# RENAL TRACT ANOMALIES IN THE HUMAN FETUS

## PRENATAL ULTRASOUND AND GENETIC ASPECTS

# AFWIJKINGEN VAN DE NIEREN EN URINEWEGEN BIJ DE HUMANE FOETUS

## PRENATALE ECHODIAGNOSTIEK EN GENETISCHE ASPECTEN

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR
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*Aan mijn ouders*
*Aan de ouders van deze kinderen*

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# Contents

Chapter 1

# Introduction to the prenatal diagnosis of fetal urinary tract malformations; definition of the study objectives.

With the advent of high-resolution real-time ultrasound scanners, the ability to image various organ systems in utero has greatly improved. This is particularly so for the urinary tract. The fetal kidneys can be visualised by transabdominal ultrasound as early as 9 to 12 weeks of gestation (Green et al.,1988). The fetal kidneys grow rapidly throughout gestation, and measurements of normal size as a function of gestational age have been established (Grannum et al.,1980; Lawson et al.,1982). The fetal bladder generally can not been seen until the 10th week of gestation, and by 12 weeks the bladder can be identified in 50 percent of cases (Green et al.,1988). Serial measurements of fetal urinary bladder volume allows calculation of hourly fetal urinary production rates (HFUPR) (Campbell et al.,1973; Wladimiroff and Campbell, 1974). Whereas HFUPR increases eight-fold during the last 15 weeks of normal gestation (van Otterloo, 1977; Wladimiroff 1978), reduced HFUPR values were established in intrauterine growth retardation due to impaired placental perfusion (Wladimiroff and Campbell, 1974; Deutinger et al.,1987).

Although there are situations in which the ultrasonographer is alerted to the possible presence of a urinary tract malformation because of a positive family history or a clinical suspicion of oligohydramnios, most urinary tract malformations are incidental findings. A reliable ultrasound diagnosis can only be obtained after investigation of both kidneys, the bladder, the amount of amniotic fluid and a careful search for non-renal defects.

The overall incidence of urinary tract malformations, excluding hypospadias, is about 3 per 1000 births (Leck et al., 1968). Renal tract anomalies account for a considerable number of prenatal anomalies discovered by ultrasound. Recently, in a prospective population study the incidence of structural renal tract abnormalities detected prenatally by ultrasound has been documented to be 0.65 per cent (Livera et al., 1989).

In our department, which is a level 3 referral centre, in the period from 1984 till 1988 a total of 469 fetal structural defects was detected prenatally by ultrasound (table 1), 26% of which had an abnormality of renal origin (renal agenesis, cystic kidney disease or obstructive uropathy). Multiple fetal structural anomalies (consisting of structural anomalies of two or more different organ systems per fetus) were present in another 15% of the total number of affected cases. In 21 of these 71 cases (29.5%) the kidneys were involved.

Table 1 Association of ultrasonically detected fetal structural defects and chromosome abnormalities (1.1.84 - 1.1.88)

| | US diagnosis | Abnormal karyotype | |
|---|---|---|---|
| Neural tube defect | 82 | 3 | (3.6%) |
| Hydrocephaly | 38 | 3 | (7.9%) |
| Multiple congenital abnormalities | 71 | 17 | (32.9%) |
| Obstructive uropathy | 67 | 2 | (3.0%) |
| Cystic kidney(s) | 34 | 1 | (2.9%) |
| Cardiac defects | 31 | 7 | (22.6%) |
| Cystic hygroma | 25 | 11 | (44.0%) |
| Bilateral renal agenesis | 23 | 1 | (4.3%) |
| Skeletal anomalies | 19 | | |
| Abdominal wall defect | 18 | | |
| Gastro-intestinal obstruction | 12 | 2 | (16.6%) |
| Diaphragmatic hernia | 5 | 1 | (20.0%) |
| Miscellaneous* | 54 | | |
| total | 469 | 48 | (10.3%) |

* hydrops, hydrothorax, teratoma, abdominal cyst, lung malformation, conjoined twins, ascites.

Two groups of pregnant women are referred to our department. The first group is the 'high-risk'group where a corresponding anomaly has been diagnosed in a previous child or a positive family history of a congenital urinary tract malformation is present. The recurrence risk may vary from very small up to 50%. The ultrasonographer has to be aware of the heterogeneity and the variability in time of onset of the abnormality. Early detection or exclusion is demanded by the couple at risk. In case of recurrence of a lethal anomaly, termination of the pregnancy can be offered. The legal, ethical and psychosocial aspects of such a decision are of great importance but a discussion of these is outside the scope of this thesis. Early exclusion of a recurrence will have a positive impact on the course of the pregnancy. It is of major importance to inform parents about the limitations of the ultrasound diagnosis. Due to possible late onset of abnormal development, some anomalies are only reliably detectable in late pregnancy. This may cause difficulties since termination of pregnancy is not feasible. Adjustment of obstetric management is the only possible option.

The second group of referrals comprises pregnancies referred because a structural anomaly was detected by ultrasound following obstetric complications or at routine examination. Here, detection is usually late in gestation. The value of ultrasound in this second group of patients is the impact of the diagnosis on further obstetric management.

After prenatal ultrasound diagnosis a few options are possible depending on the gestational age. In each individual case obstetric management has to be discussed by a multidisciplinary team consisting of an ultrasonographer, obs-

tetrician, neonatologist, geneticist and pediatric urologist. In case of a lethal malformation, termination of pregnancy or surgical abstention depending on the gestational age, is the usual policy. In malformations compatible with life, obstetric management is generally restricted to reconsidering time, mode or location of delivery.

The most significant anomaly of the urinary system is bilateral renal agenesis, which is incompatible with extra-uterine life. Diagnostic problems may arise due to severe oligohydramnios rendering optimal imaging virtually impossible. From an obstetric point of view this particular group of fetuses is important to identify since not infrequently an unnecessary caesarian section is performed because of dysmaturity, intrapartum fetal distress or malpresentation. The creation of an artificial amniotic fluid compartiment by instillation of fluid has been propagated to improve ultrasound imaging (Gembruch and Hansmann, 1988). Another technique for differentiating between fetal and placental causes of growth retardation, particularly in oligohydramnios, is the recording of bloodflow velocity waveforms in umbilical and fetal arteries (Wladimiroff et al.,1985).

A second category of urinary tract malformations is cystic kidney disease. Prenatal ultrasound diagnosis has been reported for several types of polycystic kidney disease. Autosomal Recessive Polycystic Kidney Disease (ARPKD) can only be identified prenatally by ultrasound in severely affected cases (Hobbins et al.,1979; Reilly et al.,1979). In Autosomal Dominant Polycystic Kidney Disease (ADPKD) early manifestation detectable by ultrasound in fetal or neonatal life is very rare (Shokeir, 1978; Zerres et al.,1985). In case of other types of cystic kidney disease prenatal ultrasound diagnosis is usually possible, but attention should also be focused on associated anomalies, chromosomal and metabolic studies in order to confirm or rule out genetic syndromes.

A third category of urinary tract malformations are the obstructive uropathies, suspected because of the detection of a dilated urinary tract. In the past few years, much attention has been focused on this group of fetuses in particular. In utero decompression was introduced for cases in which a bladder outlet obstruction was diagnosed. This was carried out either by open surgical diversion (Harrison et al.,1982) or by the ultrasound guided insertion of a suprapubic vesicoamniotic catheter (Berkowitz et al.,1982; Golbus et al.,1982; Rodeck and Nicolaides,1983). How the results of these decompression techniques should be interpreted is still a matter of controversy. Moreover, before in utero drainage is considered as being of any therapeutic value, questions relating to efficacy and safety still remain to be answered.

## 1.1 Objectives of the present study.

In this thesis, attention will be focused on:(i) ultrasonic imaging of normal and abnormal fetal urinary tract anatomy;(ii) the reduced diagnostic potential of ultrasound in oligohydramnios, including methods to circumvent this problem; (iii) the association of renal tract malformations and extrarenal and chromosomal anomalies which may have a decisive impact on obstetric management.

The objectives of the present study were:

a. to define the role of ultrasound in the prenatal diagnosis of fetal urinary tract malformations, with particular reference to bilateral renal agenesis, cystic kidney disease and obstructive uropathy;
b. to document the incidence and nature of associated extra-renal and chromosome anomalies;
c. to assess perinatal outcome following prenatal diagnosis of a fetal urinary tract malformation;
d. to establish the possibilities and limitations of prenatal ultrasound scanning in pregnancies at risk for a particular renal tract malformation;
e. to determine the potential of intra-uterine diversion techniques in obstructive uropathy.

Chapter 2.

# Development, anatomy and function of the fetal urinary tract.

*'The more complicated an organ in its development, the more subject it is to maldevelopment, and in this respect the kidney outranks most other organs'.*

(E.L.Potter, 1972)

## 2.1 Developmental aspects of the kidneys and urinary tract.

*Normal development.*

The kidneys and urinary tract arise from the intermediate mesoderm (kidneys and ureters) and the cloaca (urinary bladder and urethra).

Two sets of primitive kidneys (pronephros and mesonephros) develop in the human embryo and degenerate before the third eventual set, the metanephros appears. The metanephros, which persists throughout life, develops from the ureteral bud (= metanephric bud) and the metanephrogenic blastema. The ureteral bud, derived from the mesonephric (Wolffian) duct, grows towards the metanephros and induces differentiation of the nephrogenic blastema into renal parenchyma. The terminal and actively growing end of the ureteral bud, known as the ampulla, will undergo multiple divisions and induce the development of nephrons and establish communication with them. The ureteral bud gives rise to the renal pelvis, calyces, papillae, and collecting tubules, whereas the metanephric blastema gives origin to the nephron (glomeruli, proximal and distal convoluted tubules and Henle's loop).

The microdissection technique was introduced by Peter (1927), who first studied and described kidney development. Also Oliver (1962) and Osathanondh and Potter (1963) based their work on kidney development and cystic kidneys on this microdissection technique.

*Pronephros.*

The pronephros becomes first visible in the beginning of the 4th gestational gestational week, lying bilaterally between the coelom and the ventrolateral border of the somites. Medial vesicular and lateral tubular portions can be distinguished and before the end of the 4th week seven to ten pairs of vesicles and tubules can be recognised in the cervical area between the level of the fourth and the fourteenth somites. In man the earliest pronephric tubules begin to degenerate before the last appear.

*Mesonephros.*

Vesicles (glomeruli) and lateral tubules continue to be formed caudal to the pronephros and to be attached to the mesonephric (Wolffian) ducts, which are an elongation of the pronephric ducts. The mesonephric ducts reach the cloaca by the end of the fourth week. Tubules appear and develop caudally, whereas tubules degenerate in the more cephalic region resulting in a maximum of about 30 - 32 pairs of tubules. The group of glomeruli, tubules and connecting ducts present on each side of the body represent the mesonephros.

In the female the mesonephric duct will disappear and remnants may be found as epoöphoron, paraoöphoron and Gartner's duct or cysts. In the male the mesonephric duct will form the ductus deferens and the opening of the mesonephric duct will become the opening into the prostatic urethra of the ejaculatory duct.

A second longitudinal duct soon develops immediately lateral to the mesonephric duct. This is the paramesonephric or Müllerian duct which is particularly important in the female. The whole complex of mesonephros and the two ducts separates itself to some extent from the dorsal body wall so that it is suspended from the latter by a mesentery, the urogenital mesentery.

*Metanephros.*

The metanephros or final kidney develops by the simultaneous differentiation of the ureteral bud, which appears near the lower end of each mesonephric duct during the fifth week of gestation and the metanephrogenic tissue into which it grows. Soon after its appearance, the terminal end of the bud (ampulla) quickly starts with dichotomous division. Four stages of ampullar development can be recognized.

a) First stage of ampullar development.

The ampulla forms the ureter, renal pelvis, the calyces and papillae. Independent of dichotomous division, the ampullae induce the formation of nephrons in the eighth week of gestation. The initial nephrons appear as first generation collecting tubules, which represent the calices minores at a later stage. The first three to five generations of branches arising from the dichotomous division of the ampulla, eventually expand to produce the renal pelvis. The next three to five generations of branches form the calices and papillae and the succeeding seven to eight produce the collecting tubules. During the first induction of nephrons by the ampulla, initially two, but later only one are formed. Nephron induction is only possible from a newly formed ampulla. Dichotomous division of the ampulla leads to the formation of two new ampullae. Nephrons attached to the ampulla migrate alongside the elongating ampulla towards the renal capsula. This explains why the end of the first stage of ampullar activity is characterized by attachment of all last generation nephrons to the collecting tubules with the

limited presence of nephrons in the medulla. The rate of ampullary division decreases when the fetus is 13 - 14 weeks old.

b) Second stage of ampullar development.

This occurs between approximately 14 and 22 weeks of gestation. It is characterized by nephron formation with only occasional ampullar division. Each nephron attaches to the ampulla by which it was induced. But when the next nephron induced by the ampulla also attaches, the connecting piece of the first nephron shifts. The new nephron then is attached to the connecting piece instead of directly to the ampulla. In this way a succession of nephrons attached to one another is produced with only the youngest attached directly to the ampulla. These arcades, consist of four to six nephrons.

c) Third stage of ampullar development.

This stage covers most of the second half of pregnancy (± 22 -36 weeks). Ampullar division has ceased, and only further nephron formation occurs as long as no other nephron is attached to the ampulla. A total of four to six new nephrons are thus produced and attached to the collecting tubules. By the end of the third stage approximately half of the about $1.10^6$ nephrons are directly attached to the collecting tubules.

d) Fourth stage of ampullar development

This phase, extending into adulthood, is characterized by interstitial growth of tubules and an increase in blood vessels and connective tissue. Elongation takes place in all nephrogenic tubules and collecting tubules. The metanephrogenic blastema has stromatogenic and nephrogenic potential. Alongside the nephrogenic tubules both nephrons and connecting tissue are formed. Metanephrogenic blastema may only differentiate into nephrons following contact with the ampulla. The upper section of the S-shaped structure of the initial nephron connects with the collecting tubule and develops into the connecting piece, distal convoluted tubule and loop of Henle. The middle section forms one part of the proximal convoluted tubule, one-third of the lower section will become the remaining part of the proximal convoluted tubule. The other two-third of the lowest section of the S-shaped structure of the initial nephron develops into the Malpighian corpuscle, consisting of glomerulus and Bowmans capsule.
When birth takes place before the full completement of glomeruli has developed, they continue to form until an approximately normal number exists. Once nephron induction is brought to halt, it is never resumed.

The metanephros is originally located in the fetal pelvis. Rapid growth of the caudal portion of the embryo results in displacement of the kidney cephalad until they reach their normal position in the lumbar fossae. The kidney also rotates 90 degrees so that the renal pelvis faces medially instead of forwards.

*Bladder and urethra*

During the fifth week, when the ureteric bud appears, the mesonephric duct is in communication with the allantois and cloaca. In the human embryo, during the sixth week, the cloaca will become divided into two parts by a urorectal septum. The urorectal septum grows caudally and reaches the cloacal membrane. The dorsal region forms part of the hindgut, the ventral part is primitive urogenital sinus. Similarly, the cloacal membrane becomes subdivided into an anterior urogenital membrane and a posterior anal membrane. The cloacal membrane separates the hindgut from the amniotic cavity and perforates at 7-8 weeks.

The bladder is mainly derived from the endodermal vesico-urethral canal and the lower end of the mesodermal mesonephric duct. The upper part of the bladder is derived from the allantois. The allantois is relatively small in the human embryo and it does not extend far into the extra-embryonic tissues. The allantois may contribute to the apex but the major part of the allantois regresses and becomes converted into a fibrous cord, the urachus, which passes from the apex of the bladder to the umbilicus.

The whole trigone of the bladder and the posterior wall of the urethra are mesodermal in origin. This portion of the urethra corresponds to the upper half of the prostatic urethra in the male and probably the whole urethra in the female. Complicated growth changes occur so that the ureters come to open into the definitive bladder while the mesonephric ducts open lower down into the pelvic part of the definitive urogenital sinus. The fetal ureters open into the bladder with disappearance of the membrane at the junction at 9 weeks.

## 2.2 Normal anatomy and renal function of the fetal urinary tract as studied by ultrasound

### 2.2.1 *Fetal urinary tract anatomy*

*Kidneys*

The fetal kidneys and adrenal glands can be imaged by transabdominal ultrasound as early as 9 weeks of gestation (Green et al.,1988) In a transverse section through the fetal abdomen the kidneys can be visualised as two circular structures on either side of the fetal spine. The average renal dimensions in the 9th gestational week are 4 by 3 mm and those of the adrenal glands are on average 1 mm larger in the same plane. In the longitudional section the kidneys appear as two bean-shaped structures in a typical paraspinal location. The kidneys are bounded by the adrenal glands, spleen, liver and bowel. A low contrast in acoustic impedance between these surrounding organs and the adrenal parenchyma may impede identifying the renal margin. As the kidneys enlarge, they become progressively easier to identify during the second and third trimester of pregnancy. At twelve weeks of gestation, fetal kidneys and adrenal glands can be visualised by abdominal ultrasound in virtually all cases under reasonable conditions with the use of high-resolution ultrasound equipment.

The ultrasonic appearance of the kidneys changes throughout pregnancy. At 9 weeks the renal tissue is echodense and gradually becoming less echogenic until after the eleventh week. This change is possibly due to the fluid production within the renal parenchyma resulting in a different acoustic impedance. Fetal urine production starts around the ninth to twelfth week of gestation. Usually the fetal adrenal glands can be identified as an echolucent structure with an extremely echodense cortex, localised on the cranial pole of the kidney.

In the first and early second trimester, the kidneys are usually generally homogeneous in appearance, except for the central collecting structures (fig.1). An echolucent, circular pelvis can often been seen surrounded by a focal area of echogenicity. As the kidney matures, the pyelo-calyceal system appears as an echo-poor structure. The capsule becomes more visible and the distinction between the pyramids and the cortex becomes apparent during the third trimester (Fig. 1). The renal arteries can be visualised with colour coded flow mapping techniques.

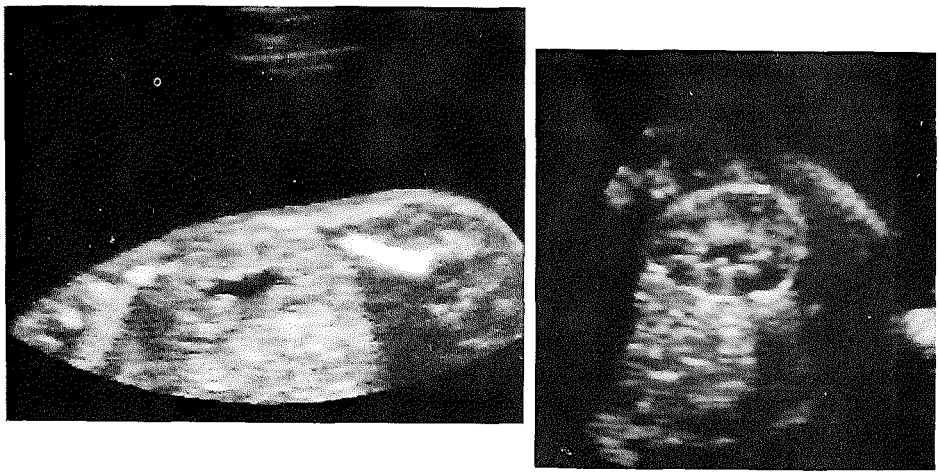

Fig. 1. Longitudinal view of a kidney in a fetus at a gestational age of 16 weeks (left) and 32 weeks (right).

*Fetal bladder*

The fetal bladder generally can not be visualised until the 10th week of gestation, but by 12 weeks the bladder can be identified in 50% of cases (Green et al.,1988). Changes in bladder size may frequently be observed during a sonographic examination, because the fetus empties its bladder every 30 to 45 minutes. The bladder wall is normally thin, but in the presence of obstruction it may undergo hyperthrophy.

*Fetal ureter*

At 30 weeks the diameter of the middle part of the fetal ureter is 1.5 mm and therefore normal ureters are rarely visible with ultrasound in the human fetus.

### 2.2.2 *Fetal renal biometry*

Different parameters have been investigated by several authors resulting in normal value curves relative to gestational age. The parameters studied include the following: kidney length, width, thickness, volume, kidney perimeter to abdominal perimeter ratio, kidney area to abdominal area ratio and the kidney circumference to abdominal circumference ratio.

All the above mentioned measurements are obtained in two different planes: First, a longitudional section of the fetus in a scan that is parallel to the long axis of the aorta. Secondly, a transverse section which is obtained at the level of the renal pelvis, if visible; otherwise it is obtained at the level where the transverse renal section is the largest.

For the first five parameters of renal size, normal data relative to gestational age are presented in Tables 1 and 2.

*Kidney length*

The kidney length is measured from the upper pole to the lower pole of the kidney in a longitudinal section.

Difficulties in measuring may be caused by uncertainty of end-points and a skewed-off axis image of the kidneys. Both will contribute significantly to measurement errors. The cranial pole may be difficult to define accurately, particularly in early gestation when the fetal adrenal glands and the fetal renal parenchyma have a very similar sonographic pattern. Later in gestation the cranial pole may become obscured by the echogenic shadow of the lower ribs. This may result in an apparent increased length of the kidney when the adrenal and kidney measurements are inadvertedly combined. Respiratory movements, when present, may be helpful to define the cleavage plane between kidneys and the surrounding organs.

Normal kidney length as a function of gestational age was originally established from 20 weeks of gestation onwards (Grannum et al.,1980; Bernaschek and Kratochwil, 1980; Lawson et al.,1981; Jeanty et al., 1982; Bertagnoli et al., 1983). These authors started their observations from the 20th week of gestation because of the slow kidney growth rate prior to that period (less than 1 mm on a diameter of 10 mm) and the problems of proper kidney boundary identification. Only Sagi et al.(1987) and Romero et al.(1988) described values from the 15th and 16th week of gestation onwards.

Table 1 Kidney perimeter to abdominal perimeter ratio

| Gestational Age (weeks) | Ratio(%) | Percentile | |
|---|---|---|---|
| | | 5th | 95th |
| <17 | 28 | 24 | 32 |
| 17-20 | 30 | 24 | 36 |
| 21-25 | 30 | 26 | 34 |
| 26-30 | 29 | 24 | 33 |
| 31-35 | 28 | 22 | 34 |
| 36-40 | 27 | 19 | 35 |

Reproduced from Jeanty, Romero: Obstetrical Ultrasound. New York, McGraw-Hill, 1983, p 146.

Table 2 Normal fetal kidney dimensions

| Gestational | Thickness (mm) | | | Width (mm) | | | Length (mm) | | | Volume ($cm^3$) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age (Weeks) | 5th | 50th | 95th | 5th | 50th | 95th | 5th | 50th | 95th | 5th | 50th | 95th |
| 16 | 2 | 6 | 10 | 5 | 10 | 13 | 7 | 13 | 18 | - | 0.4 | 2.6 |
| 17 | 3 | 7 | 11 | 6 | 10 | 14 | 10 | 15 | 20 | - | 0.6 | 2.8 |
| 18 | 4 | 8 | 12 | 6 | 10 | 14 | 12 | 17 | 22 | - | 0.7 | 2.9 |
| 19 | 5 | 9 | 13 | 7 | 10 | 14 | 14 | 19 | 24 | - | 0.9 | 3.1 |
| 20 | 6 | 10 | 13 | 7 | 11 | 15 | 15 | 21 | 26 | - | 1.1 | 3.3 |
| 21 | 6 | 10 | 14 | 8 | 12 | 15 | 17 | 22 | 28 | - | 1.4 | 3.6 |
| 22 | 7 | 11 | 15 | 8 | 12 | 16 | 19 | 24 | 29 | - | 1.7 | 3.9 |
| 23 | 8 | 12 | 16 | 9 | 13 | 17 | 21 | 26 | 31 | - | 2.1 | 4.3 |
| 24 | 9 | 13 | 17 | 10 | 14 | 18 | 22 | 28 | 33 | 0.3 | 2.5 | 4.7 |
| 25 | 10 | 14 | 18 | 11 | 15 | 19 | 24 | 29 | 34 | 0.8 | 3.0 | 5.2 |
| 26 | 11 | 15 | 19 | 12 | 16 | 19 | 25 | 31 | 36 | 1.3 | 3.5 | 5.7 |
| 27 | 11 | 15 | 19 | 12 | 16 | 20 | 27 | 32 | 37 | 1.9 | 4.1 | 6.3 |
| 28 | 12 | 16 | 20 | 13 | 17 | 21 | 28 | 33 | 38 | 2.5 | 4.7 | 6.9 |
| 29 | 13 | 17 | 21 | 14 | 18 | 22 | 29 | 35 | 40 | 3.2 | 5.4 | 7.6 |
| 30 | 14 | 18 | 22 | 15 | 19 | 23 | 31 | 36 | 41 | 3.9 | 6.1 | 8.3 |
| 31 | 14 | 18 | 22 | 16 | 20 | 24 | 32 | 37 | 42 | 4.6 | 6.8 | 9.0 |
| 32 | 15 | 19 | 23 | 17 | 20 | 24 | 33 | 38 | 43 | 5.4 | 7.5 | 9.7 |
| 33 | 16 | 20 | 23 | 17 | 21 | 25 | 34 | 39 | 44 | 6.1 | 8.3 | 10.5 |
| 34 | 16 | 20 | 24 | 18 | 22 | 26 | 35 | 40 | 45 | 6.8 | 9.0 | 11.2 |
| 35 | 17 | 21 | 25 | 18 | 22 | 26 | 35 | 41 | 46 | 7.4 | 9.6 | 11.8 |
| 36 | 17 | 21 | 25 | 19 | 23 | 27 | 36 | 41 | 47 | 8.1 | 10.2 | 12.4 |
| 37 | 18 | 22 | 26 | 19 | 23 | 27 | 37 | 42 | 47 | 8.6 | 10.8 | 13.0 |
| 38 | 18 | 22 | 26 | 19 | 23 | 27 | 37 | 43 | 48 | 9.0 | 11.2 | 13.4 |
| 39 | 19 | 23 | 27 | 19 | 23 | 27 | 38 | 43 | 48 | 9.4 | 11.6 | 13.8 |
| 40 | 19 | 23 | 27 | 19 | 23 | 27 | 38 | 44 | 49 | 9.6 | 11.8 | 14.0 |

(Reproduced with permission from the Publisher; data from Romero et al., 1989)

*Kidney width and thickness*

Kidney width and thickness are measured in a transverse section of the kidney from lateral to medial margin and anterior to posterior boundary respectively. Average renal dimensions in the 9th gestational week are 4 to 3 mm, in the 10th week 4 to 4 mm, in the 11th week 5 to 6 mm and in weeks 12 and 13, 6 to 7 mm (Green et al.,1988). Other curves have been established by Grannum et al., (1980); Bernaschek and Kratochwil, (1980); Lawson et al., (1981); Jeanty et al., (1982) and Bertagnoli et al., (1983).

*Kidney volume*

The kidney volume can be calculated using all three above mentioned parameters as follows:
kidney volume= length x width x thickness x 0.5233, whereby kidney size approximates that of an ellipsoid (Jeanty et al., 1982).

*Kidney size relative to abdominal size*

In a number of studies kidney size has been related to abdominal size; such as (i) the perimeter (width and thickness) to abdominal perimeter (antero-posterior + transverse diameter) ratio (Jeanty et al., 1982); (ii) kidney area to abdominal area ratio (Sato et al., 1985); (iii) kidney circumference to abdominal circumference ratio (Grannum et al.,1980).

In neonates ultrasonic examination of kidney length never revealed significant differences which were sex-related (Han and Babock,1985; Hangstvedt and Lundberg,1980; Fitzsimons, 1983). Significant discrepancies, however,between the length of the left and the right kidney were reported (Hangstvedt and Lundberg,1980; Fitzsimons, 1983; Rosenbaum et al., 1984) but could not be confirmed by other studies (Han and Babock,1985, de Vries and Levene, 1983). The slightly smaller size of the right kidney could be explained by the compressive effect of the liver. In the fetus no studies have been performed to compare difference in length between the sexes or between the left and right side.

*Pyelum*

At this time there is no available nomogram of renal pelvic size as a function of gestational age. Two criteria of renal pelvic measurements have been proposed:

1. Measurement of the antero-posterior diameter on a transverse cross-section of the fetal kidney. Renal pelvic diameters of less than 5 mm are normal, whereas those between 5 and 10 mm are normal in most instances but require follow up. In a study (Arger et al.,1985) of eight fetuses with a diameter above 10 mm of the renal pelvis, seven had an obstructive lesion at postnatal examination.
2. The ratio between the maximum transverse pelvic diameter and the renal diameter at the same level. Ratios above 50% would suggest hydronephrosis

(Grignon et al.,1986). However, diagnostic indices with this criterion are not available.

The measurement of the size of a pyelum can not be interpreted without relating this measurement to a normal value for the gestational age or the size of the kidney. A ratio reflects the relationship between size of the pyelum and size of the renal parenchyma. In our opinion, it is important to obtain information about possible dilatation of calyces, and whether the dilatation is mild, moderate or severe.

### 2.2.3 *Fetal urinary production*

Fetal urine is produced as soon as the first glomeruli assume a definitive form. Nephron induction starts in the 8th week and urine production starts around the 9th to 12th week. Osathanondh and Potter (1963) describe the presence of urine in the bladder of a fetus at a gestational age of 11 weeks.

Visualisation by ultrasound of fetal bladder filling and emptying was first described by Campbell in 1972 (Campbell, 1972), and a methodology was introduced for assessing fetal bladder volume and hourly fetal urinary production rate (HFUPR)(Campbell et al.1973). This method made it possible to study fetal urinary production.

Filling of the bladder occurs at a constant rate. The mean maximum bladder volume is 13.0 ml between 30 and 34 weeks, 25.4 ml between 34 and 38 weeks and 37.5 ml between 38 and 41 weeks of gestation. The minimum bladder volume varies from 1 to 5 ml. The duration of a complete bladder cycle varies from 50 to 155 minutes (Campbell et al., 1973). Similar data were later published by Kurjak et al. (1981). Circadian influences were observed in the term human fetus, with a significant decrease in bladder volume between 2400 and 0600 hours as compared to other times of the day (Chamberlain et al.,1984).

In the human the relatively low fetal glomerular filtration rate (GFR) does not appear to result in a low urine output. HFUPR is measured as an increase of bladder volume during 1 hour. In normal pregnancy a rapid increase in mean HFUPR can be observed from 3.3 to 27.4 ml between 25 and 40 weeks (Wladimiroff and Campbell, 1974). This is an absolute increase not factored for body weight. All measurements by Campbell were performed using compound B scanning. From recent reports it seems that HFUPR values are probably double the rate as reported before (Campbell, personal communication).

Between 40 and 42 weeks there appears to be a reduction in HFUPR (van Otterloo and Wladimiroff, 1977). This reduction may be explained by a reduction in GFR with concomitant unchanged tubular resorption (PTR) of water. GFR depends on the plasma flow through the glomerular capillaries, which is a result of systolic blood pressure, renal vascular resistance and hematocrit.

For a term fetus, weighing 3.5 kgs with an HFUPR value of 27.4 ml, urine production will be 7.8 ml /kg /hour. The transition for the fetus to neonatal life implies changes in renal function. In the normal term neonate, urinary production

depends on the fluid intake. On the first day of life the fluid intake will be 60 ml/kg/day resulting in a urine production of 10 ml/kg/day. For the same neonate of 3.5 kg this is 1.6 ml/kg/hour. On the seventh day of life, fluid intake is increased up to 150 ml/kg/day resulting in a urine production of 120 ml/kg/day. If the same infant still would weigh 3.5 kg, urine production will be 5 ml/kg/hour.

## 2.3 Closing remarks

Kidney growth progresses linearly throughout gestation and kidney size relative to the fetal abdomen remains constant. In general, the length of an organ should be related to body weigth or body length. For the fetus, normal values of the different parameters of kidney dimensions related to gestational age have been established. There is slight flattening of kidney growth at the end of gestation (Bernaschek and Kratochwil,1980).

Urine flow rate studies in the fetus are limited to calculation of changes in bladder dimensions by ultrasound, reflecting diuresis. Fetal urine production between 25 weeks and term measured by means of HFUPR shows an 8 fold increase.

