Management of Extremely Preterm Births in the Level III Maternity Unit at Strasbourg University Hospital Centre (CHU)

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Abstract

Introduction: Active management of extreme prematurity, defined as birth occurring before 26WG, has medical and familial repercussions on account of the uncertain future of these infants. The aim of this paper is to describe our experience in the obstetrical and paediatric management of extreme preterm births based on choices made by the families.

Methods: We retrospectively included all infants born between 22WG and 25WG+6days in our level III maternity unit in the period from January 2010 to December 2014. These births were documented along with family choices, methods of obstetrical management and birth outcomes.

Results: 166 infants were included. After 24WG, active management was requested by the parents in 90% of cases versus 13% at 23WG and none at 22WG. Corticosteroid therapy was administered in 0% of cases at 22WG, 19% at 23WG, 92% at 24WG and 94% at 25WG. Caesarean section was performed in 0% of cases before 24WG, 10% at 24WG and 48% at 25WG. Six per cent of infants at 22WG, 32% at 23WG, 89% at 24WG and 92% at 25WG were live births. The survival rate for infants admitted to neonatal intensive care was 17% at 23WG, 47% at 24WG and 71% at 25WG.

Conclusion: Optimal management of extreme preterm births requires a solidly cooperative obstetrical-paediatric team guided by respect for parental choice.

Keywords: Extreme prematurity; Family’s choice; Obstetrical management; Mode of delivery

Introduction

The World Health Organization (WHO) has defined prematurity as birth occurring before 37 completed weeks’ gestation (WG) [1]. The number of preterm births worldwide was estimated at about 15 million (95% CI (12.3-18.1)) for the year 2010, i.e., a prematurity rate of approximately 11% of live births [2]. About 5% of infants born before 37 WG can be classified as extremely preterm (<28 WG) [2]. In France, the 2010 perinatal national survey [3] registered 7.4% of births before 37 WG (live and still births), 5.9% between 32 and 36 WG and 1.5% before 32 WG. In other words, approximately 60 000 infants are born every year before 37 WG including 12 000 before 32 WG. The incidence of prematurity has slightly increased, rising from 5.9% in 1995 to 7.4% in 2010 [3].

Extreme prematurity, defined by the occurrence of a birth between 22 WG and 26 WG+6 days, accounts for 0.44% of births [4]. Follow-up of extreme preterm birth cohorts [4-7] show survival rates for infants born at 24WG ranging from 26 to 31%. At 25WG survival rates range between 44 and 63%. Survival rates without sequel range between 3 and 12% at 24WG and between 8 and 36% at 25WG [5].

While the indicators and epidemiological data which are available to us today allow groups with relatively good prognoses to be defined, there is still enormous uncertainty about the short-, mid- and long-term future of these infants. Major variations at a practical level in dealing with extreme preterm births, both internationally but also between different French centres [8], is a clear expression of a situation in which medical knowledge is far from being the sole factor which guides practice. The management of extreme prematurity poses great difficulties for medical teams and for families. How we to define what are is unreasonable? How can appropriate individual care be defined on the basis of epidemiological data which has been obtained by monitoring cohorts of preterm infants? What information should parents is given? How can we make a decision such as whether or not to resuscitate an infant at birth?

Three alternatives for delivery room management of infants born before 26 WG can be envisaged based on an appraisal of this benefit-risk ratio:

- Active management featuring life-support measures which include resuscitation procedures;
- Management without overtreatment: this approach is adapted to the infant’s condition at birth and does not involve treatment escalation (it includes intubation and surfactant administration but no external cardiac massage or adrenaline injection);
- Palliative management which consists of providing supportive care to the new-born child but no resuscitation procedures.

The objective of this paper was:
1) To describe our experience of managing extreme preterm births before 26WG over a duration of 4 years;

2) To describe choices made by families in terms of management at birth subsequent to discussion with the obstetrical-paediatric team before the actual birth;

3) And to report the immediate outcome of these births.

Materials and Methods

The Hautepierre maternity unit at Strasbourg is a type III referral centre with approximately 2800 births annually.

We enrolled all patients admitted to the delivery room whose infants were born between 22WG and 25WG+6 days over a period extending from January 2010 to December 2014.

