MEDICAL PRACTICE

Clinical Problems

Sextuplet Pregnancy

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Summary

In a sextuplet pregnancy which followed gonadotrophin therapy the principal problems were threatened abortion, premature labour, and placental insufficiency. Delivery was by caesarean section soon after the onset of labour at 32 weeks. The five liveborn babies thrived. The sixth was a macerated stillbirth.

Introduction

There is a well-known risk of hyperstimulation of the ovaries when gonadotrophins are given to induce ovulation. The sensitivity of the ovaries varies over a wide range not only among the patients but also at different times in the same patient. If hyperstimulation is suspected during a course of treatment with follicle-stimulating hormone (FSH) ovulation can be avoided by withholding chorionic gonadotrophin (HCG) and the ovaries rapidly regress without further treatment. Unfortunately attempts to diagnose hyperstimulation, even by measuring urinary oestrogen levels, have been only partially successful.

The incidence of multiple conception, abortion, premature labour, and fetal wastage has varied in reported series. Gemzell and Roos¹ treated about 100 women with human pituitary gonadotrophin and HCG and 43 pregnancies resulted. There were 20 singleton pregnancies with one abortion; 14 twin pregnancies, three ending in abortion; and two triplet, three quadruplet, one quintuplet, two sextuplet, and one septuplet

pregnancies, all but two of which ended in abortion. The incidence of multiple pregnancy including twins was 53% and excluding twins 21%.

Vande Wiele and Turksoy² reported a series of 20 patients treated with human menopausal gonadotrophin (Pergonal) and HCG. Fifteen patients conceived and 20 pregnancies resulted; eight of these ended in abortion and in the other 12 viable fetuses were delivered—seven singletons, four pairs of twins, and one set of quadruplets.

In this hospital at the time of writing 48 women have been treated with Pergonal and HCG and 26 pregnancies have resulted, the outcome of 17 being known. There were 10 singleton pregnancies (four male, four female, and two abortions), four twin pregnancies (three of mixed sex and one pair of boys), two sets of triplets (one boy with two girls and one triplet abortion, sexes unknown), and one sextuplet pregnancy (the present case—five girls and one boy). Thus the incidence of multiple pregnancy including twins so far is 41% and excluding twins 18%.

A further three pregnancies occurred after the use of pregnant mares' serum gonadotrophin for follicle stimulation. Two were singleton pregnancies (one aborted) and one was a quadruplet pregnancy (two boys, two girls). The combined multiple pregnancy rate for these two groups including twins is 40% and excluding twins 20%.

As there have been few accounts of pregnancies with more than four fetuses reaching an advanced stage of gestation (quintuplets³, sextuplets⁴) we report a sextuplet pregnancy in some detail.

Investigation and Treatment

Mrs. A.B. was first seen in August 1968 at 22 years of age. She complained of primary infertility and secondary amenorrhoea. She had been married for two years. After a menarche at the age of 12 her periods had been regular until the age of 15. She then had amenorrhoea for two years followed by scanty, irregular periods until the age of 20, when she was given intermittent courses of cyclical hormone therapy. Withdrawal bleeds occurred but there

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were no spontaneous periods. The last withdrawal bleed had been in July 1968.

Her general health was good and examination showed a normal woman. A vaginal smear was moderately hypo-oestrogenic, with mainly intermediate cells. A cervical smear was normal. Semen analysis and a postcoital test were satisfactory and tubal insufflation confirmed patency. Gynaecography showed normal-sized ovaries.

