Triplet pregnancies in women over 40 years of age
Part II

LOUIS KEITH

Abstract

Background: This paper examines a subject not specifically discussed in obstetrics and gynecology – the outcomes of triplet pregnancies in women over 40 years of age. Materials and methods: Data were available from a private perinatal database in the United States, consisting of 3288 triplet sets collected between 1988 and 2000, of which 171 mother were over age 40. These women were matched by parity on a 2:1 basis with mother age 25-29 (younger controls) and 35-39 (older controls). Data were analyzed for demographic characteristics and obstetric outcomes. Results: Mothers age 40 or older had only about 1/3 of the most dangerously preterm deliveries (< 28 weeks) compared to younger control (age 25-29) (2.3% vs. 6.4%, respectively). Older control mothers (age 35-39) were more likely to have babies > 32 weeks (p = 0.08, OR 1.5; 95% CI 1.1-2.7), compared to the younger control mothers (age 25-29). In addition, the frequency of birth at < 1 kg was 35% lower in mothers age 40 or older compared to the younger mothers (age 25-29) (4.5% vs. 7%, respectively). At the same time, individual triplet birth weights for infants A, B and C were higher for mothers over 40 years of age, and the mean total triplet weight in mothers age 40 years or older was significantly higher compared with the younger control mothers. Conclusions: Older mother of triplets did not have a poorer outcome than their younger counterparts, in terms of pregnancy length and individual and total birth weight.

Key words: multiple pregnancy, triplet, women age over 40 years

1. Introduction

The problem of the outcomes of triplet pregnancy in women over 40 years of age wasn’t specifically studied in obstetrics and gynecology. Considerable data exist regarding pregnancy in the “elderly” gravida, but mainly concerned with singleton gestations. The literature on the twin deliveries in mothers over age 40 consists of one paper. The authors of this study concluded that twin births at the age > 40 years are significantly more likely among nulliparas or para > 4. Birth weight characteristics of twins delivered to mothers of such age are not different from those delivered to 35- to 39-year-old mothers. Review of such literature shows no consistency in defining “elderly” and it does not present any information on triplet gestation.

Based on the information presented above this paper utilizes the null hypothesis that among triplet gestations, maternal age has no relation to a variety of maternal complications nor to adverse fetal outcomes.

2. Materials and methods

2.1. The database used for these studies

2.1.1. Matria

Matria, as used in this paper, is the short name for Matria Healthcare, Inc., located in Marietta, Georgia, USA. The company, through its Women’s Health division, specializes in providing a variety of outpatient surveillance services to women with high-risk pregnancies. Data were available from a nationwide perinatal database of 3288 triplet sets that had been collected between 1988 and 2000 and entered into a computerized system. Consistency of documented information was obtained using internally programmed validation ranges within the system and quarterly audits of randomly selected records. The data system demonstrated a unique characteristic, in that not only was the information collected in a prospective manner, but the data collection instrument was subject to one only major revision between 1988 and 2000.

2.1.2. The sample size in relation to all USA triplets

For the period 1989-97, the Matria triplets comprise 17.4% of all triplets delivered in the USA. This calculation aligns the Matria data with the data reported by Martin and Park [39] for the USA in the most recent governmental publication available at the time of this writing.

2.1.3. Comparison of important variables between Matria and USA Data

Figure 1 is a comparison of three important variables present in the Matria database and in recent USA
data [2]. Mean gestational age (wks), frequency of births less than 33 wks, and birth weights less than 2500 g are virtually the same in both comparison groups and without significant differences.

In contrast, small differences exist in the grouped maternal ages, although without statistical difference (Fig. 2).

To evaluate the trend in the age of triplet mothers in the USA, the data provided by Kiely and Kiely [27] were adapted for Figure 3, which shows a 2-fold increase in the number of mothers < 20 years of age during the two decades analyzed. At the same time, the number of mothers age 25-29 increased slowly and steadily, as was the case with mothers 30-34 and 35-39. In contrast, the number of mothers > 35 increased 10-fold over these years, and mothers age 45+ exhibited a 50-fold increase [27].

The Matria database showed a comparable trend for a shorter period of time (a 1990-93 to 1997-99 ratio) (Fig. 4).

A further comparison between the gestational age distribution in the USA [2] and the Matria database is shown in Figure 5. The distributions are similar, especially around the means.
Differences are seen at both tails of the gestational age distribution, relating to the effect of the Matria services, depicting a 50% decrease in deliveries at gestational age less than 28 wks and no differences in deliveries at gestational age 36 wks or more. As a result of the stability on the right side of the distribution and the difference on the left (Fig. 6), a small increase was seen in the frequency of triplets born between 28-32 wks in the Matria database compared to the USA data.

This finding (as shown in Figure 6) suggests that Matria services significantly reduced the frequency of dangerously premature triplets (i.e. < 28 wks) while not changing the mean gestational age distribution. The Matria database shows the same trend within a shorter time period (1990-99). Based on the comparisons described above, it is reasonable to conclude that the Matria database indeed is representative of the USA triplet population. The following points clarify this conclusion:

- similar distribution of gestational age at birth,
- similar frequency of births < 33 wk,
- similar frequency of birth weight < 2500 g,
- similar maternal age distribution,
- similar trend in maternal ages over time.

### 2.1.4. Descriptive statistics of the Matria Database

#### Maternal age

Maternal age is Gaussian in its distribution, with a median of 32 years (Fig. 7). Ten percent of the population is either younger than 27 or older than 37 years. Only a small component (0.5%) of the population is less than 20 years of age. Figure 8 emphasizes the differences between women age 35-39 years and those greater than age 39.

The computer-generated best-fit trend lines show marked differences in the rates of incline, in that a 20% increase (from about 20% to about 24%) is seen in the frequency of mothers 35-39 years, compared to a 700% increase in the frequency of mothers over 39 years (from about 1% to approximately 7%). Such findings support the contention that the combination of older maternal age and triplet pregnancy is a unique and therefore unknown obstetric challenge.

### Parity and gestational age

Until the mid-1980s, maternal age and parity correlated rather well. With the advent of infertility treatments to compensate for reduced fecundity from any reason, however, age no longer presents a barrier to conception, and the previous correlation no longer holds. Perhaps the most important result of this change is that the concept of “normal reproductive years” is no longer a defining term. Accordingly, the so-called “geriatric gravida” presently is well described in the literature of the USA and other developed countries, as well as in the developing world. It is important to remember that,
in traditional societies and those with little or no access to contraception, geriatric gravidas usually represent grand- or great-grand multiparas [1]. On the other hand, in the USA and other industrialized societies with access to ART, the geriatric gravida is now either a nullipara or a para 1 or 2, who, for one reason or another, has experienced a period of secondary infertility.

Figure 9 illustrates this phenomenon. Here, the ratios of nulliparas to multiparas are shown in the Matria triplet population. These findings contrast with the dotted line representing the ratio in more than 22,000 Israeli twins (courtesy of Professor Isaac Blickstein) [7], for which Matria has comparable twin data (not shown). As maternal age advances, the steep decline in the ratio. That no comparable decline is seen in the triplet ratios in the same maternal age groups suggests that many more nulliparas are having triplets, regardless of their age. Although it is a supposition, a logical explanation for this observation is that these older mothers have experienced an intervention that resulted in a triplet pregnancy.

This supposition is supported by the data presented in Figure 10, which contrast the Matria triplet nulliparous mothers with all USA nulliparas by maternal age using data from 1990, 1995, and 1998 from Ventura et al. [60]. Whereas the Matria data approximate a Gaussian distribution, those of the USA are polynomial in their nature.

The trends described above are summarized in Figure 11. This analysis depicts the ratios between the Matria nulliparas and all nulliparas in the USA by grouped maternal ages. At the far left, the likelihood of a Matria mother of triplets being age older than 29 and a nullipara is 3.4 times that of the USA nullipara. If age greater than 34 is selected, this likelihood increases by 30% to a ratio of 4.4. On the other hand, if one considers age older than 39, then the likelihood increases by an additional 50%, to give a ratio of 5.1. This trend is summarized in a statement recognizing that the age of the Matria nulliparous mother of triplets was 5 times more likely than the USA nulliparas to be older than 40 years.

The final two analyses of parity are shown in Figures 12 and 13. Figure 12 shows the frequency distribution of gestational age at birth by parity. Despite the obvious similarity, it appears that gestational age is somewhat more advanced in the Matria database.

Figure 13 emphasizes the important risk for preterm delivery among nulliparas by grouping gestational ages. The nulliparous mothers were twice as likely to deliver at a dangerously premature gestational age (less than 28 wks) compared to their multiparous counterparts. At 28 to 32 wks, however, this tendency declines by 15%. In contrast, the multiparous mothers were about 10% more likely to deliver 33-36 wks and 2.5 times more likely to deliver triplets at greater than 36 wks gestational age than were the nulliparas.
As a public health consideration, the most important finding relating to the relationship between gestational age at birth and maternal age is shown in Figure 14. Here the percent of births at less than 32 wks declines steadily in a linear fashion until age 44. The reversal in this decline after age 44 is clearly shown and highlights a central theme of this study — the greater frequency of triplets in older mother. Further, it serves to form the basis of comparison for the findings of the next two figures.

Figure 15 examines gestational age at 32-35 wks, and Figure 16 considers gestational age at week 36 or more. In neither instance does maternal age group greater than 34 years show an exaggerated effect. Rather, there is a decline at those gestational age groups, and the decline is more marked after 36 wks. Although it is an assumption, based upon the knowledge that triplet pregnancies at age 40 or older are more likely to result from ART, the data in Figure 13 may be considered alarming because of the putative association that one might make between mode of conception and extreme prematurity.

**Birth Weight**

Along with gestational age, birth weight represents an important element affecting neonatal outcome. Data from 2803 live-born triplet sets (8409 infants) were used for this analysis. A total of 435 cases was excluded for missing data, fetal death, and improbable data entries using the algorithm suggested by Kiely [28]. Two distinct numbers are analyzed: (1) the individual birth weight for each triplet, and (2) the total triplet birth weight.
weight, which is the sum of three individual weights in a given set.

Individual birth weight distribution is shown in Figure 17. Although the distribution is Gaussian at first glance, it has a negative skew in that the tail of the lower end (left) is longer than that at the upper end (right). Such a finding is indicative of a greater spread toward the higher weights, as reflected in the shift of the high point of the curve from the middle to the right.

**Fig. 17. Distribution of individual triplets birth weights – Matria Data**

**Additional neonatal data**

Data pertaining to sex were available for 3321 sets of triplets (99.5% of the sample). The female/male proportion (F/M) was 49.7:50.3, a proportion that is essentially without difference. Data were available in 2790 sets of triplets (exclusions for spurious entries) to compare gestation lengths in both sexes. The combinations are shown in Figure 18.

