

Review Article

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# Thirty Years of Perinatal Care in Portugal

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## Abstract

From the daunting figures for maternal, perinatal and infant mortalities and morbidities of the past, in the last three to four decades, Portugal has set remarkable standards of care with the gratifying results of, either overlapping or even surpassing, those of many of the western countries. This is the case for maternal mortality at just over 5-8/100,000 live births per year and perinatal mortality at below 5/1,000 live births, in the last ten years. Although a decrease in maternal and perinatal mortalities has also been achieved in all European countries Portugal was one of those with the most significant falls. Rationalization of human and financial resources was instrumental, with sophisticated technologies playing a subsidiary role for the high risk pregnancies and sick neonates. Above all, it has been a successful example of collaboration and goodwill between professionals and politicians alike regardless of the, often, conflicting interests.

**Keywords:** Maternal; Perinatal mortality; Threshold of viability

## Introduction

Maternal and infant health care should be a major priority in any country. Throughout the world, unfortunately, that is not always the case. Worldwide over 7 million perinatal deaths occur each and every year and 98% are in the less affluent countries of the world. Each year 1/2 million women die from pregnancy related complications and including unsafe abortions-once again 99% of these maternal deaths are in the same unfortunate countries. To emphasize the equation, for each maternal death in developed countries 36 women will die in developing countries from pregnancy complications and in some areas of the globe these figures will rise to 500 times those of their more privileged sisters in the western world [1-4] and the sad thing is that most of these deaths are preventable.

The development of neonatal intensive care has been shown to be effective in the survival of preterm infants without a significant increase in later morbidity, at least for the larger, more mature neonates [5-7]. In recent years, an increased survival of even the most immature infants, often at the threshold of viability, has been reported [8-10]. These are the good news, at least, for some of us in the comforts of the western world and in the developed countries. However, only 7% of all births take place in this part of the world [1-4]. When addressing the issue of under developed countries, it immediately comes to mind the dark Africa and the faraway Asian and South East Asian regions of the world. In spite of the politically correct euphemisms of semantic laundering used to classify some countries within Europe, from peripheral economies, to temporary recession, post conflict environmental emerging countries, etc the truth is that these same problems also exist in many of these countries. There are certainly many reasons for this unhealthy picture of the world, some due to our own collective wrongdoings, but equally, also due to individual faults of greed and corruption.

Against this background, Portugal, over the last 30 years has set an example of what can and, should be done, to overcome difficulties, obstructions and conflicting interests, to the enormous benefit of society as a whole and mothers and children in particular. The following report reflects what has been achieved.

## Methodology

Data is presented based on the Portuguese MOSAIC Study, the Portuguese VLBW National Register, Portuguese National Institute of Statistics and Personal Data from the Paediatric/Neonatology

Department of Sao Sebastiao Hospital. Governmental Diplomas, Regulations and Legislations are, herewith, referred as appropriate.

## Epidemiological Data

### Overall view

Maternal mortality back in the 1960's in Portugal was at 115/100,000 live births per year, similar to many developing countries at present [11]. Although, over the next 20 years, there was some improvement, nevertheless in 1980, the overall maternal mortality was still in double figures at 19/100,000. From then on, there was a significant decline and, in the last couple of decades, has remained between 5 to 8/100,000 live births, in line with most western countries [11,12]. Perinatal mortality from 28 weeks gestational age (GA) upwards was 42.2/1,000 live births in 1960. Those were the days when obstetricians and paediatricians hardly communicated with each other and, whenever that happened, were usually for the wrong reasons. Public opinion was low, obstetricians had bad reputation, which rendered obstetrics an unpopular job and paediatricians were regarded *persona non grata* within a hundred yards of the labour ward. Fortunately, after a long courtship, sometimes passionately stormy, the marriage between the two specialities was assumed and consummated leading through a troublesome pregnancy to the birth of Perinatal Medicine with the decline in perinatal mortality from 23.9/1,000 in 1980, gradually falling to 12.4, 6.2 and 3.5/1,000 per each subsequent decade up to 2010 [11]. These results, in spite of some regional asymmetries, have been consistently achieved throughout the whole country. Over the same period, although a decrease was registered in all European countries, Portugal was one of those with the most significant fall in perinatal mortality, as shown in (Figure 1) [11,12].

