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Original Article

Higher order multiple pregnancy outcomes in the Maltese islands 2000-2004

Charles Savona-Ventura, Miriam Gatt, Katya Vella, Stephen Grima

Abstract

Higher order multiple births have increased significantly in the last decades throughout the developed world. In spite of advances in obstetric care seen throughout the second half of the twentieth century, the perinatal outcomes associated with a multiple pregnancy remain associated with increased morbidity and mortality for the mother and the infants. This study attempts to assess the characteristics and outcomes of these maternities in the Maltese population. The National maternity data for 2000-2004 was analysed (19,935 maternities; 20,215 births) and various outcome parameters were statistically compared between higher order births to singleton births using the chi square test. While the twin maternity rate during the period stood at 1.26%, the triplet maternity rate stood at 0.06% and quadruplet maternities 0.01%. Artificial reproductive technology was used in 27.8% of triplets and 50.0% in quadruplets; in contrast to 0.7% in singleton maternities ($p<0.001$). High order multiple maternities were more likely to be terminated by Caesarean section (25.2% *vs* 100%; $p<0.001$) and be the result of a spontaneous or iatrogenic premature delivery (4.6% *vs* 84.0%; $p<0.001$). Infant outcome was more likely to be complicated by low birth weight under 2.5 kg (9.7% *vs* 97.6%; $p<0.001$), and the associated complications of respiratory distress (1.9% *vs* 22.0%; $p<0.001$), low Apgar score (1.4% *vs* 7.3%; $p<0.001$), and perinatal deaths (stillbirth: 0.4% *vs* 2.4%; $p<0.001$; neonatal deaths 0.4% *vs* 4.9%; $p<0.001$). There did not appear to be a greater risk of major malformations.

Key words

Multiple births, pregnancy, risk factors, complications, outcomes

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Introduction

Multiple pregnancy rates have increased throughout the developed world, mainly as a result of the increasing trend to utilise reproductive technology in cases of infertility. Part of this rise can also attributed to the changing maternal age structure of the population with a greater predisposition towards pregnancies being embarked upon in later life. This phenomenon has also been observed in the Maltese Islands. Multiple pregnancy rates in the Maltese Islands have increased significantly in the last forty years from 1.04% during the period 1960-1969 to 1.30% during 1990-1999; the rise being mainly attributable to the increasing use of fertility agents. While the perinatal mortality rates have generally taken an overall drop in the second half of the twentieth century, this drop has not been consistent in regard to multiple pregnancies.[6] This present study attempts to quantify the obstetric morbidity presented to the infants and mothers in cases of higher order multiple births.

Methods

All deliveries in the Maltese Islands during the five-year period 2000-2004 were included in the study. The study population thus included a total of 19935 maternities with a total of 20215 infants being born to these mothers. These maternities included a total of 252 twin births, 13 higher order maternities (11 triplet and 2 quadruplet births). The data was obtained in anonymous format from the National Obstetric Information System (NOIS) database managed by the Department of Health Information, Malta. This database includes all maternities registered in the Maltese Islands. The data is completed in accordance to the clinical notes after delivery, prior to discharge from hospital or until 28 days of life. This methodology may in fact give rise to an element of bias since unrecorded clinical events, e.g. use of artificial reproductive technology, will not be

registered and may thus not reflect the true picture; while any adverse outcome occurring after in the neonatal period after discharge from hospital would not be registered.

Further data regarding congenital anomalies was obtained from the Malta Congenital Anomalies Register. This database is based on the EUROCAT database which defines 'congenital anomalies' as structural defects (congenital malformations, deformations, disruptions and dysplasias), chromosomal abnormalities, inborn errors of metabolism and hereditary diseases. The database includes all diagnoses suspected or made within the first year of life of the infant. Minor congenital anomalies are not normally included in congenital anomalies registers as they would markedly swell the incidence figures and dilute the significance of major anomalies. The precise line of demarcation between anomalies to be included and those to be excluded is not clear cut and may be influenced by subjective differences in interpretation. Minor anomalies do not in themselves have serious medical or cosmetic consequences for the child. Some may nevertheless be of certain significance, since they can be predictive of major underlying pathologies. There is increasing awareness of dysmorphic syndromes which present great diagnostic difficulties, not only in their precise identification, but also in their recognition which may be delayed for many months before they are detected. EUROCAT applies a standard list of minor and commonly occurring anomalies for exclusion. This list is available on the EUROCAT web page 14. These conditions are not registered unless occurring in combination with other major anomalies.

