



The Northwestern University Twin Study VIII: On the Causes and Care of Multiple Pregnancy

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Abstract. Recent clinical literature on the causes of twin pregnancy and specific areas of antenatal care are reviewed. Controversial aspects of clinical management are discussed.

Key words: Multiple gestation, Ultrasound, Bed rest, Zygosity determination

INTRODUCTION

The numbers and types of studies involving twins is extensive [2,18,37,43,44,65,78], and the importance of the study of human twins in medical research is no longer questioned [29,81]. Nonetheless, some demographers and epidemiologists have expressed concern about a purposed decline in age-specific dizygotic (DZ) twinning rates within industrialized nations [31-33,36]. Others question whether this decline has been reversed, at least in countries such as the United Kingdom and Canada [15]. In contrast, the question of possible nonrandomization of twin births relative to space and time has received less attention [16,85]. Even if the proposed decline in the rates of DZ twinning is real and twin births indeed are clustered, these phenomena appear to have no effect on clinical obstetric practice.

A recent Medline and Medlars search obtained through the National Library of Medicine in Bethesda, MD, USA, generated 771 articles published between January, 1981,

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and July, 1986, in which the word twin(s) was the major thrust of the article. When the term twin(s) was used in a secondary position, the number of titles increased to more than 1,500. A growing portion of this recent literature is devoted to the subject of the obstetric management and outcome of mothers with multiple gestations.

Clinical reports of large numbers of twin deliveries have been published from diverse regions such as Scotland [50], Germany [22], New Zealand [10] and the United States [55,80]. The common thread which unites these and other papers [18,60,64,67,74,80,82] is the issue of the perinatal mortality rate in twins, its causes [14,28] and the means for its reduction [25,39,69,82]. An additional concern, although not voiced as frequently, is the cost of providing neonatal care to large numbers of preterm newborns [4,65,72,73,82].

Because recent reports are scattered in diverse journals and emanate from a number of countries with vastly differing systems of providing medical care, we decided to review several clinical issues that have received attention in the last several years.

THE "CAUSE" OF TWINS

Unless fertility-inducing agents are used [84] or the mother is a member of a twin-prone family [68] clinicians often are unable to explain with certainty the so-called "cause" of twinning, apart from referring to the well-known process of double ovulation for DZ cases [3]. Obviously other factors are also operational, but their elucidation in a given case is difficult. Central to the issue of "causation" in twins is the maternal FSH level. Nylander [61] not only has shown that the level of FSH is higher in African than in Caucasian women, but that this elevation persists throughout the menstrual cycle. It has been postulated that this finding underlies the high rate of twinning in African women. It is presently unknown whether this endocrinologic difference continues throughout the reproductive life of specific mothers or if it appears under special circumstances.

Other researchers approach the question of twin "causation" from different perspectives. Lazar and coworkers [45] studied preconceptional factors in an attempt to characterize women "at risk" of having a multiple pregnancy. These investigators suggested that the following parameters increased this risk: 1) maternal age between 24 and 43 years; 2) multiparity; 3) weight > 55 kg; 4) blood group O or A; 5) previous twins in the mother's family; 6) regular menstrual cycles; and 7) no prior use of oral contraceptives (OC). As the number of factors increased, so did the relative risk (RR) of bearing twins. When all seven items were present, the RR was 1.8. Considering the rather low incidence of twins in the Caucasian population, even if this risk were fully operational, the total number of twin births would remain a fraction, albeit significant, of all births.

Contrasting opinions are expressed regarding the potential effect of the prior use of OC as an antecedent to the subsequent birth of twins. One large French study [27] of 673 mothers of twins and matched singleton controls found a significant negative association with DZ twinning, with an estimated RR of 0.55 (95% confidence limits 0.39/0.78). When the same issue was assessed in a case-control study [84] conducted by postal questionnaire in Nottinghamshire, England, the RR of twinning was 1.1 (95% confidence limits 0.6/1.9) for OC users compared with all mothers. For mothers with unlike sex pairs, the RR was 2.3, but with wide confidence limits (0.8/6.4). In this latter study, there was a nonsignificant trend for the risk of twinning to rise with increased duration

of contraceptive use, whereas the interval since stopping use was without association [84].

The genetic contribution to twinning has been reviewed recently by Parisi et al [68]. These investigators concluded, in part, that not only can a propensity to DZ twinning be inherited through the maternal line, but that this propensity extends to MZ twinning as well. They also suggested that the two mechanisms of twinning may be related and that this relationship may underlie the existence of familial aggregations of both types of twinning. The possibility of polar body twinning, a once-attractive and speculative attempt to explain some of the questions confronting clinicians and parents alike, has again come under scrutiny [19]. This potential mechanism is thought to be a rare occurrence at best.

PROTOCOLS FOR MANAGEMENT OF MULTIPLE PREGNANCY

Concomitant with the increasing interest regarding the "cause(s)" of twinning, the medical community has begun to question whether it is preferable to adhere to standardized protocols for ante- and intrapartum care of mothers with multiple pregnancies [54,62]. Available data are in two categories: the first comprises general reviews with specific clinical suggestions [40,54]; the second are conclusions drawn from collected clinical experiences [10,21,22,50]. The former assist clinicians to refine their practices and take advantage of known factors which may affect outcome; the latter search for additional outcome-related factors. Both types of report focus upon the reduction of perinatal mortality, especially as it relates to prematurity, and both types should be studied concomitantly.