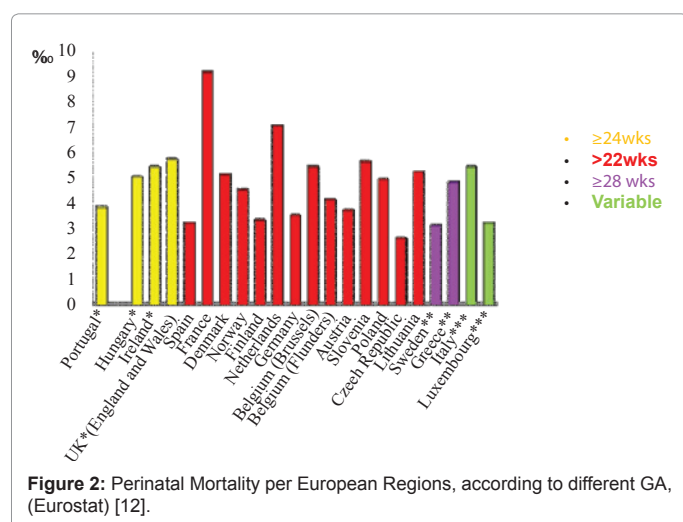
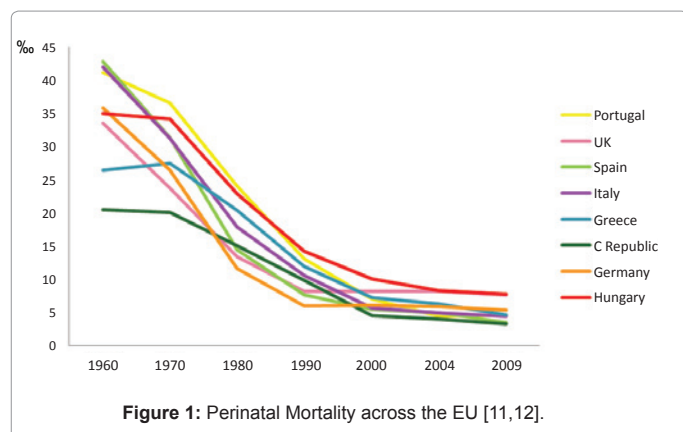
However, still remains a tremendous confusion in attempting to draw comparisons and to identify a common denominator for

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the definition of perinatal mortality, from country to country (and sometimes within the same country), has it can be inferred from (Figure 2) [12]. Portugal itself falls into the same trap because whilst the National Statistics Institute continues to report perinatal mortality from 28 weeks GA, the Official Registration of Stillbirths requires notification at 24 weeks GA [11,12] in line with the Scientific Societies of Obstetrics and Neonatology .

### A pilgrimage through success

The overall good results achieved were primarily the consequence of National Health Policies towards rationalisation of human and financial resources with modern technology playing a subsidiary role for the high risk pregnancy and neonate.

At the beginning, in the mid 1970's, a few charismatic paediatricians in Lisbon, Oporto and Coimbra, for the first time, assumed the plight of the vulnerable new-born and undertook the challenge to dedicate themselves to the special care of sick and preterm neonates. Following their pioneer efforts and dedication in 1985, there were 13 Neonatal Intensive Care Units (NICU) in the whole country, for a population of 10 million and close to 130,000 births per year. Successfully, many sick neonates and then non-viable preterms, started to survive. These examples led to the foundation of the Neonatal Branch of the Portuguese Paediatric Society in 1987 and the beginning of organized national scientific meetings.

Although only 25 years ago, Portugal was then quite a different country from what it is today with many places, however close in proximity, in reality, many hours away of the few existing reference centres. Needless to say, that for those unfortunate babies born outside these specialized hospitals and units they were, either doomed to perish or, else, to survive to a life of suffering and misery. It was amidst this kaleidoscope of asymmetries and injustices that the wisdom of a few, both inside and outside the medical profession, including the political power of the time, that the National Neonatal Transferral System was initiated, firstly in Lisbon in 1986 followed by 1987 in northern Oporto and finally in 1988 in central Coimbra [13,14]. This was a major contribution to provide available neonatal care within a reasonable geographical area and within useful time. For many years this public service of 24 hours a day 7 days a week functioned with purposely dedicated staff of neonatologists, neonatal nurses and specific ambulance crews. It was a very expensive exercise, both financial and in human resources, perhaps unobtainable today, but admittedly, a turning point in portuguese neonatal care. However, the transferral of neonates was only a substitute to *in utero* transferral, similar to today, a poor alternative at that.

