

Potential risk factors for the development of acute renal failure in preterm newborn infants: a case-control study

L Cataldi, R Leone, U Moretti, B De Mitri, V Fanos, L Ruggeri, G Sabatino, F Torcasio, V Zanardo, G Attardo, F Riccobene, C Martano, D Benini, L Cuzzolin

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Aims: To determine in a case-control study possible associations between the development of acute renal failure in preterm newborns and therapeutic interventions, particularly drug treatments.

Methods: The study population was 172 preterm infants of <38 weeks gestation; 71 had acute renal failure and 101 were controls closely matched for gestational age and birth weight. Maternal and neonatal information was collected for both groups through questionnaires and interviews. Routine data on renal variables were also collected. Univariate and multivariate logistic regression analyses were performed.

Results: Very low birthweight infants were at high risk of acute renal failure (79% of cases were <1500 g). However, the acute renal failure was transient. Mothers of infants with acute renal failure received more drugs during pregnancy and delivery (mainly antibiotics and non-steroidal anti-inflammatory drugs). Of the possible therapeutic interventions, intubation, catheterisation, and phototherapy were mainly applied to case subjects. A low Apgar score and patent ductus arteriosus were diagnosed in a greater percentage of neonates with acute renal failure. Moreover, in the first few days of life and before diagnosis of acute renal failure, case subjects received more drugs (antibiotics, non-steroidal anti-inflammatory drugs, and diuretics) and for a longer time. In the multivariate logistic analysis, medullary hyperechogenicity (odds ratio (OR) 4.491; 95% confidence interval (CI) 1.879 to 10.731) and ceftazidime administration (OR 5.082; 95% CI 1.493 to 17.297) were associated with a greater risk of acute renal failure.

Conclusions: The results suggest the need for careful monitoring of very low birthweight infants and attention to drug treatments, as it is difficult to differentiate between normality and renal failure in the first few days of life.

See end of article for authors' affiliations

Correspondence to:
Dr Cuzzolin, Department of Medicine and Public Health, Section of Pharmacology, University of Verona, Policlinico GB Rossi, Piazzale LA Scuro, 37134 Verona, Italy; laura.cuzzolin@univr.it

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Over the past 20 years, rates of survival of very low birthweight infants have increased because of improved technical and pharmacological interventions.¹ However, these treatments have contributed to an increase in the number of patients experiencing renal impairment, mainly acute renal failure (ARF), caused by the physiological and haemodynamic stressors imposed by the hostile extrauterine environment. In such cases, clinical conditions include a low Apgar score, sepsis, therapeutic interventions, and various nephrotoxic drugs.² Data in the literature on the incidence of ARF are extremely variable, mainly because of differences in the criteria used to define the disease, and range from 8%³ to 24%⁴ of all admissions to neonatal intensive care units (NICUs). Most of these conditions are transient and disappear after correction of the underlying derangement or disease, and Italian studies^{5,6} report similar values to those of Stapleton and coworkers.³ The main causes of ARF in the neonate are pre-renal mechanisms including hypovolaemia, hypotension, and hypoxaemia (more than 80% of cases). Intrinsic renal and post-renal failure are much rarer conditions (about 11% and 3% respectively).⁴

To investigate possible associations between a number of common therapeutic interventions, particularly drug treatments, and the risk of ARF in preterm newborns, we performed a case-control study among babies admitted to NICUs of several major hospitals in Italy over a period of three years. We used the standard method⁷ of selecting patients on the basis of their disease status (in our case preterm newborns with ARF) and comparing them with controls similar in all relevant ways except the disease. This is

particularly suitable in our situation in which prematurity itself is a condition predisposing to ARF.

METHODS

Study population

The study population was preterm newborn infants of <38 weeks gestation receiving care in the NICU of one of seven Italian hospitals after approval of the ethics committees. Medical care in all NICUs was provided by neonatologists working under similar policies and in accordance with common practices. Neonates were enrolled after written informed consent had been obtained from their parents: eligible newborn infants with major congenital anomalies were excluded from the study.

