

Enhancing Functional Maturity before Preterm Birth

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Key Words

Respiratory distress syndrome · Intraventricular hemorrhage · Neonatal death · Antenatal glucocorticoids

Abstract

Enhancing functional maturity of the high-risk preterm fetus is aimed at decreasing the life-threatening neonatal disorders that increase the burden of chronic disease. A course of antenatal glucocorticoids before 35 weeks of pregnancy substitutes endogenous activation of the hypothalamic-adrenal axis that spontaneously enhances functional maturity and augments cytokine-induced preterm lung maturity. It is the main fetal therapy that decreases the functional prematurity-related neonatal morbidity in the era of surfactant therapy. Tocolytic agents potentiate the effect of glucocorticoids on the fetus. Repeating an antenatal glucocorticoid course may be recommended if the preterm fetus remains undelivered for more than 7 days and very preterm birth is imminent. However, the follow-up results are still incomplete, and available preliminary studies warn against adverse neurological and metabolic consequences following several antenatal repeat courses of glucocorticoids. Administration of glucocorticoids after 34 weeks of pregnancy may be considered in selected high-risk cases, preferably with documented lung immaturity. We recommend delaying elective delivery in low-risk pregnancies without established

lung maturity until 40 weeks, unless labor starts earlier. In a selected high-risk population 17α -hydroxyprogesterone acetate decreases the prematurity rate. However, this drug has a limited impact on functional maturity of the preterm fetus and its effects on the development of the child remain to be studied further.

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Introduction

Perinatologists and neonatologists share the responsibility for treatment of the high-risk fetus and the newborn during perinatal transition. Monitoring of the fetus for the risk of common and serious diseases (infections, isoimmunization) has led to virtual eradication or drastic amelioration of some serious diseases. Visualization of fetal-placental hemodynamics and fetal morphology has become central for screening of pregnancies, follow-up of the high-risk fetus and the placental circulation. A major step beyond the aim of delivering infants without asphyxia was taken when antenatal treatment for enhancing functional maturity of the preterm fetus was introduced by Liggins and Howie [1] in 1972, and the first test for fetal functional maturity was described by Gluck et al. [2] 1 year earlier. In contrast, progress to decrease the rate of premature birth has been slow.

The present brief review will focus on a few selected antenatal practices aimed to decrease acute morbidity and improve the management and outcome of preterm infants.

Regionalization of Antenatal and Neonatal Care

Organization of healthcare varies from country to country. The weakest link in the chain of treatment provision influences outcome. The impact of regionalization in providing safe and cost-effective management of the high-risk fetus and newborn infant has become evident recently [3–6]. Consensus on the importance of regionalization is based on comparison of outcomes and healthcare costs [7–9]. Birth is a unique event associated with acute, sometimes unpredictable complications that may drastically shorten life or adversely influence its quality. Regionalized perinatal centers are designed for appropriate treatment of high- and low-risk mothers, fetuses and infants.

Resources are allocated on the basis of the level of care. The clinics, health centers and small hospitals effectively identify the high-risk pregnancies, provide early treatment and rapid maternal transport to the appropriate medical center. Effective transport of critically ill neonates is occasionally required. By analysis of gestation-adjusted antenatal and neonatal/infant mortality figures, combined with population-based follow-up data information on the appropriate referral practice may be obtained [10, 11]. Improvement in regionalization has been associated with improved outcome [12].

Mortality and morbidity have been shown to be variable, despite similar healthcare resources and apparently similar regionalization. Very large differences in population density or moderate differences in resources have a variable impact [7, 10]. Differences in perinatal outcomes among European countries are less dependent on wealth than would be expected. Besides regionalization other factors, including attitude towards treatment of extremely preterm fetuses, influence outcome [13]. Regional perinatal-neonatal management practices require further study.

Therapies Enhancing Maturity of Fetuses with Threatened Preterm Birth

Fetuses facing premature birth have risks of developing one or several immaturity-related diseases that are predictable on the basis of the length of gestation. The

Table 1. Meta-analysis of randomized trials demonstrating beneficial effects of a single antenatal glucocorticoid course on the risk of RDS, other morbidities and on mortality. The risk ratio of RDS is also given in various obstetric categories [17]

	Risk ratio	95% CI
Incidence of RDS		
All preterm infants	0.66	0.59–0.74
Subgroups, post-hoc analysis		
Drug delivery interval <24 h	0.87	0.66–1.15
Drug delivery interval 24 h–7 days	0.46	0.35–0.60
Drug delivery interval >7 days	0.82	0.53–1.28
Rupture of fetal membranes >24 h	0.68	0.51–0.90
Preeclampsia	0.50	0.35–0.72
Preterm birth <30 weeks of pregnancy	0.67	0.52–0.87
Neonatal mortality	0.69	0.58–0.81
Intraventricular hemorrhage	0.54	0.43–0.69
Necrotizing enterocolitis	0.46	0.29–0.74
Infection in neonatal intensive care unit	0.83	0.66–1.04

incidence of respiratory distress syndrome (RDS) has been reported on the basis of national registries, and data from regional centers and international networks [14–16].

