The Percutaneous shunting in Lower Urinary Tract Obstruction (PLUTO) study and randomised controlled trial: evaluation of the effectiveness, cost-effectiveness and acceptability of percutaneous vesicoamniotic shunting for lower urinary tract obstruction

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Declared competing interests of authors: Dr Hemming carried out paid peer-review work for statistical review, as statistical editor, of papers submitted to *BJOG* and she is the parent of a baby born with a lower urinary tract obstruction. Before the start of this project Dr Daniels was a co-investigator on a project grant from Wellbeing of Women to initiate the PLUTO trial. Professor Denny has received royalties for three academic textbooks on health sociology. Professor Khan provides expert reports in medical negligence cases for which a fee is paid by instructing solicitors. In addition, Professor Khan has received grants from public bodies and pharmaceutical companies in the UK and EU. Money was paid to Professor Khan and his institution from Ferring Pharmaceuticals and various universities and societies and he has received honoraria for speaking at meetings. Professor Khan has also received royalties for his books from publishers Hodder Arnold and Huber and payment for advice on medial research, and he and his institution have received sponsorship from Ferring Pharmaceuticals, Leo-Pharma, Alere, Ethicon, Hologic, Viforpharma and Preglem/ Quintiles for organising educational meetings. Before the start of this project Professor Khan was a co-investigator on a project grant from Wellbeing of Women to initiate the PLUTO trial. Before the start of this project Professor Kilby received a project grant from Wellbeing of Women to initiate the PLUTO trial. He also received a $750 honorarium for air travel to a debate in the USA on the role of fetal vesicoamniotic shunting at the Society of Maternal and Fetal Medicine, San Francisco, CA, USA in February 2013. He will be the Visiting Professor at the University of Delft and Leiden in June 2013. This will be to lead a joint meeting between fetal medicine subspecialists and paediatric urologists on congenital bladder neck obstructions. He will be paid travelling expenses and subsistence only. Professor Kilby also provides expert witness statements for medical negligence claims for which a fee is paid by instructing solicitors. All other authors declared no competing interests.

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Scientific summary

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Scientific summary

Background

Congenital lower urinary tract obstruction (LUTO) may be identified using prenatal ultrasound and is associated with a high perinatal mortality and high infant and childhood morbidity because of the prevalence of chronic renal impairment. Ultrasound-directed, in utero, vesicoamniotic shunting (VAS) bypasses the congenital urethral obstruction to potentially improve fetal outcome.

Objectives

The Percutaneous shunting in Lower Urinary Tract Obstruction (PLUTO) study aimed to determine the effectiveness, cost-effectiveness and patient acceptability of VAS for fetal LUTO.

The primary objective of the study was to determine whether intrauterine VAS to treat LUTO improves perinatal and neonatal mortality (survival to 28 days) and renal function compared with conservative, non-interventional care.

Secondary objectives included cost-effectiveness of VAS compared with conservative management; effects of VAS on short-term morbidity; survival and development of chronic renal failure at 1 year of age; identifying prognostic markers of outcome; determining clinicians' prior beliefs about the effectiveness of VAS; and assessing influences on women's decision-making with respect to opting for termination of pregnancy (TOP), randomisation and the acceptability of the intervention. We also studied the epidemiology of this condition using population-based methodology.

Methods

Randomised controlled trial and registry

A multicentre, international randomised controlled trial (RCT) was undertaken, supplemented by a register of pregnancies with LUTO not recruited to the RCT because of patient or clinician preference and an anonymous register of TOPs associated with this congenital anomaly. Expert opinions on the relative benefits of VAS and conventional treatment were elicited from fetal medicine specialists, paediatric nephrologists and paediatric urologists for use in a Bayesian analysis. The planned sample size of the trial was 150 but recruitment was abandoned after 31 women were randomised.

Setting

Fetal medicine departments across England, Scotland, Ireland and the Netherlands.

Population

Pregnant women with a singleton, male fetus with isolated LUTO.

Intervention

Randomisation was to either insertion of a VAS or conservative management. Insertion of the VAS was under continuous ultrasound examination of the fetus. During pregnancy both groups were followed with regular ultrasound scans.

Outcome measures

The primary outcome measure was survival to 28 days with secondary outcome measures being 1-year survival and renal function at 28 days and 12 months measured using serum creatinine, renal ultrasound and evidence of renal impairment. Prospective follow-up was arranged at 28 days and 12 months by paediatric nephrologists/urologists to assess these secondary outcomes.

Analysis

An intention-to-treat (ITT) approach was followed, supplemented by analysis comparing groups according to the intervention received (as treated). Intrauterine deaths and TOPs were included, classed as a death in the first instance, although a sensitivity analysis was performed excluding non-treatment-related TOP.

The relationship between gestational age at diagnosis, liquor volume at diagnosis, maternal age and survival to 28 days was assessed in a logistic regression analysis using combined data from randomised and registry patients.

