Congenital bladder neck obstruction:
Is there a role for prenatal therapy: the PLUTO Study

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Sims Black Lecturer, 2015.
Jornadas sobre Medicina Fetal.
Buenos Aires, March 2015.

High morbidity and mortality associated with:
- Fetal lower urinary tract obstruction (LUTO)
  - 30% of renal tract anomalies detected at autopsy (Brand et al 1994)
  - Heterogeneous number of pathologies:
    - Posterior urethral valves (PUV): 57%, Commonest, usually males.
    - Urethral atresia 39%
    - Cloacal plate anomalies, including megacystis microcolon syndrome
    - Prune Belly syndrome 4%
    - Unclassified

Percentage of subjects in ESRF with age, according to underlying diagnosis (UK Renal Registry, 1996-2005)

Causes of Congenital bladder neck obstruction
- Posterior urethral valves
- Urethral atresia

(Lewis MA, Semin Fetal Neonatol. 2008; 13, 118-124)
Epidemiology of LUTO

- Total prevalence of LUTO is 3.34 per 10,000 births, 2.24 per 10,000 live births
  - Prevalence significantly higher in Black and minority ethnic groups compared to British European (OR 2.38; 1.87-3.03)
  - Association of prevalence with area based deprivation measures (p<0.01)
- LUTO subtypes:
  - 179 cases (63%) posterior urethral valves
  - 48 cases (16.9%) urethral atresia/stenosis
  - 22% complex (1 in 5) (other structural/softomal anomalies)
- Prenatal detection:
  - 66.2% abnormality detected antenatally
  - 26.9% false positive diagnoses – 24.5% reflux
  - Postnatally detected cases have greater survival to one year 91% v 50% p<0.0001 (isolated)

(Morris RK et al BJOG. 2012;119(12):1455-64)

Management of LUTO

- Diagnosis:
  - Exclude other structural and chromosomal anomalies
- Prognostic indicators:
  - Fetal urinalysis
  - Ultrasound features:
    - Diagnostic.
    - Prognostic

Detection of L.U.T.O in human pregnancy

Prenatal ultrasound detecting > 60 – 70% cases

- Oligohydramnios
- Fetal hydronephrosis
- Enlarged fetal bladder
- Dilated proximal urethra
- Renal parenchymal disease
Fetal hydrenephrosis - US grading system
(Society for Fetal Urology)

Grade 0
Grade I
Grade II thin cortex
Grade IV

Dilated ureter

Urinary tract obstruction: effect on kidneys

- Time of onset
- Severity of obstruction

Postnatal renal damage
(Mahony BS, Radiology. 1984;152:143)

- Obstructive cystic dysplasia
- ↑ Echogenicity

Sensitivity 44% Specificity 100%

73% 80%
“Echogenic kidney”: microcystic change

Not all dysplastic kidneys can be detected by US

Role of vesicocentesis and urinary analyte analysis

Fetal renal maturation: effect on urinary analytes

- ↑ Tubular reabsorption $\beta_2$ microglobulin
- Urine becomes more hypotonic
- ↓ Tubular reabsorption $\text{Ca}^{++}$
- Must use gestation specific cut-offs

<table>
<thead>
<tr>
<th>Gestation (wk)</th>
<th>Osmolality</th>
<th>Sodium</th>
<th>Chloride</th>
<th>Calcium</th>
<th>Protein</th>
<th>$\beta_2$ microglobulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>&lt; 210 mOsm/L</td>
<td>&lt; 100 mg/dL</td>
<td>&lt; 90 mg/dL</td>
<td>&lt; 8 mg/dL</td>
<td>&lt; 200 mg/dL</td>
<td>&lt; 6 mg/dL</td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>36</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Normal Renal echogenicity
No oligohydramnios in early T2

LUTO - Good prognosis

Urinary electrolytes

Muller F. Clin Chem 1996;42:1855
Muller F. Obstet Gynecol. 1993;82:813

\[
\begin{align*}
\text{Na}^+ & \quad \beta_2\text{microglobulin} \\
\text{Ca}^{++} & \quad \text{Gain in Na, TP, Osm & B}2\text{-microglobulin with time.} \\
\text{Poor prognosis:} & \quad \text{No Change in urinary analytes over time.}
\end{align*}
\]

