NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of insertion of pleural-amniotic shunt for fetal pleural effusion

A fetal pleural effusion is the abnormal build up of liquid in the chest of an unborn baby, which can cause pressure on the baby's lungs and heart. It can be treated while the baby is still in the womb, by inserting a device into the baby's chest to drain the excess fluid.

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in March 2006.

Procedure name

- Fetal pleural shunt
- Fetal thoracoamniotic shunt
- Fetal pleuro-amniotic shunt

Specialty societies

- British Maternal and Fetal Medicine Society
- British Association of Perinatal Medicine
- Royal College of Paediatrics and Child Health
- Royal College of Obstetricians & Gynaecologists
- Paediatric Intensive Care Society

Description

Indications

Isolated fetal pleural effusions have an incidence rate of about 1 in 10 to 15 000 pregnancies, they may be bilateral or more commonly unilateral. They can arise in association with many problems including congenital

malformations, chromosomal abnormalities, chylothorax, anemia, heart defects, cardiac arrhythmias, and viral infections [1].

The major complication of a large persistent pleural effusion is prevention of normal lung growth and development. When effusions progress in size they can cause caval compression, leading to hydrops, which may result in fetal death. Increased lung compression associated with the effusion can cause pulmonary hypoplasia. with death soon after birth from respiratory failure. The major determinates of survival are the underlying aetiology, presence of pulmonary hypoplasia, hydrops and preterm delivery.

Current treatment and alternatives

The mother and fetus are investigated to identify any treatable underlying causes of the pleural effusion such as anaemia or cardiac arrhythmias. Some pleural effusions may resolve spontaneously before birth however if at birth the effusions are large producing respiratory compromise with or without pulmonary hypoplasia immediate drainage and intensive respiratory support are required. Pre-natal interventions include thoracocentesis and drainage of the effusions in an attempt to allow normal lung development and prevention of hydrops etc. In the some cases the fluid re-accumulates requiring repeated procedures.

Initial treatment involves needle aspiration drainage of the fluid from the fetal chest cavity; frequently either an amniocentesis or fetal blood sample will be taken at the same time to help establish an underlying aetiology. If re-accumulation is noted on repeat scans, shunting is considered.

What the procedure involves

This involves the insertion of a drainage tube though the fetal chest wall into the pleural cavity allowing continued drainage of fluid from the pleural cavity into the amniotic fluid. Different type of drainage tubes may be used including a double pigtail catheter.

Under local anesthesia and ultrasound guidance, a metal cannula on a trochar is introduced though the mother’s abdominal wall into the uterine cavity and then inserted through the fetal chest wall, into the effusion. The trochar is removed and the drainage catheter inserted into the cannula and positioned with one end in the pleural cavity and the other in the amniotic cavity. The cannula is then removed and the final position confirmed by ultrasound. The success of the procedure is determined by serial ultrasound scans, resolution of the effusion, hydrops and continued lung growth. If the effusions re-accumulate another shunt may be inserted. After delivery the chest drains are immediately clamped and removed to avoid development of pneumothorax.

Efficacy

Lung expansion

In one case series of 47 fetuses with pleural effusions treated with pleural-amntiotic shunt, effective drainage and lung expansion was achieved in 98% (46/47) of fetuses. This produced resolution (where present) of polyhydramnios in 67% (20/30) of pregnancies, and hydrops in 46% (13/28) of fetuses[2]

Post-natal respiratory function

There was no respiratory morbidity at final (post natal) follow up in any infant in two case series [1,2] at a follow up of between two months and six years. Another case series reported that none of 17 infants had respiratory symptoms at the time of final (post natal) follow up, although 35% (6/17) had demonstrated symptoms at some stage of post-natal development, requiring either bronchodilator or antibiotic medication[4]. In this series, at 12 months follow up after delivery, the mean lung functional residual capacity of the infants was 28 ml/kg, with 88% (15/17) of infants being with the normal values range for their age.

Survival

Survival past the neonatal period (period not defined in all studies) following the insertion of a shunt to drain a pleural effusion was reported across case studies to be between 47% (10/21)[1], 58% (28/48)[4], 66% (29/44)[2], 67% (6/9)[5], and 100% (3/3)[3], although the severity of effusion and underlying pathology may have varied between studies. In two case series where pleural effusions associated with hydrops were reported, survival among fetuses without associated hydrops was between 60% (3/5)[1] and 100% (15/15)[2].

