EDITORIAL

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Does Medical Intervention Affect Outcome in Infants with Trisomy 18 Or Trisomy 13?

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Two relevant and noteworthy studies are published together in this issue of the Journal [Meyer et al., 2016; Subramaniam et al., 2016]. Both articles discuss an important and timely question: Does medical and/or surgical intervention affect outcome in the care of newborns and infants with trisomy 18 or trisomy 13? In this Editorial piece, we will comment on these two papers and expound on the existing evidence regarding whether intervention influences survival in infants with these trisomy syndromes.

Subramaniam et al. [2016] conducted a retrospective cohort study of the outcome in infants with trisomy 18 in a single tertiary referral center, the University of Alabama at Birmingham, from 2004 – 2014. The authors addressed the issue of outcome by dividing the 54 live born infants in the investigation into those neonates who received "no intervention" and those who received one or more interventions; the authors further subdivided the latter group into those who received "aggressive intervention" versus "non-aggressive". Overall, neonates who received intervention had significantly increased survival compared to the "no treatment" group (p of less than 0.001). However, when the "aggressive" group was compared to the "non-aggressive" group, there was no significant difference in median survival time. The authors conclude the article by saying, "Neither aggressive obstetric or neonatal intervention increases survival of infants with T18 in our experience at a single center". Discussing neonatal intervention in particular, we would question whether the "aggressive" group truly had an intensive approach throughout the care because of the authors' oversimplified definition of aggressiveness. Aggressive intervention included any corrective surgical procedures, feeding tube placement, parenteral nutrition, cardiopulmonary resuscitation, and mechanical ventilation, aimed at prolongation of life. We have to consider in a more comprehensive way what interventions would contribute to longer survival including specific procedures (such as cesarean, mechanical ventilation, cardiac surgery) or general positive attitudes on intensive management. In the paper by Subramaniam et al. [2016], readers do have the chance to review individual patient outcomes through Table IV, which would allow more comprehensive interpretation of survival in this cohort. For example, comparison between a group managed with "palliative care at delivery" and "no mechanical ventilation" (n = 13) and a group managed with "no palliative care at birth" and "mechanical ventilation" (n = 13) would be simpler. Kaplan-Meier curves evaluated with the log-rank test demonstrated that there was significant difference in survival between these two groups (p = 0.031), with the calculated median survival time as 8 days in the former group and as 399 days in the latter. The clinical experience presented here from one of the largest neonatal intensive care units in US is very valuable, but the authors' conclusion that there was no significant difference in the two therapeutic groups has to be carefully considered.

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The second paper by Meyer et al. [2016] investigated survival of children with trisomy 18 or trisomy 13 in a multistate population study. There were 1,113 children with trisomy 18 and 693 children with trisomy 13, born during 1999 – 2007 and recruited in this study. This particular investigation is unique compared to the other population studies of the last two decades because first, the authors documented the highest 1-year survival in infants with trisomy 18 (13.4 %) and trisomy 13 (11.5%) than all prior similarly designed population studies, and secondly, they report a 5-year survival (12.3% for trisomy 18; 9.7% for trisomy 13), which has not been documented in previous work. The authors state that the higher figures are "consistent with the recent studies reporting improved survival following more aggressive medical intervention for these children".

An abbreviated version of parts of this review by John Carey appeared in the newsletter of the International Trisomy Alliance (www.internationaltrisomyalliance.com) in 2015.

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Continuing on this theme, we would like to review carefully the four lines of evidence published to date that would be critical in the discussion whether intensive management would make a difference and improve survival in trisomy 18 and trisomy 13. First, there is the seminal work by Kosho et al. [2006] who demonstrated that standard neonatal intensive treatment would improve survival compared to population studies and other hospital series. Standard neonatal intensive treatment administered in this series represented the same management routinely given to severely sick neonates without trisomy 13 or trisomy 18: appropriate respiratory care including mechanical ventilation; nutritional intervention (such as tube feeding, parenteral approach); surgery for gastrointestinal malformations; and routine management for infection or other neonatal problems. Only pharmacological treatment was performed for cardiovascular complications according to the institutional policy. Such approaches were reported to result in markedly longer 1-year survival rate (25%) and median survival time (152.5 days) in children with trisomy 18. The common underlying factors associated with death were reported to be congenital heart defects and heart failure, followed by pulmonary hypertension, and the common final modes of death were sudden cardiac or cardiopulmonary arrest and possible progressive pulmonary hypertension-related events.