From March 2000 to March 2003, potential cases of ARF were identified as the presence of high serum creatinine concentrations after the 60th hour of life (values of ≥ 114.92 and ≥ 88.40 $\mu\text{mol/l}$ were considered pathological in patients of <33 weeks and ≥ 33 weeks respectively) with or without oliguria (urine output <1 ml/kg/h) which may be absent in the first days of drug induced renal damage.⁸ Serum creatinine concentrations in the first two days of life were ignored as they reflect maternal values,⁹ whereas later persistent elevation of serum creatinine concentration is widely accepted as a diagnostic criterion of ARF.⁸ The first day on which the serum creatinine concentration was considered pathological was defined as the index date.

Abbreviations: ARF, acute renal failure; NICU, neonatal intensive care unit; PDA, patent ductus arteriosus

Table 1 Baseline characteristics of the study groups

Variable	Cases (n = 71)	Controls (n = 101)	p Value
Male	39 (55%)	62 (61%)	0.491
Gestational age (weeks)	27.83 (3.63)	28.89 (3.67)	NS
<25 weeks	12 (17%)	11 (11%)	0.361
25–28 weeks	34 (48%)	42 (42%)	0.507
29–32 weeks	14 (20%)	27 (27%)	0.378
>32 weeks	11 (15%)	20 (20%)	0.601
Birth weight (g)	1115.98 (572.36)	1275.55 (626.63)	NS
<800 g	25 (35%)	24 (24%)	0.143
800–1500 g	31 (44%)	44 (44%)	0.886
1500–2000 g	6 (8%)	16 (16%)	0.231
>2000 g	9 (13%)	16 (16%)	0.719
SGA	9 (13%)	14 (14%)	0.998
Apgar score			
1st min	4.59 (2.66)	5.12 (2.21)	NS
5th min	7.03 (1.84)	7.28 (1.79)	NS

Values are mean (SD) or number (%).

SGA, Small for gestational age (below the tenth centile).

Matching of controls (two neonates for each case) was subsequently performed according to the following criteria: same sex as the case, with a birth weight within 100 g of the case and a gestational age within one week of the case. Information on controls was taken into account at the same day interval from birth to the index date of the matched case.

Data collection

Data were collected through detailed questionnaires especially designed for the study, including information on newborns and mothers, and entered into a computerised relational database (Microsoft Access).

Basic information, biological data, clinical outcomes diagnosed or suspected, and all therapeutic interventions (particularly drugs administered) were recorded for each newborn.

Mothers were interviewed by a trained doctor within a few days of the delivery. The study was explained and an information pamphlet was provided. They were then given time to decide whether or not to participate. Mothers who could not be interviewed in hospital were contacted by phone. Women were asked about previous obstetric history, their pregnancy, and intrapartum risk factors (including

drugs administered). Information was also collected about sociodemographic variables and any family history of acute and chronic diseases, in particular those related to renal function.

Renal function

To test renal function during the observational period, serum creatinine concentrations, blood urea nitrogen and urine output of each patient were measured and recorded every two to three days throughout the first month of life. Oliguria was established on the basis of urine volumes measured over a period of 24 hours. In addition, all newborns had renal sonography examinations to evaluate the size, structure, and echogenicity of the kidneys.

Statistical analysis

The research was designed and analysed as a case-control study. Statistical analysis was performed using the Statistical Package for Social Sciences for Windows (SPSS Inc, Chicago, Illinois, USA).