Serial fetal urinalysis

Good Prognosis:

Fetal urine analysis to predict POOR: postnatal renal function in LUTO

Best: $\text{Ca}^{++} > 95\% \text{ for GA}$
$\text{Na}^+ > 95\% \text{ for GA}$
Worst: $\beta_2\text{-microglobulin} less accurate$

<table>
<thead>
<tr>
<th>Index</th>
<th>Threshold</th>
<th>LR (95% CI)</th>
<th>LR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>&gt;100 mg/dl</td>
<td>0.96 (0.51-1.84)</td>
<td>1.01 (0.54-1.90)</td>
</tr>
<tr>
<td>Sodium</td>
<td>&gt;100 mg/dl</td>
<td>0.86 (0.52-1.41)</td>
<td>1.13 (0.66-1.92)</td>
</tr>
<tr>
<td>Albumin</td>
<td>&gt;100 mg/dl</td>
<td>0.14 (0.01-0.91)</td>
<td>0.87 (0.56-1.37)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>&gt;20 mg/dl</td>
<td>0.00 (0.00-0.04)</td>
<td>0.03 (0.01-0.11)</td>
</tr>
<tr>
<td>Ammonium</td>
<td>&gt;100 mg/dl</td>
<td>0.09 (0.03-0.29)</td>
<td>0.97 (0.50-1.88)</td>
</tr>
<tr>
<td>Urea</td>
<td>&gt;100 mg/dl</td>
<td>0.00 (0.00-0.04)</td>
<td>0.01 (0.00-0.04)</td>
</tr>
</tbody>
</table>

LR+: positive likelihood ratio; LR−: negative likelihood ratio.
\(\text{CI: confidence interval.}

\begin{align*}
\text{Author} & \quad \text{Positive LR (95% CI)} & \quad \text{Negative LR (95% CI)} \\
\text{Anumba et al. 2005} & 1.25 & 0.92 & (0.38-2.32) \\
\text{Baik et al. 1996} & 7.00 & 0.54 & (0.22-1.29) \\
\text{Bussieres et al. 1995} & 2.24 & 0.09 & (0.31-1.13) \\
\text{Johnson et al. 1994} & 2.03 & 0.41 & (0.17-1.00) \\
\text{Lipitz et al. 1993} & 0.90 & 0.38 & (0.32-1.02) \\
\text{Nicolini et al. 1992} & 2.00 & 0.31 & (0.11-0.86) \\
\text{Morris et al. 1993} & 3.45 & 0.03 & (0.00-0.46) \\
\text{Nicolaides et al. 1992} & 10.07 & 0.30 & (0.18-0.50) \\
\text{Nicolaides et al. 1993} & 3.71 & 0.20 & (0.04-0.90) \\
\text{Reuss et al. 1997} & 1.57 & 0.43 & (0.07-2.03) \\
\end{align*}

a Second urine sample
b severe renal disease only

Sensitivity and specificity for predicting renal dysfunction.

Best: $\text{Ca}^{++} > 95\% \text{ for GA}$
$\text{Na}^+ > 95\% \text{ for GA}$
Worst: $\beta_2\text{-microglobulin}$ less accurate


(Morris K. Prenat Diagn 2007; 27: 900–911)
Prognostic sonographic findings in fetuses with LUTO

- Systematic review 13 articles, 205 women

<table>
<thead>
<tr>
<th>Diagnostic measure</th>
<th>Sensitivity (95% Confidence intervals)</th>
<th>Specificity (95% Confidence intervals)</th>
<th>$X^2$ test and p value</th>
<th>Area under receiver operating characteristic curve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligohydramnios</td>
<td>0.63 (0.51-0.74)</td>
<td>0.76 (0.60-0.85)</td>
<td>19.67 p=0.02</td>
<td>0.74</td>
</tr>
<tr>
<td>Renal cortical appearance</td>
<td>0.57 (0.37-0.76)</td>
<td>0.84 (0.71-0.94)</td>
<td>10.29 p=0.04</td>
<td>0.78</td>
</tr>
<tr>
<td>Gestation at diagnosis &lt;24 weeks</td>
<td>0.48 (0.26-0.71)</td>
<td>0.82 (0.66-0.92)</td>
<td>3.88 p=0.14</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Morris et al, BJOG 2009;116:1290-1299