The differences were negligible (MMM = 32.79; MMF = 32.74; FFM = 32.83; FFF = 32.91 wks). Despite these insignificant differences, the disparity between male and female birth weight averages amounts to 88 g (1793 g for females vs. 1881 g for males). The mean birth weights by sex combination were MMM = 1871, MMF = 1849, FFM = 1826, and FFF = 1804. The mean total triplet birth weight by the same sex combinations were MMM = 5614 g, MMF = 5546 g, FFM = 5477 g, and FFF = 5411 g. When mean total triplet birth weight (g) was analyzed by these same gender combinations, the heavier weight of males contributed to a 203 g difference between the total birth weight of MMM sets (5614 g) to the FFF sets (5411 g).

The proportion of admissions versus non-admissions to the Neonatal Intensive Care Unit (NICU) is shown in Figure 19. When this material was reanalyzed using the grouped maternal ages, this lack of difference remain unchanged (data not shown).

**Fig. 19. Neonatal Admissions to the NICU – Matria Data**

### 2.2. Selection of cases and controls

The data analysis of this study uses a case control methodology. The cases were all mothers of triplets in the Matria database age 40 years or more (n = 171). Two control groups were selected for the match. In the first, patients were selected from the mothers age 35-39 who represented the nearest subset of maternal age. In the second, mothers ages 25-29 comprised the cohort from which additional matches were selected. Each control group comprised 342 mothers.

It was originally anticipated that the controls would have been selected from groups age 20-29 and 30-39. It became apparent, however, that 10-year groupings might be too broad to see an age-specific effect and that a more appropriate approach would be to select the upper half of each group (younger controls age 25-29 and older controls age 35-39). Moreover, this methodology had been used with success in an earlier analysis of
Therefore, the original plan of analysis was modified. Two controls were selected for each case, matched for parity using a computer generated randomization methodology. Based on this construct, older mothers can be compared with two groups of younger mothers — the distinctly younger mothers and the nearly older mothers.

### 2.3. Statistical methods

Data were stored using a Paradox program and were extracted as a Microsoft Excel file (Microsoft Corporation, Redmont WA USA). Statistical analysis used the SPSS 8.0 (Chicago IL USA) software program. The 2-tailed student-t and Chi-square tests were used for continuous and categorical variables, respectively. The 2-tailed analytical methods were chosen because it was not known if the study group (mothers age 40 or older) would differ from the controls (younger mothers) in either the lower or the higher direction. *P*-values and 95% confidence intervals (95% CI) were calculated for each analysis. Two-tailed *p*-values less than 0.05 were considered significant. Power analyses showed that the sample size was large enough to detect differences of 5% at a power of 80%.

![Fig. 20. Percentage of married mothers](image)

**Fig. 20. Percentage of married mothers**

### 2.4. IRB approval

This studies was labeled IRB Project No. 1081-001 at Northwestern University Medical School in Chicago IL USA and declared exempt from IRB review under applicable United States regulations [45 CFR 46.101(b) with paragraph #4],

### 3. Results

Two controls were selected for each of the mothers of triplets in the Matria database age 40 years or more. In the first group, patients were randomly selected from the mothers age 35-39 who represented the nearest subset of maternal age. In the second, mothers age 25-29 represented the group from which additional random matches were selected. Two controls were selected for each mother age 40 or older. Each control was matched for parity using a computer-generated randomization methodology. A total of 171 mothers was identified using the descriptor of age 40 or older; each control group contained 342 mothers. Data were calculated from these numbers unless otherwise specified. Because data collection within Matria became more robust after 1995, the analyses of specific variables often had to be performed on fewer patients.

Table 1 shows the exact number of patients available for each of the following analyses by age group. In addition, the exact numbers in each cell are shown in the appropriate figures below (mothers age 40 or older, controls age 35-39, and controls age 25-29).

Figures 20 through 25 depict those women age 40 or older compared with the younger (age 25-29 years) controls and the older (35-39 years) controls, in terms of historical data.

Figure 20 shows marital status and reflects social rather than biological circumstances. Significantly, more women over age 40 were married, compared to the younger controls, age 25-29 (*p* = 0.005, OR 0.2; 95% CI 0.1, 0.7).

Figure 21 refers to smoking. Although the percentage of non-smoking mothers does not differ among cases and controls, this finding is important because a significant difference might at least partially account for differences in fetal size and growth restriction, if such were present.

Figure 22 shows smoking. Although the differences are not significant, a clear trend is seen in which a greater number of younger women describe a past history of preterm labor. This trend may reflect the fact that younger women were more likely to have experienced pre-term labor in a prior pregnancy that had a less than ideal outcome; therefore, they may have requested ART more frequently in the subsequent (current) pregnancy, although this interpretation is speculative.
Table 1. Number of patients for each analysis by age group

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Fig. 21. Percentage of non-smoking mothers

Fig. 22. Percentage of mothers with a history of cervical incompetence
Triplet pregnancies in women over 40 years of age. Part II

Figure 23 shows a significant difference in the prior history of abortion for mothers age 40 or older versus the younger (age 25-29) control group ($p = 0.0001$, OR 2.3; 95% CI 1.6, 3.5). This finding is logical and not unexpected, as increasing age increases the chance for both pregnancy and pregnancy loss. Unfortunately, the available data do not discriminate between spontaneous and induced losses.

Figure 24 reflects a similar trend as shown in Figure 23. Here, the younger (age 25-29) controls had a somewhat higher chance of a prior preterm birth, although it is not statistically significant.

The data shown in Figure 27 (cervical incompetence in the current pregnancy) possibly represent a combination of the interpretation of history and current physical findings. Compared with the data shown in Figure 22, the overall percentages in Figure 27 are increased for every age group, suggesting that the designation of cervical incompetence is more frequent (almost two times) when a patient is being followed for a triplet pregnancy. A rational explanation for this supposition is that it reflects intrinsic physical features of a triplet pregnancy, i.e., the tendency toward precocious dilatation and effacement, as well as funneling (dilatation of the lower uterine segment and presentation of the membranes into the internal os).

Figure 28 shows a nonsignificant difference in the numbers of mothers age 40 or older and those of either...
the younger (25-29) or older (35-39) controls who received cerclage during the index pregnancy. Regardless, at each age group, the numbers of mothers who received cerclage were more than the numbers of mothers who exhibited cervical incompetence (see Figure 27).

This discrepancy reflects the ongoing controversy regarding the use of prophylactic cerclage in triplet pregnancy. The literature on this intervention fails to provide consensus on two crucial issues: (1) whether to perform the operation at all, and (2) whether it is beneficial if performed. Critics are quick to point out that this operation is not innocuous and may lead to serious complications, regardless of whether it is performed prophylactically or only in cases with indication.

Bleeding at less than 18 weeks is generally considered a nondependent risk for adverse pregnancy outcome (Fig. 28). In this study, there is no significant difference between the cases and either control group. Because of this, bleeding can be discounted as an explanation for potential differences between groups.

The frequency of uterine irritability in mothers age 40 or older and both the younger (age 25-29) and older (age 35-39) controls is shown in Figure 31. Significant differences are present between both control groups ($p = 0.04$, OR $0.7$; 95% CI 0.5, 0.98) but not between mothers age 40 or older and either the younger (25-29 years) or the older (35-39 years) control. Whereas one might speculate that the difference between the younger (age 25-29) and older (age 35-39) controls is because of a diminution or loss of the natural propensity of the uterus to contract during pregnancy [21], one might wonder why this was not also the case for the women age 40 or older. Another potential – but not completely satisfactory explanation – is that younger women were less experienced with pregnancy-related symptoms and thus...
more likely to report them to their healthcare providers. As the Matria database did not define the criteria required for making this diagnosis, it is not possible to be more precise in explaining this finding. Regardless, it also is possible that “uterine irritability” is a default characteristic of the uterus that diminishes with age. From a teleological point of view, this is not unreasonable.

The finding depicted in Figure 34 — that there is a significant difference in the percentage of deliveries indicated for gestational hypertension in mothers age 40 or older compared to the younger (age 25-29) controls ($p = 0.03$, OR 1.9; 95% CI 1.1, 3.5) — is not unexpected. Unfortunately, however, because the Matria database collapsed various subtypes of hypertensive disease into one category — that is, gestational hypertension, the numbers of mothers with chronic hypertension in any of the patient groups are unclear.

Regardless, the numbers of mothers with HELLP syndrome did not differ significantly between the younger or older control groups (Fig. 35).
The ability to further interpret the data in Figure 34 and 35 somewhat is hampered by a lack of references for comparison, but recent commentary by Smith-Levitin [57] suggests that patients with multiples present with symptoms consistent with HELLP syndrome more frequently than do women with singleton pregnancies.

The frequency of spontaneous rupture of membranes (Fig. 36) did not differ between mothers age 40 or older and both the younger (age 25-29) and the older (age 35-39) control groups.

In fact, these numbers are quite similar and only about 25% of the respective frequencies of patients who had preterm labor (Fig. 37). It is not possible to determine the frequency with which spontaneous rupture of the membranes immediately proceeded or followed preterm labor, as these two variables were not jointly coded. Here again, the numbers in the Matria database are fewer than those cited by Luke et al. [32], either for PPROM (21%) or preterm labor (75%).

Figure 38 is of interest for two reasons: (1) it shows low rates of suspected IUGR, and (2) it shows no differences in the percentage of pregnancies with suspected IUGR between the mothers age 40 or older and the younger (age 25-29) and older (age 35-39) control groups. It is quite possible that the low rate of ascertainment of IUGR is related to lack of a uniform standard based on data gathered from triplet pregnancies.

Because of the competition for nutrients by the fetuses, the risk of IUGR increases with advancing gestation age. As noted by Luke et al. [32], by 36 weeks gestation, the mean birth weight for triplets is at 10th percentile for singletons.

The data shown in Figure 39 support the contention that triplet pregnancy does not accentuate the maternal risk of gestational diabetes. In general, these figures are somewhat lower than those cited by Luke et al. [32]. Further, they cannot explain the birth weight differences that will be discussed below.
There are no differences in pre-pregnancy Body Mass Index (BMI) between the mothers age 40 or older and both the younger (age 25-29) and older (age 35-39) control groups (Fig. 40). Indeed, the lack of either significant or clinically relevant differences is both striking and somewhat surprising, in that older women are often heavier than their younger counterparts. Moreover, one might expect that birth weight differences might in some way be related to differences in pre-pregnancy BMI, but such differences are clearly not present.