Univariate analysis was performed to identify differences between the case and the control groups using Student's *t* test (continuous data) or the χ^2 test (categorical variables) as

Table 2 Maternal characteristics: information about pregnancy and delivery

Variable	Cases (n = 71)	Controls (n = 101)	p Value
Age	31.03 (5.64)	31.92 (4.73)	NS
Renal pathologies before pregnancy	10 (14%)	7 (7%)	0.198
Renal pathologies during pregnancy	4 (6%)	9 (9%)	0.612
Primiparity	23 (32%)	36 (36%)	0.780
Smoking during pregnancy	8 (11%)	6 (6%)	0.330
Alcohol during pregnancy	17 (24%)	17 (17%)	0.338
Pre-eclampsia	8 (11%)	21 (21%)	0.159
Premature rupture of membranes	22 (31%)	20 (20%)	0.133
Maternal fever	12 (18%)	8 (8%)	0.117
Caesarean section	53 (75%)	66 (65%)	0.257
Fetal problems	31 (44%)	27 (27%)	0.032
Maternal problems	22 (31%)	39 (39%)	0.386
Twins	18 (25%)	14 (14%)	0.088
Drugs during pregnancy	53 (75%)	62 (62%)	0.039
Antibiotics	23 (32%)	13 (13%)	0.004
NSAIDs	25 (37%)	19 (19%)	0.013
Steroids	22 (31%)	25 (25%)	0.466
Drugs during delivery	60 (84%)	68 (68%)	0.018
Antibiotics	21 (30%)	14 (14%)	0.020
Steroids	3 (4%)	3 (3%)	0.984

Values are mean (SD) or number (%).

NSAID, Non-steroidal anti-inflammatory drug.

Table 3 Therapeutic interventions, diagnosed diseases, and drug treatments before onset of acute renal failure

	Cases (n = 71)	Controls (n = 101)	p Value
Endotracheal intubation	60 (85%)	70 (69%)	0.035
At birth	46 (65%)	47 (46%)	0.027
Subsequently	14 (20%)	23 (23%)	0.771
Percutaneous venous catheter	40 (56%)	36 (36%)	0.011
Duration of use (days)	18.02 (16.00)	17.61 (15.57)	NS
Umbilical artery catheter	57 (80%)	81 (80%)	0.856
Duration of use (days)	7.58 (4.39)	6.26 (2.51)	0.013
Central venous catheter	13 (18%)	21 (21%)	0.835
Duration of use (days)	14.69 (11.25)	21.28 (11.26)	<0.001
Meconium stained amniotic fluid	16 (23%)	9 (9%)	0.023
Hyperbilirubinaemia	60 (85%)	80 (79%)	0.496
Phototherapy	59 (83%)	68 (68%)	0.032
Low Apgar score	30 (42%)	27 (27%)	0.049
Respiratory distress syndrome	63 (89%)	83 (82%)	0.334
Mechanical ventilation			
Frequency	58 (82%)	73 (72%)	0.213
Length (days)	13.38 (15.07)	13.99 (16.07)	NS
Oxygen supplementation	8 (11%)	1 (1%)	0.008
Surfactant requirement	52 (73%)	61 (60%)	0.113
Patent ductus arteriosus	31 (44%)	28 (28%)	0.049
Sepsis	16 (23%)	18 (18%)	0.569

Values are mean (SD) or number (%).

appropriate: statistical significance was defined as $p \leq 0.05$. Odds ratio (OR) and 95% confidence interval (CI) were calculated for each 2×2 table. Variables that the univariate analysis showed to be significant were entered into a stepwise logistic regression model.

RESULTS

The study population included 81 consecutive cases of ARF (mainly identified on the third or fourth day of life) in preterm infants in NICUs. Six subjects were excluded from the study because of difficulty collecting information about the mothers. The parents of four newborns refused to participate. The control group consisted of 101 rather than 142 newborn infants, because it was not always possible, according to our criteria, to locate a second control for cases of low gestational age (<25 weeks).

