Long-term follow-up of adult women with urinary tract infection in childhood

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To my family

ABSTRACT

Acute pyelonephritis is common in young children and can lead to permanent renal damage. Renal damage increases the risk of complications such as hypertension and decreased renal function later in life. For women with renal damage there is also an increased risk of pregnancy complications. During the years 1982 to 1984 a long-term follow-up study was performed in women who had had urinary tract infections (UTI) in childhood. The material consisted of 111 women, born between 1950 and 1968, 54 with known renal damage detected by urography and 57 with proneness to UTI but without renal damage.

During the years 2001 to 2004, 86 of these patients were reinvestigated. The aim of the new study was to evaluate 1) if the patients with renal damage had an increased prevalence of hypertension; 2) if renal function, as measured by the glomerular filtration rate (GFR), had deteriorated since the last study; 3) if the pattern of UTI had changed with increasing age; 4) if patients with renal damage had higher prevalence of gestational hypertension, preeclampsia or other complications during their pregnancies.

Each patient was interviewed according to a structured questionnaire concerning UTI and was investigated with DMSA scan, EDTA clearance, office blood pressure, and 24-hour ambulatory blood pressure monitoring. Hospital and antenatal clinic records were also studied.

The results showed that women with bilateral or severe unilateral renal damage had higher blood pressure than those without damage. Women with bilateral damage had significantly lower GFR than those with unilateral or no damage. Decrease of GFR since the previous study was seen only in the group with bilateral damage. The proneness to febrile UTI decreased with age. Women with renal damage had significantly higher blood pressure during pregnancy but no increased frequency of other pregnancy complications.

Women with bilateral or severe unilateral renal damage associated with UTI in childhood have an increased risk of high blood pressure and decreased renal function in adult age. Follow-up of blood pressure and renal function should be considered in these women. Extra monitoring of blood pressure during pregnancy is also recommended.

Keywords: ambulatory blood pressure, blood pressure, chronic kidney disease, DMSA scan, glomerular filtration rate, hypertension, pregnancy, renal damage, renal function, urinary tract infection, vesicoureteral reflux

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SAMMANFATTNING PÅ SVENSKA

Akut njurinfektion (pyelonefrit) är vanligt hos små barn och kan leda till permanent njurskada. Förekomst av njurskada ökar risken för komplikationer i form av hypertoni eller nedsatt njurfunktion senare i livet. För kvinnor med njurskada finns en ökad risk för graviditetskomplikationer.

Under åren 1982 till 1984 gjordes en första långtidsuppföljning av kvinnor som haft urinvägsinfektioner i barndomen. Patientmaterialet bestod av 111 kvinnor, födda 1950 till 1968, 54 med känd njurskada diagnosticerad med njurröntgen (urografi) och 57 med benägenhet att insjukna i urinvägsinfektioner men utan njurskada.

Åren 2001 till 2004 undersöktes 86 av dessa kvinnor på nytt. Syftet med den nya studien var att undersöka om hypertoni var vanligare hos patienter med njurskada; om njurfunktionen försämrats sedan föregående studie; om mönstret och frekvensen av urinvägsinfektioner ändrats med stigande ålder; om patienter med njurskada löpte större risk att drabbas av graviditetshypertoni, havandeskapsförgiftning (preeklampsi) eller andra komplikationer under sina graviditeter.

Varje patient intervjuades avseende urinvägsinfektioner enligt ett standardiserat frågeformulär och undersöktes med manuell blodtrycksmätning och 24-timmars blodtrycksmätning. Njurfunktionen undersöktes också med olika metoder. Uppgifter inhämtades från graviditets- och förlossningsjournaler.

Resultaten visade att kvinnor med dubbelsidig eller svår enkelsidig njurskada hade högre blodtryck än de utan njurskada. Kvinnor med dubbelsidig skada hade signifikant lägre njurfunktion än de med enkelsidig eller ingen skada. Försämring av njurfunktionen sedan föregående studie sågs endast i gruppen med dubbelsidig njurskada. Urinvägsinfektioner med feber avtog med stigande ålder. Kvinnor med njurskada hade signifikant högre blodtryck under graviditet men ingen ökad förekomst av andra graviditetskomplikationer.

Kvinnor med dubbelsidig eller svår enkelsidig njurskada orsakad av urinvägsinfektioner i barndomen har förhöjd risk att utveckla högt blodtryck och försämrad njurfunktion i vuxen ålder. Uppföljning av blodtryck och njurfunktion bör därför övervägas hos dessa kvinnor, liksom extra kontroller av blodtryck under graviditet.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Gebäck C, Hansson S, Martinell J, Sandberg T, Jodal U. Urinary tract infection pattern in adult women followed from childhood. *Submitted.*

II. Gebäck C, Hansson S, Himmelmann A, Sandberg T, Sixt R, Jodal U. Twenty-four-hour ambulatory blood pressure in adult women with urinary tract infection in childhood. *J Hypertens 2014; 32:1658-1664.*

III. Gebäck C, Hansson S, Martinell J, Sandberg T, Sixt R, Jodal U. Renal function in adult women with urinary tract infection in childhood. *Pediatr Nephrol 2015; 30:1493-1499.*

IV. Gebäck C, Hansson S, Martinell J, Milsom I, Sandberg T, Jodal U. Obstetrical outcome in women with urinary tract infections in childhood. *Submitted.*

CONTENT

ABBREVIATIONS

ABU	Asymptomatic bacteriuria
ABPM	Ambulatory blood pressure monitoring
BP	Blood pressure
CKD	Chronic kidney disease
CI	Confidence interval
DBP	Diastolic blood pressure
DMSA	^{99m}Tc-dimercaptosuccinic acid
EDTA	^{51}Cr-edetic acid
eGFR	Estimated glomerular filtration rate
GFR	Glomerular filtration rate
LS	Least square
MCUG	Micturating cystourethrogram
OR	Odds ratio
SBP	Systolic blood pressure
SD	Standard deviation
SDS	Standard deviation score
UTI	Urinary tract infection
VUR	Vesicoureteral reflux

1 INTRODUCTION

Urinary tract infection (UTI) is one of the most common bacterial infections in females of all ages. It is the reason for many prescriptions of antibiotics. UTI in combination with fever, acute pyelonephritis, is a severe infection that can be life-threatening. In childhood, acute pyelonephritis can cause persistent renal damage that can lead to long-term consequences such as hypertension and impaired renal function (1-3). The frequency of such problems is insufficiently known, to a large extent dependent on difficulties in following patients over several decades, which is required to obtain reliable data. Previous studies have mainly focused on the outcome of patients from selected groups managed at tertiary referral centers (4-8). This investigation is population-based and covers 3-4 decades.

This thesis will cover some of the background to UTI-related renal damage and the long-term consequences in adult life, as we know them today, i.e. hypertension, reduced renal function, and pregnancy complications.

1.1 Pathophysiology of the urinary tract

1.1.1 Vesicoureteral reflux

Vesicoureteral reflux (VUR) is the backward leakage of urine from the bladder to the ureter, which usually is prevented by a valve-like mechanism in the vesicoureteral junction. VUR is most common in infants with a prevalence of 0.4-1.8% (9). There is a high rate of spontaneous resolution during childhood by maturation of the valve mechanism. VUR is graded on a five-grade scale, from I with reflux only to the ureter to V with gross dilatation of the renal pelvis (10) (Figure 1, Table 1). VUR enhances the possibility for bacteria to ascend from the bladder to the kidney and thus increases the risk of renal infection.

Figure 1. International grading of VUR.

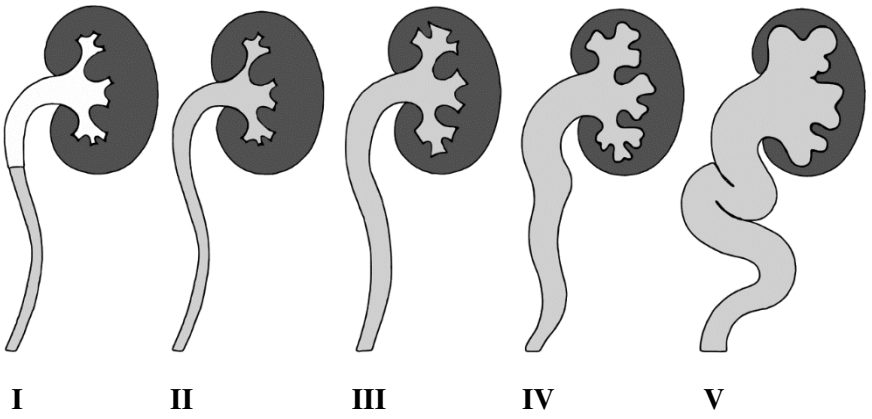


Table 1. Definitions of grading of VUR according to the International Radiographic System.

Grade	Definition
Grade I	Urine refluxing only into the ureter
Grade II	Reflux into the renal pelvis and calices but without associated dilatation of the ureter or calyces
Grade III	Mild dilatation and/or tortuosity of the ureter. Dilatation of the renal pelvis and calyces with preserved fornices of the calyces
Grade IV	Moderate dilatation and/or tortuosity of the ureter. Moderate dilatation of the renal pelvis and calyces.
Grade V	Gross dilatation and tortuosity of the ureter. Gross dilatation of the renal pelvis and calyces.

1.1.2 Urinary tract infections

Diagnostic criteria of UTI

Positive urine culture is defined as significant growth of bacteria, i.e. $\geq 10^5$ colony-forming units/mL in a urine culture.

Cystitis (lower UTI) or non-febrile UTI is defined by voiding symptoms such as dysuria, urgency and urinary frequency, in combination with a positive urine culture, in the absence of fever.

Acute pyelonephritis (upper UTI) or febrile UTI is defined by fever of at least 38.0°C, flank pain and costovertebral angle tenderness with or without voiding symptoms, and a positive urine culture.

Asymptomatic bacteriuria (ABU) is defined as significant growth, i.e. $\geq 10^5$ colony-forming units/mL, of the same bacterial species in two consecutive urine samples with at least a 2-day interval in the absence of typical symptoms of UTI.

Recurrent UTI is defined as >2 UTI during the last 6 months and/or >3 during the last year.

In the child

UTI is a common infection during childhood. The cumulative incidence of symptomatic UTI during the first two years of life has been estimated in the Swedish UTI study to be 2.5% both in boys and girls (11). During the first 6 months of life, boys are more affected but thereafter UTI occurs more often in girls. VUR in girls persists longer before resolution and that makes them more vulnerable to recurrent UTI (12). The risk of recurrent UTI is also increased by factors as the short urethra, constipation and dysfunctional voiding.

In a child who suffers from a severe episode of pyelonephritis, imaging of the urinary tract with ultrasound or ^{99m}Tc-dimercaptosuccinic acid (DMSA) scan may be performed to reveal VUR or other types of anomalies. Micturating cystourethrogram (MCUG) is only performed when ultrasound or DMSA scan shows a pathological result. If pyelonephritis is left undiagnosed and untreated in a child, there is a risk of renal damage in the growing kidney. If VUR with dilatation of the upper urinary tract (grade III to V) is present, long-term antibiotic prophylaxis is considered to avoid further episodes of

pyelonephritis and to prevent development of renal damage (13). VUR is a main risk factor for pyelonephritis in childhood but data have been presented suggesting that a genetic susceptibility may also be important (14, 15).

In the adult woman

The yearly incidence of UTI in women older than 18 years has been estimated to 10.8% to 13.3% and the lifetime incidence to 53% to 60% (16, 17). In the general practitioner's office, 75% of all UTIs are non-febrile UTIs (cystitis) (18). Approximately 20% of all women with UTI in Swedish primary care have recurrent UTI (18). Risk factors for developing cystitis are sexual activity, new sexual partner, use of spermicides, UTI during the last 12 months, diabetes mellitus, incontinence, and a family history of UTI (19-21). Pyelonephritis occurs with an incidence of 0.28% to 0.59% in adult women (20, 22).