The association between maternal pregravid BMI and birth weight was part of the study 227 mothers of triplets age 20-34 described by Yokohama and Shimizu [61]. In this study from Japan, gestational week of delivery and birth weight were significantly lower in underweight women, compared to women with normal weight. In view of the prior observations of Luke et al. [34] — that birth weight in twins is related to pre-pregnancy BMI — the differences between published observations in triplets and those in twins suggest that further studies in this area would be useful. Given these discrepancies, one can hypothesize that what appears to be true in twins may not be the case in triplets.

The lack of significant differences in maternal height between mothers age 40 or older and either the younger (age 25-29) or older (age 35-39) control group (Fig. 41) is not in agreement with the observations of Blickstein and Jacques [7] in their global analysis of the Matria triplet database. Elster et al. [15] also found that maternal height was associated with higher than average triplet birth weight but not with a more advanced gestational age at birth. However, in the construct of the present study, one should not expect that height would differ with age.

Figure 42 shows that no significant differences were found in the pre-pregnancy weight between the age groups, contradicting the widely held opinion that older women invariably are heavier than their younger counterparts. According to conventional thinking, the added weight often observed in older women is related to higher parity, which is characteristic of increased years. In this study, however, parity was a matching variable and so cannot be further considered here.

Figure 43 describes the mean gestational age at referral for Matria services. No differences are present.

Because Matria represented an outside consultation service to its referring physicians, the lack of variation in the mean is instructive to show the relative uniformity...
of concern exhibited by physicians for women at differing ages. It would appear that maternal age did not influence the time of referral.

The present epidemic of triplet gestations permits consideration of data pertaining to triplet pregnancies in ways previously not possible. Foremost is among these — and the principal aim of this studies — is to evaluate the effect of maternal age on pregnancy outcome, an analysis not previously conducted because of insufficient numbers. Figures 44 through 46 merit a common discussion, as they represent the most important findings of these studies. These figures illustrate the length of gestation and individual and total triplet birth weights.

Figure 44 shows no statistical difference in the grouped gestational age at birth for mothers age 40 or older, compared with both the younger (age 25-29) and the older (age 35-39) control groups. However, using the grouped format, the younger (age 25-29) controls had a 1-week disadvantage, compared to the mothers age 40 or older and the older (age 35-39) controls (32 weeks vs. 33 weeks).

These findings are amplified in Figure 45. Here, mothers age 40 or older had only about one-third of the most dangerously preterm deliveries (< 28 weeks) compared to the younger (age 25-29) control mothers (2.3% vs. 6.4%, respectively). Equally instructive are the pregnancies that ended at greater than 32 weeks of gestation. Statistical differences are not present between the two control groups, although the older (age 35-39) group, compared to the younger (age 25-29) group was more likely to have babies > 32 weeks (p = 0.08, OR 1.5; 95% CI 1.1, 2.7). It is also important to note that, even though mothers age 40 or older were not statistically different from older (age 35-39) control mothers with regard to the frequency of births after 32 weeks, a difference was seen.

Figure 46 describes individual triplet birth weights. A significant difference exists for the infants of mothers over 40 compared with mothers in the younger (age 25-29) control group for triplet A, triplet B, and triplet C. By examining the data for triplets baby A, baby B, and baby C individually, other important differences also become apparent. For example, although the birth weight differences between the infants of mothers age 40 or older and those of mothers age 35-39 did not reach the statistical significance, the clinical importance of such differences cannot be dismissed. Thus, the difference of 170 g between 2062 g in baby A of a mother over 40 years of age and the 1892 g of baby A of the mother age 35-39 cannot be disregarded, as it is a clinically important difference. Similarly, the difference between the 1892 g baby A of the 35- to 39-year-old mother and the 1664 g baby A of the mother age 25-29 years — 318 g — also is clinically important.
between 2069 g and 1878 g is 191 g, and the difference between 1878 g and 1678 g is 200 g. These differences also are clinically important and cannot be discounted. The patterns evident for baby A and baby B are present for baby C as well, except that all weights are diminished in comparison to baby B and baby A. Here the difference between 1942 g and 1774 g is 161 g, and the difference between 1774 g and 1567 g is 207 g. Again, these differences are clinically important, especially because the weights of baby C are smaller than the weights of baby B and baby A, regardless of maternal age.

Figure 47 is instructive for two reasons: (1) the mean total triplet birth weight is significantly higher in mothers of 40 or older compared with the younger (age 25-29) controls \( (p = 0.01) \), and (2) this finding points the way for accelerated focus in the provision of prenatal care in the younger women whose children are at risk in terms of diminished (-334 g) total birth weight compared to the children of mothers over age 40.

**Fig. 47. Comparison of mean total triplet birth weight**

Figure 45 is a prelude to Figure 48, which shows that the frequency of births at less than 28 weeks was markedly reduced (almost 2/3) in mothers age 40 or older compared to the younger (age 25-29) controls \( (2.3\% \text{ vs. } 6.4\%) \).

**Fig. 48. Comparison of frequency of birth weight categories**

Figure 48 shows that the frequency of birth at less than 1 kg is 35% lower in mothers age 40 or older compared to the younger (age 25-29) controls \( (4.5\% \text{ vs. } 7\%) \). Moreover, when births from 1.1-1.5 kg are considered, mothers age 40 or older fared better than the younger (age 25-29) control group \( (18.7\% \text{ vs. } 21.6\%) \). Thus, the findings of Figures 45 and 48 both reflect better outcomes in mothers age 40 or older.

### 4. Discussion

#### 4.1 Aristotle’s opinion

Some of the major issues of concern of these studies were discussed by Aristotle in his On the Generation of Animals (book 7, part 4) \[3\]. As was noted earlier, Aristotle observed that, whereas twins were not against nature per se, they were outside nature’s common course \( (\text{prater naturam}) \). By this, he referred specifically to what he deemed their method of conception, and in this regard his opinions were at considerable variance from what is considered the true circumstances today. At the same time, when he described length of gestation and birth weight, his comments were more in line with modern thinking, so much so that I quote them directly.

Now all other animals bring the time of pregnancy to an end in a uniform way; in other words, one single term of pregnancy is defined for each of them. But in the case of mankind alone of all animals the times are diverse; for pregnancy may be of seven months’ duration, or of eight months or of nine, and still more commonly of ten months, while some few women go even into the eleventh month.

Children that come into the world before seven months can under no circumstances survive. The seven-months’ children are the earliest that are capable of life, and most of them are weakly — for which reason, by the way, it is customary to swaddle them in wool — and many of them are born with some of the orifices of the body imperforate, for instance the ears or the nostrils. But as they get bigger they become more perfectly developed, and many of them grow up.

Such then are the differences between mankind and other animals in regard to the many various modes of completion of the term of pregnancy \( (\text{Aristotle, 4th Century BCE}) \) \[3\].

This commentary anticipates the finding of a short gestation length in triplet pregnancies and the inevitability of death in those born with extremely short
4.2. The older gravida – a concept revisited

4.2.1. Overview

The literature on pregnancy in the “older gravida” is extensive. Published reports can be divided broadly into those written before or after 1990. In either instance, reference citations are repetitive, and original conclusions are few. What is missing is a standard definition of what constitutes “older”, a consensus of whether older women inherently represent high, average, or low obstetric and neonatal risk, and a clear understanding of whether such pregnancies are or are not associated with an increased risk of adverse outcomes. Also missing is whether the older gravida is at any advantage or disadvantage compared to her younger counterpart – a circumstance leading to divided opinions.

One important exception to this knowledge deficit is a report by Mansfield and McCool [38]. Because neither author was a physician, these writers were able to approach the concept of “advanced maternal age” from a new perspective. They concluded that prior researchers failed to control for important contextual differences surrounding the pregnancy and childbirth experiences of both younger and older women in the vast majority of studies of advanced maternal age and pregnancy outcomes published until the late 1980s. They further suggested that these contextual differences accounted for a considerable portion of the differential results mistakenly ascribed merely to reproductive age. They identified three “hidden factors” affecting pregnancy outcomes: (1) older women’s increasing likelihood of having a chronic disease, (2) altered medical management of the pregnancy and labor in older women with resultant iatrogenic complications, and (3) demographic characteristics associated with healthy, middle-class postponers in contrast to women with either poverty or subfertility. Perhaps more important, their review of the literature failed to show a solid empirical basis for the generally held point of view that middle-age women, especially first-time mothers, were actually high-risk patients. Ninety percent of the 114 studies reviewed by Mansfield and McCool [38] were methodologically flawed, 61% of them seriously so. Overall, only 38% of these studies demonstrated higher pregnancy risk for mature mothers, whereas as few as 28% of the methodologically accurate studies found this result. After reviewing hidden factors, these authors concluded that, when older women experience poorer reproductive outcomes than their younger counterparts, it is often assumed that a specific feature of aging, i.e., some intrinsic biologic change that makes these women less efficient reproductively, is responsible for increased risks. In this construct, maternal age becomes a causal variable that, if lowered or raised, can produce different outcomes in the same women. According to Mansfield and McCool [38], the flaw in such logic is believing that older childbearing women differ from their younger counterparts only in their reproductive capacity.

When the same or comparable literature was reviewed by two obstetricians (O’Reilly-Green & Cohen) [44], the concept of increased maternal risk reemerges. O’Reilly-Green and Cohen concluded, after reviewing a 103 sources, that “pregnancy after age 40 involves some clearly demonstrable and even unique risks such as decreased fecundity, spontaneous abortion, genetic abnormalities, medical complications, fetal growth abnormalities, dysfunctional labor, cesarean section, and maternal/perinatal death.” After describing these topics in detail, the question is rhetorically posed whether a woman older than 40 years who is in good health, has no history of infertility, does not smoke, and has favorable sociodemographic features is still at increased risk. O’Reilly-Green and Cohen [44] answered their query in the following manner, “The best information available suggests that the healthy individual is still at increased risk on the basis of advanced age itself.”

4.2.2. Potential advantages and disadvantages of being older

Given the obvious lack of consensus in the literature, it is not unreasonable to ask if the older gravida has some advantage compared to a younger woman. If such were the case, what are some of these advantages, and how might they counter the rather “pessimistic” overview described so thoroughly by Mansfield and McCool [38]? Here, the obstetric literature is relatively silent, and clues – albeit speculative – must be obtained from life observations and the collateral medical literature [19]. Older mothers and certainly those above 40 years of age are likely to be more “mature”. Many may have finished or be at a solid midpoint in their career aspirations and thus have the ability and/or desire to devote nine months exclusively to a pregnancy. In addition, older mothers, especially those who have under-
gone IVF or ART, are likely to have had sufficient time to increase their awareness of the special needs of the unborn fetus. This also means that these mothers are more likely to seek competent obstetric advice early in the first trimester. Moreover, because older women may have a higher BMI and not be as weight-conscious as their younger counterparts, they may be more prone to eat wisely, obtain a balanced diet, decrease alcohol consumption, and avoid tobacco entirely. Such potential advantages would be associated with a greater likelihood of positive outcomes, although proving this contention with solid evidence would not be easy [44].

