Continuous subcutaneous terbutaline administration prolongs pregnancy after recurrent preterm labour

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The ambulatory administration of continuous parental subcutaneous terbutaline (SQT) to women at very high risk for early delivery was under evaluation. Women at very high risk for early delivery were those with recurrent preterm labour (PTL) before 32 weeks' gestation. The technology aimed to prevent early birth. It was compared with no therapy provided in the home on an outpatient basis.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised women with two or more episodes of PTL, who were stabilised in hospital with intravenous tocolytics and were prescribed continuous SQT on discharge. Women were excluded from the study if further continuation of the pregnancy was contraindicated. They were also excluded if they had insulin-dependent diabetes, preterm premature rupture of the membranes, allergy to beta-sympathomimetic drugs, foetal anomalies, or foetal death.

Setting
The setting of the study was community care. The authors did not clearly state where the study was carried out, but it appears to have been conducted in Jackson (MS), USA.

Dates to which data relate
The effectiveness and resource use data were collected during the 12 months from January 1, 2001, to December 31, 2001. The price year was not reported.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was undertaken prospectively on the same patient sample as that used in the effectiveness study.

Study sample
The use of power calculations to determine the sample size was not reported. The method used to select the sample was
also not reported. The sample consisted of women stabilised in hospital with intravenous tocolytics who were prescribed continuous SQT on discharge. Fifteen patients with a mean age of 26.8 years (standard deviation, SD=5.4) were included in the intervention group (continuous SQT). These were matched with 45 patients with a mean age of 25.2 years (SD=5.2) in the control group (no therapy). The authors did not report that any women were excluded from the initial sample.

Study design
This was a single-centred, prospective, cohort study. No loss to follow-up was reported. The mean duration of follow-up was also not reported.

Analysis of effectiveness
All of the patients included in the study were accounted for in the analysis of outcomes. The outcomes of interest for the women were:

- the gestational age at delivery,
- reason for the birth (if before 37 weeks),
- pregnancy prolongation after first hospital discharge,
- quantity of SQT infused and associated side effects,
- total maternal hospitalisation (first and second PTL plus delivery hospital days), and
- the route of delivery.

For the infants, data were collected on:

- the birth weight,
- NICU admission,
- need for resuscitation,
- morbidity or mortality,
- Apgar scores,
- arterial blood gas information, and
- total nursery days.

The control and intervention groups were matched for cervical dilatation, gestational age at discharge from the hospital for recurrent PTL, maternal age, and the number of prior preterm births caused by PTL or preterm rupture of the membranes. However, the two groups seemed to differ in terms of the risk factors for preterm birth.

Effectiveness results
Women in the intervention group reported more side effects than in the control group (3 tachycardia, nervousness versus 0 in the control group).

The gestational age at delivery was significantly lower in the control group (233 days) than in the intervention group (256.7 days), (p<0.001). In fact, a higher proportion of women in the intervention group delivered at term (37 or more weeks) than women in the control group (53% versus 4%; p<0.001). Also, no women in the intervention group delivered at less than 32 weeks’ gestation compared with 47% of women in the control group (odds ratio, OR=0.04).
95% confidence interval, CI: 0.00 - 0.65).

Pregnancy prolongation, from the episode of recurrent PTL, was doubled in the intervention group (49.8 days versus 24.5 days; p<0.001).

Total maternal hospitalisation was higher among the control group patients (15.9 days) than among the intervention group patients (9.8 days); (p<0.001).

Women who received ambulatory SQT had heavier infants than those in the control group (2,700 g versus 1,978 g; p<0.003). They also had fewer infants weighing less than 2,500 g (OR 0.24, 95% CI: 0.06 - 0.96).

Infants born of control group women were at a higher risk of birth complications than those born to women in the intervention group (OR 9.75, 95% CI: 1.96 - 48.49).

The number of admissions to the NICU (OR 0.27, 95% CI: 0.08 - 0.95), the duration of NICU stay (1.9 days versus 19.8 days; p<0.001), and the total days of newborn care (3.8 days versus 22.4 days; p<0.016) favoured the intervention group compared with the control group.

Clinical conclusions
The authors concluded that the use of SQT rather than no therapy significantly prolonged pregnancy, decreased serious neonatal complications, and reduced the duration of hospitalisation for both mother and infant.