We excluded medical terminations of pregnancy (MTP) for foetal malformations and in utero foetal deaths.

Sociodemographic characteristics of parents were age and parity.

Unfortunately, we do not have data about the social status, but since all the very premature birth in our region occur in this Hospital, we assume that our population is representative of the general population and that the potential selection bias is limited.

The choice of the parents concerning the management of the infant at birth was documented following the interview with the obstetrician-paediatrician duo. Discussion with the parents took place in a quiet room and included solid data on morbidity and mortality before 26 WG which set out all the difficulties caused by such extreme preterm birth. It was essential that the obstetrician and paediatrician agreed on the terms of their joint approach prior to talking with the parents. Nevertheless, if there was disagreement between the physicians’ recommendations and the family’s preferences, the treatment plan was based on the parents’ wishes. In the event of an imminent delivery prior to 26 WG which did not allow sufficient time for a thorough consideration of the issues and in the parents had not made any explicit statement in favour of palliative management, active management was provided in the birthing room the nature of which depended on adaptation to extra-uterine life.

When examining the patient records, we recorded parental preferences after the obstetrical-paediatric discussion for active management, management without overtreatment or palliative management:

- Active or intensive management entailed complete resuscitation with initiation of continuous positive-pressure ventilation or mechanical ventilation, administration of drugs and/or insertion of central vascular catheters.

- Management without overtreatment consisted of resuscitation adapted to the infant's age with intubation and surfactant administration, but no external cardiac massage or adrenaline injection.

- Palliative care was a process of minimal medical intervention with respect to the infant, which put emphasis on allowing it to be present with the parents in a quiet room; warmth and medications were provided with the sole aim of reducing suffering.

We also researched the patient records to determine whether an antenatal corticosteroid therapy has been administered to assist lung maturation and whether the foetal heart rate (FHR) had been recorded either during antenatal surveillance or in labour.

We also indexed the delivery method, whether vaginally or by caesarean section, along with indications for the latter when delivery took place before 25WG.

Results

We retrospectively enrolled 166 infants born between 220/7 and 256/7 WG in the Hautepierre type III maternity unit, with an average of 2800 deliveries a year, from January 2010 to December 2014. Of these 166 infants, we recorded 16 infants born between 220/7 and 226/7 WG, 37 infants born between 230/7 and 236/7WG, 50 infants born between 240/7 WG and 246/7 WG and 63 infants born between 250/7WG and 256/7 WG. The average of patients age was 29.95 years (SD=6.01) and the average of parity was 0.67 (SD=0.97).

Table 1 summarizes decisions made by couples about neonatal management following discussion with the obstetrical-paediatric team for these 166 new-born between 220/7 and 256/7 WG. No parental decision was collated when delivery occurred outside the maternity unit (at home or in the emergency medical service vehicle). Before 23 WG, no request for active management was solicited by the parents. At 23 WG, 5 couples (13%) requested active management. This request was qualified in 3 of these couples (60%). At 24 WG, active management was requested in 90% of cases, a figure rising slightly to 91% at 25 WG. In the vast majority of cases (91%) it was noted that the couple opted for active management but without treatment intensification. Only 10 couples (9%) among the 107 who sought active management wished for intensive neonatal resuscitation at whatever cost.

| Gestational age (weeks’ gestation) | Number of infants (n=166) | Active management (n=107) | Supportive care | No decision |
|-----------------------------------|--------------------------|--------------------------|----------------|-------------|
|                                   |                          | Intensive resuscitation (n=10) | Without treatment (n=97) | (n=54) | (n=5) |
| 22 0/7-22 6/7 WG                  | 16 (10%)                 | 0                        | 0               | 15 (94%) | 1 (6%) |
| 23 0/7-23 6/7 WG                  | 37 (22%)                 | 2 (5%)                   | 3 (8%)          | 30 (81%) | 2 (5%) |
| 24 0/7-24 6/7 WG                  | 50 (30%)                 | 2 (4%)                   | 43 (86%)        | 5 (10%)  | 0      |
| 25 0/7-25 6/7 WG                  | 63 (38%)                 | 6 (10%)                  | 51 (81%)        | 4 (6%)   | 2 (3%) |