The World Health Organisation Obstetrical Quality Indicators and Data collection (OBSQID) project had identified several pregnancy indicators relevant to multiple pregnancies.[3] These outcome indicators for twin and higher order births were compared to those in singleton births. Information relating to zygosity of multiple births was not available. Statistical analysis between singleton and higher order maternities was performed using the chi square test using a standard statistical package MedCalc. Statistical significance was assumed with a probability value <0.05. The twin pregnancy data for the same period has been previously published.[4]

Results

During the five-year period under investigation, there were a total of 19,669 singleton births, 252 twin births (1.26%), 11 triplet births (0.06%), and two quadruplet births (0.01%). Assisted reproduction, including the use of ovulatory agents, IVF-ET, ICSI, etc., was reported in only 0.7% of all singleton maternities. This contrasts significantly in the reported rates of 30.8% in higher order maternities ($p<0.001$).

A significantly increased maternal morbidity is noted in higher order births as a result of an increased incidence of pre-existing DM (0.4% *vs* 15.5%; $p<0.001$). The higher order pregnancies appeared to be more likely to be complicated by hypertensive disease (singleton: 6.5% *vs* higher order: 15.4%; $p=0.47$), though the differences did not prove to be statistically significant. There were no cases of third trimester bleeding or gestational diabetes mellitus in the higher order group (Table 1).

The presence of a high order pregnancy together with the increased antenatal complication rates result in a greater predisposition of spontaneous or iatrogenic premature delivery (singleton: 4.6% *vs* higher order: 84.7%; $p<0.001$) often requiring Caesarean section (25.2% *vs* 100%; $p<0.001$). In conformity to the oft-chosen elective mode of delivery and the greater likelihood of a spontaneous onset of premature labour in multiple births, there were no cases of induced labour in the higher order maternities ($p=0.01$). Similarly there were no cases of operative vaginal deliveries (Table 1).

The presence of a higher order maternity is associated with a greater likelihood of an adverse outcome to the infants. This is reflected by an increase in the perinatal and late neonatal death rate (0.8% in singletons *vs* 7.3% in higher order; $p<0.001$). At the end of the neonatal period, there were still a total of 21 infants (51.2%) born as higher order maternities still hospitalised and receiving care in the Special Care Baby Unit beyond 28 days of life. This is very much in excess of the rate of singleton neonates requiring prolonged specialised management (0.76%; $p<0.001$). The outcome of these infants is not followed up by the NOIS database. The NOIS database excludes miscarriages.

The greater predisposition for prematurity gives rise to prematurity-related infant problems in higher order infants including low Apgar score at 5 minutes (1.4% vs 7.3%; $p=0.01$); respiratory distress (1.9% *vs* 22.0%; $p<0.001$); and low birth weight under 2.5 kg (9.7% *vs* 97.6%; $p<0.001$).

There did not appear to be a greater risk of major malformations associated with multiple births in this series (Table 2).

Discussion

The multiple pregnancy rate in the Maltese Islands has been shown to have increased significantly in the last forty years from 1.04% during the period 1960-1969, when presumably the use of assisted reproduction was limited, to 1.30% during 1990-99 ($p<0.001$). This increase is possibly partly influenced by changes which have occurred in maternal age distribution which alone would have increased the twin pregnancy rate to only 1.07%. The 19.1% difference must be attributable to other factors, the most likely being the increasing use of pharmacological and technological reproductive aids.[6] In the 1970s, the only effective pharmacological agents available to clinicians to assist the ovulatory process were clomiphene and human chorionic gonadotrophic therapy.[1] In Malta these were supplemented by FSH/LH gonadotrophin extracts in the 1980s, therapeutic options that resulted in 1989-1990 in reports of drug-induced higher order births and ovarian hyperstimulation syndrome.[7] The introduction of these drugs alone showed a rise in multiple pregnancy rates from the "natural" 1.04% level of the 1960s to the 1.18% level of the 1980s, a 13.5% rise. The higher order birth rates rose from 0.008% to 0.018%, a 125% rise.[6] These significant rises resulted in 1992 in a call to be made by the Malta College of Obstetricians and Gynaecologists to regulate