As reported in table 1, the mean gestational age and birth weight of our 71 preterm infants with ARF were 27.83 (3.63) weeks and 1115.98 (572.36) g respectively. Very low birthweight infants (birth weight <1500 g) made up 79% (56/71) of the neonates. In addition to gestational age and birth weight, cases and controls were comparable with regard

to Apgar scores, baseline mean highest (51.14 (12.54) v 50.98 (10.51) mm Hg) and lowest (28.62 (10.04) v 28.42 (8.68) mm Hg) blood pressure and respiratory variables (FiO_2 49.59 (24.80) v 47.89 (22.48)%; Pao_2 55.72 (22.50) v 61.06 (22.38) mm Hg; $Paco_2$ 43.21 (10.13) v 43.76 (9.81) mm Hg), observed at the beginning of pharmacological treatments in the cases and on the same postnatal days in the controls.

The results of the univariate analysis show the differences between cases and controls (tables 2–5) and the relative OR with 95% CI (table 6).

The data on pregnancy and delivery (table 2) show some significant differences between mothers of case subjects and controls in relation to drugs administered during pregnancy (antibiotics and NSAIDs) and delivery (antibiotics).

Therapeutic interventions such as endotracheal intubation at birth, catheterisation, phototherapy, and oxygen supplementation were more often applied to case subjects than controls. Moreover, a low Apgar score and patent ductus arteriosus (PDA) were diagnosed in a significantly greater percentage of preterm infants with ARF (table 3). Significant differences were also observed in relation to presence of meconium stained amniotic fluid between cases and controls.

Table 4 Drugs administered to premature newborns in the first days of life (before diagnosis of acute renal failure)

	Cases (n = 71)	Controls (n = 101)	p Value
Antibiotics	61 (86%)	87 (86%)	0.856
Aminoglycosides	50 (70%)	80 (79%)	0.254
Duration of use (days)	6.35 (3.82)	6.46 (4.33)	NS
Penicillins	55 (77%)	79 (79%)	0.877
Duration of use (days)	7.09 (3.19)	7.63 (3.90)	NS
Cephalosporins	14 (19%)	5 (5%)	0.001
Duration of use (days)	8.51 (3.99)	7.20 (3.20)	0.018
Glycopeptides	2 (2.8%)	4 (4%)	0.984
Duration of use (days)	10.50 (7.78)	17.50 (9.33)	<0.001
Macrolides	5 (7%)	7 (7%)	0.783
Duration of use (days)	5.60 (0.89)	4.60 (1.34)	<0.001
Ibuprofen	22 (31%)	17 (17%)	0.046
Furosemide	17 (24%)	11 (11%)	0.038
Dopamine	41 (58%)	62 (62%)	0.576

Values are mean (SD) or number (%).

Table 5 Renal outcome

Variable	Cases (n = 71)	Controls (n = 101)
Oliguria (urine output < 1 ml/kg/h)	6 (8%)	1 (1%)
Blood urea nitrogen (mmol/l)		
Day 2	7.18 (5.56)	4.03 (2.68)***
Day 4	8.92 (6.93)	3.86 (2.40)***
Day 7	9.04 (8.23)	3.48 (2.41)***
Day 10	7.05 (6.12)	3.64 (2.70)***
Day 14	4.42 (4.54)	2.62 (2.64)***
Day 21	4.14 (4.63)	2.81 (2.80)*
Day 28	2.51 (2.70)	1.91 (2.26)
Serum creatinine (µmol/l)		
Day 2	129.95 (37.13)	79.56 (17.68)***
Day 4	143.21 (39.78)	73.37 (20.33)***
Day 7	137.91 (45.08)	68.95 (19.45)***
Day 10	113.15 (37.13)	66.30 (17.68)***
Day 14	92.82 (35.36)	60.99 (17.68)***
Day 21	81.33 (32.71)	57.46 (22.98)***
Day 28	65.42 (30.94)	47.74 (18.56)***

Values are mean (SD) or number (%).
*p < 0.05, ***p < 0.001 compared with cases (Student's *t* test).