Table 1: Parental decision in neonatal management following discussion with the obstetrical-paediatric team.
Pregnancy outcomes are summarised in Table 2. The proportion of live births went from 6% at 22 weeks, to 32% at 23 WG, then to 89% at 24 WG and finally 92% at 25 weeks. Of these live born neonates, 54% died in the delivery room at 22-23 WG, 13% at 24WG and 9% at 25 WG. The survival rate of live neonates born at 22-23 WG was 8%, 44% at 24 WG and 69% at 25WG. Of the 17 deaths which took place in the delivery room, 6 (35%) occurred after failure or cessation of neonatal resuscitation. Of the neonates admitted alive to intensive care, the survival rate was 17% at 23 WG, 47% at 24 WG and 71% at 25 WG.

Methods of obstetrical management are summarised in Table 3.

| Gestational age (weeks' gestation) | Number of infants (n=166) | Antenatal corticosteroid therapy (n=60) | FHR recording (n=111) | Delivery method | Caesarean | Vaginal |
|-----------------------------------|--------------------------|----------------------------------------|-----------------------|----------------|----------|---------|
| 22 0/7–22 6/7 WG                  | 16 (10%)                 | 0                                      | 0                     |                | 16 (100%)| 0       |
| 23 0/7–23 6/7 WG                  | 37 (22%)                 | 7 (19%)                                | 0                     |                | 37 (100%)| 0       |
| 24 0/7–24 6/7 WG                  | 50 (30%)                 | 46 (92%)                               | 30 (60%)              |                | 45 (90%) | 5 (10%) |
| ≥ 26 ΩΓ                          | 63 (38%)                 | 59 (94%)                               | 55 (87%)              |                | 33 (52%) | 30 (58%)|

Discussion

This study describes the birth conditions and immediate fate of 166 premature infants born before 26 WG between January 2010 and December 2014 in a type III maternity unit attached to Strasbourg university hospital. A live birth rate of only 6% was observed at 22WG but this rose to 92% at 25WG. Among the live born neonates, survival rates allowing transfer to neonatal intensive care were 0% at 22WG, 8% at 23WG, 44% at 24WG and 69% at 2FG. Of those neonates admitted alive to intensive care survival rates were 17% at 23WG, 47% at 24WG and 71% at 25WG.

Many epidemiological studies have assessed morbidity and mortality rates in the neonatal period and during follow-up. In the British EPICure 2 cohort, survival rates among live born neonates were 40% at 24 WG and 66% at 25 WG and for those admitted alive to intensive care 47% at 24 WG and 69% at 25 WG [5]. These results are almost identical to those obtained in our maternity unit. The Neonatal Research Network reported 18-22 month survival rates within a cohort of 4466 new-born infants of 56% (24 WG) and 81% (25 WG) [9]. Better still, the Swedish Express study (904 infants <27 WG) had administered in 4 cases on the same grounds as cited above (severe pre-eclampsia with intra-uterine growth retardation, disseminated intravascular coagulation with multiple retro-placental haematomas and 2 domiciliary deliveries). A FHR recording was obtained in 87% of cases.