Requirement for repeat shunting procedures

One study found that re-accumulation of the pleural effusion required a new stent to be inserted in 8% (4/49) of fetuses[2]. In another series repeat shunt placement was required in 33% (3/9) of fetuses, and in a third series re-accumulation of pleural effusion occurred in 6% (1/17) of fetuses[4].

Safety

Intraoperative complications

Only one study provided details of intraoperative complications, where in one fetus during insertion of a second shunt in bilateral effusion the shunt was inadvertently placed into the left pleural cavity resulting in traumatic hemothorax[3].

Intrauterine complications

The most common complications reported arose during the gestational period following insertion of a shunt.

One case series following fetuses receiving a shunt reported fetal loss as a result of shunt complications in 10% (1/10)[1]. There was one instance of fetal mortality as a result of both premature birth and shunt insertion complication

among 9 fetuses (11%) that were treated with a shunt in a case series[5]. Unilateral arm oedema in 10% (1/10) of fetuses was also reported in one case series. [1]

Intrathoracic displacement of the shunt was reported at a rate of 23% (3/13) in cases reported at three separate centres within one case series[3]. However, this analysis was based on a very selective sample of procedures only including sites where this outcome was reported. In all three procedures where the shunt inadvertently dislodged into the chest all three were asymptomatic at the final follow up despite the shunt being left in the chest[3].

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to fetal plural-amniotic shunting. Searches were conducted via the following databases, covering the period from their commencement to 15/03/2006: Medline, PreMedline, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches. (See appendix C for details of search strategy.)

The following selection criteria (Table 1) were applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good-quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patient	Patients with pleural effusion
Intervention/test	Pleuro-amniotic shunting
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on five case series[1-5]; all relevant case series identified by the search are included in Table 2.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (Table 2) are listed in appendix A.

Existing reviews on this procedure

No published reviews were identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B details the recommendations made in each piece of guidance listed below.

Interventional procedures
None applicable

Technology appraisals
None applicable

Clinical guidelines
None applicable

Public health
None applicable

Table 2 Summary of key efficacy and safety findings on insertion of pleural-amniotic shunt for fetal pleural effusion

Abbreviations used: FRC – functional residual capacity			
Study Details	**Key efficacy findings**	**Key safety findings**	**Comments**
Nicolaides K H (1990)[2] **Case series** UK **n=51 (of which 47 pleural effusions)** Study period: 1985 and 1990 Indications: Pleural effusion *(aetiology undetermined)* Population: Fetuses were diagnosed between 19-35 weeks of gestational age, by ultrasound scan due to suspicion of polyhydraminos or routine fetal anomaly scan. Bilateral effusion n=25, polyhydramnios n=30, hydrops n=28. Technique: Shunting with double pigtail catheter without maternal sedation or fetal paralysis. Monitoring with weekly ultrasound scans and insertion of new shunt where re-accumulation occurred. Delivery followed standard obstetric practice and chest drain were immediately clamped and removed after delivery. **Follow-up= 3 months to 6 years post-natally** Disclosure of interest: Not stated	**Mortality** . There were 2 intrauterine deaths, and 12 deaths during the neonatal period. Survival to infancy was 66% (29/44), including all 15 fetuses without hydrops. **Other antenatal outcomes** Rapid expansion of the lung in 98% (46/47) of fetuses. In all cases with unilateral effusions there was a simultaneous shift of the heart to its normal position. Re-accumulation of effusion requiring insertion of new shunt in 8% (4/49) of fetuses. Resolution of polyhydramnios was achieved in 67% (20/30) of fetuses, and fetal hydrops resolved in 46% (13/28) of fetuses. Four pregnancies were terminated at the parents request due to concomitant abnormalities **Other post-natal outcomes** In surviving infants there were no reported respiratory morbidity or growth deficiencies		Shunting not performed in cases with associated lethal abnormalities, where fluid accumulation did not produce major pulmonary compression or mediastinal shift, or where termination was elected. Authors state that prognostic signs of poor outcome following shunting include bilateral effusions, and presence of hydrops, although no statistical comparison of subgroups was performed. No details of case accrual are provided. Efficacy and safety of shunting for different indications was not compared.