In contrast, the disadvantages of older age are not so speculative [44]. Two major phenomena interact. First, the incidence of chronic medical conditions is higher, especially after age 40. Indeed, many such women have been infertile or subfertile for many years [25]. Second, regardless of the presence of absence of medical conditions or any degree of infertility, physicians have long tended to consider older gravidas as women who required special attention and/or special care [38]. The combination of these two factors results in older gravidas being treated differently, regardless of whether or not there is a scientific basis for such a treatment [38].

4.2.3. Comments from the literature

The older gravida

Because the literature on the older gravida is so extensive, it was deemed reasonable to review a selection of articles based upon the authors’ description of women over age 40. An exception will be made for an article published in the 1980s by Blickstein et al. [8], which is distinguished by the use of comparison groups and the separate treatment of multiparous and primiparous patients. In that study, no evidence was found that older women should be managed as high-risk patients during their gestations. These conclusions preceded the later comments of Mansfield and McCool [38] but were not cited in their paper. The literature discussed below will be described in chronological order. All articles refer to singleton pregnancies, as no reports on triplet pregnancy after age 40 have been published.

In 1992, Milner et al. [41] came to an opposite conclusion from that of Blickstein et al. [8]. Based on a study of data from 599 women age 40 or over from among 28 600 singleton deliveries conducted between January 1, 1985 and December 1, 1989 at the Rotunda Hospital in Dublin, Ireland, Milner et al. [41] concluded that it was “wiser to manage all elderly gravidas in a high risk manner”. This conclusion was based upon an analysis of 35 variables. In this study, significantly increased rates of antepartum hemorrhage, distress, low birth weight, and perinatal mortality were found in mothers age 40 or older. The authors observed that the mothers over age 40 could be divided into 2 groups: those who had postponed their pregnancy until that age and those who had continued reproducing throughout so-called middle age [41].

Bianco et al. [4] from the Mount Sinai Hospital in New York reported a retrospective cohort study of 1404 pregnant women at least 40 years of age and 6,978 controls age 20-29 years. Patients were stratified by parity (nulliparous and multiparous). Numerous differences were present in terms of demographic characteristics, medical history, and selected antepartum complications based on age as well as parity. Based on either maternal age or parity, the rates of very low birth weight (VLBW), low birth weight (LBW), small for gestational age (SGA), and delivery at less than 37 weeks or less than 32 weeks were without difference. Moreover, the number of perinatal deaths did not differ by age or parity, and the number of neonatal deaths was too small for comparison. In contrast, operative vaginal delivery and cesarean delivery were significantly higher in older women, regardless of their parity. The authors concluded that, although maternal morbidity was increased in the older gravidas, the overall neonatal outcome was not affected [4].

A retrospective review of in-hospital singleton deliveries to women > 45 years of age was conducted by Dildy et al. [13] for the 10-year period between 1985 and 1994 at four Utah (USA) tertiary hospitals. Among the 126 500 births registered during these years, 79 cases were selected for study. No controls were used, and the data analysis was limited. No outcome data for the infants were available except the median gestational age at delivery (39 weeks), with a range of 22.9 to 41.7 weeks. There were two sets of twins and no triplets. Of interest, the median gravidity was 9, with a range of 1 to 26. Although the authors did not so state, it is reasonable to speculate that most patients were Mormon women who avoided contraception and continued to become pregnant on a regular basis throughout the fourth decade of their lives. The woman who was gravida 26 was 45 years of age, and three women had their first pregnancy at 45 years, 46 years, and 53 years of age [13]. An interesting feature of this report is a literature review of ten additional studies of pregnancy in women over age 40. Of these, eight were published before 1980, and in one, the
study period began in 1927. In the others, most data referred to pregnancies before the age of modern contraception [13].

The effect of aggressive infertility treatments and the need for multifetal pregnancy reduction in women > 45 years of age was described by Evans et al. [16]. Eight of nine patients who requested pregnancy reduction were older of 45 years of age. No such requests had been evident before 1994. Four of the nine patients chose reduction to singleton gestation, citing financial and parenting issues at age 60 and 70 as the basis for the request for a singleton gestation. Outcome data was not provided [16].

An Israeli group studied the effect of advanced maternal age (44 years or more) on pregnancy outcome and rate of cesarean delivery [14]. A total of 109 women was matched to 309 controls age 20-29. Using logistic regression, an analysis showed that older women had significantly higher rates of medical complications (hypertensive disorders and diabetes) (OR 2.5; 95% CI 1.5, 4.1; p < 0.001), instrument-assisted vaginal delivery (OR 7.5; 95% CI 2.2, 25.0; p < 0.004), and cesarean delivery (OR 7.3; 95% CI 2.2, 16.7; g: 0.001). The regression model showed an increased risk for cesarean delivery associated with age of at least 44 years (OR 7.3; 95% CI 2.2, 16.7), primiparity (OR 3.5; 95% CI 1.3, 9.8), infertility treatment (OR 3.6; 95% CI 1.5, 8.8), and egg donation (OR 19.5; 95% CI 6.1, 62.2), with positive and negative predictive values of 94 and 86%, respectively [14].

The largest comparative study is that Jolly et al. [22] from the Saint Mary's Maternity Information System Database, which records maternity information from 18 hospitals within the geographical boundaries of the northwest Thames region in the United Kingdom. The obstetric risks of adverse outcome among 385 120 singleton pregnancies were computed for the years between 1988 and 1997. A total of 7331 women age > 40 years was compared to 336 462 women age 18-34 and 41 327 women age 35 to 40 years. In general, older mothers (> 40 years) had higher risks of gestational diabetes (OR 3.98, CI 3.38-4.68), placenta previa (OR 3.09, CI 2.19-4.36), pulmonary embolism (OR 2.38, CI 1.03-5.47), and elective cesarean section (OR 2.67, CI 2.42-2.95). Other complications were also higher, but the increases were not as impressive. Older women C > 40 years) were more likely to deliver before 37 weeks of gestation (OR 1.42, CI 1.26-1.60) or before 32 weeks gestation (OR 1.64, CI 1.25-2.14). Infant birth weights were not described in this report. The general conclusion was that pregnant women > 35 years of age were more likely to suffer complications of pregnancy, compared to younger women [22].

The great grand multipara

It is important to distinguish between the older mother who becomes pregnant for the first time because she had previously postponed pregnancy and the mother who continues to have repetitive pregnancies as she becomes older. Data on these latter pregnancies is far less abundant than the literature on pregnancy in older women. Much of the literature comes from countries or communities where contraception is not used because of religious or cultural barriers and/or from societies with decidedly pronatal policies. A selective review is presented at this point. The interested reader must recognize that much of this literature was published in what are considered “second tier” journals, which may not be familiar to many obstetricians residing on either side of the Atlantic Ocean. A preview of the high number of pregnancies in the Mormon community in Utah, USA, was presented above [13]. Here again, reports are cited in chronological order. As was the case with the absence of the definition of the older gravida, so it is with the grand or great-grand multipara – is it 7, 10, or 14?

Seidman et al. [54] studied a mostly homogeneous, ultra-orthodox Jewish community in Jerusalem, Israel, in an early review of grand multiparity. Of a total of 5916 deliveries in one community hospital, 893 (13%) occurred to mothers who had given birth to seven or more infants. Birth control is forbidden, fertility is extremely high, and almost two-thirds of the grand multiparous women were less than 35 years of age. All women were literate, and 99.6% were married. The ethnic origins were divided as follows: European and Anglo-Saxon Jews (Ashkenazi), 40.3%; Spanish origin (Sephardi) and Asian and Middle-Eastern Jews (Oriental), 27.8%; North African, 23.4%; non-Jews (Arabs of Muslim decent), 5.7%; and unknown, 2.8%. There was a significant decrease in the incidence of SGA infants among the grand multiparous women, compared to the controls (3.6% vs. 5.8%), which was independent of maternal age. No increase in obstetric complications or neonatal morbidity and mortality was present for the grand multiparous mothers compared to the controls. Birth weights were not reported [54].

Kaplan et al. [23] proposed the term “great grand multiparity” to describe the condition of having giving birth 10 times or more. These authors studied two prenatal and delivery units in the Tel-Aviv area that cater to the very large extremely orthodox community of Bnei-
Brak and neighboring towns, whose inhabitants avoid contraception mainly to fulfill the Old Testament precept, “Be fruitful, and multiply” (Genesis 1:22). The study group consisted of 420 women delivering for the tenth time or more between January 1, 1990 and June 30, 1994. Results were compared with those from a control group of the general population (numbers not stated). The average maternal age in the study group was 37.98 (range 33 to 47 years), 9.98 years older than the average of the controls. Parity ranged from 10 to 19, and gestational age at delivery was 39.63, compared to 38 weeks for the general population. Birth weight at the present delivery was 3523 g, compared to 3400 g for the general population, with a significantly lower rate of LBW ($p < 0.005$). The authors concluded that great grand multiparity did not present an obstetric risk. The references of this article are of interest, because they describe this clinical entity in Nigeria, Malaysia, and other developing countries in the Pacific Rim [23].

Abu-Heija and Chalabi [1] described a neighboring point of view from Jordan. Using the same definition of great grand multipara as the Israelis (para > 10), 154 study patients were compared with 308 women (para 2-5) for the time between April 16, 1994 and January 15, 1995. Highly significant differences were noted for great grand multiparas compared to multiparas in terms of age (37.9 vs. 28.5, $p < 0.0001$), parity (10.97 vs. 3.1, $p < 0.0001$), and birth weight (3552 vs. 3301, $p < 0.005$). Additionally, great grand multiparous women were found at increased risk of pre-eclampsia, intrauterine fetal death, and macrosomia. Unlike the Israeli report of Seidman et al. [54], which details a favorable socioeconomic lifestyle of the study population, this report observed that most of the study mothers did not receive regular antenatal care and were of the lower socioeconomic classes. The authors were of the opinion that the lack of antenatal care was attributable to a burden of a large family at home and that most mothers had no problems with prior pregnancies [1].