In a gonadotrophin stimulation test^{5,6} the baseline urinary excretion of oestrone⁷ was 11 $\mu\text{g}/24$ hours. On the sixth day after a single intramuscular injection of 18,000 I.U. of pregnant mares' serum gonadotrophin the oestrone excretion rose to 35.5 $\mu\text{g}/24$ hours and the pregnanediol excretion (measured by gas liquid chromatography; normal levels comparable with those given by Russell *et al.*⁸) was 0.3 mg/24 hours. As the ovaries were not palpably enlarged the patient was given 12,000 I.U. of HCG. Six days later the oestrone excretion was 28.3 $\mu\text{g}/24$ hours and that of pregnanediol 32.5 mg/24 hours and by the end of the next week these had fallen to 14.9 $\mu\text{g}/24$ hours and 2.5 mg/24 hours respectively. The basal temperature record was biphasic and a period occurred 16 days after the administration of HCG. She was then given two courses of clomiphene 100 mg daily for five days, but this produced no effect. Further treatment with gonadotrophins was therefore decided on after discussion of the risks with the patient and her husband.

In March 1969 a second gonadotrophin stimulation test showed normally responsive ovaries.

Pregnancy

On 12 May 1969 the baseline oestrone excretion was 5.1 $\mu\text{g}/24$ hours. The patient was given three intramuscular injections of 600 I.U. of Pergonal on alternate days. By 19 May the oestrone excretion was 67.5 $\mu\text{g}/24$ hours. The ovaries were not palpable on bimanual examination and 10,000 I.U. of HCG was given. The subsequent steroid excretion levels are shown in Fig. 1.

Menstruation did not occur and by 9 June the basal temperature was still raised. The patient had had abdominal pain and both ovaries were palpable abdominally. Ten days later a pregnancy test was positive and the ovaries were a little smaller. She was

admitted to hospital on 16 July with further abdominal pain and slight vaginal bleeding, nausea and vomiting, tiredness, and headaches. She was then 10 weeks pregnant (eight weeks postovulation). Her blood pressure was 110/50 mm Hg. The uterus was enlarged to 15 weeks' pregnancy size. The haemoglobin was 9.6 g/100 ml. She was treated with bed rest and iron and folic acid tablets. The pain settled and the bleeding stopped. Ultrasound examination disclosed at least four fetal sacs.

After being discharged from hospital at 16 weeks the patient was seen fortnightly in the antenatal clinic. Fetal movements were felt at 18 weeks. She was readmitted at 21 weeks with abdominal pain suggestive of premature labour. Uterine contractions were felt but stopped after treatment with an isoxsuprine infusion for a few hours. Contractions returned on two occasions during her stay in hospital until delivery but stopped with sedation and isoxsuprine infusion. During most of this time she rested in bed or sat up in a chair with her legs raised but she was up for toilet purposes and walked about a little.

As the haemoglobin level remained low a sternal marrow examination was performed at 24 weeks but showed no abnormality. Estimation of the red cell volume⁹ and the plasma volume showed that the low haemoglobin values were a dilution effect due to a large increase in plasma volume.

On an abdominal x-ray film at 25 weeks six fetal skulls were visible and the presence of a seventh was suspected. As premature labour had been threatening it was decided to keep investigations to a minimum and to repeat the x-ray examination and to localize the placenta with ultrasound at 32 weeks. Maternal weight and abdominal girth were recorded regularly, and urinary oestriol¹⁰ and pregnanediol levels were determined (Fig. 2). These, together with the falling plasma volume and the persistent softness of the abdomen alerted us to the possibility of poor placental function. It was therefore decided that the pregnancy should not go beyond 34 weeks and that delivery should be by caesarean section.

The patient and her husband were told from an early stage that there was a multiple pregnancy, with four or more fetuses. It was agreed that the other patients and most of the staff should be told that triplets were expected. This subterfuge was essential to maintain the secrecy necessary to protect the patient from publicity and harassment. The patient and her husband were warned of the high risks of abortion and premature labour. When seven fetuses were suspected the husband was told and the news

FIG. 1—Response of steroid levels to treatment.

FIG. 2—Measurements taken to monitor placental function.