- At 22WG, the sole neonate born alive received palliative management. He had not received antenatal corticosteroid therapy and was delivered vaginally. No recording of the foetal heart rate (FHR) had been made.
- At 23WG, 7 infants (i.e. 58% of live born neonates) received active management including 2 infants born in the emergency medical service vehicle. Seven (19%) had received antenatal corticosteroid therapy and none was delivered by caesarean section. No recording of the FHR had been made.
- At 24WG, 36 infants (i.e., 92% of live born neonates) received active management. Forty-six infants (92%) had received antenatal corticosteroid therapy. Four infants had not received corticosteroid therapy either because of the very unfavourable obstetrical setting (maternal salvage in a context of severe pre-eclampsia with intra-uterine growth retardation) or because of the degree of urgency (chorioamnionitis, metrorrhagia, threatened premature delivery with onset of spontaneous labour). FHR recordings had been obtained in only 60% of births. Five infants were delivered by caesarean (10%) including 4 for a foetal indication (two cases with foetal heart rate (FHR) decelerations, 2 cases with suspected retro-placental haematoma and 1 case as a live-saving measure for a mother with severe pre-eclampsia complicated by acute pulmonary oedema).
- At 25WG, 97% of live born neonates received active management. Fifty-nine received antenatal corticosteroid therapy (94%) and 30 were delivered by caesarean (48%). Corticosteroid therapy could not be
reported 1 year survival rates for all live births of 67% (24 WG) and 81% (25 WG) [10]. In the French EPIPAGE-2 cohort in 2011, survival rates were 0% at 22WG, 1% at 23WG, 31% at 24WG and 60% at 25WG [11]. Paradoxically, for these preterm neonates the long-term outcome does not appear to be such an issue of concern. In the British EPICure 2 cohort, the fate of these former preterm infants at 3 years showed favourable development rates (no or minor forms of neurosensory impairment) in 70% of infants born at 24 WG and 75% at 25 WG [12]. In the Swedish Express study, the fate of these former preterm infants at 2\textsuperscript{nd} years showed a favourable rate of development (no neurosensory anomaly or only minor forms based on Bayley 3rd edition) in 67% of infants born at 24 WG and 73% at 25 WG [13]. The French EPIPAGE-1 study in 1997 had reported a survival rate on discharge from hospital of 31% at 24 WG and 50% at 25 WG [4]. The 5-year motor outcome of these infants showed a cerebral palsy rate of 18% at 24-25WG [14]. Their cognitive status was assessed by the MPC (mental processing composite) score issued by the Kaufman Assessment Battery for Children (K-ABC). No cognitive anomaly (MPC score >85) was found in 56 % of infants born at 24-25 WG and a favourable development (no or minor anomaly with an MPC score >70) was observed in 87% of infants born at 24-25 WG [14]. It is important to note that, although morality rates are higher for extreme prematurity at 24-25 WG, neuromotor outcomes among survivors are comparable to those of less immature new-born infants. For instance, although the absence of cognitive anomaly at 5 years (MPC>85) within the EPIPAGE-1 cohort was 56% for infants born at 24-25 WG, it was only slightly higher for longer term infants (63% at 26WG, 27WG and 28WG) and even remained fairly similar for even longer term infants (69% at 29WG, 65% at 30WG) [14].

In the light of these results, it is legitimate to ask: is there a predefined age limit below which we cannot propose active management and above which active management ought to be obligatory? Relatively recent literature reviews [15,16] suggest that in reality there is no benchmark, either in legal or medical terms. A number of factors other than the gestational age appear to determine the neonatal prognosis. They are birth weight, presence of an infectious context, administration of antenatal corticosteroid therapy, sex, place of birth (out born or inborn), cause of prematurity and especially existence of an associated hypotrophy [4,17-22]. Accordingly, although the indicators and epidemiological data available to us today enable us to define situations where the prognosis is relatively good, they merely reduce but by no means dispel the enormous uncertainty about the short-, medium- and long-term future of such infants.

As a consequence, discussion about the type of management at birth cannot take place without the very close involvement of the parents. The purpose of this dialogue is to be able to make a joint decision against a backdrop of uncertainty. They hold parental authority and, given that the intention is to act in the best interests of the infant, the expression of their wishes once they have been fully informed should be taken into full consideration. It is our experience that before 24WG, the overwhelming majority of couples (100% at 22WG, 81% at 23WG) opt after discussion for palliative management. Although the decision to resuscitate is more common in the higher gestational age groups (90% at 24WG and 91% at 25WG), we were also able to observe that the majority of couples (86% at 24WG and 81% at 25WG) prefer an ethical approach without overtreatment. It therefore appears to be the case that if clear and appropriate information is provided, the great majority of couples understand the issues at stake and the risks of active management for their extreme preterm infant. Reducing the decision to a simple opposition between resuscitating and not resuscitating a preterm neonate obscures the shades of grey pertaining to resuscitation measures that may be taken at birth. Deciding to resuscitate a neonate at birth does not signify deploying the entire armamentarium available to the resuscitation physician, but knowing how to adapt measures taken to both the clinical situation and antenatal monitoring data so as not to lose a sense of perspective if treatment escalation takes place: this can lead to unreasonable obstinacy. Choosing to resuscitate an extremely preterm infant is also to set limits to resuscitation which will be put in place prospectively. In the specific case of a reasoned decision discussed in the antenatal period to undertake resuscitation at birth, it is evident that on the basis of the principle of avoiding any unreasonable obstinacy, resuscitation should not be continued if events develop adversely. It is known today that 50% [23] of deaths during resuscitation occur after a decision to discontinue intensive care, which is why we elected to make couples aware of this issue in the antenatal period whenever active management had been decided upon. In the study by Kaempf et al. [24] in 2009 which documented 121 infants born before 27WG at the PSVMC (Providence St Vincent Medical Center, Oregon), parental wishes for neonatal management on birth were also collected. Palliative management was chosen for 100% of births at 22 WG, 61% at 23WG, 38% at 24WG, 17% at 25WG and 0% at 26WG. Twenty-five women agreed to take part in a second assessment interview after a lapse of 6 to 18 months. The advisory process and guidelines were perceived by the family as readily understandable and helpful. No negative comments on these talks were expressed at the follow-up assessment. Our results, like those of Kaempf et al. [24], show that in the difficult situation of extreme preterm birth, at the limits of medical knowledge, taking decisions in close cooperation with the families appears to be the most appropriate solution. Opting for palliative management or a limited treatment is possible with families in an ambience of mutual understanding and friendliness, a long way from the medical paternalism that was still common a few years ago. Ethicists and health care providers now widely recognise parents as playing a fully active part in health decisions concerning their infant [16,25-29]. Knowing how to share this information more effectively still requires further research.