UTI is caused by bacteria originating from the woman's own microbial flora in the gut. The most common bacteria are Escherichia coli, followed by Staphylococcus saprophyticus, especially in younger women. In women with abnormal urinary tracts or history of recurrent UTI, other bacterial species as Klebsiella pneumoniae and enterococci are also common. Changes in the vaginal microbial flora caused by postmenopausal hormonal changes, use of spermicidal contraceptives, or recent antibiotic treatment increases the risk that bacteria from the gut colonize the periurethral area and ascend through the urethra to the bladder. When this happens and the bacteria carry virulence factors, acute pyelonephritis can develop even in individuals with a normal urinary tract (23, 24).

In ABU, the bacteria and the mucosal membrane in the bladder have established a symbiotic relationship where harmless bacteria protect the woman from being infected with more virulent strains (25). Eradication of ABU by antibiotics increases the risk of a subsequent symptomatic UTI episode (26). ABU should therefore be left untreated unless the woman is pregnant, see below.

In the pregnant woman

During pregnancy the tonus of the bladder and the ureters change already in the first trimester due to increasing levels of progesterone which has an

atonic effect on smooth muscle (27) and makes the bladder capacity increase. Early in the second trimester, the growing uterus can mechanically affect the ureters, resulting in retarded urine flow. The volume of the ureters increases from 10 to 30-50 mL and as the uterus enlarges, the base of the bladder is altered anatomically (28, 29). This causes the ureters to displace and the normal function of the valves at the ureterovesical junction is disturbed, making it easier for urine to regurgitate up the ureters when the intravesical pressure is increased during voiding. Also, the renal blood flow and glomerular filtration increase heavily, as does the tubular reabsorption, which results in enlargement of the kidneys (27). The urine volume can vary substantially.

These changes increase the risk that bacteria ascend to the kidneys to cause pyelonephritis. The risk of pyelonephritis is considerably higher than in non-pregnant women and a severe attack of pyelonephritis increases the risk of premature delivery.

The prevalence of ABU in pregnant women has been estimated to between 1% and 5% (30). In the end of the 1980s, Stenqvist et al found a prevalence of 2% in a material from antenatal clinics in Gothenburg (31). Pregnant women with untreated ABU have a 20% to 40% risk of developing pyelonephritis in later pregnancy (32). The risk is reduced by 80% when ABU is identified early in pregnancy and treated with antibiotics (33). The incidence of cystitis during pregnancy is 1% to 2%.

In western Sweden, according to the local guidelines for ABU and UTI during pregnancy, screening for ABU is done with a urine dipstick at the first visit to the antenatal clinic. Urine culture is performed when the nitrite test is positive. Another urine culture is done in pregnancy weeks 24-25 for any of the following reasons:

- Recurrent UTI
- Previous episode of pyelonephritis
- Known urinary tract anomaly, kidney disease or insulin-treated diabetes mellitus

If a urine culture shows significant growth of bacteria another urine culture is done to exclude or confirm the diagnosis ABU. In case of ≥ 2 episodes of ABU or cystitis or one episode of pyelonephritis, antibiotic prophylaxis is recommended during the rest of the pregnancy.

1.1.3 Renal damage

During the first half of the 20th century the term "chronic pyelonephritis" was used when urography showed scarred or small kidneys (34, 35). These were assumed to be a result of progressive destruction of the parenchyma by persistent or recurrent bacterial infections. In the 1960s interest focused on VUR after its association with renal scarring had been demonstrated (36). The association between VUR, UTI and renal scarring was generally accepted (37, 38) and the importance of VUR as a cause of renal scarring became so dominating that the term reflux nephropathy was established (39). It is now known that VUR is not a prerequisite for renal scarring but can develop in the absence of VUR (40, 41).

Bacteria leaking backwards to the kidney cause an inflammatory response in the renal tissue. This results in local ischemia and fibrosis and eventually scar formation in the infected region (42). Recurrent pyelonephritic attacks, delay of antibiotic treatment, and a genetic susceptibility for acute pyelonephritis (14, 15) are risk factors for development of renal damage in the young child. It is important to prevent pyelonephritis when the kidneys are still growing to avoid permanent renal damage. This is done by long-term antibiotic prophylaxis (13) or by having the child under strict surveillance with easy access to medical assessment in case of fever or symptoms of UTI. In the absence of urinary tract obstruction the full-grown kidney is less susceptible to injury even if exposed to recurrent episodes of pyelonephritis.

A couple of decades ago, urography was the standard method for detection of renal scarring, a diagnosis that was based on thinning of renal tissue with or without concurrent clubbing of the calyces. However, it could take up to two years for the scars to be visible on urography. Also, when renal scarring was diagnosed it was difficult to separate congenital damage from damage caused by pyelonephritis. In the 1980s, the DMSA scan (43) was introduced and proved to be a more sensitive method to detect both acute and late renal damage. Therefore the DMSA scan today is the method of choice to study renal damage (44). An abnormal scan is defined by defective uptake of the tracer, focal or generalized. It does not, however, visualize the calyces and thus does not give the typical picture of morphological scarring. Therefore the term renal damage is further used in this thesis when describing the changes seen on a DMSA scan, instead of renal scarring, the latter traditionally used when the damage is revealed by urography.

A recent review estimated the risk for permanent renal damage after febrile UTI in childhood to about 15% (45). Based on this figure and a cumulative risk of symptomatic UTI in Swedish girls of 6% (46), about 1% of young women entering adulthood should have UTI-related renal damage.

1.2 Renal function

Production of primary urine in glomeruli in the kidneys, the glomerular filtration, is the first step in the urine formation. Renal clearance of a specific marker is used to determine the glomerular filtration rate (GFR). The most common marker is creatinine, although this substance gives a falsely high value of GFR at normal kidney function and even more at a lowered renal function. It is a metabolite from the muscles which makes its concentration in the plasma dependent on the muscle mass of the patient and also the dietary intake of meat. Other extensively used markers are iohexol and isotope-labelled ^{51}Cr-edetic acid (EDTA) (47). The latter is used in Gothenburg. The radiation of this substance is so low that it can be used in children and pregnant and nursing women (48). GFR is often correlated to the body surface area (mL/min/1.73 m^2) so that obtained values can be compared to a reference interval.

GFR decreases with increasing age. In healthy individuals, GFR remains constant at a mean of 103 mL/min/1.73 m^2 until the age of 40, thereafter decreasing at a rate of approximately 10 mL/min/1.73 m^2 per decade (48, 49). A number of studies have shown no difference in GFR between men and women (48-50).

Many diseases can influence the renal function. Most well-known is diabetes mellitus and other immunological diseases. This thesis will discuss the possible impacts of UTI and renal damage on renal function. Chronic kidney disease (CKD), no matter the cause, is classified according to the international system set by the National Kidney Foundation in USA. In that system, kidney disease is divided into five stages depending on the level of GFR (Table 2) (51).

Table 2. Stages of chronic kidney disease

Stages	Description	GFR (mL/min/1.73 m^2)
Stage 1	Renal damage with normal or higher GFR	≥90
Stage 2	Renal damage with mild lowering of GFR	60-89
Stage 3	Renal damage with asymptomatic moderate lowering of GFR	30-59
Stage 4	Advanced renal insufficiency with symptomatic uremia	15-29
Stage 5	Kidney failure	<15

Renal function in pregnancy

In pregnancy, GFR normally increases markedly. In women with impaired renal function, pregnancy involves risks for both mother and fetus (52) and fetal loss may occur. Deterioration of GFR is common, especially when severe renal dysfunction is present already before the pregnancy. Concurrent hypertension increases this risk further.

There are few studies addressing the outcome of renal function in pregnant women with renal damage due to VUR and UTI (53, 54). These studies included patients with renal damage, primarily recruited from specialized nephrology centers. Jungers et al. studied 158 women (375 pregnancies) of whom 21 had diagnosed severe renal failure already at the time of conception and 24 had hypertension in combination with impaired renal function. Preeclampsia was diagnosed in 39 pregnancies (10%). During pregnancy, no deterioration of renal function was seen in women with normal function at conception. However, after delivery 9 of the patients with normal renal function both at conception and during pregnancies, later developed end-stage renal failure (ESRF). In the study by Becker et al. (53), 6 women with moderate renal failure were studied and all had a decreased renal function at the start of pregnancy. Four of the 6 patients were in ESRF within 2 years of delivery.

1.3 Hypertension

Blood pressure (BP) is maintained by a combination of mechanical, neuronal and endocrine self-regulating systems in the body. These systems regulate BP according to changes in the environment. Women have lower systolic blood pressure (SBP) levels than men in the 30- to 44 year age groups (55).

Primary hypertension has by definition no single identifiable cause although genetic and environmental factors play a role. Around 95% of all patients with high BP belong to this category (56). The prevalence of primary hypertension increases by age. Before anti-hypertensive treatment became available, renal involvement was frequent in these patients (57). With anti-hypertensive treatment the more severe renal complications are now rare but still many patients have deranged renal function, which in itself is a risk factor for cardiovascular disease (58). As a hang-over from an old belief viewing high BP as a compensatory mechanism for preserving organ function the term essential hypertension is also used (the "essential" nature of hypertension).

Secondary hypertension refers to high BP from an identifiable underlying cause, the most common being renal parenchymal disease, accounting for up to 5% of all cases (59). All different forms of glomerular disease cause hypertension when the renal function has been sufficiently damaged. The most common causes of renal parenchymal disease are diabetes mellitus and hypertension, but it can also be linked to genetic diseases like polycystic kidney disease and autoimmune diseases like lupus nephritis and IgA nephropathy. In pyelonephritis, the inflammatory process in the kidney leads to damage and decrease of nephron numbers, resulting in reduction of the filtration area. Long-term consequences of this can be hypertension and sometimes progressive renal insufficiency (60). Hypertension combined with renal disease can cause diminishing renal function and are associated with a high risk of cardiovascular disease (61-63).

Hypertension in early stages, in young individuals, is characterized by mainly elevated diastolic blood pressure (DBP), while in middle-aged persons there is predominantly an increase of SBP due to a gradual increase in peripheral vascular resistance (64).

Diagnosis of hypertension

Hypertension diagnosed with manual BP measurements is usually defined as SBP ≥140 mmHg and/or DBP ≥90 mmHg. Most guidelines recommend that this level is lowered to ≥130/80 mmHg when there is concurrent renal disease (57, 65). The reason for treating these patients more aggressively is to better preserve their renal function.

The threshold for diagnosis of hypertension by ambulatory blood pressure monitoring (ABPM) depends on the guidelines used. According to the European Society of Hypertension (ESH) guidelines from 2007 and 2013 (57, 66), hypertension can be defined either by mean daytime, night-time and 24-hour BP measurements together or separately (Table 3). However, in the National Institute for Health and Clinical Excellence (NICE) guidelines from 2011 and in the revision from 2013 (67, 68), hypertension is solely defined as a mean day-time BP ≥135/85 mmHg.

Table 3. Blood pressure thresholds for diagnosis of hypertension with ambulatory blood pressure monitoring according to ESH guidelines from 2007

BP variable	BP thresholds
Mean 24-hour BP	≥125/80 – 130/80
Mean daytime BP	≥130/85 – 135/85
Mean night-time BP	≥120/70

BP, blood pressure (mmHg)

Hypertension during pregnancy

In pregnancy BP normally decreases in the first and second trimesters, reaching values that are approximately 10 to 15 mmHg lower than before pregnancy, due to decreased systemic vascular resistance (27, 69). In the third trimester the BP returns to, or exceeds the pre-pregnancy levels. This fluctuation is normal and occurs in normotensive women as well as in those with preexisting hypertension or with gestational hypertension.

