Case Report

Trisomy 18 syndrome: Towards a balanced approach

Hasan Batis, Khalid A Altirkawi

Department of Pediatrics, College of Medicine and King Khalid University Hospital, King Saud University, Riyadh, Saudi Arabia

ABSTRACT

Trisomy 18 is a relatively common autosomal trisomy syndrome. It is due to either full or partial presence of an extra copy of chromosome 18. Its prevalence correlates positively with advanced maternal age. Affected infants usually exhibit a variable pattern of anomalies including growth restriction, marked psychomotor and cognitive disability and an array of physical findings including characteristic craniofacial features, clenched fists with overriding fingers, small fingernails, underdeveloped thumbs, short sternum and heart and kidney anomalies. The majority of these infants die within the first year of life; only 5% to 10% of them survive longer. Their death is primarily due to cardio-respiratory failure.

In this case report of trisomy 18 we tried to highlight the importance of antenatal diagnosis and to emphasize the need for proper counseling at different points of time starting from the moment the condition is suspected until the point when diagnosis is confirmed and thereafter.

Key words:

Aneuploidy; Trisomy 18; Edward's syndrome; Prenatal diagnosis; Counseling.

Correspondence to:

Khalid Altirkawi,

Assistant Professor and Consultant in Neonatology,

Department of Pediatrics (39),

College of Medicine, King Saud University

PO box 7805, Riyadh, Saudi Arabia 11472

Office: + 966 11 467 1099, Fax: + 966 11 467 1709

Email: kaltirkawi@ksu.edu.sa

How to cite this article:

Batees H, Altirkawi KA. Trisomy 18 syndrome: Towards a balanced approach. Sudanese J Paediatr 2014;14(2):76 - 84.

INTRODUCTION

Trisomy 18, or Edward's syndrome, was first recognized as a specific entity in 1960. It is the second most common autosomal trisomy syndrome, second only to trisomy 21. It is characterized by the presence of an extra copy of chromosome 18, as full, mosaic or partial trisomy 18q. The live-born prevalence is about 0.15/1000; however, the overall prevalence is believed to be higher (0.4/1000) due to the high rate of fetal loss and pregnancy termination after prenatal diagnosis [1]. The prevalence of this syndrome correlates positively with increasing maternal age. The recurrence risk for a family of a child with full trisomy 18 is about 1% [2]. White ethnicity, female Gender and being a singleton seem to increase the risk for trisomy 18 [3].

Currently, the prenatal diagnosis of this aneuploidy condition is based on maternal serum biomarkers screening and the detection of characteristic ultrasonographic abnormalities "the quadruple screening" [4]. Isolation of cell-free fetal DNA (cfDNA) in maternal serum is poised to be the test of choice in the future due to its better performance in the targeted population [5,6]. Typically, affected infants exhibit a variable pattern of anomalies including growth restriction and marked psychomotor and cognitive disability. The most frequent physical findings are heart and kidney anomalies, characteristic craniofacial features, clenched fists with overriding fingers (camptodactyly), small fingernails, underdeveloped thumbs, and short sternum [7].

Almost half of trisomy 18 infants die within the first week of life, and the majority of the remaining die in the next 12 months; only 5% to 10% of these infants survive the first year. The death usually is due to central apnea, upper airway obstruction, respiratory insufficiency, aspiration, cardiac failure, or a combination of these and other factors (including decisions for palliative care) [7].

CASE REPORT

A male preterm infant is born at 33 weeks of gestation by an emergency Caesarian section delivery due to preterm labor and fetal distress. Mother is a 45-year-old (Gravida 8, Para 7, Abortion 0) lady. Pregnancy was complicated by inadequate and late prenatal care, a long-standing systemic lupus erythematosus (SLE) diagnosed at age of 14 years and treated once with steroids but not during this gestation. She also suffers from bronchial asthma with on-demand bronchodilator inhalation therapy. Upon admission mother was well, with a history of spontaneous rupture of membranes and clear amniotic fluid for 12 hours. The records revealed her blood group of (O) Rh-negative type with pending TORCH screening. The first dose of antenatal corticosteroid course was administered four hours prior to delivery.

