CEOG Clinical and Experimental Obstetrics & Gynecology
Original Research

Advanced maternal age and neonatal outcomes in Malta

M. Collict[1], Y. Mucat Baron[1], M. Gatt[2], N. Calleja[2]

[1]Department of Obsterics and Gynaecology, Mater Dei Hospital, Msida; [2]Department of Health, Information and Research, Pieta (Malta)

Summary

Introduction: During the past three decades, significant increases in childbirth at advanced maternal age (AMA) have been noted in different high-income countries. Objective: The aim of this study is to assess for the association between AMA and different neonatal outcomes in Malta. Multivariate regression analysis was carried out. *Materials and Methods:* Data was derived from the National Obstetric Information System. All mothers of 20 years and older, who delivered singleton babies in Malta and Gozo between 1st January 2000 and 31st December 2014 were studied. *Results:* The study population included 55,943 singleton births. Our results clearly show that the percentage of preterm babies increased and the birth weight decreased with advancing maternal age. The adjusted rates of stillbirths and rates of infants that died in less than 28 days also increased with age. A significant increase in chromosomal abnormalities was also detected in mothers over 40 years. *Conclusion:* This study demonstrates that AMA in Malta significantly increases the risk for preterm births, low birth weight, still births and neonatal deaths. The set-up of a multidisciplinary specialized clinic may prove useful in improving outcome in pregnancies of women with AMA.

Key words: Preterm births; Advanced maternal age (AMA); Neonatal outcome; Malta.

Introduction

During the past three decades, significant increases in childbirth at advanced maternal age (AMA) have been noted in different high-income countries [1]. AMA is generally defined as age 35 years and older at the estimated date of delivery. The reasons motherhood is postponed are manifold and complex. All women should be supported in their decisions of whether to have children or not and when to plan childbearing. However, women also need to be counselled regarding how fertility and pregnancy outcomes change with increasing age. Several studies have been carried out evaluating the effect of AMA on the perinatal outcomes. AMA continues to be associated with a range of adverse outcomes including low birth weight, pre-term birth, and stillbirths [2, 3].

The only published study on AMA and neonatal outcomes in Malta was in 1987 by Savona Ventura and Grech on risk factors in elderly obstetric patients, in the European Study Group on Social Aspects of Human Reproduction, V annual meeting [4].

The aim of this research is to present a clearer picture of the neonatal outcomes to elderly women delivering in Malta. In this study, the authors assess the association between AMA and adverse neonatal outcomes after adjustment for confounding factors in maternal characteristics and in the obstetric history.

Materials and Methods

This research project is a large Retrospective Cohort Study which analyses maternal complications associated with AMA. All data was derived from the National Obstetric Information System (NOIS) of Malta. The NOIS was launched by the Department of Health Information and Research (DHIR) at the beginning of 1999 and now covers all hospital deliveries taking place on the islands of Malta and Gozo. The systematic data collection for NOIS commences once the mother delivers her baby. Information regarding the course and outcome of each pregnancy is recorded by the relevant appointed staff at each centre on a standard NOIS sheet. Once the data are recorded, the sheets are forwarded to the DHIR on a regular basis. At the DHIR the relevant sheets are processed and entered into the NOIS database. All data is kept in accordance with the Data Protection Act, 2001.

This research analyses almost all deliveries in Malta and Gozo over a 15-year period from the year 2000 to 2014. The study population was recruited from the NOIS according to the following inclusion and exclusion criteria. Inclusion criteria were: mothers of 20 years of age and over, singletons babies, live births or still births, births occurred either in Malta or in Gozo, and between January 1st, 2000 and December 31st, 2014.

Exclusion criteria were: mothers of less than 20 years of age, multiple pregnancies, and missing maternal age.

All the data analysis was performed by the Statistical Package for the Social Sciences (SPSS). Permission to conduct this research was obtained from the recognised University Research Ethic Committee of the University of Malta. The public health medicine consultant (MG) in charge of the NOIS performs regular validation audits on a number of variables to validate the information in the dataset.

