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Genetic syndromes and prenatally detected renal anomalies

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Summary Renal anomalies are frequently detected on the routine second trimester scan offered to all pregnant women in the UK. These anomalies may be isolated but can also be associated with other congenital anomalies. Many combinations of ultrasound scan findings constitute recognised genetic entities. Knowledge of these conditions is essential for adequate management of the pregnancy and subsequent balanced parental counselling. This short review discusses the common genetic syndromes associated with the renal abnormalities identified on the antenatal ultrasound scan, and also provides an overview of renal symptoms in chromosome imbalances and after teratogenic influences.

Introduction

Detailed obstetric ultrasound scans are routinely offered to pregnant women in the second trimester of pregnancy in the developed world. The aims of this screening procedure are to identify anomalies that are either incompatible with life, associated with expressed morbidity or long-term disability, or may require intrauterine or early neonatal intervention.[1] This allows optimal neonatal outcome and accurate counselling of expectant parents to help them make informed choices. In a multicentre study of antenatal abnormalities identified on the second trimester scan, major abnormalities were identified in 6 per 1000 fetuses.[2] If an anomaly is detected prenatally, decisions regarding the pregnancy are strongly influenced by the definitive diagnosis and prognosis of the underlying condition. It is therefore paramount for obstetricians to have insight into the various possible diagnoses and the consequences in case an anomaly is detected.

This review provides a short discussion of the most important prenatally detectable renal anomalies. In a survey of all prenatal ultrasound scans performed at a hospital in north-east England, the incidence of renal anomalies was 5 per 1000 births[3] underlining the importance of careful screening of the kidneys. We discuss here the renal symptoms of agenesis, enlargement and cysts, as well as the most common aetiologies, including their consequences and genetic aspects. In addition, renal consequences of teratogenic influences and prenatally detected chromosome anomalies are discussed.

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Oligohydramnios

Strictly speaking, oligohydramnios is not a renal anomaly. Normal renal function is required for adequate production of amniotic fluid from 8 weeks on. Initially, it was thought that only renal pathology resulted in oligohydramnios, but later it became recognised that oligohydramnios could be caused by any other urinary tract anomaly that interfered with amniotic fluid production and prolonged amniotic fluid leakage.[4] Renal causes can be renal agenesis, cystic renal dysplasia, polycystic kidney disease and renal tubular dysgenesis (see below). Irrespective of the cause, oligohydramnios was found to be accompanied by 'Potter syndrome'-flattened face with upslanted palpebral fissures and 'squashed' nose, positional limb anomalies including talipes and pulmonary hypoplasia. As these symptoms are secondary to the increased pressure on the fetus in the absence of amniotic fluid, nowadays most physicians prefer to refer to these symptoms using the term, 'oligohydramnios sequence'.

The incidence of congenital malformations in fetuses with oligohydramnios is about 11%,[5] with most being urinary tract anomalies. Additional extra-renal abnormalities were present in 32% of the fetuses with oligohydramnios and renal tract anomaly. Of these, 65% had an underlying chromosome anomaly or a recognisable genetic syndrome.[2]

Polyhydramnios

Polyhydramnios complicates between 1% and 3% of pregnancies.[5] The aetiology of polyhydramnios is unknown in two-thirds of the cases, but is associated with fetal abnormalities in up to 50% of the affected pregnancies.[5,6] There is a greater association with non-renal anomalies in polyhydramnios, particularly gastrointestinal tract abnormalities in 21%[5] and anomalies of the central nervous system (CNS) in 10%. These include structural CNS anomalies or neurological conditions, presenting as decreased fetal movements or neonatal hypotonia.

Renal agenesis

The true definition of complete renal agenesis is failure to identify any renal tissue on post-mortem examination. As both unilateral and bilateral renal agenesis is a feature of many genetic syndromes,[7] it is essential to undertake detailed scans for associated anomalies. Associated anomalies are identified in 30%[8] of the fetuses and involve, especially, genitals, hindgut, heart and limbs. The diagnosis of isolated renal agenesis is one of exclusion. The most frequent syndromes associated with renal agenesis and the main clinical features are listed in Table 1.

The incidence of isolated unilateral renal agenesis is estimated as 1 per 1000 live births.[9] Bilateral renal agenesis is less common, with an incidence of 1 in 4000. It is three times commoner in males. Autosomal dominant inheritance of isolated renal agenesis has been recognised and a parent with unilateral renal agenesis may have a baby with bilateral absent kidneys. Renal agenesis in a fetus should prompt a renal scan for the parents. The recurrence risk to parents of a baby with isolated unilateral renal agenesis is about 1% if the parental renal scans are normal. If a parent has unilateral renal agenesis, then the risk of renal abnormalities in the offspring is 7%, with a 1% possibility of bilateral renal agenesis.[10] A higher sibling recurrence risk (8%) has been suggested in bilateral renal agenesis.[7] It may be that this higher figure is caused by the inclusion of syndromes unrecognized at the time. Unless a syndromic cause can be diagnosed, prenatal diagnosis is based on detailed anomaly scans. If the family history is positive for diabetes mellitus, the renal cysts and diabetes syndrome should be considered, as renal symptoms in this entity are very variable and include renal agenesis.[11]

Enlarged kidneys

Renal enlargement may be secondary to pelvicalyceal dilatation, cystic dysplasia or enlargement of the cortex. Differential diagnosis on prenatal scans alone can be difficult and definitive diagnosis may need post-mortem examination.

Beckwith–Wiedemann syndrome (BWS)

This is an overgrowth syndrome associated with predisposition to tumour formation, especially Wilms tumour. The most important characteristics are macrosomia, macroglossia, ear lobe creases or posterior helical ear pits, umbilical hernia or omphalocele, embryonal tumours, hemihyperplasia and visceromegaly, including renal abnormalities. Other symptoms are polyhydramnios, facial naevus flammeus and neonatal hypoglycaemia.[12,13] Postnatal development is almost always normal, except in those with expressed neonatal hypoglycaemia. It results from mutations or epigenetic modifications of the imprinted region of chromosome 11p and most cases are sporadic.[12] It has been suggested that BWS and other disorders caused by a disturbed imprinting are more frequent in fetuses conceived using assisted reproduction techniques.[14] However, it has recently become clear that this is caused by a correlation between infertility and disturbance of imprinting and the correlation with assisted reproduction techniques is only secondary.[15]

Prenatal diagnosis of BWS can usually be reliably made based on the enlarged kidneys and extrarenal symptoms on antenatal scans.[16] The kidneys are typically enlarged, echogenic and with loss of corticomedullary differentiation. If standard chromosome analyses are performed, these will yield a normal result, but a molecular diagnosis can be made by specific 11p methylation studies on amniotic fluid.

Perlman syndrome

Perlman syndrome is an overgrowth syndrome, which is much less common than BWS, but shows a considerable overlap with BWS. Affected infants have macrosomia, macrocephaly and visceromegaly, including cardiomegaly. There are facial features (deep-set eyes, short nose, depressed nasal bridge), but these are usually too subtle to be visible on scans. Males have ambiguous genitalia. Postnatal cognitive development is delayed.[17] Nephroblastosis, neonatal hypoglycaemia and predisposition to Wilms tumour are further overlapping features with BWS. The