Randomized clinical trials involving more than 4,000 pregnancies have shown that a single course of antenatal steroids (ANS; either betamethasone or dexamethasone) decreases the risk of RDS in infants born before 34 weeks of pregnancy (table 1). According to meta-analysis, this benefit is also found in cases of premature rupture of the fetal membranes and in preeclampsia. ANS do not significantly influence the risk when the infant is born either <24 h or >7 days after the first steroid dose. ANS reduce mortality, intraventricular hemorrhage (IVH), and necrotizing enterocolitis and tend to protect against neonatal infections [17]. Both betamethasone and dexamethasone in the doses used are safe and efficacious [18]. The protective effects of ANS are mediated by multiple, complex mechanisms that advance structural maturity of the lung, increase surfactant secretion, and enhance the maturity of the gastrointestinal tract and cardiovascular system. ANS have multiple influences on innate immunity and on other host defenses. On the basis of meta-analysis, a single course of ANS has no major side effects for the fetus, the newborn or the mother.

Since 1994, ANS treatment of pregnant women, between 24 and 34 weeks' gestation and with threatened delivery within 7 days, has increased dramatically in most centers [19–21]. Most of the studies reported were performed prior to the surfactant era, and indeed many sur-

Table 2. Meta-analysis of randomized trials of the effects of a single antenatal glucocorticoid course on the risk of RDS, IVH and neonatal deaths

Study ^a	Statistics for each study				RDS/total		Study ^a	Statistics for each study				RDS/total	
	risk ratio	lower limit	upper limit	p value	treat-ment	con-trol		risk ratio	lower limit	upper limit	p value	treat-ment	con-trol
a Surfactant era							IVH^d						
RDS^b							Amorim 1999						
Kari 1994	0.731	0.523	1.021	0.066	34/91	46/90	0.353	0.145	0.858	0.022	6/100	17/100	
Silver 1996	0.984	0.806	1.201	0.871	43/54	34/42	0.188	0.022	1.635	0.130	1/80	4/60	
Lewis 1996	0.423	0.198	0.902	0.026	7/38	17/39	0.508	0.095	2.724	0.429	2/130	4/132	
Overall	0.877	0.742	1.036	0.122			0.638	0.346	1.176	0.150	10/33	19/40	
IVH^c							Morales 1989						
Kari 1994	0.381	0.177	0.819	0.013	7/77	18/66	0.583	0.311	1.092	0.092	13/87	20/78	
Silver 1996	1.144	0.718	1.822	0.572	25/54	17/42	0.232	0.051	1.053	0.058	2/70	8/65	
Lewis 1996	0.147	0.008	2.774	0.199	0/38	3/39	Overall	0.504	0.350	0.726	<0.001		
Overall	0.823	0.555	1.221	0.333			Neonatal deaths^d						
Neonatal deaths^d							Amorim 1999						
Kari 1994	0.645	0.188	2.207	0.484	4/91	6/88	0.500	0.280	0.892	0.019	14/100	28/100	
Silver 1996	0.681	0.268	1.726	0.418	7/54	8/42	Collaborative 1981	0.060	0.669	1.679	0.805	34/365	32/364
Lewis 1996	1.026	0.067	15.824	0.985	1/38	1/39	Dexiprom 1999	0.481	0.149	1.548	0.220	4/105	8/101
Overall	0.687	0.336	1.407	0.305			Doran 1980	0.273	0.091	0.815	0.020	4/80	11/60
b Presurfactant era reported in 1980 or later							Gamsu 1989						
RDS^d							0.836						
Amorim 1999	0.535	0.350	0.817	0.004	23/100	43/100	0.430	1.625	0.598	14/130	17/132		
Cararah 1991	1.615	0.075	34.655	0.759	1/12	0/6	Garite 1992	0.992	0.468	2.101	0.983	9/33	11/40
Carlan 1991	0.295	0.038	2.270	0.241	1/11	4/13	Morales 1989	0.784	0.298	2.64	0.623	7/87	8/78
Collaborative 1981	0.704	0.497	0.997	0.048	46/361	65/359	Nelson 1985	1.000	0.067	15.000	1.000	1/22	1/22
Dexiprom 1999	1.162	0.755	1.789	0.495	32/102	27/100	Parsons 1988	0.319	0.014	7.448	0.478	0/23	1/22
Doran 1980	0.300	0.099	0.910	0.034	4/80	10/60	Qublan 2001	0.452	0.294	0.697	0.000	19/70	39/65
Gamsu 1989	0.444	0.189	1.044	0.063	7/130	16/132	Schuttle 1980	0.234	0.070	0.787	0.019	3/62	12/58
Garite 1992	0.909	0.655	1.262	0.569	21/33	28/40	Overall	0.703	0.606	0.815	<0.001		
Morales 1989	0.503	0.334	0.757	0.001	10/22	41/78	a Surfactant was available as standard therapy.						
Nelson 1985	0.909	0.489	1.690	0.763	10/22	11/22	b Mechanical ventilation with positive end-expiratory pressure, indomethacin and caffeine/theophylline were available.						
Parsons 1988	0.957	0.216	4.243	0.953	3/23	3/22	^a Kari et al. [19] used human surfactant in established RDS and retreatment was given when the response was insufficient. Silver et al. [46]: surfactant was given in the delivery room (calf lung, bovine or synthetic surfactant) and surfactant was repeated in RDS. Lewis et al. [47]: the fetuses were born after premature rupture of fetal membranes and a single dose of synthetic surfactant was given in RDS.						
Qublan 2001	0.542	0.308	0.954	0.034	14/70	24/65	^b Heterogeneity, $p = 0.05$.						
Schuttle 1980	0.605	0.310	1.181	0.141	11/62	17/58	^c Heterogeneity, $p = 0.046$.						
Teramo 1980	1.105	0.237	5.150	0.899	3/38	3/42	^d Heterogeneity, $p > 0.10$.						
Overall	0.703	0.606	0.815	<0.001									

