of gonadotropin ampoules administered and the longer duration of follicular development also reflect less concern with uncontrolled polyovulation, permitting better timing of ovulation induction in the individual patient.

Confronted with the imminent ovulation of too many follicles, the couple has the choice of three options: cancellation of the cycle, aspiration of the follicles discarding the supernumerary oocytes, and converting the treatment strategy to IVF. Cancellation of the treatment causes a considerable loss of financial resources without issue. Conversion of the treatment cycle to IVF necessitates the unforeseen and immediate investment of considerable additional financial resources and involves extensive laboratory equipment including cryopreservation. Only a limited infrastructure is required for IUI and the technique of ultrasound-guided follicular aspiration for the prevention of multiple pregnancies is cheap and nearly free of complications. The present data demonstrate that ultrasound-guided aspiration of supernumerary follicles on a routine basis is feasible and acceptable to patients with imminent polyovulation within the organizational structure of a single treatment center.

To reduce the number of multiple pregnancies induced by clomiphene and gonadotropin stimulations by gynecologic practitioners in the city of Basel, Switzerland, we are currently preparing a centralized organization of ultrasound-guided transvaginal aspirations of supernumerary follicles whenever needed. Future experience with such a centralized setting will demonstrate to what extent aspiration of supernumerary follicles is accepted by both patients and gynecologic practitioners and whether the regional rate of multiple births can be lowered effectively.

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