Beyond 40 weeks of gestation the growth curve shows flattening and the HFUPR demonstrates a reduction. This can be explained by changes in vascular resistance of the feto-maternal unit. Under normal physiologic conditions the increase of vascular resistance of the term placenta causes a shift in distribution of circulating blood volume in the fetus. This redistribution probably will diminish the blood supply towards the fetal kidneys, resulting in a decreased of GFR. The GFR is influenced by the perfusion rate of the fetal kidneys and the tubular function does not seem to be affected. Also in cases of growth retardation due to placental insufficiency, the GFR is responsible for the reduction of HFUPR. Blood flow velocity waveform studies in the renal arteries using colour-coded Doppler may provide further information about the change in renal vascular restistance beyond term and in cases with severely impaired placental function. After birth, urine production depends on the fluid intake, and will increase from 1.6 ml/kg/hour on day one to 5 ml/kg/hour on day seven. Compared to the production in the term fetus of 7.8 ml/kg/hour, the transition to neonatal life implies a nearly 5 fold decrease on day one to an 1.5 fold decrease on day seven.

Chapter 3

# Abnormal development of the fetal urinary tract. Developmental and clinical aspects.

## Introductory remarks

Aspects of abnormal development of the fetal urinary tract will be presented in chapter 3.1. Chapter 3.2 will provide an introductory overview of the prenatal findings and fetal outcome in a first group of 239 pregnant women undergoing a scan in order to detect a fetal urinary tract anomaly at the Department of Obstetrics and Gynaecology, Dijkzigt hospital, Rotterdam, between January 1982 and December 1985. This is followed by an overview of the incidence and nature of chromosome anomalies in the presence of fetal structural malformations in general (Chapter 3.3).

## 3.1 Abnormal development.

The pathogenesis of renal congenital anomalies is poorly understood. The development of the kidney represents one of the few exceptions to the general embryologic rules that a gland that is connected to a hollow viscus by a duct, develops as an outgrowth from that viscus.

A kidney never develops in the absence of a ureter. The stimulus afforded by the presence of the ampulla (terminal end of the ureteral bud) is essential for the differentiation of the nephrogenic tissue into glomeruli and secretory tubules. Failure of induction because of an abnormal response of the metanephric blastema or because of a defective ampulla results in disorganised differentiation of the metanephric blastema. When a ureter is present, there is almost invariably some resemblance or development of kidney tissue. Glomeruli never develop in the absence of a ureter. The presence of a ureter does not automatically imply normal glomerular development.

A very early disturbance of development (usually before the 5th week of gestation) prevents the communication between ureteral bud and metanephric blastema and causes renal agenesis and secondary atrophy of the metanephric blastema. Disturbances in development occurring immediately after union of ureteral bud and metanephric blastema may result in the formation of dysplastic cystic kidneys. Renal cysts develop either through dilatation of Bowman's capsule or the convoluted tubules when they are of metanephric origin, or through dilatation of collecting tubules when of ureteric origin. Disturbances in later stages of development e.g. due to late obstruction cause dysplastic kidneys or hydronephrosis.

Heterogeneous causes have become identified as possible causes of derangement of normal renal development. The classical idea of 'timing of the insult' to be responsible for the type of anomaly has clarified some relations to normal embryonic development, but is not sufficient to assume an extraneous cause for a programming error at any fixed time for all types of abnormal renal development. Intrinsic (like genetic) causes might have identical effects. The heterogeneous causes of similar clinical types of renal tract disorders clearly examplify this point.

The mechanisms of the intricate pathways between genetically determined differentiation processes, their embryological manifestations, and contributing factors from genes and the environment have largely still to be understood. It is timely, however, to amplify the simplistic notion that renal (or other) malformations are brought about by 'an insult' at a certain embryological stage (leaving the embryologist free to hypothesize about the nature of the insult).

## 3.2 Antenatal diagnosis of renal tract anomalies by ultrasound

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### Abstract

A first group of 141 pregnant women carrying children at risk of a renal tract anomaly, because of a positive family history, was referred to our obstetrical ultrasound department. Prenatal ultrasound examination revealed an abnormality of the urinary tract in 8 %. A recurrence was observed under the following conditions: renal agenesis, cystic kidneys and urethral obstruction, but not in ureteral obstruction. In two children renal abnormalities were not detected until after birth, one child having an autosomal recessive and the other an autosomal dominant form of polycystic kidney disease. The large variation in the prenatal manifestation of cystic kidney disorders requires that predictions of possible recurrence on the basis of repeated ultrasound examinations should be made with great care. A second group of 98 pregnant women was referred because of a suspected renal abnormality found by ultrasound in the absence of a previous family history. In 64% a malformation of the urinary tract was confirmed (31 with obstructive uropathy and 32 with cystic kidneys). In almost half of the cases with subvesical obstruction or with cystic kidney disease a structural defect of extrarenal organs was present.

*Keywords* Prenatal ultrasound - Cystic kidney disease - Renal tract malformation

## Introduction

The potential of real-time ultrasound for the antenatal diagnosis of fetal structural defects is now well established. Accurate identification of fetal kidneys is possible in 90% of pregnancies by 16-17 weeks of gestation. Fetal urinary bladder filling can be visualized as early as 14-15 weeks.

This paper describes the possibilities and limitations of prenatal detection of renal tract anomalies by ultrasound in pregnancies which are known to be at risk because of a positive family history and in pregnancies referred for previously suspected renal malformations.

## Materials and methods

Between January 1982 and December 1985 a total of 2351 pregnancies was referred to our obstetrical ultrasound department for screening for fetal structural defects. A total of 239 pregnant women was examined in order to exclude or confirm the presence of renal tract anomalies in the fetus, and two groups were formed:

Group 1 (141 cases): Pregnancies at risk for fetal renal tract malformation because of a corresponding anomaly in a previous child or because of a positive family history of a congenital urinary tract malformation.

Group 2 (98 cases): Pregnancies in which a renal tract abnormality was suspected because of corresponding abnormal findings during ultrasound examination by the referring obstetrician.

All examinations were carried out using a mechanical sector scanner (Diasonics CardioVue, San Francisco, California) with a 5.0 mHz transducer and included measurements of kidney length, width and thickness. The values were plotted against normal curves for renal growth (Bertagnoli et al., 1983; Lawson et al., 1981; Jeanty et al., 1982).

The obstetric management of affected fetuses was guided by the following findings (Glick et al., 1985): gestational age at the time of diagnosis, the presence of non-renal structural defects or of a chromosomal abnormality; the effects on pulmonary function development and on fetal renal function. Whenever a renal tract anomaly was diagnosed we performed amniocentesis for fetal karyotyping as a matter of routine. When oligohydramnios was present (3 cases), fetal urine or ascites were used for chromosome analysis (Lenz et al., 1985). In two instances an artificial fluid compartment was created by intrauterine instillation of 150-200 ml of a 5% glucose solution, allowing better visualization of the fetal structures. In four cases of bladder outlet obstruction, direct assessment of renal function was attempted through fetal bladder needling for the determination of sodium, chloride, osmolarity (Glick et al., 1985) and amino acids (Lenz et al., 1985).

In each individual case obstetric management was discussed by the perinatal team which consisted of an obstetrician, a paediatric urologist, a neonatologist, an ultrasonographer and a geneticist. It was considered that management should vary from careful follow-up by serial ultrasound scanning to pregnancy termination. Neonatal follow-up was available in all cases and included at least one ultrasound examination during the first 5 days of life. Autopsy was carried out in all cases of intrauterine and neonatal death.

The diagnostic classification of renal tract anomalies in index cases (previously affected children), as well as in fetuses and neonates diagnosed in this study, was based upon available pathology reports, using criteria proposed by Zerres et al. (1984).

## Results

### Group 1

In 11 cases (7.8%) a renal tract abnormality was detected. The following subgroups were formed depending on the condition of a previous child born in the same family or other affected family members (including the mother) (Table I).

*Autosomal recessive polycystic kidney disease*

From 10 pregnancies examined because a previous child of the mother had been affected by this kidney disorder, 2 recurrences were observed. The diagnosis was made prenatally in only 1 female child, at a gestational age of 22 weeks; the parents decided to continue the pregnancy and the infant died during a premature delivery. Autopsy revealed a lesion which corresponded to Potter's type I kidney. The other patient who suffered a recurrence was observed following repeatedly normal ultrasound findings at a gestational age of 18, 24 and 30 weeks. The female infant, born at term, showed a distended abdomen and bilateral polycystic kidneys on ultrasound. This child is now 2 years of age and suffers from hypertension, intercurrent urinary tract infections and renal tubular dysfunction. The other 8 infants from this series proved to have normal ultrasound findings at birth.

*Autosomal dominant polycystic kidney disease*

Twelve pregnancies were referred because of characteristic features of this disease in the mother. Ultrasound examinations were performed and until 32 weeks of gestation was reached, no abnormalities were evident. One of the 12 newborn infants was examined by a paediatrician at age of 3 days because of a urinary tract infection; ultrasound examination showed bilateral mildly enlarged kidneys, increased echogenicity and multiple small cysts. None of the other infants in this group developed pathological ultrasound features until they reached 4 years of age.

Table I Group 1 - 141 pregnancies monitored because of increased risk of recurrence of a renal tract abnormality

| Risk | Number of referrals | Prenatal detection of recurrence | Postnatal detection of recurrence |
|---|---|---|---|
| Polycystic kidney disease, autosomal recessive | 10 | 1 | 1 |
| Polycystic kidney disease, autosomal dominant | 12 | 0 | 1 |
| Polycystic kidneys, genetically undetermined | 1 | 1 | 0 |
| Cystic kidneys, other types | 19 | 2 | 0 |
| Renal agenesis | 41 | 1 | 0 |
| Ureteral obstruction | 20 | 0 | 0 |
| Urethral obstruction | 15 | 2 | 0 |
| Miscellaneous | 23 | 4[a] | 0 |
| | 141 | 11 | 2 |

[a]Three recurrences of Meckel syndrome, one of medullary cystic disease

*Polycystic kidneys, Potter type III, genetically undetermined*

One mother from this series had previously given birth to a premature infant, who died shortly after delivery. Autopsy revealed Potter type III polycystic kidneys without any extrarenal lesions. The mother and father (aged 22 and 24 years respectively) had normal renal scans. During a subsequent pregnancy we observed bilateral polycystic kidneys, the absence of bladder filling and oligohydramnios in the fetus at 25 weeks of gestation. The parents opted for termination of the pregnancy. At autopsy Potter type III kidneys were found.

*Cystic kidneys of other origin*

A total of 19 pregnancies was referred either because the mother had a previous child with unilateral cystic kidney (n=2) or bilateral cystic kidneys (n=17), which in 18 cases were associated with histologically proven renal dysplasia (Potter kidney type II). When ultrasound examination was performed we found renal pathology in two fetuses. One mother previously had a stillborn child with a unilateral multicystic kidney and agenesis of the contralateral kidney; in a subsequent pregnancy a unilateral multicystic kidney was diagnosed, combined with a normal contralateral kidney; at the age of 6 months the male infant underwent a unilateral nephrectomy. The second mother had previously lost two children at birth: one male with bilateral cystic kidneys (Potter type $II_A$) and one female with bilateral cystic kidneys (Potter type $II_B$); in addition she had a normal child. In the fourth pregnancy a fetus was found with bilateral dilated ureters and pyela, with normal kidney and bladder size and a normal

amount of amniotic fluid at a gestational age of 22 weeks. The male infant was born at term and showed a massive vesico-ureteral reflux, which needed bilateral uretero-cutaneostomy.

*Renal agenesis*

Forty-one pregnancies were screened because the mothers had previously given birth to a child with renal agenesis (2 unilateral, 37 bilateral) or because one of the parents had unilateral renal agenesis (n=2). In only one case was bilateral renal agenesis found again by ultrasound in a subsequent pregnancy; this pregnancy was terminated at the request of the parents.

*Ureteral obstruction or vesico-ureteral reflux*

A further 20 pregnant women were examined because they previously had a child with ureteral stenosis or reflux (unilateral or bilateral). No renal abnormalities could be detected by ultrasound examination either prenatally or postnatally.

*Urethral obstruction*

In 15 pregnancies the reason for referral was a history of urethral obstruction (atresia 14, stenosis 1) in a previous child in the same family. We twice noticed the prenatal recurrence of a bladder outlet obstruction. In the first child the obstruction was due to a bladder diverticulum which had been detected in the 23rd gestational week and was resected later in life. In a second child bladder outlet obstruction became visible only at a gestational age of 30 weeks, and was due to urethral valves (Wladimiroff et al., 1985). After birth of the infant the valves were cauterized subsequent to bilateral uretero-cutaneostomy, which became necessary because of severe bladder wall hypertrophy.

*Miscellaneous*

Finally, 23 pregnant women were examined because of various renal anomalies observed in previous pregnancies (n=17) or a corresponding family history of congenital renal disorders (n=6). The kidney disorders involved were horseshoe kidney (n=4), double kidneys (n=3), branchio-oto-renal syndrome (n=2), Meckel syndrome (n=13) and medullary cystic disease (n=1). Three recurrences occurred in the Meckel syndrome group when a neural tube defect was found (n=2) and was associated with cystic kidneys (n=3); patho-anatomical examination showed Potter II kidneys once and Potter III kidneys twice. Consanguineous parents from the Cape Verde Islands had previously had an infant which died in utero with hydrocephalus and a form of cystic disease of the renal medulla. In the following pregnancy a recurrence was noted at a gestational age of 16 weeks. Autopsy confirmed hydrocephalus and a form of cystic disease of the renal medulla, probably juvenile nephronophthisis.

Group 2

In group 2, 98 pregnancies were referred because of suspected fetal renal tract pathology, without a prior family history of such abnormalities. In 63 cases (64%) abnormal findings were confirmed before birth (Table II). In the remaining 35 cases there were no renal anomalies before or after birth.

*Cystic kidneys without non-renal anomalies*

Of the 19 pregnancies in this category, 7 were unilateral and 12 bilateral. Thirteen cases were associated with oligohydramnios. One fetus displayed a unilateral multicystic kidney (histologically Potter type II) combined with agenesis of the contralateral kidney. This pregnancy was terminated at the parents request. The remaining 6 children with fetal unilateral multicystic kidneys were delivered at term and underwent nephrectomy at the age of 6-12 months. The kidneys were pathologically classified as Potter type $II_A$.

Of the 12 cases with bilateral cystic kidneys (Fig.1), one fetus presented with ascites which was aspirated; chromosome studies revealed an unbalanced translocation; the mother was found to be a carrier of a balanced translocation t(6; 9) (q23; q21.2) (Department of Human Genetics, Leiden University). Seven pregnancies were terminated after discussion with the parents; and the remaining 5 cases the infant died shortly after birth. Postmortem examinations revealed Potter type $II_A$ kidneys in 9 cases, Potter type I kidneys in 2 cases and Potter type III kidneys in 1 case. Chromosome studies were normal in 11 fetuses from this group. All parents had normal renal scans.

*Cystic kidneys combined with extrarenal structural defects*

In a further 13 pregnancies renal cysts were found in combination with non-renal structural defects. In 6 cases cystic kidneys were found to be associated with a neural tube defect; postmortem examinations revealed Meckel syndrome in all cases. Parental consanguinity was established in 2 of these 6 cases.

Seven cases presented with more than two non-renal defects. (Table 2) (skeletal abnormalities 6, omphalocoele 3, congenital heart defect 3, gastrointestinal obstruction 2, neural tube defect 2). In 4 of these 7 cases an abnormal karyotype was established by amniocentesis (trisomy 18 in 3 cases and Turner syndrome once).

*Obstructive uropathy*

In 31 cases obstructive uropathy was diagnosed either at the level of the ureter (high-level obstruction, n=14) or at the level of the urethra (low-level obstruction, n=17).

Table II Group II - 98 pregnancies monitored for suspected fetal renal tract abnormality without previous family history

| | |
|---|---|
| Cystic kidneys without non-renal anomalies (n=19) | |
| unilateral | 7 |
| bilateral | 12 |
| Cystic kidneys combined with extrarenal structural defects (n=13) | |
| neural tube defect (Meckel syndrome) | 6 |
| other structural defects | 7 |
| Obstructive uropathy (n=31) | |
| High level (ureter) | |
| unilateral | 8 |
| bilateral | 6 |
| Low level (urethra) | 17 |
| No structural abnormality of kidneys | 35 |

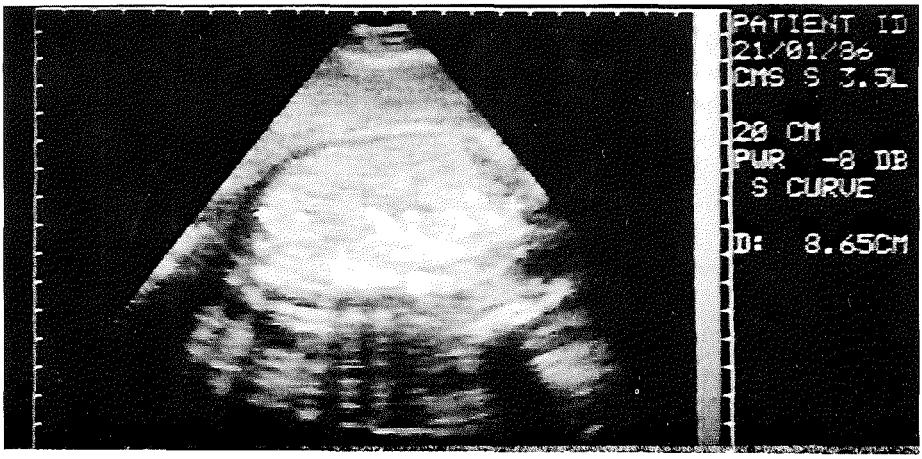


Fig.1 Polycystic kidney (Potter type III in Meckel syndrome). Prenatal ultrasonographic appearance (gestational age 28 weeks) in a fetus with hydrocephalus and polycystic kidneys

*High level obstruction*

In eight cases this condition was unilateral (Fig.2). All infants were delivered at term. In five cases ureteral stenosis was established, ureterocoele once and dilated ureters and pyela without signs of obstruction were found twice. After birth, the latter two patients were found to have bilateral vesicorenal reflux.

In the six patients with bilateral high-level obstruction, amniotic fluid volume remained normal in five cases; and one patient developed polyhydramnios. In

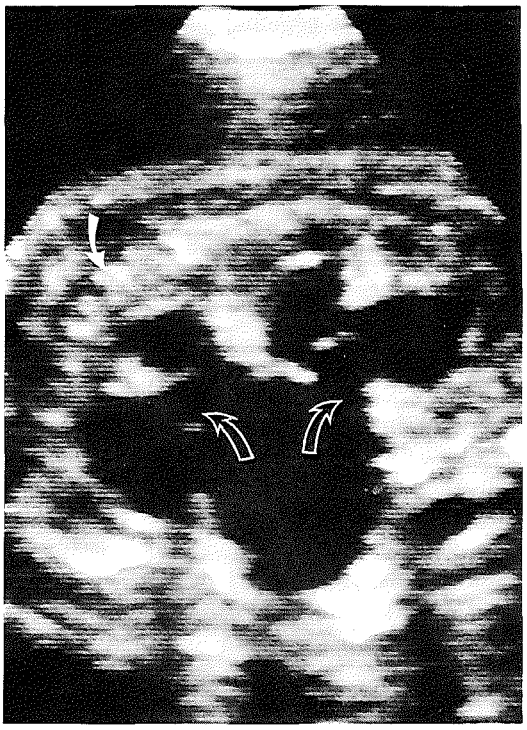

Fig.2 Hydronephrotic kidney. Prenatal ultrasonographic appearance (gestational age 26 weeks). Dilated pelvis and calyces (open arrows) with normal renal parenchyma (closed arrow)

the latter case progressive hydronephrosis resulted in the termination of the pregnancy at 22 weeks. The remaining five pregnancies progressed to term. In two cases bilateral obstruction at the pelvi-ureteral junction was confirmed postnatally and a pyeloplasty was performed. In one infant unilateral obstruction was found after birth. In two cases no anatomical lesion was established and one of these infants displayed Noonan syndrome.

*Low-level obstruction*

Oligohydramnios was observed in 12 of 17 cases with low-level obstruction; 2 cases had an increased amniotic volume and 3 a normal amniotic volume. Fetal ascites was documented in 3 cases, and an additional diaphragmatic hernia was noted once. Chromosome studies were performed twice by culturing cells from fetal urine; these showed normal male karyotypes. One abnormal karyotype (trisomy 21) was established by amniocentesis.

The outcome in the cases of low-level obstruction was generally poor.

Pregnancy was terminated in 7 cases, and in addition, there were 2 intrauterine deaths. Six infants died in the neonatal period because of pulmonary hypoplasia. Post-mortem examination of these 15 fetuses revealed urethral atresia in 14 cases and cloacal anomaly in 1 case; one of these cases had unilateral renal agenesis as well.

Other non-renal structural defects besides pulmonary hypoplasia were found in 5 out of 15 fetuses: rectal atresia (2), microcolon (1) diaphragmatic hernia (1) and cardiac defect (1). Two male infants with urethral valves survived and were successfully treated by cauterization.

## Discussion

In a group of 141 pregnancies with an increased risk for renal pathology on the basis of a positive family history for congenital renal tract malformations, a corresponding abnormality was detected prenatally in 11 cases (8%). All diagnoses were confirmed after birth. The varying age at manifestation in most conditions with cystic kidney disease requires repeated scans to appreciate its full potential for prenatal diagnosis.

Out of 10 pregnancies with an increased risk for the autosomal recessive ("infantile") type of polycystic kidney disease, we identified one recurrence in the 22nd week of gestation, but established normal kidney size and echogenicity up to the 30th week in another case, which turned out to be affected after birth. As cysts develop late in this condition a prenatal diagnosis by ultrasound is often missed before the 24th week (Luthy and Hirsch, 1985; Romero et al., 1984)). Only in those cases with early manifestation in a previous pregnancy is early detection of the cystic disease possible in a subsequent pregnancy (Zerres et al., 1984).

In the dominant (adult) type of polycystic disease, the variability in the age of manifestation is even greater and prenatal diagnosis is restricted to the rare cases with a prenatal onset of cyst formation (Zerres et al., 1982; Zerres et al., 1985; Main et al., 1983). This problem is demonstrated by a case in which the disorder was not diagnosed until the 3rd day of postnatal life. For the dominant type of polycystic kidney disease, restriction length polymorphism studies using markers for chromosome 16 may provide a more reliable prenatal diagnosis with the help of chorionic villous biopsy (Reeders et al., 1986).

Multicystic kidneys (Potter type II) and renal agenesis are anomalies with a multifactorial inheritance and a low risk of recurrence (Zerres et al., 1984). Renal ultrasound scans in the parents and a careful family history are needed to evaluate the risk of recurrence and to exclude inherited syndromes, such as the autosomal dominant branchio-oto-renal syndrome (Roodhooft et al., 1984; Bankier et al., 1985). The variable combination of multicystic kidneys with renal agenesis is demonstrated by a family with an infant suffering from unilateral Potter type II kidney and contralateral renal agenesis in the first pregnancy and unilateral type II kidney and normal contralateral kidney in the second pregnancy.

Urethral obstructions have a small risk of recurrence according to our findings. The autosomal recessive Meckel syndrome is an example where even by the combined use of alpha-fetoprotein determination in amniotic fluid and ultrasound, prenatal diagnosis may be difficult (Fraser and Lytwyn, 1981).

Precise patho-anatomical evaluation of an index case in a given family is always essential for establishing the diagnosis of a congenital renal tract anomaly and its risk of recurrence. It is also important to inform the ultrasonographer of the diagnosis of a previous renal anomaly in a family and the variability of the respective lesions to be expected. It should also be stressed that antenatal screening for renal tract anomalies should always include a complete ultrasound examination of extrarenal organs. Karyotyping by means of amniocentesis, fetal bladder puncture or cordocentesis (Daffos et al., 1985) is also essential. In our series of patients referred because a renal tract anomaly was suspected, there were 6 out of 98 fetuses with different chromosomal abnormalities.

In the second group of 98 fetuses referred because of a suspected renal tract anomaly, we were able to confirm the diagnosis by ultrasound in 64% of the pregnancies. Cystic kidney disorders and obstructive uropathy were each found in half of all pathological cases. Cystic kidneys in the absence of extrarenal structural defects were unilateral in 7 cases. If they presented with a normal contralateral kidney, no influence on the fetal prognosis was shown. In contrast, bilateral cystic kidneys were associated with a poor outcome. This is demonstrated by perinatal death in 5 cases and by termination of pregnancy in the 7 remaining cases after discussion of the prognosis with the respective parents.

A combination of bilateral cystic kidneys with non-renal structural defects was found in 13 pregnancies in our second group of fetuses. In all 6 cases associated with a neural tube defect the patho-anatomical findings were compatible with the diagnosis of Meckel syndrome (autosomal recessive).

In the total group of bilateral cystic kidneys, associated structural defects were present in 41% of cases. This high incidence demonstrates the necessity for ultrasound examination of the whole fetus in addition to the urinary tract and for additional cytogenetic studies, determination of alpha-fetoprotein in amniotic fluid and a full patho-anatomical examination at autopsy. The combined results of such a comprehensive study are essential for evaluating the prognosis of the fetus as well as for establishing an accurate diagnosis in view of the later demand for genetic counselling.

Ureteral obstructions in the fetus had a relatively good prognosis. In only 10 of 14 cases (71%) where the prenatal diagnosis of ureteral obstruction had been made was this confirmed after birth. The remaining 4 cases displayed reflux or dilatation.

Urethral obstructions were found to have a very poor outcome with a prenatal or perinatal mortality of 88%. Lung hypoplasia was the major cause of death. As reported by other authors (Lirette and Filly, 1983; Blane et al., 1983) the incidence of other non-renal abnormalities was high in our group with low-level obstructions. In groups 1 and 2 (combined) obstructive uropathy was

associated with non-renal structural defects in 35% of cases. One case of obstructive uropathy in group 2 had an abnormal karyotype. It should also be mentioned that a number of non-chromosomal syndromes exist which combine urethral obstruction with caudal regression, sirenomelia (Allen et al., 1981), microcolon (Winter and Knowles, 1986) or imperforate anus. The association of the latter with urethral obstructions was present in two cases from group 2; in both cases death occurred in the neonatal period. Finally, an urethral obstruction malformation complex exists which is different from the above associations (Pagon et al., 1979).

In all cases where there are severe morphological and functional renal tract anomalies the obstetric and prenatal diagnostic team has to consider the ethical implications. The parents have to be fully informed and decisions regarding intervention, pregnancy termination or non-intervention are made following full assessment of relevant information from the various sources (Lenz et al., 1985; Lirette and Filly, 1983; Blane et al., 1983).

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## 3.3 Prenatal Diagnosis of Chromosome Abnormalities in the Presence of Fetal Structural Defects

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A chromosomal abnormality was found in 42 (10.9%) out of 386 fetuses with a structural defect. Thirty-five of these were diagnosed prenatally, following ultrasonic detection of one or more structural anomalies and associated pathology such as marked intrauterine growth retardation and polyhydramnios. Termination of pregnancy was carried out in 16 fetuses aged <26 weeks, intrauterine and neonatal death occurred in 20 cases, the remaining 6 infants were alive at 3 months.

The poor outcome in these pregnancies emphasizes the need for prenatal chromosome analysis in the presence of a fetal structural defect.

*Keywords* congenital structural defects - intrauterine growth retardation - polyhydramnios - real-time ultrasound - prenatal chromosome studies

## Introduction

Present-day high-resolution real-time ultrasound equipment allows detection of an increasing number of fetal structural defects. Referral centres with large series of fetal structural defects have observed a relatively higher percentage of combined fetal structural and chromosome anomalies than have been documented in newborns (Platt et al., 1986).

The present communication deals with a retrospective study on the diagnosis and follow-up of fetuses with combined structural and chromosome defects in a level 3 referral centre over a period of 5 years.

## Material and methods

Structural anomalies were diagnosed in 386 fetuses. Prenatal chromosome analysis was performed in 170 of these affected fetuses (44%) on the basis of the following:

a) a specific structural anomaly, duodenal atresia, omphalocele, or cystic hygroma (38%);
b) multiple structural defects (22%);
c) intrauterine growth retardation (IUGR) as defined by an upper-abdominal circumference below the 5th centile according to Campbell (1976) (19%);
d) polyhydramnios (12%);
e) fetal non-immune hydrops (6%);
f) rare defects such as teratomas, abdominal cysts, and facial clefts (3%).

Prenatal cytogenetic analysis was mainly done in amniotic fluid (n=161); in a few cases in fetal urine (n=4) and in fetal ascites (n=2) owing to severe oligohydramnios, and in one case in a chorionic villi sample at 12 weeks of gestation (Reuss et al., 1987). Pregnancy duration at the time of chromosome analysis ranged between 12 and 20 weeks in 21%, between 21 and 30 weeks in 52% and between 31 and 40 weeks in 27%. The prenatally diagnosed structural anomalies were further examined after delivery. In case of a prenatally established abnormal chromosome pattern, a blood or skin sample was taken for confirmation.

In the remaining 56% of affected fetuses no chromosome analysis was performed since i) the structural defect was not generally associated with a chromosome anomaly (n=187), e.g., skeletal defects, unilateral renal pathology, teratomas, isolated cleft lip, Meckel's syndrome, ovarian cyste, hydrocolpos; ii) the parents and/or referring gynaecologist refused the procedure (n=19); iii) the pregnancy duration was beyond 36 weeks of gestation (n=10). Postpartum examination showed no chromosome abnormalities in this group.

## Results

A chromosome abnormality was found in 42 (10.9%) out of 386 features with a structural defect. Gestational age at referral ranged between 12 and 36 weeks (mean 24 weeks). Thirty-five chromosome abnormalities were diagnosed

prenatally, making up 20.5% of the 170 analysed pregnancies. These were autosomal trisomies (54%), monosomies (45,X) (23%); triploidy (11.5%); sex chromosome anomalies [46,X,i(Xq), 47,XXY, 47,XYY] (8.5%), and one unbalanced familial translocation (6; 9). All chromosome abnormalities could be confirmed postnatally. The remaining seven chromosome abnormalities were diagnosed after birth: i.e., trisomy 18 (2x), trisomy 21, 45,X (3x) and der(13) del(q22.3→qter). Trisomy 18 and 21 were the most common chromosome aberrations in prenatal chromosome analysis. Polyhydramnios and cardiac structural defects were the most consistent findings in the presence of these trisomies. IUGR was observed in all 7 cases of trisomy 18 beyond 25 weeks of gestation against only one case of IUGR in trisomy 21. Duodenal atresia was typically associated with trisomy 21. Oligohydramnios, IUGR, and multiple structural defects were the main clinical findings in the presence of fetal triploidy. Twice hydrocephaly was diagnosed. Hygroma colli was the structural defect most commonly observed in association with 45,X. For these cases referral nearly always took place before 20 weeks of gestation. The remaining four chromosome abnormalities (46,X,i(Xq); unbalanced translocation (6;9); 47,XYY; 47,XXY) were twice associated with cardiac structural defects, once with bilateral multicystic kidneys and once with mild hydrocephaly.

Prenatally established structural defects were confirmed postnatally in all 35 infants. Major clinical findings in the 7 postnatally established chromosome aberrations were cardiac defects and IUGR.

Termination of pregnancy was carried out by request of the parents in 16 cases (38%) with 26 weeks of gestation as the upper limit; intrauterine and neonatal death occurred in 20 cases (48%). The remaining 6 cases (14%) representing complete atrioventricular canal defect + trisomy 21 (2x); Tetralogy of Fallot + trisomy 21; duodenal atresia + trisomy 21; omphalocele + 45,X and microcephaly +der(13)del(22.3+qter) were alive at 3 months.

## Discussion

With improvement of neonatal care the relative contribution of fetal structural defects to perinatal mortality continues to increase.

Most structural defects are not detected until the second half of the second trimester of pregnancy. At that time the diagnosis is usually made only after associated pathology such as IUGR and abnormal amniotic fluid volume has been established. The principal associated findings in the presence of chromosome abnormalities were IUGR (52%) and polyhydramnios (54.5%). Multiple structural defects were present in 34%, cardiac anomalies in 40% of fetuses with a chromosome anomaly.