Revised manuscript accepted for publication February 12, 2018

Clin. Exp. Obstet. Gynecol. - ISSN: 0390-6663
XLVI, n. 2, 2019
doi: 10.12891/ceog4624.2019

7847050 Canada Inc.
www.irog.net

Published: 10 April 2019

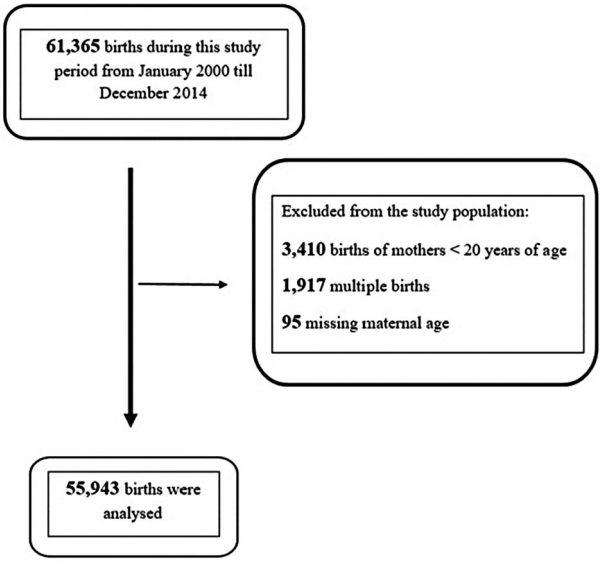

Figure 1. — Study plan.

Table 1. Patient Age Distribution

Maternal Age Groups	Number of Mothers	Percentage of Mothers
20 – 24 years	9,814	17.5%
25 – 29 years	20,417	36.5%
30 – 34 years	17,549	31.4%
35 – 39 years	6,838	12.2%
≥ 40 years	1,325	2.4%

Results

Between the year 2000 and the year 2014, a total of 61,365 deliveries were registered in Malta and Gozo. Figure 1 represents the number of births, exclusions, and the actual size of the study population. All mothers studied were divided in five different maternal age groups as shown in Table 1. The average maternal age was 29.2 (range 20-55) years. Figure 2 represents the maternal age over this 15-year period.

The maternal age and the following maternal and infant characteristics were studied. Maternal characteristics included were body mass index worked, nationality, smoking status, parity, previous live births or previous still births, hypertension, and diabetes mellitus. The infant characteristics studied are: calculated gestation at the time of delivery, infant's birth weight, Apgar score at 1 and 5 minutes, infant outcome, infant congenital malformations, and deformities.

Multivariate regression analysis was carried out for each outcome studied. The first model created was to assess for preterm delivery. Babies born before the 37 weeks of gestation were considered as preterm births. For this case, a forward stepwise logistic regression model was fitted and the significant confounders were maternal age ($p < 0.0001$), insulin-dependent diabetes mellitus (IDDM) ($p < 0.0001$), cigarette smoking ($p < 0.0001$), BMI ($p < 0.0001$), and history of stillbirth ($p < 0.0001$). The effects of ethnic origin, year of delivery, parity, and non-insulin-dependent diabetes mellitus (NIDDM) were not found to be significant. The adjusted results are represented in Table 2.

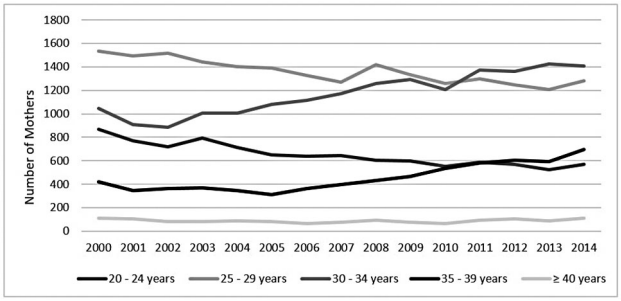

Figure 2. — Trends in maternal age in Malta from 2000 - 2014.

Table 2. Adjusted results for Preterm Delivery and Maternal Age

Preterm Delivery	Adjusted Means & Confidence Interval
20 – 24 years	20% ±2.5 (16; 26)
25 – 29 years	20% ±2.4 (16; 26)
30 – 34 years	22% ±2.6 (17; 27)
35 – 39 years	27% ±3.0 (22; 33)
40 years & older	31% ±3.9 (24; 39)

The average gestational age was 39 weeks. Figure 3 represents the different maternal age groups and the percentage of preterm and non-preterm babies. Results clearly show that the percentage of preterm babies increased with advancing maternal age. The second model created was to analyse the effects on the infants' birth weight. The model used here was forward stepwise linear regression model and the significant confounders were maternal age ($p < 0.0001$), parity ($p < 0.0001$), BMI ($p < 0.0001$), cigarette smoking ($p < 0.0001$), and history of stillbirth ($p < 0.001$). Table 3 shows the adjusted birth weights obtained for each maternal age group after the regression analysis.

The Apgar scores at one and at five minutes were also studied. The ANOVA test was used. No significant differences were found in the mean Apgar scores between different maternal age groups.