An increased risk of complications during pregnancy, such as gestational hypertension and preeclampsia, due to renal damage caused by UTIs in childhood have previously been described (70-72). Hypertensive disorders of

pregnancy is the second commonest cause of direct maternal death in the developed world (73). Hypertension is the most common medical complication during pregnancy occurring in 6% to 8% of pregnancies (74) and is associated with increased risk of intracerebral hemorrhage, placental abruption, intrauterine growth retardation, prematurity, intrauterine death (57), and gestational diabetes (75).

Studies have indicated that 24-hour ABPM could be superior to conventional manual BP measurements in predicting hypertensive causes of pre-term delivery, low infant weight at birth and general outcome of pregnancy (76, 77). Therefore, it may be useful to perform ABPM in high-risk pregnant women with hypertension, diabetes mellitus or renal disease.

Gestational hypertension or pregnancy-induced hypertension develops after 20 weeks of gestation in a previously normotensive woman. BP ≥140/90 mmHg at two occasions with at least 4 hours interval in between is required for the diagnosis. In most cases gestational hypertension resolves within 42 days postpartum.

Preeclampsia is diagnosed when the BP is ≥140/90 mmHg and <160/110 mmHg in combination with significant albuminuria, presented beyond 20 weeks of gestation. Significant albuminuria is defined as excretion of ≥300 mg albumin/24-hour urine collection, a urinary albumin/creatinine ratio greater than 30 mg/mmol, or a urine dipstick albumin grade of 1+ or greater if other methods are unavailable (78, 79). Severe preeclampsia is present when at least one of the following symptoms is added (78, 79): SBP ≥160 mmHg or DBP ≥110 mmHg at two occasions with at least 4 hours interval in between, platelet count below 100,000/μL, oliguria (<500 mL/24-hour), liver transaminases elevated to twice the normal serum concentration, pulmonary edema and cerebral or visual symptoms.

In the developed world, preeclampsia complicates approximately 3% to 5% of pregnancies (80-82). It has been shown that up to a quarter of women with preexisting hypertension will develop preeclampsia (83). Risk factors can be present on the maternal, paternal or fetal side (69). The most common risk factors in the mother are: age older than 40, interpregnancy interval less than 2 years or more than 10 years, nulliparity, preeclampsia or gestational hypertension in a prior pregnancy, hypertension or CKD.

Preeclampsia is one of the most common causes of maternal mortality and severe maternal morbidity including eclampsia, placental abruption, pulmonary edema, and acute renal failure (73, 82). Infants of mothers with

preeclampsia have an increased risk of neonatal death (84) and preterm delivery. Neonatal symptoms and signs such as low Apgar score, seizures, intrauterine growth restriction, low birth weight, and neonatal encephalopathy are also seen (82).

Eclampsia is a life-threatening development of seizures in a woman with preeclampsia. It is rare in the developed world, with an incidence of 2.7 to 5.4 cases per 10,000 births, reported from two different countries in Europe (85, 86). Eclampsia may be preceded by a history of preeclampsia or may occur unexpectedly in a woman with no major hypertension or proteinuria during pregnancy (69).

Hypertension after delivery

Typical for hypertension due to preeclampsia is that it decreases within days of delivery and BP normally returns to original levels by 12 weeks postpartum. A woman with previous preeclampsia has a 16% risk of recurrence in a subsequent pregnancy, and a 13% to 53% risk of gestational hypertension in a future pregnancy (69). For women with gestational hypertension, the risk of recurrence in a subsequent pregnancy is 16% to 47%.

Hypertension in pregnancy, regardless of type or presence of other known risk factors, increases the risk of later hypertension, cardiovascular disease, chronic kidney disease, and diabetes mellitus (87-90). Preeclampsia elevates the risk of future hypertension (91).

1.4 Results from the previous follow-up study

The 111 patients in this cohort, thoroughly described in the Patients section, were previously investigated by Martinell et al between 1982 and 1984 with the aim to study long-term complications during two decades of follow-up. The following section gives a short summary of the results as they were presented in Martinell's thesis 1999.

Pattern of urinary tract infections

In children with severe renal scarring the first symptomatic UTI was recognized at an earlier age than in children with moderate or no renal scarring (92). In 73% of the patients with renal scarring the first UTI was diagnosed as pyelonephritis. The frequency of symptomatic recurrences was high. The proportion of pyelonephritis was highest at the index infection and decreased with the number of infections and was higher in patients with VUR. The rate of pyelonephritis was significantly higher in patients with than without renal scarring.

Hypertension

Systolic and diastolic office BPs were compared between healthy controls and patients without, with moderate and severe renal scarring (93). Diastolic BP in patients with severe renal scarring was significantly higher than in controls. Hypertension during childhood was seen in two patients with severe renal scarring. Both became normotensive after nephrectomy of a damaged kidney. One patient with severe bilateral renal scarring was on anti-hypertensive treatment and had elevated BP at examination.

Renal function

In 7 patients GFR values were below -2 standard deviation scores (SDS); in 4 with severe renal scarring (70-78 mL/min/1.73 m^2) and in 3 without renal scarring (74-79 mL/min/1.73 m^2) (93). Patients with severe renal scarring had significantly lower GFR than those without renal scarring. There was no difference in the excretion of albumin between patients and controls.

Renal damage

VUR was diagnosed in 67 patients. In 14 patients a repeated micturating cystourethrogram (MCUG) showed a more severe grade of VUR than the first investigation (93, 94). No patient had VUR grade V.

Renal scarring was detected by urography in 54 patients. Grade of reflux, number of pyelonephritic attacks and age at first recognized UTI all correlated significantly with renal scarring.

Pregnancies

During first pregnancies bacteriuria with or without symptoms were significantly more common in patients with previous history of childhood UTI than in controls (37% vs. 2%) (71). Symptomatic UTI occurred only in patients and not in controls. Increased BP was diagnosed late, after the 36th gestational week. Hypertension was found in significantly more patients with severe renal scarring than in controls (36% vs. 7%). The mean diastolic BP at the last antenatal control was significantly higher in patients with severe renal scarring compared to controls while patients with moderate renal scarring were normotensive. During second and third pregnancies no woman developed hypertension and the mean BPs were not significantly different between the groups. Preeclampsia occurred in 2 of 19 with renal scarring and in 1 of 44 controls, all during first pregnancies. There was no difference between patients and controls in rate of operative delivery, prematurity, malformation or birth weight of infants.

2 AIMS OF THE STUDY

The main aim was to study complications in adult women with and without renal damage, 3 to 4 decades after UTI in childhood. Specifically focus was on:

- If the patients with renal damage had an increased prevalence of hypertension
- If kidney function had deteriorated since the previous study
- If the pattern of UTI had changed with increasing age
- If patients with renal damage had higher prevalence of gestational hypertension, preeclampsia or other complications during their pregnancies

3 PATIENTS

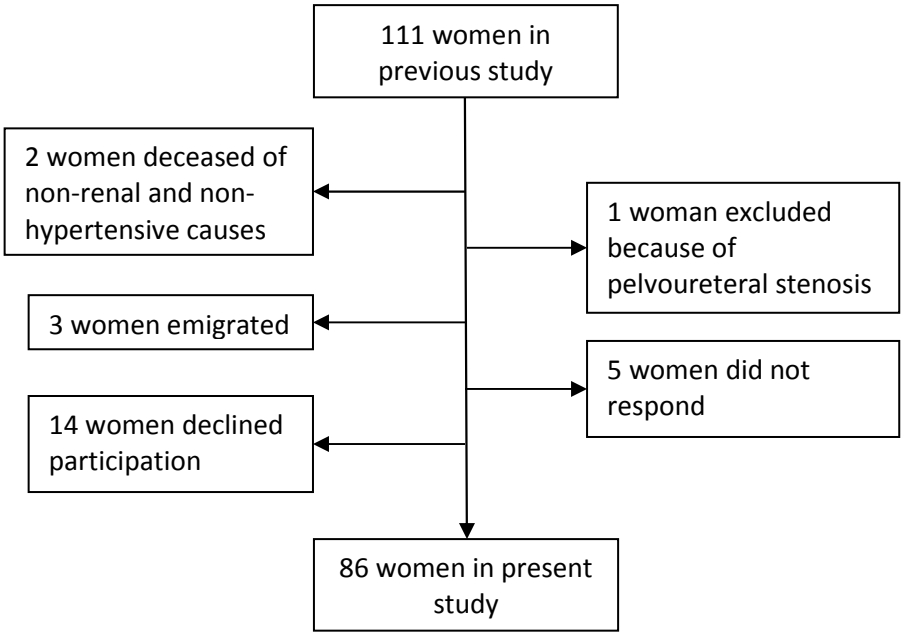
At the time of the first follow-up study, the city of Gothenburg had a population of about 420 000 inhabitants, of whom 80 000 were children below 16 years of age. In the 1960s, a special interest in childhood UTI developed at the Children's Hospital. A pediatric UTI-clinic was established aiming at close surveillance of epidemiology and long-term aspects of childhood UTI (95, 96). A similar unit for adults was established at the Department of Infectious Diseases around 1970 and a close cooperation between these two units was developed. At the age of 15-18 years, women with history of non-obstructive UTI and urographic evidence of renal damage or with persistent proneness to UTI including those with untreated ABU were referred for further follow-up to the UTI clinic for adults.

All women with UTI in childhood who had been followed from their first recognized UTI and had been referred to the Department of Infectious Diseases during the years 1975 to 1983 were included in the first follow-up study performed between 1982 and 1984 by Martinell et al (92-94). A total of 111 women, born between 1950 and 1968, fulfilled these criteria. The mean age of the women was 27.5 years. The classification of their renal damage was based on the most recent urography. Fifty-four had been referred because of renal damage and 57 because of proneness to UTI or ABU. The index UTI was symptomatic in 87 subjects while in 24 the first UTI had been asymptomatic and detected at school screening.

From the initial cohort of 111 women, 105 were asked to participate in the present study by letter and personal telephone calls. Two were deceased of non-hypertensive and non-renal causes, one was found to have pelvoureteral stenosis in childhood and was erroneously included in the former study, and three had moved out of the country. In five cases there was no response and 14 declined participation. Thus 86 women accepted to take part and completed the study protocol (Figure 2).

Median age of the participating 86 women was 41 years (range 35 to 51) and median follow-up time 35 years since the first recognized UTI (range 23 to 50). Of the 25 women of the original cohort who did not participate in the study, one had bilateral renal damage, 9 unilateral damage, one pelvoureteral stenosis, and 14 normal urography. The severity of urographic renal damage in the women who did not participate was not different from that in those who participated.

Figure 2. Flow chart of the participating patients



4 METHODS

4.1 Imaging methods

No radiologic examination was performed in this follow-up study but the results from previous investigations were used. Therefore a short summary of the techniques is presented here.

Micturating cystourethrogram (MCUG)

MCUG is a radiological method to examine VUR from the urinary bladder to the ureters. Contrast medium is infused into the bladder via a urethral catheter which is then removed and the patient voids. Repeated images are obtained at partial filling of the bladder, when the bladder is full, when voiding and immediately after voiding to see if any urine leaks backwards up the ureters to the kidneys. The images are then assessed and graded I through V according to the International System of Radiographic Grading of VUR (10), see Table 1, page 6.

Urography

Urography is a radiological method aiming to visualize abnormalities of the urinary system, including the kidneys, ureters and bladder. X-ray contrast medium is given intravenously. The contrast is excreted from the blood stream via the kidneys, and becomes visible on fluoroscopy almost immediately after the injection. The anatomy of the kidneys can then be studied with the focus on anatomical abnormalities, such as renal scarring, congenital or acquired.