The high frequency of chromosome abnormalities in the presence of above-mentioned structural defects and associated pathology together with the high fetal wastage emphasizes the need for prenatal chromosome analysis in the management of the pregnancies. First, unnecessary surgical intervention can be avoided in the presence of a chromosome abnormality. This is particularly

important with respect to fetal surgical procedures before fetal viability is reached. On the other hand, the knowledge that the fetus is cytogenetically normal would allow the parents and those involved in the obstetric management to discuss alternatives and choose the appropriate time, mode and place of delivery. Second, the high incidence of intrauterine death with subsequent fetal maceration will render postpartum chromosome analysis impossible and counseling of a recurrence risk difficult. In the group of postnatally established abnormal chromosome patterns, amniocentesis for prenatal cytogenetic analysis was planned but not carried-out owing either to refusal to undergo the procedure or to the very short time interval between ultrasound documentation of fetal structural pathology and delivery.

In conclusion, our data emphasize the need for prenatal chromosome analysis in the presence of a fetal structural defect. In particular, cardiac anomalies, duodenal atresia, omphalocele, and hygroma colli; multiple structural defects; and additional pathology such as marked IUGR and polyhydramnios should be considered markers for possible associated chromosome abnormalities.

### 3.4 Closing remarks.

Prenatal ultrasound describes morphology, and therefore will only be able to detect the presence of a renal abnormality if maldevelopment resulted in morphologic changes.

In pregnancies at risk for renal tract abnormalities because of a corresponding anomaly in a previous infant or a positive family history of congenital urinary tract anomalies, a recurrence was detected prenatally in 8 per cent. Two infants (1.4%) were born with polycystic kidney disease (once autosomal recessive and in the other case autosomal dominant type) while ultrasound findings were eventful up to the beginning of the third trimester. In one case the recurrence of a bladder outlet obstruction was only detected as late as the beginning of the third trimester. Some renal abnormalities are not detectable by ultrasound in the second and / or third trimester due to the late onset of maldevelopment, variability in onset or late manifestation of symptoms, such as urinary tract dilatation and oligohydramnios. These limitations of prenatal monitoring in 'high-risk' pregnancies should be pointed out at genetic counselling.

In general, associated non-renal malformations are not always detectable prenatally and strongly influence morbidity and mortality. Chromosomal anomalies were present in 10.9 per cent of fetuses with structural anomalies, which included extra-renal anomalies. The combined presence of fetal structural and chromosomal anomalies resulted in a mortality of 85 per cent.

These data emphasize the need for a careful search for associated defects and prenatal chromosome analysis in the presence of a fetal structural defect.

Chapter 4

# Sonographic, clinical and genetic aspects of prenatal diagnosis of fetal renal agenesis.

## Introductory remarks.

Bilateral renal agenesis (BRA) with an incidence of 1 to 2 per 10.000 births (Carter et al., 1979), is a rather common malformation not compatible with postnatal life. This is distinct from unilateral renal agenesis (URA) which might be etiologically related to BRA. The spectrum of renal agenesis varies from a minimal form of isolated URA to the lethal form of BRA. URA and BRA may present as an isolated malformation or in association with other anomalies.

BRA is the result of a disturbance affecting the mesonephric ducts, which inhibits the outgrowth of the metanephric buds. As a result, the metanephric blastema fails to differentiate and both ureters and kidneys are absent (Potter, 1965). This disturbance occurs between the 25th and 28th fetal day (Curry et al., 1984), when there is a close spatial relationship between the lower cervical somites and the promesonephric duct. Since paramesonephric duct (Müllerian duct) formation is also dependent upon normal mesonephric duct development, associated uterine and vaginal abnormalities can be explained similarly. This explains the frequent association of Müllerian duct anomalies, renal agenesis and cervical thoracic vertebral anomalies. Duncan et al. (1979) postulated the term MURCS-association (Müllerian duct anomalies, Renal agenesis, Cervical and thoracic vertebral anomalies). Potter found only one infant with a normal vagina and uterus among 12 females with this syndrome. In males, abnormalities of the vas deferens and seminal vesicle occur as consequence of their derivation from the mesonephric duct.

From the great variety of associated malformations it has been suggested that they are all the result of the exogeneous action exerted at a critical period during embryonic development (Potter, 1975). Nowadays, it is suggested that the classical idea of the timing of the insult should not imply only exogeneous factors. Gene mutations involved in differentiation processes and morphogenesis of the kidney may also have similar effects. BRA should be differentiated from bilateral renal aplasia, bilateral renal hypoplasia and small dysplastic kidneys. In all these cases the presence of the ureter (absent in renal agenesis), abnormalities of the ureter, absence of the kidney (agenesis), presence of non-functioning dysplastic tissue (dysplasia and in the extreme form aplasia) or a small kidney with less than a normal amount of nephrons without dysplastic elements (hypoplasia) has to be carefully assessed. Potter (1965) has suggested that the term BRA be reserved for those patients in whom kidneys, ureters and renal arteries are absent in combination with a hypoplastic bladder lacking ureteral orifices.

## 4.1. Ultrasound diagnosis.

Prenatal detection of BRA is important, because of its incompatibility with postnatal life, and offers options for pregnancy termination in early pregnancy and non-intervention in the third trimester. URA in the presence of a normal contralateral kidney has no consequences for the obstetric management. Emphasis will be placed on the ultrasound diagnosis of BRA. Garrett et al. (1970), Campbell (1974) and Hansmann et al. (1975) suggested the potential of prenatal diagnosis of BRA by ultrasound studies, and thereafter case reports were published (Kaffe et al., 1977; Keirse and Meerman, 1978; Hansmann et al., 1979). The prenatal ultrasound diagnosis of BRA is based on the combination of severe oligohydramnios, absence of fetal bladder filling and failure to identify fetal kidneys. Reduced fetal growth is common. Oligohydramnios which is the result of lack of urine production, is usually detectable after 16 - 18 weeks of gestation. It has been suggested that prior to 16 weeks of gestation the contribution of fetal urine to amniotic fluid volume is minor (Saunders and Rhodes,1975). For that reason oligohydramnios is not invariably present in BRA in the early mid trimester. Moreover, cases of BRA without oligohydramnios have been reported in association with other defects that impair the disposition of amniotic fluid, like oesophageal atresia and severe central nervous system defects affecting the neural control of swallowing (Bain and Scott, 1960; Thomas and Smith, 1974).

Severe oligohydramnios and the degree of fetal flexion that acompanies this condition makes visualization of the renal area difficult. One side is often in the shadow of the spine. Retroperitoneal paraspinal masses can represent adrenals instead of kidneys. This potential source of confusion has been previously recognized in fetuses (Dubbins et al., 1981) and neonates (Silverman et al., 1980). Potter (1972) has suggested that the adrenal glands in BRA adopt an oval disk shape presumably because of the absence of a compressive effect by the normal kidney. This shape can grossly simulate the morphology of a normal fetal kidney. Criteria that may be helpful in distinguishing between these two organs include clear identification of the renal capsule and consistent imaging of the renal pelvis (Romero et al., 1985).

*Additional techniques to improve the diagnostic accuracy of fetal anomalies in the presence of severe oligohydramnios.*

A particular diagnostic dilemma may arise in the presence of intrauterine growth retardation (IUGR) and severe oligohydramnios. Here, IUGR due to impaired placental perfusion has to be differentiated from IUGR associated with fetal structural pathology in particular renal pathology, like BRA.

Maternal intraveneous administration of 60 mg of furosemide causes an increase in fetal urinary production from 80 - 150% in normal third trimester pregnancies (Wladimiroff, 1975). Based on these furosemide studies in normal pregnancy, a furosemide challenge test (Wladimiroff, 1975) was advocated for evaluation of fetal renal function in growth retarded fetuses. Recently, the

reliability of furosemide-induced diureses to differentiate between BRA and other cases of intrauterine failure has been questioned (Romero et al., 1985; Gembruch et al., 1988).

Furthermore, in fetal lambs Chamberlain et al. (1985) could not demonstrate augmented fetal urine production after maternal furosemide administration. It seems, therefore, that the results of the furosemide challenge test should be interpreted with caution when they are used to evaluate human fetal renal function.

The following procedures may, however, may add to the diagnostic accuracy of fetal anomalies in the presence of oligohydramnios, in particular renal anomalies such as agenesis.

First, the creation of an artificial amniotic fluid compartment (Gembruch and Hansmann, 1988). Instillation of 100 - 200 ml of a 5% glucose / 0.9% saline solution into the empty amniotic cavity will allow more optimal visualization of fetal structures including the renal area. Subsequent fetal swallowing will result in fetal stomach and bladder filling when one or two functional kidneys are present. However, rupture of membranes and preterm labour occured in 10.5 per cent of cases following a single intra-amniotic infusion. When also the cases with multiple infusions are taken into account, this complication occured in 28.9 per cent .

The second approach consists of the recording of umbilical artery and fetal internal carotid artery waveforms, using pulsed Doppler equipment (Reuwer et al., 1984; Trudinger et al., 1985; Wladimiroff et al., 1986). Typical waveform changes in these vessels characterized by a reduced end-diastolic flow velocity in the umbilical artery and an elevated end-diastolic flow velocity in the fetal internal carotid artery may be observed in impaired placental perfusion reflecting circulatory centralization and subsequent brain-sparing in the hypoxic fetus. However, normal flow velocity waveforms have been documented, especially in the fetal internal carotid artery in case of a fetal structural malformation.

At ultrasound examination a cord loop between the flexed fetal leggs and the anterior abdominal wall may mimick the presence of a small bladder 'inside' the fetus. Doppler flow investigation can also be helpful in distinguishing between a fetal bladder and a cord loop by recordings of velocity waveforms in the latter.

Recently, intraperitoneal instillation of saline has been suggested as an alternative to improve visualisation of fetal intra-abdominal organs (Nicolini et al., 1989) in the presence of severe oligohydramnios.

In chapter 4.2 the differentiation between IUGR due to impaired placental perfusion and IUGR associated with fetal renal pathology, in particular BRA will be discussed. A more recent observation of an abnormal umbilical artery flow velocity waveform in the presence of fetal BRA which became normal following the formation of an artificial amniotic fluid compartment has pointed at the possibility of umbilical cord compression in severe oligohydramnios. This limites the diagnostic value of umbilical artery waveforms when BRA is suspected. This will be discussed in more detail in chapter 4.3.

## 4.2 Fetal renal anomalies, a diagnostic dilemma in the presence of intrauterine growth retardation and oligohydramnios

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### Abstract

Measurement of the head-to-abdomen (H/A) ratio for differentiating between symmetrical and asymmetrical IUGR may be difficult in the presence of marked oligohydramnios. A total of 76 cases of IUGR with various degrees of oligohydramnios was studied. Sixteen (59%) out of 27 structural defects represented bilateral renal agenesis, 11 of which were diagnosed prenatally. When only the H/A ratio was measured (n=29) the sensitivity in picking up a structural defect was 50%. Calculation of the pulsatility index in the umbilical artery and fetal internal carotid artery (n=47), whether or not combined with amnioinfusion (n=5), resulted in a sensitivity of 76%. It is suggested that the latter two techniques may provide valuable additional information as to the cause of IUGR.

*Keywords* - Oligohydramnios - Renal agenesis - Head-to-abdomen ratio - Fetal blood flow - amnioinfusion

### Introduction

Severe intrauterine growth retardation (IUGR) associated with marked oligohydramnios constitutes a considerable problem with respect to establishing the cause of IUGR and subsequent obstetric management. Particularly in the presence of fetal structural and/or chromosomal anomalies, IUGR is associated with a poor fetal outcome. Whereas prenatal ultrasound has been shown to be of considerable value in the detection of fetal structural anomalies, the presence of marked oligohydramnios may greatly restrict the quality of fetal imaging even with present high resolution real-time scanners. This is of particular clinical importance when renal pathology such as polycystic or hypoplastic kidneys or renal agenesis is suspected. Calculation of the head-to-abdomen circumference (H/A) ratio (Campbell and Thoms, 1977) has been helpful in differentiating between asymmetrical and symmetrical growth retardation. Whereas the former usually is a result of diminished uteroplacental function, the latter usually suggests a fetal origin of the growth restriction. In the presence of severe IUGR, particularly associated with marked oligohydramnios, it may however be difficult to obtain a reliable measurement of the head and/or abdominal circumference. There are two alternative methods which may be helpful in determining the cause of IUGR when marked oligohydramnios is present: first, improvement of fetal imaging has been reported by creating an artificial amniotic fluid compartment (Gembruch and Hansmann, 1988); second, reduced end-diastolic blood flow

velocity values at the lower thoracic level of the fetal descending aorta (Jouppila and Kirkinen, 1984; Griffin et al., 1984) and in the umbilical artery (Reuwer et al., 1984; Trudinger et al., 1985) together with raised end-diastolic values in the fetal internal carotid artery (Wladimiroff et al., 1986) have been documented in the presence of IUGR secondary to reduced uteroplacental perfusion. In the present study the significance of both methods in differentiating between placental and fetal origin of severe IUGR in the presence of marked oligohydramnios will be discussed.

## Material and methods

Between 1 January 1984 and 31 December 1986 a total of 146 pregnancies with suspected IUGR was referred to our Ultrasound Division in order to exclude or confirm the presence of fetal structural defects, in particular renal abnormalities. Gestational age was certain, as determined by early crown-rump length or biparietal diameter (BPD) measurement and varied between 23 and 38 weeks (mean 30.1 weeks).

IUGR was confirmed in 76 out of 146 pregnancies (52%) on the basis of:

1. A clinical discrepancy of more than two weeks in fundal height on two successive antenatal appointments combined with ultrasonic findings of upper-abdominal and /or head circumference measurements below the 5th percentile according to the normograms established by Campbell and Wilkin (1975) and Campbell (1976). If feasible, head-to-abdominal (H /A) ratio values were subsequently calculated according to the method of Campbell and Thoms (1977).
2. A birthweight below the 5th percentile for gestational age according to Kloosterman's Table (Kloosterman, 1970), corrected for maternal parity and fetal sex.

Following maternal blood screening for toxoplasmosis, cytomegalovirus, herpes, rubella and syphilis, a detailed 2D real-time search for the presence of fetal structural anomalies was carried out in each subject using a mechanical sector scanner (Diasonics Cardio Vue 100; 5 MHz transducer). Amniotic fluid volume was considered normal, reduced or virtually absent. A reduced amniotic fluid volume was present if a pocket of liquor greater than 1 cm in broadest diameter was not revealed on real-time scanning (Manning et al., 1981). Amniocentesis was considered in each case. Twenty-nine out of 76 pregnancies (38%) were referred during the first 18 months of the three-year study period (Group I). No Doppler flow measurements were performed. Gestational age varied between 23 and 37 weeks (mean 29.5 weeks). The remaining 47 pregnancies (62%) (Group II) were referred during the last 18 months of the study period at a gestational age ranging 26 and 33 weeks (mean: 30.7 weeks). During this period the blood flow velocity waveform in the umbilical artery (Reuwer et al., 1984; Trudinger et al., 1985) and fetal internal carotid artery (Wladimiroff et al., 1986) was recorded over at least five consecutive cardiac cycles using

a combined mechanical and pulsed Doppler system (Diasonics Cardio Vue 400, 5 MHz Doppler transducer) for calculation of the Pulsatility Index (PI) as first described by Gosling and King (1975). A PI in the umbilical artery above the 2SD limit of the normogram was considered abnormal, reflecting increased vascular resistance at placental level; a PI in the internal carotid artery below the 2SD of the normogram suggested a brain-sparing effect. In five cases in which no amniotic fluid was observed and the presence of fetal kidneys was not established with certainty, an artificial amniotic fluid compartment was created by installation of 150-200 ml of 5% glucose solution allowing more optimal visualization of fetal structures, particularly the kidneys and urinary bladder and collection of fetal cells for karyotyping. In case of pregnancy termination, intrauterine or neonatal death, a postmortem examination was performed. All live-born infants were seen by a pediatrician.

## Results

*Group I (n=29)*

This group comprised a total number of 10 structural defects, i.e. an incidence of 34.5%. Only five of these defects were diagnosed prenatally resulting in a sensitivity of 50%. There were no false positive diagnoses. The negative predictive value was 79% Twice an associated abnormal karyotype (69, XXX; trisomy 13) was established, once an abnormal karyotype was diagnosed without overt structural pathology. The nature of the structural defects, the associated findings and fetal outcome are represented in Table I. Bilateral renal pathology was responsible for half of all anomalies in Group I. Symmetrical IUGR reflected

Table 1. Structural defects, associated findings and fetal outcome in Group 1.

| | | Antenatal findings | | | |
|---|---|---|---|---|---|
| Patient no. | Gest.age (wks) | H/A ratio | AFV | Structural/chromosomal defects | Fetal outcome |
| 1 | 22 | S | — | BRA | TOP, ♂ BRA |
| 2 | 23 | S | — | Bilateral multicystic kidneys | TOP, ♂ Potter type IIA |
| 3 | 24 | ? | ± | Hydrocephaly; 69, XXX | TOP, ♂ hydrocephaly |
| 4 | 25 | ? | ± | — | IUD, ♀ horseshoe kidney |
| 5 | 28 | A | — | 69, XXX | IUD, ♂ spina bifida; 69, XXX |
| 6 | 28 | S | — | — | ND, ♂ BRA |
| 7 | 32 | A | + | Hydrometrocolpos | ♀ Hydrometrocolpos, alive at 3 months |
| 8 | 33 | A | ± | — | ND, ♀ bilateral hypoplastic kidneys |
| 9 | 33 | ? | ± | ASD, VSD; trisomy 13 | ND, ♀ ASD, VSD; trisomy 13 |
| 10 | 33 | S | — | — | ND, ♀ BRA |

H/A=head-to-abdomen circumference; S=symmetrical, A=asymmetrical, ?=not measured, AFV=amniotic fluid volume, +=normal, ±=reduced, —=absent, TOP=termination of pregnancy, IUD=intrauterine death, ND=neonatal death, ASD=atrial septal defect, VSD=ventricular septal defect, BRA=bilateral renal agenesis.

by normal H/A ratios was documented in three, asymmetrical IUGR in four fetuses with a structural defect. No H/A ratio was obtained in the remaining three fetuses. Amniotic fluid was considered virtually absent in five, reduced in four and normal in one case. Termination of pregnancy was requested in three out of five prenatally diagnosed structural defects (bilateral renal pathology 2x; severe hydrocephaly), intrauterine death occurred once (atrial and ventricular septal defect, trisomy 13). The infant with hydrometrocolpos was alive and well at the age of three months. Pregnancy outcome in the five postnatally established defects was intrauterine death in two (horseshoe kidney; spina bifida) and neonatal death in the remaining three cases (bilateral renal pathology).

In the remaining 19 pregnancies, there were four cases of pregnancy induced hypertension, in the other 15 cases no overt cause for the IUGR could be established. Asymmetrical IUGR was observed in 18 fetuses, no H/A ratio was obtained in one case. Amniotic fluid was considered virtually absent in five, reduced in 10 and normal in four cases. There were seven cases of intrauterine death and one case of neonatal death; 11 infants were alive and well at the age of three months.

*Group II (n=47)*

In this group there were 17 fetal structural defects, i.e. an incidence of 36%. The nature of these structural defects, the associated findings and fetal outcome are presented in Table II. According to the PI values calculated from the flow velocity waveforms in the umbilical and fetal internal carotid artery two subgroups could be recognized.

*Subgroup 2a*

Normal PI values in the umbilical and fetal internal carotid artery were established in 21 pregnancies (45%), including all 17 cases with a fetal structural defect. Bilateral renal pathology was responsible for the majority (76%) of these anomalies. Two abnormal karyotypes (69,XXX; trisomy 18) were diagnosed in amniotic fluid without overt structural pathology. Thirteen structural anomalies were diagnosed prenatally, resulting in a sensitivity of 76%. There were no false positive diagnoses. The negative predictive value was 88%. When excluding the two cases of fetal microcephaly, IUGR was symmetrical in 14 cases and asymmetrical in four cases. In one pregnancy no H/A ratio value could be obtained. Amniotic fluid volume was absent in 15 pregnancies suggesting bilateral renal agenesis. In five of these pregnancies an artificial amniotic fluid compartment was produced to confirm the diagnosis. Amniotic fluid volume was reduced in one and normal in the remaining five pregnancies. Termination of pregnancy was requested in seven out of 13 prenatally diagnosed structural defects (Table II). Four infants died during the neonatal period from renal pathology (bilateral renal agenesis, hypoplastic kidneys, n=3) or microcephaly (n=1). Two infants (CHD and trisomy 21; microcephaly and der(13)del (q22.3->qter)) were alive at the age of three months.

Table 2. Structural defects, associated findings and fetal outcome in Group 2.

| Patient no. | Gest. age (wks) | Antenatal findings: H/A ratio | AFV | PI UA; ICA | Amnio-infusion | Structural chromosomal defects | Fetal outcome |
|---|---|---|---|---|---|---|---|
| 1 | 20 | S | — | N | + | BRA | TOP, ♂ BRA |
| 2 | 23 | S | — | N | — | BRA | TOP, ♀ BRA |
| 3 | 23 | S | — | N | — | BRA | ND, ♂ BRA |
| 4 | 26 | S | + | N | — | CHD; trisomy 21 | ♀, CHD; trisomy 21, + alive at 3 months |
| 5 | 29 | S | — | N | + | BRA | ND, ♀ bilateral hypoplastic kidneys |
| 6 | 29 | S | — | N | — | — | ND, ♀ BRA |
| 7 | 29 | A | — | N | + | BRA | TOP, ♂ BRA |
| 8 | 29 | S | — | N | — | BRA | TOP, ♂ BRA |
| 9 | 29 | S | — | N | + | BRA | TOP, ♂ BRA |
| 10 | 29 | S | — | N | + | BRA | TOP, ♂ BRA |
| 11 | 30 | S | — | N | — | BRA | TOP, ♂ BRA |
| 12 | 31 | A | — | N | — | — | ND, ♂ BRA |
| 13 | 31 | A | — | N | — | — | ND, ♀ VSD; trisomy 18 |
| 14 | 32 | ? | ± | N | — | Microcephaly | ND, ♂ microcephaly |
| 15 | 34 | S | — | N | — | — | ND, ♂ BRA |
| 16 | 36 | S | — | N | — | BRA | ND, ♂ BRA + MCA |
| 17 | 38 | ? | + | N | — | Microcephaly | ♂ microcephaly; der(13)del (q22.3—>qter) alive at 3 months |

H/A = head-to-abdomen circumference; S = symmetrical, A = asymmetrical, ? = not measured; AFV = amniotic fluid volume; + = normal, ± = reduced, — = absent; TOP = termination of pregnancy; ND = neonatal death; CHD = congenital heart disease; BRA = bilateral renal agenesis; PI UA, ICA = pulsatility index in umbilical artery and fetal internal carotid artery.

In the six pregnancies in which no prenatal diagnosis of a structural defect was made, four infants died neonatally from either bilateral renal agenesis (3x) or trisomy 18 with a ventricular septal defect. In two of the undiagnosed cases of fetal bilateral renal agenesis, either the adrenals (fig.1) or the testis imposed as kidneys. The remaining infants were alive and well at the age of three months.

*Subgroup 2b*

Raised PI values were documented in the umbilical artery in 26 pregnancies, 21 of which (81%) combined with a reduced PI in the fetal internal carotid artery. There were four cases of pregnancy induced hypertension, in the other 22 cases no overt cause for the IUGR was found. Asymmetrical IUGR was demonstrated in 25 cases; in one pregnancy no H/A ratio value could be obtained. Amniotic fluid volume was considered virtually absent in two, reduced in 16 and normal in eight pregnancies. In none of the pregnancies a prenatal diagnosis of structural defects was made.

There were six intrauterine deaths. From the 20 live born infants, three died during the neonatal period: twice due to the prematurity and severety of IUGR, and once as a result of sepsis. One female infant demonstrated a webbed neck, the karyotype was 45, X. The remaining 16 infants were alive and well at the age of three months.

## Discussion

IUGR was studied over a three year period by either ultrasound assessment of fetal structure and measurement of H/A ratio alone (Group I, n=29) or by additional methods such as Doppler blood flow velocity waveforms in the umbilical and fetal internal carotid artery whether or not combined with amnioinfusion (Group II, n=47). Both groups are comparable with respect to mean gestational age. (29.5 versus 30.4 weeks) and incidence of extreme oligohydramnios (35% versus 36%), fetal structural anomalies (34% versus 36%), abnormal karyotypes (11% versus 13%) and perinatal mortality (62% versus 55%).

In the presence of fetal structural defects, a H/A ratio measurement could not be obtained in 30% of the cases in Group I and in 12% of the cases in Group II. When the H/A ratio was available the percentage of symmetrical IUGR was only 57% in Group I and 80% in Group II. These data suggest a limited relationship between symmetrical IUGR and the presence of structural defect. Of interest is that failure in obtaining a H/A ratio measurement was generally associated with only moderate oligohydramnios. A much more close relationship was established between asymmetrical IUGR and reduced uteroplacental perfusion. Following the introduction of Doppler blood flow measurements and amnioinfusion, the sensitivity in the prenatal detection of structural defects increased from 50% to 76%, and the negative predictive value rose from 79% to 88%. Specificity, and positive predictive value were 100% during both study periods.

Of interest is that normal PI values in the umbilical and fetal internal carotid artery (Subgroup IIa) were highly associated with fetal structural anomalies (81%); an abnormal karyotype was established in 24%. As expected, the vast majority of IUGR cases was of the symmetric type, twice microcephaly was present. No fetal structural defects were documented in the presence of abnormal umbilical and fetal internal carotid arterial PI values. IUGR was nearly always of the asymmetric type (96%). The high mortality rate of 88% in Subgroup IIa as opposed to 45% in Subgroup IIb underlines the extremely poor fetal outcome in the presence of a structural and/or chromosomal defect. The present data indicate that blood flow velocity waveform studies in the umbilical and fetal internal carotid artery may be helpful in the differentiating between IUGR resulting from impaired uteroplacental perfusion and IUGR due to a reduced potential of cell division in the presence of a structural and/or chromosomal defect. The data collected in the present study are to some extend at variance with those reported by Trudinger and Cook (1985). They observed a raised placental resistance, as expressed by an increased systolic/diastolic ratio in a number of patients. They postulated that in these patients there is a process of obliteration of small arteries in the placenta that is triggered by the abnormal fetus. This difference may be partly determined by the fact that in the present study a slightly different population of structurally abnormal pregnancies was examined, i.e. severe IUGR associated with various degrees of oligohydramnios.

Over the entire study period 18 (66%) out of 27 structural defects were of renal origin, 16 of which represented bilateral renal agenesis. Eleven out of these 16 cases of bilateral renal agenesis were correctly diagnosed during the antenatal period. In five instances the correct diagnosis was only made after amnioinfusion of a 5% glucose solution. Here, the advantage of improved fetal imaging should be weighed up against possible risks due to the procedure such as premature labour, infection, fetal damage and premature rupture of the membranes, the latter being observed once in the present study.

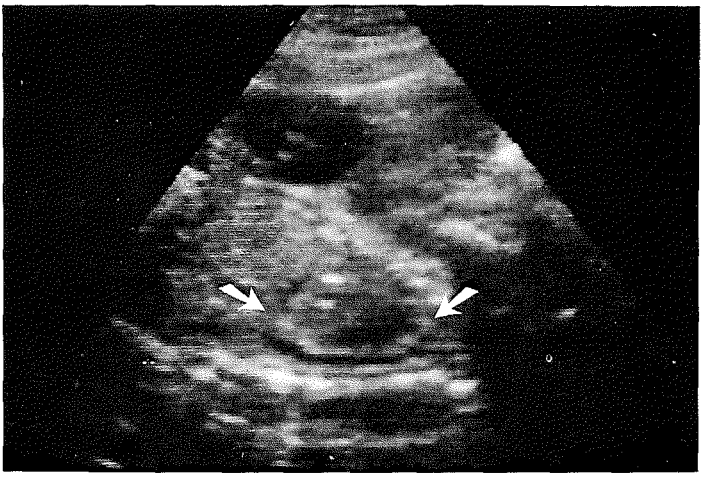

Fig. 1. Longitudinal view of a paraspinal mass representing the fetal adrenal gland in a 28 week old fetus with bilateral renal agenesis. Not the absence of a clear outline of the renal capsule (closed arrows) and renal pelvis. The open arrow represents the fetal spine.

It should be realized that retroperitoneal paraspinal masses can represent adrenals instead of kidneys, as was the case in one of our fetuses (Fig.1). This potential source of confusion has been previously recognized in fetuses (Dubbins et al., 1981) and neonates (Silverman et al., 1980). Potter (1972) has suggested that the adrenal glands in the presence of bilateral renal agenesis adopt an oval disk shape presumably because of the absence of a compressive effect by the normal kidney. This shape can grossly simulate the morphology of a normal fetal kidney. Criteria that may be helpful in distinguishing between kidneys and adrenals include clear identification of the renal capsule and consistent imaging of the renal pelvis (Romero et al., 1985). In the present study, postmortem examination revealed bilaterally enlarged adrenals in four out of five false negative cases.

It can be concluded that in the presence of IUGR particularly in combination with marked oligohydramnios, calculation of the PI in umbilical and fetal internal carotid artery may provide valuable additional information as to the cause of

the growth retardation. If normal PI values are present, a careful search for structural and chromosomal anomalies is needed. If bilateral renal agenesis is suspected, amnioinfusion with a 5% glucose solution may be employed to secure the diagnosis. In the presence of abnormal PI values impaired uteroplacental perfusion is likely.

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## 4.3 Effect of amnioinfusion on the umbilical Doppler flow velocity waveform: A case report

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*Keywords* - Intrauterine growth retardation - Oligohydramnios - Renal agenesis - Amnioinfusion - Doppler ultrasound - Umbilical artery velocity waveform

**Abstract**

A case of intrauterine growth retardation with marked oligohydramnios is presented in which, following amnioinfusion of 200 ml of a 5% glucose solution, the diagnosis of bilateral renal agenesis was established. Doppler flow study in the umbilical artery revealed a high resistance flow velocity waveform which became normal following amnioinfusion, suggesting cord compression rather than poor uteroplacental perfusion. Abnormal Doppler flow velocity waveforms in the umbilical artery in the presence of severe oligohydramnios should be interpreted with caution.

**Introduction**

Ultrasound plays a major role in monitoring fetal growth. Whereas intrauterine growth retardation (IUGR) often results from impaired uteroplacental perfusion, an alternative cause may be a fetal structural/chromosomal defect. IUGR associated with marked oligohydramnios may, therefore, in advanced pregnancy present with an obstetric dilemma. In the presence of poor uteroplacental perfusion, premature delivery may be indicated to salvage the hypoxic infant.

On the other hand, in a pregnancy characterized by a lethal fetal structural / chromosomal defect, one should generally abstain from any form of intervention.

Marked oligohydramnios may seriously hamper optimal visualization of fetal anatomy rendering accurate diagnosis of a structural defect often possible. Instillation of a 5% glucose solution into the amniotic cavity has been reported to considerably improve image resolution (Gembruch and Hansmann, 1988). Moreover, recently umbilical artery (Trudinger and Cook, 1985) and fetal internal carotid artery flow velocity waveforms (Wladimiroff et al., 1986) have been studied in an effort to differentiate between various causes of IUGR.

*Case report*

A 21-year-old gravida I, para O was referred to our department at 28 weeks of gestation for ultrasound assessment of fetal anatomy and growth. Pregnancy was uneventful until 26 weeks. At this time IUGR and marked oligohydramnios were established. Maternal blood pressure was 130 /80. Ultrasound examination revealed a single viable fetus. Biparietal diameter (6.1 cm), upper abdominal circumference (20.5 cm) and femur length (4.1 cm) were situated below the 5th percentile of the normal charts according to Campbell and Newman (1971) and Campbell (1974) and Jeanty et al. (1981). There appeared to be a total absence of liquor. Although no gross structural anomalies could be visualized, no information could be obtained on the fetal kidneys. The fetal urinary bladder was empty; there was no bladder filling over a period of 45 min. Doppler flow study of the umbilical artery showed a flow velocity profile with a pulsatility index (PI)(Gosling and King, 1975) above the +2SD cutoff level of the normogram according to Wladimiroff et al.(Wladimiroff et al., 1987)(fig.1).

