

Antenatal betamethasone and incidence of neonatal respiratory distress after elective caesarean section: pragmatic randomised trial

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Abstract

Objective To test whether steroids reduce respiratory distress in babies born by elective caesarean section at term.

Design Multicentre pragmatic randomised trial.

Setting Ten maternity units.

Participants 998 consenting women randomised at decision to deliver by elective caesarean section; 503 randomised to treatment group.

Interventions The treatment group received two intramuscular doses of 12 mg betamethasone in the 48 hours before delivery. The control group received treatment as usual.

Outcome measures The primary outcome was admission to special care baby unit with respiratory distress. Secondary outcomes were severity of respiratory distress and level of care in response.

Results Sex, birth weight, and gestation were not different between the two groups. Of the 35 babies admitted to special baby units with respiratory distress, 24 were in the control group and 11 in the intervention group ($P = 0.02$). The incidence of admission with respiratory distress was 0.051 in the control group and 0.024 in the treatment group (relative risk 0.46, 95% confidence interval 0.23 to 0.93). The incidence of transient tachypnoea of the newborn was 0.040 in the control group and 0.021 in the treatment group (0.54, 0.26 to 1.12). The incidence of respiratory distress syndrome was 0.011 in the control group and 0.002 in the treatment group (0.21, 0.03 to 1.32).

Conclusions Antenatal betamethasone and delaying delivery until 39 weeks both reduce admissions to a special care baby unit with respiratory distress after elective caesarean section at term.

Introduction

The rate of caesarean section in England rose from 9% in 1980 to 22% in 2003 as a result of changing practice in the management of previous caesarean and breech presentation as well as increased choice for women.^{1 2} This increase has included some women who have opted for caesarean section at socially convenient times, without medical reasons.³ The consequences of elective caesarean section at term for the baby have received little attention. The incidence of respiratory distress is much higher than in vaginal delivery (0.036 v 0.0053).³ Other risk factors for respiratory distress include gestational age, mode of delivery, male sex, fetal asphyxia, maternal asthma and diabetes, and type of anaesthesia given during delivery (regional or general).⁴⁻⁷ The development of respiratory distress leads to admission to a special care baby unit or neonatal intensive care unit, often at a distance, and

separation from the mother potentially disrupting bonding.⁸ It may increase the cost of care and the risk of complications⁹ and increases the risk of asthma in childhood.¹⁰

Antenatal corticosteroids reduce the incidence of respiratory distress in preterm babies,¹¹ but their effect later in gestation is unknown. The antenatal steroids for term caesarean section (ASTECS) randomised trial sought to evaluate whether giving two doses of betamethasone before delivery¹² reduces the incidence of respiratory distress in babies delivered by elective caesarean section at term.

Methods

Between 1995 and 2002, 998 women entered the study. Mothers were eligible for the trial if elective caesarean section was planned at 37 weeks' gestation or beyond. Exclusion criteria included severe maternal hypertension, history of peptic ulceration, severe fetal rhesus sensitisation, and evidence of intrauterine infection. Please see www.bmj.com for more details. In the 48 hours before elective caesarean section, women received either two intramuscular doses of 12 mg of betamethasone, separated by 24 hours, or treatment as usual, without antenatal steroids.

Outcome measures

The primary outcome was admission to a special care baby unit with respiratory distress. Secondary outcomes were severity of respiratory distress and level of care needed.¹³ Respiratory distress was defined as tachypnoea (more than 60 breaths per minute) with grunting, recession, or nasal flaring within 24 hours of birth. We graded respiratory distress as mild if the baby received less than 30% oxygen, severe if he received more than 70% oxygen or ventilatory support, otherwise moderate. We asked for chest radiographs of babies admitted with respiratory distress. Two neonatal radiologists independently assessed these for the radiological features of transient tachypnoea of the newborn or the reticular granular pattern of respiratory distress syndrome.¹⁴

Sample size and analysis

We based our power calculation on the reduction in the percentage of babies admitted to a special baby unit with respiratory distress from 8% to 4% when a 5% significance level was used. Analysis was by intention to treat.