A final and more recent Israeli commentary was published Maymon et al. (1998). In this study of 12 296 multiparous women (6 singleton deliveries or more), 78% (9587) were classified as grand multiparas, and the remaining 2709 were characterized as “huge” multiparous women (> 10 singleton deliveries). High birth order remained strongly associated with the occurrence of peripartum complications, and huge multiparity was associated with a higher rate of maternal and peripartum complications than grand multiparity. Theirs was the largest study of its kind [40].

### 4.3. The findings of this studies

The composite results of the analyses performed for these studies are shown in Table 2. Data are segregated into the following subsections: historical, medical conditions of the current pregnancy, anthropometric status, and obstetric outcomes. The figure number of each separate analytic factor is also presented, so the reader may refer back to the results section as desired. As shown in the right column, significant differences are present between the mothers age 40 or older and either one or both of the control groups (C1, mothers age 35-39; and C2, mothers age 25-29) for some of the factors studied. In these analyses, the null hypothesis is rejected. In the remainder, the null hypothesis that the maternal age is not related to X, Y, or Z is accepted.

Some of the variables in which the null hypothesis is accepted are of considerable medical importance. Among the historical maternal data, for example, the history of prior abortions has medical and statistical importance in terms of the study outcomes. The same may be said for the uterine activity and cervical change, uterine irritability, and the higher number of admissions into the hospital, all of which may be connected and related via one or more of the possible explanations offered in the next section. At the same time, bleeding < 18 weeks and delivery for gestational hypertension may relate to inherent age related differences.

By far, the most clinically important and totally unexpected finding is the rejection of the null hypothesis in terms of the individual triplet birth weights (Fig. 46), the mean total triplet birth weight (Fig. 47), and the frequency of birth weights < 1000 g and > 2500 g (Fig. 48) in mothers greater than 40 years of age.

Given the findings cited above, these studies add important and previously unknown and unexpected data to the debate surrounding the issue of whether pregnancy at age 40 or older is inherently at higher risk than pregnancy at a younger age. Considering the available parameters of the dataset used in these studies, one might say that mothers age 40 or older in this study group exhibited advantageous outcomes in many important variables. This finding may be of great value in the future as the techniques of ART become even more refined, whereby older women (age 50 or older) become pregnant via oocyte donation [48, 51].

### 4.4. Confirmatory findings from the NCHS Matched Multiple Data File

Because the null hypothesis was accepted in terms of advanced maternal age not being related to adverse
fetal outcomes, it was deemed useful to attempt to confirm this finding. To the best of this author’s knowledge, no existing publications could provide data that would either confirm or refute the findings of these studies. The one potential but yet unpublished source was held by the National Center for Health Statistics of the Centers for Disease Control and Prevention in the United States Department of Health and Human Services in the form of the Matched Multiple Birth File [39]. This data set has not been widely circulated.

Accordingly, the author requested Amy Branum, assistant to Dr. John L. Kiely (Senior Research Scientist for Perinatal Epidemiology and Chief, Infant and Child Health Studies Branch, of the NCHS) to perform a special run on the Matched Multiple Birth File that could be used for comparison with the results of these studies. She provided the following methodology as a complement for results shown in Table 2.

**Methods**

The NCHS Matched Multiple Data File was used for analysis. These data consist of all twin and triplet fetal deaths, births, and infant deaths in the United States between 1995 and 1997 [39]. For this analysis, all complete sets of triplet births with no missing information on gestational age or birth weight were selected initially (N = 5,238 sets). Next, only triplet sets with all live born infants (i.e., no fetal deaths) were selected (n = 5125 sets). Those triplet sets were then stratified by parity (nulliparous or no previous live births); any set with missing or inaccurate parity information were excluded (n = 465 sets). The final sample size consisted of 4,660 triplet sets.

Maternal age was coded in five categories: younger than 25, 25-29, 30-34, 35-39, and 40 and older. In this data set, there were 212 mothers age 40 or older. It was requested that two controls be selected from both the 25-29 and 35-39 age groups for every one triplet set born to a mother 40 or older, based on same parity. There were 49 nulliparous 40+ mothers and 163 multiparous 40+ mothers. This resulted in a random selection of 98 nulliparous mothers and 326 multiparous mothers from both of the control age groups. Random controls were generated using a function of SAS (V. 8.02, SAS Institute, Cary NC USA). Mean gestational age, total triplet birth weight, individual triplet birth weight, and standard deviations were generated using SAS. Frequency charts for individual and total triplet birth weights were generated using PROC CHART in SAS.

(A. Branum, Personal Communication, 2002)

The data from the NCHS, as shown in Table 3, confirm some of the most important findings of these studies. In terms of the nulliparous mothers, the mean gestational age of mothers age 40 years or older is 33.9 weeks, compared to 32.5 weeks for mothers age 35-39 and 32.0 weeks for mothers age 25-29. Similarly, the mean total triplet birth weight for mothers age 40 or older is 5558.5 g, compared to 5153.4 g for mothers age 35-39 and 4951.1 g for mothers age 25-29. At the same time, the mean individual birth weight of triplets born to mothers age 40 or older is 1852.8 g, compared to 1699.5 g for mothers age 35-39 and 1624.2 g for mothers age 25-29. With regard to multiparous mothers, the mean gestational age for women age 40 or older 33.0 weeks compared to 32.8 weeks for mothers age 35-39 and 32.2 weeks for mothers age 25-29. Mean total triplet birth weight in mothers age 40 or older is 5538.9 g compared to 5399.3 g in mothers age 35-39 and 5069.4 g in mothers age 25-29. Mean individual triplet birth weight is 1846.3 g in mothers age 40 or older, compared to 1,799.8 g in mothers age 35-39 and 1689.8 g for mothers age 25-29. Other findings, including the mean individual and total triplet birth weight at < 28 weeks, 28-32 weeks, and 32+ weeks for nulliparous and multiparous mothers, also are shown in Table 3.

Because no other benchmark comparisons for the findings of these studies are available in the literature, the data provided by the NCHS confirm what the author considers the most important finding of his work – that the triplet infants of mothers age 40 or older actually do better, both from a statistical and a clinical point of view, compared with the triplet infants of either the younger (age 25-29) controls or the older (age 35-39) controls.

### 4.5. Possible explanations

The findings of these studies require some explanation, but that explanation is elusive. Given the confirmatory findings from NCHS, it is unlikely that the study finding is incorrect or spurious. Rather, it is useful to consider the findings broadly, while recognizing that the explanations offered below are only potential explanations and that others may also exist, reflecting that our knowledge of uterine physiology and, indeed, of labor itself is far from complete.

Simply stated, triplet pregnancy in women over age 40 has not adequately been studied. Under this circumstance, it is reasonable to ask whether the major finding relates to an advantage if one is older and pregnant with triplets or to a disadvantage if one is younger.
Table 2. Findings of these studies – current pregnancy, medical conditions, anthropometric status, & obstetric outcomes

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<th>C2</th>
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<td>Uterine activity &amp; cervical change</td>
<td>26</td>
<td>19.3</td>
<td>26.7</td>
<td>32.9</td>
<td>40+ vs. 25-29: $p = 0.002$; OR 0.5; 95% CI 0.3, 0.8</td>
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<td>Cervical incompetence</td>
<td>27</td>
<td>9.4</td>
<td>10.6</td>
<td>9.3</td>
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<td>Cerclage</td>
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<td>15.8</td>
<td>10.6</td>
<td>9.3</td>
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<td>Bleeding &lt; 18 weeks</td>
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<td>2.9</td>
<td>5.6</td>
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<td>NS</td>
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<td>Placenta previa</td>
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<td>0.0</td>
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<td>3.2</td>
<td>40+ vs. 25-29: $p = 0.01$; Fisher exact test</td>
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<td>Uterine irritability</td>
<td>31</td>
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<td>35-39 vs. 25-29: $p = 0.04$; OR 0.7; 95% CI 0.5, 0.98</td>
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<td>1 admission</td>
<td>33</td>
<td>67.6</td>
<td>53.3</td>
<td>58.3</td>
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<tr>
<td>2 admissions</td>
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<td>29.7</td>
<td>27.5</td>
<td>NS</td>
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<td>&gt; 2 admissions</td>
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<td>4.2</td>
<td>16.5</td>
<td>14.2</td>
<td>40+ vs. 35-39: $p = 0.001$; OR 0.2; 95% CI 0.1, 0.6; 40+ vs. 25-29: $p = 0.007$; OR 0.3; 95% CI 0.1, 0.7</td>
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<td>34</td>
<td>78.4</td>
<td>70.8</td>
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<td>Spontaneous rupture of membranes</td>
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<td>70.8</td>
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<td>Pre-pregnancy BMI</td>
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<td>90.1</td>
<td>90.4</td>
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<td>Height</td>
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<td>Pre-pregnancy weight</td>
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<td>Mean gestational age at referral</td>
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<td>Grouped gestational age at birth</td>
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<td>Gestational age &lt; 28 weeks</td>
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<td>Gestational age 28-32 weeks</td>
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<td>Gestational age &gt; 32 weeks</td>
<td>45</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>35-39 vs. 25-29: $p = 0.08$, OR 1.5; 95% CI 1.1, 2.7</td>
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<td>Individual triplet birth weights – A</td>
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<td>100.0</td>
<td>100.0</td>
<td>40 vs. 25-29: $p = 0.16$</td>
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<td>Individual triplet birth weights – B</td>
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<td>40 vs. 25-29: $p = 0.01$</td>
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<td>Individual triplet birth weights – C</td>
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<td>100.0</td>
<td>100.0</td>
<td>40+ vs. 25-29: $p = 0.03$</td>
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<td>Mean total triplet birth weights</td>
<td>47</td>
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<td>100.0</td>
<td>100.0</td>
<td>40+ vs. 25-29: $p = 0.01$</td>
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<td>Frequency of birth weight categories</td>
<td>48</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
<td>40+ vs. 25-29, at &gt; 2.5 kg, $p = 0.005$, OR 1.8; 95% CI 1.2, 2.7</td>
</tr>
</tbody>
</table>

Cases = 171 mothers age 40 or older, control C1 – 342 mothers age 35-39, control C2 – 342 mothers age 25-39
Table 3. Results from NCHS Matched Multiple Data File (Courtesy, Amy Branum)

