HIGH ORDER MULTIPLE BIRTHS IN THE MALTESE POPULATION

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ABSTRACT

Triplets are a relatively rare, occurrence being encountered in the Maltese Islands with an overall incidence of about 0.1 per 1000 maternities. The incidence appears to be on the increase over the last twenty years rising from the 0.08 per 1000 maternities in the decade 1960-69 to 0.11 per 1000 maternities in the following two decades. This increase has been correlated with the increasing use of ovulation induction agents, as has the occurrence of two quadruplets and one octuplet pregnancies in 1988-90. Triplets are shown to occur more frequently in elderly mothers, but no relationship to parity could be identified. Higher order births are shown to have a high incidence of antenatal and intrpartum problems, and are associated with a higher fetal loss than singleton pregnancies.

INTRODUCTION

Twinning occurs often enough to constitute an important biological event. High order multiple births occur less frequently, though the increasing use of ovulation-inducing agents have increased the frequency of triplets and even higher order births. The Maltese archipelago consists of a group of islands which in 1989 had a total population of 352,430. During that year there were a total of 5773 live births and 44 stillbirths. The crude birth rate stood at 15.8 per thousand population being the average rate for the last decade [1]. The epidemiology and clinical features of twin births in the Maltese Islands have been previously reported to show that the incidence of twin births approximated 10.2 per 1000 maternities during the period 1959-1982. There did not appear to be any marked increase in multiple pregnancy rates during the period reviewed [2]. Clinical data about conjoined twins from Malta in the last years have also been reported [3]. The data on higher order multiple births is scanty due to their decreased frequency. This study attempts to outline the incidence trends and clinical features of these high order births on the Islands. In addition the case reports of two quadruplet pregnancies and the one octuplet maternity are detailed.

MATERIAL AND METHODS

Demographic registration relating to multiple births dates back only to 1959, though this registration must be considered incomplete since it records only those cases terminating in a livebirth or stillbirth, and excludes abortions and fetus papyraceous. The published data makes available information relating to number of cases per year, number of livebirths and stillbirths, and the maternal age. A total of 22 triplet maternities are recorded for the period 1959-1989, of which 6 cases occurred during 1980-1989 [1,4]. Further information was obtained by reviewing the Labour Ward Registers of St. Luke's Hospital (Malta) and Gozo General Hospital (Gozo) for the years 1980-1989. During these ten years there were recorded in the hospitals a total of 8 triplets, two quadruplet pregnancies - one in a foreign patient, and one octuplet pregnancy. The hospital files of these eleven patients were reviewed.

INCIDENCE TRENDS

The overall incidence of triplet maternities in the Maltese Islands for the period 1959-1982 has been estimated at 0.13 per 1000 maternities. Triplet pregnancies appeared to be commoner with increasing age rising in women aged 30 years or more [2]. In the ninteenth century twins were reported to be common but triplets were so rare that not one instance had been heard of by medical men for at least 30 years previous to 1821 [5]. The first recorded quadruplet pregnancy in Malta was born on 19 January 1826 as evidenced by an ex-voto on the wall of the sacristy of Tal-Hlas Church at Qormi [6]. Prof GB Schembri in his lectures to midwives in 1896 makes a passing reference to triplet pregnancies and their management [7]. Table 1 shows the incidence trends over 10 year periods for multiple births since 1960 [1,4]. The twin pregnancy rates over the thirty year period shows no definite pattern but may have shown a slight increase particularly in the 1980's. Triplet maternities have shown a definite increase in incidence rates from 0.08 per 1000 maternities in the 1960-69 period to 0.11 in 1980-89. The only two quadruplet pregnancies recorded during the thirty year period under review occurred in 1988 and 1989. The increase in the triplet maternity rates and the occurrence of two quadruplet maternities in a period of two years, together with the octuplet maternity during 1990 may be a result of the increasing use of ovulation-induction agents. Review of the hospital data shows that while only two cases of the eight triplets delivered in the hospital are recorded as having received ovulation induction, both mothers with quadruplets and the case of octuplet pregnancy received this therapy.

CLINICAL CHARACTERISTICS

Patients having twin pregnancies have been shown to be generally elderly and multiparous, while the pregnancy outcome was more likely to be complicated by an operative delivery and a higher perinatal mortality and morbidity. Triplet maternities similarly appeared to be more common in the elderly patient [2]. Table 2 shows the age related incidence of all registered triplet cases including the two hospital cases not included in the national statistics since one of the infants was a fetus papyraceous. The table confirms that the incidence of triplet maternities increases with increasing age of the mother, thus rising markedly after the age of 35 years. The hospital data for 1980-89 shows a similar though less marked pattern. The mean maternal age for mothers delivering triplets in the hospital was 30.5 years. The quadruplet pregnancies occurred in mothers aged 26 and 30 years, while the octuplet pregnancy occurred in a mother aged 36 years. All these latter higher order cases were artificially induced ones.