Abbreviations used: FRC – functional residual capacity

Study Details	Key efficacy findings	Key safety findings	Comments
Smith R P (2005)[1] **Case series** UK **n=21** Study period: 1997 to 2003 Indications: Severe fetal hydrothorax Population: Median age at diagnosis =20 weeks gestation, median age at shunting = 24 weeks gestation. Associated hydrops n=16. Bilateral effusion n=15. Technique: Aspiration of effusion with a 20-22 gauge needle under ultra-sound guidance and rescanning after 2 to 3 days and if re-accumulation shunting under US guidance using a 14G trochar and pigtail shunt and prophylactic antibiotics. **Mean follow-up= 2 months to 2 years post-natally** . Disclosure of interest: not stated	**Mortality** There were eight intrauterine deaths and three neonatal deaths following delivery at <32 weeks gestation. All those born after 32 weeks gestation survived 47% (10/21). Of the seven fetuses with post-mortem information was available, three had concomitant abnormalities suggestive of an underlying congenital syndrome. Survival was 44% (7/16) among fetuses with associated hydrops, and 60% (3/5) among those without hydrops. **Other post-natal outcomes** None of the surviving infants was reported to have residual chest problems.	**Operative complications** None stated **Postoperative complications** Preterm birth (<37 weeks)* — Rate (n=10 survivors) 70% (7/10) Post natal chest drain required* — 40 % (4/10) Surgery to remove a stuck shunt — 10% (1/10) Unilateral arm oedema — 10% (1/10) Overall fetal loss as a result of shunt complications* — 10% (2/21) * For these outcomes, attribution of causality is uncertain, as they may in part relate to underlying condition and concomitant pathology	Retrospective analysis of case notes Cases with mild to moderate effusions were not shunted and thus this series represents the worst end of the spectrum. For shunted cases that resulted in intrauterine death, pathology records were used to confirm diagnosis Among survivors, some underlying genetic conditions may not have been apparent after birth, and hence not ascertained. Authors state that outcome after shunting is influenced by the presence of hydrops and gestational age of delivery.

Abbreviations used: FRC – functional residual capacity			
Study Details	**Key efficacy findings**	**Key safety findings**	**Comments**
Thompson P J (1993)[4] **Case series** UK **n=17** Study period: 1985 to1990. Indications: Fetuses with pleural effusions Population: Mean age at shunting = 29 weeks, mean gestational age at delivery =37 weeks, bilateral pleural effusion n=8, hydrops n=12. Technique: Not stated. **Median follow-up = 12 months** Disclosure of interest: supported by the UK Medical Research Council	**Mortality** Not applicable, as this study follows up 17 of the patients who survived the neonatal period following fetal pleural shunt at a success rate of 58% (28/48) from the total population treated at the centre **Other-antenatal outcomes** Pleural effusion re-accumulated in 6% (1/17) of fetuses, this was presumed to be due to inadvertent removal of the shunt by the fetus. **Respiratory** None of the 17 infants were symptomatic at the time of evaluation. 35% (6/17) had previously demonstrated respiratory symptoms, and had been treated with bronchiodiltor or antibiotic medication. All of the symptomatic infants had hydrops at time of shunt insertion. The mean lung Functional Residual Capacity (FRC) of the infants was 28 ml/kg, and 88% (15/17) were within the normal range for their age. There was no statistically significant difference in the FRC scores of infants with bilateral or unilateral shunts inserted, or with and without hydrops.		A selected sample out of 48 fetuses originally treated who were available for follow up (loss to follow-up 65%). However, there was no significant difference in age at shunt insertion and gestational age at delivery between fetuses that were followed up and those lost to follow-up. Lung function residual capacity was assessed by spirometry by one investigator blinded to the intervention. Relatively old case series, and the technique may have evolved since. No definition of how severity of pleural effusion was assessed at baseline.

