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Original article

Renal failure in the neonate associated with in utero exposure to non-steroidal anti-inflammatory agents

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Abstract. In utero exposure to non-steroidal anti-inflammatory agents (NSAIAs) can produce combinations of oligohydramnios, a bleeding diathesis, ileal perforation, premature closure of the ductus, and acute or chronic renal injury. NSAIAs induce renal dysgenesis in fetal monkeys and renal structural abnormalities in the developing human fetus. We report oligohydramnios and renal failure associated with in utero exposure to early, prolonged, high-dose indomethacin in four neonates, and to ibuprofen in one neonate. Four of the affected neonates were one of twins. In each set of twins, only one of the pair was affected. One set of twins was proven to be identical, whereas the other three sets seemed to be identical. It is possible that the histopathological findings of uncertain or incomplete tubular differentiation may be the result of a direct effect of NSAIAs on developing or "immature" tubules. Therefore, the advantages of NSAIAs as tocolytics need to be weighed against the complication of severe renal injury.

Key words: Renal failure – Fetus and neonate – Indomethacin

Introduction

Prostaglandin synthetase inhibitors are used as tocolytics to treat premature labor or polyhydramnios. They cross the placenta and can attain high levels in the fetal circulation. Indications for treatment with indomethacin are refractory premature labor caused by polyhydramnios, uterine fibroids, or multiple gestation. When indomethacin is given in large doses for weeks to months to prevent spontaneous labor, there is usually no apparent fetal damage [1]. However, acute renal failure is reported in neonates exposed in utero to indomethacin for more than 48 h [1–3]. Additional complications are premature narrowing of the ductus arteriosus, oligohydramnios, hydrops fetalis, ileal perforation, bleeding, persistent neonatal pulmonary hypertension, and stillbirth [2–5]. We have reported oligohydramnios, bleeding, renal insufficiency, renal tubular dysfunction, and renal dysgenesis in one of identical twins born after prolonged in utero exposure to large doses of indomethacin [6]. The same association has been reported in six neonates from Europe [7] and in one from The United States [8]. The purpose of this report is to describe our observations in four additional neonates. It is our impression that non-steroidal anti-inflammatory agents (NSAIAs) may cause a renal embryopathy syndrome that includes severe renal injury.

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Case reports

The five patients are summarized in Table 1.

Case 1

A 37-year-old G4,P1,Ab2 woman had polyhydramnios affecting both fetuses at 16 weeks' gestation. Despite treatment with 150 mg of indomethacin/day from 22 weeks, the amniotic fluid volume increased. The dose of indomethacin was increased to 300 mg/day and terbutaline was added to treat premature uterine contractions. Polyhydramnios resolved by 26 weeks' gestation, at which time the fetal kidneys appeared normal by ultrasonography. The dose of indomethacin was decreased and then discontinued at 32 weeks because of oligohydramnios in both twins. Delivery was by cesarean section at 36 weeks. Twin A weighed 2,310 g with Apgar scores of 7 at 1 min and 8 at 5 min; twin B weighed 2,075 g and her Apgar scores were 8 at 1 min and 9 at 5 min. Twin A had no complications. The twins were monochorionic and diamniotic. They were subsequently shown to have identical major blood groups, were rhesus positive, had identical HLA typing for A and D loci, and were identical according to DAN fingerprinting.

Bilateral flank masses were palpated on admission of twin B (case 1) to a neonatal intensive care unit for mild respiratory distress. From day 5 she had gross hematuria, hypertension, and non-oliguric renal failure with a maximum serum creatinine concentration of 6.5 mg/dl. Electrolyte derangements included: hyperkalemia (serum potassium 8.3 mEq/1), metabolic acidosis (serum bicarbonate 19 mEq/1), and

Table 1. In utero exposure to non-steroidal anti-inflammatory agents (NSAIAs)

	Case 1	Case 2	Case 3	Case 4	Case 5
Twin/singleton	Twin	Singleton	Twin	Twin	Twin
Onset of NSAIA	22 weeks	24 weeks	21 weeks	25 weeks	21 weeks
Indomethacin	150–300 mg/day for 16 weeks	100 mg/day for 12 weeks	100 mg/day for 11 weeks	200 mg/day for 2 days, ibuprofen 2,400 mg/day for 4 weeks	50–200 mg/day for 11 weeks
Birth	36 weeks	32 weeks	32 weeks	30 weeks	32 weeks
Birth weights Singleton		2.773 kg			
Affected twin	2.075 kg		1.490 kg	1.68 kg	1.54 kg
Unaffected twin	2.301 kg		1.930 kg	0.955 kg	2.246 kg
Apgar 1 min	8	3	6	4	7
5 min	9	8	5	7	5
Problems at birth	Flank masses, mild respiratory distress, hematuria, hypertension, non-oliguric renal failure, coagulopathy	Acute renal failure	Respiratory distress, hypotension, hypoglycemia, renal failure	Respiratory distress, renal failure, hypothyroidism	Respiratory distress, renal failure
Peak serum creatinine	6.5 mg/dl	2.3 mg/dl	3.5 mg/dl		3.4 mg/dl