Red Cell Antigens and Red Cell and Placental Enzymes in Parents and Babies

Subject/ Sex	Red Cells																Placenta Enzymes										
	Antigens												Enzymes														
	ABO	C	c	D	E	e	M	N	S	s	Lu ^a	K	Fy ^a	Jk ^a	Ac.P.	PGM ₁	A.K.	Peptidase				ADA	Dia.	Alk.P.	PGM ₁	PGM ₂	
																		A	B	C	D						
Father	O	+	—	+	—	+	+	+	—	+	—	—	+	+	BA	1	1	1	1	1	1	1	1	1	..	..	..
Mother	O	+	+	+	—	+	+	+	—	+	—	—	—	+	BA	2-1	1	1	1	1	1	1	1	1	..	..	..
Babies:																											
F.	O	+	+	+	—	+	—	+	—	+	—	—	—	+	BA	1	1	1	1	1	1	1	1	1	S	1	2-1
F.	O	+	+	+	—	+	+	+	+	+	—	—	+	+	BA	2-1	1	1	1	1	1	1	1	1	S	2-1	2-1
F.*	O	+	..	+	—	+	..	+	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	S	1	2-1
F.	O	+	+	+	—	+	+	+	+	+	—	—	—	+	BA	2-1	1	1	1	1	1	1	1	1	S	2-1	2-1
F.	O	+	+	+	—	+	—	+	—	+	—	—	—	+	A	1	1	1	1	1	1	1	1	..	S	1	2-1
M.	O	+	+	+	—	+	+	+	+	+	—	—	—	+	BA	1	1	1	1	1	1	1	1	1	FS	1	2
F.	O	+	+	+	—	+	+	—	+	—	—	—	—	+	BA	1	1	1	1	1	1	1	1	1	1	1	2

*Stillborn.

Red cell enzymes: Ac.P. = Acid phosphatase; PGM₁ = Phosphoglucosyltransferase (locus 1); A.K. = Adenylate kinase; ADA = Adenosine deaminase; Dia. = Diaphorase. Placental enzymes: Alk.P. = Placental alkaline phosphatase; PGM₁ = Phosphoglucosyltransferase (locus 1); PGM₃ = Phosphoglucosyltransferase (locus 3). + = Positive reaction. — = Negative reaction. .. = Not tested.

was gently broken to the patient. After some discussion the husband sought expert professional advice in handling the important financial implications.

Delivery

On 11 December there was a small vaginal blood loss and on the 14th contractions began at about 7.30 a.m. They became moderate in strength every three to four minutes. An isoxsuprine infusion was instituted and the contractions ceased during the morning but started again in the evening and became stronger, at three-minute intervals, continuing despite the isoxsuprine infusion. Caesarean section was therefore performed in the early hours of 15 December (30 weeks after ovulation). The earlier planning ensured that events ran smoothly.

The patient was anaesthetized in the operating theatre using preoxygenation, methohexitone, suxamethonium chloride, endotracheal intubation, nitrous oxide and oxygen, and pancuronium bromide. As the lower uterine segment was easily accessible a routine lower segment caesarean section was performed. The skin incision was made at 12.35 a.m. and the uterine incision at 12.37 a.m. The abdominal wall was noted to be very oedematous and there was blood-stained fluid in the peritoneal cavity. No placenta was found beneath the uterine incision. The babies were delivered in the following order: 12.37½ a.m., live girl weighing 1,270 g (2 lb 13 oz) by the vertex; 12.38 a.m., live girl weighing 1,160 g (2 lb 9 oz) by the breech; 12.38½ a.m., macerated stillborn girl weighing 580 g (1 lb 4 oz) by the vertex; 12.39 a.m., live girl weighing 1,100 g (2 lb 7 oz) by the vertex; 12.39½ a.m., live boy weighing 780 g (1 lb 11½ oz) by the breech; and 12.40½ a.m., live girl weighing 930 g (2 lb 1 oz) by the breech.

