NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedures overview of therapeutic amnioinfusion for oligohydramnios during pregnancy (excluding labour)

Oligohydramnios is a condition in which an abnormally low volume of fluid surrounds an unborn baby in the womb. Amnioinfusion involves infusion of fluid by a needle inserted into the womb and the space surrounding the unborn baby, to increase the amount of amniotic 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 April 2006

Procedure name

- Therapeutic amnioinfusion for oligohydramnios during pregnancy (excluding labour)

Specialty societies

- British Association of Perinatal Medicine
- British Maternal and Fetal Medicine Society

Description

Indications

Oligohydramnios during pregnancy.

An abnormally low volume of amniotic fluid (AF) surrounding the fetus is termed oligohydramnios. The condition is commonly defined as an amniotic fluid index (AFI) of less than 5 cm. Ultrasound is used to measure the depth of

the amniotic fluid in four quadrants of the uterus and combined to produce the AFI. A normal AFI is considered to be between about 8 and 18 cm.

Oligohydramnios may be the result of decreased fetal urine production or excretion, or excessive amniotic fluid loss. The condition can occur at any stage of pregnancy but it is most common in the last trimester. The earlier in pregnancy oligohydramnios occurs, the poorer the prognosis. Causes of oligohydramnios include premature rupture of membranes,congenital abnormalities of the urinary tract of the fetus, placental insufficiency, twin–twin transfusion syndrome, post-maturity (more than 42 weeks of gestation), certain maternal health problems such as high blood pressure, and certain medications.

Amniotic fluid serves a number of functions for the developing fetus. It allows freedom of movement to help musculoskeletal development; it cushions the fetus from external forces; and plays an important role in the normal development of the respiratory system. Severe oligohydramnios in early pregnancy, therefore, may lead to the underdevelopment of fetal lung tissue (pulmonary hypoplasia) and limb defects and is associated with poor fetal growth. There is also an increased risk of miscarriage, premature birth and stillbirth. During labour, oligohydramnios could cause fetal distress due to compression of the umbilical cord.

Current treatment and alternatives

Oligohydramnios is not routinely treated during pregnancy. There is some evidence that maternal hydration can increase the volume of amniotic fluid, but the clinical benefits of this have not yet been established.[1]

What the procedure involves

Under ultrasound guidance, a needle is inserted through the uterine wall and the amniotic cavity and isotonic fluid, such as normal saline or Ringer's lactate, is infused until the volume of amniotic fluid is normalised. The procedure may be repeated on a regular basis if oligohydramnios recurs (serial amnioinfusion).

Amnioinfusion may be used during labour, and also for diagnostic purposes, to facilitate ultrasound scanning of the embryo. However, this overview only considers its use as a therapeutic intervention during pregnancy, before labour, and for therapeutic (as opposed to diagnostic) purposes.

Efficacy

The efficacy evidence presented in this overview relates to one randomised controlled trial[2], four non-randomised controlled trials[3-6] and two case series[8,9].

The Specialist Advisors stated that key efficacy outcomes include prolongation of gestation, reduced incidence of pulmonary hypoplasia and improved neonatal survival.

Pulmonary hypoplasia

A randomised controlled trial of 34 pregnant women reported a statistically significantly lower incidence of pulmonary hypoplasia among fetuses of pregnancies treated with amnioinfusion compared with the controls (12% [2/17] versus 53% [9/17], relative risk 0.22, 95% confidence interval 0.05 to 0.87).[2] A non-randomised comparative study reported a pulmonary hypoplasia rate in live births to be 23% (6/26) in the treated group compared with 31% (4/13) in the control group (p = not significant, exact value not given).[3]

Neonatal mortality

In the randomised controlled trial, neonatal mortality was 6% (1/17) in both the treated group and the control group.[2] A non-randomised controlled study reported neonatal mortality was 18% (2/11) in the treated group compared with 71% (5/7) in the controls (p = 0.05).[5] In another non-randomised comparative study, mortality within the first week of life was 23% (6/26) in the treated group compared with 38% (5/13) in the controls (p = not significant, exact value not given).[3] A third non-randomised comparative study reported a neonatal survival rate of 73% (8/11) for cases treated with amnioinfusion and 21% (6/29) for controls (p < 0.05).[7]

Retention of infused fluid

Two case series reported that 24% (4/17) and 30% (11/36) of women successfully retained the infused fluid for 48 hours or longer after an initial amnioinfusion.[8,9]

Latency period between premature rupture of membranes and delivery

The randomised controlled trial of 34 women reported a significantly longer interval between premature rupture of membranes and delivery (latency period) for cases treated with amnioinfusion than for controls who were conservatively managed (21 days versus 8 days, p < 0.05). Two non-randomised comparative studies also reported a significantly longer latency period for cases treated with amnioinfusion compared with controls (37 days versus 9 days, p < 0.001 and 34 days versus 9 days, p < 0.05).[3,7]

Gestational age at delivery

The randomised controlled trial reported similar mean gestational age at delivery for cases and controls (27 weeks versus 29 weeks, p = 0.16). One non-randomised comparative study reported older gestational age at delivery for fetuses of women treated with amnioinfusion compared with controls managed expectantly (26.4 weeks versus 21.9 weeks, p < 0.0001).[3] Three other non-randomised comparative studies reported no significant differences in gestational age at delivery.[4,5,6]

Safety

The safety evidence presented in this overview relates to five non-randomised controlled trials and two case series.