<table>
<thead>
<tr>
<th></th>
<th>25-29</th>
<th></th>
<th>35-39</th>
<th></th>
<th>40+</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>mean ± SD</td>
<td>n</td>
<td>mean ± SD</td>
<td>n</td>
<td>mean ± SD</td>
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<tr>
<td>Nulliparous mothers</td>
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<tr>
<td>Mean gestational age</td>
<td>98</td>
<td>32.0 ± 3.6</td>
<td>98</td>
<td>32.5 ± 3.4</td>
<td>49</td>
<td>33.9 ± 3.6</td>
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<tr>
<td>Mean total triplet birth wt</td>
<td>98</td>
<td>4951.1 ± 1507.3</td>
<td>98</td>
<td>5153.4 ± 1671.8</td>
<td>49</td>
<td>5558.5 ± 1466.3</td>
</tr>
<tr>
<td>Mean ind triplet birth wt</td>
<td>294</td>
<td>1624.2 ± 543.6</td>
<td>294</td>
<td>1699.5 ± 596.5</td>
<td>147</td>
<td>1852.8 ± 524.3</td>
</tr>
<tr>
<td>Mean ind triplet birth wt @ &lt; 28 weeks</td>
<td>27</td>
<td>713.3 ± 299.0</td>
<td>24</td>
<td>594.3 ± 133.0</td>
<td>6</td>
<td>837.7 ± 168.2</td>
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<tr>
<td>Mean ind triplet birth wt @ 28-32 weeks</td>
<td>90</td>
<td>1383.6 ± 328.5</td>
<td>66</td>
<td>1307.3 ± 316.4</td>
<td>30</td>
<td>1355.9 ± 226.2</td>
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<tr>
<td>Mean ind triplet birth wt @ 32+ weeks</td>
<td>177</td>
<td>1928.9 ± 407.2</td>
<td>204</td>
<td>1982.7 ± 454.5</td>
<td>111</td>
<td>2042.0 ± 436.4</td>
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<tr>
<td>Mean total triplet birth wt @ &lt; 28 weeks</td>
<td>9</td>
<td>2139.0 ± 917.0</td>
<td>9</td>
<td>1782.9 ± 391.4</td>
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<td>2513.0 ± 610.9</td>
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<tr>
<td>Mean total triplet birth wt @ 28-32 weeks</td>
<td>30</td>
<td>4150.8 ± 889.0</td>
<td>22</td>
<td>3922.0 ± 831.9</td>
<td>10</td>
<td>4067.4 ± 412.7</td>
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<tr>
<td>Mean total triplet birth wt @ 32+ weeks</td>
<td>59</td>
<td>5786.8 ± 1010.1</td>
<td>68</td>
<td>59948.3 ± 1148.0</td>
<td>37</td>
<td>6126.0 ± 1162.0</td>
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<tr>
<td>Multiparous mothers</td>
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<tr>
<td>Mean gestational age</td>
<td>326</td>
<td>32.2 ± 3.8</td>
<td>326</td>
<td>32.8 ± 3.6</td>
<td>163</td>
<td>33.0 ± 3.4</td>
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<tr>
<td>Mean total triplet birth wt</td>
<td>326</td>
<td>5069.4 ± 1638.7</td>
<td>326</td>
<td>5399.3 ± 1596.6</td>
<td>163</td>
<td>5538.9 ± 1570.9</td>
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<tr>
<td>Mean ind triplet birth wt</td>
<td>978</td>
<td>1689.8 ± 584.9</td>
<td>978</td>
<td>1799.8 ± 565.6</td>
<td>489</td>
<td>1846.3 ± 559.7</td>
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<tr>
<td>Mean ind triplet birth wt @ &lt; 28 weeks</td>
<td>114</td>
<td>706.3 ± 253.8</td>
<td>69</td>
<td>758.1 ± 233.2</td>
<td>27</td>
<td>645.7 ± 229.8</td>
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<tr>
<td>Mean ind triplet birth wt @ 28-32 weeks</td>
<td>225</td>
<td>1364.6 ± 359.1</td>
<td>207</td>
<td>1337.2 ± 335.0</td>
<td>99</td>
<td>1357.5 ± 355.4</td>
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<tr>
<td>Mean ind triplet birth wt @ 32+ weeks</td>
<td>639</td>
<td>1979.7 ± 394.0</td>
<td>702</td>
<td>2038.6 ± 425.0</td>
<td>363</td>
<td>2068.9 ± 402.2</td>
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<tr>
<td>Mean total triplet birth wt @ &lt; 28 weeks</td>
<td>38</td>
<td>2118.9 ± 694.2</td>
<td>23</td>
<td>2274.4 ± 655.7</td>
<td>9</td>
<td>1937.1 ± 693.7</td>
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<tr>
<td>Mean total triplet birth wt @ 28-32 weeks</td>
<td>75</td>
<td>4093.9 ± 954.5</td>
<td>69</td>
<td>4011.7 ± 876.7</td>
<td>33</td>
<td>4072.6 ± 950.1</td>
</tr>
<tr>
<td>Mean total triplet birth wt @ 32+ weeks</td>
<td>213</td>
<td>5939.2 ± 1028.2</td>
<td>234</td>
<td>6115.7 ± 1114.0</td>
<td>121</td>
<td>6206.7 ± 1022.1</td>
</tr>
</tbody>
</table>

If one accepts that these data indicate that younger women are disadvantaged compared to their older counterparts, then one must also ask why this is so.

A potential answer to this latter question relates to uterine volume in terms of prior pregnancy experience. Clinicians generally have no difficulty in manually distinguishing the relative difference in size of the uterus of a woman who has never been pregnant from that of a woman who has been pregnant many times, provided that the women’s stature is such that the abdominal wall does not interfere with the clinician’s tactile perception. Having said this, it is reasonable to ask, then, what the exact difference is in size between the never pregnant and repeatedly pregnant uterus and why this difference might exist. The answer to these questions is surprisingly obscure if one’s only source is modern textbooks that tend to describe the uterine anatomy in terms of ranges of size and ranges of weight. For example, the most widely read American text on obstetrics states that the size of the uterus of adult nulliparous women is from 6-8 cm in length, compared with 9-10 cm in multiparous women [11]. Dickinson [12], writing in Human Sexual Anatomy, is far more specific and cites several references, some of which go back to the late 19th Century. The following two paragraphs are quoted in their entirety. Dickinson does not relate these findings to maternal parity or age.

The figures of the total length of the cavity of the parous uterus show a wide variation among books on anatomy, gynecology and obstetrics, the largest being 9.4 cm, as given by Tandler (1923, p. 273), and the smallest 5.7 cm as given by Testut and Jacob (1914), a difference of 3.7 cm, the average of the findings in about 450 cases reported being 7.39 cm. The figures for the nulliparous uterus show the same wide disparity, the largest figure again being Tandler’s 8.1 cm and the smallest being that given by Webster (1892), 3.2 cm. Meaker (1930) writes me that he finds in 67 cases, mostly nulliparous, an average of 7.4 cm for the total uterine cavity.

In contrast, Langlois [29] describes uterine weight in relation to age and parity. His article also presents numerous references that describe further variations in size in addition to those noted by Dickinson [12]. The
The younger (age 25-29) control group (p = 0.00001, OR older had a history of abortion compared with 39.6% of as shown in Figure 24, 52% of the mothers age 40 or reasonable to relate to findings of this studies because, consequently switch from proliferation to hypertrophy thereby creating a “pool” of myometrial cells that sub-

which induce myocyte proliferation early in pregnancy, hormonally changes in pregnancy. These include increa-

et al., uterine growth is intimately related to specific matrix synthesis, and remodeling [36]. According to Lye cell-proliferation, hypertrophy, apoptosis, differentiation, matrix synthesis, and remodeling [36]. According to Lye et al., uterine growth is intimately related to specific hormonal changes in pregnancy. These include increases in growth factors, such as IGF-1 and EGF, both of which induce myocyte proliferation early in pregnancy, thereby creating a “pool” of myometrial cells that sub-

sequently switch from proliferation to hypertrophy under the influence of progesterone and are thus “remo-
deled” [36]. This recent physiological explanation is reasonable to relate to findings of this studies because, as shown in Figure 24, 52% of the mothers age 40 or older had a history of abortion compared with 39.6% of the younger (age 25-29) control group (p = 0.00001, OR 2.3; 95% CI 1.6, 3.5). By having abortions, older mothers may have been more likely to possess “remodeled” uteri that were more able to withstand the rigors of distention as the pregnancy progressed. This latter statement is compatible with the finding, as shown in Figure 41, that the frequency of the uterine irritability among mothers age 40 or older was less than the frequency of the uterine irritability among the mothers in the younger (age 25-29) control group (40.3% vs. 47.1%).

If one accepts the concept that the uterus is “re-

dodeled” by the pregnancy experience, one can then expect that even a remodeled uterus will determine an optimal uterine volume at which its activity is maximal and from which the process of “adaptation” cannot proceed further without facing inherent restrictions from overdistension [10]. Indeed, one of the most commonly circulated explanations in the obstetric literature for the onset of preterm labor in multiple gestations is that the uterus has an inherent upper limit of expansion, after which labor must ensue. This clinical precept does not consider the effect of “uterine remodeling”; however, the increased weight of the uterus based on gravidity, as shown by Langlois [29], is evidence that even pregnancy that ends in abortion results in cell prolifera-

which may ultimately affect uterine performance.

In these studies, we find that, although the length of gestation is essentially the same for mothers age 40 or older and for the younger (age 25-29) and the older (age 35-39) control groups, the older mothers had a clinical advantage (Fig. 44) compared to the younger (age 25-29) controls. At the same time, however, the total triplet birth weight of the mothers age 40 or older is signi-

antly higher than the birth weights the younger (age 25-29) control group (p = 0.01). Could it be that “extra cells” representing the result of uterine cell prolifera-

tion, assist in nourishing the infants of the older mother because there are more of them? There is precedence for this thinking if one considers the well-established fact of more efficient labor of the multipara compared to the primipara. Could it also be that the “extra cells” that result from the process of cell proliferation and clearly are visible on cut section of the uterus (Cunningham et al. [11]; Dickinson [12]) add to the tensile strength of the uterus and interfere with physical signals that normally provoke irritability in the uterus of different physical dimensions. Finally, one should not forget that the ratio of the corpus to the cervix changes from 1/2 in the nulligravid patients to 2/3 to 1/3 in the multipara [11]). Taken together, the points discussed above suggest that the uterus of a 45-year-old woman who is gravida 4 para 0 at the time she becomes pregnant with triplets is in-

herently different and thus behaves differently from the uterus of a 25-year-old gravida 0 para 0 who becomes pregnant with triplets.

A final, although totally speculative, potential expla-

nation for the outcome differences is that the mothers age 40 or older might have been more likely to have undergone egg donation as part of their IVF experien-

ces. As attractive as this concept is, the available data are insufficient to test it.

