Case Reports

COMBINED PREGNANCY AFTER GONADOTROPIN THERAPY

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Three cases of combined pregnancy are described after gonadotropin therapy; two cases after human pituitary gonadotropin and one after human menopausal gonadotropin administration. In each case the intrauterine gestation was a multiple pregnancy. After salpingectomy, two of the women have proceeded to the delivery of healthy infants; the third woman aborted. In each case the gonadotropin stimulation regimen was ceased at the appropriate stage when the estriol excretion was between 60 and 125 μg/day, but the subsequent rate of rise of estriol was 2.3- to 3.2-fold during the coasting phase before the human chorionic gonadotropin trigger when the estriol excretion rate was 140 to 350 μg/day. (*Obstet Gynecol 64:855, 1984*)

The simultaneous presence of an intrauterine and extrauterine gestation is known as a heterotopic or combined pregnancy. It is generally thought to be a rare event with an incidence of around one in 30,000.[1] This figure was derived by calculating the proportion of ectopic pregnancies expected in cases of dizygotic twins. The incidence figures applied by De Voe and Pratt[1] were 0.37 and 0.8%, respectively, and were derived from a review of the literature. It readily can be appreciated that the natural incidence in any community is most dependent upon the rate of ectopic pregnancy, as there appears to be little fluctuation in the rate of spontaneous twinning. Figures derived from the major hospitals in Western Australia over the last five years reveal an increase in admissions for ectopic pregnancy, consistent with a rate closer to that reported by Kitchin et al[2] of around 0.8%. This would raise the spontaneous rate of combined pregnancy to around one in 15,000. As the other variable is the multiple pregnancy rate derived from separate ovulations, it may be expected that combined pregnancies will arise more often after ovulation induction. The present report documents three such cases arising in a program of ovulation induction using gonadotropin therapy, both with human menopausal gonadotropin and human pituitary gonadotropin. Some of the reported cases of combined pregnancy have arisen after ovulation induction with clomiphene[3,4] and gonadotropin therapy,[4–6] including a case of simultaneous tubal and intrauterine multiple pregnancy following human menopausal gonadotropin administration.[7]

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Materials and Methods

Three patients who experienced combined pregnancy were derived from a group of 42 women undergoing gonadotropin therapy for the induction of ovulation over a three-year period beginning in 1980. Of the 26 pregnancies from this group, five were multiple gestations, three of which proved to be combined. The three women, aged between 28 and 38 years, had long-standing infertility (longer than five years), and each was shown to be anovulatory with oligomenorrheic cycles. They had never used an intrauterine device, and each underwent preliminary laparoscopic appraisal before ovulation induction therapy. No woman had any evidence of pelvic pathology. The fallopian tubes were anatomically normal, and there was no evidence of endometriosis, pelvic inflammatory disease, or adhesions. One woman had 6-cm polycystic ovaries with mildly elevated serum luteinizing hormone (LH) levels, but otherwise the serum prolactin and gonadotropin estimations were normal in each case. Each had previously been treated with clomiphene and clomiphene/human chorionic gonadotropin (hCG) without success, and one had undergone three months' treatment with a gonadotropin-releasing hormone pulsatile pump. The treatment schedule for all patients was the incremental regimen advised by Brown and associates.[8,9] Human pituitary gonadotropin was supplied by the Australian Pituitary Advisory Committee, and levels are expressed in IU per gland (average yield, 75 to 100 IU follicle-stimulating hormone [FSH] per gland) as assessed by the

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Table 1. Treatment Details and Outcome of Three Women with Combined Pregnancy

Subject no.	FSH/LH preparation	FSH (IU)		Estriol (μg/day)		hCG (IU)	Ultrasound follicle sizes on day of hCG	Midluteal progesterone (nmol/L)	Pregnancy outcome	
		Maximum dose per day	Total dose	Day of last FSH/LH	Day of hCG					
1	hPG	370	1500	125	320	3000	<1.4 cm (several)	160	Salpingectomy Abortion	11 wk 14 wk
2	hMG	375	2925	60	140	5000	Not performed	591	Salpingectomy Healthy triplets	8 wk 36 wk
3	hPG	420	1250	110	350	3000	1.8 cm (3) 1.4–1.6 cm (2)	273	Salpingectomy Healthy twins	8 wk 36 wk

FSH = follicle-stimulating hormone; LH = luteinizing hormone; hCG = human chorionic gonadotropin; hPG = human pituitary gonadotropin; hMG = human menopausal gonadotropin.

Steelman-Pohley bioassay against a Commonwealth Serum Laboratories working standard of pituitary FSH (primary standard: First International Reference Preparation of hPG, FSH, and LH, for bioassay). Human pituitary gonadotropin* contains 75 IU of FSH and 75 IU of LH measured by biologic assay standardized in terms of the Second International Reference Preparation for hMG. The dose of hCG† is estimated by a biologic assay standardized in terms of the Second International Reference Standard.