Management of LUTO

- Diagnosis:
  - Exclude other structural and chromosomal anomalies
- Prognostic indicators:
  - Fetal urinalysis
  - Ultrasound features
- Intervention:
  - Vesico-amniotic shunting (VAS)
  - Fetal cystoscopy

Therapeutic options (1) - Cystoscopy

- Cystoscopy with endoscopic ablation of PUV:
  - Allows restoration of normal fetal bladder dynamics and option for diagnosis
  - Systematic review n=4 papers:
    * Improved diagnosis 25-36.4%
  - Search updated Jan 2012 no new papers

**Therapeutic options (1) - Cystoscopy**

Table 4: Outcome data for fetuses with confirmed posterior urethral valves (voluntary termination of pregnancy excluded)

<table>
<thead>
<tr>
<th></th>
<th>Therapeutic cystoscopy (n=10)</th>
<th>Vesico-amniotic shunting (n=10)</th>
<th>No intervention (n=5)</th>
<th>Cystoscopy v no intervention VAS</th>
<th>Cystoscopy v no intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival (%)</td>
<td>100 (10/10)</td>
<td>60 (6/10)</td>
<td>20 (1/5)</td>
<td>0.5</td>
<td>0.19</td>
</tr>
<tr>
<td>Survived with renal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>impairment* (%)</td>
<td>30 (3/10)</td>
<td>83 (5/6)</td>
<td>0 (0/1)</td>
<td>0.29</td>
<td>0.79</td>
</tr>
<tr>
<td>Perinatal mortality (%)</td>
<td>0 (0/10)</td>
<td>40 (4/10)</td>
<td>80 (4/5)</td>
<td>0.09</td>
<td>0.03</td>
</tr>
</tbody>
</table>

* renal impairment was defined in two papers as serum creatinine >50mg/dl at 12 months of age and not defined in two papers

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**Therapeutic options (2) - Vesico-amniotic shunting (VAS)**

### Intervention v no treatment - Perinatal survival

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Favour treatment</th>
<th>Favour no treatment</th>
<th>Odds ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor prognosis</td>
<td>Shunting overall perinatal survival OR 3.86 (2.00-7.45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor prognosis</td>
<td>Shunting overall perinatal survival OR 26.19 (4.39-156.25)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Intervention v no treatment – Survival with normal renal function

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Favour treatment</th>
<th>Favour no treatment</th>
<th>Odds ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor prognosis</td>
<td>Shunting Postnatal survival with normal renal function OR 0.50 (0.13-1.90)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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(Morris et al Ultrasound Obstet Gynecol 2011;37(6):629-3)
Percutaneous shunt in L.U.T.O (PLUTO)

- **Objectives:**
  - **Primary:**
    - To determine whether vesico-amniotic shunting for LUTO, compared with conservative care, improves prenatal and perinatal mortality and renal function.
  - **Secondary:**
    - Perinatal morbidity, prognostic risk assessment at diagnosis, long-term outcomes for infants to 5 years.
- **Design:**
  - Multicentre randomised controlled trial including a prospective registry

**Trial Algorithm**

- **Population:**
  - Pregnant women with singleton, male fetus with isolated lower urinary tract obstruction
- **Setting:**
  - 21 fetal medicine centres within UK, National Maternity Hospital Dublin and University Medical Centre, Leiden, Netherlands.
Percutaneous shunt in L.U.T.O (PLUTO)

• Outcome measures:
  • Pregnancy outcome:
    - Perinatal mortality, admission to SCBU, length of stay, oxygen dependency at discharge, birth weight, serum creatinine/renal USS
  • At 4-6 weeks:
    - Renal USS findings, weight, serum creatinine, surgery, MCUG
  • At 1 year:
    - as 4-6 weeks, need for dialysis/transplantation, UTIs, BP, weight and height
  • At 2 years:
    - renal function, developmental questionnaire (PARCA)
  • At 5 years:
    - as 2 years with micturition questionnaire and Quality of life assessment (PedsQL)