The infant, with a birth weight of 1,300 g, was profoundly depressed at birth. Initial resuscitation steps of dryness, suction, stimulation and warming followed by free oxygen flow then PPV for 2 minutes were needed. He eventually improved and maintained normal Oxygen saturation. Apgar's scores were 5 and 8 at 1 and 5 minutes respectively. Infant was then shifted to neonatal intensive care unit (NICU) on Nasal continuous positive-air-way-pressure (CPAP) support.

On examination, infant was active, pink and not in respiratory distress, his vital signs were within normal limits. He looked dysmorphic with frontal bossing, pointed and up-turned nose, small mouth, triangular hairy face, low set ears, micrognathia, bilateral camptodactaly, rocker-bottom feet; features which are suggestive of Trisomy 18 (Figure 1). He appeared small for gestational age (weight, length and head circumference all were bellow 5th centile.) The rest of examination was remarkable for umbilical hernia and pan-systolic, non-radiating murmur of grade 3/6, best heard at lower left sternal border.

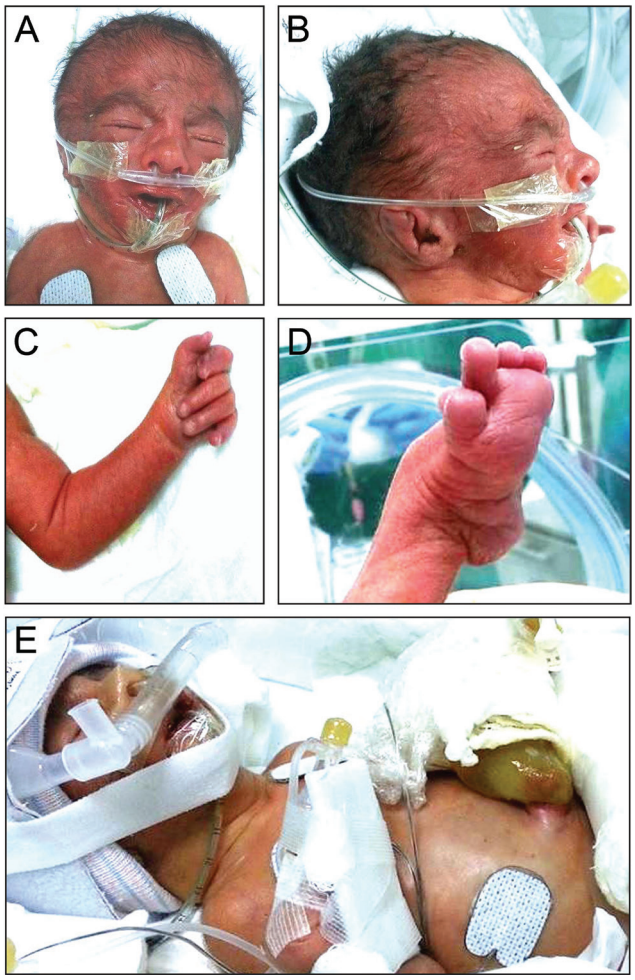

Figure 1 – The phenotype. (A) Notice triangular hairy face, frontal bossing, pointed and up-turned nose, small mouth. (B) Low-set ears and micrognathia. (C) camptodactaly (fisting). (D) Rocker-bottom foot. (E) Omphalocele.

An orogastric tube could not be inserted beyond 7 cm mark, radiographic evaluation showed the tip of this tube at the level of the 3rd thoracic vertebra suggesting the diagnosis of esophageal atresia (EA) with possible tracheo-esophageal fistula (TEF) (Figure 2).