The surgeon had two assistants, the first of whom held each baby below the level of the placenta, while the second, using numbered clamps, doubly clamped and cut each cord. A recorder noted the times and details of delivery. Each baby was in a separate sac, none of which contained more than a small amount of murky liquor. The placentae were on the anterior and posterior walls of the body of the uterus in two separate groups of three. The uterus contracted efficiently and the placentae which separated spontaneously were delivered at 12.43 a.m. after 0.5 mg of ergometrine had been given intravenously. The operation was completed in the routine fashion. Although blood loss was probably less than 600 ml 1 pint (570 ml) of whole blood was transfused during the operation. The ovaries were large (about 7 cm by 5 cm by 2.5 cm) and their appearance suggested that a large number of follicles had ruptured.

Puerperium and Subsequent Progress

The postoperative course was initially satisfactory. The patient had wanted to breast feed but as lactation was indifferent did not persist with it. On the seventh postoperative day she developed a pyrexia of 101°F (38.3°C) and evidence of an upper respiratory tract infection. This settled without treatment and she went home on the fifteenth postoperative day. She was readmitted five days later with pneumococcal lobar pneumonia but made a rapid recovery with antibiotic treatment and physiotherapy. She was seen at the postnatal clinic one month after delivery and was asymptomatic. The abdominal wall was well healed and the uterus was completely involuted.

Amenorrhoea persisted until August 1970, when a spontaneous period occurred; she had two further periods at intervals of two months and subsequently menstruation occurred monthly.

Babies

Since it was anticipated that seven babies needing active resuscitation at birth might be delivered simultaneously seven resuscitation trolleys were provided and 14 paediatricians and neonatal nurses trained in resuscitation were present at delivery. Group O Rh-negative blood was available in case any of the babies should bleed at delivery.⁴

The five live babies were all in excellent condition at birth. None required endotracheal intubation and they were all breathing spontaneously within two minutes. They were immediately transferred to incubators and maintained in the neutral thermal range. They appeared dysmature (four weighed less than the 10th percentile for gestation), with neurological development appropriate to their gestation. Arterial oxygen and carbon dioxide tensions and pH measured in samples taken from radial or brachial arteries, and blood glucose levels measured with Dextrostix on heel-prick samples, were normal. Because of chest wall retractions suggesting the possible development of hyaline membrane disease umbilical artery catheters were inserted in two babies and intravenous infusions were set up in the other three. All were given intravenous 10% dextrose in an electrolyte solution to maintain hydration and normoglycaemia. Breathing was monitored with apnoea alarm mattresses.¹¹

Nasogastric tubes were passed within a few hours of birth and feeding was started with expressed human milk or a cow's milk formula. Tube-feeding was well tolerated and the infusions were stopped within 12 to 24 hours of birth. Chest wall retractions stopped during the first six hours and chest x-ray appearances were normal. All the infants developed minor apnoeic attacks due to "apnoea of prematurity." These were detected within 10 to 15 seconds and could always be terminated by peripheral stimulation. Dextrostix measurements of blood sugar were continued for 10 days and values were always above 45 mg/100 ml. except in the smallest baby, who became asymptotically hypoglycaemic on the third day (blood glucose 13 mg/100 ml). After treatment with intravenous dextrose solution for 24 hours hypoglycaemia did not recur. The results of other investigations were normal.

The babies all weighed more than their birth weights at 2½ weeks of age and subsequently did well. They were totally bottle-fed by 6 to 8 weeks and were discharged home weighing 2,480 and 3,245 g at from 8 to 13 weeks. They were seen many times in the follow-up clinic and were developing normally.¹² At the "real" age of 20 months (that is, chronological age of 22 months less the 8 weeks that they were born before term), they weighed between 8.0 kg. and 10.9 kg. (<3rd percentile to 25th percentile) and their developmental quotients were between 90 and 100. Red cell antigen and red cell and placental enzyme studies¹³ showed that the five live-born babies differed in sex or in one or more of the genetic markers (see Table) and hence they arose from separate zygotes and were "non-identical."