TABLE 1:
MULTIPLE BIRTH RATES ACCORDING TO REGISTRATION

YEAR	All maternities	TWINS		TRIPLETS		QUADRUPLETS	
		No	Rate	No	Rate	No	Rate
1960-69	63792	659	10.33	5	0.08	0	0.0
1970-79	57342	564	9.84	6	0.11	0	0.0
1980-89	56639	643	11.35	6*	0.11	0*	0.0

* Hospital data: triplets n = 8 rate 0.14 per 1000
quadruplets n = 2 rate 0.04 per 1000

TABLE 2:
AGE RELATED TRIPLET MATERNITY RATES PER 1000 MATERNITIES

MATERNAL AGE	TOTAL MATERNITIES	TRIPLET MATERNITIES	
		No.	Rate
under 25	57810	3	0.05
25 - 29	62993	6	0.10
30 - 34	39010	6	0.15
35 - 39	20161	7	0.35
over 40	6277	2	0.32
TOTAL	186288*	24	0.13

(* data 1959-89 unknown age n = 37)

Data regarding parity was only available for the triplet pregnancies delivering in the hospitals during 1980-89. The mean parity of these eight mothers was 0.9 (range 0 - 2). Though the data is too scanty for statistical evaluation, there does not appear to be a trend towards an increasing risk of higher order maternities with increasing maternal parity. It is likely that the observation that twin pregnancies were more likely to occur in multiparous mothers was an indirect relationship to the tendency of multiparous patients being of an older age group.

The diagnosis of a higher order pregnancy was often made early on the basis of a uterus which was markedly bigger than dates and confirmed by ultrasound. The antenatal course was relatively uneventful though the patients were distressed by their abdominal distension. three triplet maternities were complicated with a haemoglobin under 11 g/dl in spite of prophylactic haematemics. Two pregnancies were complicated by mild to moderate hypertensive disease of pregnancy (Table 3). The two quadruplets had no antenatal complications. The octuplet pregnancy was complicated by anaemia.

Labour commenced prematurely in 7 cases of triplet maternities at a mean gestational age of 34.5 weeks. In some cases attempts were made to relax the uterus by the use of oral B-sympathomimetics. The two quadruplets showed a wide variation in onset of labour. One case terminated at 22 weeks gestation in spite of rithodrine infusion, while the second terminated at 37 weeks of gestation. The octuplet pregnancy terminated at 23 weeks after delivering one fetus at 17 weeks gestation. The mode of delivery varied markedly from a vaginal delivery to Caesarean section. The latter form of delivery was more likely to be undertaken in the latter years of the ten year period. Thus prior to 1987 all but one triplet delivered vaginally, whereas after 1987 both triplet deliveries were terminated by Caesarean section. This reflects the modern attitude towards multiple deliveries with the increasing tendency towards undertaking abdominal delivery. Malpresentation was frequently encountered with six breech presentations, two transverse lies, and the remainder cephalic presentations. The two fetus papyraceus delivered spontaneously in their sacs.

The perinatal mortality was noted to be higher in twin pregnancies as compared to singleton births [2]. This appears to be more marked in triplets and other higher order births. Thus using the 1959-1989 national and hospital data of 24 triplet maternities with 72 infants, there appeared to be two early fetal losses (2.8%) and five stillbirths (6.9%). These figures are markedly in excess of those reported for the Maltese Islands where the stillbirth rate for 1989 was reported as 7.8 per 1000 total births [1]. No data is available about the early neonatal death rate for triplet maternities, however all the triplets delivered alive at the hospital during 1980-89 survived the early neonatal period. The two quadruplet pregnancies had a very bad perinatal outcome. the one delivering at term had one of the infants stillborn, while the one delivering prematurely had four early neonatal deaths. The octuplet pregnancy terminated in the loss of all the infants who died from intrapartum stress or severe prematurity soon after delivery.