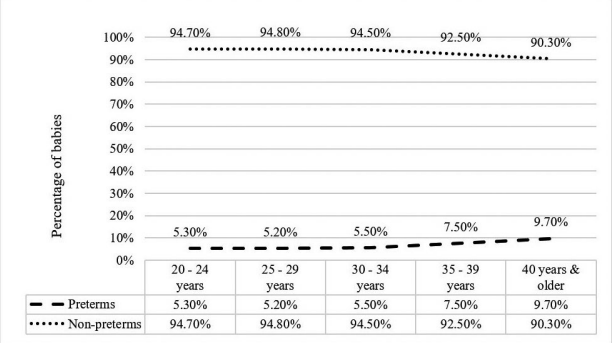

Figure 3. — Preterms, non-preterms, and maternal age.

Table 3. Adjusted birth weight and maternal age groups

Infant Birth weight	Adjusted Means (grams)	Standard Error	Confidence Interval (Lower)	Confidence Interval (Upper)
20 – 24 years	3119.82	19.204	3082.18	3157.46
25 – 29 years	3131.21	18.702	3094.55	3167.87
30 – 34 years	3136.95	18.801	3100.10	3173.80
35 – 39 years	3136.85	19.542	3098.55	3175.15
40 years & older	3090.73	25.202	3041.34	3140.12

The third model created analysed the infant outcome. In this case, forward stepwise multinomial regression analysis was carried out and the significant confounders were maternal age ($p = 0.02$) and IDDM ($p < 0.0001$). Table 4 represents the adjusted rates of stillbirths and the adjusted rates of infants that died within the first 28 days of life. These results were obtained after multinomial regression analysis was carried out by SPSS and the reference group used for this analysis was live births and births of mother of 40 years and older.

As part of the pregnancy outcome, the number and type of congenital malformations and deformities in infants were also studied. Table 5 summarises all the congenital problems detected in this 15-year study period in each maternal age group. Down's syndrome or trisomy 21 was the commonest chromosomal abnormality detected. Over the 15-year study period, 62 cases of Down's syndrome were found. Thirty-one cases of Down's syndrome were children of mothers with AMA. Figure 4 represents the percentage of infants with Down's syndrome according to the maternal age.

Discussion

In the Western world, the average maternal age at which mothers are giving birth is continually rising. The main purpose of this study was to analyse the Maltese local data.

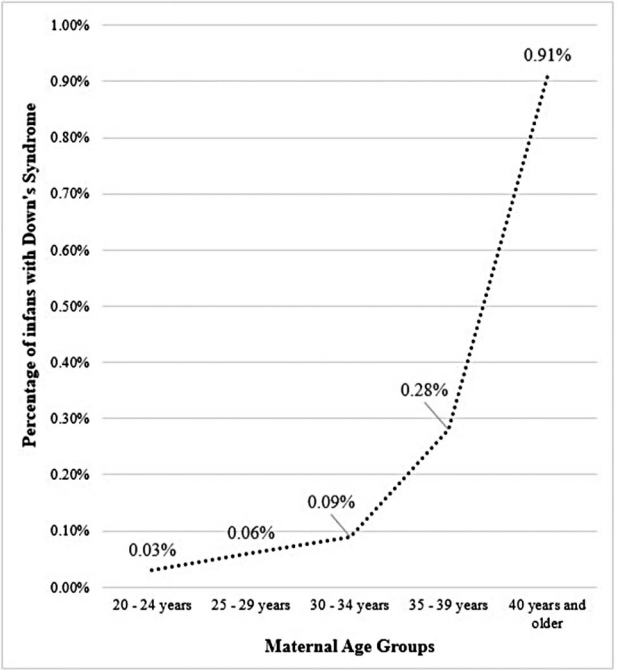

Figure 4. — Infants with Down's syndrome and maternal age.

Table 4. Adjusted rates of Infant Outcomes

Infant Outcomes	Adjusted Rates of Stillbirths	Adjusted Rates of Infants that Died < 28 days
20 – 24 years	0.432%	0.381%
25 – 29 years	0.440%	0.387%
30 – 34 years	0.494%	0.408%
35 – 39 years	0.696%	0.455%
40 years & older	N/A	N/A

The importance of this research lies in the fact that it is the first recent research of its kind carried out locally after the study published by Savona-Ventura and Grech in 1987 [4].

The sample size chosen for this research was large enough to reach the main aim of the study. Malta, similar to Europe, UK, and United States [5], has noticed an increase in percentage of women giving birth at age 35 years and over. According to the yearly annual reports published by NOIS, the average maternal age in Malta was 28 years from the year 2000 until 2007; this increased to 29 years from 2008 to 2012, and increased further to 30 years in the from 2013 and 2014.