In the previous study, investigations by urography were performed using standard technique (42). Renal damage was classified according to Smellie et al: type A – one or two scars, type B – more than two scars but with some parenchyma remaining, type C – generalized parenchymal reduction and type D – an end-stage shrunken kidney (37). Patients with severe renal scarring included those with unilateral damage of type C or D and with bilateral damage of at least type B on one side.

^{99m}Tc-dimercaptosuccinic acid (DMSA)

The current method to visualize acute pyelonephritis and renal damage is static scintigraphy with DMSA (44, 97). DMSA is rich in sulphydryl groups and is irreversibly bound to proximal tubular cellular proteins via disulfide bonding (44). The uptake is dependent on the renal perfusion and the amount of functioning renal cortical mass. Almost no DMSA is secreted in the urine and therefore only one image is routinely taken no less than two hours after injection, preferably three hours.

The uptake of DMSA will be reduced in acutely inflamed or scarred kidney areas. Interpretation of DMSA images includes assessment of renal size and identification of uptake defects. Renal damage, congenital or acquired, is characterized by fibrosis giving various degrees of irregular outline of the kidney, distortion of the local anatomy and a focal reduction of kidney function. In adults, measurement of differential renal function is also important.

The DMSA scans of the patients in the study was done according to a standardized method used at the Department of Clinical Physiology for adults at Sahlgrenska University Hospital. The images were then assessed by both a clinical physiologist at that department and one at the Department of Pediatric Clinical Physiology.

4.2 Evaluation and classification of renal damage

In the previous study urographic damage was defined as reduction of parenchymal thickness to <2 SDS with corresponding calyceal deformity (98, 99). Since calyceal deformity is not visualized on a DMSA scan, the urographic data were reanalyzed using a definition of renal damage set at reduction of parenchymal thickness to $\leq$ 2.5 SDS, which is the definition of renal damage used in the International Reflux Study in Children (100, 101).

In the present study, renal damage was investigated by DMSA scan with posterior, anterior and posterior oblique views (102, 103). A kidney without uptake defect and a relative (split) function of 45% or more was classified as normal. Abnormal DMSA scan was defined as presence of focal or generalized uptake defects or relative uptake (split function) of DMSA of a kidney to <45%. Split function was calculated as a geometric mean value of

the background subtracted kidney uptake from the posterior and anterior view. The extent of damage of the most severely affected kidney of each patient was graded: class 1 represented split function ≥45% together with focal uptake defect; class 2 40-44% and class 3 <40% function, both irrespective of focal damage (104). In cases with bilateral renal damage the kidneys were individually classified by an experienced nuclear medicine specialist and classified according to the most severely affected kidney. In the following analyses, the kidney with more pronounced involvement was chosen to represent the patient.

4.3 ^{51}Cr-edetic acid (EDTA) clearance

EDTA clearance was used to determine GFR. A single injection was given intravenously and plasma concentrations of EDTA were measured 180, 195, 210, 225 and 240 minutes thereafter. The plasma clearance values of EDTA were then correlated to body surface area and expressed as mL/min/1.73 m^2 (105). The same method was used in the previous study of these patients. This method has limitations only if the patient has marked edema (8-10 kg) or has a severely reduced renal function (GFR <20 mL/min) (48). Neither was the case in this study cohort.

To estimate GFR of the individual kidneys, the total GFR was multiplied by the percentage side function calculated as a geometric mean value of the background subtracted kidney uptake from the posterior and anterior view. In patients with bilateral renal damage, the kidney with the lowest function was chosen to represent the patient.

4.4 Blood pressure measurements

BP is influenced by a wide range of factors, for example age, ethnicity, disease, emotions, posture, drugs, meals and exercise (106). Therefore it is important to standardize the circumstances in which the BP is measured. This has been done by using a strict protocol for manual and ambulatory BP measurements. All measurements were performed by the same biomedical assistant.

Most previous studies of BP in individuals with UTI-related renal damage used casual office BP measurement (1, 3), usually at a single visit to the clinic. In our study both manual BP measurement and 24-hour ABPM was used, the latter a more complicated method requiring special recording apparatus but with several advantages compared to manual measurement. ABPM provides repeated measurements, ideally more than 60, which are recorded while the subject is allowed a near normal life. Since the measurements are automatic, the variability and observer bias is reduced compared to office measurements, even if the latter are repeated on a number of occasions (107, 108). It has also been shown that hypertension associated with end-organ damage correlates better with 24-hour mean BP than with single office measurements (109). In addition, ABPM provides information about both daytime and night-time BP profiles and day-night BP differences (110). The situation when some individuals present themselves as hypertensive when BP is measured manually in the clinic but are normotensive otherwise, so called "White Coat Hypertension" (111, 112), is also possible to avoid by using ABPM. The opposite, "masked hypertension", when casual office BP is normal but measurements by ABPM is elevated is also detected.

Some women had hypertension and were taking anti-hypertensive medication at study entry. The diagnosis of hypertension in these patients was thus made by the patient's ordinary physician and was not questioned or reevaluated during the study. The anti-hypertensive medication was not discontinued before the assessment of BP.

Manual blood pressure

For manual measurement of BP a cuff was used, encircling the right arm and adjusted to its size. The SBP was recorded in Korotkoff phase I when the pulse was first heard and the DBP in Korotkoff phase V when the pulse sounds disappeared completely. Three office BP measurements were recorded in a seated position after 30 minutes of rest and the mean of the recordings was used for analysis. Usually a resting time of 5-10 minutes before the BP measurement is chosen (57) but the resting time of 30 minutes in this study was chosen to be consistent with the previous investigation of these women (92, 93).

24-hour ABPM

The 24-hour ABPM was performed with a non-invasive ambulatory recorder (Dansjö model 90207-30) programmed to measure every 20 minutes during daytime (06.00-22.00) and every 30 minutes during night-time (22.00-06.00). The recordings were performed on weekdays, Monday to Friday. The subjects were instructed to carry out normal daily activities, but physical exercise was restrained. Analysis of all ABPMs was conducted to identify subjects with incomplete ABPMs, i.e. with less than 14 measurements during the day, and less than 7 measurements at night, according to the recommendations issued by the European Society of Hypertension (ESH) working group on BP monitoring (113).

4.5 Questionnaire and personal interview

At the visit to the hospital each patient met with one of the physicians in the study and was interviewed according to a structured questionnaire. The issues that were addressed concerned general health, smoking and alcohol habits, physical training, medication and family history of hypertension, cardiovascular disease, cerebral stroke, hyperlipidemia, diabetes and pregnancies.

The protocol also included detailed questions about UTIs since the first study. When possible, patient records from hospitals and outpatient clinics were collected and reviewed retrospectively to confirm the anamnestic information. Focus was on evaluating the severity of the UTIs and a febrile episode required temperature of at least 38.0° C.

Data concerning pregnancies, deliveries and any UTI during pregnancy, both febrile and non-febrile, were collected retrospectively by studying hospital and antenatal records. The diagnoses of pregnancy-related hypertension and preeclampsia followed currently accepted international definitions based on information obtained from the medical records and were not reassessed in this study.

4.6 Evaluation of bladder function

Bladder function was evaluated anamnestically. A questionnaire focusing on bladder emptying was attached to the invitation letter. The questions concerned difficulties to start and need to strain at voiding, and feeling of incomplete emptying. Patients affirming all three questions were considered to have problems with bladder emptying.

4.7 Urine analyses and blood tests

Urine creatinine and serum creatinine was determined by an enzymatic technique and urine albumin by an immunochemical method (turbidimetry). Estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft-Gault formula (114). Albuminuria was defined as an albumin/creatinine ratio of more than 5 g/mol creatinine.

4.8 Statistical methods

All tests were two-tailed and conducted at 0.05 significance level. Statistical analyses were performed with the SAS® 9.2. Package (Cary, NC).

For tests between two groups with respect to continuous variables Mann-Whitney U-test was used and for two dichotomous variables Fisher's Exact test. The relation between an ordered categorical variable and a dichotomous or an ordered categorical variable was tested with the Mantel-Haenszel Chi-square test. For comparison between more than two groups the Kruskal-Wallis test was used for continuous variables.

In paper I Generalized Estimating Equations (GEE) models were used to allow for adjustment of within-individual correlations. Prediction of UTI was analyzed using logistic regression. Odds ratio (OR) was presented with a 95% confidence interval (CI).

In paper II Jonckheere-Terpstra test was used for comparison between ordered groups.

In paper III the correlation was described by using Spearman's correlation coefficient (r_s). Multivariable analysis of continuous variables was performed

by using Analysis of Covariance (ANCOVA). It has been checked that the assumption of normal distribution is satisfied for the dependent variable. The Least Square (LS) means and 95% CI were presented for descriptive purpose. Changes of continuous variables over time were tested by using Wilcoxon Signed Rank test.

In paper IV comparison between presence and absence of renal damage regarding SBP and DBP where there were several measures a Mixed Model Covariance Pattern Model for Repeated Measurement with covariance structure compound symmetry with presence or absence of renal damage as fixed effects was used.

4.9 Ethical approval and informed consent

The study was approved by the Ethics Committee of the Medical Faculty of the University of Gothenburg (Ö 164-00). Written consent was obtained from all patients before attending the study.

5 RESULTS

5.1 MCUG

The VUR results originate from the previous study by Martinell et al. since MCUG was not repeated in this study.

MCUG was performed at least once in 84 patients. VUR was found in 51 with maximum grade IV in 14, grade III in 14, grade II in 15 and grade I in 8, according to the international classification system (10). Surgical re-implantation was performed in 18 patients by varying techniques. In 12 of these VUR was resolved after surgery and in the rest the VUR grade was improved even though it remained. When the last MCUG was performed in late childhood at median age 14 years (range 4 to 33) 24 patients had persistent VUR, 4 grade III, 9 grade II, and 11 grade I.

5.2 Questionnaire

Seven women had hypertension and were taking anti-hypertensive medication at entry. One woman had had a stroke without a neurological sequel related to use of birth control pills. Three patients were intermittently taking non-steroidal anti-inflammatory drugs, four antidepressants and one anxiolytic medicine. Autoimmune disease was diagnosed in three women, two of whom were on immunosuppressive medication. No correlation was found between higher BP and such medication, hereditary or lifestyle factors in the structured questionnaire.

No other medication that could compromise renal function was recorded. No disease that could influence the obstetrical outcome or make the patients more prone to UTI or bladder dysfunction was found.

5.3 Renal damage

All 86 women had undergone urography as part of the previous study, the last investigation at a median age of 23 years (range 15 to 36). Two women with previously identified bilateral urographic damage had had unilateral

nephrectomy, one at age 10 because of a shrunken kidney and severe hypertension, and the other at age 33 because of recurrent febrile UTIs. In the statistical analyses the two nephrectomized patients were included in the group with bilateral renal damage since the remaining kidney was damaged.

DMSA scan showed renal damage in 58 women, 9 with bilateral, 47 with unilateral, and 2 with damage in a single kidney (after nephrectomy). Nine had renal damage class 1, 15 class 2, and 34 class 3 in the remaining most severely damaged kidney.

Nine patients with damage on DMSA scan had normal urography. The UTI pattern and VUR status of these patients are listed in Table 4. Only one of these patients had a febrile UTI in adulthood but five had one or more non-febrile UTIs. At the first MCUG in Martinell's study, VUR was seen in five of these patients, persisting in three of them at the last MCUG. Progress of VUR was not seen in any of these patients.

Ten women had renal damage detected by urography but not visible on DMSA scan. The mean GFR of this group was 108 mL/min/1.73 m² (range 80 to 125 mL/min/1.73 m²).