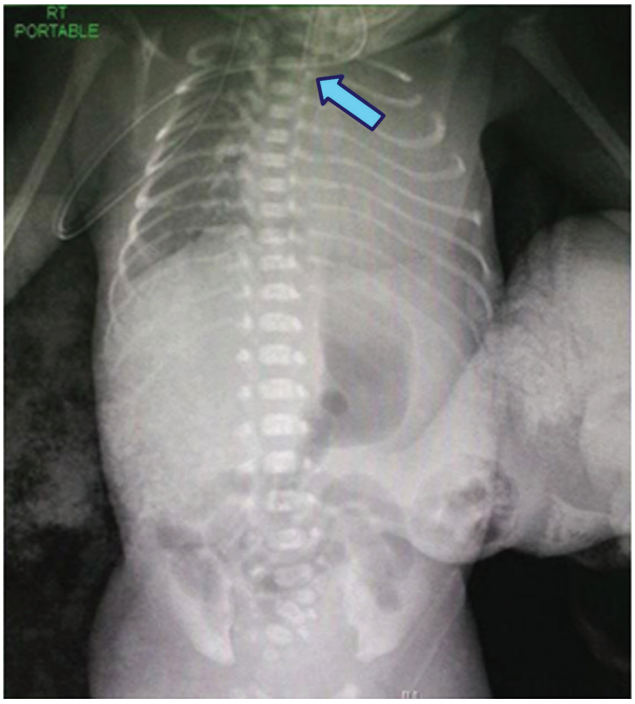

Figure 2 - Chest Roentgenogram. Notice the orogastric tube position in the med-esophagus (arrow).

The initial laboratory investigations including complete blood counts, hepatic and renal function panels and bony profiles were all within normal limits. The laboratory evaluation for sepsis was reported later as negative. Subsequent abdominal ultrasonogram revealed a left sided hydronephrosis. Echocardiogram confirmed the presence of multiple small ventricular septal defects (VSD), patent ductus arteriosus (PDA) of moderate size and markers of pulmonary hypertension.

After discussion with surgical services two management options were considered; the first was surgical intervention to facilitate patient care and possibly ameliorate the course of illness and the second was the expectant conservative management. As the long-term outcomes were dependant on the final diagnosis, parents and treating team opted for no surgical intervention at this stage. The following days were significant for gradual deterioration of

respiratory functions requiring mechanical ventilation whereas circulatory status remained stable.

At the age of one week, the result of chromosomal analysis confirmed the diagnosis of Trisomy 18 (Figure 3). Parents were counseled once again regarding the final diagnosis and expected long-term outcomes, quality of life, and the prospects of poor prognosis even with the multiple surgical interventions. Parents expressed their desire not to further escalate the therapy (a DNR status). Infant was weaned off mechanical ventilation and kept on palliative care including oxygen flow via nasal cannula (NC). He finally passed away at age of 31 days.

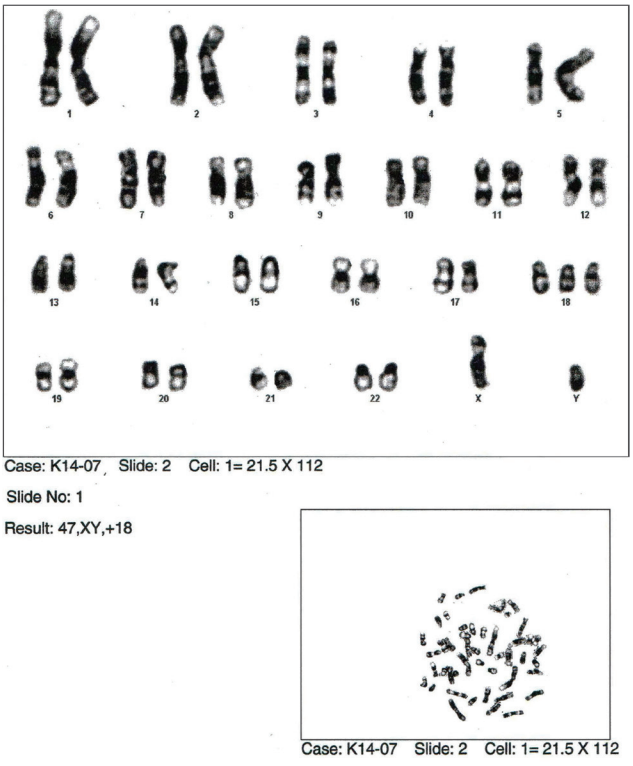

Figure 3 - Patient's karyotype showing the presence of three copies of chromosome 18.