Abbreviations used: FRC – functional residual capacity			
Study Details	**Key efficacy findings**	**Key safety findings**	**Comments**
Wilson R D (2004)[5] **Case series** USA **n=19 (of which 9 pleural effusion)** Study period: 1998 to 2001 Indications: Primary pleural effusion, in fetuses with hydrops or at risk of developing pulmonary hypoplasia, and negative viral evaluation of amniotic fluid. Population: Mean age of shunt placement =26 weeks, male =89%, mean gestational age at delivery = 36 weeks, associated hydrops n=3, polyhydramnios n=9, bilateral effusion n=3. Technique: patients underwent one or two thoracenteses and if re-accumulation occurred the effusion was shunted using a double pigtail catheter under continuous ultrasound and with intravenous sedation of mother and fetus. Delivery followed standard obstetric practice **Mean follow-up:** Not stated. Authors report that no long term follow up is available on the study population at present. Disclosure of interest: Not stated	**Mortality** There was one intrauterine death, and two neonatal deaths – means that overall survival to a post-neonatal period was 67% (6/9). The gestational age at time of shunting was not related to survival outcome. **Other antenatal outcomes** Repeat shunt placement was required in 33% (3/9) fetuses.		Retrospective study The study also reported outcome in 10 fetuses with congenital cystic adenomatoid malformations, with survival of 70% (7/10). A single obstetrician placed 24/26 of the shunts. Severity of pleural effusion at baseline is not documented, although all case are described as “primary pleural effusion”.

Abbreviations used: FRC – functional residual capacity			
Study Details	**Key efficacy findings**	**Key safety findings**	**Comments**
Sepulveda W (2005)[3] **Case series** Chile, Venezuela, Spain **n=13 total (only 3 cases described in the text which demonstrated complications)** Indications: Fetuses with pleural effusion, with bilateral shunting required in two fetuses. Population: No additional details provided for all fetuses treated. Technique: Operative technique may have varied between the three participating centres, but thoracentesis was attempted before shunt insertion in each of the cases reported. **Mean follow-up: not stated range 10 months to 2 years.** Disclosure of interest: Supported by the Chilean Society of Fetal Medicine.	**Mortality** All three fetuses survived to final follow up and were asymptomatic despite having the shunt remaining in the chest.	**Operative complications** Intrathoracic displacement of the shunt occurred in 23% (3/13) fetuses, or in 20% (3/15) of procedures. In one fetus with bilateral pleural effusion, the second shunt was inadvertently inserted into the left pleural cavity, resulting in traumatic hemothorax.	Cases came from three centres. Dislodgement of the shunt into the fetal chest may occur due to growing chest size or fetal movements, or due to improper placement of the device. Authors state that the rate of shunt displacement reported may be unrepresentative of true rate, as data was only collected from centres where this complication was seen. A number of different shunts catheters were used across the three participating centres. It is not clear whether the cases reported represent initial clinical experience at each site

Validity and generalisability of the studies

- A number of different shunts / catheters have been used (sometimes even within one study report).
- Post-natal follow-up described only in some studies
- Some studies report experience from over 10 years ago and technique, and patient selection criteria, may have changed since

Specialist advisors' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College.

Dr A Cameraon, Mr T Overton, Dr W Martin, Dr S Kumar, Prof. N Fisk, Mr S Walkinshaw, Mr M Taylor, Prof. S Robson

- The potential benefits of shunting are a swift resolution of the effusion, leading to reversal of hydrops or polyhydramnios, to provide better neonatal outcomes, without the need for repeat needle aspiration.
- All advisors considered pleural shunting for effusions to be an established procedure.
- Advisors noted a range of adverse events that have been reported in the literature and seen anecdotally. These included complications related tot the shunt, both dislodgement, and blockage, trauma to the fetus, maternal infection, and incidents of preterm labour and intrauterine fetal death.
- In addition, the procedure may result in fetal bradycardia or puncture of the heart that would require immediate delivery, fetal limb entanglement, and maternal vessel injury.
- Advisors commented that in some instances fetal pleural effusions may spontaneously resolve, and a balance has to be made between treatment and natural progression of the effusion.
- Almost all advisors commented that case selection may be related to outcome, and that indications for the procedure are not yet well established. Factors to be considered include whether hydrops is present or not, and the gestational age with particular concern about the period when the lungs are developing.
- The procedure requires good ultrasound guidance, and practitioners should be trained in invasive fetal medicine and be familiar with the range of shunts available. This was thought likely to come from sites with appropriate experience, and most advisors though that the procedure will only be carried out in less then 10 specialist centres
- Audit criteria to monitor the procedure should include complications of shunt dislodgement maternal pain, and emergency delivery, with out comes to include intrauterine and neo-natal death, preterm labour, and factors relating to infant respiratory function such as long term oxygen requirement and exercise tolerance. Case mix variables such as presence of hydrops, and concomitant surgery undertaken should also be recorded.