If we consider drugs administered to our preterm infants in the first days of life—that is, before diagnosis of ARF (table 4)—cases received more drugs (cephalosporins, ibuprofen, and furosemide) often given in association and, in some situations, for a longer period of time. Single antibiotics, such as ceftazidime and ampicillin, were more often administered to case subjects.

Regarding the renal function tests shown in table 5, a greater percentage of oliguria (8% *v* 1%) and significantly higher blood urea nitrogen concentrations were observed in cases than controls. Moreover, significantly higher levels of serum creatinine were persistent in cases throughout the first month of life. The other routine biochemical and haematological variables showed no significant differences between the two study groups.

Kidneys were within the normal range for size and shape. Compared with controls, a significantly higher percentage of preterm infants of the case group showed medullary hyperechogenicity (25% (18/71) *v* 5% (5/101); $\chi^2 = 13.271$, *p* < 0.001). A similar percentage of neonates with a mild urinary tract dilatation (pyelectasis) was observed in the two groups (7% (5/71) *v* 5% (5/101)).

Rates of survival at one month were divergent in the two groups, with an 11% mortality in the case group compared with a 2% mortality in the control group. The most common causes of death were overwhelming sepsis (six cases) and necrotising enterocolitis (two cases).

Table 6 Univariate analysis of neonatal course

	OR	95% CI
Drugs during pregnancy	1.998	1.016 to 3.930
Antibiotics	2.299	1.043 to 5.069
NSAIDs	2.346	1.168 to 4.710
Drugs during delivery	2.647	1.231 to 5.692
Antibiotics	2.610	1.220 to 5.583
Endotracheal intubation	2.114	1.132 to 3.948
Percutaneous catheter	2.433	1.305 to 4.536
Phototherapy	2.386	1.130 to 5.037
Low Apgar score	2.005	1.052 to 3.822
Drugs given to the newborns		
Ceftazidime	4.716	1.614 to 13.782
Ampicillin	2.156	1.143 to 4.069
Ibuprofen	2.218	1.075 to 4.578
Furosemide	2.576	1.123 to 5.907
Medullary hyperechogenicity	4.360	1.919 to 9.906

NSAID, Non-steroidal anti-inflammatory drug.

The multivariate logistic regression analysis included all variables with *p* < 0.05 observed in the univariate analysis (drugs given to the mothers during pregnancy and the delivery, endotracheal intubation, percutaneous catheter, phototherapy, low Apgar score, drugs given to the newborns, medullary hyperechogenicity). Table 7 shows the results. Ceftazidime administration (OR 5.082; 95% CI 1.493 to 17.297) and medullary hyperechogenicity (OR 4.491; 95% CI 1.879 to 10.731) were associated with a greater risk of ARF, whereas for the other variables (low Apgar score, ampicillin, ibuprofen) the risk was lower.

DISCUSSION

Few data are available on ARF in the neonatal period, particularly with regard to preterm infants with a low gestational age. It is also difficult to compare information because of differences in the populations examined and the criteria used to estimate renal function.

This is the first study in which case and control subjects were closely matched for gestational age and birth weight, minimising the confounding effects of these factors. Moreover, with our study it has been possible to quantify all risk factors involved in ARF development in a population of preterm newborns on the basis of multiple sources of information, including maternal interviews. Previous studies have generally lacked a comparison group or maternal information^{10 11} which may be important for elucidating other possible risks such as prenatal drugs.