A list of collaborators is on bmj.com



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Results

Follow-up continued until December 2002, when all babies had left hospital (see www.bmj.com for participants' flow through the trial). Altogether 942 babies were available for intention to treat analysis, 467 in the treatment group and 475 in the control group. These two groups were similar in mothers' age, asthma, and smoking, and in babies' sex and birth weight (table 1). Eighty six (9.1%) were born at 37 weeks' working gestation, 434 (46.1%) at 38 weeks, 357 (37.9%) at 39 weeks, 46 (4.9%) at 40 weeks, 13 (1.4%) at 41 weeks, and 6 (0.6%) at 42 or more weeks.

Primary outcome: admission to special care baby unit

Table 2 shows that 35 babies entered these units with respiratory distress, 24 in the control group and 11 in the treatment group ($P=0.021$). The incidence of admission with respiratory distress was 0.051 in the control group and 0.024 in the treatment group—a relative risk of 0.46 in favour of treatment (95% confidence interval 0.23 to 0.93).

Secondary outcomes

The severity of respiratory distress in babies admitted to a special care baby unit was similar in both groups. We received radiographs relating to 22 of the 35 babies admitted with respiratory distress. The remaining 13 babies had diagnoses of transient tachypnoea of the newborn on discharge. Nineteen control babies had transient tachypnoea of the newborn and five had respiratory distress syndrome, compared with 10 treated babies with transient tachypnoea and one with respiratory distress syndrome. The incidence of respiratory distress syndrome was therefore 0.011 in the control group and 0.002 in the treatment group (relative risk 0.21, 0.03 to 1.32), and the incidence of transient tachypnoea of the newborn was 0.040 in the control group and 0.021 in the treatment group (0.54, 0.26 to 1.12).

The predicted probability of admission to a special care baby unit with respiratory distress at 37 weeks gestational age was 11.4% in the control group and 5.2% in the treatment group, at 38 weeks it was 6.2% and 2.8%, respectively, and at 39 weeks it was 1.5% and 0.6%.

Adverse effects

Reports of side effects came from seven mothers in the treatment group who had received two doses of

Table 1 Mothers' and babies' characteristics by intention to treat

Binary characteristics*	Betamethasone group	Control group	Total
Male baby	234/467 (50.1)	243/475 (51.2)	477/942 (50.6)
Maternal asthma	44/467 (9.4)	58/475 (12.2)	102/942 (10.8)
Maternal smoking	89/467 (19.1)	110/475 (23.2)	199/942 (21.1)
General anaesthetic	42/455 (9.2)	26/458 (5.7)	68/913 (7.4)
Quantitative characteristics†			
Maternal age (years)	31.1 (5.2)	30.5 (5.1)	30.9 (5.2)
Birth weight (g)	3260 (460)	3320 (470)	3290 (460)
Working gestation (days)	269 (5.9)	269 (5.9)	269 (5.9)
Corrected gestation (days)	269 (6.7)	269 (6.6)	269 (6.6)

*Values are numbers (percentages). Denominator varies according to number of valid responses.

†Values are means (standard deviations).

betamethasone and one who had received only one. Five reported generalised flushing, one nausea, one tenderness at the injection site, and one increased energy with difficulty in sleeping. No such reports came from the control group. No reports were made of wound infection or neonatal sepsis.

Discussion

Betamethasone given immediately before elective caesarean section at term reduces respiratory distress and admission to a special care baby unit. The rate of such admission was 0.050 in the control group and 0.024 in the treatment group. This rate falls with increasing gestation, supporting the recommendation to delay elective caesarean section until the 39th week.⁴ Nevertheless, the benefits of antenatal steroids persist until 39 weeks.

Strengths and weaknesses of the trial

We designed ASTECS as a pragmatic trial to estimate the effectiveness of betamethasone for caesarean section at term in routine practice in 10 diverse maternity units. Blinding participants and professionals was therefore neither desirable nor possible. Similarly the use of placebos was not practical. Furthermore, the primary outcome, respiratory distress requiring admission to a special care baby unit, is hardly susceptible to maternal influence.

To simplify, and thus increase, recruitment we did not stratify treatment allocation by gestation or centre; no imbalance in allocation resulted.