Discussion

Gonadotrophin therapy for treating infertility should be undertaken only for definite indications and in a special centre

where precautions can be taken to minimize the likelihood of hyperstimulation.⁵⁻⁶ Unfortunately the responsiveness of the ovaries, even in a particular patient, is not constant, and even with careful monitoring—by measuring urinary oestrogen levels—it is not always possible to avoid hyperstimulation of the ovaries and multiple conception.

The first indications in this patient that a high multiple conception had occurred were the high urinary excretion levels of oestrone and pregnanediol (Fig. 1). The uterus was large for dates and the diagnosis was confirmed by ultrasound. The main hazards that were expected were abortion or premature labour with neonatal death, placental insufficiency with intrauterine death, and pre-eclampsia. It was thought that rest would be the most helpful prophylactic treatment for these problems, and fortunately it was possible to achieve a satisfactory compromise between rest and activity. The isoxsuprine infusions used when contractions occurred may have helped to prevent abortion and premature labour.

Placental function was monitored by measuring girth and weight and the levels of oestriol and pregnanediol in 24-hour urine specimens.

Anaemia was more apparent than real and due primarily to a dilution effect. Pre-eclampsia was not a problem in this pregnancy (nor in that described by Liggins and Ibbertson.³), though it was in two other gonadotrophin-induced multiple pregnancies managed in this hospital and in the sextuplet pregnancy described by Aiken.⁴

Planning for the delivery was of vital importance in ensuring that events ran smoothly when the time came. Adequate numbers of obstetric and paediatric personnel remained on call permanently for several weeks beforehand. Other preparations included preparing seven pairs of numbered clamps, blood cross-matched for the mother and for the babies, and equipment for the reception, resuscitation, and future management of seven premature babies.

Caesarean section was decided on because of possible hypoxia during labour and possible entanglement and premature placental separation during delivery. Fortunately we had easy access to the lower segment; this was not so in the case described by Aiken,⁴ where a classical caesarean section had to be performed, with damage to one of the placentae and loss of a baby through haemorrhage from the placenta.

We were also fortunate that the five liveborn babies were in such good condition at birth and that none developed hyaline

membrane disease. The preponderance of girls may have been partly responsible for the absence of this disease, since it occurs more often in boys. We have not, however, previously observed any evidence of hyaline membrane disease in premature babies born in this hospital after gonadotrophin therapy and possibly therefore, some factor, perhaps hormonal, is acting to mature the enzymes responsible for the synthesis of pulmonary surfactant before delivery in these fetuses.

We were successful in avoiding publicity before delivery, but subsequently arrangements had to be made for dealing with several hundred journalists. A large room was set aside for press conferences and extra telephones were installed. In general the press remained most co-operative and respected our wish to avoid personal publicity. On several occasions, however, attempts were made by journalists to force an entry into the obstetric hospital. For this reason it was necessary to post guards on the door.

We are grateful to Miss A. Stoten and Mr. H. Shah for performing the steroid assays, to Mr. Asta for preparing the Figures, to members of the Medical Research Council Human Biochemical Genetics Unit for details of the red cell antigen and enzyme studies, and to the staff of the obstetric hospital for all their help in caring for the patient and her babies.

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Clinical Endocrinology

Delayed Puberty

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Puberty is defined as the state of having become functionally capable of procreating and in England is legally recognized to be at the age of 12 in girls and 14 in boys. In clinical practice it is an event in transition from childhood to maturity charac-

terized by changes in somatic and sexual development that take place over a number of years. Moreover, true reproductive capability is probably not achieved, particularly in girls, until late in adolescence and not until the beginning of the third decade in some.

The onset of puberty depends on the activation of the testes or ovaries by pituitary gonadotrophin. The increased production of this hormone at this time is now believed to be due to the maturing of higher centres and the relaxing of the inhibitory influences exerted on the pituitary during childhood.

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