The Specialist Advisors listed potential adverse events to include premature labour and delivery, fetal loss, fetal trauma, infection, uterine perforation and premature rupture of membranes.

Premature labour

A non-randomised comparative study including 45 women treated with amnioinfusion reported onset of labour shortly after the procedure for 2% (1/45) of cases.[3]

Fetal loss (and miscarriage)

One non-randomised comparative study reported spontaneous abortion or miscarriage in 11% (3/28) of women with unruptured membranes treated with amnioinfusion and 21% (5/24) of women with ruptured membranes.[4] A second non-randomised comparative study reported miscarriage in 12% (2/17) of cases.[8] Four studies reported rates of intrauterine deaths between 0% (0/15) and 14% (4/18) for cases treated with amnioinfusion, and between 0% (0/14) and 38% (11/29) for controls managed expectantly.[4,5,6,7]

Placental abruption

Placental abruption was reported in 0% (0/11) to 25% (3/12) of cases.[4,5,8,9]

Chorioamnionitis

Chorioamnionitis was reported in 0% (0/11) to 32% (8/25) of cases.[4,5,8,9]

Fetal trauma

A study including 12 women treated with amnioinfusion reported that one neonate had a laceration on the leg that required sutures, which was attributed to the procedure.[5]

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to amnioinfusion for oligohydramnios during pregnancy. Searches were conducted via the following databases, covering the period from their commencement to February 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	Pregnant women with oligohydramnios
Intervention/test	Amnioinfusion during pregnancy
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 one randomised controlled trial[2], five non-randomised comparative studies[3-7] and two case series[8,9]. Five studies included only women with preterm premature rupture of membranes (PPROM) and oligohydramnios.[2,3,5,8,9] One study compared outcomes for women with and without PPROM.[4] The two case series compared outcomes for successful amnioinfusion procedures with unsuccessful procedures (cases with persistent oligohydramnios).[8,9]

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

Existing reviews on this procedure

A review on antepartum amnioinfusion studies between 1987 and 2002 was published in 2003.[10] The relevant studies in the review have all been included in this overview, either in Table 2 or the appendix. The review concluded that amnioinfusion seems to offer several benefits in terms of both prenatal diagnosis and favourable perinatal outcome but prospective randomised trials, subdivided by the cause of the oligohydramnios, should be encouraged before it is introduced into routine practice. Reported complications in the literature included chorioamnionitis, premature rupture of membranes, placental abruption and premature delivery within 24 hours of the procedure.

Related NICE guidance

There is no published NICE guidance related to this procedure.

Table 2 Summary of key efficacy and safety findings on amnioinfusion for oligohydramnios during pregnancy

Abbreviations used: AFI, amniotic fluid index; CI, confidence interval; LBR, live birth rate; NS, not significant; PPROM = preterm premature rupture of membranes.

Study details	Key efficacy findings	Key safety findings	Comments
Tranquilli AL et al. (2005)[2] Randomised controlled trial Italy (Ancona) Study period: 2002 n =34 Population: 34 women with PPROM • 50% (17/34) treated with serial amnioinfusions (treatment group) • 50% (17/34) expectant management (control group) Mean maternal age: • treatment group = 33 years • control group = 33 years Indications: women with singleton pregnancies, gestational age between 24 and 33 weeks; evidence of PPROM within 24 hours of admission; oligohydramnios (AFI < 10th centile); absence of uterine contractions; no evidence of clinical chorioamnionitis; no evidence of placental anomalies or major structural fetal anomalies; normal cardiotocography. Follow-up: neonatal outcomes were assessed after delivery and after 3 months. Technique: amnioinfusion was repeated weekly if AFI fell below the 5th centile and/or a median pocket of amniotic fluid was < 2 cm. Disclosure of interest: none specified	**Median PPROM-to-delivery interval**: • treatment group = 21 days (range 15–29) • control group = 8 days (range 3–14), p < 0.05 **Mean gestational age at delivery**: • treatment group = 27 weeks • control group = 29 weeks, p = 0.155 **Neonatal mortality**: • treatment group = 6% (1/17) • control group = 6% (1/17), p = NS, exact value not given **Pulmonary hypoplasia**: • treatment group = 12% (2/17) • control group = 53% (9/17) Relative risk 0.22, 95%CI 0.05 to 0.87, p < 0.05 **Abnormal neurological outcome** (defined as cerebral palsy, spastic diplegia or tetraplegia, unilateral or bilateral deafness or blindness): • treatment group = 6% (1/17) • control group = 23.5% (4/17) Relative risk 0.24, 95% confidence interval 0.03 to 1.97, p = NS (exact value not given)	None reported	Randomisation described. Women were randomised to each group 24 hours after admission to hospital. All women were treated with bed rest and antibiotic prophylaxis. Both neonatal deaths were attributed to pulmonary hypoplasia. Small sample size. There appears to be a discrepancy between the median PPROM-to-delivery interval and the mean gestational age at delivery.

Abbreviations used: AFI, amniotic fluid index; CI, confidence interval; LBR, live birth rate; NS, not significant; PPROM = preterm premature rupture of membranes.