Following the initial steps, under the direct responsibility of the Minister of Health, the First National Commission for Maternal and Neonatal Care (FNCMNC) was empowered in 1989 [13]. A combined effort between obstetricians, neonatologists and politicians, the FNCMNC proved to be a successful example of common sense and an expression of goodwill between the parties even, sometimes, in spite of the conflicting interests. It was thanks to the hard work of these few people that a whole map of available resources and, above all, of missing essentials was drawn. This field work was the basis for the comprehensive regionalization of maternal and infant health care in Portugal. As a consequence, some of the measures undertaken were quite unpopular, albeit courageous, often in open confrontation with local interests and feuds: 1. closure of small, inefficient maternities, throughout the country; 2. rationalization of hospitals into two groups only, according to the number of deliveries per year and technical differentiation: Perinatal Hospitals assigned to deliver between 1500-3000 births per year and capable of supplying special care for both mothers and babies everyday of the week and Advanced Perinatal Hospitals responsible for 3000 or more deliveries per year and capable of offering intensive care to both the mother and the neonate; 3. implementation of regional administrative units to liaise between primary health care and hospital services [15,16]. This differentiation into Perinatal and Advanced Perinatal Hospitals, besides making birth a safe event also had the advantage of eliminating misunderstandings of whatever constitutes I, II (IIA, IIB, etc) or III level Units based, sometimes, on individual arbitrary criteria of standards of care. As it stands, these health policies allocated to the Perinatal Hospitals the responsibility to provide obstetric care for pregnancies over 32 weeks gestation as well as neonatal care, including short term assisted ventilation. Advanced Perinatal Hospitals were, therefore, reserved mostly for the high risk pregnancies and neonates, often at the lower limit of viability and/or, with major surgical or heart problems. In 2006, the Ministry of Health reporting on the National Perinatal Network identified 28 Perinatal Hospitals and 19 Advanced Perinatal Hospitals [17]. For a declining birth rate, at present under 100,000 births per year, they are in excess of the needs and adjustments are, obviously required. Portugal being a geographical small country and a limited population with a modern network of roads, contrary to the past, should prove to be not too difficult to make ends meet. However, these reforms must be thoughtful, sensible, equated to the needs and not subject to

the reckless whims of bureaucrats in distant ivory towers of equivocal power. In spite of the continuous financial constraints and restraints let's hope that the excellent work done so far will not be jeopardised in the future.

Regionalization and allocation of resources alone could not be the only answer to the overall equations of achievements. Of paramount importance and, it must be emphasised, in addition to the general strategies of the equitable distribution of health care over the last 30 years, continuous medical and nursing education has always been a priority and has been clearly instrumental in reducing maternal and perinatal mortalities.