Bayesian analysis for the randomised controlled trial

Expert opinions on the relative benefits of VAS and conventional treatment were elicited from fetal medicine specialists, paediatric nephrologists and paediatric urologists. Bayesian models were used to estimate the effectiveness of VAS at 28 days (a logistic model) and survival to 1 year of age (a Cox regression model). Bayesian prior distributions utilising evidence elicited from experts in the field and enthusiastic, sceptical and uninformative priors were used. The same priors were incorporated into the Cox proportional hazards regression analysis, excluding the elicited priors as these were obtained for perinatal survival only.

Economic analysis for the randomised controlled trial

A model-based economic evaluation, based on a decision tree utilising data inputs on resource use and outcomes from the RCT, assessed the cost-effectiveness of VAS compared with standard conservative management. Unit costs from routine sources were applied to resource use.

The model adopted a time horizon of 1 year. All analyses took the perspective of the NHS and results are presented in terms of cost per additional survivor at 28 days, cost per survivor at 1 year and cost of disability-free survival. We conducted deterministic and probabilistic sensitivity analyses to explore data uncertainty and the robustness of the results.

Patient acceptability study

A patient acceptability study using a phenomenological approach was used to explore the ways in which women make sense of their experiences and to elicit their motivations for participation in the RCT. A series of semistructured interviews were undertaken with a purposive sample of RCT and registry patients to elicit the lived experience of women.

Epidemiological study

A retrospective study identified a population of fetuses affected by LUTO delivering between 1995 and 2007 and recorded in the West Midlands Congenital Anomaly Register (WMCAR). Cases were selected using *International Classification of Diseases*, 10th Edition (ICD-10) codes and keyword terms and diagnoses were validated using additional data sets from regional fetal medicine, perinatal pathology and paediatric services. Outcome measures were incidence, prenatal diagnosis rates and mortality.

Results

Results of the randomised controlled trial and registry study

A total of 31 women from seven centres were randomised between October 2006 and October 2010. Of those randomised to VAS, 3/16 (19%) did not receive the intervention and, of those randomised to

conservative management, 2/15 (13%) received a VAS. There were 12 live births in each arm [12/16 (75%) for VAS vs. 12/15 (80%) for conservative management]. Eight out of 16 (50%) of the babies randomised to VAS survived to 28 days compared with 4/15 (27%) of those randomised to conservative management, giving an ITT analysis relative risk (RR) of 1.88 [95% confidence interval (CI) 0.71 to 4.96] in the direction of benefit with VAS. One baby in each arm died after 28 days giving a RR of 2.19 (95% CI 0.69 to 6.94) at 1 year, again in the direction of benefit with VAS but not excluding harm. Of those babies who survived to 1 year, only two had no evidence of renal impairment (VAS arm), with four in the VAS arm and two in the conservative arm requiring medical management. One baby in the conservative arm had end-stage renal failure at 1 year.

A total of 45 women were entered onto the registry of whom the majority (78%) had conservative management. Those women who entered the study registry and had conservative management were more likely to have a normal liquor volume at diagnosis (greater than the fifth centile) than those receiving VAS ($p = 0.07$) or those randomised ($p = 0.05$). There was also a higher proportion with gestational age at diagnosis of ≥ 24 weeks among these women than among those randomised ($p = 0.003$). These variables were strongly associated with improved survival to 28 days in a multivariable logistic regression analysis.

Over the period of recruitment 68 TOPs for LUTO were notified to the trial office.

Results of the Bayesian analysis

In total, 52 experts provided information on their beliefs about change in perinatal mortality as a result of intrauterine VAS. The elicited opinions combined over all experts gave a prior odds ratio (OR) of 1.22 [95% credible interval (CrI) 0.52 to 2.92] for survival to 28 days with VAS, which, when compared with the trial results in a Bayesian analysis, yielded a RR of 1.31 (95% 0.84 to 2.18), slightly increasing the average and focusing the range of values that can be considered as likely estimates of effect. The possibility that VAS may have a harmful effect could not be ruled out. Combining the trial data and the elicited priors gave a probability of 25% that VAS had a large clinically important effect (a relative increase in survival of 55% or more).

The analysis of survival to 1 year showed VAS to have an effect in the direction of harm [hazard ratio (HR) > 1 favours treatment] from randomisation to birth (36.5 weeks) (HR 0.90, 95% CrI 0.25 to 3.04) and in the direction of benefit between birth and 1 year (HR 1.75, 95% CrI 0.51 to 6.84).

Results of the health economic analysis

The use of VAS was more expensive. In the ITT analysis insertion of VAS incurred an additional cost of approximately £15,500 per survivor at 1 year. The additional cost of VAS per disability-free survival at the end of 1 year was much higher, at about £43,900.

Results of the patient acceptability study

The acceptability study found that various factors were influential to women when they were deciding whether to take part in research during pregnancy. Positive influences were visualisation of the fetus during ultrasound scanning and perceiving a benefit from the trial, but women were similarly motivated to participate for altruistic reasons. Fear of VAS and the perceived severity of LUTO in the baby tended to result in non-participation in the study. The need for more detailed information about the condition and its implications during pregnancy and following delivery was a further important finding of this research.