factant trials were performed with infants who barely had been exposed to ANS. According to animal experiments and a retrospective analysis of a large randomized clinical trial of surfactant supplementation, the effects of ANS and exogenous surfactant in improving gas exchange and lung mechanics are additive [22]. In order to evaluate the impact of ANS in the era of surfactant therapy, randomized clinical trials reported from 1980 were divided into those performed during the presurfactant era and those conducted when exogenous surfactant was available as a standard therapy (table 2). ANS decreased the risk of RDS, IVH and neonatal mortality during the presurfactant era. In the surfactant era similar effects were evident but they were not statistically significant. This may be due to the small size of the trials and there was some hetero-

geneity among the individual trials. The surfactants used in two of the three trials are no longer available and the dose was low in at least one trial (table 2). Although equipoise is still evident concerning ANS during the surfactant era, it is difficult to justify placebo-controlled trials in threatened very preterm delivery.

The efficacy of weekly or biweekly repeated betamethasone courses compared to a single course followed by weekly placebo for prevention of RDS has been studied in several randomized trials. One study showed that repeated courses decreased RDS [23] whereas the others had a similar but non-significant trend [24–26]. Repeated courses compared to a single course of ANS did not decrease the risk of IVH or neonatal death. However, an association between exposure to multiple courses of ANS

and a reduction in head circumference and perinatal weight gain was reported [23, 25, 26]. Follow-up studies on the efficacy and safety of repeated ANS are available for the two large trials. There were no significant differences in neurological development or growth during the first 2 years of life [27–29]. However, there was an almost significant association between multiple ANS courses and the risk of cerebral palsy ($p = 0.06$) [27].

The randomized trials studying the effect of a single repeat course of betamethasone showed a decrease in the risk of RDS, without early growth retardation and no evidence on adverse neurological outcome at the corrected age of two years [28, 30, 31]. The follow-up studies are not complete yet. On the basis of present knowledge, it appears that a course of ANS more than 7 days after the first course is indicated in cases where birth is imminent before 35 weeks of gestation.

Prevention of RDS in Late Preterm and Early Term Pregnancy

A significant number of near-term infants would develop RDS if delivered electively before the onset of labor. One estimate is based on analysis of the surfactant profile from amniotic fluid and has been confirmed by clinical observations [32, 33]. Labor tends to protect against RDS as it decreases lung liquid secretion and increases surfactant fluid-filled peripheral airways before birth. Secretion of fetal surfactant is highly variable on the basis of genetic and environmental factors. Therefore some late preterm and early term infants develop RDS that is sometimes complicated by persistence of fetal circulation. These infants additionally have a significant risk of spontaneous pneumothorax or transient tachypnea (wet lung syndrome).