In order to obtain better information about the fetal renal area, 200 ml of a 5% glucose solution was instilled into the amniotic cavity under ultrasound guidance according to the method first described by Gembruch and Hansmann (1988). On ultrasound examination enough liquor was present to ensure optimal visualization of fetal anatomy. The kidneys appeared to be absent; again no bladder filling was observed over a period of 60 min. A diagnosis of bilateral renal agenesis was made. Flow studies of the umbilical artery, which were carried out within 1 h following the amnioinfusion, revealed a pronounced change in the velocity waveform in that the PI was now situated within the normal range (fig.1).

Five days later, the ultrasound examination was repeated as a follow-up of the amnioinfusion. There again was virtual absence of liquor and the PI in the umbilical artery had returned to well above the +2SD cutoff level of the normogram (fig.1).

At a gestational age of 31 weeks, the patient went into premature labor. A stillborn male fetus, showing the typical features of the Potter syndrome, was delivered. Birth weight was 825 g, which is below the 5th percentile according to Kloosterman's (1970) tables corrected for maternal parity and fetal sex.

Autopsy confirmed the diagnosis of bilateral renal agenesis accompanied by severe hypoplasia of the lungs.

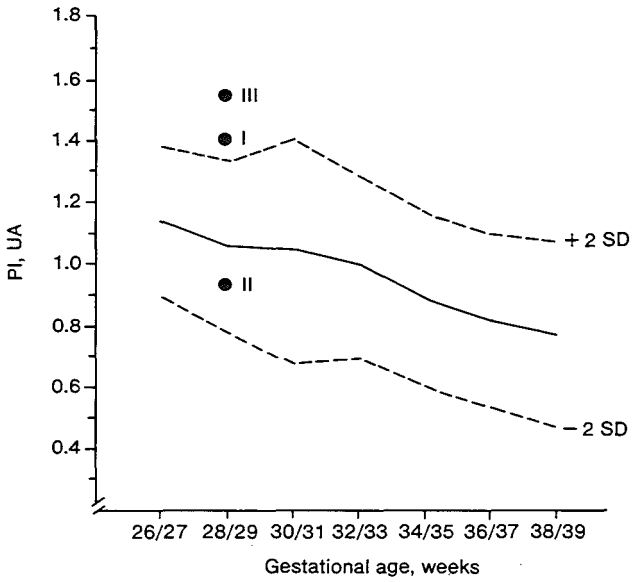


Fig. 1. PI values in the umbilical artery relative to the normogram (Wladimiroff et al., 1987) immediately before (I), 60 min after (II) and 5 days after amnioinfusion (III).

## Discussion

When ultrasound reveals marked oligohydramnios one should consider premature rupture of the membranes and IUGR, the latter particularly in association with bilateral renal pathology, in the differential diagnosis. While in the presence of ruptured membranes there is usually a history of amniotic fluid leakage, serial measurements of head and upper abdominal circumference are necessary to establish IUGR. The technique of amnioinfusion, first described by Gembruch and Hansmann (1988), generally considerably improves image resolution, resulting in a more accurate assessment of fetal anatomy. Moreover, amnioinfusion provides information on fetal renal function in that fetal urinary bladder filling should be seen over a period of 45-60 min following this procedure. In our case, the absence of a clear renal outline and any bladder filling strongly suggested bilateral renal agenesis. Whereas maternal administration of frusemide results in increased fetal urinary output in normal pregnancy (Wladimiroff, 1975), this is not so in severe IUGR associated with poor placental perfusion. This makes frusemide administration useless in the distinction between reduced fetal renal function due to chronic fetal hypoxia and bilateral renal agenesis. Risks attached

to the amnioinfusion technique are small, only rupture of the membranes was reported in a limited number of cases in the study of Gembruch and Hansmann (1988) and was encountered in 1 out of 9 procedures in our unit.

Doppler blood flow velocity waveform studies are increasingly being used in the evaluation of fetal growth retardation. Several authors have described the typical waveform pattern with low end-diastolic velocity in the umbilical arteries (Reuwer et al., 1984; Trudinger et al., 1985; Schulmann et al., 1984) as a consequence of high placental resistance, while in cases of major fetal abnormality both waveforms with normal and elevated pulsatility indices have been described (Trudinger and Cook, 1985; Wladimiroff et al., 1987). In our patient an abnormal waveform characterized by a reduced end-diastolic velocity, hence a raised PI, was established. However, after amnioinfusion the waveform became completely normal, whereas 5 days later, after resorption of the instilled fluid, again a waveform with elevated PI was observed.

In the literature, the well-known non-renal features of Potter's syndrome are frequently being attributed to compression of the fetus due to extreme oligohydramnios (Thomas and Smith, 1974). Our findings suggest that also the umbilical cord, which is normally prevented from compression by the amniotic fluid acting as a fluid cushion (Gabbe et al., 1976), can be compressed in case of severe oligohydramnios, resulting in high-resistance velocity waveforms in the umbilical artery. Support for this hypothesis may be found in the study of Miyazaki and Navarez (1985), in which repetitive variable decelerations in the first stage of labor, suggesting cord compressing in the presence of oligohydramnios, were successfully relieved by saline amnioinfusion.

In conclusion, it is suggested that abnormal Doppler flow velocity waveform in the umbilical artery in severe oligohydramnios complicated by IUGR should be interpreted with caution.

**Acknowledgement**

The authors wish to thank C.A.Bloemsma, MD, PhD, for referring the patient to our unit.

### 4.4. Genetic aspects.

Renal agenesis, both bilateral and unilateral, are at the extreme end of a spectrum of ureteric bud malformations and most studies indicate a common cause of these conditions. Renal agenesis is etiologically heterogeneous and may be classified in several different ways: unilateral or bilateral, with or without ureteric remnants, isolated or associated with other malformations. It has been suggested that each of these distinctions was etiologically significant (Potter 1965; Buchta et al., 1973), and yet within each classification each type may occur within the same family. A single family may have both unilateral and bilateral cases, or affected individuals with or without ureteric remnants. Agenesis of one kidney may be associated with dysplasia of the other kidney in the same

individual, or in other members of the same family. Horseshoe and duplex kidney may also occur in other family members. This wide spectrum of expression within families makes genetic classification on phenotypic criteria very difficult.

Renal agenesis may be associated with genital, hindgut or caudal skeletal defects, including as an extreme form, sirenomelia. Renal agenesis may also occur in association with malformations of non-caudal structures as part of a malformation syndrome (Table 1) or a chromosomal disorder. The two most common groups of malformations seen in association with renal agenesis are those involving either the genital tract or the ear. Some such syndromes are genetically determined and for others the etiology is unknown.

BRA has an incidence of one to two per 10,000 births (Carter et al., 1979; Wilson and Baird, 1985; Sangal et al., 1986). Infants with BRA are still-born in 25 - 40% of cases (Welch, 1958; Potter, 1965; Bergsma, 1979; Wilson and Baird, 1985). Males account for about 70% of BRA cases (Davidson and Ross, 1954; Potter, 1965; Wilson and Baird, 1985). URA is more common than BRA, both Warkany (1971) and Museles and associates (1971) giving figures of 1 in 600 for the former. An ultrasound survey of 682 adults found a prevalence of URA of 3 per thousand (Roodhooft et al., 1984). Individuals with URA had additional anomalies in 82% of the studied population (Wilson and Baird, 1985). The percentage of still births was 9%. In URA sexes were equally affected. Clinical manifestations in URA can be similar to those found in BRA regarding additional anomalies, notably of the skeletal, gastrointestinal and central nervous system (Wilson and Baird, 1985).

*Renal agenesis as an isolated malformation.*

Commonly renal agenesis and dysplasia are understood as a multifactorial determined disorder with a low recurrence risk (Buchta et al., 1973) up to 2-3%.

Carter et al. (1979) in a review of 103 patients with BRA in their families found a recurrence risk of 3.5%, which was higher than expected for multifactorial inheritance and concluded that there may be autosomal dominant and autosomal recessive patterns of inheritance. This study was undertaken in a time before ultrasound imaging of the renal tract had become widely available. They may have substantially underestimated the incidence of URA and other occult renal malformations among the relatives of their index cases, as recognized by Carter (1984).

Based on recurrent familial cases and observations of an increased frequency of urogenital malformations in siblings and relatives of affected infants some authors have suggested an autosomal dominant inheritance in some families (Buchta et al., 1973; Curry et al., 1984; Biedel et al., 1984; Monn and Nordhus, 1984). Bankier et al.(1985) reported that recurrences of BRA in families were limited to those in which affected infants had BRA without anomalies in other systems. Curry et al. (1984) emphasized that the occurrence of renal agenesis

in a female with Müllerian duct abnormalities might suggest autosomal dominant inheritance. Buchta et al. (1973) suggested BRA without ureteric remnants is multifactorial, while BRA with ureteric remnants is due to autosomal dominant inheritance.

Unilateral /bilateral agenesis and renal dysplasia may occur within the same sibship, with an autosomal dominant inheritance pattern with variable expression, hence the term heriditary renal adysplasia (Buchta et al., 1973). Schimke and King (1980) suggested that developmental defects in the mesonephric and paramesonephric ducts may have a common genetic basis. They suggested the designation hereditary urogenital adysplasia for the combination of anomalies of the Müllerian duct with developmental errors of the urinary tract.

Buchta et al. (1973) interpreted the variability in some familial cases as evidence for autosomal dominant inheritance with incomplete penetrance. Others have proposed that the variation in developmental renal anomalies can be explained by means of the developmental field concept (Gilbert and Opitz, 1979). It remains unclear whether complete BRA differs embryologically and /or genetically from cases of renal dysplasia (Curry et al., 1984). Variations from complete agenesis to dysplasia might represent a developmental continuum rather than separate entities (Gilbert and Opitz, 1979; Al Saadi et al., 1984; Curry et al., 1984; Wilson and Baird, 1985). This might explain familial cases involving BRA in one sibling and URA with cystic dysplasia with or without ureters in another sibling (Hack et al., 1974; Cain et al., 1974; Carter et al., 1979; Schmidt et al., 1982; Curry et al., 1984; Bankier et al., 1985).

Roodhooft et al. (1984) showed that frequency of renal malformations in parents and siblings of probands with BRA or URA or renal dysplasia was significantly higher than that in a matched control group (9% versus 0.3%). Of interest is that in this study, 30% of parents with more than one previously affected infant had a "silent" genito-urinary malformation themselves. This in contrast to 7.4% of the parents who had only one affected infant.

A single family has been reported compatible with X-linked recessive inheritance (Pashayan et al.,1977).

*Renal agenesis as part of syndromes or chromosomal disorders.*

The remaining cases of renal agenesis are considered syndromic, with normal or abnormal chromosomes. A few cases of BRA with abnormal karyotypes have been reported (Machin, 1978; Yunis et al., 1980; Coté et al., 1981; Pflueger et al., 1984; Clark, 1984), although the majority of patients studied have had normal chromosome patterns. However, isolated BRA may be part of a monogenic syndrome and accordingly higher risks of recurrence, also for non-renal malformations, may be associated with these situations. The autosomal dominant Branchio-Oto-Renal (BOR) syndrome is an example. The affected individuals may have pre-auricular pits, lacrimal duct stenosis, hearing loss, branchial fistulas or cysts, structural defects of the outer, middle and inner ear and renal anomalies, which may range from mild hypoplasia to BRA (Melnick et al., 1975, 1978;

Fitch and Srolovitz, 1976; Carmi et al., 1983). Fraser et al. (1978) estimated a 6% risk for gene carriers to have severe anomalies. The high variability of this syndrome is to be considered in genetic counselling and when attempting prenatal diagnosis. Recently, a fetus was detected with right renal agenesis and severe left renal hypoplasia in a family with a BOR syndrome (Greenberg et al., 1988).
Other syndromes with renal agenesis are listed in table 1.

Table 1. Syndromic and Non-syndromic associations of renal agenesis (excluding chromosomal disorders)

| | inheritance |
|---|---|
| MURCS association | mfr |
| Mayer-Rokitansky-Kuester anomaly | mfr, a.d. |
| Goldenhar syndrome | mfr, a.d. |
| BOR (branchio-oto-renal) syndrome | a.d. |
| Oto-renal syndrome | a.d. |
| Oto-renal genital syndrome | a.r. |
| Acro-renal syndrome | a.d. |
| Fraser syndrome | a.r. |
| Auricular-renal adysplasia-hypospadia syndrome | a.d. |
| Polydactyly,cleft lip,hamartoma,renal,deafness, retardation syndrome | a.r. |
| DK-phocomelia-trombocytopenia syndrome | mfr |
| Donnai-Young syndrome | a.r. |
| Cerebro-oculo-facio-skeletal (COFS) syndrome | a.r. |
| Fanconi's pancytopenia | a.r. |
| Multiple lentigenes syndrome | a.d. |
| Miller-Diecker syndrome | a.r. |
| Lenz-microphthalmia | X-linked |
| Darier's disease | a.d. |
| VATER association | mfr |
| McKusick-Kaufmann | a.r. |
| Caudal regression syndrome | a.r.,terat. |
| Klippel-Feil sequence | mfr, a.d. |

a.r.= autosomal recessive, a.d.= autosomal dominant, mfr= multifactorial inherited, X-linked= X chromosomal linked inherited, terat.= teratogenic.

*Oligohydramnios sequence.*

It is now recognised that the term 'Potter syndrome' is the consequence of any condition leading to oligohydramnios, hence the term 'oligohydramnios sequence'. The equivalent terms 'renal non-functioning sequence'and 'Potter sequence', describe a fetal or neonatal phenotype of heterogeneous aetiology due to the influence of longstanding oligohydramnios or anhydramnios. The genetic interpretation depends on the underlying pathology (Table 2.)

Table 2 Syndromes and diseases which may be associated with the oligohydramnios sequence.

| | | inheritance |
|---|---|---|
| Autosomal recessive PKD | | a.r. |
| Autosomal dominant PKD | | a.d. |
| Renal agenesis,hypoplasia,dysplasia or combination | | mfr, a.d. |
| Meckel syndrome | | a.r. |
| VATER association | | mfr |
| Caudal regression syndrome | (usually) | n.i. |
| Cerebro-oculo-facio-skeletal syndrome | | a.r. |
| Fraser crypthophtalmos syndrome | | a.r. |
| Branchio-oto-renal syndrome | | a.d. |
| Prune Belly | | different modes |
| Chromosomal disorders | | - |

a.r.=autosomal recessive, a.d.=autosomal dominant, n.i.=not inherited, PKD= polycystic kidney disease, mfr=multifactorial
(adapted from Zerres, 1987)

Potter (1946) drew attention to facial characteristics of infants with bilateral renal agenesis:'The principal change consists of a mild increase in width between the eyes, a very prominent fold of skin arising at the inner canthus, a flattening of the nose, mild retraction of the lower jaw, and large, low-lying ears with incomplete cartilaginous development'. Additional malformations are: malformations of the spine, bowing of the legs, club feet, large hands, reduction in bones of lower extremities including sirenomelous deformity, pulmonary hypoplasia and others.

Oligohydramnios has been considered causal to some of the deformations present, in particularly the Potter "facies", abnormal ears, pulmonary hypoplasia, some musculo-skeletal deformaties and some external genital malformations. The presence of central nervous system, cardiac and gastrointestinal anomalies indicates that a more primary developmental defect must be considered. Page and Stocker (1982) proposed a possible primary mesenchymal defect affecting multiple organ systems, with oligohydramnios being an associated rather than a causal phenomenon. Even a spectrum of malformations involving a disturbance of caudal mesoderm resulting in BRA has been proposed, the pulmonary and facial changes being a cranial extention of such a basic defect (Källén and Winberg, 1974).

From all the above-mentioned reports, it is clear that recurrence risk estimation remains difficult. This stresses the need for thorough evaluation of patients and their families (Morse et al., 1987), as well as a detailed autopsy report of the index case.

BRA has a significant empiric recurrence risk. Because of the variable

recurrence risk in cases of BRA, ultrasound should be offered in all subsequent pregnancies. A complete anomaly scan is essential, since associated anomalies have been reported in BRA, notably, respiratory and musculo-skeletal, cardiac, gastrointestinal and central nervous system defects (Potter, 1965; Carter et al., 1979; Wilson and Baird, 1985).

It is obvious, that the parents must be made aware of the possibility of an associated genito-urinary anomaly in parents and siblings and of the chance of recurrence in a subsequent pregnancy, not only for a fetus with BRA with an uniformly fatal outcome. Ultrasound is of paramount importance in the clinical investigation and management of patients with BRA and their families.

### 4.5. Closing remarks.

Renal agenesis, both bilateral and unilateral, can be pathologically related, and are at the extreme end of a spectrum of ureteric bud malformations. The ultrasound diagnosis prenatally of renal agenesis is of importance on two occasions. Firstly, to obtain a final diagnosis on small non-functioning or absent kidneys, after the incidental finding of oligohydramnios. Secondly, a pregnancy may be known to be at risk because of a corresponding anomaly in the previous infant or one of the parents. The variability of the condition, the status of the parents, the evidence for a syndromal association or association with chromosomal anomalies should all be considered when genetic counselling is provided.

In URA, obstetric management and fetal outcome will be mainly determined by the condition of the contralateral system and the presence and severity of associated anomalies. A complete fetal anomaly scan will, therefore, always be necessary. Here too one should look for familial genito-urinary tract anomalies and offer ultrasound examinations in subsequent pregnancies.

There are limitations to the prenatal diagnosis of BRA. These are mainly determined by the severe oligohydramnios rendering optimal visualisation of the renal area virtually impossible. The often enlarged adrenal gland may pose as a kidney. The furosemide challenge test should be considered with reservation. The creation of an artificial amniotic fluid compartment (Gembruch and Hansmann, 1988) can greatly improve visualization of fetal abdominal structures but has a considerable risk of complications like rupture of membranes or premature delivery. Therefore, it should be performed only when obvious diagnostic benefit regarding further management is expected. Blood flow velocity waveform studies in the umbilical and internal carotid artery may provide additional support in establishing or refuting BRA. The presence of fetal growth retardation and severe oligohydramnios in combination with normal PI values in the fetal arteries, is strongly suspicious of fetal structural and /or chromosomal anomalies. Colour coded Doppler allows visualization of the fetal renal arteries. The potential of this device in establishing BRA should be examined.

If the diagnosis of BRA can not be given with certainty, then in our opinion the fetus should be given the benefit of the doubt.

The cause of recurrent BRA is uncertain and has been postulated to variously

represent a polygenic multifactorial, autosomal dominant, autosomal recessive or sex-linked recessive trait.

The term Potter syndrome should not be used since it does not comprise any information about the cause of this phenotype, instead the term oligohydramnios sequence is preferred. Careful post-mortem examination of the index case including karyotyping and a search for "silent" genito-urinary tract malformations in parents and siblings are prerequisites for effective genetic counselling in case of BRA. Serial ultrasound examinations should be offered in all subsequent pregnancies.

Chapter 5

# Sonographic, clinical and genetic aspects of prenatal diagnosis of cystic kidney disease.

## Introductory remarks

Cystic kidney disease plays a major role among the inherited renal diseases. The knowledge about cystic kidneys is still incomplete, and the extensive literature uses a complex and often contradictory nomenclature. The lack of a universal classification contributes to the confusion.

In this chapter only those entities will be discussed in which the perinatal manifestation of cystic kidney disease may offer possibilities for a prenatal ultrasound diagnosis. Standard ultrasound parameters are provided in chapter 5.1. The classification of renal cystic disease is presented in chapter 5.2. An overview of genetic forms of cystic kidney disease is given in chapter 5.3: autosomal recessive polycystic kidney disease (chapter 5.3.1), autosomal dominant polycystic kidney disease (chapter 5.3.2), the differential diagnosis (chapter 5.3.3), and congenital nephrosis (chapter 5.3.4).

Cystic kidneys can be part of a malformation syndrome and in chapter 5.3.5 the differential diagnosis is presented. In chapter 5.3.6 a report is presented of six cases of prenatal diagnosis of cystic kidney disease with ventriculomegaly in two related sibships in order to illustrate the difficulties of morphologic classification. Multifactorially inherited cystic disease of the kidneys is discussed in chapter 5.4.

## 5.1 Ultrasound diagnosis

Since great variety exists in clinical and patho-anatomical findings of cystic kidney disease the macroscopic ultrasound picture is also variable. The macroscopic description of the kidneys by ultrasound should include: (1) shape of the kidney ;(2) kidney size ;(3) symmetry; (4) aspect of the parenchyma;(5) the presence, location and diameter of cysts.

Information should be obtained about the presence of bladder filling and the amount of amniotic fluid since these parameters reflect urine production. The specific features of the different kinds of cystic kidney disease will be discussed in the following chapters.

## 5.2 Classification of renal cystic disease

A cyst is referred to as a closed epithelium-lined sac or cavity, normal or abnormal, usually containing liquid or semisolid material. In some renal conditions the cysts are ectatic collecting tubules in continuity with the nephron, while

in others the cysts are saccular or fusiform diverticulum-like structures at various locations in a nephron. The cyst is lined with epithelial cells and may be microscopic or macroscopic, with or without communication to the glomerulus, collecting duct or calyx. In some conditions cysts are accompanied by dysplastic elements and in others evidence of dysplasia is absent.

Dysplasia is defined as abnormal metanephric differentiation and it is diagnosed histologically. Dysplasia may be diffuse, segmental or focal. Cysts may or may not be present and they may vary in size. Irrefutable evidence of dysplasia is the presence of primitive ducts and nests of metaplastic cartilage (Bernstein, 1968). Primitive ducts are found in the renal medulla and sometimes in the medullary rays. The duct is surrounded by a collar of concentric rings of connective tissue containing occasional smooth muscle cells and collagen but not elastine.

A number of classifications have been proposed based on clinical, morphological and radiological observations. The classification of Osathanondh and Potter (1964) was based upon findings from microdissection including morphologic and pathogenetic criteria. In this latter classification some clinically different entities fell into the same category, making the classification of little clinical use. The pathologist may meet difficulties when classifying microscopic specimens using criteria from microdissection findings to microscopic specimens. Also the types of cystic kidneys are genetically heterogeneous. Nonetheless several clear entities can be defined on the basis of pathological features and inheritance. The classification in table 1 is based on predominantly genetic considerations (Glassberg et al.,1987).

Table 1. Cystic disease of the kidney

| |
|---|
| Genetic |
| Autosomal recessive (infantile) polycystic kidneys |
| Autosomal dominant (adult) polycystic kidneys |
| Juvenile nephronophtisis-medullary cystic disease complex: |
| Juvenile nephronophtisis (autosomal recessive) |
| Medullary cystic disease (autosomal dominant) |
| Congenital nephrosis (autosomal recessive) Finnish type |
| Cysts associated with multiple malformation syndromes (table 2) |
| Nongenetic or multifactorial |
| Multicystic kidney (multicystic dysplasia) |
| Multilocular cyst (multilocular cystic nephroma) |
| Simple cyst |
| Medullary sponge kidneys (less than 5% inherited) |
| Acquired renal cystic disease in chronic hemodialysis patients |
| Caliceal diverticulum (pyelogenic cyst) |

## 5.3 Genetic Cystic disease

*'In surviving individuals, cystic kidneys are inherited dominantly. In non-viable individuals, cystic kidneys are recessive'.*

(W.Marquardt, 1935)

*Polycystic kidneys.*

The term polycystic kidneys should not be confused with multicystic kidneys nor should it be used as a general term to describe kidneys with multiple cysts. The term applies to two separate inherited disorders and in neither evidence of dysplasia is found. The two disorders have previously been referred to as infantile polycystic kidney disease and adult polycystic kidney disease. Both terms are misnomers, since the infantile form may manifest in adolescence and the adult form may manifest in infancy (Shokeir, 1978; Zerres et al.,1985; Fryns et al., 1986). The so-called infantile form is transmitted as an autosomal recessive trait and the adult form as an autosomal dominant trait. Therefore, it is suggested that the terms autosomal recessive polycystic kidney disease (ARPKD) and autosomal dominant polycystic kidney disease (ADPKD) should be used.

### 5.3.1 *Prenatal diagnosis by ultrasound in pregnancies at risk for autosomal recessive polycystic kidney disease*

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Submitted for publication

#### Summary

In 15 pregnancies at risk of the autosomal recessive type of polycystic kidney disease (ARPKD), there were six recurrences (40%), five of which were diagnosed prenatally between 17 and 26 weeks (mean 22 weeks). In the remaining affected case normal kidney size and echogenicity was still present at 30 weeks of gestation. Fetal kidney enlargement and increased echogenicity are the key ultrasonographic signs for the detection of ARPKD. Absent fetal bladder filling and oligohydramnios were only documented in two of the six affected pregnancies.

The variability in onset, the intrafamilial variability and the limitations of excluding ARPKD by second trimester ultrasound have to be considered when counselling a couple at risk for this particular disorder.

#### Introduction

The estimated incidence of autosomal recessive polycystic kidney disease (ARPKD) is about 1 : 40.000 (Zerres et al.,1984). ARPKD is characterized by cystic dilatation of different proportions of the renal collecting ducts invariably

associated with congenital hepatic fibrosis (Potter 1972). Qualitative variation in tubular dilatation allows the distinction of a perinatal group (most common, $>90\%$ of tubules affected), a neonatal group (60% of tubules affected), an infantile group (25% of tubules affected) and a juvenile group ($<10\%$ of tubules affected), with hepatic fibrosis increasing with prolonged survival in cases of mild renal changes (Blyth and Ockenden 1971; Zerres et al.,1984). In the perinatal group, respiratory insufficiency related to kidney enlargement and lung hypoplasia, is the most common cause of death. Renal failure and portal hypertension occur in the neonatal and juvenile group. Although kidneys in ARPKD are often grossly enlarged at birth, prenatal sonographic diagnosis of this entity is not always possible (Zerres et al.,1988). This communication reports on our experience in prenatal sonographic diagnosis of ARPKD in a high-risk population.

## Patients and methods

Between January 1980 and January 1988, a total of 15 pregnancies from seven families at risk for ARPKD was referred to our ultrasound department. In each family at least one earlier affected infant with ARPKD was born. Nearly all of the live-born affected infants died within six hours after delivery, only two died at the age of five and seven months. The final diagnosis was made at patho-anatomical examination.

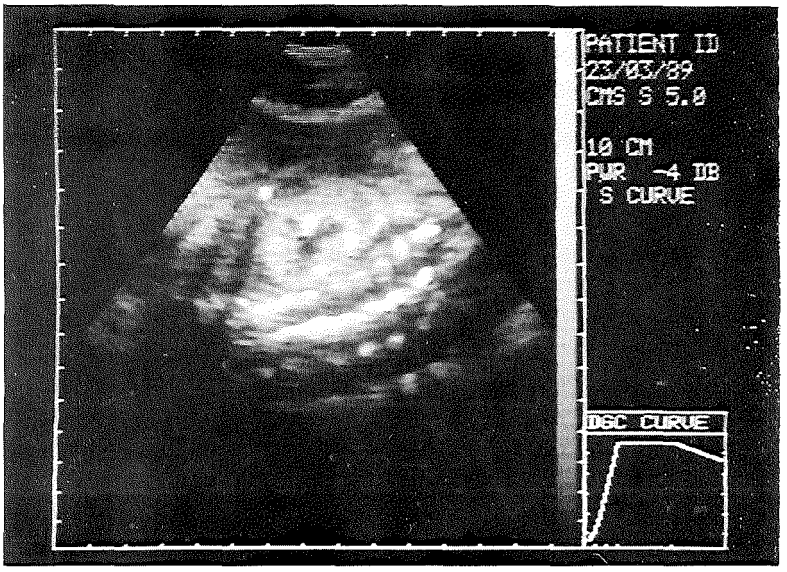


Fig. 1. Longitudinal scan of a fetus with ARPKD at 23 weeks. The kidney displays increased echogenicity; kidney length is situated on the 95th percentile of the reference curve according to Jeanty et al (1982).
Amniotic fluid volume and bladder filling were normal.

Three couples were consanguineous. The number of pregnancies per family studied varied from 1 to 5. The sonographic examinations were performed using a real-time mechanical sector scanner with a 5 MHz transducer (Diasonics Cardio Vue 100). Each examination included measurement of kidney size, study of the echogenicity of the renal parenchyma, and a careful search for non-renal defects. Individual values for kidney length were related to the normal range for this parameter according to Jeanty et al, 1982. The presence or absence of oligohydramnios and fetal urinary bladder filling were also documented. A recurrence was diagnosed in the presence of enlarged fetal kidneys with the typical hyperechogenic texture (Figure 1). In all cases follow-up was available. Autopsy was carried out in three of six cases with fetal or neonatal death. All live-born infants were seen by a pediatrician, with a follow-up period varying from ten months to seven years.

## Results

Tables I and II present the prenatal and postnatal findings in all 15 pregnancies. A first ultrasound examination was performed between 17 and 21 weeks of gestation in 11 pregnancies, at 23 weeks in three pregnancies and at 26 weeks in the remaining pregnancy. A recurrence of ARPKD was established in five out of 15 pregnancies. Gestational age at the time of detection ranged between 17 and 26 weeks (mean 22 weeks). At the time of diagnosis, all five affected pregnancies displayed enlarged fetal kidneys with increased echogenicity. Normal urinary bladder filling was observed in three and a normal amount of amniotic fluid was documented in four out of five pregnancies. Associated hydrocephaly was diagnosed in one case (no.IV,7).

Termination of pregnancy was requested in two cases before 24 weeks of gestation. Of the remaining three affected pregnancies which were continued, one was regularly scanned in our unit. In this particular case (no.IV, 4; Table 1), there was renal enlargement, increased echogenicity of the renal parenchyma and absence of bladder filling at 22 weeks; oligohydramnios had only developed at 28 weeks. These three affected pregnancies delivered spontaneously at 36-37 weeks. Neonatal death from respiratory insufficiency occurred in each instance. Permission for autopsy was only given in two (no.III,5; no.IV,7) out of these five affected pregnancies. In both cases, mildly enlarged kidneys with cystic dilatation of the collecting tubules was documented. Normal calyces, pyela and ureters were present. The bladder was small. Histology of the liver revealed periportal fibrosis and bile duct proliferation. One fetus (no.III,5) displayed multiple small cysts in the pancreas. In the other case (no.IV.7), the prenatal diagnosis of associated hydrocephaly was confirmed. Both fetuses had low set ears. There were no signs of lung hypoplasia.

A distended abdomen with a palpable mass in both flanks was noted in the remaining three affected infants in which no autopsy was permitted (nos.IV,4; V,3; VII,14).

Normal prenatal ultrasound findings of the fetal kidneys were present in 10

Table I Prenatal renal findings in 15 pregnancies from seven families at risk of ARPKD

| Pat. no. | Pregnancy no. | Consanguinity | Gest.age (wks) at recurrence | Renal enlargement | Increased echogenicity | Postnatal findings |
|---|---|---|---|---|---|---|
| I | 2 | + | — | — | — | A & W |
| | 3 | + | — | — | — | A & W |
| II | 2 | - | — | — | — | affected |
| III | 3 | + | — | — | — | A & W |
| | 4 | + | — | — | — | A & W |
| | 5 | + | 23 | + | + | affected |
| IV | 3 | + | — | — | — | A & W |
| | 4 | + | 22 | + | + | affected |
| | 5 | + | — | — | — | hydrocephaly |
| | 6 | + | — | — | — | A & W |
| | 7 | + | 17 | + | + | affected + hydrocephaly |
| V | 2 | - | — | — | — | A & W |
| | 3 | - | 23 | + | + | affected |
| VI | 3 | - | — | — | — | A & W |
| VII | 14 | - | 26 | + | + | affected |

Table II Prenatal extra-renal and postnatal findings in 15 pregnancies from seven families at risk of ARPKD.

| Pat. no. | Pregnancy no. | No bladder filling | Oligo-hydramnios | Other anomalies | Postnatal findings |
|---|---|---|---|---|---|
| I | 2 | — | — | — | ♀, A & W |
| | 3 | — | — | — | ♀, A & W |
| II | 2 | — | — | — | ♀, affected |
| III | 3 | — | — | — | ♂, A & W |
| | 4 | — | — | — | ♀, A & W |
| | 5 | — | — | — | TOP, ♂, affected |
| IV | 3 | — | — | — | ♂, A & W |
| | 4 | + (22 wks) | + (28 wks) | — | ♀, †, affected |
| | 5 | — | — | hydrocephaly | TOP, ♂, † |
| | 6 | — | — | — | ♀, A & W |
| | 7 | — | — | hydrocephaly | TOP, ♂, affected |
| V | 2 | — | — | — | ♂, A & W |
| | 3 | — | — | — | ♀, †, affected |
| VI | 3 | — | — | — | ♀, A & W |
| VII | 14 | + | + | — | ♂, †, affected |

TOP= termination of pregnancy
A & W =alive and well.

out of 15 pregnancies. Serial scans were carried out in all ten cases, seven of which into the third trimester of pregnancy. There was one case of isolated hydrocephaly diagnosed at 16 weeks (no.IV,5). Pregnancy was terminated and the abnormality confirmed, the kidneys and liver were histologically normal.