Issues for consideration by IPAC

- No comparative data compared to conservative management is available.

- The major safety concerns are in utero death or pre-term delivery. However, in the absence of controlled studies, attribution of causality is difficult, as some of these events may relate to underlying concomitant pathology.
- A minority of fetuses requires additional shunting procedures.
- The condition is rare, and relates to many different underlying syndromes and conditions. Therefore it is likely that there is clinical heterogeneity between the patients included in studies.
- All relevant case series are extracted in Table 2 (except for those where there is duplicate publication of the same cases.
- Two non-English case series were identified but not included in Table 2.
- Indications of hydrothorax and chlylothorax were considered relevant.
- All specialist advisors have undertaken the procedure.

References

1. Smith RP, Illanes S, Denbow ML et al. (2005) Outcome of fetal pleural effusions treated by thoracoamniotic shunting. *Ultrasound in Obstetrics & Gynecology* 26:63–6.

2. Nicolaides KH, Azar GB. (1990) Thoraco-amniotic shunting. *Fetal Diagnosis & Therapy* 5:153–64.

3. Sepulveda W, Galindo A, Sosa A et al. (2005) Intrathoracic dislodgement of pleuro-amniotic shunt. Three case reports with long -term follow-up. *Fetal Diagnosis & Therapy* 20:102–5.

4. Thompson PJ, Greenough A, Nicolaides KH. (1993) Respiratory function in infancy following pleuro-amniotic shunting. *Fetal Diagnosis & Therapy* 8:79–83.

5. Wilson RD, Baxter JK, Johnson MP et al. (2004) Thoracoamniotic shunts: fetal treatment of pleural effusions and congenital cystic adenomatoid malformations. *Fetal Diagnosis & Therapy* 19:413–20.

Appendix A: Additional papers on insertion of pleural-amniotic shunt for fetal pleural effusion not included in summary Table 2

The following table outlines studies that are considered potentially relevant to the overview but were not included in the main data extraction table (Table 2). It is by no means an exhaustive list of potentially relevant studies.