DISCUSSION

Prenatal Diagnosis and parental Counseling

The prenatal diagnosis of a seriously malformed fetus is a stressful event in the life of the expecting parents. Counseling offered by competent physicians in this situation seems helpful as current literature reveals.

The effective counseling would deliver the facts related to the illness without imposing the physician's personal preferences upon the families [8]. In a study on parental perceptions of the antenatal counseling offered to families of prenatally diagnosed infants with serious congenital anomalies, Miquel-Verges et al [9] reported that mothers found a consultation with a neonatologist helpful; it made them better prepared for the perinatal course. These mothers looked for realistic information, no matter how grim, provided it was pertinent to their condition and tailored to their knowledge base. They pointed out that conflicting information from different physicians increased their anxiety and diminished their confidence. On the other hand, mothers valued touring the NICU during the consultation despite being an emotionally difficult experience. More importantly, all mothers said they would recommend a prenatal consultation with a neonatologist. These findings concur with the conclusions of an older report by Halamek [10] that a consultation with a neonatologist can provide parents with a unique perspective other subspecialists may not afford.

Showing empathy by physicians seems of a paramount importance; Mothers, as reported by Menahem and Grimwade [11], expected health care providers, irrespective of their level of technical competence, to be empathetic and sensitive, they wanted to know all possible scenarios, what to expect, and what the management plan would be. Interestingly enough, they were more concerned with the plan for the pregnancy and perinatal care than the details about the anomaly itself. Furthermore, mothers emphasized the importance of allowing hope, regardless of the prognosis. Boss et al. [12] reported that Parents whose infant suffered of "lethal" anomalies or extreme prematurity also appreciated

the importance of maintaining hope. Apparently, this requires in addition to a continuous communication with the parents a good deal of time spent in listening and answering questions. Howard [13] claims that the time constraints and pressures of a busy workplace can interfere with performing these badly needed tasks. She suggested that adequate preparation in advance, by reviewing available studies and previous consultations, along with allocating enough time to set down and try to answer parents' queries is very important; it would convey a positive message of empathy and readiness to offer the professional help needed. In a relatively recent study, Walker et al. [14] in a report on health-care experiences of families given the prenatal diagnosis of trisomy 18 found that these families satisfaction depends, ultimately, on expression of empathy from providers, continuity of care, good communication, valuing the fetus and participation in medical decision-making.

Based on the information obtained from parents who continued their pregnancy after a diagnosis of Trisomy13 or trisomy18, Guon et al. [15] suggested the following to help physicians optimize the prenatal care:

*Be honest; provide parents with accurate survival figures and inform them about the positive feelings of other parents who elected to continue pregnancy despite the diagnosis of the trisomy 18 syndrome.

*Whatever choices the parents make, be supportive not judgmental.

*Avoid "value-laden" descriptions; such as "lethal" or "incompatible with life".

*Always refer to the unborn infant as a person, preferably by a name, not as a diagnosis.

*Tell the parents the relevant information about their own infant not about the disease.

*Offer hope within the limits of reality. Be transparent about any hospital policy that restricts certain interventions to babies born with such illness.

*Continue to provide prenatal care as for any other pregnancy; this entails guiding parents in formulating a birth plan suitable for the infant and family.