From the analysis of the non-clinical characteristics of our premature infants, it emerges that a very low birthweight infant is at specific risk of ARF (79% of our case subjects weighed < 1500 g at birth), and this may explain the

Table 7 Results of multivariate logistic regression analysis of risk factors for development of acute renal failure

Variable	OR	95% CI
Low Apgar score	2.143	1.065 to 4.313
Medullary hyperechogenicity	4.491	1.879 to 10.731
Ampicillin	2.368	1.098 to 5.104
Ceftazidime	5.082	1.493 to 17.297
Ibuprofen	2.885	1.229 to 6.775

problems that we encountered in identifying matched controls with the same characteristics as the case subjects but without renal problems, as also reported by Ojala *et al.*¹² It also confirms that prematurity must be considered one of the main risk factors for ARF development.⁴

ARF was usually transient. In most cases, serum creatinine concentrations progressively decreased to normal over the first 14 days of life (93%), persisting at high levels in only five cases (7%) after one month. In these five patients, concentrations had returned to normal in the 2nd month of life. These data seem to confirm the pre-renal origin of ARF⁴ related to drugs, therapeutic interventions, or diseases which cause hypoperfusion of functioning kidneys. The condition is reversible in parallel with the resolution of the underlying problems or the suspension of certain treatments.

The ecographic data revealed no differences in the percentage of subjects with pyelectasis (a urinary tract dilatation rarely considered pathological and usually not requiring any particular therapeutic measure¹³), whereas a significantly higher percentage of cases showed medullary hyperechogenicity, generally considered an index of aspecific renal stress.

Analysis of information related to the mothers revealed distinct patterns of risk for certain antepartum and intrapartum variables. Case status was associated with drugs taken by the mothers during pregnancy (NSAIDs, antibiotics) or delivery (antibiotics), confirming the influence of maternal pharmacological treatments on the fetus or newborn. Several cases of severe and sometimes irreversible renal insufficiency have been described in neonates after prenatal exposure to NSAIDs.^{14–16} As far as antibiotics are concerned, it is known that β lactams and aminoglycosides cross the placenta, and adverse renal effects have been observed in newborn animals.^{17–18}

If we examine the therapeutic interventions applied to our preterm infants, intubation and catheterisation have also previously been indicated as risk factors for ARF development.² In particular, the placement of arterial and venous catheters and duration of their use were found to be risk factors correlated with renal abnormalities.¹² Phototherapy remains the standard treatment of hyperbilirubinaemia in newborns,¹⁹ even though hydration status should be monitored. It has been reported that this practice may cause renal problems in the newborn.²

As expected, a significant correlation was observed between ARF development and the presence of a low Apgar score and PDA. Although the data available in the literature on low Apgar scores are conflicting, our results are in agreement with those of Gouyon and Guignard,²⁰ who reported a clear relation between renal problems and the presence of a low Apgar score. In the case of PDA diagnosis, its association with ARF development may be due to the disease itself, but also to its treatment. In fact, a severe PDA causes hypovolaemia, predisposing the newborn to renal problems.² Moreover, during significant left to right shunting through the open ductus, circulatory failure and large aortic run-off lead to a decreased renal perfusion with subsequent stimulation of the renin-angiotensin system. Thus renal perfusion becomes dependent on the release of vasodilating prostaglandins. Consequently, administration of NSAIDs results in decreased renal perfusion and urine output.²¹

Respiratory distress syndrome is considered one of the main causes of pre-renal failure, as it reduces glomerular filtration rate and renal plasma flow.⁴ The percentage of respiratory distress syndrome was not significantly different between our two groups. Rather, we observed a significant difference between cases and controls with regard to the severity of the disease, accounted for by the greater percentage of treatments and complications observed in

neonates with ARF. This correlates well with the fact that an effect of respiratory distress syndrome on renal function in neonates is the inability to maintain adequate adjustment of circulatory and respiratory functions.⁴

Finally, drug toxicity is involved in 50% of ARF cases in preterm infants,²² determining both intrinsic and pre-renal failure from vasoconstriction. As confirmed by our data, this is particularly true for NSAIDs and diuretics. These drugs, often used in premature newborns in the treatment of PDA and in fluid/electrolyte management respectively, can directly affect renal function. Their mechanism of action implies inhibition of vasodilating prostaglandins and stimulation of the vasoconstricting renin-angiotensin system.^{12–23–24}