these pharmacological ovulatory agents and to limit their use to qualified specialists only. This call was taken up by the Department of Health in a general circular issued the subsequent year. (DOH circular No.2/94). Unfortunately, these medications continued to be used by non-specialist physicians. The 1990s saw the introduction of further technological advances in assisted reproduction techniques which have continued to contribute to a rise in multiple pregnancy rates by about a further 10.2% for twins and 83.3% for higher order births.[6] These reported temporal trends conform with the observations in this study which has shown a statistically significant difference in the proportion of pregnant women whose pregnancy was achieved by artificial reproductive pharmacological with/out technological techniques. Thus while only 0.7% of women having singleton pregnancies were reported to have availed themselves of these techniques, a higher proportion amounting to 9.1% for those having twin births[4] and 30.8% for those having higher order births reported having availed themselves of these procedures. These figures may in fact be underestimates since a proportion of couples may be unwilling and reluctant to report their having required interventions to assist their fertility. The relationship between increasing multiple pregnancy rates and subfertility treatments has been assumed in a number of communities, but there are few quantitative assessments to assess this. A definite correlation has been shown in the Oxford Record Linkage Study area, where the proportions following subfertility treatment have been documented. National data on prescriptions for subfertility treatments have reinforced the view that they have had a major effect on the trends, and currently perhaps 60% of triplet and higher order births and 15% of twins follow their use in Britain.[8]

The occurrence of a multiple pregnancy remains fraught with adverse outcomes and in spite of the advances in obstetric antenatal surveillance and easier recourse to early delivery, the

Table 1: *Maternal morbidity parameters*

Maternal Problems	***Singleton births (N=19669)***		***Higher Order (N=13)***		
	number	***% (CI)***	***number***	***% (CI)***	
Assisted Reproduction	142	0.7 (0.6-0.9)	4	30.8 (10.4-61.1)	$p<0.001$
Hypertensive disease	1277	6.5 (6.2-6.9)	2	15.4 (2.7-46.3)	$p=0.47$
Pre-existing DM	80	0.4 (0.3-0.5)	2	15.4 (2.7-46.3)	$p<0.001$
Gestational DM	385	2.0 (1.8-2.2)	0	-	
Third trimester bleeding	334	1.7 (1.5-2.0)	0	-	
Delivery Complications					
Very Preterm births (<32 wks)	118	0.6 (0.5-0.7)	2	15.4 (2.7-46.3)	$p<0.001$
Preterm births (32-36 wks)	790	4.0 (3.8-4.3)	11	84.7	
Induced labour	7552	38.4 (37.7-39.1)	0	-	$p=0.01$
Operative vaginal deliveries	778	4.0 (3.8-4.3)	0	-	$p=0.99$
Elective LSCS	1842	9.4 (9.2-9.6)	6	46.2 (20.4-73.9)	$p=<0.001$
Emergency LSCS	3104	15.8 (15.5-16.1)	7	53.8 (26.8-81.0)	

Table 2: *Infant morbidity parameters*

Adverse Pregnancy Outcome	*Singleton births (N=19669)*		*Higher Order (N=41)*		*p value*
	No	*% (CI)*	*No*	*% (CI)*	
Stillbirth deaths (>22 wks)	79	0.4 (0.3-0.5)	1	2.4 (0.1-14.4)	
Early Neonatal deaths	59	0.3 (0.2-0.4)	2	4.9 (0.9-17.8)	
Late Neonatal deaths	18	0.1 (0.06-0.15)	0	0	*p*<0.001
Apgar <=6 @ 5 min	283	1.4 (1.3-1.6)	3	7.3 (1.9-21.0)	*p*=0.01
Infant with RDS	379	1.9 (1.7-2.1)	9	22.0 (11.1-38.0)	*p*<0.001
Malformations*	655	3.3 (3.1-3.6)	0v	0	*p*=0.46
Birth weight <500 gm	4	0.02 (0.01-0.06)	0	0	
Birth weight 500-1499 gm	181	0.9 (0.8-1.1)	12	29.3 (16.7-45.7)	*p*<0.001
Birth weight 1500-2499 gm	1723	8.8 (8.4-9.2)	28	68.3 (51.8-81.4)	
Infants receiving care in SCBU beyond 28 days of life	149	0.8 (0.6-0.9)	21	51.2 (35.4-66.9)	*p*<0.001