Study details	Key efficacy findings	Key safety findings	Comments
De Carolis M et al. (2004)[3] Non-randomised comparative study Italy (Rome) Study period: 1990 – 1999 n = 99 Population: 99 women with preterm premature rupture of membranes: • 45% (45/99) treated with serial amnioinfusions (treatment group) • 44% (44/99) expectant management (control group) Mean maternal age: • treatment group = 31.9 ± 5.2 years • control group = 33.0 ± 5.0 years Mean gestational age at rupture: • treatment group = 19.1 ± 2.7 weeks • control group = 19.8 ± 2.9 weeks Indications: patients with PPROM prior to the 26th week of gestational age; severe oligohydramnios (AFI < 3 mm); no signs of labour; no infections. Exclusion criteria: multiple births; fetal malformations; obstetric complications; maternal medical problems; lack of consent. Technique: infusion of saline solution was carried out with antibiotic prophylaxis. Mean number of amnioinfusions per patient = 3.8 ± 2.8. Disclosure of interest: none specified	**Median latency period**: • treatment group = 37 days (range 5–139) • control group = 9 days (range 2–62), p < 0.001 **Mean gestational age at delivery**: • treatment group = 26.4 ± 4 weeks • control group = 21.9 ± 3 weeks, p < 0.0001 **LBR:** • treatment group = 57.7% (26/45) • control group = 29.5% (13/44), p < 0.014 **LBR (PPROM prior to 20 weeks gestation):** • treatment group = 60.8% (14/23) • control group = 5.3% (1/19), p < 0.0001 **LBR (PPROM after 20 weeks gestation)**: • treatment group = 54.5% (12/22) • control group = 48% (12/25), p = NS **Sepsis within 72 hours of delivery (neonates):** • treatment group = 7.7% (2/26) • control group = 7.7% (1/13) **Pneumonia within 72 hours of delivery (neonates):** • treatment group = 7.7% (2/26) • control group = 7.7% (1/13) **Pulmonary hypoplasia (in live births):** • treatment group = 23.1% (6/26) • control group = 30.7% (4/13), p = NS **Mortality during 1st week of life:** • treatment group = 23.1% (6/26) • control group = 38.5% (5/13), p = NS Logistic regression showed that increasing gestational age at rupture significantly decreases the probability of developing pulmonary hypoplasia in both groups independent of treatment, but the probability is much lower in the treatment group (odds ratio 0.08, 95% CI 0.006 to 1.19, p < 0.05).	Onset of labour shortly after procedure = 2.2% (1/45)	Patients were assigned 'on the basis of consent', however the two study groups are reported as being similar in terms of maternal age, parity and gestational age at rupture. In the treatment group, no case of pulmonary hypoplasia was found when PPROM occurred after the 18th gestational week. When the p value was described as not significant (NS) in the paper, the exact value was not given.

Abbreviations used: AFI, amniotic fluid index; CI, confidence interval; LBR, live birth rate; NS, not significant; PPROM = preterm premature rupture of membranes.

Study details	Key efficacy findings	Key safety findings	Comments
Gramellini D et al. (2003)[4] Non-randomised comparative study with historical controls Italy (Parma) Study period: 1994–2000 n = 95 Population: 95 women hospitalised for oligohydramnios: 56% (53/95) had PPROM, 44% (42/95) without PPROM Of those with PPROM: • 45% (24/53) amnioinfusion (treatment group) • 55% (29/53) conservative management (control group) Of those without PPROM: • 67% (28/42) amnioinfusion (treatment group) • 33% (13/42) conservative management (control group) Indications: < 34 weeks gestational age with ultrasound verification within 20th week; singleton pregnancy; oligohydramnios (AFI ≤ 5 cm) upon hospitalisation. Exclusion criteria: active labour; placental abruption; chorioamnionitis. Technique: all women received corticosteroid therapy after 24 weeks gestation. Antibiotic prophylaxis was given to approximately 90% of women with PPROM and 93% of women without PPROM who were being treated with amnioinfusion. Amnioinfusion was repeated whenever AFI fell below 5 cm more than 12 hours after previous infusion Disclosure of interest: none specified	*Women with ruptured membranes* **Gestational age at delivery**: • treatment group = 27 weeks (range 18–35) • control group = 28 weeks (range 20–39) **Latency period**: • treatment group = 22 days (range 1–94) • control group = 11 days (range 1–72) *Women with unruptured membranes* **Gestational age at delivery**: • treatment group = 31 weeks (range 26–41) • control group = 30 weeks (range 24–35) **Latency period**: • treatment group = 30 days (range 1–122) • control group = 9 days (range 1–22)	*Women with ruptured membranes* **Post-partum endometritis**: • treatment group = 13% (3/24) • control group = 17% (5/29) **Spontaneous abortion (< 22 weeks):** • treatment group = 21% (5/24) • control group = 10% (3/29) **Vaginal bleeding**: • treatment group = 21% (5/24) • control group = 7% (2/29) **Caesarean section for placental abruption:** • treatment group = 4% (1/24) • control group = 7% (2/29) **Caesarean section for fetal distress:** • treatment group = 8% (1/24) • control group = 31% (9/29) **Intrauterine death (< 22 weeks):** • treatment group = 13% (3/24) • control group = 3% (1/29) *Women with unruptured membranes* **Post-partum endometritis:** • treatment group = 4% (1/28) • control group = 7% (1/14) **Spontaneous abortion (< 22 weeks):** • treatment group = 11% (3/28) • control group = 0% (0/14) **Vaginal bleeding:** • treatment group = 0% (0/28) • control group = 7% (1/14) **Caesarean section for placental abruption:** • treatment group = 4% (1/28) • control group = 0% (0/14) **Caesarean section for fetal distress:** • treatment group = 11% (3/28) • control group = 50% (7/14), p < 0.05 **Intrauterine death (< 22 weeks):** • treatment group = 14% (4/28) • control group = 14% (2/14)	The study aim is described as aiming to evaluate maternal complications of amnioinfusion. Women in the control group were hospitalised between 1994 and 1996 before amnioinfusion was in use, whereas women in the treatment group were hospitalised between 1997 and 2000. The study population originally included 113 women but 18 opted for pregnancy termination and were excluded from further statistical analysis. In PPROM group, the mean gestational age on admission was significantly lower for the treatment group than for control group (24 weeks vs 27 weeks, p < 0.05). In the non-PPROM related group, the only significant difference between groups was that prophylactic antibiotic therapy was given to 15 treated patients vs 1 control (54% vs 7%, p < 0.01). Small sample sizes in subgroups.