4.6. Risks of higher order multiple pregnancies

4.6.1. Traditional

The “pessimistic” attitude toward maternal and fetal outcomes described as early as 1989 by Mansfield and McCool [38] is amplified in two recent publications. The first, by Sebire et al. [53], used essentially the same data.
set as that used by Jolly et plurality into singletons, twins, and triplets instead of by age categories, as was the case in the Sebire et al. [53] publication. After exclusions, the study group included 417 542 singletons, 5416 twin pairs, and 149 triplet pregnancies. The ethnic representation of the study group essentially reflected that of the present UK population in which Caucasians are most prevalent, followed by Indian/Pakistani, Afro-Caribbean, Mediterranean, and Oriental. Maternal age averaged 28 years in the singletons (range 12-54), 30 in the twins (range 15-51), and 32 in the triplets (range 17-47). Multiparas were more common among the singleton and twin mothers, whereas almost two-thirds of the triplet mothers were primiparas.

For most variables examined, the magnitude of risk increased with the number of fetuses. This increase was particularly striking in terms of two of the most important precursors of maternal mortality, i.e., preeclampsia and anemia (0.8%, 2.9%, 4.7% for preeclampsia in singletons, twins, and triplets, respectively, and 4.3%, 17.2%, 24.8% for anemia in singletons, twins, and triplets, respectively). This finding is in agreement with Skariah et al. [55], who analyzed conditions predisposing maternal mortality in twins and singletons using the 1989 USA birth cohort. It also adds strength to Blickstein’s [9] suggestion that multiple pregnancy is an important and unrecognized potential antecedent of maternal mortality. Sebire et al. [53] also documented increasing rates of delivery at less than 32 weeks by plurality (1.1%, 8.5%, 34.9% for singletons, twins, and triplets, respectively) and birth weight less than 2500 g (6%, 52.3%, 93.3% for singletons, twins, and triplets, respectively).

The second large-scale discussion of maternal complications by plurality is provided by Luke [34] in *Multifetal Pregnancy: A Handbook for Care of the Pregnant Patient*, a book she co-edited with Newman. Luke reviewed more than 40 recent publications to synthesize the data she presented in her tables. Her approach was somewhat different from that of Sebire et al. [53]. For example, whereas triplets had twice as frequent antenatal hospital admissions compared to twins (53 vs. 27), the range of the length of stay was almost triple for the triplets compared to the twins (10-42 days vs. 11-16.5 days). The percentage of cerclage (13%) was comparable to the findings of the present study [34]. However, the relative risk of this operation was 3.7 times greater for triplets compared to twins. In terms of infant outcomes, the available literature was grouped as follows: 10 studies beginning in 1958 through 1980 and 12 studies between 1980 through 2000 [34]. Although she did not describe the ages of the mother in terms of infant outcome, she observed a decline in the average birth weight of each triplet infant from mid-1800 g in the earlier years to mid-1700 g in the later years. This decline may represent the effect of the greater willingness of physicians to terminate triplet pregnancy for maternal indications such as toxemia, or fetal indications such as poor growth.

### 4.6.2. Special – cerebral palsy

In the past, comments regarding the differential risk of cerebral palsy in multiples compared to singletons were hampered by biases related to the inability to provide long-term follow-up on all potential cases. This statement was true regardless of whether it was believed that the condition might relate etiologically to prior preterm delivery, intrauterine growth restriction, or intrapartum hypoxia. Recent data from western Australia circumvent all of these problems, because of a system of ascertainment set in place more than two decades ago.

An analysis of gestational-age-specific cerebral palsy rates for all infants (regardless of plurality) born in western Australia between 1980 and 1994 shows a strong inverse relationship between the risk of cerebral palsy and advancing gestational age through 41 weeks [49]. Of interest, during the years of study, 78% of the triplets with cerebral palsy were delivered before 33 weeks. In an earlier publication from this group, which analyzed data from 1990 through 1999, the relative risk of cerebral palsy (per 1,000 neonatal survivors) in singletons, twins, and triplets was 1.6, 7.4, and 28.0, respectively [49].

The importance of population-based data is underscored by the work of Pharoah and Cooke [50], who described similar data from Mercey in the UK for the birth cohort for the years 1982-89. In this study, the relative risks of cerebral palsy for singletons, twins, and triplets was 2.3, 12.6, and 44.8, respectively. In a widely quoted Japanese study by Yokoyama et al. [61], the risk of cerebral palsy for singletons was not reported. However, the relative risk for twins, triplets, and quadruplets was 8.5, 31.4, and 111.1, respectively.

Blickstein [7] recently summarized the literature on cerebral palsy and multiple gestations in the following manner, “The increased risk of cerebral palsy among multiples has no geographical restrictions... The data clearly indicate that the higher the number of fetuses, the greater is the prevalence of cerebral palsy. Moreover, the increase in cerebral palsy with the number of fetuses is exponential.”
4.7. The effect of ART on outcomes

One of the major concerns of recent years regarding infants born after conceptions using ART is whether they were associated with low birth weight. This concern is of particular importance for triplet gestations because of the high likelihood that triplets born after 1985 resulted from ART [35]. Several studies cited recently by Schieve et al. [52] suggest that there is a higher rate of low birth weight among singleton infants conceived after ART compared to natural conceptions or among all infants in the general population. These authors further observed that it was unclear whether the risk of low birth weight of ART singletons was a direct effect of the procedure or reflected some aspect of the couple’s underlying infertility. Therefore, they studied 42,463 infants born in 1996 and 1997 after ART and compared them with 3,389,098 infants born in 1997. Data were obtained from the Society for Assisted Reproductive Technology reports to the CDC. In one of the analyses, the age of the mother was stratified, and the percentage of infants with low birth weight (< 2500 g) in singletons, twins, and triplets was calculated. For mothers age 40-44 years, the percentages were 13.5%, 51.3%, and 91%, respectively. These figures were not substantially different for mothers age 20-29 years (12.4%, 61.7%, and 92.4%) [52]. The likelihood of birth below 1500 g and before 32 weeks of gestation was not addressed.

A second and equally important concern of recent years is whether there is an increased risk of having a major birth defect after an ART conception, compared with spontaneous pregnancy. Whereas early reports did not show any increased risk, a recent review by Hansen et al. [18] summarizes deficiencies of these early studies. These include methodological problems, such as inadequate sample size and variations in the definition of major birth defects. The analysis by Hansen et al. [18] using data from three registries in western Australia assessing rates of malformation in infants born between 1993 and 1997 is quite clear. At the end of one year, the cumulative prevalence of major birth defects is twice as high after intracytoplasmic sperm injection and in vitro fertilization, compared to natural conceptions. The data used for these studies did not contain information on either antenatal or postnatal detection of birth defects.

4.8. Nutritional considerations

The importance of prenatal nutrition cannot be overstressed. The origins of dietary recommendations in pregnancy until about 1960 were based primarily upon the writings of the German obstetrician Prochownik, who practiced in the latter half of the 19th century. The Prochownik diet was based on the need to produce smaller infants who were more likely to pass through deformed, contracted rachitic pelvises. The “starvation mentality” remained part of the medical armamentarium until about 1970, when advice began to appear suggesting a more liberal diet; most of the available information dealt with singleton pregnancy, however.

It was not until 1990 that the USA National Academy of Science published nutritional guidelines in Nutrition in Pregnancy. This publication was unique for two reasons: (1) it recommended a range of weight gain based upon the mother’s pregravid weight, and (2) it recommended, for die first time, a 35- to 45-pound weight gain for normal women with twin pregnancies. No recommendations were made for triplet pregnancies [42]. Seven years later, an expert working group was convened by the National Center for Education in Maternal and Child Health to determine whether a formal revision of the 1990 weight gain recommendations of the National Academy of Science was warranted [59]. Even though the panel members concluded that such a revision was not needed, they reaffirmed, that for multiple births, the optimal range of birth weight and the gestational age associated with the lowest morbidity was achieved earlier than for singleton births. For twins, this optimal range is estimated to be 2500-2800 g at 36-37 weeks and for triplets, 1900-2200 g at 34-36 weeks [33].

Luke utilized these recommendations in a series of widely quoted studies relating to triplets. Among her contributions was the recognition that the pattern of the weight gain based upon the Body Mass Index (BMI) was particularly important in view of the expected shortened duration of multiple gestations. In this construct, it became necessary for mothers of triplets to gain most rapidly because their gestation length was, on average, shorter than for twins and far shorter than for singletons. Thus, Luke et al. [32] advised a 50- to 60-pound total weight gain for mothers of triplets and a weight gain of 36 lbs. by the 24th week. Better intrauterine growth was achieved when maternal weight gains were equal to or greater than 1.5 pounds per week before 24 weeks of gestation [32]. The publications of Luke et al. [32] have been reviewed extensively [24, 30]. In these studies, no attempt was made to correlate fetal outcomes with maternal BMI.

4.9. Costs

One cannot discuss triplets or higher order multiple gestations without considering the enormous expense,
which has several components. These include the financial costs associated with becoming pregnant, maintaining pregnancy, delivery, and neonatal intensive care, as well as the lifetime costs of aftercare, should one or more of the multiples have either developmental or neurological handicaps. The body of literature on costs associated with multiple births is relatively limited, considering their large numbers in recent years. Part of this knowledge deficit may relate to the difficulty of differentiating between hospital costs and hospital charges, which is even more difficult in studies that attempt to look at monetary expenditures on a national basis.

One exception is a study by Luke et al. [31], in which one of the authors was the vice president for finance at a major university hospital in Chicago. The study focused on the true cost as opposed to the patient charge [31]. In that report, which looked at twins and singletons, the predominant cost factor at birth was prematurity rather than plurality. Moreover, the cost was magnified if intrauterine growth retardation or congenital anomalies were present.

A more recent study of the impact of gestational age at delivery on the economics of triplet pregnancy was published by Malone et al. [37], who found a significant inverse relationship between gestational age at delivery and total charges per triplet family, with a decrease of $16,584 for each additional gestational week reached (p = 0.006). The total pregnancy charge averaged almost $190,000, not including the cost of becoming pregnant or any follow-up infant care.

The long-term outpatient costs of a multiple birth were calculated by Henderson and Petrou [20], using the same database in the UK that has previously been described for the work of Jolly et al. [22] and Sebire et al. [53]. In this evaluation, the antenatal, intrapartum, and long-term costs were exponentially related to plurality, with costs for triplets greater than costs for twins, which were greater than costs for singletons. No cost data — antenatal, intrapartum, or postnatal — were available for this study. Similarly, the costs of the Matria service are not known to the author of these studies.