hyponatremia (serum sodium 128 mEq/1). Renal sodium wasting (fractional excretion of sodium of 13%) was demonstrated in the presence of a serum sodium concentration of 126 mEq/1. She also had a transient, severe coagulopathy with spontaneous bleeding from venepuncture sites that could not be controlled by exerting pressure. The coagulopathy was not well characterized because the baby was exsanguinating. It was treated with blood transfusion, fresh plasma, cryoprecipitate, and 1-Desamino-8-arginine vasopressin. Ultrasonography revealed that both kidneys were large with increased echogenicity and poor corticomedullary differentiation. A percutaneous kidney biopsy was performed on day 9. A liver biopsy specimen taken the same day was normal. Over the subsequent 4 years her renal function gradually improved and remained stable with serum creatinine levels of 1.5–1.8 mg/dl, until the age of 6 years when the serum creatinine concentration increased rapidly. She was started on chronic peritoneal dialysis at age 6 years.

Case 2

A 28-year-old G3,P2 white female, pregnant with a single fetus, developed polyhydramnios and premature uterine contractions at 24 weeks' gestation. She was treated with 100 mg of indomethacin and 30 mg of terbutaline/day. Amniocentesis was performed 25 times to remove excess fluid. The infant was born at 32 weeks' gestation by a normal spontaneous delivery. Birth weight was 2,773 g and Apgar scores were 3 at 1 min and 8 at 5 min. The neonate was admitted to an intensive care unit because of severe abdominal distention and non-oliguric renal failure. She required multiple surgical procedures and long-term central alimentation for treatment of a severe congenital secretory diarrhea [9]. The serum creatinine concentration peaked at 2.3 mg/dl and gradually decreased to normal values. A renal sonogram demonstrated increased echotexture.

Case 3

A G1,P0 woman aged 39 years had an ultrasound examination at 13 weeks for an amniocentesis to exclude genetic disorders. Twin pregnancy was suspected. At 16 weeks polyhydramnios was detected in the larger twin and oligohydramnios was noted in the smaller twin. Treatment was started at 21 weeks with indomethacin in a dose of 100 mg/day and continued throughout pregnancy. Gestational diabetes was treated with insulin. Several therapeutic amniocenteses were performed to remove fluid from the larger twin with polyhydramnios. Premature uterine contractions began after an amniocentesis at 28 weeks and treatment was started with terbutaline. At 32 weeks a cesarean section was performed because fetal monitoring indicated heart rate variability in the smaller baby.

Twin A, a premature male, weighed 1,930 g; Apgar scores were 2 at 1 min and 1 at 5 min. He was intubated in the delivery room because of pallor and poor respiratory effort. Physical examination revealed a hyperdynamic precordium, a heart murmur, and an S3 gallop. Both kidneys were palpable, the left larger than the right. Blood pressure was 54/23 mmHg and the initial hematocrit was 40.7%. The hospital course was complicated by transient respiratory distress and hypoglycemia. A cardiac echocardiogram revealed tricuspid regurgitation and dilated ventricles. An abdominal ultrasound examination showed left hydronephrosis and a hypertrophied bladder wall. A voiding cystourethrogram was normal. His respiratory, status improved and he was discharged from hospital. At 9 months he was thriving and had no evidence of renal dysfunction.

Twin B (case 3), a male, weighed 1,490 g and had Apgar scores of 6 at 1 min and 5 at 5 min. Physical examination was normal. The blood pressure was 32/18 mmHg and the hematocrit was 45.9%. The hospital course was complicated by respiratory distress, hypotension, hypoglycemia, and renal insufficiency. The initial blood urea nitrogen was 27 mg/dl, the serum creatinine was 1.5 mg/dl, sodium 129 mEq/1, and potassium 7.9 mEq/1. He was treated with peritoneal dialysis for oliguria, generalized anasarca, and cardiopulmonary failure. Examination of the kidneys by renal ultrasonography showed increased echogenicity. A renal biopsy was not performed.

He was treated with peritoneal dialysis for 3 months. Although the serum creatinine initially stabilized at 3.5 mg/dl, renal function gradually deteriorated and he received a renal allograft from his father at 20 months of age.