In this research a significant difference was noted in the birth weight of babies of mothers from different maternal age groups ($p < 0.0001$). In this study, it was noted that the mean birth weight increased with advancing maternal age up to the 35–39 age group. The mean birth weight of babies

Table 5. Congenital problems and Maternal Age

ICD 10 Congenital Malformations, Deformations, Chromosomal Abnormalities	20 – 24 years	25 – 29 years	30 – 34 years	35 – 39 years	≥ 40 years
Q00 – 07 (Nervous System)	0.08% (8)	0.17% (34)	0.18% (32)	0.16% (11)	0.23% (3)
Q 10 – 18 (Eye, Ear, Face, Neck)	0.17% (17)	0.15% (30)	0.13% (22)	0.12% (8)	0.08% (1)
Q 20 – 28 (Circulatory System)	0.35% (34)	0.25% (52)	0.32% (57)	0.28% (19)	0.38% (5)
Q 30 – 34 (Respiratory System)	0% (0)	0.02% (5)	0.02% (4)	0.04% (3)	0% (0)
Q 35 – 45 (Digestive System)	0.23% (23)	0.25% (51)	0.25% (43)	0.34% (23)	0.38% (5)
Q 50 – 56 (Genital Organs)	0.63% (62)	0.44% (89)	0.36% (64)	0.31% (21)	0.60% (8)
Q 60 – 64 (Urinary System)	0.11% (11)	0.15% (31)	0.09% (16)	0.06% (4)	0.08% (1)
Q 65 – 79 (Musculoskeletal System)	1.5% (147)	1.40% (285)	1.13% (198)	1.17% (80)	0.83% (11)
Q 80 – 89 (Other)	1.13% (111)	1.03% (211)	1.10% (193)	0.98% (67)	1.89% (25)
Q 90 – 99 (Chromosomal Abnormalities)	0.04% (4)	0.06% (13)	0.14% (24)	0.5% (34)	1.89% (25)

born to mothers aged 40 years and older was 3,225.5 grams, and this was the lowest mean birth weight. Similar findings were obtained after the regression analysis was carried out. In 2014, Jacquemyn, Martens, and Martens also reported low birth weights in mothers of 45 years and older [6]. Low birth weights for infants of mothers with AMA was also reported in the study carried out by Savona-Ventura and Grech [4].

In this study, statistically significant results were found between prematurity and maternal age ($p < 0.0001$). In the 40 years and older maternal age group, 9.7% of babies were born before the 37 weeks of gestation. Jacquemyn, Martens, and Martens reported similar results in their retrospective cohort study published in 2014 [6]. On the other hand, in a smaller study published by Weersekra and Udugama in 2003 where only 150 women of 40 years and older were studied, no significant differences in the incidence of premature deliveries and birth weight were detected [7].

No significant difference was found in this population between the Apgar score at one ($p = 0.28$) and at five minutes ($p = 0.099$) and different maternal age groups. This contrast with Savona-Ventura and Grech's study published in 1987, where infants of elderly mothers were statistically more likely to have low Apgar scores at delivery [3]. On the other hand, Weerasekera and Udugama also concluded that in their study carried out in 2003 in Sri Lanka, they found no significant difference in the fiver-minute Apgar score [8].

In this research, elderly mothers in Malta had statistically higher rates of stillbirths. Increased stillbirth rates among elderly mothers was also reported by Salihu *et al.* in their study carried out on 1,313,677 singleton deliveries [9], and by Lehmann and Chism back in 1987 in their retrospective analysis on 183 elderly women.[10] In 2013, the Royal College of Obstetricians and Gynaecologists released a Scientific Impact Paper on 'Induction of Labour at Term in Older Mothers' [2]. They concluded suggesting that offering induction of labour at 39–40 weeks of gestation to women of 40 years of age and older would reduce late antenatal stillbirths and maternal risks of an ongoing pregnancy such as pre–eclampsia [11]. This argument was found to be stronger when there are concurrent medical problems, nulliparity, or Afrocaribbean ethnicity, which all are known to have higher rates of stillbirths [11].

The neonatal deaths were also analysed and a sharp rise was found among babies delivered from mothers of 40 years and older. Many other studies reported increase in perinatal mortality. Jacquemyn, Martens, and Martens [6], Lehmann and Chism [10], Berkowitz *et al.* [12], and Jacobsson, Lafors, and Milsom [13], all reported in their respective studies significantly increase in perinatal mortality.

Congenital anomaly is defined by the World Health Organisation as structural or functional anomalies that occur during intrauterine life. In this study population, apart from the higher percentage of chromosomal anomalies detected in infants of mothers with AMA, higher percentages of digestive system problems were noted in mothers of 35 years and older.