### How are we doing with tiny babies?

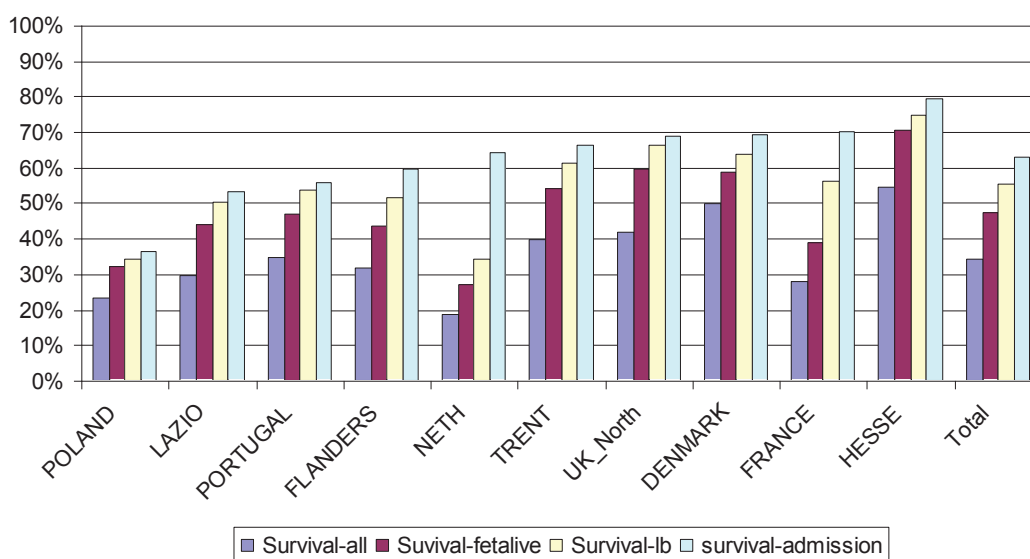
Data from the Portuguese National VLBW Register shows that out of a total of over 9700 live born babies less than 31 weeks and 6 days GA, over a 12 year period between 2000 and 2011 in Portugal, the survival rate stands at 83.6% and that of those less than 27 weeks and 6 days, 63% survived to discharge [18]. After 22 weeks, GA there are no survivors, but survival of 18.4%, 35.5% and 56.6% has been observed at 23, 24 and 25 weeks respectively [18]. Data from our own institution over the same period shows 33.3%, 61.5% and 83.3% for the same gestational ages. It is quite obvious that obstetric and neonatal practices, as well as available resources and facilities, are playing a major role in the survival of these very immature infants but, both human and financial resources apart, why should there be a discrepancy for reported survival rates at the threshold of viability? There can be several reasons and explanations, but whilst the National Register is a population based study ours is a single individual perinatal centre with few numbers as a whole. However, both these studies include only live born neonates. Data regarding the outcome of pregnancy from the beginning of labour might be quite different as shown by the MOSAIC study of 2003 involving the Northern Portuguese Region (Figure 3) [19]. Particularly important, this data comparing results, also illustrates both the similarities and the discrepancies which in turn might reflect different obstetrical and neonatal practices at this very and extremely low gestational ages.

Survival is not (and should not be) the only goal in perinatal medicine

when attempting to establish a 'lower limit of viability'. Outcome and quality of life should be a major priority. Severe neurological injury, ROP and BPD are often a heavy burden. Although most of the severe sequel at the time of discharge are seen in babies at the lower limit of viability, paradoxically, the higher number of disabilities observed with advancing gestational age, especially, at around 26 weeks gestation are the reflection of the increasing survival with age [18,20,21].

It is quite plausible that some of the adverse outcome in survivors at these low gestational ages may not be just the direct effect of prematurity and/or low birth weight *per se* but also the result of the hostile intrauterine milieu leading to preterm delivery from inflammatory mediators, to IUGR, hypoxic-ischaemic insults, metabolic imbalances, etc [22]. Postnatal events, from nosocomial infection to anaemia and haemodynamic instability, metabolic derangements of hyper/hypoglycaemia and electrolytic disturbances, etc. may also play an adjuvant role in the overall picture of survival with multiple handicaps. But one area in particular should call for special caution: the possible role of iatrogenically-induced disability. Many of these tiny babies are, from the very early start, often subjected to whole panoply of manoeuvres and medications known to alter haemodynamics, blood flow and perfusion, from xantines to NSAID, diuretics, volume expanders, antimicrobials with known toxic side-effects, paralysing agents and sedatives, etc. etc. On a positive note, antenatal corticosteroids (ANCS) have been shown to be associated with a significant reduction of RDS, neonatal death and intra/periventricular haemorrhage [23-25] with a possible synergistic effect with post natal surfactant therapy [26]. On this score, Portugal performs quite well with 83.9 to 90.1% of women with pregnancies ending at less than 31 weeks and 6 days being given ANCS [18].

The need to establish a perceivable prognosis at discharge from NICU is quite understandable. Evaluation at the time of discharge, however, may be hindered and fraught with many imponderables to serve as a clear guidance for the future of these babies. Indeed, assessments are often distorted by the stormy incidents of complicated perineonatal events charged with bias and uncertainties coupled with the fast physiological changes and adaptations of prematurity itself. Cranial ultrasounds (US) in the neonatal period are, increasingly, being used to forecast outcome [27-32]. However, in our own experience,



**Figure 3:** Survival to discharge, births <28 weeks GA. Adapted from ref [19] for Portuguese MOSAIC.



unless there are major, devastating abnormalities, US should not be used for guidance or parental counseling. Magnetic resonance imaging (MRI) may add further information in this context [30, 32-40] but our data also shows that even abnormal MRI may be compatible with normal outcome (11.4%) or mild neurosensorial impairment and slight psychomotor development delay (77.1%). Therefore, clinical judgement should prevail at all times and guarded follow up will be required throughout childhood into adult life.