The second line of evidence comes from recent studies that report outcomes in children who have had cardiac surgery. Presently, there are over 160 children reported in these various studies who have had cardiac surgery with about 85% leaving the hospital [reviewed by Carey et al., 2012; Lorenz and Hardart, 2014]. Generally, cardiac surgery including palliative procedures (pulmonary artery banding, ductus ligation) and intracardiac repair (closure of ventricular septal defect in most) was performed safely and seemed to contribute to longer survival in children with trisomy 18 or trisomy 13. This was demonstrated in a cohort of the multicenter Pediatric Cardiac Care Consortium in US [Graham et al., 2004]; in a tertiary medical center in Japan, the Japanese Red Cross Medical Center [Kaneko et al., 2008, 2009; Kobayashi et al., 2010]; in a tertiary medical center in Japan, Kyushu Koseinenkin Hospital [Muneuchi et al., 2011]; in a multicenter registry of the Japanese Society of Pediatric Cardiology and Cardiac Surgery [Maeda et al., 2011]; in a tertiary medical center in Washington, DC, Children's National Health System [Costello et al., 2015]; in the Tracking Rare Incidence Syndromes (TRIS) project [Bruns and Martinez, 2016]; and in a tertiary medical center in Japan, Nagoya City University Hospital [Nakai et al., 2016].

Two other recent investigations are relevant to this discourse on outcomes after surgery and other interventions. Both support this notion that intervention improves outcome: 1. the article by Nishi et al. [2014] compared different approaches to the treatment of children with trisomy 18 and esophageal atresia in two tertiary medical center in Japan (Nagano Children's Hospital, Central Hospital, Aichi Human Service Center); those having complete repair ("radical" surgery) did better than those only having palliative treatments (1-year survival rate, 27% v.s. 0%, respectively). 2. The paper by Nelson et al. [2012] showed an increasing number of inpatient hospital stays and numerous therapeutic procedures performed on children with trisomy 18, many of whom were older than a year, in the US over time. The authors state that despite "the conventional understanding of these syndromes as lethal, a substantial number of children are living longer than 1 year and undergoing medical and surgical procedures as part of their treatment".

The third line of evidence comes from an analysis of the published survival studies in population series that suggest improved survival in recent times compared to the past. The authors of the paper by Meyer et al. propose this as mentioned above. In addition, examination of outcome data from the population studies of the United Kingdom over the last 20 years shows improved survival over time [Carey, 2012]. The recent paper from the UK by Wu et al. [2013] had the largest number of cases of live born infants with both syndromes compared to the previous investigations (326 for trisomy 18 and 142 with trisomy 13) and documented 8% 1-year survival rate for both conditions. The 1-year survival rate in the Meyer et al. study was 13.4% and 11.5%, the highest of any of the previous work using this methodology.

Finally, quality of life of children with trisomy 18 or trisomy 13 as well as parental feelings would have to be considered in the management of individuals with the syndromes. Janvier et al. [2012] reported the experiences and perspectives of parents of children with trisomy 18 or trisomy 13 who belonged to support groups. Despite being told by healthcare providers that their child was "incompatible with life" (87%), would live a life of suffering (57%), would be a "vegetable" (50%), or might have a short meaningful life (60%), 30% of parents requested "full" intervention and 97% described their child as a happy child. Through a questionnaire-based comprehensive study of children with trisomy 18 and their parents in collaboration with a Japanese trisomy 18 support group, half of the mothers were reported to have a cesarean, one-third of the families were offered intensive treatment, and half of the children received intermittent mechanical ventilation. Parents were reported to be positive about caring for their children, and the children seemed to interact with parents and siblings as long as they lived, resulting in quality family time [Kosho et al., 2013]. Kosho et al. [2013] implicated that these positive parental feelings together with recent evidence of efficacy in intensive management could justify an intensive approach in the care of children with trisomy 18, adjusted to individual physical conditions and considering parental feelings.

While more investigation needs to be accomplished to help address this question including risk stratification of patients with trisomy 18 or trisomy 13 in view of surgical intervention, the body of work indicates that intervention does make a difference in terms of survival in infants with trisomy 13 or trisomy 18 and could be a reasonable option in discussion of care in a prenatal or postnatal session with parents.

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