Resuscitation at birth

Current literature suggests that the vast majority of trisomy 18 patients, especially the very low birth weight (VLBW) ones who are not treated intensively would die soon and their outcomes would not improve even with intensive care management and corrective surgeries. Until recently, there was a near consensus among health care providers that trisomy 18 represents a lethal condition for which resuscitation at birth is not indicated. This view of letting these infants go originated probably from the dismal prognosis they have. Nonetheless, the current Neonatal Resuscitation Program (NRP) guidelines [16] do not identify Trisomy 18 as a condition in which withholding resuscitative efforts may be considered reasonable. This sentiment in the ranks of the neonatologists seems picking up; McGraw and perlman [17] reported that 44% of US-based neonatologists indicated that they would consider initiation of resuscitation of an infant with trisomy 18 and known congenital heart disease. 70% of the respondents to the survey cited maternal preference as the primary reason for choosing to do so. The condition of the neonate in the delivery room (appearing vigorous or having a heart rate of 100 beats per minute) was the second most cited reason (46%), whereas legal concerns, surprisingly, came in the third place (25%). Thus, full medical support seems a reasonable recommendation until the confirmatory karyotype result is in.

Postnatal counseling and management

Withholding or withdrawal of intensive treatment has been recommended due to the observed short life span of these infants; Median survival time was

14.5 days (95% CI: 8–28), the survival rate at age of one year was 5%–10%, [18] and due to profound mental retardation as well [19]. These figures are based on data derived from a population of patient cared for mainly in the "standard" approach. More recently, Kosho [20] described the natural history of infants with trisomy 18 who received intensive care, he documented an improved survival; the median survival time is 152.5 days and a survival rate at age of one year is 25%. Reports such as this one constitute the basis for a more "individualized" approach to the management, whereby the intensive treatment options could be considered, placing significant weight on parental choices in the context of the "best interests of the child" [17,21].

Counseling considerations

For a counseling process to be effective and to end up in a fruitful decision making several basic principles need to be observed, these principles may be summarized in the following:

*The "best interest of the patient" should always be at the core of any intervention; this means that improving patient's quality of life and minimizing the potential for suffering inflected on the infant is of prime importance.

*Parental autonomy must be respected irrespective of their faith, ethnicity or cultural preferences.

*Health care providers need to be mindful of the judicious allocation of the available resources.

It is conceivable that high neonatal and infant mortality and "poor" quality of life in children suffering of this syndrome compelled many physicians to advocate a non-intervention/comfort care [19]. However, voices of dissent are getting louder; some argued that currently, 5%-10% of infants with trisomy 18 survive to their first birthday; thus the description "LETHAL" is a misplaced and misleading one. Furthermore, parents and families of children with trisomy 18 are, generally, resilient and cope well; they appreciate the "unique" quality of life in their children, value their children deeply, and want to be a part of the decisions made around their care [22]. This view has been further supported by the report of Janvier et al. [8] who surveyed parents of children with trisomy 18; almost all the parents reported that their child affected with the syndrome has enriched their life and had a positive effect on siblings and parents.

These arguments do lay the foundation for a change whereby the focus may be shifted from prognosis-related issues and pursuing a futile objective of full cure to a more realistic, yet hopeful, goals. Merritt et al. [16] provide a review of those important themes that can be discussed and a list of questions to be considered during counseling. The concluding remarks of their paper constitute a great summation of this trend "*transforming hope for cure to hope for the child and the family to be relieved from suffering, and to experience love and care in their infant's lifetime, should be the primary goal*."

As mentioned earlier, parents should participate actively in the discussion to delineate the best interest of the neonate after the required stabilization period [23,24]. If the parents choose intensive management, then appropriate respiratory, cardiovascular, and nutritional support, as well as prevention of infection, is initiated based on the standard NICU protocol and evidence specific to this condition [25-27]. Continued discussions with the parents help not only in keeping them engaged but it facilitates making adjustments in patient's care when the need for this arises. Although demanding, such approach is an incumbent one, it relay a positive message of respect to patients and their families [24].