### Do we have a lower limit of viability?

It is quite obvious that a threshold exists for each and every one, whatever it might be. However, commendable the pursuit and quest to emulate the best results, for the meantime, individual thresholds must be recognized. It is within this reality that decisions can be made when faced with the extremely pre-term infant, and that an educated prognosis can be discussed with parents. Improvements can then be pursued based upon continuous self-auditing, in strict adherence to the moral conduct of good medical practice towards the most vulnerable of all patients, the sick and extremely preterm infant.

### Ethical Issues

Laws vary from country to country and sometimes between states within the same country. Widespread philosophical, religious and moral views across the globe concur to enhance the complexity of the equation and must also to be taken into consideration. It would appear to be quite unrealistic to argue the attainability of a common denominator, to frame it within the various legal requirements, to dictate the codes of rules and to expect it to be internationally accepted, yet that is the essence of Ethics and Portugal cannot be exempted.

Worldwide, reports of survival at 22 weeks gestation [41-43] and less than 400 grams birth weight [44] have led to a change in legislation [45] and to a redefinition of the "Perinatal Period" [46] and the aim for the survival of the most immature of babies became only natural and pressing. In Portugal, there has never been one single survivor at 22 weeks GA [18]. And what about at 23 weeks (or 23 weeks and a couple of days)? From here on, it is an open game and the stakes are high, with survival rates from just over 18% to 33%, whilst at 24 and 25 weeks the numbers rise sharply up to 80% or more [18]. It is quite clear that there are enormous geographical asymmetries even within our country with similar demographics and it is not surprising that some of us may place the lower limit of viability at 24-25weeks GA.

The ethical questions to practising neonatologists are whether they should accept their own reality of survival and try to improve on quality rather than quantity, or whether they should try to compete with the more advanced centres and aim for the threshold of viability? Who should decide on that? Should it be an individual (local) decision or a matter of national (regional) policy? What are the ethics and moral implications of these decisions? Could it possibly be that in practice new technologies would change matters? What would be the financial resources needed, could they be afforded, and, again, what would be the ethical implications of discrimination on financial grounds? On one issue at least, everyone would agree, that whatever the dilemmas and however difficult, decisions must never be taken upon account of sex, eugenics, religious or economic prejudice, and never based on a doctor's own cultural or religious beliefs [47-49].

Futile treatment is currently used in medicine to mean that any treatment beyond a certain point would be unjustifiable. Neonatologists, often young, are frequently faced in the middle of the night with the crucial decision (based very often upon inaccurate information

on gestational age) of whether or not to initiate active, aggressive management of the extremely immature infant at the threshold of viability. In doubt, active resuscitative measures should be started in the labour ward. The decision to further continue intensive care can always be reversed after reevaluation and counseling to the parents but this does not imply that decisions to continue or withdraw treatment should rest upon them.

Advancing technologies can often cause procrastination over medical decisions which, when based on a particularly sophisticated tool, may be mistaken for good medical practice. It might assist but must not replace clinical judgement.

### Conclusions

Although a fall in maternal and perinatal mortalities has been achieved in all European countries, Portugal was one of those with the most significant decreases. Major steps to achieve these goals were: 1. regionalization and national policies including the closure of small, obsolete hospitals, rendering pregnancies and birth a safe experience and providing uniformity and quality of care throughout the country; 2. establishing a National Neonatal Transferal System with purposely dedicated staff to cover for those deliveries outside referral Units and for whom *in utero* transferal could not be provided on time; 3. direct involvement of professionals and politicians alike regardless of personal or conflicting interests.

Above all, besides the immediate and obvious needs in medical care, the emphasis was also on continuous medical and nursing education through the different scientific societies, a very rewarding and gratifying achievement for the benefit of all, especially for mothers and their offspring.

A success story and a tribute to a generation of professionals that made perinatal care an example of citizenship well beyond the role of duty. Let's hope that the new financial "gurus" will not jeopardize what has taken such a great deal of effort to achieve.

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### References

1. Kurjak A, Bekavac I (2001) Perinatal problems in developing countries. Lessons Learned and Future Challenges. J Perinat Med 29: 179-187.
2. González EF (2006) Preface in Maternal and Infant Health in the World, WAPM and Matres Mundi International. 15-16.