TABLE 3: CLINICAL NOTES FOR TRIPLET MATERNITIES: 1980 - 1989

YEAR	MATERNAL CHARACTERISTICS	INFANTS NOTES
1980	Age 28, P1+0, no history of infertility. Booked at 27 wks and diagnosed triplets by ultrasound. HB 10.0 g/dl. Mild BP rise noted at 30 wks managed by rest and anti-hypertensives. Fetal growth by U/S adequate. SROM at 36 wks. Normal labour first stage lasting 3 hrs 15 min. Total 2nd stage lasted 25 min. First infant born OA spontaneously, 2nd and 3rd infant assisted breech deliveries. Third stage occurred 5 min after syntometrin. Overall placental wieght 1.75kg. Pyrexia postpartum treated by antibiotics.	*First infant male 2.12 kg 2nd infant male 2.25 kg 3rd infant female 1.8 kg All survived first week of life.*
1981	Age 30, P1+0, no history of infertility. Booked at 18 wks and diagnosed triplets by ultrasound. Hb 10.8g/dl treated with TDI at 26 wks. Third infant diagnosed IUD by U/S at 28 wks. Uterine contractions noted at 30 wks, patient given alupent. Subsequent adequate fetal growth for remaining two infants. Onset of labour at 34 wks. Total duration of labour 2 hrs 15 min, complicated by mild intrapartum bleeding. First infant born ROA spontaneously, 2nd assisted breech delivery, 3rd spontaneously with unruptured mem branes.	*First infant female 1.7 kg 2nd infant female 1.8 kg Both survived first week of life. 3rd infant male 0.23 kg macerated abortion.*

YEAR	MATERNAL CHARACTERISTICS	INFANTS NOTES
1982	Age 36, P2+0, no history of infertility. Booked at 27 wks and diagnosed triplets by U/S. History of marked hyperemesis. Hb 12.7 g/dl. SROM at 35 wks. First stage lasted 3 hrs 15 min after augmen tation with syntocinon. 2nd stage overall lasted 30 min. First infant born OA forceps delivery, remaining two cephalic OA positions. third stage lasted 5 min after syntometrin. Placental weight 2 kg. No postpartum problems.	*First infant female 2.25 kg, 2nd infant female 1.62 kg, 3rd infant female 1.97 kg. All survived first week of life.*
1983	Age 35, P1+2, no history of infertility. Booked at 17 wks and diagnosed triplets by U/S. Hb 13.9 g/dl. Spontaneous onset of labour at 32 wks. First stage lasted 4 hrs 10 min. 2nd stage overall lasted 15 min. First infant assisted breech delivery, 2nd OA cephalic delivery, 3rd OP cephalic delivery. Third stage 10 min after syntometrin. Placenta 1.2 kg. Readmitted for secondary PPH followed by ERPC.	*First infant female 2.3 kg, 2nd infant male 2.3 kg, 3rd infant male 2.6 kg. All survived first week of life.*
1983	Age 26, P1+0. Spontaneous onset of labour at 33 wks. Emergency LSCS, first and 2nd infants cephalic, 3rd transverse.	*First infant female 2.31 kg, 2nd infant female 2.0 kg, 3rd infant male 2.13 kg All survived first week of life.*
1984	Age 26, PO+O, no history of infertility. Booked at 26 wks and diagnosed triplets by U/S. Hb 13.4 g/dl. U/S at 26 wks showed growth discrepancy of third fetus with BPD of 5.4 cm while other two showed BPD of 6.8 cm. IUD of 3rd fetus diagnosed by U/S at 31 wks. Spontaneous onset of labour at 35 wks. Dexamethasone given. Duration of labour 12 hrs 15 min after augmentation with ARM and syntocinon. First two infants born cephalic, third spontaneous after membrane rupture.	*First infant male 1.87 kg. 2nd infant male 2.65 kg. Both survived first week of life. 3rd infant sex? 0.8 kg macerated stilbirth.*
1987	Age 25, PO+O. Given clomiphene. Booked with private specialist early and diagnosed triplets by U/S early. Cervical cerclage and Ventolin given prophylactically. Hb 10.3 g/dl. Vaginal spotting at 8 wks. At 33 wks found hypertensive with proteinuria, managed by bed rest. Spontaneous onset of labour at 34 wks, given dexamethasone. Emergency LSCS, first cephalic, remaining two breech. Placental weight 1.2 kg.	*First infant female 1.77 kg, 2nd infant female 1.9 kg, 3rd infant male 1.415 kg. All survived first week of life.*
1988	Age 38, P1+O. Given 1 dose of clomiphene for 10 yrs infertility. Booked at 22 wks and diagnosed triplets by U/S. No antenatal problems. Admitted for rest at 34 wks and given Ventolin prophylactically. Elective LSCS at 37 wks. First infant cephalic, remaining two breech. Placental weight 1.5 kg.	*First infant male 3.39 kg, 2nd infant male 2.35 kg, 3rd infant male 2.125 kg. All survived first week of life.*