Results of the epidemiological study

There were 284 LUTO cases among 851,419 total births in the West Midlands region from 1 January 1995 to 31 December 1997, giving an incidence of 3.34 (95% CI 2.95 to 3.72) per 10,000 total births, which was observed to be stable over time. The incidence of LUTO was significantly higher in black and minority ethnic groups and was associated with area-based deprivation measures ($p < 0.01$). Of the 284 cases, 221 (77.8%) were isolated and the remainder were associated with other structural or chromosomal anomalies. There were 211 (74.3%) cases of isolated, non-female, singleton foetuses, which would fit the

trial eligibility criteria, but only 46.9% (99/211) had been diagnosed prenatally and thus would be suitable for inclusion in the trial.

Conclusions

The PLUTO trial stopped early because of poor recruitment. The conclusions that can be drawn from the study concerning the relative effectiveness of VAS are uncertain as they are based on only 31 participants. Survival to 28 days and 1 year appeared to be higher with VAS but the uncertainty in the direction and magnitude of the effect is high and it is not possible to conclude benefit. However, prognosis in both arms (conservative and VAS) at 12 months is poor, with only two babies overall surviving to 1 year of age with no renal impairment. This finding reinforces the natural pathogenesis of this fetal disease as one of severe and significant mortality and morbidity independent of treatment and suggests that, even if perinatal survival is increased, VAS may not have a long-term benefit. A high number of women did not receive the treatment allocated because of clinician choice or a changing clinical picture. Relatively few women were willing to consider randomisation and opted instead for either entry onto the registry or TOP.

The analysis of expert opinion concerning the value of VAS for 28-day mortality showed that experts have uncertainty of its value. Combining expert opinion with the trial data suggests that the data should persuade experts to hold a more positive view, but not to rule out the possibility of harm.

Data from the whole cohort (RCT and registry) demonstrated that normal liquor volume (greater than the fifth centile) and age at diagnosis of ≥ 24 weeks are associated with increased probability of survival at 28 days in fetuses with a confirmed diagnosis of LUTO.

Patients in the VAS arm accrued more expenses than those in the conservative management arm, mainly because of costs associated with additional surgery and intensive care. The observed increase in survival at 28 days and 1 year, if real, needs to be considered in relation to this increase in cost. The cost-effectiveness analysis suggested that these costs are likely to be very high for the benefits observed up to 1 year. Long-term follow-up data are needed to complete this analysis.

Why was it difficult to recruit?

Influences on women's participation in the RCT were perceived benefit, altruism and to increase scientific knowledge and understanding. Fear of the shunting procedure, personal faith and perceived extent of the condition were reasons suggested as influential in non-participation in the RCT. The ability to have open, detailed and ongoing communication with a health professional dedicated to the study appeared to be a positive influence on participation in this research. The finding that the expert clinicians who took part in the Bayesian elicitation exercise were quite pessimistic suggests that many clinicians may not have referred patients for inclusion in the PLUTO trial because of preconceived opinions that the intervention was not beneficial. The epidemiological study also noted the incidence of LUTO to be lower than previously reported, with a high percentage of cases not detected antenatally and thus unable to be included in the trial. Parental choice of TOP was not insignificant in this cohort (and indeed in those pregnancies with apparently isolated LUTO). Bureaucratic barriers and delays were also experienced, related to governance, insurance and approvals for an international trial in this field.

Implications for health care

The results of the RCT suggest that VAS may improve overall perinatal survival compared with conservative management but that the long-term prognosis for these babies into infant life is poor (with high rates of mortality and morbidity). Although VAS may increase survival compare with conservative management, it is

unlikely to be a cost-effective option. Parents should be counselled about the risks of pregnancy loss with or without VAS insertion. The National Institute for Health and Care Excellence (NICE) interventional procedures guidance (IPG 202) should be updated to reflect this new evidence.

Women (and their families) faced with a difficult diagnosis in pregnancy should be appropriately counselled (by professionals from different disciplines/specialties) and supported and, when considering entry into research studies, the recruitment process should ideally use an individualised approach with a dedicated research midwife/clinician.

Recommendations for future research

Ideally, a larger RCT would be performed but it is unlikely that this would be funded or delivered. Thus, it is imperative that the babies recruited into the PLUTO trial are prospectively followed up throughout childhood to determine the effects of VAS on outcomes such as renal function, incontinence, cognitive development and quality of life. Further research should look at ways to overcome the barriers to recruitment identified within this study, namely the methodology of RCTs in rare diseases (especially relating to pregnancy). Higher education institutions and funders must work hard to resolve the issue of indemnity and sponsorship to allow international collaboration in the research into rare diseases.
The factors that appear to influence decision-making with regard to participation in an RCT may be used to tailor future research designs to meet the needs of pregnant women and address the issues of importance to them around this difficult time.

Trial registration

This trial is registered as ISRCTN53328556.

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