4.10. Special considerations – the rate of dangerously preterm births as a measure of the quality of prenatal care

Among the many contributions to the literature on multiple gestations by Papiernik is his call for assessment of the efficacy of prenatal care [26]. This proposal merits particular consideration in terms of the findings of these studies, because Papiernik advocates early aggressive interventions, including the use of a special twin clinic, lifestyle modification, and delivery at level 3 hospitals [46]. In an examination of the results of 733 twin pregnancies followed and delivered at the Maternite Port Royale in Paris (where he was affiliated) between 1993 and 1998, several important trends became clear. First, the rate of delivery at the time of dangerous prematurity (week 22-27) was directly related to the time the patients came under care and the degree of care they received. Thus, the rate of preterm delivery was 0.2% for women who were followed at the hospital from the inception of their pregnancy (before 20 weeks). In contrast, women who were referred by their obstetrician for advice and remained in the care system had a preterm delivery rate of 1.3%. Finally, those who came for the intrapartum transfer as an emergency had a rate of dangerously preterm delivery of 19.5%. When the same groups were examined for delivery between 28-32 weeks, the corresponding rates were 1.1%, 6.9%, and 47.8%, respectively [47]. Of equal interest, when all twin live births were considered, the neonatal death rate for the early-referred patients was 17%, compared to 80% among the late referrals or transferred mothers. Finally, the rate of transfer to the NICU was 20.3% among the women who came early, compared to 69.3% among the late referred or transferred mothers. Papiernik [47] suggests that the decrease of neonatal deaths is perhaps a singular goal, which must be used to counterbalance the admittedly higher rates of preterm deliveries that often are conducted by physicians for worsening maternal or fetal conditions.

A novel approach to the care of triplet pregnancy, which resulted in a marked decrease (p = 0.02) in the number of deliveries <28 weeks, was described in a recent report from Croatia [56]. In this study of 79 triplet pregnancies, preventive hospitalization was offered to all women at the beginning of the second trimester. It was chosen by 55, and the remaining 24 elected standard outpatient care for multiple pregnancy until week the 28th week, when they also were admitted to the hospital. The gestational age at delivery was significantly higher for those who had early hospitalization, compared to those who did not (34.1 vs. 30.3, p < 0.001). Mean birth weight was higher for the early-hospitalized mothers compared to the others (1652 g vs. 1228 g, p < 0.001). Finally, deliveries before the 28th week were infrequent in the group that had elected early hospitalization, compared to those for whom it was applied at the later date (p = 0.02). These findings are in substantial agreement with reports emanating from countries in which
health care was freely disbursed by governments in the mid-1960s and 1970s [24].

5. Limitations

These studies are not without certain limitations, foremost of which is the lack of neonatal follow-up. This deficiency stems from Matria being a private service provider, consulting with numerous physicians throughout the USA. Because Matria did not have access to individual newborn hospital records, it is not possible to describe important outcome variables such as rates of Apgar Scores, NICU admission, days of ventilation, and perinatal mortality for the infants born to the mothers who comprise the study population. Despite this limitation, however, the section entitled “Comparison of Important Variables Between Matria and USA Data” (Section 2.1.3) shows that the Matria database is very similar to USA data. Accordingly, a special run of the NCHS Matched Multiple Data File (Table 4) was performed to determine recent neonatal mortality rates. This analysis demonstrates a strong inverse correlation in the neonatal mortality rate and increasing maternal age for the USA birth cohort in the years between 1995 and 1997.

A second limitation of these studies is that the data file used was not accompanied by similar data for singletons and/or twins collected during the same time period. Thus, no calculations can be made to corroborate or disagree with the recent observations of Blickstein et al. [6] regarding maternal age and birth weight characteristics among nulliparous mothers. In this study, nulliparous mothers age 40 or older were less likely to have a twin pair with a total birth weight of < 2999 g, compared to mothers age 35-39 or 25-29 (9.7% vs. 11.9% and 10.3%). Similarly, mothers age 40 or older were less likely to have two infants of very low birth weight, compared to control mothers age 35-39 or 25-29 (6.7% vs. 8.9% and 8.2%).

A third limitation is that it is not possible to compare the findings of these studies to any other published data. The entity of triplet pregnancy in mothers over 40 is so uncommon that even centers that normally attract large numbers of mothers of multiples for treatment and obstetric care have not had sufficient numbers of cases to compare outcomes of these mothers with those of younger mothers.

Finally, a decision was made not to consider maternal ethnicity or race for the following reasons: (1) no accepted definition of race exists; (2) in the USA, many individuals now have what can best be described as “mixed racial background”; and (3) the selection of race is always made based on the respondent’s answer, regardless of whether this has any relation to the respondent’s phenotype. A full discussion of the recent debate on race-neutral and race-specific designations is provided by Oleszczuk et al. [45].

6. Conclusions

Students of demography and epidemiology are aware that the patterns of births within a given country change over time. In the USA, the number of births rose substantially after World War II (1940-1945) and the Korean mobilization (1955-1960). Individuals born in these years are often characterized as “baby boomers”. The so-called “boom” ended around 1975, after which time births began to rise again when the “baby boomers” themselves began to have children. Figure 1 shows these trends and the effect of the introduction of ovulation-inducing agents and assisted reproductive technologies in the 1970s and 1980s. As a result, the rates of increase in the numbers of twin and triplet births outstripped the rate of increase in the singletons for the first time since birth recording began in the USA. In this manner, the so-called “epidemic of multiple births” began. A detailed summary of some features of this epidemic are described elsewhere [24].

Two other important phenomena are not shown in Figure 1: (I) the proportion of births to women age 30 and older, and (2) the proportion of first births to women at these ages. Data from the National Vital Statistics Reports, which analyzes births occurring in 1998 [60], clearly establishes that the rate of increase in the number of triplets and higher order births after 1990 has been dramatic. These increases include substantial numbers of women having their first births. Many of these women are age 30 or older. Among these individuals, the use of ART and/or IVF is not uncommon.

<table>
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<tr>
<th></th>
<th>25-29 years</th>
<th>35-39 years</th>
<th>40+ years</th>
<th>All</th>
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<tr>
<td><strong>Triplets</strong></td>
<td></td>
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<tr>
<td>Neonatal death Rate (per 1000)</td>
<td>195</td>
<td>54.8</td>
<td>90</td>
<td>26.3</td>
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<tr>
<td><strong>Twins</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Neonatal death Rate (per 1000)</td>
<td>1631</td>
<td>20.5</td>
<td>638</td>
<td>14.7</td>
</tr>
</tbody>
</table>
Thus, it is reasonable to conclude that pregnancy after age 40 represents a new obstetric entity and one in which many mothers will have twins or triplets as a result of their use ART and/or IVF. Although it was anticipated, based upon historical perceptions, that mothers of triplets would have a poorer outcome than their younger counterparts in terms of pregnancy length and individual and total triplet birth weight, this was not the case in the data analyzed for these studies. Indeed, younger mothers were found to be disadvantaged in these regards. That this observation was confirmed by the analysis of population-based data from the NCHS strongly suggests that the findings of these studies are real and can be verified.

The findings of these studies are based upon a case-control matched study design in which parity was the matching factor. Thus, the findings do not conflict with the data presented for the entire Matria group as shown in Figure 14 for three reasons. First, the age group of 45 and older is limited, and conclusions cannot be drawn with sufficient statistical power. Second, it is possible that the figures of the age group 40-44 obscure the figures of the women age 45 and older. Finally, it is not known if the difference is in this direction because, with a higher number, it could change.

The findings of these studies also support the contention that, unlike the ovary, the uterus does not lose its ability to function with age. As a corollary to this statement, it is likely that any prior pregnancy, including abortion, may affect the ability of the uterus to function in a subsequent pregnancy, either by providing better nourishment or by affecting its ability to respond to the mechanical stimuli that may promote the onset of labor.

Further study in this area is clearly needed, preferably using a database that combines maternal and neonatal data. Jolly et al. [22] and Sebire et al. [53] suggest that the Saint Mary's Maternity Information System database for the northwest Thames region in the UK might be able to accomplish this with existing data. The same may be said for the 1995-97 Matched Multiple Data File of the National Center of Health Statistics in the USA [43]. Additional study is also needed to clarify the impressions that are now emerging that short- and long-term infant outcomes in the older mother or in mothers who have had IVF may not be as advantageous as the outcomes of infants born to younger mothers. In one Canadian study of the risk of fetal death at advanced maternal age, for example, the odds ratio for women age 40 or older was 2.4 (1.3-4.5) [17]. Another study showed that children born after IVF in Sweden had 3 times the rate of cerebral palsy compared with children in the general population [58]. The Swedish authors noted that the risks described in their study were largely because of the high frequency of twin pregnancies, low birth weight, and prematurity among babies born after IVF.

These latter issues are important, because mothers of any age want healthy children. To be pregnant with triplets after ART or IVF may not represent an ideal choice for many couples that had desperately wanted a single child. It may be comforting for these women to know, however, that there is solid evidence that the birth outcome of their pregnancy should be no worse than it would have been had they not waited to become pregnant.

Older mother of triplets did not have a poorer outcome than their younger counterparts, in terms of pregnancy length and individual and total birth weight.

References

Sauer M.V., Paulson R.J., Lobo R.A. (1995) Pregnancy in women 50 or more years of age: Outcomes of 22 consecu-
tively established pregnancies from oocyte donation. Fer-
tility and Sterility 64: 111-115.

Schieve L.A., Meikle S.F., Ferre C. et al. (2002) Low and
very low birth weight in infants conceived with use of as-
sisted reproductive technology. N. Engl. J. Med. 346: 731-
737.

Sebire N.J., Jolly M., Harris J. et al. (2001) Risks of obstet-
tric complications in multiple pregnancies: an analysis of
more than 400,000 pregnancies in the LTK. Prenat. Neo-
nat. Med. 6: 89-94.

Seidman D., Arm on Y., Roll D. et al. (1988) Grand mul-
tiparity: An obstetric or neonatal risk factor? Am. J. Obs-

Skariah J., Jost S., Oleszczuk J.J. et al. (2000) Conditions
predisposing to maternal mortality in twins and single-

Skrablin S., Kuvacic I., Jukic P. et al. (2002) Hospitaliza-
tion vs. outpatient care in the management of triplet ges-

Smith-Levitin M. (2001) Reduced and non-reduced twin
pregnancies: are they the same? In: Blickstein I., Keith
L.G. (eds), Iatrogenic multiple pregnancy: Clinical impli-

Stromberg B., Dahlquist G., Ericson A. et al. (2002) Neu-
rological sequelae in children born after in vitro fertiliza-

expert work group. National Center for Education in Ma-
ternal & Child Health, Arlington VA.


of cerebral palsy in twins, triplets, and quadruplets. Int. J.
Epidemiol. 24: 943-948.