The most common chromosomal disorder detected in this study was Down's syndrome, and the percentage of infants with Down's syndrome increased with advancing maternal age. The prevalence of Down's syndrome is reported to increase as the mother's age increases [14]. In a study carried out to analyse the trends of Down's syndrome in UK and Wales between 1989 and 2008, it was found that the small increase in the number of older mothers has a large effect on the number of Down's syndrome pregnancies. In fact, it was found that the risk for a 40-year-old mother is around 16 times that for a 25-year-old mother [15]. In this study by Morris and Alberman, it was reported that increases in maternal age would have caused a 48% increase in births with Down's syndrome in the absence of terminations between 1989 and 2007 [15]. However, terminations of pregnancies with Down's syndrome have caused the number of live births with Down's syndrome to remain constant in these countries [15]. This does not apply locally, as termination of pregnancy is illegal in Malta.

Conclusion

This study demonstrates that AMA in Malta significantly increases the risk for preterm births, low birth weight, still births, and neonatal deaths. With the persistent rise in the number of mothers having their children at advanced age in Malta, the set-up of a multidisciplinary specialized clinic for pre-conception, antenatal, and postnatal care for these

mothers may prove useful in improving outcome in pregnancies of women with AMA.

References

[1] Mathews T.J., Hamilton B.E.: "First births to older women continue to rise". Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Center for Health statistics. May 2014. Available at: http://www.cdc.gov/nchs/data/databriefs/db152.pdf

[2] Jolly M., Sebire N., Harris J., Robinson S., Regan L.: "The risks associated with pregnancy in women aged 35 years or older". *Hum. Reprod.*, 2000, *15*, 2433.

[3] Joseph K.S., Allen A.C., Dodds L., Turner L.A., Scott H., Liston R.: "The perinatal effects of delayed childbearing". *Obstet. Gynecol.*, 2005, *105*, 1410.

[4] Savona–Ventura S., Grech E.S.: "Risk factors in elderly patients". *In:* European Study Group on Social Aspects on Human Reproduction". V annual meeting, Malta: September 1987, 41.

[5] Matthews T.J., Hamilton B.E.: "Delayed childbearing: more women are having their first child later in life". *NCHS Data Brief*, 2009, *21*, 1.

[6] Jacquemyn Y., Martens E., Martens G.: "Pregnancy at late premenopausal age: outcome of pregnancies at 45 years and older in Flanders, Belgium". *J. Obstet. Gynaecol*., 2014, *34*, 479.

[7] Skaźnik-Wikieł M., Czajkowski K., Kugaudo M., Teliga-Czajkowska J.: "Assessment of pregnancy and labour outcome and the condition of the newborn in primiparous women aged 35 and older". *Ginekol. Pol*., 2003, *74*, 607.

[8] Weerasekera D.S., Udugama S.G.: "Pregnancy at 40 and over: a case-control study in a developing country". *J. Obstet. Gynaecol*., 2003, *23*, 625.

[9] Salihu H.M., Wilson R.E., Alio A.P., Kirby R.S.: "Advanced maternal age and risk of antepartum and intrapartum stillbirth". *J. Obstet. Gynaecol. Res*., 2008, *34*, 843.

[10] Lehmann D.K., Chism J.: 'Pregnancy outcome in medically complicated and uncomplicated patients aged 40 years or older". *Am. J. Obstet. Gynecol*., 1987, *157*, 738.

[11] Royal College of Obstetricians and Gynaecology: RCOG statement on later maternal age". Available at: https://www.rcog.org.uk/en/news/rcogstatement-on-later-maternal-age/

[12] Berkowitz G.S., Skovron M.L., Lapinski R.H., Berkowitz R.L.: "Delayed childbearing and the outcome of pregnancy". *N. Engl. J. Med*., 1990, *322*, 659.

[13] Jacobsson B., Ladfors L., Milsom I.: "Advanced maternal age and adverse perinatal outcome". *Obstet Gynecol*., 2004, *104*, 727.

[14] "Birth Defects". Available at: http://www.cdc.gov/ncbddd/birthdefects/downsyndrome/data.html

[15] Morris J.K., Alberman E.: "Trends in Down's syndrome live births and antenatal diagnoses in England and Wales from 1989 to 2008: analysis of data from the National Down Syndrome Cytogenetic Register". *BMJ*, 2009, *339*, b3794.

Corresponding Author:
M. COLLICT, M.D., MSc, MRCSEd
Mater Dei Hospital
Geranium, Joseph Pace Street
Gudja GDJ1141 (Malta)
e-mail: mandy.caruana@gov.mt