Most French neonatologists still tend to take the view however that active management of preterm infants at 26 WG or more is widely recommended whereas intensive care of neonates before 24WG is perceived as unreasonable or not recommended in specific instances [9,15,16,30]. This position however differs considerably from country to country. The “grey area” of major prognostic uncertainty below which active management is considered as unreasonable varies from 22-23WG in Germany [31] to 23-24WG in the United States [32].

If parents did not voice any opposition to active management of their infant, the discussion held with them and within the care-providing team itself turned on 3 key issues:

- The timing of corticosteroid therapy.

An injection of corticosteroids at 23WG is practicable in order to ensure the best possible conditions for management of a foetus at 24WG [33]. Antenatal administration of corticosteroid therapy produces a significant reduction in neonatal mortality, intraventricular haemorrhages and necrosing enterocolitis [33].

In any event, administration of a corticosteroid therapy does not necessarily predetermine the type of management at birth. In our cohort, for instance, only 19% of infants born at 23WG (representing 100% of infants born at 23WG for whom active management had been
chosen beforehand) had received an antenatal corticosteroid therapy, and none born before 23WG.

- Monitoring of the FHR starting at 25WG.

According to our results 60% of infants born at 24WG and 87% of those born at 25WG underwent monitoring.

- Thirdly, the type of delivery: this is probably the most difficult decision to take since it has to be balanced between the potential benefit of caesarean for the unborn infant and post-caesarean risks for the mother’s health and her future childbearing projects. The challenge in giving birth to these extreme preterm infants is related more closely to the fact that induction is often impossible and that unless spontaneous labour had begun a caesarean section is often required when birth is imminent [34].

We observed in our results that vaginal deliveries were highly preponderant up to 25WG (100% at 22WG and 23WG and 90% at 24WG) whereas the rate of caesarean at 25WG was 58%. This type of delivery does not appear to be beneficial at this very early term for either mother or foetus. In the first place the technical difficulties associated with this procedure have to be surmounted: anatomically the inferior segment is often poorly formed at a term of 24-25WG. Furthermore, there may be placental abnormalities which render extraction difficult, e.g. pelvic varices or an anterior placenta. The surgical procedure is therefore most certainly not devoid of risk for the uterus and the patient herself [35], especially when performed as an emergency [36].

A recent meta-analysis which was not specifically concerned with preterm neonates <26WG confirmed this rise in maternal risk associated with caesarean section (RR=7.21; 95% CI: 1.37–38.08) without a significantly improved neonatal morbidity [37]. Aside from the technical difficulties and maternal risks, another limit associated with caesarean is the fact that there is no obvious advantage attached to this method of extraction in many situations. Whether in the event of breech presentation, a scarred uterus, twins, IUGR, prematurity or for a relatively non-severe FHR anomaly, the delivery method remains controversial: there is no obvious foetal benefit in performing a routine caesarean in such cases when it is a source of respiratory complications [36]. For breech-presenting foetuses between 24 and 26 WG, caesarean section also fails to provide any neonatal benefit and may increase the risk of haemorrhage and maternal infection [38].