Case 4

A G4,P1 mother aged 32 years developed premature uterine contractions at 25 weeks. Antenatal ultrasonography demonstrated polyhydramnios in one fetal sac and oligohydramnios in the other. The

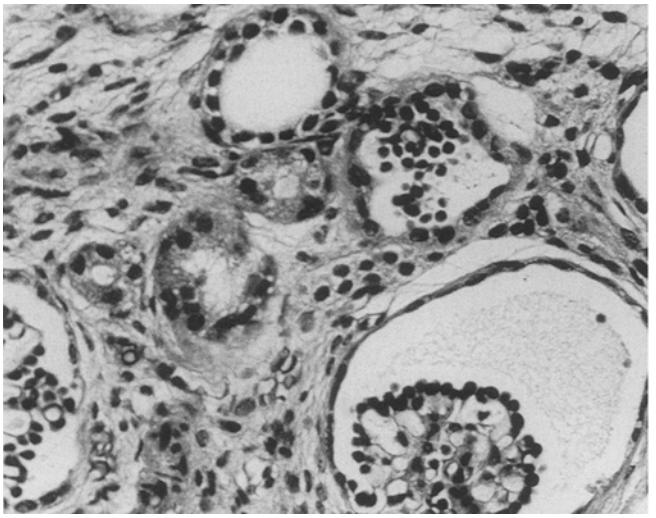

Fig. 1. Renal biopsy specimen from case 2 (hematoxylin and eosin, ×375). Note small glomerulus with glomerular cyst. The proximal tubules have no brush borders. There is an increase in the interstitium

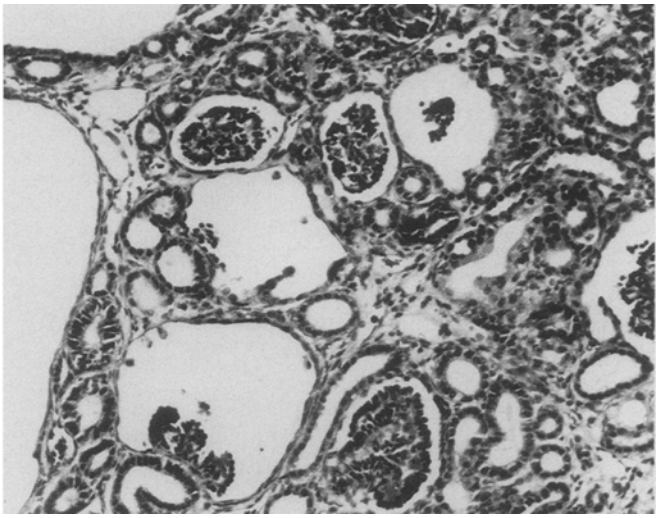

Fig. 2. Renal biopsy from case 1 (hematoxylin and eosin, ×200). There are glomerular cysts with normal-sized and rudimentary glomeruli. Some tubules are dilated and lined with poorly differentiated epithelium

mother was treated with indomethacin in a dose of 200 mg/day for 2 days. Indomethacin was discontinued because she developed hematuria. She was then treated with ibuprofen in a dose of 2,400 mg/day from week 26 until delivery by cesarean section at week 30. During the month before delivery she underwent seven amniocenteses to remove fluid from the polyhydramniotic sac. Twin A weighed 1,680 g with Apgar scores of 3 at 1 min and 8 at 5 min, and twin B weighed 955 g with Apgar scores of 4 at 1 min and 7 at 5 min. There were two amnions and one chorion.

Twin A, who occupied the polyhydramniotic sac, was admitted to the intensive care unit because of plethora, cyanosis, and poor respiratory efforts. His blood pressure was increased to 123/61 mmHg. The hospital course was complicated by congestive heart failure with poor cardiac function and a transient coagulopathy. He also had acute non-oliguric renal failure, mild proteinuria, and microscopic hematuria. Examination of the kidneys by ultrasonography showed that the echotexture was normal but that they were at the upper limit of normal for size. By the time of discharge the serum creatinine concentration was 0.4 mg/dl.

Twin B (case 4) was also admitted to the intensive care unit after delivery. He had severe respiratory distress treated with mechanical ventilation, acute renal failure, and hypothyroidism. He was anuric for the 1st week and required peritoneal dialysis. An isotope scan failed to reveal renal uptake. Increased echogenicity of the kidneys was noted by ultrasonography. He died 3 weeks after birth from severe respiratory failure while on peritoneal dialysis.