CASE REPORTS

The first reported case of quadruplet pregnancy occurred in 1988 in a Libyan national. The patient was aged 26 years and was nulliparous. She had received two courses of clomiphene prior to conception. At 20 weeks gestation she was noted to be larger than dates and an ultrasound scan showed four gestational sacs but only three fetuses were noted all with a BPD of 5.1 cm. A previous scan performed in Libya had confirmed four viable fetuses. The mother complained of marked abdominal discomfort resulting from the excessive distension. At 22 weeks she was started on prophy-

lactic salbutamol. She required admission for rest at 28 weeks gestation. There appeared to be no evidence of polyhydramnios, hypertension or oedema. Adequate fetal growth was noted by serial ultrasound, though only three fetuses were noted in a total of five scans. The last BPD four days prior to delivery averaged 9.3 cm. At 37 weeks of gestation the patient had a spontaneous onset of labour. An emergency LSCS was performed. The first two infants were born in the breech position, which the remaining two in the cephalic position. All infants were in separate sacs. The second infant was a fresh stillborn child, the remaining three children were liveborn and survived the neonatal period. The overall placental weight was 4.0 kg. The patient's post-operative period was uneventful.

The second case of a quadruplet pregnancy occurred in 1989 in a Maltese national aged 30 years P1+1. She had been treated by her general practitioner with human menopausal gonadotrophin for a supposedly secondary infertility. She had had her previous child six months before. She was referred by her general practitioner for a triplet pregnancy diagnosed by ultrasound at 22 weeks. She had been prescribed duphastone besides iron and vitamin supplements. She was admitted at 22 weeks with premature contractions. Ultrasound scan confirmed a triplet pregnancy and showed evidence of cervical dilatation. She was started on ritordrine infusion, but progressed with spontaneous labour and delivery four days after admission. In view of her highly anxious mental state, she was allowed to progress spontaneously. The second stage of labour lasted 2 hours 10 minutes. After the birth of the third fetus, three placentae with their sacs and cords were delivered. At this stage a fourth pregnancy was identified, and the fourth fetus delivered followed by its placenta and sac. All four infants were in separate sacs. The first infant weighed 400 grams while the remaining three weighed 500 grams each. The overall placenta weighed 650 grams. The fetuses died within 20 minutes of delivery.

The octuplet pregnancy was reported in 1990. The patient was a 36 year old nulliparous women who suffered from polycystic ovarian disease with infertility, hirsutism and mild obesity. She had been originally seen in gynaecological consultation for irregular menstruation and infertility. She was initially started on clomiphene with no adequate response. She was thus started on gonadotrophin regime using HMG and HCG. The dose was increased gradualy to achieve ovulation reaching a dose of 2 ampules HMG for 10 days followed by 10000 units HCG on the 12th day. This dose gave rise to hyperstimulation with enlarged ovaries and mild-moderate abdominal pain. This settled with conservative management. As a result of a misunderstanding, the patient took a repeat course in her subsequent cycle using 2 ampoules of HMG and 5000 units HCG. She became pregnant during this cycle. Her hormone profile taken on the 25th day of her cycle showed a very high progesterone level (>127 nmol/1) and an elevated testosterone level (35.5 pmol/1). Her LH was 42.1 U/1, FSH was 2.2 U/1, and prolactin was 455 mU/1. She was seen at 11 weeks gestation when she was noted to be larger than her dates. An ultrasound scan confirmed the presence of at least five fetuses. She was admitted to the hospital for rest and observation. She was prophylactically given Gravibinan injections, Ventolin tablets, besides high doses of iron and folic acid. Serial ultrasound showed adequate fetal growth. The markedly distended uterus caused marked discomfort to the patient. At 17 weeks gestation, she gave birth to one fetus following spontaneous rupture of membranes without experiencing contractions. The stillborn abortus was male with a crown-rump length of 13.0 cm. Delivery of the other fetuses did not proceed spontaneously and the patient was restricted to bed and covered with broad-spectrum antibiotics. The umbilical cord was allowed to dry up and was pulled off without difficulty three days later. Pregnancy was allowed to continue. The patient's haemoglobin fell to 9.8 g/dl and she was transfused with blood to achieve normal haemoglobin levels. Labour started again at 23 weeks gestation. Examination found the patient to be fully dilated, and she was augmented with ARM and syntocinon infusion. The first four infants were born spontaneously and alive. Three died in the immediate neonatal period, while the fourth died the next day. The fifth and sixth infants were born using forceps and were stillborn. The placenta was delivered after the sixth fetus. The seventh fetus was stillborn with its placenta. The infants weight ranged between 400 - 500 grams. Examination of the placental mass weighing 1.25 kg, showed this to consist of five placentae enclosed in one sac of membranes. These contained eight umbilical cord insertions. The first placenta measuring 11 x 8 x 2.5 cm had one umbilical cord with a velementous insertion. The second placenta measuring 16 x 12 x 3 cm contained three umbilical cords with acentric velamentous insertion. The third placenta measured 11 x 7 x 2 cm had one umbilical cord with a velamentous insertion. The fourth placenta measured 16 x 9 x 2 cm and had a velamentously inserted umbilical cord, while the fifth placenta measured 12 x 10 x 2 cm had two umbilical cord insertions. The mother had an uneventful puerperal course receiving prophylactic antibiotics, ergometrin, and bromocriptine.