One of the major limits in the issue of the delivery method for extremely preterm infants is the lack of any randomised trial and the frequent impossibility of distinguishing spontaneous deliveries from medically induced deliveries. In their analysis, Werner et al. [38] concluded that for low-birth weight neonates and preterms at 28-32WG, the delivery method did not modify the neonatal condition, but that for terms of less than 26WG, vaginal delivery accounted for only 1% of the cohort studied although it was strongly preferred. A retrospective study conducted between 1994 and 2003 in 2466 vertex-presenting singleton new-borns weighing less than 1500g compared vaginal and caesarean births [39]. In the specific subpopulation of neonates of gestational age <26 WG (n=439), caesarean showed no advantage in terms of neonatal mortality (OR 0.89; 95% CI: 0.54–1.46) [39]. With regard to morbidity in the overall cohort, caesarean was reported not to confer any benefit for either infectious risk (OR 0.78; 95%CI: 0.61–1.01) or risk of respiratory distress (RR 1.23 [0.99-1.51]), although there was a benefit relating to the risk of cerebral haemorrhage (OR 0.73; 95% CI: 0.55-0.97) [40].

In the latest clinical practice guidelines of 2016 [41], routine caesarean for preterm infants is therefore not recommended for vertex presentation, given that there is no empirical evidence that the neonatal prognosis is improved by caesarean section. There is no recommendation concerning the delivery method for breech presentation [41].

Analysing the data in our project has helped us to draw up protocols for obstetrical and neonatal management in cases of extreme prematurity. They are summarized in Table 4. Accordingly, we do not recommend active management for infants born before 24WG because, firstly, the risk of death during resuscitation or severe neurological impairment is estimated to be more than 50% and, secondly, we do not consider that it is either fair or reasonable to insist on the resuscitation of an infant who risks developing severe long-term sequel. After discussing the matter and obtaining informed consent from the parents, we are able to consider active management before 24WG if so requested by the families, but never before 23WG. We recommend active management after 24WG, although we respect a parental decision to opt for palliative management. Concerning corticosteroid therapy for pulmonary maturation, we recommend it from 23WG onwards. Monitoring of the FHR is carried out from 25WG. Finally, regarding the delivery method, we do not recommend a caesarean for foetal indications before 25WG.

| Gestational age | Obstetrical management | Neonatal management |
|-----------------|------------------------|---------------------|
| <23 WG1         | Tocolysis possible     | Supportive care     |
|                 | No corticosteroid therapy for lung maturation | No resuscitation |
|                 | No FHR recording2      |                     |
|                 | No caesarean for foetal indication |                     |
| 230/7–236/7 WG  | Tocolysis              | Supportive care     |
|                 | Corticosteroid therapy for lung maturation (twin pregnancy: 23½+5 WG) | Resuscitation if requested by the parents (excluding emergency and twin pregnancy) |
|                 | No FHR recording2      |                     |
|                 | No caesarean for foetal indication |                     |
| 240/7–246/7 WG  | Tocolysis              | Resuscitation       |
Table 4: Management protocol for extremely preterm infants at Hautepierre Teaching Hospital Centre (CHU).

| Gestational Age | Tocolysis       | Resuscitation |
|-----------------|----------------|--------------|
| 250/7–256/7 WG  | Corticosteroid therapy for lung maturation | Supportive care if requested by the parents |
|                 | FHR recording2 not recommended |             |
|                 | Caesarean for foetal indication not recommended |             |
| ≥ 26 QWG        | Tocolysis       | Resuscitation |
|                 | Corticosteroid therapy for lung maturation | Supportive care if requested by the parents |
|                 | FHR recording2 and/or adverse criteria present |             |
|                 | Caesarean for foetal indication3 |             |

**Conclusion**

Methods of managing preterm neonates <26 WG raise many ethical, human and medical issues. They give rise to much legitimate self-questioning within neonatal care teams. In the sole aim of fostering a more standardised approach, we propose a protocol for managing preterm infants born before 26WG. In these situations at the limits of medical knowledge, we believe it is of prime importance to involve the families in choosing how to manage their infant at birth.

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