The human menopausal gonadotropin or human pituitary gonadotropin preparation (FSH/LH) was given by intramuscular injection each day with daily monitoring of urinary estriol excretion. The last dose was given when the urinary estriol levels on the previous day were between 60 and 125 μg/day. An injection of hCG was then given after a coasting phase of 48 hours at a dose of 3000 IU (subjects 1 and 3) or 5000 IU (subject 2) if the previous response was unsatisfactory. Three booster injections of 1000 IU were given 6, 9, and 12 days later in the luteal phase. The urine collections were ceased at or soon after the time of the initial hCG trigger for ovulation, and a midluteal plasma progesterone level was estimated in each case. Serum β-hCG estimations were performed when the luteal phase was longer than 19 days, and these women invariably proved to be pregnant. Two of the women with combined pregnancy underwent a preovulatory ultrasound examination* to check the number and size of follicles within the ovaries.

Urinary estriol was measured by radioimmunoassay.[10] Urinary estriol has been shown to have a high correlation ($r = .896$) with the technique of determining total urinary estrogens described by Brown and associates.[11] Plasma progesterone levels were assayed by Coat-A-Count solid-phase radioimmunoassay.†

* Pergonal, Serono, Italy.
† Primogonyl, Schering Pty. Ltd, Australia.
* Diasonics DRF 1, Nuclear Enterprises, California.
† Diagnostic Products Corporation, California.

Results

Multiple pregnancies occurred in five of the 26 patients who conceived (19%), and three of the five proved to have combined pregnancy. The details of their management are outlined in Table 1. In each case the intrauterine pregnancy was diagnosed before the ectopic gestation by an ultrasound scan performed in the seventh or eighth week. One woman (subject 1) had no premonitory symptoms but simply collapsed at home with an acute abdomen. She was admitted to the hospital severely hypotensive and required a two-L blood transfusion. At laparotomy, a ruptured left ectopic pregnancy was treated by salpingectomy. Subsequently, her intrauterine twins aborted. The other two women presented a similar picture of persistent vaginal bleeding and constant pelvic pain. Each had an ectopic gestation diagnosed at laparoscopy in the ninth week of pregnancy. One was undergoing a tubal abortion treated by salpingectomy together with a 1-L blood transfusion. The other was found to have a discrete midtubal swelling with less than 50 mL of blood loss via the fallopian tube; hence a relatively conservative midtubal resection was performed. Those two patients proceeded to 36 weeks' gestation. Subject 2 delivered healthy triplets and subject 3 delivered healthy twins, both by cesarian section performed for obstetric reasons. The urinary estriol excretion and the timing of the hCG trigger are displayed in Figure 1. In each case the FSH/LH injection was ceased when urinary estriol excretion was 125 μg/day or less. It can be seen that ovulation was triggered within the safe range in subject 2 and at excessive levels (more than 200 μg/day), likely to be associated with multiple pregnancy,[9] in subjects 1 and 3. Regardless of the actual levels, the rise in estriol excretion level was 2.3- to 3.2-fold in the coasting phase between the last FSH/LH injection and subsequent hCG injections. In reviewing the singleton pregnancies for gonadotropin therapy, the rise was invariably no greater than 2.0-fold. Patients were aware and accepted the risks of

multiple pregnancy before electing to continue with ovulation induction. The three patients were all examined in the midluteal phase and although there was no clinical evidence of hyperstimulation, the levels of midluteal progesterone were excessive.[12]

Discussion

For a phenomenon considered to be an obstetric rarity, the finding of three combined pregnancies within a short series by one clinician was highly unexpected. In recent years a number of reports of such pregnancies have appeared, and the incidence appears to be dependent upon the rates of ectopic gestation and multiple pregnancy. The risk of the latter after gonadotropin therapy is known to be high, with rates varying between 15 and 40%.[13,14] In this series, a rate of 19% was documented. The prevention of multiple pregnancy after gonadotropin therapy requires the avoidance of both intercourse and introduction of the hCG ovulation trigger when the urinary estrogen levels are excessive or the rate of rise is too steep.[9] The FSH/LH preparation was ceased in the three studied subjects at acceptable levels of estriol excretion (60 to 125 μg/day), but it was noted that the subsequent rate of rise was steep (2.3- to 3.2-fold) in the interval before the hCG injection.

It might have been expected that pelvic ultrasound scan would be helpful in predicting multiple pregnancy by displaying the number of large mature follicles available for ovulation. Indeed, the authors have found ultrasonic detection of ovarian follicles to correlate closely with the detected number and size at the time of laparoscopic aspiration in their in vitro fertilization and embryo transfer program,[15] and whereas it was prognostically useful in one woman (subject 3), mature follicles were not detected in the other women who were scanned. There was no technical information forthcoming to explain this discrepancy, but it is possible that the follicles were at an early stage of development and that their full maturation and ovulation actually occurred some days later. Ultrasound scan applied during pregnancy was helpful in determining the number of intrauterine gestational sacs, but tended to create false reassurance and provided no definitive ability to diagnose the tubal gestations.