ULTRASONIC EXAMINATION

In the past decade, ultrasonic examinations have become an indispensable part of the ante- and intrapartum management of twin gestations in those locales where this technology is available [40]. Ultrasonography has three distinct roles in the multiple pregnancy: 1) the detection and verification of the pregnancy per se [43]; 2) the characterization of intrauterine growth patterns [9]; and 3) the determination of the fetal position, either immediately prior to delivery or after the delivery of the first twin [8,63].

The availability of ultrasound has made it possible to survey large populations of pregnant women and confirm or reject the presence of a "vanishing twin" or a reduction in the number of gestational sacs. Landy et al [43] reviewed the literature pertaining and confirmed the reality of this phenomenon [44]. At present, the use of ultrasound to screen all pregnancies, as begun in Sweden in 1973 and reported in 1978 by Grennert and Persson [20] and in 1979 by Persson and Grennert [69,70], is not performed in many areas where ultrasound is available [41]. The routine use of ultrasound in twin pregnancies has made it possible to: 1) develop standards for the evaluation of intrauterine growth [47,70,76] as well as to characterize growth disturbances [30,48]; 2) point to possible etiological factors of such disturbances [5]; and 3) make the diagnosis of the MZ condition in the first trimester [52]. Today, the use of ultrasound in the delivery room is increasingly

common, especially in those cases in which intrauterine manipulation of the second twin must be performed [8,22,63].

GESTATIONAL AGE DISCREPANCIES

The accurate determination of gestational age is difficult. Factors which contribute to discrepancies include: 1) inaccurate maternal recall of the last menstrual period (LMP); 2) ovulation at a date other than 14 days after the onset of the LMP; 3) variations in ultrasonic dating systems and the errors inherent to these systems; ie, a late initial scan after the 24-26th week; and finally, 4) intrapair weight differences at the time of birth.

No single parameter for assessment of gestational age is as effective as two or more parameters used in combination. Thus, birth weight alone is not as effective an index of neonatal risk as is birth weight in combination with gestational age [75]. Stated another way, the mortality rate for small-for-date infants is higher than the rate obtained for low birth weight infants. Unfortunately, little correlation exists between the methods available for assessing gestational age in twins, and intrapair discrepancies are common [75]. All too frequently, one classification scheme regards a specified infant as premature, whereas another calls it term. Since intrapair weight discrepancies are not uncommon [58,71,75], the pediatrician may be placed in a position of uncertainty. In many circumstances, immediate neonatal assessments have equally important clinical implications [2,6,7,53].

THE VALUE OF BED REST

A major concern of our earlier publications [4,41] was the purported value of bed rest in reducing perinatal mortality. A side issue was the cost of providing this intervention [4]. At the meeting of the Working Party on Multiple Pregnancy of the International Society for Twin Studies held in Paris, France, in 1982, Professor MacGillivray correctly noted that the efficacy of this treatment had not been proven by randomized controlled trials. In the years subsequent to this meeting, such trials have not been undertaken, and the various published studies addressing this issue have not reached a consensus [23,25,39]. What has become clear, however, is that maternal erect posture [77] increases the frequency of uterine contractions and that these contractions can be measured accurately on an ambulatory basis [57]. In addition, the importance of heavy physical exertion in causing premature labor has been clarified [83], and the social costs of preterm twin pregnancies have been amply documented [65,72,73,83]. Thus, while it seems reasonable to agree with Hartikainen-Sorri and Jouppila [24] that hospitalization per se may not be required in all uncomplicated twin pregnancies, reduction of maternal activity appears warranted in almost every case [82], as is bed rest at home [39], home visits by members of the health care team [1,83], careful evaluation of the cervical state for effacement and dilatation [40,66], and the use of ambulatory uterine contraction monitoring devices where possible [57].

ZYGOSITY DETERMINATION

Many recent reports [10,22,55,64,67,74,82], fail to consider twin zygosity. Some investigators, principally from Scotland or Nigeria [50,59,60], consistently determine zygosity. When zygosity is accurately determined, it can be an important analytic tool [11,26]. The underutilization of accurate zygosity determination by clinicians is perhaps related to the absence of a universally agreed-upon method to assess zygosity and the potential costs of some of the available tests. The period immediately after birth appears to be the most logical moment to initiate an investigation to determine zygosity [34], as numerous techniques can be used concomitantly. Among these are sex determination, assessment of fetal membranes, determination of umbilical cord blood groups, quantitation of placental alkaline phosphatase and the use of DNA probes [12]. In contrast, if zygosity determinations are not performed at this time, the likelihood for error increases, especially as the twin population ages and is overcome by disease or death [34,51]. In recent years, numerous formulas have been advocated for zygosity determination based upon analyses of blood or other tissues [46,49,56], and some studies have utilized combinations of analytic methods [42,51]. In the absence of other data, Weinberg's formula can be used, but its validity is not universally accepted [37]. Since many of the major twin study groups have been assembled long after the births of their members [29,78], it seems likely that the problem of inaccurate zygosity determination will continue to exert a bias in the literature for years to come [34,79].

DATA ANALYSIS

The growing number of publications on twins has made the lack of uniform data reporting obvious. Not only are outcome statistics reported differently in most publications, but these differences impair direct comparisons of different populations unless published rates are recalculated. Since many maternal and obstetric factors may simultaneously affect a given pregnancy, sophisticated computerized analytical methodologies [13] and programs have been recommended for data analysis. However, even with the availability of these analytical tools, some studies resort to specialized methods of data presentation, such as chi-square curves [22]. It is hoped that the sophistication of these analytic methods will not serve as a deterrent to potential readers or neophyte research workers and that standards for data presentation will be developed in the near future.

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