Abbreviations used: AFI, amniotic fluid index; CI, confidence interval; LBR, live birth rate; NS, not significant; PPROM = preterm premature rupture of membranes.

Study details	Key efficacy findings	Key safety findings	Comments
Ogunyemi D and Thompson W (2002)[5] Non-randomised comparative study USA Study period: 1996–1999 n = 24 Population: 24 women with PPROM and oligohydramnios: • 50% (12/24) serial amnioinfusions (treatment group) • 50% (12/24) expectant management (control group) Mean maternal age: • treatment group = 27.8 years • control group = 33.6 years, p = 0.006 Mean gestational age at PPROM: • treatment group = 21.7 weeks • control group = 22.6 weeks, p = NS Indications: gestational age ≤ 27 weeks; AFI < 5 cm; normal fetal anatomical scan; absence of gross infection; stable mother and fetus. Exclusion criteria: active labour; clinical chorioamnionitis. Technique: all patients received antibiotic prophylaxis. Intravenous magnesium sulphate was administered during the procedure and discontinued after 12 hours if preterm labour did not ensue. Ampicillin was added to the infusion solution. Disclosure of interest: none specified	**Mean gestational age at delivery:** • treatment group = 27 weeks • control group = 25 weeks, p = NS **Mean latency period**: • treatment group = 42.4 days • control group = 16.2 days, p = 0.024 **Pulmonary hypoplasia (diagnosed at autopsy):** • treatment group = 8.3% (1/12) • control group = 16.7% (2/12) **Neonatal sepsis (excluding stillbirths):** • treatment group = 27% (3/11) • control group = 86% (6/7), p = 0.049 (odds ratio 0.32, 95% CI 0.12 to 0.87) **Neonatal mortality (excluding stillbirths):** • treatment group = 18% (2/11) • control group = 71% (5/7), p = 0.049 **Total mortality (stillbirths and infant deaths occurring before discharge from NICU) :** • treatment group = 42% (5/12) • control group = 83% (10/12), p = 0.035 (odds ratio = 0.14, 95% CI 0.02 to 0.96) Using logistic regression, the only significant variables for infant survival were gestational age at delivery, odds ratio = 0.63 (p = 0.022), and transabdominal amnioinfusion, odds ratio = 0.52 (p = 0.045).	**Fetal trauma:** one neonate had a laceration on the leg that required sutures and one had a superficial chest scar that healed spontaneously. **Fetal demise:** • treatment group = 0% (0/12) • control group = 25.0% (3/12) *Reasons for delivery* **Established labour**: • treatment group = 25.0% (3/12) • control group = 33.3% (4/12) **Fetal demise**: • treatment group = 0% (0/12) • control group = 8.3% (1/12) **Fetal compromise**: • treatment group = 33.3% (4/12) • control group = 16.7% (2/12) **Cord prolapse**: • treatment group = 8.3% (1/12) • control group = 8.3% (1/12) **Abruption**: • treatment group = 25.0% (3/12) • control group = 8.3% (1/12) **Chorioamnionitis:** • treatment group = 8.3% (1/12) • control group = 25.0% (3/12)	Case selection is unclear. Controls were retrospectively chosen from the pool of patients admitted with PPROM ≤ 27 weeks during the study period, matched to treated cases by gestational age ± 2 weeks, year of delivery and presence of AFI < 5 cm. The mean age of the treatment group was significantly lower than the control group. Small sample size. Corticosteroid therapy was administered after 24 weeks gestation. Diagnosis of pulmonary hypoplasia was not attempted in surviving neonates. The authors state that this is a technically difficult procedure and should be performed by skilled and experienced personnel.

Abbreviations used: AFI, amniotic fluid index; CI, confidence interval; LBR, live birth rate; NS, not significant; PPROM = preterm premature rupture of membranes.