Article title	Number of patients/ follow-up (FU)	Direction of conclusions	Reasons for non-inclusion in Table 2
Ahmad FK, Sherman SJ, Hagglund KH et al. (1996) Isolated unilateral fetal pleural effusion: the role of sonographic surveillance and in utero therapy. *Fetal Diagnosis & Therapy* 11(6):383–9.	n = 1 Case report FU = 1 year	Near complete drainage of effusion, resolution of hydrops; excellent postnatal outcome	Case report where series is included in Table 2
Becker R, Arabin B, Novak A et al. (1993) Successful treatment of primary fetal hydrothorax by long-time drainage from week 23. Case report and review of the literature. [Review] [26 refs]. *Fetal Diagnosis & Therapy* 8(5):331–7.	n = 1 Case report FU = 8 days	Premature rupture of membranes and spontaneous onset of labour at 36 weeks; healthy infant with good perinatal outcome	Case report where series is included in Table 2
Blott M, Nicolaides KH, Greenough A. (1988) Pleuroamniotic shunting for decompression of fetal pleural effusions. *Obstetrics & Gynecology* 71(5):798–800.	n = 11 Case series FU = ?	8/11 (73%) fetuses survived to delivery and had no evidence of pulmonary hypoplasia	Same cases as included in Nicolaides et al (1990)
Brown R, Nicolaides K. (2000) Constriction band of the arm following insertion of a pleuro-amniotic shunt. *Ultrasound in Obstetrics & Gynecology* 15(5):439–40.	n = 1 Case report FU = 6 months	Successful shunt but one end of the shunt was constricting the arm on delivery	Case report where series is included in Table 2
Chan V, Greenough A, Nicolaides KN. (1996) Antenatal and postnatal treatment of pleural effusion and extra-lobar pulmonary sequestration. *Journal of Perinatal Medicine* 24(4):335–338	n = 1 Case report FU = 15 days	Lung function normal at 15 days	Case report where series is included in Table 2. Possibly same case as reported in Nicolaides (1990).
Grisaru-Granovsky S, Seaward PG, Windrim R et al. (2000) Mid-trimester thoracoamniotic shunting for the treatment of fetal primary pleural effusions in a twin pregnancy. a case report. *Fetal Diagnosis & Therapy* 15(4):209–11.	n = 1 Case report FU = 1 year	One fetus of twins had shunt for pleural effusion; both infants healthy at 1 year follow-up.	Case report where series is included in Table 2
Koike T, Minakami H, Kosuge S et al. (2000) Severe hypoproteinemia in a fetus after pleuro-amniotic shunts with double-basket catheters for treatment of chylothorax. *Journal of Obstetrics & Gynaecology Research* 26(5):373–6.	n = 1 Case report FU = 6 hours	Infant born at 29 weeks' gestation died from cardiac failure and pulmonary hypoplasia	Case report where series is included in Table 2
Sase M, Miwa I, Hasegawa K et al. (2002) Successful treatment of primary fetal hydrothorax with a double basket catheter. *American Journal of Perinatology* 19(8):405–411	n = 1 Case report FU=6 months	Successful drainage; healthy at delivery	Case report where series is included in Table 2

Appendix B: Related published NICE guidance for insertion of pleural-amniotic shunt for fetal pleural effusion

Guidance	Recommendation
Interventional procedures	None applicable
Technology appraisals	None applicable
Clinical guidelines	None applicable
Public health	None applicable

Appendix C: Literature search for insertion of pleural-amniotic shunt for fetal pleural effusion

IP: 333 Fetal Pleural Shunt		
Database	**Version searched**	**Date searched**
Cochrane Library	February 2006	15/3/2006
CRD databases	2006 Issue 1	15/3/2006
Embase	1980 to 2006 Week 10	15/3/2006
Medline	1966 to March Week 1 2006	15/3/2006
Premedline	March 14, 2006	15/3/2006
CINAHL	1982 to March Week 2 2006	15/3/2006
British Library Inside Conferences	1993 to date (limit to current year)	15/3/2006
NRR	2006 Issue 1	15/3/2006
Controlled Trials Registry		15/3/2006

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in other databases.

1 (Thoracoamniotic adj3 shunt$).tw.
2 (thorac$ adj3 shunt$).tw.
3 (amniotic adj3 shunt$).tw.
4 (pleur$ adj3 shunt$).tw.
5 ((thorac$ or chest) adj2 decompression$).tw.
6 (utero adj3 shunt$).tw.
7 (intrauterine adj3 shunt$).tw.
8 (pigtail adj1 (catheter$ or shunt$)).tw.
9 (silastic adj1 (catheter$ or shunt$)).tw.
10 (drain$ adj2 (catheter$ or shunt$)).tw.
11 or/1-10
12 Pleural Effusion/ or pleur$ effus$.tw.
13 Hydrothorax/
14 (pulmonary adj1 (hypoplasia or cyst$)).tw.
15 hydrop$.tw.
16 Polyhydramnios/
17 Polyhydramnio$.tw.
18 Pleur$ fluid$.tw.
19 Pulmonary Edema/
20 (edema$ or oedema$).tw.
21 "Cystic Adenomatoid Malformation of Lung, Congenital"/
22 CCAM.tw.
23 or/12-22
24 (fet$4 or foet$4 or utero$ or intrauterine).tw.
25 Fetal Diseases/su [Surgery]
26 Fetus/su [Surgery]
27 or/24-26
28 23 and 27
29 Hydrops Fetalis/
30 28 or 29
31 11 and 30
32 Animals/
33 Humans/
34 32 not (32 and 33)
35 31 not 34