In a fresh view from Japan, Kosho [20] presents an elaborate list of guidelines devised to help both physicians and families in the process of deciding on the care plan of serious illnesses such as trisomy 18. In the following is a summary of the most salient

points:

*All infants have the right for protection and to receive appropriate medical care.

*Parents have the right and the obligation to choose the course of their infant's medical treatment.

*The course of medical treatment must be based on the ''best interests of the child''. Parents and physicians must discuss all available options in this regard.

*Building a trusting relationship with families is a must. Parents need to be treated as equal partners in this process.

*Providers may present their opinions and express their emotions concerning the treatment of newborns. However, they have the obligation to provide parents with all information relevant to their infant's condition and all available treatment options in an easy to understand language.

*The infant's prognosis should be based on the latest medical information available. Consultation with other specialists of other disciplines may be necessary.

*Withdrawal of life-sustaining medical treatment must be discussed with extreme caution. This means to exchange opinions with as many physicians as possible in the presence of parents and other team members. When the decision is reached an appropriate documentation should be made.

*Changes in the plan may be introduced at any time depending on changes in the infant's condition or based on the wishes of the family. This option has to be articulated clearly and in advance to the parents.

CONCLUSIONS

Trisomy 18 is relatively a common syndrome. Affected infants suffer of a multitude of physical anomalies and significant psychomotor developmental delay. The majority of these infants die before reaching their first birthday; only 5% to 10% of them survive longer. Their death is usually due to cardio-respiratory failure. Until recently, the perception of trisomy 18 as a lethal condition was the norm. This view is currently facing a serious challenge. Authorities such as American Academy of Pediatrics are no longer advocating withholding active management including resuscitation interventions in the delivery room. Furthermore, reports from units providing intensive care to these infants indicate an improved survival rates and probably a better quality of life. This trend found its way into the many guidelines formulated to help physicians and families in their efforts to optimize the care of these infants and hopefully to have a true improvement in their outcomes.

ACKNOWLEDGEMENTS

We thank Dr. Adnan Hadeed for his kind gesture and providing us with the pictures of this patient

REFERENCES

1. Bianchi DW, Parker RL, Wentworth J, Madankumar R, Saffer C, Das AF, et al. DNA Sequencing versus Standard Prenatal Aneuploidy Screening. New England Journal of Medicine 2014; 370:799–808.
2. Cereda A, Carey J. The trisomy 18 syndrome. Orphanet Journal of Rare Diseases 2012; 7:81.
3. Boghossian NS, Hansen NI, Bell EF, Stoll BJ, Murray JC, Carey JC, et al. Mortality and Morbidity of VLBW Infants With Trisomy 13 or Trisomy 18. Pediatrics 2014; 133:226–35.