Study details	Key efficacy findings	Key safety findings	Comments
Turhan NO and Atacan N. (2002)[6] Non-randomised comparative study Turkey Study period: 1999–2000 n = 29 Population: 29 women with oligohydramnios: • 52% (15/29) amnioinfusion (treatment group) • 48% (14/29) expectant management (control group) Median maternal age: • treatment group = 25 years • control group = 25.5 years, p = 0.87 Median gestational age (weeks): • treatment group = 30.6 (range 23.3–35) • control group = 33.4 (range 30–35), p = 0.01 Median AFI on admission (cm): • treatment group = 6 (range 3–10) • control group = 7.5 (range 4–10), p = 0.04 Indications: women with pregnancies complicated by oligohydramnios. Exclusion criteria of the study group: multiple pregnancy; uterine anomalies; diabetes mellitus; placenta praevia; bleeding consistent with placental abruption; cervical cerclage; pre-eclampsia; major structural fetal anomalies; clinical chorioamnionitis. Technique: amnioinfusion was repeated in two patients. If uterine contractions started after amnionifusion, tocolytic treatment was administered. Disclosure of interest: none specified	**Median gestational age at delivery:** • treatment group = 33.4 weeks (range 30.1–38.4) • control group = 34.8 weeks (range 31–37.2), p = 0.10 **Median latency period:** • treatment group = 15 days (range 1–51) • control group = 8 days (range 2–23), p = 0.05 No fetal malformations were observed at delivery.	**Tocolytic therapy administration;** • treatment group = 67% (10/15) • control group = 21% (3/14), p = 0.04 Tocolytic therapy was administered more frequently in the treatment group because of procedure-related uterine contractions. No intrauterine fetal deaths were observed in either group. **Preterm delivery**: • treatment group = 93% (14/15) • control group = 71% (10/14), p = 0.28 **Caesarean delivery for fetal distress**: • treatment group = 20% (3/15) • control group = 21% (3/14), p = 0.72	No randomisation. Case selection is unclear. Controls were recruited from patients attending the same clinic. The median gestational age and AFI were significantly lower in the treatment group than the control group. Clinically diagnosed PPROM, haemorrhage in the 2nd and/or 3rd trimesters and intrauterine growth restriction were similar in the two groups. The paper stated that the exclusion criteria were applied to the study group but it is not clear if the same criteria were applied to the control group. Small sample size. Oligohydramnios was defined as an AFI below the 5th percentile. Corticosteroids were administered in all cases after the 26th week of gestation. Antibiotic treatment was administered prophylactically in all cases with PPROM or in cases without PPROM but with elevated maternal infection markers.

Abbreviations used: AFI, amniotic fluid index; CI, confidence interval; LBR, live birth rate; NS, not significant; PPROM = preterm premature rupture of membranes.

Study details	Key efficacy findings	Key safety findings	Comments
Chen M et al. (2005)[7] Non-randomised comparative study (prospective) Taiwan Study period: 2002–2005 n = 40 Population: 40 women with oligohydramnios • 27.5% (11/40) amnioinfusion (treatment group) • 72.5% (29/40) expectant management (control group) PPROM: • treatment group = 36% (4/11) • control group = 45% (13/29) Mean maternal age (years): • treatment group = 32 (range 23–41) • control group = 33 (range 20–43) Mean gestational age at diagnosis (weeks): • treatment group = 23 (range 17–26) • control group = 23 (range 15–29) Exclusion criteria: active labour; maternal temperature > 38°C; maternal leukocytosis; history of cervical incompetence; cervical length < 4 mm; maternal/placental problems including hyperthyroidism, pregnancy-induced hypertension, gestational diabetes or placental tumours; fetus with bilateral renal agenesis, obstructive uropathy or multiple anomalies. Technique: patients treated with amnioinfusions were also treated with tocolytics to prevent preterm delivery before and after the invasive procedure. Mean number of serial infusions = 3.9 (range 1–8). Disclosure of interest: none specified	**Mean gestational age at delivery:** • treatment group = 31 weeks (range 24–33) • control group = 26 weeks (range 16–30) **Mean latency period**: • treatment group = 34 days (range 11–59) • control group = 9 days (range 2–19), p < 0.05 **Neonatal survival rate**: • treatment group = 73% (8/11) • control group = 21% (6/29), p < 0.05	**Intrauterine fetal death:** • treatment group = 9% (1/11) • control group = 38% (11/29), p < 0.05 **Fever after diagnosis**: • treatment group = 18% (2/11) • control group = 41% (12/29), p < 0.05 The study noted no serious maternal complication in any of the subjects.	Controls were enrolled prospectively at the same two hospitals, matched by maternal age, gestational age at diagnosis and percentage of PPROM. All patients received prophylactic antibiotics. Four patients in the treatment group with PPROM were also treated with cerclage. One of these patients was also treated with amniopatch, which was considered to be successful. Karyotype was known and normal for all women in treatment group. It was only known for 20 women in control group and 5 were abnormal.

Abbreviations used: AFI, amniotic fluid index; CI, confidence interval; LBR, live birth rate; NS, not significant; PPROM = preterm premature rupture of membranes.