According to available evidence, ANS in near-term pregnancies do not offer a statistically significant protection from RDS [17]. In high-risk late preterm pregnancies, elective delivery is indicated after balancing the risks of continuing the pregnancy against early delivery. In maternal diabetes, severe metabolic disease, obstetric bleeding, placental diseases causing severe intrauterine growth restriction or hemodynamic abnormalities, in serious isoimmunization and other rare diseases, elective late preterm delivery may be indicated. Since RDS and other forms of respiratory distress are rare diseases in late preterm infants, expanding routine indications of ANS beyond the 35th week of pregnancy requires evidence of considerable risk of RDS (e.g. previous near-

term RDS in the family). In these cases, documentation of fetal lung immaturity may be helpful to guide ANS treatment.

The rationale of antenatal surfactant diagnostics is based on evidence that the amniotic surfactant pool increases with imminent functional maturity of the fetal lung as a sign of increasing surfactant secretion from the fetal lung. Surfactant indices (lecithin/sphingomyelin ratio, phosphatidylglycerol, the lung profile including several surfactant components, lamellar bodies) are analyzed in amniotic fluid specimens, evaluating the risk of RDS in the unborn fetus [32]. This is indicated when there is a need to balance between the risks of continuing a pregnancy against the risk of iatrogenic RDS after elective birth. The reported specificity and sensitivity of surfactant indices in amniotic fluid ranges from 92 to 100% and from 30 to 90%, respectively.

Prevention of Preterm Births

The prematurity rate has remained constant or has increased by 10–40% in several countries during the past 20 years. Teenage pregnancies contribute to the high rate. Increase in multiples due to implantation of multiple embryos during assisted conception is responsible for most of this increase. Preeclampsia and pregnancy-induced glucose intolerance are more prevalent among pregnant mothers who tend to be older and more obese than in previous years. However, at the same time management of placental insufficiency and intrauterine growth restriction has become more sophisticated improving the optimal timing of elective preterm births.

Spontaneous preterm labor is a cause of 60–90% of very preterm births. Despite several therapeutic trials using progesterone, progesterone derivatives, various inhibitors of prostaglandin synthesis and several other tocolytic agents, antiseptic agents and antibiotics, the reduction in preterm birth has been at best very modest [34, 35]. It has been known since the 1970s that administration of progesterone in pregnancies with previous spontaneous preterm births increases the length of pregnancy [36]. According to a meta-analysis of randomized trials with 17α -hydroxyprogesterone caproate, treatment increases the duration of high-risk pregnancies and decreases serious neonatal morbidity [37]. These encouraging results have led to further trials using different dosage, routes of administration or different progesterone metabolites in threatened preterm birth due to spontaneous onset of labor, in premature rupture of the fetal mem-

branes and in multiple pregnancies. The results have been variable [34] and follow-up studies of exposed fetuses are pending.

Comment

Increase in sophistication of neonatology requires more consideration of factors preceding birth. Antenatal therapies enhancing maturity or prolonging pregnancy are potentially very effective in preventing serious diseases due to immaturity. Although some drugs have modest efficacy, unexpected adverse effects on the newborn have been observed [38]. Several drugs are multi-functional hormones, influencing expression of thousands of genes and with epigenetic involvement [39]. Long-term follow-up of the exposed infants is therefore mandatory.

Early exposure to diethylstilbestrol to manage threatened abortion or preterm birth was found to be teratogenic and to increase the risk of cervical adenocarcinoma in young adults [40]. Concerns about possible side effects of progesterone, and 17 α -hydroxyprogesterone acetate for prevention of premature birth have been raised. The proven efficacy of the drug has been limited to high-risk groups [41, 42]. A single follow-up study that did not reveal side effects needs to be extended [43].

Despite concern about the adverse neurological consequences of a single course of ANS, neurodevelopmental and neurological problems may have decreased rather than increased, reflecting observed decreases in neonatal morbidities. Long-term follow-up studies of infants treated with repeated courses of ANS are ongoing. Evidence of a possible increase in cerebral palsy and altered temperament has been reported following several repeated courses of ANS. Besides neurological problems, steroid-induced metabolic programming may alter metabolic responses in later life. The recipients of a single course of steroids in the original study of Liggins and Howie [1] had a small but significant increase in insulin levels following glucose tolerance test [44]. The observed decrease in fetal body and head growth, following repeat courses of ANS appears to be transient but there is a need to continue longer follow-up of these trials.

Antenatal therapies aimed to improve acute neonatal adaptation should represent a cost-effective aim to improve survival and quality of later life [45]. However, at the same time this approach is a challenge to the pediatric community since diligent follow-up studies during the neonatal period and in later life are required. These concerns should not result in abandonment of carefully planned trials that are based on appropriate basic and translational research.

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