4. Spencer K. Aneuploidy screening in the first trimester. Am. J. Med. Genet. 2007; 145C:18–32.
5. Russo ML, Blakemore KJ. A historical and practical review of first trimester aneuploidy screening. Seminars in Fetal and Neonatal Medicine 19:183–7.
6. Irving C, Richmond S, Wren C, Longster C, Embleton ND. Changes in fetal prevalence and outcome for trisomies 13 and 18: a population-based study over 23 years. Journal of Maternal-Fetal and Neonatal Medicine 2011; 24:137–41.
7. Lyons Jones K. Smith's Recognizable Patterns of Human Malformation [Internet]. 7th ed. Phladelphia, USA: Elsevier Saunders; 2013. Available from: http://www.us.elsevierhealth.com/pediatrics/smith-recognizable-patterns-of-human-malformation-expert-consult/9781455738113/
8. Janvier A, Okah F, Farlow B, Lantos JD. An Infant With Trisomy 18 and a Ventricular Septal Defect. Pediatrics 2011; 127:754–9.
9. Miquel-Verges F, Woods SL, Aucott SW, Boss RD, Sulpar LJ, Donohue PK. Prenatal Consultation With a Neonatologist for Congenital Anomalies: Parental Perceptions. Pediatrics 2009; 124:e573–9.
10. Halamek LP. The advantages of prenatal consultation by a neonatologist. J Perinatol 2001; 21:116–20.
11. Menahem S, Grimwade J. Pre-natal counselling—helping couples make decisions following the diagnosis of severe heart disease. Early Human Development 81:601–7.
12. Boss RD, Hutton N, Sulpar LJ, West AM, Donohue PK. Values Parents Apply to Decision-Making Regarding Delivery Room Resuscitation for High-Risk Newborns. Pediatrics 2008; 122:583–9.
13. Howard ED. Family-centered care in the context of fetal abnormality. J Perinat Neonatal Nurs 2006; 20:237–42.
14. Walker LV, Miller VJ, Dalton VK. The health-care experiences of families given the prenatal diagnosis of trisomy 18. J Perinatol 2007; 28:12–9.
15. Guon J, Wilfond BS, Farlow B, Brazg T, Janvier A. Our children are not a diagnosis: The experience of parents who continue their pregnancy after a prenatal diagnosis of trisomy 13 or 18. American Journal of Medical Genetics Part A 2014; 164:308–18.
16. American Academy of Pediatrics. Textbook of Neonatal Resuscitation. 5th ed. Elk Grove Village, USA: American Academy of Pediatrics; 2010.
17. McGraw MP, Perlman JM. Attitudes of Neonatologists Toward Delivery Room Management of Confirmed Trisomy 18: Potential Factors Influencing a Changing Dynamic. Pediatrics 2008; 121:1106–10.
18. Rasmussen SA, Wong L-YC, Yang Q, May KM, Friedman JM. Population-Based Analyses of Mortality in Trisomy 13 and Trisomy 18. Pediatrics 2003; 111:777–84.
19. Bos AP, Broers CJM, Hazebroek FWJ, Tibboel D, Molenaar JC, van Hemel JO, et al. Avoidance of emergency surgery in newborn infants with trisomy 18. The Lancet 1992; 339:913–5.
20. Kosho T, Nakamura T, Kawame H, Baba A, Tamura M, Fukushima Y. Neonatal management of trisomy 18: Clinical details of 24 patients receiving intensive treatment. American Journal of Medical Genetics Part A 2006; 140A:937–44.
21. Carey JC. Perspectives on the care and management of infants with trisomy 18 and trisomy 13: striving for balance. Current Opinion in Pediatrics 2012; 24:672–8 10.1097/MOP.0b013e3283595031.
22. Wilfond BS, Carey JC. Parental requests for intervention in children with lethal conditions [Internet]. In: Clinical Ethics in Pediatrics. Cambridge University Press; 2011. page 174–80.Available from: http://dx.doi.org/10.1017/CBO9780511740336.031
23. Thiele P, Blair S. Destined to die. BMJ 2011; 343:d3625–d3625.
24. Carey JC. Attitudes of Neonatologists Toward Delivery Room Management of Confirmed Trisomy 18: Potential Factors Influencing a Changing Dynamic. Pediatrics 2009; 123:e547–8.

25. Kaneko Y, Kobayashi J, Yamamoto Y, Yoda H, Kanetaka Y, Nakajima Y, et al. Intensive cardiac management in patients with trisomy 13 or trisomy 18. Am. J. Med. Genet. A 2008; 146A:1372–80.
26. Maeda J, Yamagishi H, Furutani Y, Kamisago M, Waragai T, Oana S, et al. The impact of cardiac surgery in patients with trisomy 18 and trisomy 13 in Japan. Am. J. Med. Genet. A 2011; 155A:2641–6.
27. Graham EM, Bradley SM, Shirali GS, Hills CB, Atz AM. Effectiveness of cardiac surgery in trisomies 13 and 18 (from the Pediatric Cardiac Care Consortium). American Journal of Cardiology 93:801–3.