Study details	Key efficacy findings	Key safety findings	Comments
Tan LK et al. (2003)[8] Retrospective case series UK Study period: 1992–2000 n = 19 Population: 19 women with oligohydramnios and confirmed PPROM Median gestation = 19 weeks (range 15–22) Median AFI = 1 cm (range 0–3) Indications: women with PPROM and severe oligohydramnios. Exclusion criteria: fetuses with syndromic features; lethal anomalies (including renal agenesis, lower urinary tract obstruction and severe intrauterine growth restriction). Technique: if fluid was retained for 48 hours or more, repeat amnioinfusions were undertaken if the AFI fell below 5 cm. Disclosure of interest: none specified	**Successful test amnioinfusions** = 89% (2 infusions were abandoned because of fetal bradycardia during the procedure and both mothers opted to terminate their pregnancies) **Retention of fluid following successful test amnioinfusion** = 24% (4/17) *Women who retained fluid after test amnioinfusion (n = 4):* • **Median PPROM to delivery interval**: 8 weeks (range 4–14) • **Pulmonary hypoplasia** = 0% (0/3) • **Neonatal survival** = 67% (2/3) (Of the 4 women who retained fluid during the test amnioinfusion, 1 miscarried at 19 weeks before serial amnioinfusion could be started). *Women who leaked fluid within 2 days of test amnioinfusion (n = 13):* • **Median PPROM to delivery interval**: 10 weeks (range 8–12) • **Pulmonary hypoplasia** = 67% (2/3) • **Neonatal survival** = 67% (2/3) **Overall neonatal survival** = 20% (4/20)	• **Placental abruption** = 6% (1/17) • **Chorioamnionitis** = 6% (1/17) • **Miscarriage** = 12% (2/17)	41 women with oligohydramnios were excluded from this study (18 obstructive uropathy, 10 renal agenesis, 7 multiple fetal anomalies, 2 multicystic kidneys, 2 twin–twin transfusion syndrome and 2 intrauterine growth restriction). Study was designed to identify patients in whom, if fluid from a test amnioinfusion was retained, serial amnioinfusion may be of benefit. 9 women who did not retain the infused fluid for 48 hours opted to terminate their pregnancies. It is difficult to determine the frequency of pulmonary hypoplasia because of the large number of women who opted for termination. The authors conclude that therapeutic amnioinfusion will only restore amniotic fluid volume in a minority of patients and the overall prognosis remains poor; an initial test amnioinfusion may identify the small proportion of women who may benefit from serial infusions.

Abbreviations used: AFI, amniotic fluid index; CI, confidence interval; LBR, live birth rate; NS, not significant; PPROM = preterm premature rupture of membranes.

Study details	Key efficacy findings	Key safety findings	Comments
Vergani P et al. (2004)[9] Case series Italy (Monza) Study period: 1991–2001 n = 36 Population: 36 women with PPROM and oligohydramnios Indications: singleton pregnancies with PPROM at < 26 weeks and lasting 4 days or longer. Technique: patients with persistent (> 4 days) oligohydramnios received serial amnioinfusions to maintain amniotic volume above 2 cm. Disclosure of interest: none specified	**Successful amnioinfusion (infused fluid retained for 48 hours)** = 30% (11/36) *Patients with successful amnioinfusion (n = 11):* **Median PPROM to delivery interval** = 89 days (range 48–139) **Median gestational age at delivery** = 29.4 weeks (range 22.0–35.3) **Pulmonary hypoplasia** = 10% (1/10) **Postural deformities** = 18% (2/11) **Neonatal survival** = 73% (8/11) **Abnormal neurological outcome** = 0% (0/8) *Patients with persistent oligohydramnios (n = 25):* **Median PPROM to delivery interval** = 22 days (range 9–105) **Median gestational age at delivery** = 24.4 weeks (range 17.0–29.0) **Pulmonary hypoplasia** = 62% (13/21) **Postural deformities** = 16% (4/25) **Neonatal survival** = 20% (5/25) **Abnormal neurological outcome** = 60% (3/5) Gestational age at delivery was significantly lower for women with persistent oligohydramnios. Using logistic regression, the only independent predictors of perinatal survival were successful amnioinfusion and steroid administration; 22% of perinatal survival was predicted by successful amnioinfusion and an additional 17% was predicted by administration of steroids.	*Patients with successful amnioinfusion (n = 11):* • **chorioamnionitis** = 0% (0/11) • **placental abruption** = 0% (0/11) *Patients with persistent oligohydramnios (n = 25):* • **chorioamnionitis = 32% (8/25)** • **placental abruption = 16% (4/25)**	Study also included 13 women who had PPROM but without oligohydramnios. All patients were placed on hospital bed rest for the first week and antibiotic prophylaxis was administered. Corticosteroid therapy was administered after 25 weeks gestation. Tocolytic therapy was administered in the presence of preterm labour without clinical amnionitis or placental abruption. All patients who were offered amnioinfusion consented to the procedure. Oligohydramnios was defined as maximum cord-free pocket of amniotic fluid ≤ 2 cm. Authors stated that patients who retained the infused solution for more than 48 hours benefited the most from the procedure. Small sample sizes in subgroups.

Validity and generalisability of the studies

- All the studies are small and the single randomised controlled trial included only 17 patients in each study group.[2]
- Three of the five non-randomised comparative studies reported statistically significant differences between the cases and controls in terms of maternal age or gestational age at diagnosis.[4,5,6]
- Five of the eight studies included only pregnancies with PPROM and oligohydramnios.[2,3,5,8,9] There may be different efficacy and safety profiles for women with oligohydramnios in the absence of ruptured membranes. In fact, PPROM is described as a complication of the procedure.[10]
- Six of the studies excluded cases with major structural fetal anomalies.[2,3,5,6,7,8]
- All of the studies treated at least a proportion of cases with serial amnioinfusion. The number of procedures undertaken by an individual may have an effect on the safety and efficacy.
- Only two studies reported the proportion of cases who retained the infused fluid for more than 48 hours. The authors of both these studies suggest that the procedure is more beneficial for this subgroup of patients.[8,9]
- One study diagnosed pulmonary hypoplasia only at autopsy. The investigators did not attempt to diagnose the condition in live neonates.[5]
- The definition of oligohydramnios varied between studies.