Table 4. Patients with renal damage on DMSA scan but normal urography.

	Febrile UTI in adulthood	Non-febrile UTI in adulthood	VUR grade at first MCUG	VUR grade at last MCUG	Class of renal damage on DMSA scan	GFR
Pat 1	No	Single	II	I	2	117
Pat 2	No	Recurrent	II	II	3	109
Pat 3	No	Single	0	0	1	138
Pat 4	No	No	0	0	2	109
Pat 5	No	Recurrent	I	0	1	148
Pat 6	No	No	III	0	2	121
Pat 7	No	No	0	0	2	110
Pat 8	Yes	Recurrent	0	0	2	99
Pat 9	No	No	II	I	2	78

DMSA, ^{99m}Tc-dimercaptosuccinic acid; GFR, glomerular filtration rate (mL/min/1.73 m²); MCUG, micturating cystourethrogram; UTI, urinary tract infection; VUR, vesicoureteral reflux

5.4 Renal function

The mean eGFR for women without and with renal damage were 120.8 ± 30.1 (SD) and 104.4 ± 25.4 mL/min, respectively (p=0.01). Of the 58 women with renal damage, 2 had CKD stage 3, 14 CKD stage 2, and 42 CKD stage 1.

Glomerular filtration rate

In the previous study the mean GFR for women without and with renal damage were 113 and 106 mL/min/1.73 m^2, respectively. Women with unilateral renal damage had mean GFR 109 and those with bilateral renal damage 93 mL/min/1.73 m². Re-examination of the same cohort with the same technique in the present study showed the corresponding values to be 113, 100, 104 and 81 mL/min/1.73 m², respectively (Table 5). Between the two studies, there was a significant decrease of GFR of 12.4 mL/min/1.73 m^2 only in the group with bilateral renal scarring (p=0.01) (Table 5, Figure 3).

There was no significant decrease of GFR between the two studies in patients with pyelonephritis (p=0.15) or frequent UTIs (p=0.11) in adulthood.

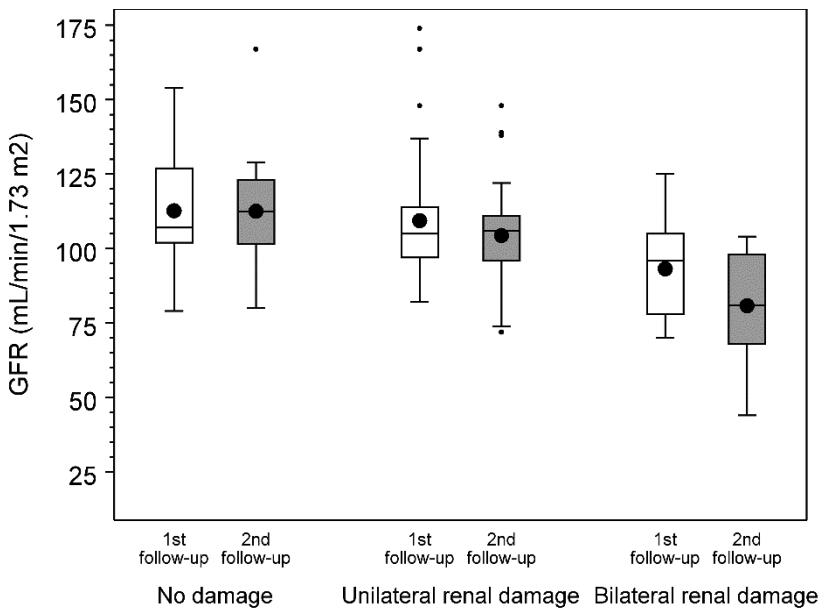
In this study, women with bilateral renal damage had significantly lower GFR than women with no or unilateral damage (mean 81 vs. 107 mL/min/1.73 m^2; p<0.0001). Women with class 3 damage had numerically but not significantly lower GFR compared to women with class 1 or 2 renal damage (mean 100 vs. 107 mL/min/1.73 m^2; p=0.07). Of the 58 women with renal damage, 1 had CKD stage 3, 14 CKD stage 2 and 43 CKD stage 1.

Table 5. GFR determined by EDTA clearance at the 1st and 2nd follow-up investigation in adult age.

Renal damage	Patients	GFR, mean (SD), median (range)			
		1st follow-up	2nd follow-up	Change from 1st to 2nd follow-up	p-value
None	28	113 (18)	113 (17)	-0.3 (18.6)	0.85
		107 (79; 154)	113 (80; 167)	-1.0 (-41.0; 40.0)	
Unilateral	47	109 (19)	104 (16)	-5.0 (16.7)	0.07
		105 (82; 174)	106 (72; 148)	-3.0 (-50.0; 39.0)	
Bilateral	11	93 (16)	81 (18)	-12.4 (13.4)	0.01
		96 (70; 125)	81 (44; 104)	-10.0 (-40.0; 5.0)	

EDTA, ^{51}Cr-edetic acid; GFR, glomerular filtration rate (mL/min/1.73 m²)

Figure 3. Glomerular filtration rate (GFR) at the 1st and 2nd follow-up investigation in adult age according to type of renal damage.



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The four patients with the most severe persistent VUR at the last MCUG (grade III) did not have any marked decrease of GFR between the two studies. There was, however, a significant correlation between severity of VUR in childhood and low GFR in adult age (r_s=-0.26, p=0.02). GFR in the 26 patients with hypertension diagnosed by ABPM was lower than in those with normal BP but did not reach the significance level (mean 98 vs. 107 mL/min/1.73 m^2; p=0.06). Twenty-two of the patients above with both hypertension and renal damage, had significantly lower GFR when compared with the other patients in the cohort (mean 96 vs. 107 mL/min/1.73 m^2; p=0.04) but not when compared with the 36 patients with renal damage but without hypertension (mean 96 vs. 102 mL/min/1.73 m^2; p=0.38).

The multivariable analyses revealed that the effect of higher maximum grade of VUR on lower GFR persisted also when adjusted for hypertension and age (LS mean -3.4, 95% CI -6.1 to -0.8, p=0.01). However, when also including grade of renal damage in the model, there was a non-significant relation to GFR for both variables (p=0.10 for maximum grade VUR and p=0.36 for grade of renal damage, respectively) because of a strong association between these two variables (p<0.0001).

Individual kidney GFR

The distribution of individual kidney GFR is shown in Table 6. In 38 (44%) patients individual kidney GFR was less than 40 mL/min/1.73 m² in one of the kidneys. The lowest individual kidney GFR of the 26 hypertensive patients was significantly lower than that in those without hypertension (mean 36 vs. 43 mL/min/1.73 m^2; p=0.03). Maximum grade VUR in childhood was significantly correlated to low individual GFR of the corresponding kidney in adult age (r_s=-0.55, p<0.0001).

Table 6. Distribution of individual GFR in the kidney with the lowest function in 86 patients according to type of renal damage.

Individual GFR in the kidney with the lowest function	Patients with no renal damage n=28	Patients with unilateral renal damage n=47	Patients with bilateral renal damage n=11
< 10	0	3 (6.4%)	2 (18.2%)
10-19	0	3 (6.4%)	2 (18.2%)
20-29	0	4 (8.5%)	1 (9.1%)
30-39	1 (3.6%)	18 (38.3%)	4 (36.4%)
≥ 40	27 (96.4%)	19 (40.4%)	2 (18.2%)

GFR, glomerular filtration rate (mL/min/1.73 m²)

5.5 Blood pressure

Seven women had hypertension and were taking anti-hypertensive medication at entry to the study. Clinical information on the patients with and without renal damage is presented in table 7.

Table 7. Clinical characteristics of women without and with renal damage

	Without renal damage n=28	With renal damage n=50	p-value
Age (years)	40.2 ± 2.6 (35.7; 46.1)	41.7 ± 3.8 (34.6; 51.1)	0.09
Height (m)	1.67 ± 0.06 (1.52; 1.77)	1.67 ± 0.06 (1.50; 1.81)	0.99
Weight (kg)	70.0 ± 12.6 (56.0; 116.0)	70.5 ± 12.0 (50.0; 111.0)	0.44
BMI	25.1 ± 4.9 (19.0; 44.0)	25.2 ± 3.8 (20.0; 36.0)	0.55
Mean office systolic BP	111.3 ± 10.4 (91.7; 146.7)	113.9 ± 12.8 (86.7; 146.7)	0.31
Mean office diastolic BP	71.7 ± 8.1 (55.0; 88.3)	72.8 ± 10.1 (56.7; 98.3)	0.75

Data: Mean ± SD (range). BMI, body mass index (kg/m^2); BP, blood pressure (mmHg)

Manual blood pressure

In addition to the 7 women who had hypertension and were taking anti-hypertensive medication at entry, another 6 women were found to have elevated BP based on office measurements: 2 had SBP as well as DBP ≥140/≥90 mmHg, 2 SBP ≥140 mmHg, and 2 DBP ≥90 mmHg. No significant difference was seen between the groups without or with renal damage (Table 7).

24-hour blood pressure

Two women who had undergone nephrectomy and seven with known hypertension (one woman fulfilled both criteria) were excluded, leaving BP measurements of 78 women for analysis. We also performed a sensitivity analysis including all women (n=86). Hypertension was defined according to ESH guidelines issued in 2007 (57), using both the lower and higher threshold, and also according to the NICE guidelines from 2011 (68), see Introduction. Incomplete ABPMs were seen in 11 women.

Four of six cases with elevated BP detected at office measurements were also recognized at ABPM. The two remaining cases had normal ABPM and were therefore considered not to have hypertension.

Analysis according to the ESH guidelines identified 19 women with hypertension by the lower and 15 by the higher threshold (Table 8). Of these, 15 and 12, respectively had renal damage. Analysis according to the NICE guidelines, revealed 11 new hypertensive women of whom eight had renal damage.

Together with the 7 women with hypertension diagnosed before entry, the lower ESH threshold found 26 (30%) women with hypertension, 4 of 28 (14%) without and 22 of 58 (38%) with renal damage (p=0.04). With the higher BP threshold, there were a total of 22 (26%) women with hypertension, three of 28 (11%) without and 19 of 58 (33%) with renal damage (p=0.046). With the NICE guidelines, there were a total of 18 (21%) with hypertension, three of 28 (11%) without and 15 of 58 (26%) with renal damage (p=0.18).