** Malformations data based on Malta Congenital Anomalies Register*

stillbirth rates and neonatal mortality in multiple maternities have remained markedly elevated contrasting with the fall in the singleton rates. The national stillbirth rate for singleton births has dropped from the 17.06% average 10-year rate in the 1960s to the 4.05% average 10-year rate in the 1990s. This drop has been the result of a general improvement in the socioeconomic situation of the population supplemented by an improvement in the available obstetric services. In spite of the fact that similar factors have influenced mothers having multiple births, the corresponding stillbirth rates for twin births have remained approximately similar in the two decades at 28.07% and 30.97% respectively. During both decades, there were no registered stillbirths in triplet maternities.[6] Though national demographic data is unavailable, comparative mortality analysis studies carried out by the Department of Obstetrics-Gynaecology in the 1979-87 and 2000-04 have confirmed that the early neonatal mortality in multiple births has also remained about 7.5 times greater than that registered for singleton births, but has shown a proportional decrease.[2,5,6] The present study has confirmed the overall higher stillbirth-neonatal loss being registered at only 0.8% for singletons, but 4.6% for twins[4] and 7.3% for higher order births. These figures must be conservative since a number of infants were still undergoing intensive treatment in the Special Care Baby Unit beyond one month of life. The long-term morbidity of the surviving infants has not been measured. The main cause for the increasing morbidity and mortality arises from the medical problems of prematurity and low birth weight. A significantly high proportion of infants born in multiple birth circumstances have a weight less than 1500 gm. The medical management of these infants is highly demanding and places excessive strains to the limited facilities of the one and only Special Care Baby Unit in the main hospital. This is compounded by the immeasurable emotional strains placed on the medical and paramedical staff of these units. The higher perinatal mortality and morbidity rates associated with multiple births have long been documented. In spite of advances in obstetric management, these higher mortality rates have been maintained. During 2000-2003, the confidential enquiry into stillbirths and neonatal and post-neonatal deaths in England, Wales and N. Ireland reports that multiple births have a stillbirth

rate over three times that of singleton births and a neonatal mortality rate nearly seven times that of singleton births.[9]

Multiple births also increased the morbidity to the mother, especially when one considers the non-obstetrical complications arising from them having had recourse to artificial reproduction intervention. These latter risks include hyperstimulation syndrome which can have very severe adverse medical consequences. During pregnancy, the morbidity of the mothers is significantly increased by the greater likelihood of the development of hypertensive disease and antepartum haemorrhage. Compared with singleton gestations, women with multiple gestations in Uruguay during 1985-1997 have been shown to have higher risks for eclampsia, preeclampsia, and postpartum haemorrhage. Likewise, there was significant association between multiple gestation and increased incidence of preterm labour, anaemia, urinary tract infection, puerperal endometritis, and caesarean delivery. In contrast, there were no increased risks for third trimester haemorrhage in these women.[10] A definite risk for third trimester bleeding in multiple births has however been demonstrated.[11] In addition, one must also take into account the emotional and psychological trauma experienced by these couples both during their intensive treatment for their infertility and also when faced with the mortality or morbidity of their child as a result of the interventions they had undergone.

Recommendations

The problems posed by the infertile couple and the wish to help as effectively as is possible to assist such unfortunate couples to achieve a pregnancy must be tempered by good adequate advice and psychological support. The uncontrolled use of ovulatory agents known to be directly responsible for stimulating superovulation must be regulated and restricted only to accredited specialists in the field. Similarly, the technological treatment options available to our population must be reviewed and adequate measures should be considered to advise the number of fertilised ova inserted during each cycle. Because of the documented risks of higher order births, it is recommendable that not more than two fertilized ova should be inserted each cycle.[12] Unfortunately, the present system in the Maltese Islands is currently based in the private sector and this makes it more difficult for any regulatory body to ensure adherence to regulations which may be instituted. It may be opportune to consider the expansion of the government free-health service to encompass a broader infertility service. The availability of a government-based service could allow for a better regulatory process possibly decreasing the incidence of higher order births and consequent complications. The financial benefits from decreasing the costs of intensive managing of the sick premature low-weight child have been shown to far surpass the cost of introducing a government-based infertility service that ensures elective single embryo transfer versus two-embryo transfer in first IVF/ICSI cycles.[13]

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