Specialist Advisors' opinions

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

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- The use of amnioinfusion for diagnostic purposes is well established but the role of the procedure in reducing the incidence of pulmonary hypoplasia is still uncertain.
- The potential impact of this procedure on the NHS, in terms of numbers of patients eligible for treatment and use of resources, is minor.
- Training in fetal medicine is important.

Issues for consideration by IPAC

- It is difficult to ascertain which adverse outcomes should be attributed to the amnioinfusion procedure rather than being the result of oligohydramnios itself, or the result of linked underlying conditions causing oligohydramnios.
- The majority of cases described were treated with serial amnioinfusions. One of the studies suggests that serial amnioinfusions should only be offered to women after a successful test infusion in which the fluid is retained for 48 hours or longer.
- This overview has only considered the evidence regarding the therapeutic application of amnioinfusion during pregnancy.

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3. De Carolis MP, Romagnoli C, De Santis M et al. (2004) Is there significant improvement in neonatal outcome after treating pPROM mothers with amnio-infusion? *Biology of the Neonate* 86(4): 222–229.
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8. Tan LK, Kumar S, Jolly M et al. (2003) Test amnioinfusion to determine suitability for serial therapeutic amnioinfusion in midtrimester premature rupture of membranes. *Fetal Diagnosis and Therapy* 18(3): 183–189.
9. Vergani P, Locatelli A, Verderio M et al. (2004) Premature rupture of the membranes at <26 weeks' gestation: role of amnioinfusion in the management of oligohydramnios. *Acta Bio-Medica de l Ateneo Parmense* 75 Suppl 1: 62–66.
10. Gramellini D, Fieni S, Kaihura C et al. (2003) Antepartum amnioinfusion: a review. *The Journal of Maternal-Fetal and Neonatal Medicine* 14: 291–296.

Appendix A: Additional papers on amnioinfusion for oligohydramnios during pregnancy not included in summary Table 2

The following table outlines the 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	Direction of conclusions	Reasons for non-inclusion in Table 2
De Santis M, Scavo M, Noia G et al. (2003) Transabdominal amnioinfusion treatment of severe oligohydramnios in preterm premature rupture of membranes at less than 26 gestational weeks. *Fetal Diagnosis and Therapy* 18(6): 412–417.	71 patients	Amnioinfusion is a low fetal and maternal risk technique that improves fetal intrauterine stay and survival.	A more recent and larger study from the same centre is included.[2]
Feldman B, Hassan S, Kramer RL et al. (1999) Amnioinfusion in the evaluation of fetal obstructive uropathy: the effect of antibiotic prophylaxis on complication rates. *Fetal Diagnosis and Therapy* 14(3): 172–175.	30 patients	Oral prophylactic antibiotics reduce the risk of post-amnioinfusion complications (chorio-amnionitis and PPROM or preterm labour)	More recent studies are included in Table 2. This study focuses on the use of prophylactic antibiotics.
Fisk NM, Ronderos-Dumit D, Soliani A et al. (1991) Diagnostic and therapeutic transabdominal amnioinfusion in oligohydramnios. *Obstetrics and Gynecology* 78(2): 270–278.	9 patients treated with serial infusions for therapeutic purposes.	44% (4/9) preterm labour 67% (6/9) live births 33% (3/9) neonates survived	Study mainly focuses on amnioinfusion as an aid to diagnosis. A more recent study from the same centre is included in Table 2.[5]
Garzetti GG, Ciavattini A, De Cristofaro F et al. (1997) Prophylactic transabdominal amnioinfusion in oligohydramnios for preterm premature rupture of membranes: increase of amniotic fluid index during latency period. *Gynecologic and Obstetric Investigation* 44(4): 249–254.	36 women.	Mean latency period was significantly longer in patients who underwent amnioinfusion than controls (4.1 vs 1.7 weeks, $p < 0.001$).	More recent studies are included.
Gramellini D, Piantelli G, Delle CL et al. (1998) Amnioinfusion in the management of oligohydramnios. *Journal of Perinatal Medicine* 26(4): 293–301	80 patients	Amnioinfusion significantly prolonged gestation and reduced neonatal mortality.	A more recent and larger study from the same centre is included.[4]