Analysis of the RCT

• Intention to treat analysis
• Risk ratios and confidence intervals for survival
• Multi-level modelling for continuous repeated variables e.g. Creatinine clearance
• Sub-group analysis: gestational age at diagnosis, liquor volume, maternal age, learning curve effects
• Secondary research:
  - Bayesian priors
  - Qualitative research
  - Epidemiology study
  - Economic analysis

Results (1) – baseline characteristics

• Recruitment Sep 2005 – Dec 2010
• Cohort n= 145
  - Randomised n=31
  - Registered n=46
  - TOP n= 68

Randomised to shunt:
• N=16 [received n=15 (13 allocation, 2 crossovers)]
• Median GA 142 days (IQR 112-154) (range 98-224) p=0.71
• Liquor volume MPD median 1.6cm (IQR 0-2.93) (range 0-4.4); 62.5% <5th centile p=0.72
• 43.8% urinalysis
• 25% karyotype

Randomised to conservative:
• N=15 [received n=16 (13 allocation, 3 crossovers)]
• Median GA 151 days (IQR 133-160) (range 112-296)
• Liquor volume MPD median 1.0cm (IQR 0.3-2.5) (range 0-9.4); 60% <5th centile
• None had urinalysis
• 26.7% karyotype

Results (2) – Pregnancy outcome

Allocated to shunt n=16
All NND were within 24 hours of birth
2 TOP's treatment related

Termination of pregnancy
Intra-uterine death <24 weeks
Neonatal death <28 days
Alive >28 days

Median interval randomisation to delivery 88.5 days (IQR 30.5-115) (range 1-164)
Median GA at delivery live births 254 days (IQR 238.5-263) (range 188-267)
### Results (3) – Pregnancy outcome

**Allocated to conservative n=15**
- 7/8 NND all within 24 hours
- 2, 13%
- 8, 53%
- 4, 27%
- 1, 7%

- Termination of pregnancy
- Intra-uterine death <24 weeks
- Neonatal death <28 days
- Alive >28 days

Median interval randomisation to delivery 105 days (IQR 64-115) (range 14-124)
Median GA at delivery live births 255.5 days (IQR 241.5-264) (range 232-281)

### Results (4) – Complications

- **Preterm delivery <34 weeks (n=4)**, 2 in each arm, 1 in shunt arm <28 weeks
  - No significant difference mode of delivery
  - Vaginal delivery shunt v cons 66.7% v 58.3%
  - No significant difference between arms in birth weight median or <10th centile
    - shunt v cons 41.7% v 33.3%

### Results (5) – Live birth rate

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Shunt</th>
<th>Conservative</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>AllITT</td>
<td>12</td>
<td>16</td>
<td>0.94 (0.34, 1.77)</td>
<td>0.94 (0.34, 1.77)</td>
</tr>
<tr>
<td>Excluding crossover and non-treatment related TPUs</td>
<td>8</td>
<td>12</td>
<td>0.92 (0.37, 1.23)</td>
<td>0.92 (0.37, 1.23)</td>
</tr>
</tbody>
</table>

NNT to prevent a pregnancy loss = 20 harm

**As treated analysis RR 0.90 (0.61-1.33)**

### Results (6) – Survival to 28 days

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Shunt</th>
<th>Conservative</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>AllITT</td>
<td>8</td>
<td>16</td>
<td>1.00 (0.71, 1.43)</td>
<td>1.00 (0.71, 1.43)</td>
</tr>
<tr>
<td>Excluding crossover and non-treatment related TPUs</td>
<td>7</td>
<td>12</td>
<td>1.27 (0.61, 2.64)</td>
<td>1.27 (0.61, 2.64)</td>
</tr>
</tbody>
</table>

Perinatal mortality NNT=5

**As treated analysis RR 3.20 (1.06-9.62) p=0.03**
Results (7) – Survival to 1 year

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Shunt</th>
<th>Conservative</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLUTO</td>
<td>7</td>
<td>15</td>
<td>4.27</td>
<td>1.07-17.0</td>
</tr>
<tr>
<td>PLUTO (excluding cross-overs and non-randomized related TaPs)</td>
<td>6</td>
<td>12</td>
<td>1</td>
<td>11</td>
</tr>
</tbody>
</table>