The course of the remaining nine pregnancies was uneventful. After delivery one infant (no.II,2) which showed negative scans up to 30 weeks, revealed a distended abdomen at postnatal examination, caused by bilaterally enlarged kidneys. A subsequent renal scan showed polycystic kidneys. This female infant is now three years old and suffers from hypertension, intercurrent urinary tract infections and renal tubular dysfunction. The remaining eight infants are alive and well, their age varying between ten months and seven years.

## Discussion

The principal problems relating the prenatal diagnosis of ARPKD are the variability in onset and the limitation of excluding the disease with certainty by early pregnancy ultrasound examination (Simpson et al., 1982; Romero et al., 1984; Luthy and Hirsch, 1985). Since the disorder does not involve the ureteral bud and affects already well developed collecting ducts after normal or completed branching, manifestation of ARPKD may not occur early in pregnancy (Zerres et al.,1984; 1988). This must be clearly stated during genetic counselling and may influence the parents attitude towards the ultrasound examination. One of the couples in our study refused scans during the second half of the second trimester of pregnancy because of potential psychological problems arising from a possible late detection.

In the present study, six out of 15 monitored pregnancies (40%) displayed a recurrence of ARPKD. Retrospectively, the seven investigated couples had a total of 30 off-spring, 14 (47%) of which were documented to be affected. This latter percentage significantly exceeds the expected 25% based on a recessive autosomal inheritance pattern ($p < 0.05$, binomial test). Prenatal diagnosis of a recurrence of ARPKD was made in five out of six cases, four of which before 24 weeks of gestation. Although autopsy was only carried out in two affected infants, the clinical findings in the remaining three cases were as such that ARPKD could be assumed to be present.

In all five prenatally diagnosed cases, the recognition of ARPKD was based on a combination of renal enlargement and increased parenchymal echogenicity. The echogenicity of the renal parenchyma is increased in both renal cortex and medulla. This hyperechogenic texture is attributed to sound enhancement by the microscopic cystic structures, present in the renal parenchyma.

Oligohydramnios associated with ARPKD has been reported as early as 16 - 20 weeks of gestation (Morin et al.,1981; Jung et al.,1982; Romero et al.,1984; Luthy and Hirsch 1985; Zerres et al.,1988). On the other hand normal amounts of amniotic fluid have been described even in cases belonging to the perinatal type (Weiss et al.,1981; Simpson et al.,1982; Romero et al.,1984). Of the six affected pregnancies in our study only two presented with absent fetal bladder

filling and oligohydramnios. In both instances pregnancy had advanced into the second half of the second or early third trimester. Therefore, the prenatal diagnosis of ARPKD should be based on the typical hyperechogenic texture of the kidneys and not, as postulated (Romero et al., 1988), on the presence of oligohydramnios and the absence of bladder filling. The latter two parameters reflect urine production and provide valuable adjunctive information.

When prenatal ultrasound reveals the presence of polycystic kidneys, the differential diagnosis should include ARPKD, early manifestation of autosomal dominant polycystic kidney disease and the Meckel Syndrome (Zerres et al.,1984; 1988). A detailed family history and a sonographic search for other manifestations of the Meckel Syndrome like polydactyly and encephalocele should lead to the correct diagnosis. In the present study, patient IV (Table I) may have been at risk of a separate entity of polycystic kidney syndrome associated with hydrocephaly. Since one male fetus was affected by hydrocephaly only (no.IV,5) and the other male fetus (no.IV,7) had hydrocephaly, polycystic kidneys and liver abnormalities there may have been a risk for two different genetic disorders as a result of consanguinity. Alternatively, X linked hydrocephaly might be considered as a separate genetic risk in this family. Different expression of one entity can also be considered. Metabolic studies in the index case or affected infant were not performed.

Although the degree of severity of ARPKD is said to be fairly constant within a given family, the possibility of intrafamilial variability has to be borne in mind (Zerres et al.,1984; Kaplan et al.,1988). The variability in time of onset in utero can also be quite considerable within one and the same family (Luthy and Hirsch 1985). Even in case of a proven early ARPKD in a previous infant, a valid and early prenatal diagnostic exclusion by ultrasound in a subsequent pregnancy cannot be guaranteed. Moreover, the disease represents a continuum of renal and hepatic disease rather than precise clinical, pathological and genetic variants.

The variability of ARPKD makes a long-term follow up of all off-springs necessary. In such a follow up, emphasis should not only be put on renal function, but should also include possible development of isolated hepatic fibrosis.

In conclusion, recurrence of ARPKD may be diagnosed prenatally by ultrasound, but the variability in onset, the intrafamilial variability and limitations in excluding a recurrence of ARPKD during the second and third trimester of pregnancy remains a difficult problem concerning the reliability of prenatal diagnosis. In the light of the awareness of a high-recurrence risk, all these factors may result in an ambivalent and emotional attitude of couples towards serial ultrasound scanning during pregnancy. This should be kept in mind when genetic counselling is provided.

**Acknowledgement**

We are grateful to the Clinical Genetics Foundation Rotterdam for their financial support.

### 5.3.2 *Autosomal dominant polycystic kidney disease*

Dominant polycystic kidney disease is the most common form of renal cystic disease with a frequency of 1 per 1000 (Spence et al.,1957). It is characterized by bilateral involvement and progressive enlargement of renal cysts. The cysts vary in size, and are usually connected to some part of the nephron or collecting duct. Up to 50% of the patients have cysts of the liver, cysts in other organs occur less frequently (pancreas, spleen, lungs, ovaries and testes) and rarely have clinical sequelae. Aneurysms of the circle of Willis (berry aneurysms) occur in 10-30 per cent of the patients (Levey et al., 1983).

Dominant polycystic kidney disease may manifest clinically at any age but most often a diagnosis is made after 30 years of age. With the advent of sonography, presymptomatic diagnosis becomes possible at earlier age.

Dominant polycystic kidney disease is rarely discovered in the infant or the fetus. Its outcome is variable. Some patients die during the first year of life. The diagnosis of dominant PKD in a symptomatic infant identified with cystic kidney disease may be difficult and will need confirmation by identifying an affected parent or grandparent.

The gene of ADPKD has been localised on the short arm of chromosome 16 (Reeders et al.,1985) and prenatal diagnosis of ADPKD has been performed using the closely linked polymorphic DNA marker (Reeders et al.,1986). The demonstration of microscopic changes in these kidneys at a gestational age of 12 weeks gives insight into the pathogenesis of cystic kidneys.

Genetic heterogeneity, however, is present and in some families there is no linkage to the gene on chromosome 16 (Romeo et al., 1988).

*Ultrasound diagnosis.*

Prenatal ultrasound diagnosis of a fetus with an early manifestation of ADPKD has been reported by Zerres et al.(1982). Therefore, prenatal examination of fetal kidneys at risk for ADPKD seems to be indicated since an early manifestation may occur. The kidneys may be of normal size or enlarged. In adults the onset is often asymmetric. The size of the cysts may vary from small to grossly visible. However, normal ultrasound findings do not exclude ADPKD. The only reliable prenatal diagnosis can be provided by restriction length polymorphism studies using markers on chromosome 16 with the help of chorionic villus biopsy. With the use of flanking markers, the risk of recombination between the markers and the disease locus resulting in an false diagnosis is less than 1 per cent (Breuning et al., 1987).

The variability of the disease, the lack of perception of its potential severity, and the tendency of medical specialists caring for ADPKD patients to be reluctant about genetic counseling are all factors that have a negative effect on utilisation of genetic counselling services in ADPKD families.

### 5.3.3 *Polycystic kidney disease in the fetus or the infant.*

*Considerations regarding the differential diagnosis between the dominant and the recessive type.*

The symptoms and findings of ADPKD and ARPKD in the fetus or infant may be confusingly similar. Both seperate entities have a great variability in age of manifestation. In infants, the incidence of early manifestation of ADPKD is more frequent than the incidence of ARPKD. The manifestation of ADPKD in childhood is probably more common than thought before.

Imaging studies, morphologic studies, clinical data and family study are essential for the differential diagnosis. Examination of both liver and kidneys is indicated since major constant differences between ADPKD and ARPKD exist in liver pathology. Also in sporadic cases a distinction between ADPKD and ARPKD may be provided after investigation of the type of liver involvement and of the family. In perinatal lethal cases histology is necessary. In childeren who survive, imaging studies usually solve the diagnosis and histological studies are seldom needed (Kääriäinen, 1988).

In imaging studies, macroscopic kidney cysts are seen in ADPKD at ultrasound or computed tomography (CT). However in ARPKD typical kidney involvement can change in cases of survival beyond the first months of life. Cysts become different in size, larger cysts begin to compress the renal pelvis (resembling the changes in ADPKD). Enlargement of collecting tubules in intraveneous pyelography, strongly enhanced renal echogenicity and cortical accentuation of contrast in CT are typical but not pathognomonic for ARPKD.

In morphologic studies, the variable cyst epithelium and presence of also glomerular cysts are typical for ADPKD. Patients with ARPKD do not have berry aneurysms or cysts of the liver or any other organ as occurs in ADPKD. The liver of infants with ARPKD has varying degrees of bile duct proliferation, dilatation and abnormal branching, in addition to varying amounts of periportal fibrosis.

The final diagnosis is not only of importance for the determination of the inheritance pattern but also has its impact on the prognosis. Some authors state a better prognosis for infants with ADPKD than for those with ARPKD (Loh et al.,1977), while others (Zerres et al.,1987) describe a usually more insidious course in the dominant than in the recessive type of disease.

Nowadays, genetic marker studies can be performed for the dominant type of PKD. But in isolated cases this can not be regarded at as a diagnostic tool.

### 5.3.4 *Congenital nephrosis (Finnish type).*

Congenital nephrosis of the Finnish type is an autosomal recessive disease characterised by a placenta weighing more than 1 /4th of the birthweight and cystic dilatation of the proximal tubules in both kidneys. Tubular dilatation may not be present initially (Hallman et al., 1973). Excessive amounts of protein loss in the urine already are detectable in most cases in the second trimester

by the elevation of alpha-feto-protein (AFP) in amniotic fluid (Wiggelinkhuizen et al., 1976). The proteinuria is unresponsive to therapy and death usually occurs within the first 2 years of life. The differential diagnosis includes Galloway syndrome (congenital nephrosis with microcephaly) which does not show prenatal elevation of amniotic fluid AFP.

*Ultrasound picture.*

The detection of structural renal changes by ultrasound during pregnancy is not possible. In some cases a thickenend and edemateous placenta may be established.

### 5.3.5 *Syndromal associations of renal cystic disease.*

Renal cystic changes occur with a varying incidence in numerous syndromes (Table 1). The morphologic findings in the kidneys are very heterogeneous. Many syndromes reveal very discrete changes of the kidneys. Cystic kidneys can be the only symptom in Meckel syndrome, tuberous sclerosis or von Hippel-Lindau syndrome. Therefore, in all cases with renal cystic changes, genetic syndromes and non-hereditary malformation complexes should be taken into consideration.

*Ultrasound picture.*

The picture is variable since the macroscopic description of the renal abnormalities depends on the microscopic changes, which are multiform.

Table 1. Multiple malformation syndromes associated with cystic kidneys

| | Inheritance |
|---|---|
| Meckel syndrome | a.r. |
| Short rib polydactyly syndromes | a.r. |
| Zellweger syndrome | a.r. |
| Tuberous sclerosis | a.d. |
| von Hippel-Lindau syndrome | a.d. |
| VATER association | variable |
| Retina renal dysplasia syndromes | a.r. |
| Ivemark syndrome | a.r.,mfr. |
| Fryns syndrome | a.r. |
| Different chromosomal disorders | - |
| Asphyxiating thoracic dystrophy (Jeune) | a.r. |
| Oral-facial-digital syndrome I | X-l |
| Laurence-Moon-Bardet-Biedl syndrome | a.r. |
| Kaufman-McKusick syndrome | a.r. |
| Hypothalamic hamartoma syndrome | n.i.? |
| Lissencephaly syndromes | variable |
| Prune Belly syndrome | variable |
| Ehler-Danlos syndromes | variable |
| Branchio-oto-renal syndrome | a.d. |
| Roberts syndrome | a.r. |
| DiGeorge syndrome | variable |
| Smith-Lemli-Opitz syndrome | a.r. |
| Wiedemann-Beckwith syndrome | mfr, a.d. |

a.r.= autosomal recessive, a.d.= autosomal dominant, n.i.= not inherited, X-l= X linked, mfr.= multifactorial inheritence. (adapted from Zerres, 1987)

## 5.3.6 *Prenatal diagnosis of cystic kidney disease with ventriculomegaly. A report of six cases in two related sibships.*

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Department of Obstetrics and Gynecology (A.R., J.W.W.), Department of Pathology (J.C.den H.), Department of Clinical Genetics (M.F.N., O.P.van D., D.L., F.J.L.), Erasmus University Rotterdam, Rotterdam, The Netherlands.
American Journal of Medical Genetics: in press


**Summary**

In two consanguineous relationships, a Cape Verdian man fathered six fetuses (5 male) with fetal ventriculomegaly and echodense fetal kidneys as visualised by ultrasonography between 16 and 32 weeks.

During prenatal monitoring, an increased alpha-fetoprotein level and abnormal acetylcholinesterase were detected at amniocentesis in 5 of 6 affected fetuses. Chromosomes were normal. Five pregnancies resulted in elective termination; one child was still-born prematurely. Hydrocephalus and cystic disease of the (renal) corticomedullary areas were found. One fetus had polydactyly. The differential diagnosis and prenatal diagnosis of this presumably autosomal recessive syndrome are discussed.

*Keywords* - Alpha-fetoprotein - acetylcholinesterase - ventriculomegaly - renal cystic disease - prenatal ultrasonography - autosomal recessive inheritance - consanguinity.

*Clinical reports*

Mrs.IV-1, a healthy 30 year old primigravida (Fig.1), originating from the Cape Verde Islands, was seen for an ultrasound scan at a gestational age of 32 weeks because of a large-for-date uterus. A fetus with ventriculomegaly, normal-sized very echodense kidneys and an increased amount of amniotic fluid was found at ultrasound examination (Table I). Shortly thereafter the male infant was stillborn. Postmortem examination showed normal sized kidneys with cystic tubular dilatation in the corticomedullary area and renal medulla containing eosinophilic (Haematoxylin-azophloxin) staining amorphous proteineous material. Brain had autolysed and was unsuitable for further analysis. The placenta weighed 400 grams, 25% of the infants weight, and was otherwise unremarkable.

In four subsequent pregnancies amniocentesis and ultrasound examination were performed. In 3 pregnancies we found a markedly elevated alpha-fetoprotein (AFP) level and abnormal acetylcholinesterase (AChE) (Fig.2) with a normal male or female chromosome constitution. Ultrasonography in these 3 pregnancies demonstrated severe ventriculomegaly and normal-sized, very echodense kidneys (Fig. 3). Bladder filling was observed and the amount of amniotic fluid was normal.

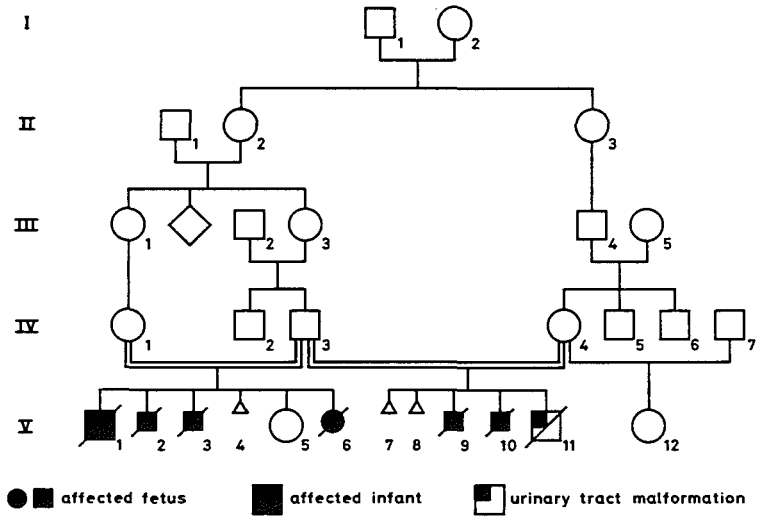


Fig. 1. Pedigree.

Table 1. Clinical Manifestations

| | Prenatal findings | | | | Postnatal findings | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Pregnancy | Gest.age at diagnosis(wk) | AFP µg/ml | AChE | Ultrasound findings | Gest.age at delivery(wk) | Sex | Kidneys micr.abn. | Ventriculo-megaly | Associated anomalies |
| V-1 | 32 | NS | NS | v.e.k. | 32 | ♂ | + | + | — |
| V-2 | 16 | 1239 | + | v.e.k. | 18 | ♂ | + | + | — |
| V-3 | 16 | 1500 | + | v.e.k. | 18 | ♂ | + | + | — |
| V-5 | 16 | 21 | — | normal | 39 | ♀ | — | — | — |
| V-6 | 17 | 1438 | + | v.e.k. | 18 | ♀ | + | + | polydactyly |
| V-9 | 19 | 1111 | + | v.e.k. | 20 | ♂ | + | + | - |
| V-10 | 17 | 1806 | + | v.e.k. | 19 | ♂ | + | + | — |
| V-11 | 16 | 30 | — | normal | 22 | ♂ | unilat.double collecting system | — | — |

V-2: other partner, healthy female infant; V-4: spontaneous abortion; V7+8: pregnancy termination for social reasons; v.e.k.: ventriculomegaly, echodense kidneys; AChe: acetylcholinesterase, the isoenzyme in amniotic fluid associated with neural tube defects; NS: not studied.

Pregnancy termination was requested by the parents in all 3 cases. The autopsy findings confirmed the prenatal diagnosis of cerebral and renal anomalies. The brain showed dilatation of the lateral ventricles and focal hyperplasia of the chorioid plexus. No obvious obstruction as cause for the hydrocephaly could be found. The normal-sized kidneys demonstrated multiple small cysts in the corticomedullary area and in the renal medulla (Fig.4). No further anomalies

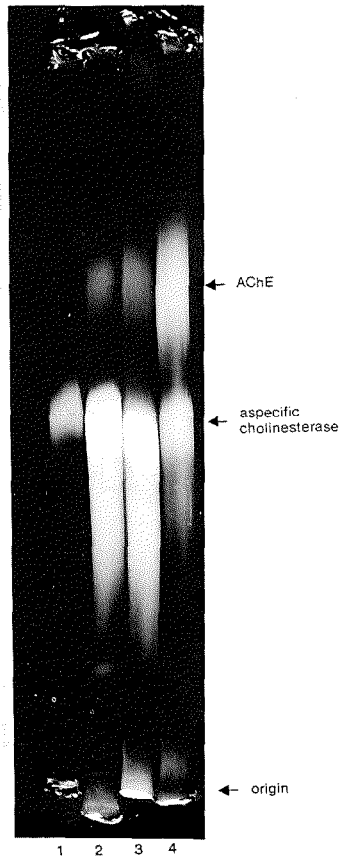


Fig. 2. Analysis of acetylcholinesterase (AChE) from amniotic fluid.
Acetylcholinesterase was separated by polyacrylamide gel-electrophoresis and stained according to Brock and Hayworth, 1980. Amniotic fluid samples: normal (1); pregnancy V-2 (2); pregnancy V-9 (3); and, spina bifida (4).

were found at macroscopic and microscopic examination except postaxial polydactyly was present in one fetus (V-6). One fetus (V-5) had normal chromosomes and ultrasound findings; a healthy girl was born at term.

IV-4 is a healthy, 30-year-old gravida 4 para 1 woman who was seen at a gestational age of 19 weeks for routine ultrasound examination. She had a healthy girl from a previous relationship. Two further pregnancies were terminated for social reasons.

In the present pregnancy, a single fetus (V-9) with ventriculomegaly, normal-sized echodense kidneys and a normal amniotic fluid volume was observed.

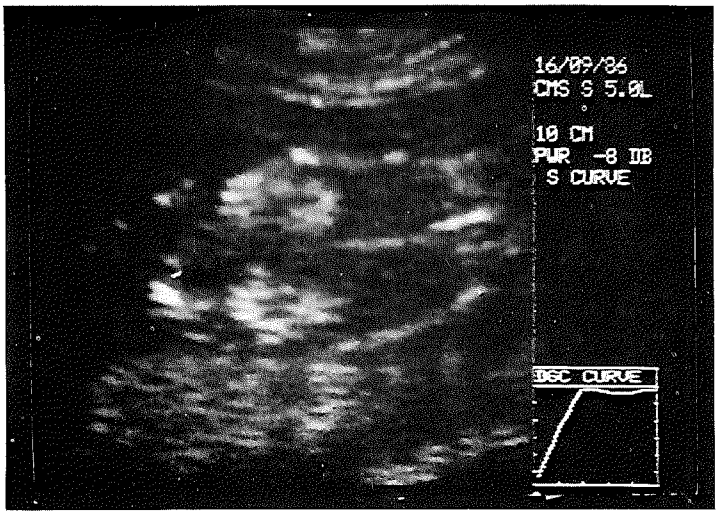


Fig. 3. Ultrasound image of a longitudinal cross-section through the fetal abdomen. Both kidneys have a very echodense aspect.

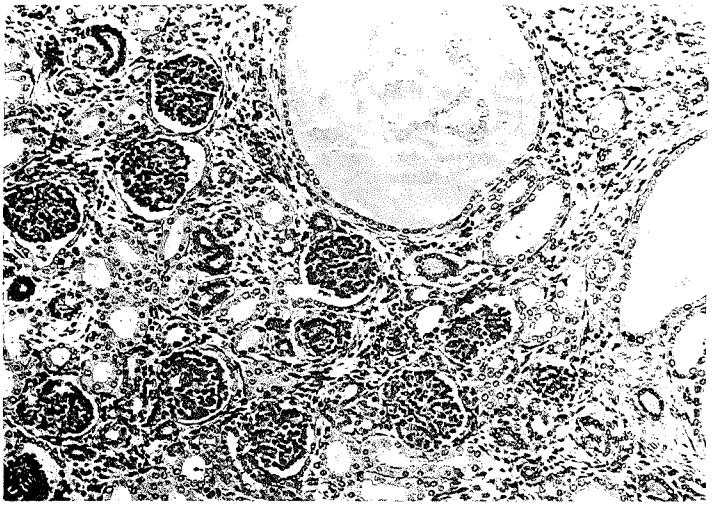

Fig. 4. Photomicrograph of the kidney of Fig. 3.

After amniocentesis, an elevated AFP, abnormal AChE (Fig.2) and normal chromosomes were established. The pregnancy was terminated at the request of the parents. At autopsy dilatation of the lateral ventricles was found in

combination with normal-sized kidneys containing multiple cysts in the corticomedullary area and medulla with strongly eosinophilic staining amorphous proteineous material.

In the following pregnancy amniocentesis at a gestational age of 17 weeks showed normal chromosomes, an elevated AFP and abnormal AChE. Ultrasonography showed ventriculomegaly and normal-sized, echodense kidneys. The parents elected for pregnancy termination. At autopsy hydrocephaly and multiple cysts in the corticomedullary and medullar zone were confirmed. Zellweger syndrome and other peroxisomal disorders were considered. Cultured fibroblasts showed normal very long chain fatty acid oxidation. In the 6th pregnancy normal amniotic fluid AFP and ultrasound findings were documented. However, premature rupture of membranes resulted in the delivery of a stillborn male at 22 weeks (V-11).

At autopsy the right kidney was slightly enlarged due to a duplication of the kidney and proximal ureter. The contralateral kidney showed no abnormalities and both kidneys were microscopically normal.

## Discussion

The 6 abnormal fetuses of both sexes from two consanguineous relationships of the same father showed an identical pattern of brain and kidney malformations. Wrights coefficient of inbreeding (F) is 1/16 for the first and 1/64 for the second sibship.

Prenatally the fetuses had ventriculomegaly and very echodense kidneys at ultrasound examination. The amniotic fluids contained elevated amounts of AFP and AChE. The levels of AFP were much higher than those found in neural tube defects (anencephaly included) and appear to be characteristic for severe renal defects (Brock et al. 1980). AChE was also abnormal, but the levels were lower than those found in spina bifida; fetuses with hydrocephaly do not show an abnormal AChE (Crandall et al. 1982). Therefore it is concluded that the AChE, like AFP, originates in this syndrome from fetal blood and enters the amniotic fluid compartment through the defective kidneys. This combination of abnormal AChE and increased AFP in the presence of renal abnormalities has not been reported previously (Brock et al. 1980; Crandall et al. 1980, Aitken et al. 1984 and Crandall and Matsumoto, 1986).

At autopsy all fetuses showed a variable dilatation of the lateral cerebral ventricles. No anatomical or histological cause for the hydrocephaly could be found. The size and weight of the kidneys of the affected fetuses was normal.

At microscopic examination an identical pattern of cystic dilatation of the renal tubules was seen. The cysts were localised in the corticomedullary area and in the renal medulla; they had a maximum diameter of approximately 0.1 cm and were lined with one layer of cuboidal epithelium. They contained an eosinophilic staining amorphous proteineous material. These renal changes can

not be classified according to the Potter classification. No further anomalies were found at macroscopic and microscopic examination except postaxial polydactyly was present in one fetus. No signs of hepatic fibrosis or abnormal cystic bile duct proliferation were present.

Renal cystic changes have been described in many syndromes (Zerres et al. 1984), and often constitute very discrete changes of the kidneys. With reference to minimal renal changes Potter's classification is particularly limited.

In the differential diagnosis the Meckel syndrome, Smith-Lemli-Opitz (SLO) syndrome, Zellweger syndrome or some other association of hydrocephaly and cystic kidneys or congenital nephrosis were considered.

In the 6 fetuses described above the renal changes were essentially different from those seen in the Meckel syndrome. The absence of hepatic lesions (Zerres, 1981) and the unique occurrence of postaxial polydactyly do not justify the diagnosis of Meckel syndrome.

Zellweger syndrome (Wilson, 1986) and the pseudo-Zellweger syndrome (Goldfischer, 1986) were excluded since normal very long chain fatty acid oxidation was shown (fetus V-10).

In the SLO syndrome, the kidneys, if abnormal, tend to be hypoplastic, and small cysts may be seen confined to the cortex. Other more nonspecific urinary tract abnormalities include ectopic kidney, hydronephrosis, bifid collecting system and renal agenesis (Lowry, 1983).

Congenital nephrosis of the Finnish type is a distinct entity showing an elevated AFP level at amniocentesis (Wiggelinkhuizen et al. 1976), a placenta weighing more than 1 /4 of the birth weight and renal histology revealing cystic dilatation of the tubulus particularly in the juxta-medullary area (Hallman et al. 1973). The distribution of the cysts in our two families seems similar but quantity and size are not.

Sinclair-Smith et al. (1980) describe the renal histology from two sibs with similar abnormalities consisting of isolated hydrocephalus with associated familial nephrotic syndrome. The latter had a milder course than the Finnish type of congenital nephrosis and was diagnosed antenatally by elevated AFP levels at amniocentesis. However, at histologic examinations of the kidneys only in one case cysts were present, mainly in the deep cortical area. Also the presence of glomerular cysts was noted. In the other surviving case no cysts were present. In our cases the presentation of renal pathology was identical in all affected fetuses, the cysts were mainly localised in de medulla and no glomerular cysts were present.

The relation between renal and brain pathology as evidenced by this and other syndromes has been supposed to originate from a common mesoectodermal dysplasia (Kornguth et al. 1977). It is still speculative, if defects of cell adhesion molecules, shared by brain and kidneys like N-CAM (neural cell adhesion molecule) might explain pathological changes in different organs (Edelman, 1984; Rutishauer and Goridis, 1986).

To our knowledge, the combination of anomalies in the 6 fetuses, i.e.

hydrocephaly and cystic dilatation of the renal tubules in the corticomedullary area and the medulla, has not been described. The expression of this syndrome was remarkably consistent in all affected pregnancies. The inheritance pattern of this syndrome is most probably autosomal recessive, in view of parental consanguinity and absence of renal disease in the parents.

Prenatal diagnosis is specifically possible on the basis of the combined findings of ventriculomegaly of early onset, echodense kidneys of normal size at ultrasound, and abnormally elevated levels of AFP and AChE.

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## 5.4 Multifactorial inherited cystic kidney disease.

*Multicystic dysplasia (multicystic kidney).*

Multicystic dysplasia is the most common form of cystic disease in infants. Dysplasia represents a variable picture, and results from abnormal metanephric development. Involvement may by unilateral, bilateral or segmental. The kidneys range from being extremely large with large cysts and little stroma to extremely small having microscopic cysts and more stroma. Potter referred to the large cystic variety as type IIA and the small variety as type IIB cystic disease. Both entities show cysts, whether large or small, and primitive ducts. Mature glomeruli may be present although sparse. The liver is not involved.

Multicystic kidneys are associated with a nonpatent drainage system in which there is either pelvi-infundibular atresia, or an absent or atretic ureter. Contralateral hydronephrosis is present occasionally, which usually is due to obstruction at the pelvico-ureteric junction. Multicystic kidneys appear on the left side more frequently, a finding associated with some obstructive conditions, such as uretero-pelvic junction obstruction and primary obstructive megaureter (Glassberg and Filmer, 1985).

Bilateral disease is incompatible with life, and can be associated with oligohydramnios, pulmonary hypoplasia and the features of the oligohydramnios sequence.

Since multicystic kidneys are associated with a nonpatent drainage system, various authors have debated their etiology, particular as to whether they are secondary to early severe obstruction. Current research is aimed at determining why kidneys associated with obstruction of the ureter are predominantly hy-

dronephrotic and those with ureteral atresia are mainly dysplastic.

The role of genetic factors in cystic dysplasia remains unclear. The overall risk of recurrence after the birth of one affected child is low, probably less than 10 %, suggesting multifactorial inheritance (Zerres et al., 1984). Manifestation may occur as unilateral or bilateral agenesis, unilateral or bilateral dysplasia, or a combination of both (unilateral agenesis and contralateral dysplasia) known as heriditary renal adysplasia (Buchta et al.,1973). One known teratogenic factor for renal dysplasia is maternal diabetes (Soler, 1976).

*Ultrasound picture.*

Frequently the findings are asymmetric. Unilateral cystic kidney nearly always belongs to the dysplastic type. The size of the kidney may vary from small to enlarged. The size of the cysts are also variable from small (hardly visible at ultrasound examination) to extremely large. The shape of the kidney can still be reniform but sometimes it is replaced by an enormous cystic mass without any recognisable kidney tissue (Fig.1). Only if both kidneys are non-functioning, oligohydramnios will be present.

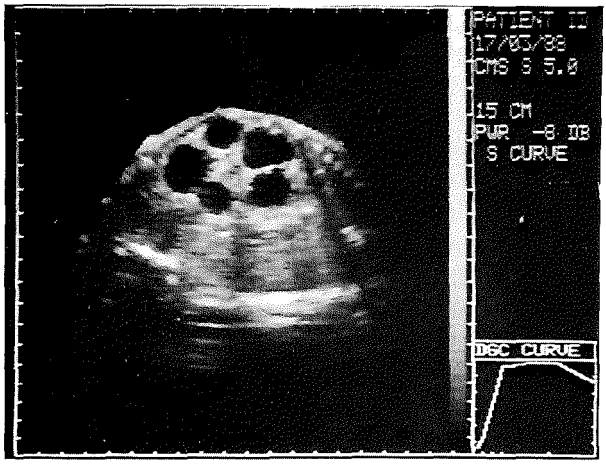


Fig.1 Ultrasonic picture of a multicystic kidney in a fetus of a gestational age of 26 weeks

## 5.5 Closing remarks.

Depending on kidney changes, the pathological, macroscopical and clinical picture of cystic kidney disease can be extremely variable. No classification exists in which all the entities can be seperately defined according to pathologic, morphological, clinical and genetical criteria. Imaging studies, like ultrasound provide a macroscopic description of the kidneys. The combination of examination of kidneys and liver, clinical data, family history and the presence of associated anomalies is mandatory to obtain a final diagnosis.