3. (2005) World health report 2005 statistical annex. The world health report.
4. (2006) The State of the world's children. UNICEF
5. Ciaran SP, Laurence CB, Aaron BC, Beate D, Susan KS, et al. (2007) Level and volume of neonatal intensive care and mortality in very-low-birth-weight infants. *N Engl J Med* 356: 2165-2175.
6. Rogowski JA, Staiger DO, Horbar JD (2004) Variations in the quality of care for very-low-birthweight infants: implications for policy. *Health Aff (Millwood)* 23: 88-97.
7. Stark AR (2004) Levels of neonatal care. *Pediatrics* 114: 1341-1347.
8. Fischer N, Steurer MA, Adams M, Berger TM (2009) Survival rates of extremely preterm infants (gestational age <26 weeks) in Switzerland: impact of the Swiss guidelines for the care of infants born at the limit of viability. *Arch Dis Child Fetal Neonatal Ed* 94: F407-F413.
9. Pignotti MS, G Donzelli (2008) Perinatal care at the threshold of viability: an international comparison of practical guidelines for the treatment of extremely preterm births. *Pediatrics* 121: e193-e198.
10. Saigal S, LW Doyle (2008) An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet* 371: 261-269.
11. (2011) Base de dados Portugal contemporaneo. PORDATA.
12. (2010) The European Perinatal Health Report 2010. EURO PERISTAT.
13. Ministério da Saúde-Despacho 8/89 17-03-1989.
14. Ministério da Saúde-Despacho 20/91. 13-09-1991.
15. Ministério da Saúde-Despacho 6/91. 20-06-1991.
16. Ministério da Saúde-Despacho 12 917/98 27-07-1998.
17. (2006) Relatório do Ministério da Saúde, Organização Perinatal Nacional, Capítulo 3, Rede de Referência Hospitalar.
18. VLBW portuguese national register 2000-2011 official but unpublished data.
19. Zeitlin J, Draper ES, Kollée L, Milligan D, Boerch K, et al. (2008) Differences in rates and short-term outcome of live births before 32 weeks of gestation in Europe in 2003: results from the MOSAIC cohort. *Pediatrics* 121: e936-e944.
20. Fellman, Hellström-Westas L, Norman M, Westgren M, Källén K, et al. (2009) One-year survival of extremely preterm infants after active perinatal care in Sweden. *JAMA* 301: 2225-2233.
21. KL Costeloe, EM Hennessy, S Haider, Stacey F, N Marlow, et al. (2013) Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies) *Tijdschrift voor Kindergeneeskunde* 81: 48-49.
22. Draper ES, Manktelow B, Field DJ, James D (1999) Prediction of survival for preterm births by weight and gestational age: retrospective population based study. *BMJ*. 319: 1093-1097.
23. Crowley P (2000) Prophylactic corticosteroids for preterm birth. *Cochrane Database Syst Rev* 2: CD000065.
24. (1995) Effect of corticosteroids for fetal maturation on perinatal outcomes. NIH Consensus Development Panel on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes. *JAMA*. 273: 413-418.
25. Wright LL, Horbar JD, Gunkel H, Verter J, Younes N, et al. (1995) Evidence from multicenter networks on the current use and effectiveness of antenatal corticosteroids in low birth weight infants. *Am J Obstet Gynecol* 173: 263-269.
26. Jobe AH, Mitchell BR, Gunkel JH (1993) Beneficial effects of the combined use of prenatal corticosteroids and postnatal surfactant on preterm infants. *Am J Obstet Gynecol* 168: 508-513.
27. Orcesi S, Olivieri I, Longo S, Perotti G, La Piana R, et al. (2012) Neurodevelopmental outcome of preterm very low birth weight infants born from 2005 to 2007. *Eur J Paediatr Neurol* 16: 716-723.
28. Kristen Kobaly BS, Mark Schluchter, Nori Minich, Harriet Friedman, Hudson Gerry Taylor, et al. (2008) Outcomes of extremely low birth weight (<1 kg) and extremely low gestational age (<28 weeks) infants with bronchopulmonary dysplasia: effects of practice changes in 2000 to 2003. *Pediatrics* 121: 73-81.
29. Farooqi A, Hägglöf B, Sedin G, Serenius F (2011) Impact at age 11 years of major neonatal morbidities in children born extremely preterm. *Pediatrics* 127: e1247-1257.