Table 8. Hypertension detected before entry and by ABPM according to extent of renal damage in the most severely damaged kidney as evaluated by DMSA scan

	Hypertension detected before entry	Hypertension detected by ABPM according to different guidelines		
Type of renal damage		ESH 2007 lower threshold*	ESH 2007 higher threshold**	NICE 2011***
Without damage	0	4	3	3
Class 1	1	2	2	1
Class 2	2	4	4	2
Class 3	4	9	6	5
Total	7	19	15	11

*Mean 24-h BP ≥125/≥80 mmHg, mean daytime BP ≥130/≥85 mmHg and mean night-time BP ≥120/≥70 mmHg (57)

**Mean 24-h BP ≥130/≥80 mmHg, mean daytime BP ≥135/≥85 mmHg and mean night-time ≥120/≥70 mmHg (57)

*** Mean daytime BP ≥135/≥85 mmHg (68)

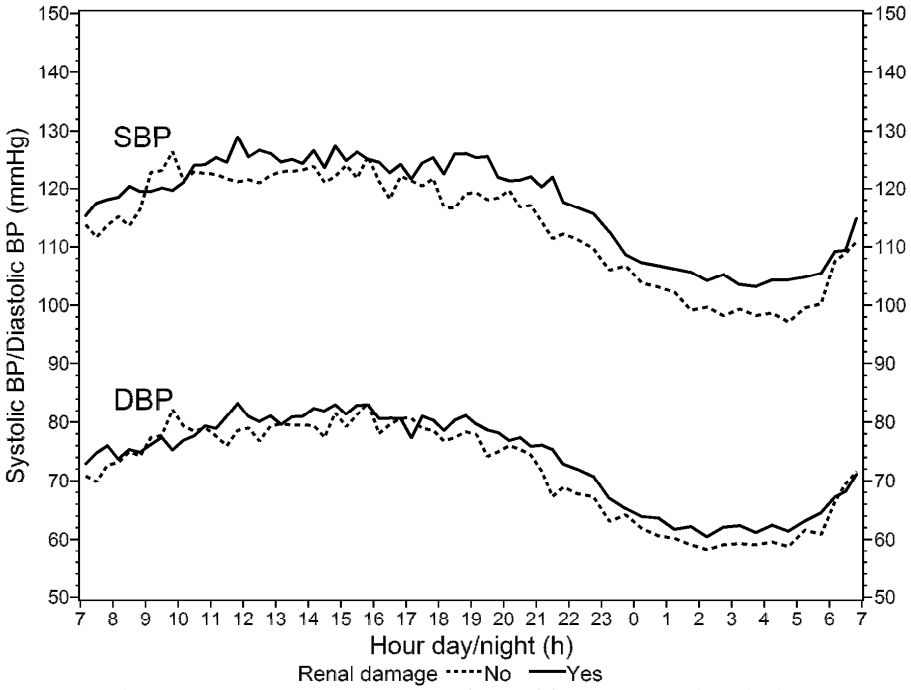
Table 9. Ambulatory blood pressure in women without and with renal damage.

	Without renal damage n=28	With renal damage n=50	p-value
Mean 24-hour SBP	114.2 ± 11.2 (99.9; 156.5)	117.6 ± 10.1 (93.7; 140.4)	0.03
Mean 24-hour DBP	72.3 ± 7.0 (62.1; 95.3)	73.8 ± 8.0 (58.0; 98.0)	0.27
Mean daytime SBP	118.4 ± 11.6 (103.5; 160.6)	121.2 ± 10.6 (94.2; 148.6)	0.04
Mean daytime DBP	76.1 ± 7.2 (66.2; 98.0)	77.2 ± 8.3 (59.2; 104.6)	0.27
Mean night-time SBP	101.7 ± 11.2 (89.1; 145.3)	106.5 ± 9.9 (88.4; 128.9)	0.01
Mean night-time DBP	60.8 ± 7.6 (51.8; 87.7)	63.6 ± 8.4 (50.6; 84.4)	0.10

Data: Mean ± SD (range). DBP, diastolic blood pressure (mmHg); SBP, systolic blood pressure (mmHg)

The ABPMs of the 78 patients were correlated to renal damage. Women without and with renal damage had significantly different mean BP for systolic 24-hour, systolic daytime and systolic night-time measurement (p=0.03; p=0.04 and p=0.01, respectively) (Figure 4, Table 9).

Figure 4. 24-hour ambulatory systolic and diastolic blood pressure (BP) monitoring in patients without (n=28) and with renal damage (n=50). Significance was found for systolic BP (p=0.03).



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The BP was also related to the extent of renal damage. Women without renal damage compared with those with class 1, class 2 and class 3 damage differed significantly concerning mean BP for systolic 24-hour, systolic daytime and systolic night-time measurement (p=0.01; p=0.02 and p=0.008, respectively) (Table 10).

Table 10. Ambulatory blood pressure in women according to extent of renal damage.

	Renal damage Class 1 n=7	Renal damage Class 2 n=13	Renal damage Class 3 n= 30	p-value
Mean 24-hour SBP	114.8 ± 10.5 (93.7; 127.5)	115.6 ± 12.2 (96.9; 138.8)	119.1 ± 9.0 (105.9; 140.4)	0.01
Mean 24-hour DBP	73.2 ± 8.6 (58.2; 84.3)	72.2 ± 8.6 (58.0; 86.8)	74.6 ± 7.8 (61.8; 98.0)	0.25
Mean daytime SBP	118.0 ± 11.1 (94.2; 127.8)	118.7 ± 13.0 (98.5; 140.9)	123.1 ± 9.2 (108.9; 148.6)	0.02
Mean daytime DBP	76.4 ± 8.9 (59.2; 85.7)	74.9 ± 8.8 (59.4; 88.2)	78.3 ± 8.0 (63.8; 104.6)	0.17
Mean night-time SBP	104.6 ± 11.1 (91.9; 126.6)	105.7 ± 11.6 (88.4; 128.9)	107.3 ± 9.0 (94.2; 128.0)	0.008
Mean night-time DBP	62.8 ± 9.6 (51.2; 80.6)	63.6 ± 9.6 (50.6; 80.4)	63.8 ± 7.8 (52.0; 84.4)	0.10

Data: Mean ± SD (range). DBP, diastolic blood pressure (mmHg); SBP, systolic blood pressure (mmHg). P-values were obtained comparing all 4 groups (no renal damage and class 1-3 renal damage).

Analysis excluding the 11 patients with incomplete ABPMs was also performed (n=67). The difference between the groups without and with renal damage persisted for systolic night-time measurement (102.7 ± 12.1 vs. 107.1 ± 9.6 mmHg; p=0.03). Also, the difference between the groups without renal damage compared with those with class 1, class 2 and class 3 damage persisted (102.7 ± 12.1 vs. 104.6 ± 11.1 vs. 108.3 ± 10.6 vs. 107.2 ± 9.0 mmHg; p=0.04). Similar results were obtained in a sensitivity analysis including all 86 women.

The diurnal pattern of each patient's ABPM was also analyzed and a non-dipping BP pattern was defined as a <10 % nocturnal BP fall (110). Eight women had a both systolic and diastolic non-dipping BP pattern. Of these, 5 were defined as hypertensive in the study according to the lower threshold in the ESH guidelines and 3 had normal ABPM (7 had renal damage). Twelve women had a systolic non-dipping BP pattern. Of these, 3 were defined as hypertensive in the study according to the lower threshold in the ESH guidelines and 9 had normal ABPM (7 had renal damage). One woman with renal damage had reverse-dipping but otherwise normal ABPM.

5.6 Urinary tract infections and bladder dysfunction

A short summary of the results from paper I is presented here.

The UTI pattern in adulthood of the 86 patients, i.e. from the age of 20 years, is described. Twenty-two patients had had no UTI, 35 had had occasional UTI and 29 frequent UTI. Pyelonephritis occurred in 22 patients, once in 15 and two or more times in 7 patients. The pattern of symptomatic UTI represented by the most severe episode for each 5-year period is shown in Figure 1, paper I. The risk of pyelonephritis decreased with increasing age in patients both with and without renal damage. Bladder emptying problems were significantly more common in women with frequent non-febrile UTI.

5.7 Urine analyses

Measurement of urinary albumin was done in 83 patients. Three patients had albuminuria. The first woman excreted 9.82 g/mol creatinine, had a GFR of 97 mL/min/1.73 m² and no renal damage. The second excreted 10.8 g/mol creatinine, had a GFR of 44 mL/min/1.73 m² and had been nephrectomized in adult age with renal damage in the remaining kidney. The third excreted 20 g/mol creatinine, had a GFR of 68 mL/min/1.73 m² and bilateral renal damage.

5.8 Pregnancies

When this cohort was previously investigated, a primary purpose was to study pregnancy complications (71). Since then, another 30 women had given birth and the number of pregnancies had more than doubled. No women had diabetes mellitus or any other serious systemic disease that could influence the obstetrical outcome.

Of the 86 women investigated, 72 had given birth to one or more children. Median time from the last delivery to the present study was 11 years (range 1 to 28 years). There were a total of 151 deliveries, but no twin pregnancies (Table 11). Two children died, one intrauterine in week 38 of unknown cause in a woman with unilateral renal damage, the other due to infection after a premature delivery in week 25 in a woman without renal damage. The

women made their first visit to the antenatal clinic at median week 12 (range 9 to 19 weeks).

Complications

There were no significant differences in birth weight, birth height, premature birth or cesarean delivery between women with and without renal damage (Table 11). Neither when subdividing those with damage into unilateral and bilateral, or class 1 to 3, nor when comparing no damage to both bilateral and class 3 damage together, any differences were found.

No woman had hypertension before the first pregnancy. Gestational hypertension was diagnosed in seven women (10 pregnancies), all of whom had renal damage. Four of these seven women had hypertension detectable with 24-hour ABPM in the present study. The other 18 women with hypertension in this study had BP within the normal range during the pregnancies. One woman with gestational hypertension was treated with anti-hypertensive medication during the pregnancy which was then discontinued.

Four women, of whom 3 with renal damage, developed preeclampsia during their first pregnancy. One woman with bilateral damage had preeclampsia in both her pregnancies. The prevalence of preeclampsia in the pregnancies in the whole study cohort was 3%, and in the group with renal damage 4%. Two women with preeclampsia continued anti-hypertensive medication after pregnancy.

Table 11. Clinical details and obstetric data of the women who had a live birth grouped according to renal damage

	No renal damage n=24	Renal damage n=48	p-value
1st delivery	24	48	0.99
2nd delivery	18	37	0.99
3rd delivery	6	14	0.99
4th to 6th deliveries	1	3	1.00
Length of pregnancy	39.4 ± 1.8	39.5 ± 1.9	0.90
(weeks)	40.0 (34.3; 42.0)	40.0 (30.0; 42.0)	
Age at first pregnancy	28.0 ± 5.0	27.8 ± 5.1	0.880
(years)	25.9 (20.4; 37.6)	27.5 (19.0; 44.9)	
Birth weight	3517 ± 517	3492 ± 539	1.00
(g)	3515 (2600; 4565)	3528 (1450; 4680)	
Birth height	50.2 ± 2.0	50.6 ± 2.3	0.380
(cm)	50.0 (46.5; 54.0)	50.3 (41.0; 55.5)	
Caesarean section			
1st delivery	4	9	
2nd delivery	4	0	
3rd delivery	0	1	0.120
Number of pregnancies with delivery before pregnancy week 37	3	3	0.370

Data: mean ± SD/Median (range)

Urinary tract infections

Among the 48 women with renal damage, 15 had persistent VUR at the last MCUG, two grade III, six grade II, and seven grade I. Antibiotic prophylaxis was given to these women in 12 pregnancies, mainly first pregnancies. Pyelonephritis occurred in two women with grade II reflux and in one without VUR. Among the 24 women without renal damage, four had VUR – one grade III, one grade II and two grade I. Antibiotic prophylaxis was given in 11 pregnancies to these women. No pyelonephritis occurred in this group. There was no difference in use of prophylaxis between the groups with and without renal damage (p=0.730). There were no differences in the frequency of non-febrile or febrile UTI between women with and without renal damage (p=0.80). Women with history of UTI in adulthood, both occasional and recurrent, were more prone to UTI during their pregnancies compared to those without UTI (p=0.023).

Blood pressure

When the BP registrations from every antenatal visit were analyzed, SBP was significantly higher in women with renal damage compared to those without. This was evident for the first pregnancy as well as the subsequent ones (p=0.0005 and p=0.034, respectively) (Table 12). The difference persisted when the group without damage was compared to the groups with class 1-3 damage (p=0.003 and p=0.015, respectively). The 22 women found to have hypertension in this study had significantly higher SBP and DBP when compared to the rest of the women only when pregnancies 2-6 were analyzed (p=0.003 and p=0.009, respectively).