The risk of ectopic pregnancy after gonadotropin therapy appears to be around 3%;[6,16] this complication has been related to the level of urinary estrogens excreted. McBain and associates[6] demonstrated an ectopic risk level of 12.5% when the estrogen excretion exceeded 200 μg/24 hours on the day of hCG trigger. Under correct stimulation, the estrogen values do continue to rise after the last dose of FSH/LH and reach a peak of up to 200 μg/24 hours on the day the hCG is given.[9] From Figure 1 it can be seen that two of the women were at risk of ectopic gestation because of excessive estrogen levels. The mechanisms responsible for tubal conception are unknown but are assumed to relate either to anatomic anomalies within the fallopian tube, causing embryo entrapment, or to abnormal tubal motility function, preventing appropriate transport of the embryo into the uterus. The main predisposing condition is conventionally but not unanimously regarded to be that of pelvic inflammatory disease.[17] Most women undergoing gonadotropin induction of

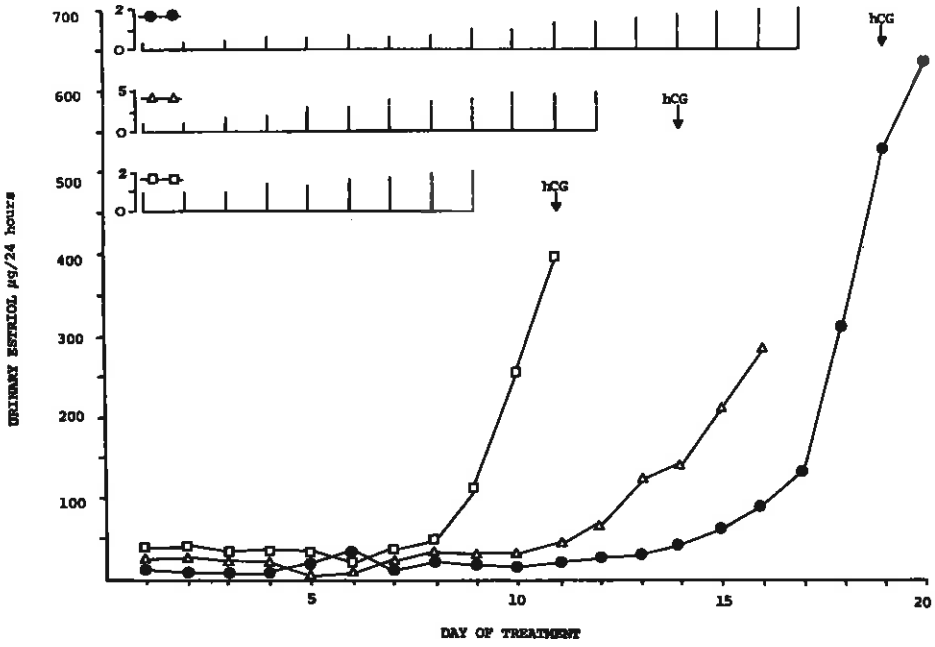

Figure 1. Gonadotropin treatment schedule for three women who developed combined pregnancy. Inserts indicate dose of either human pituitary gonadotropin (*circles, squares*) in pituitary glands per day (75 to 100 IU FSH per gland) or human menopausal gonadotropin (*triangles*) in ampoules per day (75 IU FSH; 75 IU LH/ampoule).

ovulation, including the present combined pregnancy cases, have no evidence of underlying tubal disease. Thus a more attractive theory in such cases is that of a functional disturbance of the transport mechanism induced by high circulating estrogen levels. An increased risk of ectopic gestation has been noted after failed postcoital contraception with high-dose estrogen therapy.[18] Although there is some definitive experimental support for this theory,[19] it is possible that the association with estrogen is indirect.

After the authors' experience of three combined conceptions from a series of 26 gonadotropin-induced pregnancies, they would recommend that the enthusiasm to generate an increased pregnancy rate by triggering ovulation when the estrogen levels are at or above 140 μg/24 hr, or when the rate of rise has more than doubled during the coasting phase, should be tempered by the knowledge that ectopic and combined pregnancies are a relatively likely outcome. The problem is potentially lethal; a maternal mortality of 35% has been reported.[20] Two of the three subjects required a blood transfusion, and one of the women was deeply shocked on admission. However, earlier recourse to laparoscopy in pregnant patients who conceive after gonadotropin therapy and who experience pelvic pain combined with uterine bleeding regardless of an intrauterine pregnancy demonstrable on ultrasound scan, will minimize maternal mortality and improve the outcome for the intrauterine conceptus. Hypotension with diminished uterine and placental perfusion appears to be the main risk prejudicing the outcome of the intrauterine pregnancy.

Women treated for infertility should be considered at greater risk for combined pregnancy, especially if they are known to be at increased risk for ectopic gestation and multiple pregnancy.

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