Polycystic kidney disease encompasses two rather circumscript genetic entities, ARPKD and ADPKD. Both forms of polycystic kidney disease demonstrate a marked variablity in onset and intrafamilial variability. Major differences are found in liver pathology and family history.

The recessive form represents a continuum of renal cysts and hepatic fibrosis rather than precise clinical, pathological and genetic variants. There appears to be an inverse relationship of recessive polycystic kidney disease with congenital hepatic fibrosis (Zerres et al., 1984). The use of ultrasound to monitor pregnancies at risk for this particular disease is limited and this should be pointed out at genetic counselling. On the basis of the typical hyperechogenic texture of the kidneys, a recurrence can be detected early in pregnancy, but may not be excluded. Still ultrasound is the only known method to provide some information during pregnancy about a possible recurrence. Therefore, referral to a centre with particular ultrasound experience in this field should be offered to parents at risk after careful explanation of the limitations.

For pregnancies known to be at risk for ADPKD the use of prenatal ultrasound is also limited. A reliable prenatal diagnosis can only be provided by DNA-studies after chorionic villus sampling. Prenatal ultrasound diagnosis may only be of some value for the detection of a rare occurrence of a severly affected offspring known to be at risk. If a fetus displays cystic kidneys, other diagnostic possibilities remain like a sporadic occurrence or an affected infant of a parent not yet identified as having cystic kidney disease.

In polycystic kidney disease the kidneys are affected symmetrically. The dominant form, although, may present in adults with a picture of assymmetric affection at the onset of the disease.

Cystic kidneys may also occur as part of a syndrome or may be the only manifestation of a syndrome.

Dysplastic kidneys occur often unilateral, and are often associated with ureteral obstruction. Malformations of the contralateral system may be present, strongly influencing the prognosis. In contrast with polycystic kidney disease liver changes are not present in cystic dysplasia. Frequently cystic dysplasia presents as part of a syndrome.

In case of bilateral disease the oligohydramnios sequence will be present, and the prognosis is uniformly poor. In unilateral cystic dysplasia the function of the contralateral kidney and the possible presence of associated anomalies will determine the prognosis. Ultrasound study during pregnancy will easily reveal the presence of a huge dysplastic kidney. Small dysplastic kidneys may be difficult to identify at prenatal ultrasound. The kidney mass is small and the aspect is abnormal. In the presence of oligohydramnios, absent bladder filling and if no normal renal tissue is identified, bilateral renal agenesis or cystic dysplasia may be suspected. It may be difficult to differentiate ultrasonically between these two entities, which is not of major importance for the prognosis of the affected fetus. Also genetically these two entities are related since renal dysplasia and agenesis may occur within one individual and within one family.

Chapter 6

# Sonographic, clinical and genetic aspects of prenatal diagnosis of fetal obstructive uropathy.

## Introductory remarks

Urinary tract obstruction, vesico-ureteral reflux and parenchymal dysplasia are the most frequent congenital lesions of the uropoietic system. They represent 30-40% of all cases of chronic renal insufficiency. In Europe, the prevalence of this condition is estimated to be 20 in 100.000 children between 0-15 years (proceedings of the European Dialysis and transplantation Association, 1980).

Dilatation is not synonymous with obstruction. The term obstructive uropathy encompasses a wide variety of different pathological conditions characterized by dilatation of part or all of the urinary tract. The reason for an obstruction can be structural or functional. The localisation can be high (level of ureter) or low (level of urethra). The obstruction can be complete or partial.

The consequences of an obstructive uropathy for the kidney and the upper urinary tract, mainly depend on the severity of the obstruction. These consequences consist of dilation of the urinary tract above the level of obstruction and increase of pressure inside the kidney, possibly resulting in structural or functional changes. Especially distal tubulus and collecting tubulus function are threatened causing a disturbance of the concentrating capabilities (salt-losing and renal acidosis of the distal type). In case of a more severe obstruction also a decrease of glomerular function is noted resulting in a reduced clearance.

The moment of detection of a congenital obstructive uropathy depends on the localisation and the severity of the obstruction. The clinical manifestation of the infra-vesical obstruction varies from acute oliguric renal insufficiency in the neonate to micturition problems in the older infant. In high-level obstruction the presentation may vary from a palpable abdominal mass to hematuria. Some of these anomalies are detected during the study of a child following diagnosis of a particular abnormality known to be often associated with urinary tract pathology (e.g. congenital cardiac anomalies).

The prognosis of obstructive uropathy depends on the localisation, severity and time of obstruction. Early recognition and early decompression of an obstructive uropathy have been a widely accepted postulate for many years. The aims of postnatal management are the preservation of renal function and the prevention of infection.

Following this introduction attention will first be focused on the significance of ultrasound in imaging high and low level fetal obstructive uropathies (Chapter 6.1). This will be followed by a first account of the prenatal management and

outcome of fetal obstructive uropathies in our department between January 1982 and January 1986 (Chapter 6.2). The role of fetal urinary electrolyte determinations in assessing renal function in the presence of obstructive uropathy will be examined in Chapter 6.3. The outcome of 43 consecutive cases of fetal bladder outlet obstruction in which no in utero decompression was undertaken, will be discussed in Chapter 6.4. Also the impact of associated extra-renal structural and /or chromosomal anomalies on fetal outcome will be determined. Chapter 6.5 will provide a short overview on the genetic aspects of obstructive uropathy. In Chapter 6.6 there will be a general comment on the pathophysiology, diagnosis and the possibilities of in utero decompression of fetal obstructive uropathy. Closing remarks will be presented in chapter 6.7.

## 6.1 Ultrasound diagnosis.

Obstructive uropathies can be divided into upper and lower level obstruction. In both instances, hydronephrosis (unilateral or bilateral) may develop. Prenatal ultrasound can accurately establish the presence and level of an urinary tract anomaly.

The site of the obstruction is classified as high (level of ureter) or low (level of urethra). High level obstructions are diagnosed by identifying an isolated dilated renal pelvis or /and the presence of ureteral dilatation. This includes cases of dilated ureters with or without dilatation of the renal pelvis. Low level obstructions are identified by dilatation of the bladder and proximal urinary tract. Sometimes, a dilated urethra can be demonstrated.

A morphological classification has been presented by Grignon et al. (1986), who recognised five grades of hydronephrosis in the fetus:

grade I: physiological calyceal dilatation and size of the renal pelvis less than 10 mm;
grade II: normal calyces and size of renal pelvis 10-15 mm;
grade III: slight calyceal dilatation and size of the renal pelvis $>$ 15 mm;
grade IV: moderate dilatation of the calyces, with easily identified residual renal cortex and size of pelvis $>$15 mm;
grade V: severe dilatation of the calyces with atrophic cortex and size of the pelvis $>$ 15 mm.

Grade I should be considered normal. Grades II and III constitute an intermediate hydronephrosis. Grade IV and V are clearly pathologic.

The degree of dilatation of the renal pelvis is variable. In some patients, there may be severe obstruction and renal dysplasia in the absence of marked distension of the renal pelvis. This can be explained by:(i) renal dysplasia resulting in decreased urinary production; (ii) rupture at the level of the bladder or any other point along the urinary tract resulting in decompression of the renal pelvis;(iii) pelvi-ureteric atresia.

Mild transient hydronephrosis has been described in the fetus without the evidence of renal tract anomalies after birth (Deutinger et al., 1984). Therefore,

also normal physiological changes in the size of the pyelum have to be considered, as has been also reported in neonates (Homsy et al., 1986).

The presence of a dilated urinary tract can be variable in time. If reflux is occuring, dilatation may not be detectable permanently. Also no further information can be obtained about time, pressure and duration of the occuring reflux. Intermittent uretero-pelvic junction obstruction has been described in infants and adults as the Dietl syndrome, often associated with an aberrant vessel to the lower pole of the kidney (Flotte, 1988). Serial ultrasound scans are required to obtain information about the presence and performance of the dilated system.

Ureteral dilatation is considered when the ureter becomes visible which is usually at a diameter of 3 mm or more. Hydroureters can be easily identified as tortuous structures.

Low level obstruction will be characterized by a distended urinary bladder with or without increased bladder wall thickness and a dilated proximal urinary tract. Bladder distension is diagnosed when its size fills the true and false pelvis without clear evidence of complete bladder emptying. A bladder wall thickness of 4 mm or more is classified as hypertrophic. Dilated kidneys, ureters, bladder and prostatic urethra suggest the presence of posterior urethral valves.

In the male fetus, sometimes abnormalities of the external genitalia can be visualized e.g. hypospadia or scrotum bifidum.

Oligohydramnios is not an invariable finding and is related to the severity and duration of the obstruction. The presence of severe oligohydramnios is considered a poor prognostic sign; conversely, a normal amount of amniotic fluid is a good prognostic sign.

The most important consideration with regard to the kidney involves the prenatal detection of dysplasia. Renal dysplasia may occur with both small or enlarged kidneys. The sonographic signs of renal dysplasia are multiple cortical cysts and hyperechogenicity of the renal parenchyma. The detection of renal cysts is relatively insensitive (sensitivity 44%, specificity 100%). Renal echogenicity is more sensitive (sensitivity 73%) but also less specific (specificity 80%) (Mahoney et al., 1984). Increased renal echogenicity can also be the result of increased pressure inside the kidney due to an obstruction. After drainage of the kidney by urine aspiration, disappearance of the increased echogenicity has been demonstrated.

The ultrasound scan should be concluded with a careful search for non-renal defects. The presence of ascites or perirenal urinomas should also be documented. It must be remembered that the sonographic diagnosis is based on the presence of dilatation of the urinary tract. It may be difficult to determine whether the cause of an obstructive uropathy is of functional or structural origin. However, reduced bladder emptying or progressive hydronephrosis suggest a functionally important obstruction. Severe oligohydramnios is the result of inadequate passage of urine or severely impaired renal function. Prenatal ultrasound does not accurately differentiate between obstructive and non-obstructive causes of hydronephrosis.

To obtain better insight into the diagnosis of different types of obstruction, the high level and low level obstructions will be discussed separately.

### 6.1.1 *High-level obstructive uropathy*

Upper urinary tract obstruction can be subdivided into uretero-pelvic junction obstruction (UPJ) and uretero-vesical junction obstruction (UVJ)(Table 1). In both UPJ and UVJ, the bladder is not dilated. In UPJ obstruction there will be hydronephrosis without dilatation of the ureter. In UVJ obstruction there will be hydronephrosis and dilatation of the ureter.

Table 1. High level obstructive uropathy (uni or bilateral).

| |
|---|
| Uretero-pelvic junction obstruction |
| anatomical causes (fibrous adhesions, bands, kinks, ureteral valves, aberrant low pole vessels, abnormal ureteral insertion, unusual shapes of the pyelo-ureteral outlet, ureterocele, bladder diverticulum.) |
| functional causes |
| Uretero-vesical junction obstruction |
| primary obstructive megaureter |
| secondary obstructive megaureter |
| primary refluxing megaureter |
| secondary refluxing megaureter |
| primary non-obstructive non-refluxing megaureter |
| secondary non-obstructive non-refluxing megaureter |

UPJ obstruction is the most common cause of hydronephrosis in the neonate and the child (Johnston et al. 1977). The pathogenesis of this condition is unknown. Anatomical causes for UPJ obstruction are only seen in a fraction of patients. In most instances of UPJ obstruction the junction is anatomically patent to the passage of a probe; the problem, therefore, seems to be of a functional nature. Abnormal development of the interwoven muscularis of the ureter would impair bolus formation and propulsion of urine. Other possible causes of the picture of a dilated system include normal variants like an extrarenal pelvis.

The condition of UPJ obstruction occurs bilaterally in 30% of cases, usually with an asymmetrical involvement of the kidneys. Abnormality of the contralateral kidney in the presence of unilateral UPJ obstruction may vary from renal agenesis to multicystic dysplasia (Scholtmeyer and van der Harten, 1975), the latter probably representing complete obstruction during morphogenesis. If unilateral, UPJ obstruction occurs more frequently on the left side.

In the fetus, unilateral UPJ obstruction in the presence of a normal contralateral system does not affect bladder dynamics nor the amount of amniotic fluid. Sometimes the compensatory function of the normal kidney can result in a slight dilatation of its pyelum.

UVJ obstruction also causes hydronephrosis, but in addition there is an associated hydroureter. Ureteral dilatation may be caused by obstruction to the flow of urine, vesicoureteral reflux or conditions in which neither obstruction nor reflux is present. Distinction between these different conditions is important, since treatment will vary.

Obstructive or refluxing hydroureter requires surgical correction, whereas non-refluxing non-obstructive megaureters can be managed expectantly. Primary obstructive megaureter is caused either by narrowing of a ureteral segment or, more commonly, by a ureteral segment that does not dilate or transmit the peristaltic wave. In secondary obstructive megaureter, ureterectasis is due to extrinsic pressure (vessel or tumour). Primary refluxing megaureter is due to an abnormality of the uretero-vesical junction leading to failure of the antireflux mechanism. Secondary refluxing megaureter is due to reflux associated with a coexistent abnormality.

Primary non-refluxing non-obstructive megaureter is an idiopathic dilatation, and secondary non-refluxing non-obstructive megaureter is found with high rates of urine formation and in ureters that remain wide after cessation of vesico-ureteric reflux.

### 6.1.2 *Low-level obstructive uropathy*

Whereas upper urinary tract obstruction may result in unilateral hydronephrosis, infravesical obstruction will lead to bilateral dilatation of the upper urinary tract. As alternate pathways for the passage of urine, fistulas may be present (e.g. urachal, cloacal). Low-level obstructive uropathy may be the result of anatomical and /or functional causes (Table 2). The differential diagnosis may not be possible in utero.

Table 2. Low level obstructive uropathy.

| | |
|---|---|
| Bladder: | Bladder neck obstruction (bladder wall hypertrophy caused by an infra-vesical obstruction, Marion's disease due to an idiopathic functional muscular disorder of the internal sphincteric area, ureterocele). |
| | Neurogenic bladder. |
| Urethra: | Agenesis (congenital absence). |
| | Atresia (congenital segmental agenesis). |
| | Anterior urethral valves. |
| | Posterior urethral valves. |
| | Congenital urethral polyps. |
| | Hypoplasia of membraneous urethra. |
| | Meatus stenosis. |
| | Urethral diverticulum. |
| | Urethral fibroelastosis (Bodian's disease). |
| | Cloacal anomaly. |
| Prune-Belly syndrome | |
| Megacystis-Microcolon-Intestinal Hypoperistalsis syndrome | |
| Variants of the caudal regression sydrome | |

Posterior urethral valves (PUV) are one of the most common causes of congenital urethral obstruction in boys and result from the development of the prostatic urethra. According to the anatomical variation these valves may vary from very thin to thick structures, causing partial or total occlusion. The spectrum of this disease ranges from minimal, non-obstructive lesions to marked obstruction with advanced hydroureteronephrosis. Sometimes it is possible to demonstrate the dilated posterior urethra proximal to the valves in utero. Compensatory detrusor hypertrophy can result in bladder neck hypertrophy. Distension of the bladder eventually leads to vesicoureteral reflux and hydronephrosis. In neonatal series reflux is usually unilateral, mainly on the left side. Spontaneous decompression of the bladder in utero may occur through bladder rupture , through a patent urachus, spontaneous perforation of the obstructed urethral valve or the wall of the bladder or ureter. Anomalies of the genito-urinary system that are often associated with PUV include duplication of the urethra, megalourethra, cryptorchidism and hypospadia.

Distension of bladder and proximal urinary tract may have effects on morphogenesis of abdominal wall muscles and become associated with the Prune Belly syndrome. Prune-Belly syndrome (Eagle-Barrett syndrome) was first described by Frohlich (1839) and has an incidence of 1 in 30.000 live births in the Caucasian population (Baird and MacDonald, 1981). This syndrome is associated with abdominal wall muscle deficiency, dilatation of the urinary tract and failure of the testicular descent. The vast majority (96%) are males and in the rare female occurrences the urinary tract anomalies are nearly always mild. The causes are heterogeneous and it seems that the Prune-Belly syndrome is causally non-specific and secondary to (fetal) abdominal distension (Pagon et al., 1979). The muscular deficiency is the result of physical forces that cause abnormal stretching. Others (Ives 1974) proposed that the marked abdominal laxity results from disordered mesodermal development during early embryogenesis. Urethral obstruction, a common cause of fetal abdominal distension, is commonly associated with a Prune-Belly. The Prune-Belly syndrome has a wide spectrum of severity. Some infants with severe oligohydramnios die in the neonatal period because of pulmonary hypoplasia. Others survive the neonatal period and may develop renal failure if urinary obstruction was the cause of the sequence. The mild cases may have incomplete renal features of the syndrome; the uropathy is less severe, and renal function is stable. However, urodynamic studies in boys with a Prune-Belly fail to show a pressure gradient between bladder and urethral bulb in many patients, implying no obstruction at the urethral level. In addition many boys with urethral valves do not have lax abdominal muscles.

Causes of lower urinary tract obstruction in females include agenesis of the urethra, Megacystis-Microcolon-Intestinal Hypoperistalsis syndrome (MMIHS) and variants of the caudal regression syndrome. MMIHS was first described by Berdon et al.(1976) and affects female infants in the majority of cases. Prenatally it is characterized by a massively dilated, thick-walled bladder, normal or increased amount of amniotic fluid, dilatation of the stomach, bilateral

hydronephrosis with no signs of renal damage. The microcolon and intestinal hypoperistalsis can not be diagnosed prenatally. In the early neonatal period the functional obstruction of bladder and shortened intestine becomes apparent resulting in alimentation problems requiring hyperalimentation. The outcome has been uniformely fatal before the age of 3 years.

### 6.1.3 *Management of obstructive uropathy*

Appropriate management of any patient with urinary tract obstruction requires knowledge of the presence or absence of an obstruction, the degree of hydronephrosis, assessment of renal function and, if possible, insight in the potential recoverability of renal function. This is particularly so for low level obstructive uropathy since this condition may lead to bilateral dilatation of the urinary tract. Associated structural and /or chromosomal anomalies have a strong impact on the prognosis and should therefore also be considered.

Infants with bilateral dysplastic kidneys have a uniformly poor prognosis. Although sonographic detection of cortical cystic changes has excellent specificity, its sensitivity is relatively poor. Therefore infants with normal kidneys on ultrasound may still be born with non-functioning kidneys. Since fetal urine production is a significant component of amniotic fluid it provides a measure albeit crude, of the presence of renal function. Bilateral hydronephrosis without oligohydramnios does not require change of the obstetric management. Serial sonographic assessment of amniotic fluid volume should be performed if oligohydramnios appears to be questionable. Severe oligohydramnios which will result from reduced or absent voiding due to bladder outlet obstruction and / or subsequent impairment of renal function, may lead to pulmonary hypoplasia. There is some controversy, however, as to whether pulmonary hypoplasia is secondary to oligohydramnios and thoracic compression (Thomas and Smith, 1974) or due to a primary pulmonary malformation (Reid, 1977).

Exact methods of determining fetal renal function are not yet available. Ultrasound does allow non-invasive measurement of fetal urine production (Campbell et al.,1973; Wladimiroff and Campbell, 1974). Hourly fetal urinary production rates, however, are only a crude reflection of fetal diuresis and should not be used under pathological circumstances. Recently, biochemical studies in fetal urine were introduced (Glick et al.,1985; Appelman and Golbus, 1986). Fetal urine was obtained through ultrasound guided bladder needling for urinary electrolyte determination. Separate sampling from each kidney rather than the bladder was suggested on the assumption that bilateral renal damage secondary to low level obstructive uropathy is not necessarily symmetrical in severity (Nicolini et al,1987).

Glick et al.(1985) based their concept on the assumption that 'fetal urine remains constant throughout gestation until just before term'. From the fetal lamb model it was already known that sodium and chloride concentrations decline contineously with fetal age (Alexander et al., 1958). Therefore, human fetal urinary electrolytes should be related to the gestational age. However, normal

values for electrolytes in fetal urine according to the gestational age have not been established and/or published yet.

In view of the obstetric management several options are available, including pregnancy termination, in utero decompression, induced delivery when the lungs are mature with postnatal management of the newborn or observation with delivery at term and postnatal management of the newborn.

In case of an unilateral obstructive uropathy the pregnancy should be allowed to progress to term.

Pregnancy termination may be considered when the congenital abnormality is believed to be incompatible with life and the gestational age allows pregnancy termination.

Preterm delivery is possible after lung maturity is achieved. The rationale for preterm delivery involves attempting to limit the renal damage in utero by earlier treatment of the malformed urinary tract postnatally. The most commonly chosen option is observation of the fetus with a dilated urinary tract until near term because of the belief that the value of early decompression is as yet unproved (Arthur et al., 1989). Immediately after birth these infants should be thoroughly evaluated urologically to undergo appropriate management and treatment. Urodynamics in the neonate is different from that in the fetus. Decrease in urine flow rate will also affect possible pressure and resistance due to an obstruction.

In general it can be stated that;(i) prenatal ultrasound cannot correctly diagnose the primary cause of an low-level obstructive uropathy;(ii) renal function tests predicting the prognosis of the neonatal renal function are not available yet;(iii) associated primary and secondary structural anomalies are difficult to identify in the presence of oligohydramnios.

In our opinion, in the absence of oligohydramnios the fetus should be given the benefit of the doubt. If its karyotype is normal and no further associated structural anomalies are detected, serial ultrasound scans and a term delivery with immediate postnatal care provided by a neonatologist and pediatric urologist is indicated.

## 6.2 Prenatal evaluation and outcome of fetal obstructive uropathies

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### Summary

Between January 1982 and January 1986, 76 pregnant women between 15

and 40 weeks of gestation were referred because of suspected fetal obstructive urinary tract pathology. A total of 14 high-level (ureter) and 17 low-level (urethral) obstructions were diagnosed. High-level obstructions were at the uretero-pelvic obstruction in 11 and at the uretero-vesical level in 3 cases. Increased amniotic fluid volume was observed in 28 per cent. The survival rate was 86 per cent.

In the 17 cases of urethral obstruction, oligohydramnios was present in 70 per cent, associated structural defects in 30 per cent, and an abnormal karyotype in 6 per cent. Pregnancy was terminated because of progressive massive hydronephrosis in 41 per cent; intra uterine or neonatal death occurred in 47 per cent, resulting in a survival rate of only 12 per cent.

*Key words* - Fetal obstructive uropathy - diagnostic ultrasound

## Introduction

The potential of real-time ultrasound in the detection of fetal structural defects is now well established. Accurate identification of fetal kidneys is now possible in up to 90 per cent of pregnancies by 16-17 weeks of gestation. Fetal urinary bladder filling can be visualized as early as 14-15 weeks. This enables early screening of those pregnancies which are at increased risk of severe urinary tract abnormalities.

The prenatal management of obstructive uropathies may vary from a careful follow-up by serial ultrasound scanning to intrauterine diversion procedures, the success rate of the latter depending very much on proper selection of affected fetuses (Berkowitz et al., 1982; Hobbins et al., 1984; McFayden, 1984). The selection criteria used are determined by the severity of the existing renal damage and the potential for recovery of renal and pulmonary function if the obstruction is relieved. Coexistent chromosome disorders and other severe congenital malformations must be ruled out. Although the amount of amniotic fluid reasonably reflects the functional status of the kidneys, more precise information is mandatory for appropriate prenatal management of obstructive uropathies. Direct needling of the fetal urinary bladder allows collection and biochemical analysis of fetal urine and therefore more accurate assessment of renal function (Glick et al., 1985).

In this paper we present the data of retrospective analysis of fetal obstructive uropathies. The prenatal ultrasonic appearance and the functional state of the affected urinary tract were correlated with the fetal outcome.

## Material and methods

Between January 1982 and January 1986, 76 pregnant women were referred to our ultrasound unit because of suspected fetal obstructive urinary tract pathology. Ultrasound examinations were performed using a real-time mechanical sector scanner (Diasonics CV 100) with a 5 MHz transducer. Gestational age was assessed on the basis of maternal menstrual dates and/or measurements

of the fetal biparietal diameter and femur length. In each fetus, the following sonographic features were documented:
a) the size of the renal pelvis; dilatation (caliectasis) was classified according to pelvic diameter as absent (<5mm), mild/moderate (5-15mm), and marked (>15mm);
b) the width of the ureter(s); dilatation (ureterectasis) was considered when the ureter became visible, which usually was at a diameter of 3 mm or more;
c) the size of the urinary bladder; bladder distension (megacystis) was diagnosed when its size filled the true and false pelvis into the abdomen without clear evidence of bladder emptying. A bladder wall thickness of 4 mm or more was classified as hypertrophy;
d) the presence of urine ascites;
e) the amount of amniotic fluid; normal reduced or increased;
f) the presence of associated abnormalities.

The site of the obstruction was classified as high or low and as uni- or bilateral. A high-level obstruction presented with caliectasis (uretero-pelvic junction obstruction) or was characterized by ureterectasis with or without caliectasis (uretero-vesical junction obstruction). A unilateral obstruction was established in the presence of a normal size bladder and one sided dilatation of the proximal urinary tract. A low-level obstruction (urethra) was diagnosed when a distended urinary bladder with or without increased bladder wall thickness and a dilated proximal urinary tract was present. In four cases, direct assessment of renal function was attempted through fetal bladder needling for urine sodium, chloride and osmolarity determination. In two instances, the content of the amino acids valine, methionine, isoleucine, leucine and arginine involved in the process of tubular reabsorption (Lenz et al., 1985) was also studied. In two patients, fetal urine was cultured for possible cytogenetic analysis.

Each ultrasound scan was concluded with a careful search for non-renal defects. As soon as the diagnosis of obstructive uropathy was made, obstetric management was discussed by the perinatal team consisting of an obstetrician, a pediatric urologist, a neonatologist and an ultrasonographist. Neonatal follow-up was available in all cases. Autopsy was carried out in all cases of intrauterine and neonatal death.

## Results

In 31 cases, a fetal obstructive uropathy was diagnosed. The obstruction was diagnosed at high level in 14 and at low level in 17 cases. The condition was considered unilateral in eight and bilateral in 23 cases. Table 1 summarizes the ultrasonic findings and fetal outcome in the 31 cases.

### *Uretero-pelvic junction obstruction (n=11)*

There were 6 unilateral and 5 bilateral uretero-pelvic junction obstructions. Gestational age at diagnosis ranged between 21 and 37 weeks (mean 27 weeks).

Table I Summary of ultrasound findings and fetal outcome in 31 cases of fetal obstructive uropathy

| | Uretero-pelvic junction obstruction | | Uretero-vesical obstruction | | Urethral obstruction |
|---|---|---|---|---|---|
| | Unilateral (n=6) | Bilateral (n=5) | Unilateral (n=2) | Bilateral (n=1) | (n=17) |
| *Gestational age (weeks) at first presentation* | | | | | |
| 15-20 | - | - | - | - | 5 |
| 21-30 | 2 | 4 | 2 | 1 | 9 |
| 31-40 | 4 | 1 | - | - | 3 |
| *Caliectasis* | | | | | |
| None | - | - | - | - | 3 |
| Mild /moderate | 2 | 1 | - | - | 2 |
| Marked | 4 | 4 | 2 | 1 | 12 |
| Ureterectasis | - | - | 2 | 1 | 17 |
| Megacystis | - | - | - | - | 15 |
| Urine ascites | - | - | - | - | 2 |
| *Amniotic fluid volume* | | | | | |
| Normal | 5 | 4 | - | 1 | 3 |
| Reduced (oligo) | - | - | - | - | 12 |
| Increased | 1 | 1 | 2 | - | 2 |
| Associated defects | - | 1 | - | - | 5 |
| *Fetal birth weight* | | | | | |
| reduced (<10 per cent) | - | - | - | - | 3 |
| Normal | 6 | 5 | 2 | 1 | 14 |
| *Sex* | | | | | |
| Male | 3 | 4 | 1 | - | 16 |
| Female | 3 | 1 | 1 | 1 | 1 |
| *Fetal outcome* | | | | | |
| Pregnancy termination | - | 1 | - | - | 7 |
| Intrauterine /neonatal death | - | - | - | 1 | 8 |
| Survival | 6 | 4 | 2 | - | 2 |

Amniotic fluid volume remained normal in 5 out of 6 unilateral cases; polyhydramnios was observed in one case.

Expectant management through serial scanning was employed. All infants underwent spontaneous delivery at term and birth weight was within the normal range for gestational age (Kloosterman, 1970). Unilateral uretero-pelvic obstruction was confirmed postnatally in 5 out of 6 infants. There was one case of right-sided extra-renal pelvis, which needed no treatment. Two infants underwent pyeloplasty, one reimplantation of the right ureter and one removal of the left kidney due to severe renal dysplasia.

In the 5 cases of bilateral uretero-pelvic junction obstruction, gestational age

varied between 21 and 36 weeks (mean 27 weeks). Amniotic fluid volume remained normal in 4 and developed into polyhydramnios in one case. In the latter case, progressive massive hydronephrosis resulted in pregnancy termination at 22 weeks; post-mortem examination revealed bilateral uretero-pelvic obstruction and Potter type IV kidneys.

The remaining four pregnancies progressed to term. The mothers delivered spontaneously and birth weights were within the normal range for gestational age (Kloosterman, 1970). In two instances, bilateral uretero-pelvic obstruction was confirmed postnatally and a pyeloplasty was carried out at the age of 3 months. In the remaining two infants, either a unilateral obstruction or no anatomical lesion was established. One of these infants displayed Noonan syndrome characterized by webbing of the neck, pectus excavatum, cryptorchism and pulmonary stenosis. In all infants, renal function was satisfactory.

*Uretero-vesical obstruction (n=3)*

The unilateral form of uretero-vesical junction obstruction was diagnosed in two, the bilateral form in one case. Gestational age at diagnosis varied between 23 and 30 weeks. The amount of amniotic fluid remained normal in one and was increased in two pregnancies. All infants were delivered spontaneously at term. In the two unilateral obstructions, the affected kidney appeared to be non-functional; a dysplastic kidney was removed. Infant development was subsequently normal. In the case of bilateral uretero-vesical obstruction, the infant demonstrated a massive vesico-ureteral reflux and died from persistent fetal circulation.

*Urethral obstruction (n=17)*

A generally poor outcome was found in 17 cases of low-level obstructions. Gestational age at first presentation varied between 15 and 36 weeks, with more than 50 per cent between 21 and 30 weeks. The majority demonstrated a marked caliectasis, ureterectasis and megacystis. In 5 instances, there was only mild or no caliectasis. Oligohydramnios was observed in 12 (70 per cent), increased amniotic volume in two (12 per cent) and normal amniotic volume in three patients (18 per cent). Fetal ascites was documented in 3 cases.

Pregnancy termination was carried out in seven instances (41 per cent) because of progressive massive caliectasis either associated with marked oligohydramnios (n=5) or an increased amniotic fluid content (n=2) between 15 and 27 weeks of gestation (mean 22 weeks). Post-mortem examination revealed urethral atresia in 6 and no anatomical explanation for the severe bilateral caliectasis and oligohydramnios in one infant. Associated structural defects (imperforate anus(2); atrial septal defect (1); microcolon (1); diaphragmatic hernia (1)) were established in 5 cases.

The pregnancy outcome in the remaining 10 infants was poor; 2 intrauterine and 6 neonatal deaths, the latter all due to severe pulmonary hypoplasia. Post-mortem examination revealed urethral atresia in 7 infants, in one case associated

with imperforate anus. The only female infant died from an undefined neurological disorder resulting in severe bladder dysfunction. Only 2 infants developed normally. Both displayed normal amniotic fluid volumes throughout pregnancy; urethral valves were diagnosed postnatally and treated successfully by cauterization. Birth weight was normal in 14 cases and reduced (<10 per cent) in the remaining 3 cases.