30. Horsch S, Skiöld B, Hallberg B, Nordell B, Nordell A, et al. (2010) Cranial ultrasound and MRI at term age in extremely preterm infants. *Arch Dis Child Fetal Neonatal Ed* 95: F310-314.
31. O'Shea TM, Kuban KC, Allred EN, Paneth N, Pagano M, et al. (2008) Neonatal cranial ultrasound lesions and developmental delays at 2 years of age among extremely low gestational age children. *Pediatrics* 122: 2008-0594.
32. Bassan H, Limperopoulos C, Visconti K, Mayer DL, Feldman HA, et al. (2007) Neurodevelopmental outcome in survivors of periventricular hemorrhagic infarction. *Pediatrics* 120: 785-792.
33. Woodward LJ, Anderson PJ, Austin NC, Howard K, Inder TE, et al. (2006) Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. *N Engl J Med* 355: 685-694.
34. Nosarti C, Giouroukou E, Healy E, Rifkin L, Walshe M, et al. (2008) Grey and white matter distribution in very preterm adolescents mediates neurodevelopmental outcome. *Brain* 131: 205-217.
35. Allin M, Henderson M, Suckling J, Nosarti C, Rushe T, et al. (2004) Effects of very low birthweight on brain structure in adulthood. *Dev Med Child Neurol* 46: 46-53.
36. Fearon P, O'Connell P, Frangou S, Aquino P, Nosarti C, et al. (2004) Brain volumes in adult survivors of very low birth weight: a sibling-controlled study. *Pediatrics* 114: 367-371.
37. Nosarti C, Rushe TM, Woodruff PW, Stewart AL, Rifkin L, et al. (2004) Corpus callosum size and very preterm birth: relationship to neuropsychological outcome. *Brain* 127: 2080-2089.
38. Nosarti C, Al-Asady MH, Frangou S, Stewart AL, Rifkin L et al. (2002) Adolescents who were born very preterm have decreased brain volumes. *Brain* 125: 1616-1623.
39. Maalouf EF, Duggan PJ, Rutherford MA, Counsell SJ, Fletcher AM, et al. (1999) Magnetic resonance imaging of the brain in a cohort of extremely preterm infants. *J Pediatr* 135: 351-357.
40. Skiöld B, Vollmer B, Böhm B, Hallberg B, Horsch S, et al. (2012) Neonatal magnetic resonance imaging and outcome at age 30 months in extremely preterm infants. *J Pediatr* 160: 559-566.
41. Bottoms SF, Paul RH, Iams JD, Mercer BM, Thom EA, et al. (1997) Obstetric determinants of neonatal survival: influence of willingness to perform cesarean delivery on survival of extremely low-birth-weight infants. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *Am J Obstet Gynecol* 176: 960-966.
42. James A. Lemons, Charles R. Bauer, William Oh, Sheldon B. Korones, Lu-Ann Papile, et al. (2001) Very low birth weight outcomes of the National Institute of Child health and human development neonatal research network, January 1995 through December 1996. NICHD Neonatal Research Network. *Pediatrics*.107: E1.
43. Chan K, Ohlsson A, Synnes A, Lee DS, Chien LY, et al. (2001) Survival, morbidity, and resource use of infants of 25 weeks' gestational age or less. *Am J Obstet Gynecol* 185: 220-226.
44. Ginsberg HG, Goldsmith JP, Stedman CM (1992) Hospital care techniques resulting in intact survival of a 380-g infant. *Acta Paediatr Suppl* 382: 13-15.
45. Nishida H, Y Ishizuka (1992) Survival rate of extremely low birthweight infants and its effect on the amendment of the Eugenic Protection Act in Japan. *Acta Paediatr Jpn* 34: 612-616.
46. Dunn PM, Mclwaine G (1996) Perinatal Audit: A Report produced for the European Association of Perinatal Medicine 43.
47. Schenker JG (2003) Codes of perinatal ethics: an international perspective. *Clin Perinatol* 30: 45-65.
48. (1994) Recommendations on ethical issues in Obstetrics and Gynecology by the FIGO Committee for the study of ethical aspects of human reproduction: Ethical aspects in the management of severely malformed infants, 1994: London: FIGO.
49. Carrapato M (2009) Ethical Aspects in Neonatal Medicine, "Ethics in Perinatal Medicine", ed J Schenker.