Table 12. Blood pressure measurements during pregnancies in the study population, grouped according to renal damage

	No renal damage	Unilateral renal damage	Bilateral renal damage	p-value
First pregnancy	n=24	n=39	n=9	
SBP	114.0 ± 9.3	117.8 ± 9.7	126.0 ± 13.9	0.0005
	110.0	120.0	120.0	
	(90.0; 145.0)	(95.0; 145.0)	(105.0; 160.0)	
DBP	69.3 ± 8.4	70.2 ± 9.5	75.7 ± 13.7	0.073
	70.0	70.0	75.0	
	(50.0; 95.0)	(40.0; 100.0)	(60.0; 115.0)	
Pregnancies 2-6	n=25	n=44	n=10	
SBP	111.9 ± 8.9	112.7 ± 12.7	122.9 ± 13.3	0.034
	110.0	110.0	120.0	
	(90.0; 130.0)	(80.0; 160.0)	(100.0; 155.0)	
DBP	67.4 ± 7.1	68.0 ± 9.5	76.0 ± 11.0	0.093
	70.0	70.0	75.0	
	(55.0; 90.0)	(40.0; 100.0)	(55.0; 100.0)	
All pregnancies	n=49	n=83	n=19	
SBP	112.8 ± 9.1	115.0 ± 11.7	124.1 ± 13.6	0.002
	110.0	115.0	120.0	
	(90.0; 145.0)	(80.0; 160.0)	(100.0; 160.0)	
DBP	68.2 ± 7.8	69.0 ± 9.6	75.9 ± 12.1	0.061
	70.0	70.0	75.0	
	(50.0; 95.0)	(40.0; 100.0)	(55.0; 115.0)	

Data: mean ± SD/Median (range)
DBP, diastolic blood pressure (mmHg); SBP, systolic blood pressure (mmHg)

At the last antenatal visit of the first pregnancy, women with unilateral and bilateral damage had significantly higher SBP than those without damage (p=0.005), while there was no significant difference regarding DBP (Table 13). During pregnancies 2-6 the difference persisted for SBP and was seen also for DBP. Comparing BP at the last antenatal visit of the first pregnancy and of the subsequent ones in women without damage and those with class 1-3 damage, there was a significant difference in SBP (p=0.002 and p=0.030, respectively) but not in DBP. The 22 women found to have hypertension in the present study had significantly higher SBP already at the last antenatal visit of pregnancies 2-6 (p=0.019). When SBP and DBP at the first and the last trimester were compared there was no significant difference between women with and without renal damage.

Table 13. Blood pressure measured at last antenatal visit in the study population, grouped according to renal damage

	No renal damage	Unilateral renal damage	Bilateral renal damage	p-value
First pregnancy	n=24	n=39	n=9	
SBP	115.7 ± 9.2	120.1 ± 10.9	133.8 ± 13.6	0.005
	115.0	120.0	135.0	
	(100.0; 130.0)	(95.0; 145.0)	(115.0; 155.0)	
DBP	73.6 ± 7.9	75.3 ± 11.9	86.9 ± 17.5	0.140
	70.0	75.0	85.0	
	(60.0; 90.0)	(50.0; 100.0)	(65.0; 115.0)	
Pregnancies 2-6	n=25	n=44	n=10	
SBP	115.7 ± 8.4	114.3 ± 11.5	127.2 ± 11.8	0.017
	118.0	112.5	125.0	
	(100.0; 130.0)	(90.0; 135.0)	(115.0; 155.0)	
DBP	71.9 ± 8.3	69.1 ± 8.6	80.0 ± 12.7	0.031
	70.0	70.0	80.0	
	(60.0; 90.0)	(50.0; 90.0)	(60.0; 100.0)	
All pregnancies	n=49	n=83	n=19	
SBP	115.7 ± 8.7	117.2 ± 11.5	130.3 ± 12.7	0.0007
	115.0	120.0	130.0	
	(100.0; 130.0)	(90.0; 145.0)	(115.0; 155.0)	
DBP	72.7 ± 8.1	72.1 ± 10.8	83.2 ± 15.1	0.013
	70.0	70.0	80.0	
	(60.0; 90.0)	(50.0; 100.0)	(60.0; 115.0)	

Data: mean ± SD/Median (range)
DBP, diastolic blood pressure (mmHg); SBP, systolic blood pressure (mmHg)

6 DISCUSSION

Some 15% of children with pyelonephritis will have permanent renal damage (45). Preventing febrile UTI and possible renal damage in children is an important issue in pediatric medicine. The management of VUR and the possible techniques to do so is under debate. It is of concern how these patients should be followed in adulthood in order to prevent long-term consequences of UTI-related renal damage. There are few studies addressing how the follow-up in adulthood should be designed.

Some review articles try to condense the knowledge about the known long-term effects; renal damage, hypertension, impaired renal function and pregnancy complications (1, 115-119). In one the prevalence of patients with impaired renal function in the included studies varied between 0% and 56%, reflecting the great heterogeneity in the studies in this area (117). It was concluded that there was a low risk of hypertension in these patients and that it was associated with renal damage but that there were no clear data to establish other long-term consequences following UTI during childhood. Concerning pregnancy-related complications, it was concluded that the few available data on the subject seemed to exclude major influence of UTI (117). Another review concentrated on the outcome of pregnancy in women with a history of VUR and concluded that the evidence did not support that low-grade VUR in girls without renal damage should be operated on solely to reduce pregnancy complications (118). It was also concluded that renal damage rather than the presence or absence of VUR was the principal determinant of morbidity during pregnancy. Data on long-term outcome in children with UTI-related renal damage is important to outline modern guidelines in follow-up and to avoid unnecessarily extensive investigations and arrangements for these children (116).

We chose not to include MCUG in the protocol since most patients feel that it is an unpleasant investigation and long-term surveillance has shown diminishing grade of VUR and a general tendency of disappearance over the decades (120). Therefore the reflux status of the patients had probably not worsened but more likely improved since the last MCUG. Instead we used the results of the most recent MCUG performed in the previous follow-up study. Internationally, the handling of patients with UTI-related renal damage, tends to focus much on VUR in childhood. In contrast, we chose to concentrate on renal damage rather than on grade of VUR. In our study there was a correlation between severe grade of VUR in early childhood and low GFR in adulthood, both for total GFR and individual kidney GFR. It can be

discussed, however, whether it is meaningful to follow women with persistent VUR and normal GFR into adulthood. Future monitoring should instead be based on the severity of renal damage.

This study did not include any control group which would have been an advantage, especially regarding BP measurements, but also concerning analyses of renal function and pregnancy outcome. Instead, many of the comparisons in the study were done between the groups with and without renal damage, using the latter group as a reference.

6.1 Urinary tract infections

All patients in this study were followed since childhood according to a strict protocol for diagnosis, treatment, investigation and follow-up of UTIs. (95, 96). After the previous study some patients were lost because of relocation or refusal to continue supervision. Registration of UTIs was therefore not as thorough as before. The patients were asked about any UTI since the previous study, but in many cases it was not possible to confirm such episodes. Thus, recall bias concerning UTIs in adulthood could not be excluded.

Bladder emptying problems can lead to residual urine which predisposes to bacterial growth and subsequent risk of UTI. Indeed, problems with bladder emptying were associated with recurrent UTI. The odds of having pyelonephritis decreased with increasing age in all patients, although pyelonephritis in adulthood was more common in women with than without renal damage. Genetic susceptibility to pyelonephritis in these individuals could be one of the explanations for this (14, 15) as well as persisting VUR since childhood.

Non-febrile UTI still occurred in patients both with and without renal damage with increasing age. This is the scenario for many women and probably this was partly due to a genetic predisposition for UTI in some of the women (14, 15, 21). In the future it may be possible to use genetic testing in UTI-prone patients to improve diagnosis and to assess the risk for chronic sequels such as impaired renal function, hypertension and renal damage (14).

6.2 Renal damage

In the previous study by Martinell et al., renal damage was diagnosed with urography. The frequency of urographic renal damage after pyelonephritis in childhood varies between 5% and 10% (96, 121). With DMSA scan, which today is the standard method used for detection of renal damage, some 15% of children with pyelonephritis will have permanent damage (45). This technique was used in our study. Since renal damage was evaluated by two different methods in the two studies, a strict comparison between the results was not possible. In order to make some sort of comparison, the results obtained by urography in the previous study were reevaluated. Reduction of parenchymal thickness to ≤2.5 SDS (100, 101) was classified as renal damage to compensate for the fact that calyceal clubbing could not be evaluated on the DMSA scan.

When the results of the two studies were compared, nine patients had renal damage when examined with DMSA scan despite previous normal urography. Since only one of these patients had experienced an episode of pyelonephritis in adulthood it seems unlikely that this damage was acquired between the two studies but was rather due to a more sensitive examination method. The VUR status of these patients had not worsened at the last MCUG but remained unchanged or improved.

Ten women had urographic renal damage not visible on DMSA scan. The GFR of these 10 women did not differ from that in the rest of the study cohort. This highlights the problem of comparing two different methods to examine renal damage, e.g. urography versus DMSA scan. Urography is a better technique to evaluate morphological damage such as clubbing while DMSA scan provides a better functional picture of the kidney. If both kidneys are damaged there is a risk of missing this fact when evaluating the DMSA scan results as much of the interpretation is made by comparing the kidneys with each other. It is harder to find focal damage when there is no healthy kidney to compare with. It is also possible that severe damage of one kidney masks less severe damage of the other. It can be assumed, however, that it probably is more important to know the function of the kidneys than to have an exact view of the morphology.

6.3 Renal function

GFR decreases gradually with increasing age (49). In patients with UTI-related renal damage one could expect an increased risk of decreased GFR which is indicated by some previous studies (2, 3). These studies, however, were often performed in tertiary referral centers on patients with more severe renal damage. Our investigation, on the other hand, was population-based and covered 3 to 4 decades. In a similar study on patients with a mean age of 24.5 years (122), there was no difference in the decrease of GFR between patients with or without renal damage over a median period of 22 years. In our patients, who were older with a mean age of 41 years, there was a significantly reduced GFR among patients with bilateral renal damage but not among those with unilateral or no damage. Women with bilateral renal damage also had significantly lower GFR than those with no or unilateral renal damage. There was a tendency to, but not significantly, lower GFR in women with class 3 damage compared to the other patients in the cohort. This indicates that women with bilateral or more severe grade of renal damage are more likely to develop decreased renal function over time and that follow-up should be focused on these patients.

According to the classification of chronic kidney disease (51), 14 women had CKD stage 2 and only one woman CKD stage 3. Albuminuria was seen in only three patients. The woman with the most severe albuminuria had CKD stage 2 and bilateral renal damage. The second patient with borderline albuminuria had no renal damage, normal GFR and no other disease or medication that might explain her albuminuria. The third woman had CKD stage 3 (GFR 44 mL/min/1.73 m^2). She was nephrectomized at 33 years of age because of recurrent febrile UTIs. She also had preeclampsia in her first and only pregnancy at the age of 21 years and hypertension since the age of 28 years. She was the only patient in our study with severely decreased renal function, renal damage and hypertension.

Albuminuria is an indicator of progressive renal failure and is easily screened for in an out-patient clinic by using a urine dipstick. It is therefore easy to include in the screening of patients with renal damage. A more accurate measure is done by collecting urine during 24 hours which can be considered in patients where the urine dipstick indicates albuminuria. Therefore monitoring of albuminuria should be considered in the follow-up of women with bilateral or severe unilateral renal damage.

In paper II presenting the BP results, eGFR results was also reported (114). This was almost identical to the results of the EDTA clearance. Calculating

eGFR gives a better estimate of the renal function than just using serum creatinine. Another advantage of eGFR is that it is more cost- and time-effective than EDTA or iohexol clearance (47). However, EDTA or iohexol clearance are methods of choice to more accurately measure the renal function and they should be considered in patients with elevated serum creatinine values.