A fetal urine sample was collected through bladder needling in 4 cases of low-level obstruction (table 2). Sodium (>100 mEq/l) and osmolarity (>210 mosm) were raised according to the normograms by Glick et al. (1985) in 3 samples; Sodium level was normal in one sample. The chloride level was once raised (>90 mEq/l), twice normal and once not determined. Raised amino acid levels were established in 2 urine samples. Of the 3 pregnancies with abnormal fetal urine biochemistry, two were terminated because of progressive massive caliectasis and the other went into premature labour, resulting in the delivery of a severely affected infant which died from pulmonary hypoplasia. In one patient with normal fetal urine biochemistry at 28 weeks, increasing massive caliectasis necessitated Caesarean section 6 weeks later. Fetal urine sampling

Table II. Fetal urine obtained by ultrasound-guided intrauterine transabdominal vesical aspiration in four cases of low-level obstruction with oligohydramnios

| | Case 1 | Case 2 | Case 3 | Case 4 |
|---|---|---|---|---|
| *Gestational age (weeks) at first presentation* | 21 | 22 | 27 | 30 |
| *Fetal urine* | | | | |
| Na+(mEq/l) | 130 | 104 | 72 | 130 |
| Cl—(mEq/l) | - | 82 | 66 | 107 |
| Osmolarity(mosm) | 273 | 211 | - | 273 |
| Amino acids | raised | raised | - | - |
| *Obstetric management* | Pregnancy termination at 22 wks | Pregnancy termination at 22 wks | S.C. at 34 weeks | Vaginal delivery at 30 wks |
| *Fetal outcome* | † 595 g | † ? g | 2000 g respiratory insufficiency † 5 days | † 1500 g |
| *Post-mortem examination* | Urethral atresia<br>Potter type IV kidneys pulmonary hypoplasia | Urethral atresia cloacal anomaly<br>Potter type IV kidneys pulmonary hypoplasia | Urethral atresia<br>Potter type IV kidneys pulmonary hypoplasia | Urethral atresia<br>Potter type IV kidneys pulmonary hypoplasia |

was not repeated; the infant died from pulmonary hypoplasia. Fetal karyotyping was successful in 2 urine samples (46XY). Post-mortem examination revealed, besides pulmonary hypoplasia, renal dysplasia (histologically: Potter type IV) in all 4 cases.

## Discussion

To obtain better insight into the outcome of different types of obstruction pregnancies were classified according to the level of obstruction as established during repeated observations. This also enabled comparison with the approach in neonatal pediatric urological management.

The low (urethral) obstructions tended to manifest themselves earlier, with a more serious prognosis for eventual kidney function. In the high obstructions (uretero-pelvic and uretero-vesical), unilateral and bilateral cases were analysed separately.

In the present material, there were 14 cases (45 per cent) of high-level obstruction, eight of which were unilateral. Of these unilateral cases, half were diagnosed between 21 and 30 weeks, the other half even later in pregnancy. Despite marked caliectasis in six out of the eight unilateral obstructions, amniotic fluid volume was normal or even increased (three cases), most likely reflecting compensatory action of the opposite normal kidney. In three cases, marked unilateral caliectasis and a non-functioning kidney necessitated postnatal nephrectomy. One may, therefore, make an argument for intrauterine unilateral decompression to prevent further deterioration of an affected kidney. It is clear, however, that the risks of in utero shunting are currently too high to justify such an approach. The suggestion that an increased amniotic fluid content in the presence of unilateral uretero-pelvic obstruction may result from a large gastrointestinal obstruction (Golbus et al., 1985) could not be confirmed in our series. The six bilateral obstructions were mainly at the uretero-pelvic level. Pregnancies were allowed to progress to term on the basis of normal amniotic fluid volumes. Fetal outcome was, however, less favourable than in the unilateral obstructions. One pregnancy was terminated at 21 weeks because of progressive massive hydronephrosis; one infant died from persistent fetal circulation.

Although bilateral hydronephrosis was confirmed postnatally in al six infants, an anatomical obstruction was established only in four cases, two of which were bilateral and two only unilateral (at the uretero-pelvic level). In the latter instance, the caliectasis on the contralateral side was probably due to a compensatory action of the non-affected kidney.

The survival rate in the group of low-level (urethral) obstructions was extremely poor (12 per cent). In the majority of cases, a combination of bilateral caliectasis, ureterectasis, and megacystis was observed. Three times, however, there was a discrepancy between urethral obstruction and lack of ureterectasis or caliectasis. Autopsy revealed renal dysplasia, indicating a disturbance of renal development very early in pregnancy. Beck (1971) performed ureteral ligation as well as contralateral nephrectomy in lambs from 62 to 84 days of gestation. When

the ureter was ligated prior to 60-70 days of gestation, the result was renal dysplasia, whereas during the last half of gestation simple hydronephrosis developed. Recently, Bellinger et al., (1986) in their model of induced ureteral obstruction in the fetal lamb observed the duration of obstruction to be proportional to the histological damage. Their physiological studies showed that the damaged kidney, even after decompression, produced a larger volume, lost more sodium than the control kidney, and displayed a significantly lower creatinine clearance.

Early diagnosis of obstructive uropathy should therefore be attempted. In our study, only five out of 17 cases (30 per cent) were referred before 20 weeks. Centres which practice early second trimester ultrasound screening of their obstetric population should pick up a considerable number of these affected cases. It should be stressed though that in a limited number of urethral obstructions, ureterectasis and caliectasis may develop as late in the third trimester of pregnancy (Wladimiroff et al., 1985).

Oligohydramnios is a poor prognostic indicator, as shown in several studies (Hobbins et al., 1984; Golbus et al., 1985; Mahoney et al., 1985; Quinlan et al., 1986). In our study it was associated with five pregnancy terminations, two intrauterine deaths, and five neonatal deaths, the latter being the result of severe pulmonary hypoplasia. A normal amniotic fluid volume may suggest a good outcome, as was the case in the only two survivors with low-level obstruction in our study. The success of obstetric management in the presence of a low-level obstruction will depend on information on possible associated defects, the karyotype, and renal function. One abnormal karyotype was established after amniocentesis (trisomy 21). A high incidence of associated structural abnormalities in low-level obstruction has been reported (Lirette and Filly, 1983; Blane et al., 1983); in the present study, the incidence was 30 per cent.

Caudal regression syndrome is frequently associated with low-level obstructive uropathy. The spectrum of its manifestation may vary between sirenomelia (Allen et al., 1981) and imperforate anus. The latter defect was established in two of our neonatal deaths. No cases of megacystis-microcolon-intestinal hypoperistalis syndrome were present in our material. The megacystis-microcolon-intestinal hypoperistalis syndrome (Winter et al., 1986) usually presenting with normal to increased amount of amniotic fluid, should be carefully distinguished from the urethral obstruction malformation complex (Pagon et al., 1979) regarding its autosomal recessive inheritance pattern. The presence of oligohydramnios usually severely hampers a firm diagnosis of associated defects and collection of amniotic fluid for fetal karyotyping. Instead, fetal urine through bladder needling can be a useful alternative for fetal karyotyping (Lenz et al., 1985), as was demonstrated in two fetuses in the present study. Fetal urine collection will also permit determination of sodium, chloride, and osmolarity levels in the assessment of renal function (Glick et al., 1985). Abnormal levels were found in three out of four urine samples; raised amino acid levels reflecting reduced tubular reabsorption (Lenz et al., 1985) were documented in two urine samples.

Obstetric management will only become influenced by fetal urinary studies when centres have established normal data.

Ultrasonic measurement of fetal urine production may be another diagnostic approach to obtain insight into fetal renal development (Campbell et al., 1973; Wladimiroff and Campbell, 1974). A single hourly urinary production rate value is, however, time-consuming and not indicative of renal function in the case of moderate or severe urethral obstruction. Only serial measurements may demonstrate a progressive reduction in hourly fetal urinary production as evidence for declining renal function.

Reduced fetal birth weight (found in 18 per cent) did not contribute to the prognosis of low-level obstructions. The predominance of the male sex in low-level obstructions is in agreement with previous observations (Mahoney et al., 1985; Quinlan et al., 1986). A functional rather than an anatomical urethral obstruction was diagnosed postnatally in the only female infant, which died of an undefined neurological disorder resulting in severe bladder dysfunction.

There seems to be an essential difference in causes and outcome between prenatally and neonatally established urinary tract disorders (Quinlan et al., 1986).

In neonatal series (Lebowitz and Griscom, 1977), posterior urethral valves are the most frequent cause of low-level obstructions. Both in Quinlan's antenatal series and our present study, the urethral obstruction was nearly always (88 per cent) secondary to urethral atresia or urethral stenosis resulting in a very poor fetal outcome.

Posterior urethral valves were diagnosed only in the two surviving cases. Although the outcome of the majority of low-level obstructive uropathies is still poor, encouraging signs seem to come from catheter-shunt procedures in well-selected cases. In 73 cases of fetal urethral obstruction reported to the International Fetal Surgery Registery (Manning et al., 1986), attempts to decompress the obstructed fetal urinary tract yielded 30 survivals (41 per cent) and a procedure related death rate of 4-6 per cent. Pulmonary hypoplasia remained the major cause of history of fetal urinary tract obstructions. Both the fetal lamb model (Harrison et al., 1982b) and clinical experience (Harrison et al., 1982a; Manning et al., 1986) indicate that the severity of renal and pulmonary damage appears to vary with the timing and the type of obstruction. Particularly early severe obstructions often produce irreversible damage, whereas partial obstructions at a later stage in pregnancy result in less pronounced and often reversible damage. Proper patient selection based on a search for associated defects, karyotyping, and biochemical analysis of urine will remain the key for successful prenatal treatment of obstructive uropathies.

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## 6.3 Fetal Urinary Electrolytes in Bladder Outlet Obstruction

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*Keywords* - Obstructive uropathy - Urinary electrolyte studies - Renal dysplasia

### Abstract

Ultrasound findings and urinary electrolytes in the fetus were correlated with fetal outcome and postmortem findings in 8 cases of fetal bladder outlet obstructions. one of the two fetuses, suggesting normal renal function according to urinary electrolytes, displayed renal dysplasia at birth. Six fetuses were predicted to have poor renal function, 5 of these were found to have renal dysplasia at autopsy. The interpretation of fetal urinary electrolytes as a prognostic indication for the presence or absence or renal dysplasia needs to be clarified.

### Introduction

Present diagnostic ultrasound equipment allows early detection of bilateral fetal hydronephrosis, which usually is the result of bladder outlet obstruction. The assessment of fetal renal function has important implications for obstetric management which may vary from an expectant attitude to in utero surgery. The in utero evaluation of renal function depends on the ultrasonic detection of renal cystic dysplasia, urinary electrolyte studies and the amount of amniotic fluid.

The aim of the present study was to correlate fetal ultrasound and urinary electrolytes with fetal outcome and postmortem findings in 8 cases of fetal bladder outlet obstruction.

### Patients and methods

Urinary electrolytes were studied in fetal urine samples from 8 consecutive pregnancies with fetal bladder outlet obstruction. Gestational age varied between 20 and 37 weeks (mean 26 weeks). Bladder outlet obstruction was diagnosed in the presence of dilatation of the bladder and proximal tract (Hobbins et al., 1984) using a real-time mechanical sector scanner (Diasonics CV 100) with a 5-MHz transducer. A careful search for nonrenal defects was carried out. Chromosomal studies were performed in 5 of 8 cases.

In each case a fetal urine sample was obtained through fetal bladder puncture under ultrasound guidance for determination of sodium and chloride levels and osmolality. Poor renal function was predicted when values were above two standard deviations from the mean of the fetuses with good predicted renal function according to Glick et al. (1985) (Table I).

Table I. Prognostic criteria for the fetus with bilateral obstructive uropathy

| Predicted renal function | Amniotic fluid status at the time of initial presentation | Sonographic appearance of kidneys | Fetal urine | | |
|---|---|---|---|---|---|
| | | | sodium mEq/l | chloride mEq/l | osmolality mosm/kg water |
| Poor | moderate to severely decreased | echogenic to cystic | >100 | >90 | >210 |
| Good | normal to moderately decreased | normal to echogenic | <100 | <90 | <210 |

According to Glick et al. (1985)

Obstetric management was subsequently discussed by the perinatal team consisting of an obstetrician, pediatric urologist, neonatologist and ultrasonographist. In case of intrauterine or neonatal death, autopsy was performed.

## Results

The ultrasound findings, fetal urinary electrolytes and fetal outcome are listed in Tables II-IV. In 2 fetuses (Nos. 1 and 2) urinary electrolytes were within the range values which are associated with normal neonatal renal function. In both cases the kidneys displayed normal echogenicity.

One of these fetuses also presented with a diaphragmatic hernia, ascites and polyhydramnios. In this case pregnancy termination was elected by the parents at 21 weeks of gestation. Autopsy revealed urethral atresia, histologically normal kidneys, diaphragmatic hernia and lung hypoplasia.

In the other fetus serial ultrasound scanning showed a decreasing amount of amniotic fluid. For this reason caesarean section was performed at 34 weeks. A male infant was delivered with bilateral club feet. He died on day 5 from respiratory insufficiency. Histologically the kidneys were classified as Potter type IV and lung hypoplasia was documented.

In 6 fetuses urinary electrolyte levels were consistent with poor renal function. Five fetuses (Nos. 3-7) displayed very echodense kidneys suggestive of cystic dysplasia; there was severe oligohydramnios. Normal echogenic kidneys and a normal amount of amniotic fluid was observed in one pregnancy (No.8). In 3 cases the presence of ascites was noted. In the 5 fetuses with renal cystic dysplasia, chromosome analysis was performed in amniotic fluid (n=3) and fetal urine (n=2), demonstrating normal male karyotypes. Three pregnancies were terminated electively, the remaining two ended in spontaneous vaginal delivery of a dead fetus. Postmortem examination revealed urethral atresia and dysplastic kidneys in all 5 cases and lung hypoplasia in 4 cases. In 1 fetus urethral atresia was associated with anal atresia and the descending colon ending in the fetal bladder. One male infant born at term is alive at the age of 6 months. Urethral valves were diagnosed postnatally and the bladder was drained by a suprapubic catheter. Because of respiratory problems the infant was artificially ventilated

Table II. Prenatal findings

| Patient No. | Gestational age at sampling weeks | Fetal urine biochemistry prognosis | Ultrasonic appearance of kidneys | Amniotic fluid volume | Other findings |
|---|---|---|---|---|---|
| 1 | 21 | good | normal | polyhydramnios | ascites / diaphragmatic hernia |
| 2 | 27 | good | normal | moderate oligohydramnios | - |
| 3 | 21 | poor | cystic dysplasia | severe oligohydramnios | - |
| 4 | 22 | poor | cystic dysplasia | severe oligohydramnios | ascites |
| 5 | 23 | poor | cystic dysplasia | severe oligohydramnios | |
| 6 | 29 | poor | cystic dysplasia | severe oligohydramnios | - |
| 7 | 30 | poor | cystic dysplasia | severe oligohydramnios | ascites |
| 8 | 37 | poor | normal | normal | ascites |

for 8 weeks. Currently, 1 kidney displays reflux and impaired function, the contralateral kidney is normal. Valve resection was performed at the age of 5 months.

## Discussion

It has been suggested that in the case of fetal low level obstructive uropathy, abnormal urine levels of sodium, chloride and osmolarity correlate well with the presence of cystic dysplasia and poor renal function (Glick et al., 1985). However, a recent report (Wilkins et al., 1988) pointed out the discrepancies between renal function predicted from fetal urinary electrolyte studies and the presence of renal dysplasia at histological examination. It was concluded that the presence of fetal urinary electrolyte levels predicting good renal function did not reliably exclude the finding of dysplasia or evidence of severe renal dysfunction during the neonatal period and vice versa.

In our material, 1 of the 2 fetuses with predicted good renal function according to urinary electrolytes displayed renal dysplasia at birth. The delay of 7 weeks between fetal urine sampling and delivery may have invalidated the urinary parameters, since these are a reflection of the current status of the fetus. On the other hand, the postmortem histological finding of severe dysplasia implies

Table III. Fetal urine biochemistry and fetal outcome

| Patient No. | Fetal urine biochemistry | | | Fetal outcome |
|---|---|---|---|---|
| | sodium mEq /l | chloride mEq /l | osmolality mosm /kg water | |
| 1 | 75 | 61 | 163 | TOP, 21 weeks |
| 2 | 72 | 66 | NA | CS at 34 weeks, neonatal death |
| 3 | 130 | 105 | 273 | TOP, 21 weeks |
| 4 | 104 | 82 | 211 | TOP, 22 weeks |
| 5 | 115 | 97 | 242 | TOP, 23 weeks |
| 6 | 100 | NA | 218 | spontaneous vaginal delivery at 30 weeks |
| 7 | 130 | 107 | 273 | spontaneous vaginal delivery at 30 weeks |
| 8 | 146 | 111 | 284 | spontaneous vaginal delivery at 37 weeks alive and well at 6 months |

TOP=Termination of pregnancy; NA=not available; CS=cesarean section.

Table IV. Necropsy findings

| Patient No. | Urethral obstruction | Renal dysplasia | Lung hypoplasia | Other anomalies |
|---|---|---|---|---|
| 1 | + | - | + | diaphragmatic hernia |
| 2 | + | + (Potter type IV) | + | - |
| 3 | + | + (Potter type II) | - | - |
| 4 | + | + (Potter type IV) | + | cloaca anomaly |
| 5 | + | + (Potter type IV) | + | - |
| 6 | + | + (Potter type IV) | + | - |
| 7 | + | + (Potter type IV) | + | - |
| 8 | + | - | - | - |

an early, profound insult that is not just the result of progressive disease in the third trimester.

Six fetuses were predicted to have poor renal function, 5 of these were found to have renal dysplasia at autopsy. One infant is alive, and unilateral reflux with impaired renal function and a normally functioning contralateral kidney was diagnosed in the presence of urethral valves. Since the bladder content is a mixture of urine produced by both kidneys, electrolyte studies in fetal urine obtained from the bladder are not of prognostic value in cases in which renal involvement is not symmetrical. As suggested by Nicolini et al. (1987) sampling urine from each kidney rather than the bladder alone provides more reliable information in the evaluation of possible renal damage. Unilateral and asymmetrical vesicoureteral reflux may account for the ultrasound picture of bilateral hydronephrosis in cases with low level obstructive uropathy. Oligohydramnios in the presence of low level obstruction correlated uniformly with a poor prognosis, even if oligohydramnios developed later in gestation.

The retrospectively derived prognostic criteria for good or poor renal function just by determination of fetal urinary electrolytes can be challenged on physiological grounds. Glick et al. (1985) based their concept on the assumption that 'fetal urine remains constant throughout gestation until just before term'. In 1958, however, Alexander et al. (1958) already reported that in the fetal lamb both sodium and chloride concentrations in fetal urine decline continuously with fetal age. Between days 57 and 142, the average concentrations drop from about 100 to 20 mmol/l. A similar finding was later reported by Mellor and Slater (1972). This latter paper was quoted by Glick et al. (1985) as evidence in favor of the constancy of fetal urine composition. Unfortunately, relevant data about the changes in composition of human fetal urine are lacking. We think that the use of fetal urinary electrolyte data to predict renal outcome, oversimplifies the changes in glomerular and tubular function occurring during the last trimester of gestation. A more dynamic approach to assess fetal function is necessary.

Associated structural anomalies were present in 2 of 8 cases: only 1 of these anomalies (diaphragmatic hernia) was detected antenatally by ultrasound. The incidence of associated structural anomalies in this small group does not essentially differ from the 35% established in our total patient material with low level obstructive uropathy (Reuss et al., 1987).

Based on the concept that an obstructive-maldevelopment sequence consisting of oligohydramnios, hypoplastic lungs and possible renal dysplasia is reversible after diversion, it has been suggested that the fetus with a bladder outlet obstruction is a potential candidate for in utero intervention. The difficulty is an adequate fetal evaluation and the possibility that either organ damage occurs so early that it precludes corrective surgery, or the development is not secondary to obstruction but rather a primary mesodermal defect. Such a defect involving the renal-ureteral unit and lung may cause bladder outlet obstruction. Back pressure and oligohydramnios could be contributing rather than necessarily initiating factors concerning renal dysplasia and lung hypoplasia. This explanation is also likely to cause the association of obstruction and multicystic dysplasia (Potter type IIa) since these kidneys lack differentiated nephrons capable of producing urine throughout gestation.

The argument for an obstructive etiology appears more plausible for dysplasia limited to the capsular zone as in Potter type IV. This zone represents the most recently formed nephron elements. It seems likely that renal dysplasia with bladder outlet obstruction constitutes a heterogeneous group. There may be a spectrum of dysplasia secondary to pure obstruction, but its antenatal identification remains problematic.

## 6.4 Non-invasive management of fetal obstructive uropathy.

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### Summary

Fetal outcome was studied in 43 consecutive cases of fetal obstructive uropathy in which no prenatal treatment was undertaken: 12 babies survived. In the 31 who did not survive, oligohydramnios was present in 24 and urethral atresia was the most common cause of obstruction (in 27). At necropsy, bilateral renal dysplasia was found in 23 and pulmonary hypoplasia in 13; 16 had structural or chromosomal anomalies, less than half of which were detected by prenatal ultrasound. In the survivors, 8 had posterior urethral valves, 1 had oligohydramnios, and 2 had associated anomalies. Obstructive uropathy is often associated with other anomalies which may escape prenatal ultrasound detection, and studies to determine the efficacy of intrauterine decompression techniques must allow for this observation.

### Introduction.

Prenatal management of fetal obstructive uropathy ranges from careful follow-up by serial ultrasound scans to surgical decompression intended to prevent progressive renal damage and pulmonary hypoplasia (Harrison et al., 1982). The treatment chosen depends upon the severity of renal damage and the potential for recovery of renal and pulmonary function if the obstruction is relieved, but associated structural and chromosomal anomalies must be excluded. Manning and co-workers from the International Fetal Surgery Registry (Manning et al., 1986) reported on 73 vesico-amniotic shunts placements for fetal obstructive uropathy: they suggested an encouraging outcome for the intervention in selected fetuses with posterior urethral valve syndrome, but the efficacy of the procedure could not be fully established because of the selection bias. Moreover, the lack of a comparable series of non-treated affected infants limits interpretation of possible therapeutic benefits (Elder et al., 1987; Furlong et al., 1986). We report the fetal outcome in 43 consecutive cases of obstructive uropathy who did not undergo prenatal decompression.

### Patients and Methods

During the last 5 years, 43 pregnant women were referred because of suspected fetal obstructive uropathy on routine ultrasound examination. The mean gestational age was 26 weeks (range 13-37); 3 were twin pregnancies with a

normal co-twin; and 2 mothers had had a previous infant with a bladder outlet obstruction.

A real-time mechanical sector scanner (Diasonics' Cardio Vue 100') with a 5 MHz transducer was used. Obstructive uropathy was diagnosed when a distended bladder (with or without increased bladder wall thickness) and a dilated proximal urinary tract were seen. The amount of amniotic fluid was considered normal, reduced (largest fluid pocket less than 2 cm), or increased (largest fluid pocket greater than 8 cm). Each ultrasound examination included a careful search for extrarenal abnormalities. Prenatal karyotyping was done in 19 cases: from amniotic fluid in 13, fetal blood (cordocentesis) in 2, transabdominal placental biopsy in 2, or fetal urine in 2. In the other cases the karyotype was determined postnatally from blood or fibroblasts. All liveborn infants were seen by a paediatric urologist, and all cases of intrauterine or neonatal death underwent necropsy. Urethral atresia was defined as complete absence of orifice; the diagnosis of renal dysplasia was established according to Osathanondh and Potter (1965).

## Results

Fetal obstructive uropathy was confirmed in all 43 pregnancies. Other renal and extrarenal abnormalities were present in 18 fetuses (42%, see table), including 5 abnormal karyotypes (2 had trisomy 13, 2 had trisomy 18, and 1 had trisomy 21). Amniotic fluid volume was normal in 30%, reduced in 58%, and increased in 12%. 31 died and 12 survived.

### *Non-survivors*

This group consisted of 29 males and 2 females: amniotic fluid was reduced in 24, and urinary ascites was observed in 7. Associated structural or chromosomal anomalies were found in 16(see table 1): these were extra-renal in 12, renal in 1 (unilateral renal agenesis), and combined in 2. The remaining case had trisomy 21 without structural malformations. In 3 of 16 cases, the prenatal diagnosis of anomalies was incomplete; in 8 cases, the anomalies were only diagnosed postnatally.

Elective abortion (before 28 weeks) was carried out in 13 cases, in 2 because of the severity of associated anomalies (large diaphragmatic hernia, trisomy 21). In the other 11, severe impairment of renal function was suspected because of abnormal ultrasonic appearance of the kidneys together with complete absence of amniotic fluid. Intrauterine death had occurred in 7. Neonatal death occurred in 11: 5 due to respiratory distress,5 because of severe extra-renal anomalies and 1 from renal failure. Necropsy showed urethral atresia in 27; severe dilatation of the urinary tract without obstruction in 3; posterior urethral valves in 1. 23 had bilateral renal dysplasia and 13 had pulmonary hypoplasia.

### *Survivors*

8 boys and 4 girls survived. Amniotic fluid volume was reduced in only 1,

Table 1. Anomalies associated with fetal obstructive uropathy

| Patient | Gestational age (wks) | Prenatal diagnosis | Postnatal diagnosis |
|---|---|---|---|
| *Non-Survivors* | | | |
| 1 | 15 | - | Microcolon |
| 2 | 16 | URA | URA |
| 3 | 17 | URA | URA, unilateral lung agenesis, AEG |
| 4 | 19 | Diaphragmatic hernia | Diaphragmatic hernia |
| 5 | 20 | - | Anal atresia |
| 6 | 21 | CHD, URA | CHD, polydactyly, anal atresia, URA |
| 7 | 22 | - | Anal atresia |
| 8 | 22 | - | Cloacal anomaly |
| 9 | 24 | - | CHD |
| 10 | 25 | CHD, microcephaly | CHD, microcephaly, polydactyly, trisomy 13 |
| 11 | 27 | Trisomy 21 | Trisomy 21 |
| 12 | 28 | - | Anal atresia |
| 13 | 31 | - | Anal and oesophageal atresia, AEG |
| 14 | 33 | CHD, cleft-lip and palate, trisomy 13 | CHD, cleft-lip and palate, trisomy 13 |
| 15 | 37 | - | CHD, trisomy 18 |
| 16 | 37 | CHD, omphalocele, trisomy 18 | CHD, omphalocele, trisomy 18 |
| *Survivors* | | | |
| 17 | 23 | - | CHD |
| 18 | 26 | Abnormal leg position | Congenital hip and knee subluxation |

URA=unilateral renal agenesis; AEG=abnormal external genitalia; CHD=congenital heart disease.

with urinary ascites in 2. 2 had extrarenal anomalies, only one of which was recognised prenatally (see table). Urethral valves were diagnosed in all 8 male infants and were treated by resection. 1 girl with prune belly syndrome is now 3 years old, and needed orthopaedic correction for congenital hip and knee subluxation. 2 other girls now 5 and 18 months old, respectively, have the megacystis-microcolon-intestinal hypoperistalsis syndrome. The remaining girl, now 3.5 years old had resection of a bladder diverticulum and surgery for a cardiac defect. All 12 infants are alive and well at present.

## Discussion

We found that most fetuses (31 of 43) with obstructive uropathy did not survive. Perinatal survival was strongly related to the type of obstructive uropathy. All 27 fetuses with urethral atresia died; 9 fetuses had posterior urethral valves of which 8 (89%) survived. Survival was better among the female fetuses (4 of 6) than among male fetuses (8 of 37), as was also found in the International Fetal Surgery Registry (Manning et al., 1986). Non-survival in our study was mainly caused by bilateral renal dysplasia (23 of 31) and lunghypoplasia (13

of 31). The presence of bilateral renal dysplasia indicates a disturbance of renal development very early in pregnancy. Fetal lamb studies have shown that duration of urethral obstruction is proportional to the histological damage (Beck, 1971). Ligation of the ureter before 60-70 days of gestation causes renal dysplasia. The timing, type, and duration of obstruction seem to be crucial to the severity of renal and pulmonary damage and therefore early diagnosis of obstructive uropathy is essential. However, the renal damage may occur so early as to preclude corrective therapy or the maldevelopment may not be the result of obstruction but a primary mesodermal defect. Only 9 women in our study were referred for an ultrasound scan before 20 weeks of gestation. The other 34 women were first scanned during the second half of the second trimester or even as late as the third trimester. Associated structural and chromosomal anomalies were found in over half of the non-survivors and 2 of the 12 survivors, and may contribute substantially to fetal outcome (as was the case in 5 infants who died soon after birth). In 9 cases of the 18 abnormal fetuses the extrarenal anomalies were not detected by prenatal ultrasound scanning: the most common anomalies were congenital heart disease, anal atresia, polydactyly, and abnormal external genital organs. The type of anomaly and the presence of oligohydramnios are probably responsible for this poor detection rate. 5 had chromosomal anomalies, so the karyotype should be determined in obstructive uropathy. Placental biopsy (Nicolaides et al., 1986; Pijpers et al., 1988) and cordocentesis (Daffos et al., 1985) allow a rapid karyotype determination in second and third trimester pregnancies.

In view of the type of obstruction, the reduced amount of amniotic fluid, and the presence of severe associated structural or chromosomal anomalies, most fetuses in this study would not have benefitted from invasive intrauterine intervention. Most of the non-survivors were not viable; a low fetal morbidity and mortality occurred when there was a normal amount of amniotic fluid and other anomalies had been excluded. We found a spectrum of primary defects not merely an isolated primary lesion at the level of the urethra with secondary renal dysplasia and pulmonary hypoplasia. The high incidence of associated anomalies and the potential inaccuracies of prenatal ultrasound diagnosis should be remembered in the management of patients with obstructive uropathy and the assessment of efficacy of vesico-amniotic shunt placements. Management may be helped by electrolyte analysis of fetal urine samples obtained by ultrasound-guided bladder puncture (Nicolaides and Rodeck 1985; Glick et al., 1985), or from each kidney (Nicolini et al., 1987).

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## 6.5 In utero decompression of fetal low-level obstructive uropathy.

Early surgical manoeuvers to correct or improve the underlying pathology have been said to reduce the severity of secondary effects. Bladder outlet

obstruction, with its inherent risk to renal function, became a potential indication for in-utero decompression either by open surgical diversion (Harrison, 1982) or by the ultrasound-guided insertion of suprapubic vesico-amniotic shunts (Berkowitz et al. 1982; Golbus et al.,1982; Rodeck and Nicolaides, 1983). Decompression in-utero of bilateral hydronephrosis will be beneficial only to fetuses with obstructive bladder outlet obstruction, whose kidneys have not suffered irreversible damage. Appropriate selection, therefore, requires accurate assessment of fetal renal function. Fetal hydronephrosis associated with normal amounts of amniotic fluid does not require intrauterine decompression. Appropriate treatment after birth should lead to normal renal function in the majority of patients. The indications to drain an obstructed and dilated urinary tract in the fetus remain to be established. The rationale for such drainage is that decompressing the obstructed urinary tract into the amniotic cavity will thereby minimize further renal deterioration and the sequelae of oligohydramnios. However, before accepting this rationale several underlying assumptions must be evaluated:(a) the antenatal diagnosis of fetal urologic abnormalities is accurate;(b) intervention will benefit the fetus by minimizing the loss of renal function;(c) antenatal testing is capable of differentiating the upper urinary tract that is dilated consequent to obstructive uropathy from the upper urinary tract that is dilated on the basis of a non-obstructive cause (vesicoureteral reflux, Prune Belly syndrome);(d) improvement of the renal function by antenatal intervention is better than improvement in renal function by postnatal intervention and (e) intervention will be valuable when applied at the time the malformation is discovered. The value of prenatal surgery for hydronephrosis rests on our ability to demonstrate greater recoverability of renal function (and perhaps pulmonary function) by intervention in utero rather than in the neonatal period.

The International fetal Surgery Registry Report (Manning et al., 1986) describes the outcome of 58 live-born infants with obstructive uropathy treated in utero: 25 of these 58 live-borns (43%) died in the immediate newborn period from respiratory insufficiency caused by pulmonary hypoplasia. Similar survival rates are reported for treated fetuses with and without oligohydramnios (41% versus 40%). In 15 % lethal associated anomalies were reported. No final diagnosis was obtained in 33 of the total of 73 cases (45%) treated in utero.