In many NICUs, antibiotics are often prescribed in the first days of life to prevent or cure early and late onset sepsis caused by maternal infections or invasive devices such as central catheter positioning or endotracheal intubation, and contrasting data exist on their nephrotoxicity.^{10–25–26} In our neonates with ARF, we found a significantly greater use of ceftazidime and ampicillin, whereas aminoglycosides and glycopeptides (potentially nephrotoxic) were administered in a similar manner to both case subjects and controls. Another factor to be considered in our cases was the longer duration of cephalosporin treatment, even in the presence of negative cultures, despite international recommendations that treatments should be prolonged in the presence of proven infection.²⁷

The multivariate analysis confirmed the association between some drugs (particularly ceftazidime, but also ibuprofen) and ARF development in very low birthweight infants with a predisposing situation of aspecific renal stress such as medullary hyperechogenicity. The low glomerular filtration rate of the neonatal kidney, sufficient for growth under normal conditions, limits the postnatal renal functional adaptation to endogenous and exogenous stress. Such stress may take the form, in our case subjects, of a low Apgar score and exposure to drugs. This condition becomes even more problematic when these factors occur in combination.

Data on survival of preterm infants are extremely variable, depending mainly on gestational age and birth weight of the subjects and the period of observation. In our study, the observed percentages are comparable to the results of other studies in Western countries.^{28–29} However, attention should be paid to the different survival rates observed in our two groups. Even though the causes of death were various, renal problems and risk factors evident in this study may also have contributed to the lower percentage survival of our case subjects. Therefore, even though ARF is usually reversible in these subjects, as also confirmed by our data, attention should be paid to preterm newborns who experience a slight increase in serum creatinine. Careful monitoring is necessary, as this condition is not rare in NICUs, and the line between normality and ARF is very thin in the first days of life. Given that long term studies do not exist and renal insufficiency may amplify other common diseases observed in preterm infants, it is important, in our opinion, to underline the multifactorial origin of ARF, as some risk factors such as a low Apgar score cannot be prevented, whereas iatrogenic effects from drug treatments could be avoided.³⁰

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What is already known on this topic

- Acute renal failure in the newborn is a common problem mainly due to hypoxic ischaemic injury and/or toxic insults, but few data are available because of the difficulty of comparing information
- Such alterations in renal function are often reversible and recovery is highly dependent on the underlying causes and prompt and correct therapeutic intervention.

What this study adds

- This case-control study, by using multiple sources of information including maternal data, shows a multifactorial origin of acute renal failure in the newborn
- The multivariate logistic regression analysis underlines that some risk factors observed in our preterm neonates, such as iatrogenic effects from drug treatments, could be avoided

Authors' affiliations

L Cataldi, Department of Pediatrics, University of Sacred Heart, Rome, Italy

R Leone, U Moretti, L Cuzzolin, Department of Medicine and Public Health, Section of Pharmacology and Clinical Pharmacology Unit, University of Verona, Verona, Italy

B De Mitri, Pediatric Division, Section of Neonatal Intensive Care Unit, A Di Summa Hospital, Brindisi, Italy

V Fanos, L Ruggeri, Department of Pediatrics and Clinical Medicine, Section of Neonatal Intensive Care Unit, University of Cagliari, Cagliari, Italy

G Sabatino, Neonatal Intensive Care Unit, University G D'Annunzio, Chieti, Italy

F Torcasio, Neonatal Intensive Care Unit, Niguarda Ca' Granda Hospital, Milano, Italy

V Zanardo, Pediatric Division, University of Padova, Padova, Italy

G Attardo, Neonatal Unit, Civic Hospital, Palermo, Italy

F Riccobene, Neonatology Division, Neonatal Intensive Care Unit, S Camillo Hospital, Roma, Italy

C Martano, Neonatal Pathology Division, University of Torino, Torino, Italy

D Benini, Pediatric Division, Negrar Hospital, Verona, Italy

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