PRETERM LABOR IN MULTIPLES: ARE WE DOING ENOUGH?

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All mothers of multiples are at considerably greater risk of preterm labor and delivery, and, quite often, preterm contractions with or without cervical changes necessitate tocolytic treatment. Many prophylactic measures, including progestatives, cervical sutures (cerclage), beta-sympathomymetics, forced bed rest, and hospitalization, were proposed to reduce the preterm birth rates. Regrettably, all *prophylactic* measures failed to significantly reduce this common complication of multiple pregnancy. Nevertheless, expecting mothers of multiples are frequently asked to leave work and to conduct a more sedentary lifestyle.

The population-based analysis of Alexander et al,[1] the more recent data of Ventura et al,[2] and the Matched Multiple Birth Files derived by National Center for Health Statistics[3] demonstrate the axiomatic concept that triplets fare worse than twins, both in terms of gestational duration and birth weight.[3] In particular, triplets are over-representation among extremely LBW (less than 1000 g, ELBW) infants, whereby the risk is 10 times higher than that in the general population.[4,5] We calculated the odds of delivering one, two, or three ELBW triplet infants by parity. The odds of having at least one ELBW triplet were 1: 9, with significantly higher odds among nulliparas (1:8) than among multiparas (1:14).[6] The odds of having at least two ELBW triplets were 1:20, with significantly higher odds among nulliparas (1:16) compared to multiparas (1:31). In 100 sets, all three infants were ELBW, without significant difference between nulliparas and multiparas (3.4 vs. 2.5%).[6] A similar study was carried out in twins, but at this time the risk was assessed for having one or two very LBW (<1500 g, VLBW) twins.[7] The overall risk of having at least one VLBW twin is almost the same as having one ELBW triplet (1:9). However, the difference between being very and extremely LBW is that the latter is associated with significant morbidity, namely 24 to 25 % major neurological abnormalities, 37 to 42 % subnormal (<70) Bayley Mental Developmental Index, and 29 % of subnormal (<70) Psychomotor Developmental Index among ELBW infants.[5,8]

At the same time that that prophylactic measures to reduce prematurity among multiples seem futile, modern neonatal intensive care units have almost 100% survival rates for infants delivered at more than 28 weeks. This fact makes this gestational age a clinical target in the management of multiples. As a result, it was proposed that one should aim for a realistic gestational age at which neonatal mortality is lowest, rather than postponing triplet births until "term" or until the average gestational age. [Papiernik E, The 13th Workshop on Multiple Pregnancy, Porto, Portugal, June 2000, unpublished].

It is unknown to which extent are we able to change the natural distribution of gestational ages or birth weight in triplets. A recent study by the National Institute of Child Health and Human Development (NICHD) found, surprisingly, that triplets born to older mothers actually fare better than triplets born to younger mothers, a pattern that was not recognized in singletons and twins[9] Of importance, however, is the observation that this trend was found primarily in women who are more likely to conceive using assisted reproduction, and as the authors note, these women are likely to receive better prenatal care, and their infants are likely to receive a high

standard of care as newborns.[9] Consequently, it appears that the special attention, which all multiples deserve, may be the prerogative of mothers of the affluent social class.[10] The finding of Zhang et al[9] supports previous findings from an extensive study of more than 3200 triplet sets.[11,12] The comparison of Matria triplet pregnancies – a company that specializes in providing outpatient surveillance to privately insured women with high-risk pregnancies – with the United States data from the NCHS Matched Multiple Data File revealed 50% fewer extremely premature triplets (<28 weeks) and 17.7% more deliveries at 28-32 and 33-36 weeks in the former group.[11]

Another potential way to reduce prematurity, comes from the study of Luke et al who reported that maternal weight gain early during pregnancy may improve outcomes of triplets.[13-14] When the greater nutritional requirements due to greater need and metabolism are appropriately met, improved outcomes have been seen in prolonging length of gestation and in larger birth weights.[13-14] The recommended daily calories intake for a pregnant woman carrying triplets is more than twice than that for the non-pregnant state, 80% that of a singleton pregnancy, and 30% more than during a twin gestation.[15] Moreover, it has been emphasized that early weight gain is more important because there is not enough time to gain weight during the shorter triplet gestation. One must realize, however, that nausea and vomiting are more frequent during early stages of triplet gestations, and therefore, adequate maternal weight gain is even more difficult. Since the desired weight gain seems difficult to attain, we looked at the real weight gain of more than 3200 mothers of triplets, and showed 40% of normally built women gained less than the average mother of triplets that irrespective of parity and timing of referral to special care. [Sharma G, Kalish RB, Rhea DJ, Keith LG, Blicktsein I; unpublished]. Regardless, mothers of triplets who gained weight gain more than the average had significantly lower frequencies of VLBW of infants.

Finally, numerous studies described an "ideal" female phenotype selected by Nature to have twins, and characterized by being older, parous, heavily built, and with a familial or racial predisposition. Because triplets are very rare in spontaneous conceptions, it is unknown if the same phenotype also describes mothers of triplets. It goes without saying that iatrogenic pregnancies – which cause the majority of triplets – occur in women who are less "ideal" to carry twins, and surely less "ideal" to carry triplets. We recently estimated the likelihood of adverse outcomes in 2,887 triplet sets by a score comprising pregravid maternal characteristics.[16] A scoring system was constructed, assigning 1 point for the presence of a risk factor (nulliparity, stature <165 cm, and age <35 years) and 0 for the absence of a risk factor. We identified 18% of triplets' mothers (score 3) in whom the likelihood for adverse results (total triplet birth weight <4,500 and delivery at 27-32 weeks) is 50%-90% higher and the likelihood for optimal results (total triplet birth weight >6,000 g and delivery at >32 weeks) is 40% to 70% lower than background rates. It could be envisioned that a pregravid maternal profile could estimate the likelihood of adverse outcomes and be used for consulting patients at risk of having or carrying a triplet pregnancy.

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