Case 5

A G4,P2 woman aged 21 years was evaluated at 21 weeks' gestation for premature uterine contractions during the course of a twin pregnancy. An antenatal ultrasonogram revealed polyhydramnios in one of the fetal sacs and adequate fluid in the other sac. She was treated with indomethacin (50 mg/day) at 21 weeks' gestation and the dose was increased to 200 mg/day by 26 weeks. Three amniocenteses were performed to remove fluid from the polyhydramniotic sac. The twin boys were delivered at 32 weeks by cesarean section. Twin A weighed 1,540 g with Apgar scores of 7 at 1 min and 5 at 5 min and twin B weighed 2,246 g and had Apgar scores of 1 at 1 min and 8 at 5 min. Twin B's neonatal course was uncomplicated. An ultrasound examination showed mild dilatation of both collecting systems, a voiding cystourethrogram revealed a thick bladder wall but no ureteric reflux, and a renal isotope scan was normal.

Twin A (case 5) was admitted to the intensive care unit with respiratory distress and was ventilated mechanically for a week. He had non-oliguric renal failure with a peak serum creatinine concentration of 3.4 mg/dl. A ultrasonogram examination showed increased echogenicity of both kidneys. There was poor uptake and excretion of isotope on the renal scan. He did not require dialysis. The serum creatinine concentration was 1.4 mg/dl at 3 months.

Histopathological examination

Two biopsy specimens (cases 1 and 2) and one autopsy specimen (case 4) were available for examination. Sections were stained with hematoxylin and eosin and with periodic acid-Schiff. Tubular differentiation in all specimens was abnormal in that most tubules were lined with cells not characterizable as either proximal or distal. The epithelial cells in some tubules contained abundant granular or vacuolated eosinophilic cytoplasm, but brush borders were only focally present (Fig. 1). Tubular cells in case 4 were columnar, considerably taller and thinner than normal proximal tubular cells, and they contained crowded, darkly stained, basilar nuclei. Distal tubules were specifically identified only in relation to the macula densa. Increased interstitium, with fibrosis and apparent edema, was also present in cases 1 and 4. The glomeruli seemed smaller than normal, and almost all of them were covered by cuboidal or peg-shaped podocytes crowded together on the surfaces of the capillary segments. Many glomerular cysts were present in case 1 (Fig. 2), and a few were noted in case 2 (Fig. 1). Blood vessels seemed slightly more prominent than normal, with mild medial thickening. Inflammation was not present.

Discussion

In a previous more detailed report of our index case (case 1) [6] we used the term renal dysgenesis. However, the use

of this term may best be restricted to a condition first described by Allanson et al. [10] in which there is autosomal recessive inheritance of renal tubular dysgenesis with absent proximal tubules and late onset of oligohydramnios [11]. Our index case had a constellation of findings that had not previously been described: bilateral renal enlargement, reduced glomerular filtration rate, hypertension, hyponatremia, hyperkalemia, metabolic acidosis, renal salt wasting, and a coagulopathy. In addition, she had chronic renal histological changes that were induced prenatally and subsequently had moderate chronic renal failure. We speculated that these findings may have been the result of exposure, while in utero, to large doses of indomethacin. Further support for this hypothesis came from studies in fetal monkeys in which similar changes were induced by maternal administration of indomethacin [12]. Pregnant rhesus monkeys treated with indomethacin for more than 48 h developed oligohydramnios and oliguria, and incomplete nephrogenesis occurred in the fetal monkeys [12]. We also suggested that indomethacin may have reduced umbilical artery blood flow to the affected twin, but could not offer an explanation for the occurrence of renal injury in only one of the twins.

Gubler et al. [7] presented additional information on six infants whose mothers were treated with NSAIAs during pregnancy. The renal histological changes were remarkably similar to those reported in our index case. Furthermore, three of the affected infants were from twin pregnancies. In each case the other twin had no apparent renal disease. Therefore, we are now aware of 13 infants ([8]; Drut et al., personal communication) in whom administration of a NSAIA during pregnancy caused acute renal insufficiency in neonates, and subsequent death or chronic renal insufficiency in infancy.

Prostaglandin inhibitors can reduce renal blood flow and glomerular filtraton rate, cause sodium and water retention and hyperkalemia, and reduce urine output in the fetus [13, 14], and, rarely, transient renal failure in neonates [15]. However, short-term studies have failed to demonstrate changes in renal blood flow in fetuses exposed to indomethacin [16]. The exact cause of the renal injury is unknown, but may depend on gestational age, doses, and duration of treatment. The histopathological abnormality consisted principally of altered differentiation, with a loss of histological features that characterized tubules as proximal or distal. There was variable tubular and glomerular dilatation and interstitial fibrosis. These histopathological findings of uncertain or incomplete tubular differentiation suggest that NSAIAs may have a direct effect on developing or "immature" tubules. It is also possible that the pathological changes may have resulted from decreased renal blood flow, because similar abnormalities have been found in the kidneys of babies exposed to angiotensin converting enzyme inhibitors in utero [17].