Article title	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in Table 2
Gramellini D, Fieni S, Kaihura C, et al. Antepartum amnioinfusion: a review. The Journal of Maternal-Fetal and Neonatal Medicine 2003; 14: 291–296.	Review	Amnioinfusion seems to offer several benefits and most studies report that it is safe. Randomised controlled studies subdivided on the basis of the cause of oligohydramnios would be helpful.	Not a systematic review. All the relevant studies have already been included, either in Table 2 or in the appendix.
Locatelli A, Vergani P, Di Pirro G et al. (2000) Role of amnioinfusion in the management of premature rupture of the membranes at <26 weeks' gestation. *American Journal of Obstetrics and Gynecology* 183(4): 878–882.	36 women with oligo-hydramnios	Same results reported as reference no. 8 in Table 2.	A more recent study from the same centre is included.[8]
Vergani P, Locatelli A, Strobelt N et al. (1997) Amnioinfusion for prevention of pulmonary hypoplasia in second-trimester rupture of membranes. *American Journal of Perinatology* 14(6): 325–329.	34 women with PPROM and persistent oligo-hydramnios	Prevalence of pulmonary hypoplasia was significantly lower among aminoinfused cases compared with controls (46% vs 86%, OR=0.4, 95% CI 0.2 to 0.9)	A more recent study from the same centre is included.[8] Cases were compared with historic controls.
Cameron D, Lupton BA, Farquharson D et al. (1994) Amnioinfusions in renal agenesis. *Obstetrics and Gynecology* 83(5 Pt 2):872–876.	1 case (renal agenesis)	Infant died at 23 days old. Authors conclude that amnioinfusion is not an appropriate intervention for renal agenesis.	Case report.
Dommergues M, Ansker Y, Aubry MC et al. (1996) Serial transabdominal amnioinfusion in the management of gastroschisis with severe oligohydramnios.[see comment]. *Journal of Pediatric Surgery* 31(9): 1297–1299.	2 cases of severe oligo-hydramnios (fetuses had gastroschisis)	In both cases, premature rupture of membranes occurred at 36 weeks and neonates were born free of complications due to chronic exposure to severe oligohydramnios.	Only 2 cases.
Fisk NM, Talbert DG, Nicolini U et al. (1992) Fetal breathing movements in oligohydramnios are not increased by aminoinfusion. *British Journal of Obstetrics and Gynaecology* 99(6): 464–468.	16 women	Amnioinfusion did not affect the incidence of fetal breathing movements.	Study focused on fetal breathing movements. Same study centre as ref. 5.

Article title	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in Table 2
Hansmann M, Chatterjee MS, Schuh S et al. (1991) Multiple antepartum amnioinfusions in selected cases of oligohydramnios. *Journal of Reproductive Medicine* 36(12): 847–851.	38 women	LBR = 31.6% (12/38) Intrauterine fetal death = 13% (5/38) Neonatal death = 31.6% (12/38) Termination of pregnancy or spontaneous abortion = 23.7% (9/38)	More recent studies are included. Case selection is unclear.
Imanaka M, Ogita S, Sugawa T. (1989) Saline solution amnioinfusion for oligohydramnios after premature rupture of the membranes. A preliminary report. *American Journal of Obstetrics and Gynecology* 161(1): 102–106.	10 women	Fluid infused via a cervical indwelling catheter. Perinatal death = 30% (3/10)	Small case series.
Olsen ME, Taslimi MM. (1993) Permanent resolution of severe second trimester oligohydramnios after transabdominal amnioinfusion. *Journal of the Tennessee Medical Association* 86(1): 7–8.	1 case	Amniotic fluid spontaneously reaccumulated after amnioinfusion.	Case report.
Plachouras N, Sotiriadis A, Stefos T et al. (2003) Early amnioinfusion for anhydramnios after CVS. *Prenatal Diagnosis* 23(5): 430–431.	1 case	Amnioinfusion allowed visualisation of intact urinary system. Live birth at 37 weeks.	Case report.
Buek JD, McVearry I, Lim E et al. (2005) Successful external cephalic version after amnioinfusion in a patient with preterm premature rupture of membranes. *American Journal of Obstetrics and Gynecology* 192: 2063–4.	1 case	Amnioinfusion successfully facilitated external cephalic version, enabling the patient to deliver vaginally.	Case report.
Sarno AP, Polzin WJ, Feinstein SJ et al. (1995) Transabdominal amnioinfusion in preterm pregnancies complicated by fetal growth restriction, oligohydramnios and umbilical cord compression. *Fetal Diagnosis and Therapy* 10: 408–414.	4 cases	Pregnancy was prolonged for 9, 10, 22 and 38 days. Cord compression relieved in all cases.	Larger and more recent studies are included.
Stefos T, Staikos I, Plachouras N, et al. (2005) Serial saline amnioinfusion from 16th week of gestation resulted in successful outcome of pregnancy: report of two cases. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 122(2): 250–251.	2 cases	Serial normal saline amnioinfusions resulted in vital, normal and almost full-term neonates.	Only 2 cases.

Appendix B: Related published NICE guidance for amnioinfusion for oligohydramnios in pregnancy

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

Appendix C: Literature search for amnioinfusion for oligohydramnios during pregnancy

Databases	Version searched (if applicable)	Date searched
The Cochrane Library	Issue 1:2006	10.04.06
CRD	-	20.02.06
Embase	1980 – week 7 2006	10.04.06
Medline	1966 – Feb week 2 2006	10.04.06
Premedline	-	10.04.06
CINAHL	1982 – Feb week 2 2006	10.04.06
British Library Inside Conferences (limited to current year only)	-	20.02.06
National Research Register	Issue 1: 2006	20.02.06
Controlled Trials Registry	-	20.02.06

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

1. Oligohydramnios/
2. oligohydramnios.tw.
3. ((low or decreas$) adj amniotic fluid$).tw.
4. or/1-3
5. amnioinfus$.tw.
6. fluid therapy/
7. (saline or sodium chloride).tw.
8. amnio infus$.tw.
9. or/5-8
10. exp Fetal Membranes, Premature Rupture/
11.((premature$ or preterm or early) adj3 ruptur$ adj3 membrane$).tw.
12. pPROM.tw.
13. PROM.tw.
14. or/10-13
15. (4 or 14) and 9