Infant death NNT=5

As treated analysis RR 4.27 (1.07-17.0) p=0.02

Results (8)-Long-term follow-up

<table>
<thead>
<tr>
<th>Group</th>
<th>Diagnosis</th>
<th>Outcome (Final follow-up)</th>
<th>Renal Function at Final follow-up (Nadir Cr µmol/l)</th>
<th>Dialysis</th>
<th>Transplant</th>
<th>Surgery</th>
<th>Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shunt</td>
<td>PUV</td>
<td>Alive (3 years)</td>
<td>Moderate impairment (88)</td>
<td>No</td>
<td>No</td>
<td>Resection of valves, orchiopexy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50th centile height and weight; 2 UTIS; DMSA 50% function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urethral atresia</td>
<td>Alive (2 years)</td>
<td>No impairment (34)</td>
<td>No</td>
<td>No</td>
<td>Resection of valves, orchiopexy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 years significant motor and cognitive impairment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No shunt</td>
<td>PUV</td>
<td>Alive (1 year)</td>
<td>Moderate (119)</td>
<td>No</td>
<td>Resection of valves</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dialysis, transplantation, first 6 weeks 19 days in hospital</td>
<td></td>
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</tr>
</tbody>
</table>

RCT and observational data – abnormal perinatal renal function

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Favours no intervention</th>
<th>Favours intervention</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anumba et al 2005</td>
<td></td>
<td></td>
<td>0.50 (0.40, 0.67)</td>
</tr>
<tr>
<td>Freedman et al 1986</td>
<td></td>
<td></td>
<td>1.26 (0.91, 1.72)</td>
</tr>
<tr>
<td>Hutton et al 1997</td>
<td></td>
<td></td>
<td>1.70 (1.35, 2.17)</td>
</tr>
<tr>
<td>Lipitz et al 1993</td>
<td></td>
<td></td>
<td>0.37 (0.22, 0.63)</td>
</tr>
<tr>
<td>McFadyen et al 1984</td>
<td></td>
<td></td>
<td>0.57 (0.40, 0.71)</td>
</tr>
<tr>
<td>PLUSTO trial 2012</td>
<td></td>
<td></td>
<td>0.86 (0.59, 1.25)</td>
</tr>
<tr>
<td>Combined RR EPI</td>
<td></td>
<td></td>
<td>1.13 (0.65, 1.94)</td>
</tr>
</tbody>
</table>

Bayesian analysis

Bayesian prior and posterior estimates of relative risk of survival to age 28 days. The prior distribution:
- (a) was obtained by eliciting prior distributions from 52 experts, averaging the distributions, and fitting a normal distribution.
- The posterior distribution:
  - (b) is based on combining the elicited prior with the observed ITT results.
  - (c) is based on combining an informative prior with the observed ITT results.

The probabilities quoted are based on results of analysis in winBUGS.
Kaplan-Meier survival: PLUTO

• RCT data trend towards improved perinatal survival with shunting but with an increased risk of pregnancy loss. In RCT, the *as treated analysis* demonstrated that VAS improved perinatal survival to 60% as compared to no intervention (19%, p=0.03).

• At 2 years of age only 2 babies of 7 (28%) survivors post-VAS were alive with no renal impairment. (Morris et al, Lancet. 2013;382(9903):1496-506)

Conclusion

• LUTO amenable to treatment is a rare condition
• PLUTO trial closed early due to poor recruitment:
  - Rare condition
  - Patients opting for TOP (53.4%)
  - Clinicians not in equipoise
• Preliminary results:
  - Observational and RCT data trend towards improved perinatal survival with shunting but with an increased risk of pregnancy loss
  - Evidence for improvement of renal function is inconclusive but at 2 years of age only 2 babies of 7 (28%) survivors post-VAS were alive with no renal impairment (1 shunt, 1 cons.)
• Future:
  - Long term FU to determine infant mortality and morbidity
  - Economic analysis with decision analytic modeling with long term data

Acknowledgments

• PLUTO Collaborative Group
• HTA and Wellbeing of Women
• The women and babies who agreed to take part in our research

Results (A) – characteristics randomised v registry

Elected conservative more likely to be later gestation p=0.004
Elected conservative more likely to have a normal liquor volume p=0.92
Qualitative Research