6.4 Hypertension

Many of the control functions in maintaining normal BP are located to the kidneys and therefore hypertension is a well-known complication of renal disease. UTI-associated renal damage is also a well-studied and accepted reason for hypertension (2, 3, 7, 93, 123-126). Wennerström et al (123) conducted a similar study using ABPM in 100 patients (73 females and 27 males), 16-26 years after their first UTI in childhood. Fifty-three of these had renal damage. No difference in SBP or DBP between the non-damaged and the damaged group was seen. The patients in that study, however, had a median age of 25 years compared to 41 years in our study, which could be a possible explanation for the difference between the two studies.

When this cohort was investigated earlier at median age 27.5 years, the diastolic office BP was higher in females with severely scarred kidneys than in controls and hypertension was detected in 3 of 54 (6%) women with renal damage (93). Our results showed no relation between office BP and renal damage. We used a 30-minute resting period before the three office BP measurements, which may have caused some elevated office BP values to normalize before measurement. We chose to define hypertension as office BP ≥140/90 mmHg, even though anti-hypertensive treatment in clinical practice often is given to patients with renal damage at lower levels (≥130/80 mmHg), since renal damage in itself is a risk factor for cardiovascular disease (57, 65). The fact that the higher BP in the patients with renal damage was not detected by office BP shows the importance of considering 24-hour ABPMs in this specific group of patients.

We had many patients with “masked hypertension”, i.e. normal office BP but elevated BP at ABPM. The 30-minute resting period used in the study may have contributed to this observed high frequency. Depending on the definition of hypertension used when interpreting the ABPM results, the number of hypertensive patients in the study varied. The NICE guidelines (67, 68) are based on a simplified model using only mean daytime BP, and

subsequently detected a lower number of women with hypertension. Of the 58 women with renal damage, 22 (38%) and 19 (33%), respectively had hypertension according to the ESH guidelines with the two different cut-off levels (57), to be compared to 4 of 28 (14%) and 3 of 28 (11%), respectively in those without damage. Thus, the prevalence of hypertension was significantly higher in women with than without renal damage. Only 7 of the 26 women with hypertension were taking anti-hypertensive medication at entry to the study. The others were undetected which means that they were at increased risk of cardiovascular complications. It is therefore desirable to monitor BP in women with renal damage, especially those with severe damage. With higher age there is an increasing risk of hypertension, regardless of renal damage, and anti-hypertensive treatment should be considered to prevent not only cardiovascular illness and stroke, but also progression of renal failure (57).

The BP variable that remained highly significant throughout all subgroups of renal damage was the mean night-time SBP which should be a good marker for hypertension. The significant relation between high BP and renal damage persisted even after exclusion of patients with incomplete ABPMs. This emphasizes the robust results of this long-term follow-up, despite the limited number of women in the study. Non-invasive methods for BP measurement are sub-optimal for diastolic readings and could thus explain the poorer association between the DBP and renal damage. Echocardiography would have been useful by providing evidence of left ventricular hypertrophy or the lack of it (127). However, echocardiography was not analyzed in this study.

A recent review estimated the cumulative risk for permanent renal damage after febrile childhood UTI to about 15% (45). Based on this figure and a 6% risk of symptomatic UTI in Swedish girls (46), about 1% of young women entering adulthood should have UTI-related renal damage. In our study the prevalence of hypertension according to office BP was 13%. The prevalence of hypertension in women within the age-group 40-49 years is much higher. In 1999 a 23% prevalence of hypertension by office measurement in women and men aged 40-49 years was shown in the MONICA sample from northern Sweden (128). In the I998 Health Survey in England there was a 22% prevalence of hypertension by office measurement in women in the same age-group (129). Since the prevalence of hypertension is much higher than the prevalence of renal damage, the latter is not the major cause of hypertension in the population. This study suggests, however, that renal damage may be causally related to hypertension in women with UTI during childhood.

The lower prevalence of hypertension diagnosed by office BP may be explained by the fact that the women in this study were controlled medically since childhood and therefore had a healthier life style and an increased awareness of risk factors for hypertension compared to the public in general. It is also possible that the long resting-time before measuring office BP caused some elevated office BP values to normalize before measurement. Concerning the MONICA study, it included both men and women while our study group consisted of women only. Women have lower SBP levels than men in the 30- to 44 year age groups (55), which could explain the difference in prevalence between the studies. However, SBP rises more steeply in women than in men with increasing age, resulting in higher BP in women at or beyond 60 years of age and also a higher prevalence of hypertension when this age has been reached (64). This supports continued follow-up of BP in the women in this cohort as they grow older.

There were eight women who had both a systolic and a diastolic non-dipping BP pattern. Five of these were found to be hypertensive. Concerning other cardiovascular illness, only one of the women had had a stroke, considered to be caused by birth control pills; she was, however, not in the non-dipping or hypertensive group. It is well known that subjects in whom nocturnal decrease in blood pressure is blunted (non-dippers) have a greater prevalence of organ damage and a less favorable outcome (110). Such events were not seen in the women in this study who were mostly in the age-span 40-49 years. Other studies have indicated less of a night-time BP decline in postmenopausal women (110, 130). However, none of the women was yet menopausal, and this factor cannot explain the observed non-dipping patterns.

6.5 Pregnancies

There are some previous studies looking at the outcome of pregnancies in women with renal damage due to VUR and UTI (2-7, 53, 54, 71). Except for our study, investigating the same patients as Martinell et al., these studies mostly included either patients from tertiary referral centers or patients with known VUR, often surgically treated. In our study none of the women, irrespective of renal damage had hypertension or were taking anti-hypertensive medication before their first pregnancy. Also, no woman had GFR less than 60 mL/min/1.73 m^2 before pregnancy.

Previous studies reported a higher incidence of UTI during pregnancy in patients with VUR or renal damage (3, 6, 7, 71). Our study showed no differences in UTI frequency, including both febrile and non-febrile episodes, between the groups with or without renal damage. Only three women in our study had pyelonephritis during pregnancy, all with renal damage and two of them also VUR at the last MCUG in late childhood.

Two of the studies looked specifically at prevalence of pregnancy-related hypertension (3, 71). Both studies showed that it was more common in patients with renal damage, in Martinell's study only during first pregnancies (71). Our study showed that gestational hypertension was more common in women with renal damage when looking at all pregnancies. Gestational hypertension was diagnosed in seven women (10 pregnancies), all of whom had renal damage. Four of the seven women with pregnancy-related hypertension had hypertension detectable with 24-hour ABPM. This supports what other studies have already shown; that hypertension in pregnancy, regardless of type or presence of other known risk factors increases the risk of later hypertension (87-90). SBP during the whole pregnancy was also significantly higher in women with unilateral and bilateral renal damage compared to that in women without renal damage in the first pregnancies and also in the subsequent ones.

Some previous studies reported a high prevalence of preeclampsia in women with renal scarring (70, 72). El-Khatib et al. reported preeclampsia in 24% of the pregnancies in women with bilateral scarring, and Sacks et al. in 31%. Other studies showed lower figures; Martinell et al. 2 of 32, 6% (71), Jacobson et al. 2 of 26, 8% (2), and Jungers et al. 39 of 375 pregnancies, 10% (54). Other studies focused on women with surgically treated VUR, not necessarily with renal scarring; preeclampsia was reported by Mor et al. in 7 of 49, 7% (7), Beetz et al. in 3 of 46, 7% (4), and Bukowski et al. in 4 of 77 pregnancies, 5% (5).

In our study preeclampsia occurred in 5 of 151 pregnancies (3%) in the total study population, and in 4 of 102 pregnancies (4%) in the women with renal damage (Paper IV). Prevalence of preeclampsia in pregnancies usually varies between 3-5% in industrialized countries (82). The reason for the high numbers in some of the older studies could be explained by inclusion of patients from tertiary referral centers, with severe renal damage and impaired renal function already before pregnancy. In contrast, our study was population based and therefore presented a lower prevalence of preeclampsia, as would be expected.

In our study, renal function was not routinely measured before, during or after the pregnancies, neither with serum creatinine or GFR. Since the time span between the last deliveries to the present study when GFR was measured, varied between one and 28 years, we chose not to correlate GFR data with pregnancies to see if pregnancy in itself decreased renal function in the patients. Only one patient in our study had a severely reduced renal function and CKD stage 3 at the present study. She had had only one pregnancy, which was complicated by preeclampsia.

7 CONCLUDING REMARKS AND CLINICAL USEFULNESS OF THE STUDY

Studies like this on a population-based cohort of women with and without renal damage and proneness to UTI are rare. It is small but unique in its long follow-up time of 35 years. This makes the results important since they are not biased by having a selected patient group. The women were investigated with sensitive methods both concerning renal damage and BP. This made it possible to show significant correlations between BP, renal function and UTI-related renal damage although the material is limited in size.

Today children with VUR, UTI and UTI-related renal damage in Sweden are investigated and monitored regularly at pediatric clinics. At the age of 18, the patients are offered transferal to adult health care. For this type of patients there are no specialized clinics to which they can be referred. Many of these patients are considered too healthy to be followed at hospital clinics. Thus, there is no obvious plan for follow-up in adulthood.

Development of hypertension and decreased renal function was seen only in a few patients at the first follow-up study of this cohort of patients when the median age of the patients was 27.5 years. The present study, performed at a median age of 41 years, showed that women with UTI-associated bilateral or severe unilateral renal damage since childhood were at increased risk of hypertension before reaching the menopause. A relationship between severe renal damage and a lowered GFR was also observed. These findings suggest that this type of patients should be monitored concerning BP and renal function as they grow older. Patients with ongoing proneness to UTI also need easy access to a general practitioner that is well acquainted with the patient for rapid investigation and treatment of their UTI, especially if those are recurrent.

We suggest a follow-up plan with regular check-ups of patients with bilateral or severe unilateral renal damage which should include measurement of BP and control of renal function. It is reasonable that BP is measured in the office using a standard equipment and procedure, i.e. allow the patients to sit for 3-5 minutes before beginning BP measurements (66). The most recent guidelines from ESH/ESC state that it is generally accepted that out-of-office BP is an important adjunct to conventional office BP measurement (66). Thus, if the patient has bilateral or severe unilateral renal damage, ABPM

may be considered every second to third year, in order to detect "masked hypertension" and/or nocturnal hypertension (131). Night-time SBP was the BP variable that remained highly significant throughout all subgroups of renal damage. Renal function is most easily measured by serum creatinine and assessment of eGFR with the locally accepted method. A more extensive investigation of GFR with EDTA or iohexol clearance may be considered every five years, or when eGFR indicates decreased renal function.

UTI should be treated according to national guidelines. If the patient has one or more episodes of pyelonephritis, extra check-ups should be done. Radiological examinations with ultrasound or computer tomography are recommended only when urinary tract stones, treatment failure or renal abscess is suspected. Repeated DMSA scans are seldom indicated.

There was no increased incidence of fetal complications or preeclampsia in women with renal damage in our cohort. Check-ups concerning this should take place in any pregnancy, no matter if renal damage is present or not. In our region of Sweden, extra urine cultures are recommended if the pregnant woman has a history of UTI or renal damage. Treatment of ABU or UTI during pregnancy should follow the guidelines previously discussed in this thesis. Women with renal damage had increased BP during pregnancy which emphasizes that BP monitoring during pregnancy is important.

Today, no patient in our study cohort is followed at the Department of Infectious Diseases. The two nephrectomized women, because of impaired GFR, hypertension and the fact that they have only one remaining kidney, attend the adult Nephrology Unit at Sahlgrenska University Hospital. All other patients with bilateral or severe unilateral renal damage have been referred to their general practitioners for further follow-up.

As this cohort of women is special and unique in the meaning that it is population-based and has been followed for several decades, another follow-up after further 10 to 20 years could be of interest. The aim of that study would be to again evaluate BP, renal function and pattern of UTI.

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