Despite the current and limited use of antenatal interventions in the dilated urinary tract, the above mentioned assumptions remain unproven. The reasons for selection and lack of details about the patients involved make interpretation of any possible benefit difficult. Furthermore, since diagnosis is often obtained late in gestation or, referral to a centre is delayed, the likelihood of obtaining benefit from antenatal drainage is reduced. Even when the diagnosis is correct, there are no criteria to determine which fetus would benefit from such intervention and to predict response to fetal urinary tract decompression. Since the available technology does not accurately differentiate between obstructive and non-obstructive cause of hydronephrosis, invasive procedures do not seem justified. Relieving the symptoms of dilatation does not imply that we are curing the patient.

Several conditions may simulate obstructive hydronephrosis. Enlarged bladders have been identified in both obstructed and non-obstructed hydronephrosis cases. Non-obstructive conditions, which include vesico-ureteral reflux, neurogenic bladder and Prune Belly syndrome without obstruction, will not be aided by decompressive surgery. Some conditions might be aided by decompressive surgery, such as uretero-pelvic junction obstruction and obstruction of the upper pole of a duplicated collecting system. There is an additional group of renal lesions such as renal dysplasia, Prune Belly syndrome variants, and multicystic dysplastic kidneys that is believed to be due to in-utero obstruction of the urinary tract. However, the patho-physiologic insult may occur so early in gestation that surgical intervention at a later stage will not change the outcome. Multicystic dysplasia, often associated with pelvo-infundibular atresia, is thought to occur at 8 to 10 weeks of gestation. In the imperforate cloacal plate malformation sequence, the developmental aberration leading to obstruction of the urinary tract occurs even earlier, at 6 weeks of gestation. Benefit can be expected from therapeutic intervention only in cases of obstructive hydronephrosis if the surgery is performed early enough to prevent or correct the consequences of the obstructive lesion.

Caution must be advocated at this time for any prenatal therapeutic manoeuvres that are undertaken in the absence of proven and remediable obstruction. Because 80 to 90 percent of the renal mass develops during the third trimester, one might anticipate impairment of nephron formation due to back pressure from urinary obstruction during this period. While longstanding fetal hydronephrosis undoubtly causes thinning of the renal parenchyma, the length of time that the fetal kidney can be obstructed before irreversible damage occurs has not been demonstrated experimentally. Backward pressure of urine is thought to be a contributing factor for the development of dysplasia. But like in neonates and infants, not all dilated systems display high pressure.

In cases with obstructive uropathy, the effect of sterile urine might be different from that of infected urine. The Birmingham Reflux Study Group (1987) reported that renal scarring associated with reflux begins at the time of the first urinary tract infection. The assessment of potential gain by in utero drainage becomes more critical as complications of the procedure accumulate. Those reported include induction of premature labor, fetal bowel perforation, hemorrhage and infections. The (fetal) death rate directly attributed to the procedure is 4.7%, as reported by the International fetal Surgery society in Bonn (1988).

The success of fetal intervention for hydronephrosis relies upon further improvements in the understanding of fetal renal physiology as well as the pathogenesis of renal dysplasia, fetal hydronephrosis and pulmonary hypoplasia. In addition, we must demonstrate experimentally that in-utero drainage is of significant benefit to the development of the kidneys and lung.

## 6.6 Genetic aspects.

The causes of obstructive uropathy are heterogeneous. Precise clinical and patho-anatomical evaluation of an index case in a given family is always essential

to establish the correct diagnosis of a congenital renal tract anomaly, and its risk of recurrence.

Familial occurence of hydronephrosis due to subpelvine obstruction has been reported (Crawfurd, 1988). Also in combination with other malformations of the urinary tract like: duplication or vesicoureteral reflux. Prenatal detection of an autosomal dominant type of congenital hydronephrosis by ultrasound has been reported (McCormack, 1982). Congenital hydronephrosis may also occur as part of a malformation syndrome (Table 3).

Table 3. Syndromic associations with hydronephrosis

| | inheritance |
|---|---|
| Johanson-Blizzard syndrome | a.r. |
| Russel-Silver syndrome | mfr, a.d. |
| Congenital lipodystrophic diabetes with acanthosis nigricans | a.r. |
| Ectromelia-ichthyosis syndrome | a.r. |
| Ochoa syndrome | a.r. |
| Apert syndrome | a.d. |
| Ectrodactyly (EEC) syndrome | a.d. |
| Laurence-Moon-Biedel syndrome | a.r. |
| Multiple lentigenes syndrome | a.d. |
| Rubinstein-Taybi | a.r. |
| Female hermaphroditism | mfr,variable |
| Schinzel-Giedion syndrome | a.r. |
| Sotos syndrome | mfr, a.d. |
| Ehlers-Danlos | a.d. |
| Warburg (HARD.E) syndrome | a.r. |
| Weyer's syndrome | a.r. |
| Townes syndrome | a.d. |

a.r.=autosomal recessive, a.d.=autosomal dominant, mfr=multifactorial.

For vesico-ureteral reflux, sporadic and familial cases are known and the genetic mechanism may be either autosomal dominant (with variable expression) or multifactorial (Crawfurd, 1988). For genetic counselling purposes Bois et al. (1975) estimate a 4 per cent risk of reflux for first-degree relatives of index patients with vesico-ureteral reflux. A higher risk would presumably be appropriate when there is a strong family history. Vesicoureteral reflux may be part of a syndrome, as for example in the Townes syndrome (Townes and Brock, 1972; Reid and Turner, 1976; Kurnit et al., 1978). This autosomal dominant syndrome consists of: imperforate anus, renal hypoplasia, vesicoureteral reflux or urethral valves, anomalies of hand, feet and ear (deafness, abnormalities of the external ear).

For the Prune Belly syndrome as isolated malformation complex, autosomal recessive, autosomal dominant or multifactorial inheritance has been suggested (Crawfurd, 1988). Care should be taken to distinguish the autosomal recessive MMIHS (Winter and Knowles, 1986) from the isolated Prune Belly syndrome

which is predominantly found in males and has a low recurrence risk. It is possible that the high female to male sex ratio in the MMIHS is due to underdiagnosis in males, because of the tendancy to misdiagnose such a case as isolated Prune Belly.

The sirenomelia sequence occurs in about 1 in 60.000 live births, consisting of imperforate anus, sacral agenesis, variable degree of fusion of the lower limbs and a single umbilical artery. All degrees of severity are observed. The variable consequences are often called the caudal regression syndrome. The urinary tract lesion in the majority of cases is a bilateral renal agenesis. Less extreme forms of caudal regression may occur in association with renal or other malformations. Conceivably, imperforate anus and/or urethral atresia might represent a minor degree of this type of defect.

A structural low-level obstruction of the urethra can be caused by atresia or valves. In our series (Chapter 3.2), recurrence of urethral obstructions was observed in 2 out of 15 cases. Presumably, the inheritance pattern is autosomal dominant (with variable expression) or multifactorial.

Ultrasonic exclusion of a recurrence of an obstructive uropathy is not always possible early in the second trimester since the features of a dilated renal tract, e.g. due to urethral valves may become visible as late as the third trimester (Wladimiroff et al., 1985).

## 6.7 Closing remarks

It has become clear from the data presented in this chapter that obstructive uropathy may have many different causes and may be associated with a wide variation in kidney involvement, ranging from mild hydronephrosis to renal dysplasia. Other primary and/or secondary anomalies may strongly influence the neonatal outcome. In summary, the presence and level of a fetal obstructive uropathy can be accurately identified. However, the primary cause of the dilatation of the renal tract, which can be obstructive or nonobstructive, may not be recognised by ultrasound. Dilatation is not synonymous with obstruction. Moreover, no reliable tests are available to predict renal function of a fetus nor its neonatal function. Without this information, management in accordance with a predictable outcome is not possible. Therefore, a conservative management is advocated.

A final urologic diagnosis depends upon the use of cystography and isotopes, which are only available postnatally.

The rationale for intervention is prevention of further renal damage of the renal parenchyma. Early delivery of an affected infant, adding the risk of prematurity, transfers the problem to the paediatrician. Results of in utero diversion procedures do not provide answers to the question as to whether the risks weighs up against the possible benefits. Both after a favourable and unfavourable outcome questions arise. What is the effect of in-utero procedures? Can damage really be prevented? What is the natural history and outcome of conservatively managed fetuses? Which fetus really benefits from these procedures on a long term basis?

Aren't we just postponing the time of onset of end-stage renal disease and mortality?

The first conclusion which can be drawn is that our diagnostic capabilities have to be refined. In this aspect knowledge of genetic syndromes is necessary. Secondly, the approach of prenatal function testing of the fetal kidney by means of urine electrolyte determination is an oversimplification. Thirdly, studies dealing with the outcome of fetuses with prenatally detected dilatation of the urinary tract lack an amazing amount of details on prenatal course and postnatal follow-up, especially regarding patho-anatomical examinations (incomplete, no final diagnosis). Therefore, whenever prenatal abnormalities are detected, the first priority postnatally is to confirm the diagnosis. As a major key for answering questions about optimal prediction and management of fetal obstructive uropathies, exact diagnosis and extensive long term follow up to assess the ultimate outcome of renal function is mandatory. The presence of associated fetal anomalies in a large number of cases and the impossibility to predict renal function prenatally all warrant against agressive intrauterine management. Moreover, the initial maldevelopment process will have had its onset long before these effects become detectable by ultrasound. Attention should be focused on conservative management. Prenatal ultrasound detection of fetal obstructive uropathy is confined to identifying those fetuses in which adjustment of pre and postnatal management is required, because a lethal anomaly is present or the affected infant will benefit from immediate postnatal care or will be asymptomatic in the neonatal period.

Chapter 7

# General conclusions.

The aim of this study was to define the role of ultrasound in the prenatal diagnosis of fetal urinary tract malformations, with particular reference to renal agenesis, cystic kidney disease and obstructive uropathy. Many of the more severe urinary tract malformations are detectable by diagnostic ultrasound. More than 25% of the fetal structural abnormalities detected prenatally in our prenatal unit are of renal origin, either as an isolated malformation or as part of a syndrome.

Heterogeneous causes have been identified as possible mechanisms for derangement of normal renal development. The traditional viewpoint of the 'timing of the insult' being responsible for the type of anomaly, implies not only exogeneous factors. Gene mutations involved in differentiation processes and morphogenesis of the kidney may have similar effects. The onset of maldevelopment is variable and may occur, immediately or later in life, as is the case in autosomal dominant polycystic kidney disease. The subclinical or clinical manifestation of a disorder may be variable and will largely depend on diagnostic capabilities. Technical limitations in fetal imaging may be determined by the amount of maternal subcutaneous fat, amniotic fluid volume and fetal position. Other aspects which have to be considered are the stage of fetal development at which errors in renal morphogenesis and function become detectable.

Renal agenesis, results from a very early non-union of the ureteric bud an the metanephric blastema. Ultrasound diagnosis may, therefore, be possible at the end of the first trimester of pregnancy. Diagnostic criteria are the absence of kidneys and bladder filling. Oligohydramnios usually develops between 16-20 weeks of gestation. If bilateral renal agenesis is suspected at ultrasound examination, additional techniques such as the creation of an artificial amniotic fluid compartment and Doppler recordings of fetal arteries may be helpful to confirm the diagnosis or to detect associated anomalies. The creation of an artificial amniotic fluid compartment adds a risk for rupture of membranes and premature delivery. Therefore, the technique should only be applied in cases in which an obvious improvement of visualization of fetal organs is expected and the findings will be of paramount importance for reconsidering obstetric management. Normal flow velocity waveform recordings in the fetal arteries strongly indicate a fetal origin (structural and/or chromosomal anomalies) for the growth retardation and oligohydramnios. Nevertheless, bilateral renal agenesis remains a difficult diagnostic problem even in experienced hands. For renal agenesis the genetic mechanism is probably multifactorial with a low reccurence risk. Renal agenesis as an 'isolated' malformation may be part of a monogenic

syndrome with higher risks of recurrence, also for non-renal malformations associated with this entity. For the purpose of genetic counselling, the recurrence risk will depend on the family history, ultrasound examination of the kidneys of the parents and autopsy findings of the affected fetus /infant. In pregnancies at risk for renal agenesis because of a corresponding anomaly in a previous infant, normal ultrasound findings will not rule out minor forms of structural urinary tract pathology, for which the risk may be increased.

Cystic kidney disease presents a very heterogeneous group of malformations. No classification exists in which all the entities can be seperately defined according to pathologic, morphologic, clinical and genetic criteria. Nonetheless, several clear forms can de defined on the basis of pathologic features and inheritance. An autosomal dominant and recessive form of polycystic kidney disease exists. Major differences between these two entities are found in liver pathology and family history. A reliable prenatal diagnosis is possible for the dominant form by DNA studies on chorion villi. For the recessive type, only prenatal ultrasound monitoring can be offered to detect the typical hyperechogenic texture of the fetal kidneys. Exclusion of an affected fetus is not possible because of the variability in time of onset and the intrafamilial variability. Renal dysplasia often occurs unilateral; the presence of an unaffected contra-lateral kidney will allow normal obstetric management. Cystic kidneys may also occur as part of a syndrome or may be the only manifestation of a syndrome.

In general it has to be stressed that prenatal ultrasound describes morphology and not necessarily function. However, as soon as morphologic abnormalities are suspected, the question arises as to whether this bears any relationship to the function of the affected organ system or any other organ system. This is particularly so for fetal obstructive uropathies. Prenatal ultrasound can accurately detect the presence and level of urinary tract obstructions. However, it is not possible to distinguish between causes of obstructive and non-obstructive origin. At this stage the possible benefit of prenatal detection of obstructive uropathy is limited. It is confined to identifying fetuses with a lethal abnormality, or fetuses which will benefit from immediate postnatal care or of affected fetuses which will be asymptomatic in the neonatal period. Adjustment of the pre and postnatal management is then required. To date, there are no clear criteria to determine which fetus would benefit from in-utero drainage in the presence of obstructive uropathy.

Increasing resolution of Ultrasound equipment did not only result in further diagnostic refinement but also lead to a better understanding of inheritance patterns. Family studies have been recently undertaken utilizing ultrasound and intravenous pyelography to detect subclinical renal anomalies. Close relatives of most previously described 'sporadic' cases may not have received adequate renal evaluation.

The possibilities and limitations of first trimester diagnosis of fetal structural defects using vaginal ultrasonography, are not yet well established. Future studies on the efficacy of vaginal scanning in this particular field of prenatal diagnosis seems justified.

The spectrum of anomalies observed prenatally using ultrasound clearly differs from that seen during the neonatal period. One of the main reasons for this is the fact that many fetuses die in-utero. This thesis reflects the need for a multdisciplinary approach and underlines the need for careful prenatal and postnatal investigation and adequate documentation of fetal renal anomalies. Precise patho-anatomical evaluation of an index case and a well-documented family history are essential for establishing the correct diagnosis of a congenital renal tract anomaly, its recurrence risk and the possibilities for prenatal diagnosis in subsequent pregnancies. Whenever genetic counselling is provided, variability in time of onset, intrafamilial variability, and the heterogeneity of a malformation have to be taken into account especially in view of early diagnostic procedures in future pregnancies.

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# Summary


## Chapter 1

A general introduction on the role of ultrasound for the detection of fetal structural defects is given.

The objective of the study, as described in this chapter, was to evaluate the possibilities and limitations of the prenatal sonographic detection of renal anomalies. Renal tract anomalies are common malformations; more than 25% of the fetuses in which anomalies were detected in our prenatal ultrasound unit, displayed anomalies of renal origin. For isolated renal tract malformations the incidence of associated chromosomal anomalies is 3.2%.

## Chapter 2

A review on normal kidney development, ultrasonic renal anatomy and biometry of the fetal kidney and fetal urine production is provided. Kidney growth progresses linearly throughout gestation with a slight flattening at the end of gestation. For the human fetus, normal values of different parameters of kidney dimensions related to gestational age have been established. Urine flow rate studies in the fetus are limited to calculation of changes of bladder dimensions by ultrasound. The transition from fetal to neonatal life implies a change in haemodynamics and vascular resistance with consequences for the urine production, resulting in a decreased urinary production rate for the neonate when compared with the fetus.

## Chapter 3

Abnormal development of the renal tract is discussed.

In a 'high-risk'group of 141 pregnant women with a known increased risk for an offspring with renal tract anomalies, a recurrence was observed prenatally in 8 per cent. A recurrence was observed under the following conditions: renal agenesis, cystic kidney disease and urethral obstruction. In two infants of this group (1.4%) the recurrence was not discovered before birth due to the nature and the late manifestation of the disease (autosomal dominant and autosomal recessive polycystic kidney disease).

In a second group of pregnant women (n=98), referred because of the presence of fetal renal pathology in the absence of a positive family history, in almost half of the cases with sub-vesical obstruction (n=17) or with cystic kidney disease (n=32) also a structural defect of extra-renal origin was present.

Fetal outcome is strongly influenced by the presence of associated structural and/or chromosomal defects. In general, the overall incidence of chromosome anomalies in the presence of fetal structural defects is 10.9 per cent. The mortality

of 85 per cent, in the presence of combined structural and chromosomal anomalies emphasizes the need for prenatal karyotyping.

## Chapter 4

Severe oligohydramnios and IUGR are often associated with renal anomalies, in particular bilateral renal agenesis.

The presence of marked oligohydramnios may greatly restrict the quality of fetal imaging. Additional techniques such as the creation of an artificial amniotic fluid compartiment, doppler studies in fetal arteries and intraperitoneal instillation of saline are available to obtain information as to whether the condition is the result of impaired placental perfusion or fetal abnormalities. When additional techniques were applied (Doppler investigation of fetal arteries and in selected cases also creation of an amniotic fluid compartment) the sensitivity of picking up a structural defect increased from 50 to 76%. A close relationship between asymmetrical IUGR and reduced placental perfusion was established. Normal PI values in the fetal arteries (n=21) were highly associated with prenatal detection of fetal structural anomalies (62%), postnatally in 81 per cent of cases structural abnormalities were present. Only 2 out of these 21 (9.5%) fetuses displayed no structural and/or chromosomal abnormalities after birth. More than half of the anomalies (59%) represented bilateral renal agenesis. In 5 cases a false negative diagnosis of bilateral renal agenesis was made, 4 of these infants displayed enlarged adrenals at autopsy.

Both for renal agenesis as part of a syndrome and for the oligohydramnios sequence a differential diagnosis is given as starting point for additional investigations and prognosis.

## Chapter 5

Cystic kidneys or renal cystic disease are a morphologic description for an etiological heterogeneous group of disorders ranging from solitary cysts to several forms of multicystic and polycystic kidneys. In a group of pregnancies at risk for autosomal recessive polycystic kidney disease, 5 out of 6 recurrences were diagnosed prenatally before 26 weeks of gestation. The diagnosis was based on the typical hyperechogenic aspect of the kidneys. Oligohydramnios was only present in 2 out of 6 cases and should therefore not be used as a diagnostic criterium but only as a reflection of absent or decreased diuresis. Cystic kidney disease may present as part of different syndromes, an overview is given of the complex differential diagnosis. The prenatally established combination of combined cystic kidney disease and hydrocephaly lead to the documentation of a possibly new autosomal recessive syndrome after exclusion of other possible causes (family study, chromosomal and biochemical investigation) for this "Ventriculomegaly-polycystic kidney syndrome". The heterogeneity of pathology associated with renal cystic disease is emphasized.

## Chapter 6

Obstructive uropathy in the fetus is discussed. Urinary tract obstructions can be divided into high-level (ureter) and low-level (urethra) obstructions. Presence and level of a urinary tract obstruction can be accurately identified. The outcome of high-level obstructive uropathy in the fetus is relatively good (survival 86 %), in contrast with low-level uropathy.

In fetal low-level obstructive uropathy, electrolyte studies in urine obtained from fetal bladder aspiration have been reported to be predictive of the presence or absence of renal dysplasia in the fetus. In the present study discrepancies were observed in some instances between the electrolyte result and the presence of renal dysplasia after birth. Therefore, urinary electrolyte results should be interpreted with caution.

Finally, in a group of 43 consecutive cases of low-level obstructive uropathy the overall survival rate was 27 per cent (males with urethral valves survived in 89 per cent). Associated non-renal defects were present in 48 per cent of the cases, half of which were not detectable by prenatal ultrasound. Therefore, it is suggested that we are not dealing with an isolated primary lesion at the level of the urethra with secondary development of renal dysplasia and lung hypoplasia but with a spectrum of primary defects. A multidisciplinary approach (prenatal team consisting of: obstetrician, ultrasonographer, neonatologist, paediatric urologist, paediatric surgeon, paediatric pathologist and geneticist) is therefore advocated when prenatal ultrasound reveals fetal structural anomalies. This is of importance regarding further diagnostic procedures, possible interventions, obstetric management, prognosis and calculation of recurrence risk. An overview is given of genetic syndromes associated with hydronephrosis. The possibility of multiple non-renal defects has to be taken into account whenever an obstructive uropathy is diagnosed prenatally until the contrary is proven.

# Samenvatting

## Hoofdstuk 1

Dit hoofdstuk geeft een algemene inleiding over de rol van ultrageluid bij detectie van foetale structurele afwijkingen.

Het doel van het beschreven onderzoek was de evaluatie van mogelijkheden en beperkingen van het echoscopisch vaststellen van nierafwijkingen bij de foetus. Nierafwijkingen zijn niet zeldzaam; meer dan 25% van het totale aantal ongeborenen bij wie op onze afdeling voor prenatale echodiagnostiek afwijkingen werden vastgesteld, hadden afwijkingen van renale aard. In een groep van ongeborenen met een geisoleerde nierafwijking bedroeg het percentage geassocieerde chromosoom afwijkingen 3.2%.

## Hoofdstuk 2

Een overzicht wordt gegeven van de normale nierontwikkeling, echoscopische renale anatomie en biometrie bij de foetus en van de foetale urine productie. Tijdens de zwangerschap neemt de groei van de nier lineair toe en aan het einde van het laatste zwangerschapstrimester kan een afvlakking van de groeicurve van de nier worden gezien. Voor de humane foetus zijn normaal curves samengesteld die de verschillende parameters van de nierafmetingen correleren aan de zwangerschapsduur. Studies van de foetale urineproduktie beperken zich tot het vastleggen van verschillen in blaasgrootte met behulp van ultrageluid. De overgang van de foetale naar de neonatale situatie brengt grote haemodynamische veranderingen met zich mee die van invloed zijn op de urine produktie. Wordt de urine produktie van de neonaat vergeleken wordt met die van de foetus dan is er sprake van een afname.

## Hoofdstuk 3

In dit hoofdstuk wordt afwijkende ontwikkeling van de nieren besproken.

In een 'high-risk' groep van 141 zwangeren, met een bekend verhoogd risiko op het krijgen van een kind met een afwijking van de nieren en hun afvoerwegen, werd prenataal bij 8% een aangedane foetus vastgesteld. Het betrof hernieuwd optreden van renale agenesie, cystenier(en) en urethra obstructie. Twee verdere kinderen in deze groep (1.4%) bleken na de geboorte eveneens een nierafwijking te hebben welke prenataal niet kon worden vastgesteld gezien de aard en de late manifestatie van de afwijking (autosomaal recessieve en autosomaal dominante polycysteuze nieren).

Bij een tweede groep zwangere vrouwen (n=98) met een blanco voorgeschiedenis, verwezen in verband met de aanwezigheid van foetale renale pathologie, werd bij bijna de helft van de subvesicale obstructies (n=17) en de cystenieren (n= 32) ook geassocieerde pathologie van niet renale origine gevonden.

De prognose voor een foetus wordt in grote mate bepaald door de aanwezigheid van geassocieerde structurele en /of chromosomale afwijkingen. In het algemeen werd bij aanwezigheid van foetale structurele defecten in 10.9% een geassocieerde chromosomale afwijking gevonden. Was er een combinatie aanwezig van structurele en chromosomale pathologie, dan bedroeg de mortaliteit 85% hetgeen de noodzaak van prenatale karyotypering onderstreept.

**Hoofdstuk 4**

Een ernstig oligohydramnion (verminderde hoeveelheid vruchtwater) in combinatie met een groeiachterstand wordt vaak veroorzaakt door nierpathologie, met name renale agenesie. Diagnostische evaluatie van de foetus met echografie wordt bemoeilijkt door het oligohydramnion.

Additionele technieken zoals het aanleggen van een artificieel vruchtwater compartiment, Doppler studies in de foetale arterien of het intraperitonaal inbrengen van fysiologisch zout kunnen een waardevolle bijdrage leveren om informatie te verkrijgen of deze situatie veroorzaakt wordt door placentaire of foetale oorzaken. Met gebruik van deze additionele technieken (Doppler studies en in enkele gevallen ook het aanbrengen van een artificieel vruchtwater compartiment) steeg de sensitiviteit van de detectie van de structurele afwijkingen van 50 naar 76%.

Er werd een nauwe relatie gevonden tussen asymmetrisch groeivertraagde foetussen en verminderde placentaire doorbloeding. In aanwezigheid van een normale Pulsatiliteits Index in het bloedstroom snelheidsprofiel van de arteria umbilicalis en foetale arteria carotis interna (n=21) werd prenataal bij 62% een of meerdere structurele afwijkingen vastgesteld, terwijl postnataal het percentage 81% bleek te zijn. Slechts bij 2 van deze 21 (9.5%) ongeborenen bleek na de geboorte geen structurele en /of chromosomale afwijking aanwezig te zijn. Bij meer dan de helft van de afwijkingen (59%) was er sprake van bilaterale renale agenesie. Slechte visualisatie van de nierregio ten gevolge van het oligohydramnion vergroot het risico dat nieren voor bijnieren worden aangezien. Vijfmaal werd de diagnose bilaterale renale agenesie niet prenataal onderkend. Post-partum werd bij vier van deze vijf kinderen met een foutnegatieve bevinding bij obductie sterk vergrote bijnieren gevonden.

Een differentiaal diagnose voor de renale agenesie als onderdeel van een syndroom en voor de oligohydramnion sequentie worden gepresenteerd als een onmisbaar uitgangspunt voor aanvullend onderzoek en prognose stelling.

**Hoofdstuk 5**

Cystenieren is een beschrijvende term voor etiologisch zeer heterogene aandoeningen variërend van een solitaire cyste tot verscheidene vormen van multicysteuze en polycysteuze nieren.

In een groep zwangerschappen met een verhoogd risico op het krijgen van een kind met polycysteuze nieren van het autosomaal recessieve type werden

5 van de 6 opnieuw aangedane foetussen prenataal vastgesteld door middel van echoscopisch onderzoek, voor de 26e zwangerschapsweek. De diagnose werd gesteld op basis van het typische hyperechogene aspect van beide nieren. Bij het zesde kind traden pas later verschijnselen op. Er was slechts bij 2 van de 6 aangedane zwangerschappen sprake van een oligohydramnion. Het oligohydramnion moet niet als diagnostisch criterium voor deze afwijking gehanteerd worden maar als weerspiegeling van afwezige of verminderde diurese. Ook andere in de literatuur genoemde criteria blijken minder goed bruikbaar om de diagnose dmv. echografie met zekerheid te kunnen uitsluiten voor de 20 a 26ste week.

Cystenieren kunnen deel uit maken van verscheidene syndromen en een overzicht van deze complexe differentiaal diagnose wordt gegeven. De prenatale onderkenning van een met cystenieren geassocieerde hydrocefalie leidde tot de vaststelling van een mogelijk nieuw autosomaal recessief syndroom nadat gegevens van familie-onderzoek, chromosomaal en biochemisch onderzoek eventueel bekende oorzaken voor dit "Ventriculomegaly-polycystic kidney syndrome" hadden uitgesloten. De heterogeniteit van met nierafwijkingen geassocieerde pathologie wordt hierdoor benadrukt.

## Hoofdstuk 6

Urineweg obstructies kunnen worden ingedeeld in hoge obstructies (niveau van de ureter) en lage obstructies (niveau van de urethra). Prenataal kan de aanwezigheid en het niveau van een obstructie exact worden geidentificeerd. De prognose van prenataal gediagnostiseerde hoge urineweg afsluitingen is gunstig (overlevingskans 86%), in tegenstelling tot de lage urineweg afsluitingen.

Volgens sommige onderzoekers zou bepaling van electrolyten in geaspireerde foetale urine waardevol zijn bij het voorspellen van de aanwezigheid van dysplastische nieren bij een obstructieve uropathie. In een groep van 8 patienten vonden wij discrepanties tussen de electrolyt waarden en de aanwezigheid van dysplastische nieren, zodat de voorspellende waarde van deze bepaling betwijfeld wordt.

In een groep van 43 opeenvolgende foetale lage urineweg obstructies werd een overlevingspercentagen van 27% gevonden (voor de jongens met urethrakleppen bedroeg dit percentage 89%). Geassocieerde niet-renale afwijkingen waren aanwezig bij 48%, en slechts de helft van deze afwijkingen kon prenataal worden vastgesteld. Foetale lage urineweg obstructies lijken niet zozeer uit geisoleerde primaire afwijkingen op het niveau van de urethra met mogelijk secundaire ontwikkeling van nierdysplasie en longhypoplasie te bestaan, maar het betreft eerder een spectrum van primaire defecten van zowel renale als niet-renale oorsprong. Daarom is een multidisciplinaire benadering (prenataal team bestaande uit: gynaecoloog, echografist, kinderuroloog, kinderchirurg, neonatoloog, kinderpatholoog en klinisch geneticus) van belang voor zowel het diagnostische beleid als voor de eventuele interventies, prognose bepaling, obstetrisch beleid en de bepaling van een herhalingskans. Er wordt een overzicht gegeven van genetische syndromen welke gepaard kunnen gaan met hydronephrose. Indien bij een foetus een lage urineweg obstructie wordt vastgesteld dan moet met

de mogelijkheid van geassocieerde prenataal zichtbare en onzichtbare structurele afwijkingen en chromosoomafwijkingen rekening gehouden worden tot het tegendeel bewezen is.

# Curriculum Vitae

1958 geboren te Leiden
1976 eindexamen aan de scholengemeenschap Nebo-Marienbosch, Nijmegen.
1976 inschrijving aan de Katholieke Universiteit, Nijmegen.
1984 artsexamen.
1984 wetenschappelijk medewerker afdeling verloskunde /gynecologie van de Katholieke universiteit te Nijmegen (hoofd Prof Dr TKAB Eskes).

Sedert oktober 1984 in dienst van de Stichting Klinische Genetica Rotterdam, werkzaam in de prenatale diagnostiek (Prof Dr JW Wladimiroff) binnen de afdeling verloskunde /gynecologie Dijkzigt ziekenhuis, Erasmus universiteit Rotterdam (hoofd Prof Dr AC Drogendijk).

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Prof AC Drogendijk schiep de voorwaarden waardoor prenataal echografisch onderzoek van aangeboren misvormingen mogelijk werd binnen de Stichting Klinische Genetica regio Rotterdam en de afdeling Verloskunde-Gynecologie van het academisch Ziekenhuis Dijkzigt.

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Met Patricia Stewart, echocardiografiste, deel ik meer dan alleen echokamer 2. Zij was in "hart en nieren" betrokken bij alle gebeurtenissen.

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Prof RJ Scholtmeyer en Rien Nijman, afd.Kinderurologie Sophia kinderziekenhuis, zagen het merendeel van de kinderen en hun ouders voor en na de geboorte.

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De patholoog anatomen Jan den Hollander, Erasmus Universiteit, en Hans Gaillard, Cyto-diagnostisch Centrum, verrichten het post-mortem onderzoek.

Leonie Flick stelde haar tekstverwerker veelvuldig ter beschikking.

Paula Vogelaar corrigeerde het manuscript.

De verwijzende gynaecologen informeerden ons over de follow-up van de

zwangerschappen en droegen zo bij aan een van de wezenlijkste facetten van dit onderzoek.

Vervolgens noem ik alle mensen in mijn persoonlijke omgeving, met name mijn ouders, die altijd geintereseerd zijn geweest in de stand van zaken en mijn echo's weerkaatsten.

In het bijzonder waren de ouders die voor echodiagnostiek kwamen van belang als grootste drijfveer om de individuele patienten ervaringen en inzichten van de problematiek zoals beschreven in dit proefschrift, af te ronden en op schrift te stellen.