DISCUSSION

High order multiple birth are a comparatively a rarity. Thus according to Hellin's Law, twin births occur in 1:80 pregnancies, triplets in $1:80^2$, quadruplets in $1:80^3$, quintuplets in $1:80^4$, and so on. The frequency is increased in women who receive ovulation-induction agents. Women receiving clomiphene have a multiple birth rate of 6 - 8.4% usually twins [8,9]. The frequency is very much higher reaching 44% when gonadotrophins are used giving rise predominantly to dizygotic twinning, but also to numerous triplets and higher order births [10]. Nonatuplets produced by this method is apparently the record [11]. The increasing use of ovulation-induction agents in the Maltese Islands, particularly the indiscriminate use of the gonadotrophins by non-

specialists, are a definite contribution to the rise in triplet incidence in the last decade. This also accounts for the two quadruplet pregnancies and the octuplet pregnancy recorded in a period of three years. One quadruplet pregnancy resulted after the administration by a non-specialist of gonadotrophins to a women who had had a previous pregnancy only six months previously, and hence cannot be said to have been infertile. Hyperstimulation syndrome resulting from gonadotrophin administration may present with a marked cystic enlargement of the ovaries resulting in abdominal pain and distension, and with marked systemic and haemotological changes. This picture is variable, but severe cases have been admitted after indiscriminate and uncontrolled use of these powerful ovulation-induction agents.

Triplet maternities appear to be commoner in the elderly patient, particularly in women aged more than 35 years. This observation, which has also been reported for twin pregnancies in the Maltese Islands [2], can be attributed to the increasing pituitary FSH production which occurs as a result of increasing ovarian resistance with age [11]. Increasing parity does not appear to have an increased risk for triplet maternities.

High order pregnancies carry a significantly higher risk of fetal or neonatal loss from placental insufficiency, prematurity, and complications of delivery associated with malpresentation. Efforts need to be made to decrease the perinatal loss from these causes. Early diagnosis is essential and can only be confirmed by ultrasonography. Even so, in higher order birth, confirmation can be difficult especially after the first trimester. Hospitalization is ideal since it assures prolonged rest periods and allows the early institution of pharmacological measures to control premature labour. These measures are often ineffective in the long-term, but ensure that the infants are born timely in an environment where expert neonatal care is easily available. The development of neonatal life-supporting capabilities has done much to improve neonatal survival. An earlier recourse to operative abdominal delivery for high order births has done much to decrease the intrapartum risks. Placental insufficiency in high order pregnancies remains a difficult problem of diagnosis and management. Intrauterine growth retardation occurs at a given total weight of all fetuses regardless of the number. Thus symmetrical IUGR appears in each fetus later in gestation in triplets than in quadruplets and still later in twins. A more ominous form of IUGR is asymmetrical IUGR of one or more infants. Clinical examination of the uterine size alone is useless in identifying poor fetal growth in high order births. Fetal growth is best monitored by serial ultrasonic measurements of head-abdominal ratios so that asymmetrical growth in one or more infants can be identified early. Biophysical profiles and doppler wave forms of each infant can further help assess fetal well-being though they are difficult to perform in all infants simultaneously. Any signs of impending fetal demise are suggestive of timely delivery which must be weighed against the risk of prematurity. The decision may become more difficult when only one fetus is compromised.

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