Measure of benefits used in the economic analysis
No summary measure of benefit was used in the economic analysis. In effect, a cost-consequences analysis was performed.

Direct costs
The perspective of the study was unclear, but only hospital costs were considered. The direct costs were for newborn care in both the hospital nursery and the NICU. Resource use consisted of the total number of days spent by the infant in the nursery and the NICU, and was recorded prospectively in the study. The unit costs were not reported, nor was their source. The resource use and the costs were reported separately for NICU stay but not for nursery stay. Discounting was not performed because the follow-up was less than 2 years and no extrapolation beyond this point was performed. The price year was not reported.

Statistical analysis of costs
The data were treated stochastically. Means with SDs were provided for each estimate and statistical tests of significance were used (Student's t-test).

Indirect Costs
No indirect costs were included in the analysis.

Currency
US dollars ($).

Sensitivity analysis
The authors did not report any sensitivity analysis in the study.
Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The total cost of newborn care in the intervention group ($6,995, SD=14,822) was significantly lower than in the control group ($62,033, SD=89,978), (p<0.0002). However, the hospital nursery costs between the two groups were not statistically different, (p=0.899).

The costs of adverse events related to the intervention were not included in the study.

Synthesis of costs and benefits
The costs and benefits were not combined as, in effect, a cost-consequences analysis was performed.

Authors' conclusions
Compared with no therapy, the use of ambulatory subcutaneous terbutaline (SQT) with effective pharmacology consultation was associated with substantial cost-savings, and was advantageous in singleton pregnancies complicated by recurrent preterm labour (PTL).

CRD COMMENTARY - Selection of comparators
The comparator used was justified on the grounds that other alternatives failed to be effective (oral medication) or were too costly to be undertaken on a national scale (continuous hospitalisation). You should decide if this is a widely used health technology in your own setting.

Validity of estimate of measure of effectiveness
The analysis was based on a cohort study with a very small sample. This was not entirely appropriate for the study question since it is vulnerable to bias, confounding and chance. A randomised clinical trial with a much larger sample size would have been the most appropriate design to handle a study of this type. The authors acknowledged this limitation and used matched controls to control confounding. However, even though the two groups were shown to be comparable for most characteristics, the intervention group was at a higher risk of preterm birth than the control group. No explanation for this situation, and/or its implication in the analysis, was provided. The selection criteria for the intervention group, which may or may not have involved potential selection bias, were not explained. The authors did not perform any power calculations and, with such a small sample, it is possible that the results were due to chance. There was no information on how representative the study sample was of the study population. In addition, it was unclear whether race was an issue as the majority of women in both groups were of African-American ethnicity. This may limit the generalisability of the results. In conclusion, the nature of the study represents a limitation to the internal validity.

Validity of estimate of measure of benefit
No summary measure of health benefit was derived.

Validity of estimate of costs
The study perspective was not stated, but the cost analysis included only those health care costs related to the care of the infants. The costs and the quantities were reported separately for NICU stay, which will enhance generalisability to other settings, but not for hospital nursery care. However, relevant costs were omitted from the analysis. For example, the costs of the drugs, pharmacy consultation to determine the dosage schedule, training of the intervention group in the use of the SQT pump, the daily nurse follow-up in the intervention group, SQT-related adverse events, and maternal hospitalisation. No justification was provided for these exclusions and their omission might have led to the underestimation of the true costs of ambulatory SQT therapy. The source and unit costs were not stated, which will
compromise generalisability to other settings. A statistical analysis of the costs was performed. However, the price year was not reported, which will hamper reflation exercises.

**Other issues**
The authors made appropriate comparisons of their findings with those from other studies, finding their results to be consistent with prior studies. The issue of generalisability to other settings was not discussed. The authors do not appear to have presented their results selectively. In addition, they acknowledged several limitations to their study. First, the small study sample. Second, the study was not a randomised controlled trial. Third, tocolytic treatments were allowed to vary at the discretion of the attending physician. Finally, the extended maternal hospitalisation in the control group was at the choice of the attending physician.

**Implications of the study**
The authors stated that the ambulatory SQT model of treatment should be considered in patients who are at high risk for early delivery and remote from term, such as women with recurrent PTL, with advanced cervical dilatation, or with multifetal gestation. However, the concerns of the validity of the evidence used in the economic evaluation, as discussed in the commentary, should be borne in mind when considering this recommendation.

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