Because the half-life of indomethacin is longer in premature infants than in adults [18, 19], it is possible that a fetus may be exposed to higher concentrations for a prolonged period when the mother is given indomethacin several times a day. Clearly other factors are important because only one baby in each twin pair was affected. However, it is possible that monozygotic fetuses may be affected differently by environmental insults, and nonidentical twins are affected discordantly by indomethacin [5]. Twins seem to be affected more often than singletons, and although prematurity and polyhydramnios are more common in twins, this cannot be the entire explanation because premature singletons account for a larger percentage of premature births than do twins. It is possible that umbilical and therefore renal blood flow is not equal in all twins and that this accounts for increased delivery of indomethacin to the twin who initially has greater blood flow than its sibling.

In our first report we considered the possibility that indomethacin had not caused the adverse affects. It has also been suggested that the renal abnormalities reported in our index case occurred as a result of twin-to-twin transfusion [20]. We did not dispute the possibility that there was twin-to-twin transfusion but had no evidence that this occurred. Furthermore, it is difficult to explain the development of acute renal failure, a tubulopathy, hypertension, the severe coagulopathy, and chronic renal failure in twins and singletons on the basis of twin-to-twin transfusion [21]. And yet, because the pathogenesis of apparent NSAIA-induced renal injury has not been elucidated clearly and beyond doubt, we believe that it is important to continue to document examples of this phenomenon. We have also included case 2, who clearly has the other confounding variable of polyhydramnios caused by a secretory diarrhea [9]. We are aware of the importance of not confounding association with causation [22] and realize that careful epidemiological studies must be performed before indomethacin can be implicated unequivocally in the pathogenesis of the renal injury that we and Gubler et al. [7] have observed.

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Literature abstracts

Nephron (1994) 66: 219–224

Focal glomerular sclerosis and nephrotic syndrome in spondyloepiphyseal dysplasia

Radovan Bogdanović, Pravdoljub Komar, Angelina Cvorić, Vesna Nikolić, Miodrag Sinotić, Dragan Zdravković, Miloš Ognjanović, and Mario Abinun

The association of a spondyloepiphyseal dysplasia and disproportionate short stature with focal glomerular sclerosis is reported in two girls. Renal disease manifested by proteinuria at the age of 2.5 and 11 years, leading to treatment-resistant nephrotic syndrome over 15 and 45 months, respectively. One patient went into end-stage renal failure shortly after nephrotic syndrome developed, the other died from sepsis. The association of spondyloepiphyseal dysplasia and focal glomerular sclerosis with nephrotic syndrome may represent a distinct disease entity.

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Childhood-onset systemic lupus erythematosus: antiphospholipid antibodies in 37 patients and their first-degree relatives

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Objective. Antiphospholipid antibodies (aPL) are noted with increased frequency in patients with systemic lupus erythematosus (SLE). The main manifestations found to be associated with aPL are arterial and venous thrombotic events, thrombocytopenia, and recurrent pregnancy loss. This study is an attempt to define the incidence of aPL in patients with childhood-onset SLE and in their relatives and to correlate their presence with clinical manifestations, and especially, to evaluate the risk of thrombosis in aPL-positive subjects.

Methodology. We studied 37 unrelated patients and 107 of their first-degree relatives. VDRL, IgG and IgM anticardiolipin, and IgG antiphosphatidylethanolamine antibodies were studied in all probands during periods of clinical remission and in first-degree relatives at the time of interview. Lupus anticoagulant had only been studied in probands during an SLE flare-up.

Results. Thirty-eight percent of probands and 19% of relatives were positive for at least one aPL, with little overlap between the different aPL studied. – No aPL-negative proband developed thrombosis. Two of the aPL-positive probands had thrombotic events before testing, and a third one showed thrombosis after testing. Only two probands had high levels of IgG aCL and showed thrombosis. The occurrence of aPL positivity in relatives was not always related to its presence in probands. None of the aPL-positive relatives had had thrombosis, but recurrent fetal loss was noted in one aPL-positive mother with SLE. Although there was a high frequency of SLE, SLE-like disease, auto-immune disorders or positive serological findings for lupus in first-degree relatives, many of these relatives did not test positive for aPL.

Conclusion. The high levels of IgG aCL may be considered a risk factor for thrombosis. Findings in relatives suggest a multifactorial origin for autoimmune disease and antibody production.