Meaning of the study

Independent radiological review confirmed that antenatal betamethasone reduced the incidence of

Table 2 Outcomes by group

Outcomes	Betamethasone group	Control group	Net benefit from steroid (95% CI)
Binary*			
Resuscitated	44/467 (9.4)	54/475 (11.4)	2.0 (-2.0 to 6.0)
Resuscitation:			
Mask ventilation	22/467 (4.7)	20/475 (4.2)	-0.5 (-3.3 to 2.2)
Intubation	4/467 (0.9)	1/475 (0.2)	-0.6 (-2.0 to 0.4)
Admitted to special care baby unit with respiratory distress	11/467 (2.4)	24/475 (5.1)	2.7 (0.3 to 5.3)
Quantitative†			
Apgar score at 1 minute	8.48 (0.07)	8.57 (0.05)	-0.09 (-0.26 to 0.08)
Apgar score at 5 minutes	9.27 (0.06)	9.29 (0.05)	-0.02 (-0.18 to 0.14)
Time in special care baby unit in days	0.18 (0.05)	0.35 (0.09)	0.18 (-0.02 to 0.37)
Time on oxygen in hours	0.64 (0.35)	3.44 (1.20)	2.80 (0.34 to 5.25)
Maximum inspired oxygen concentration in %	21.29 (0.13)	21.99 (0.31)	0.68 (0.12 to 1.42)

*Values are numbers (percentages). Denominator varies according to number of valid responses. Net benefit is percentage in control group minus percentage in treatment group.

†Values are means (standard errors). Net benefit is difference between control mean and treatment mean with negative sign when controls performed better.

What is already known on this topic

Two antenatal doses of betamethasone reduce the incidence of respiratory distress syndrome by more than 50% in babies born before 34 weeks' gestation, thus reducing morbidity and mortality

The treatment's effect is thought to be mediated through increased surfactant production, a shortage of which leads to respiratory distress syndrome, which is common in preterm babies

What this study adds

Babies born after 37 weeks by elective caesarean section also benefit from antenatal betamethasone

This reduces the incidence of respiratory distress by more than 50%, mainly by reducing transient tachypnoea of the newborn

The likely benefits of antenatal betamethasone should be compared with those of delaying caesarean section until 39 weeks when possible

transient tachypnoea of the newborn from 4% of elective caesarean sections to 2.1% and that of respiratory distress syndrome from 1.1% to 0.2%. To our knowledge this is the first report that antenatal steroids prevent transient tachypnoea. During labour and at birth, the mature lung switches from active chloride and fluid secretion to active sodium and fluid absorption.¹⁵⁻¹⁷ The reduced incidence of transient tachypnoea in the steroid group is consistent with the hypothesis that corticosteroids, increased in mother and fetus through the stress of labour, encourage the expression of the epithelial channel gene and allow the lung to switch from fluid secretion to fluid absorption. Without another source of corticosteroid, elective caesarean section will disrupt this process.

Conclusion

Antenatal betamethasone is effective in reducing admission to a special care baby unit with respiratory distress after elective caesarean section at term. In planning elec-

tive caesareans, the risk of respiratory distress should be considered and the likely benefits of antenatal corticosteroids should be compared with those of delaying delivery until 39 weeks when possible.

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Contributors: For members of the ASTEC research team and collaborators see bmj.com

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Unexpected feedback

As the only independent body in Europe investigating clinical research fraud and training researchers in its detection, we talk to various groups. One example I describe of publication fraud is the case of William McBride, the Australian physician who was one of the first to raise concerns about the teratogenicity of thalidomide. In the early 1980s he published a paper reporting work with the active substance of the drug Debendox in pregnant animals, showing it to be a teratogen, and he later alleged in court that it also caused physical defects and mental retardation in children. The drug, used for nausea and sickness in early pregnancy, was withdrawn, but it wasn't until some years later that his research results were exposed as fiction. I finish the story by saying that, not only was McBride's career effectively finished by the exposure of the fraud, but countless women must have continued their pregnancy in fear and dread that they might give birth to a deformed child; I want to make the point that there are many victims in cases of research fraud.

After one training session for members of research ethics committees, one of the women on the course came up to me, took my hands, and said rather emotionally that she wanted to thank me. She had taken Debendox during pregnancy and for 28 years had been tortured by the fear that she might have damaged her son in some way. Although he seemed in all respects to be normal, she always dreaded that some weakness would one day become apparent because of her taking the drug, or that her hoped for grandchildren would have birth defects. She knew of the research, but not of the retraction, and told me I had made her burden of guilt vanish and that she felt years younger.

It had never occurred to me that a case of fraud could have such long term consequences. She told me I had made her day, but I felt rather that she had made mine.

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