- **Aim:**
  - To gain an insight into the experiences of pregnant women approached to take part in PLUTO
- **Sample:**
  - Purposeful sample of six women
- **Methods:**
  - Semi-structured interviews analysed using a phenomenological interpretive and thematic approach
- **Findings:**
  - Data saturation was not achieved hence further interviews will be undertaken
  - Four themes have been identified so far:
    - Antenatal diagnosis
    - Participation in the study
    - Emotional impact of diagnosis
    - Sources of Support

Economic Evaluation

- **Within study analysis:**
  - No QALY as no consensus re methodology in children
  - Outcome expressed as ‘Cost per additional disability free life year gained’
  - Patient specific resource use and costs
- **Model based analysis:**
  - Will allow projection of costs and benefits beyond trial follow up period
  - Data from the epidemiology study and systematic review of shunt outcome studies will provide additional data to inform the model

Bayesian priors

Results (B) – Survival to 28 days – gestational age at diagnosis
**Results (C) – Survival to 28 days liquor volume at diagnosis**

<table>
<thead>
<tr>
<th>Prognostic feature</th>
<th>Allocated to shunt n=16</th>
<th>Outcome</th>
<th>Allocated to conservative n=15</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age at diagnosis &lt; 24 weeks</td>
<td>13/16 (81.3%)</td>
<td>8/13 (61.5%)</td>
<td>14/15 (93.3%)</td>
<td>11/14 (78.6%)</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>4/13 (30.8%)</td>
<td>7/13 (53.8%)</td>
<td>14/15 (93.3%)</td>
<td>12/14 (85.7%)</td>
</tr>
<tr>
<td>Survival to 28 days with CRF</td>
<td>4/5 (80%)</td>
<td>1/5 (20%)</td>
<td>3/3 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>Survival to 28 days and well</td>
<td>1/5 (20%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gestational age at diagnosis ≥ 24 weeks</td>
<td>3/16 (18.8%)</td>
<td>2/3 (66.7%)</td>
<td>1/15 (6.7%)</td>
<td>1/1 (100%)</td>
</tr>
<tr>
<td>Alive at 28 days</td>
<td>2/3 (66.7%)</td>
<td>1/1 (100%)</td>
<td>1/1 (100%)</td>
<td>1/1 (100%)</td>
</tr>
<tr>
<td>Survival to 28 days with normal renal function</td>
<td>1/2 (50%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Poor prognosis for pulmonary hypoplasia at randomisation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>3 NND, TOP, alive and well at 28 days</td>
<td>5</td>
<td>4 NND, TOP, alive and well at 28 days</td>
<td>5</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 NND due to PH, IUD at 16 weeks, 3 alive and well at 28 days</td>
<td>2</td>
<td>1 NND due to PH, IUD, 2 alive and well at 28 days</td>
<td>2</td>
</tr>
<tr>
<td>Mild</td>
<td>6 4 alive at 28 days, 2 TOP 6</td>
<td>2</td>
<td>2 alive at 28 days, 1 NND due to PH, I IUD, 2 TOP</td>
<td>2</td>
</tr>
<tr>
<td>Antenatal progression of poor prognosis for pulmonary hypoplasia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsening of prognosis to high</td>
<td>5</td>
<td>1 TOP, 2 NND due to PH, 2 alive at 28 days</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Improvement in prognosis high to moderate</td>
<td>2 Alive at 28 days</td>
<td>2 Alive at 28 days</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Poor prognosis for renal function at randomisation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>4 2 CRF at 6-8 weeks, 2 alive and well at 1 year</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>1 CRF at 28 days, peritoneal dialysis, died at 10 months</td>
<td>2</td>
<td>2 CRF at 1 year awaiting transplant at 2 years; CRF at 28 days died at 7 weeks</td>
<td>2</td>
</tr>
<tr>
<td>Mild</td>
<td>3 1 alive and well at 2 years, 1 CRF at 2 years, 1 CRF at 28 days</td>
<td>1</td>
<td>1 CRF at 28 days</td>
<td>1</td>
</tr>
</tbody>
</table>

**Antenatal progression of poor prognosis for renal function in survivors**

| Worsening moderate to high | 1 CRF with persistent albumin at 24 hrs | 1 CRF at 21 days | 1 CRF at 1 year |
| Improvement in prognosis high to moderate | 1 | 1 CRF at 21 days | 1 CRF at 1 year |