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Original Article

A Single-Center Review of the Outcomes and Safety of Renal Biopsy in Pregnancy

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ABSTRACT

Purpose: Renal disease is rare in pregnancy but presents a clinical dilemma with the safety profile of kidney biopsies during pregnancy unclear. Current guidelines have no consensus on the indication and timing, or criteria for selecting patients on, whom the benefits of a renal biopsy during pregnancy outweigh the risks of performing a safe renal biopsy. The aims of our research study were to determine the impact and safety of renal biopsy in the management of pregnant patients with renal diseases at Tygerberg Hospital from 1990 to 2019.

Methods: A series of percutaneous renal biopsies performed in 21 pregnant women with renal disease presenting during pregnancy over the past 30 years (1990–2019) were reviewed. Indications, timing, post-biopsy complications, histopathologic findings, management, and maternal and fetal outcome were reviewed for each case.

Results: The main indication for renal biopsy was suspected of glomerular diseases (81%). The median gestational age at the time of biopsy was fifteen weeks and six days in the range of 2-32 weeks. No patient developed any bleeding post renal biopsy (hematuria, subcapsular renal bleed , retroperitoneal bleed) . Most of the women had a glomerular disorder on renal biopsy, with mesangiocapillary glomerulonephritis (MCGN) being the most common histological diagnosis (23.8%). Six patients required conservative treatment only, while 14 patients required additional steroids, and only one patient required both steroids and an immunosuppressive agent. Out of 21 women patients, 14 (66.7%) had developed chronic kidney disease, while seven (33.3%) patients had normal kidney function. Eleven (52.5%) of the pregnant women had a normal delivery, while seven (33.3%) had a termination of pregnancy (MTOR), two premature deliveries after 33 weeks to save the kidneys during delivery, and one miscarriage .

Conclusions: A renal biopsy performed during pregnancy is not contraindicated, and pregnancy didn't lead to an increased risk of biopsy bleeding in our study, Results of histopathological studies are useful to and, in advising continuation or termination of pregnancy, recommend specific therapeutic modalities.

Keywords: Pregnancy, glomerulonephritis, pre-eclampsia, hypertension.

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INTRODUCTION

Pregnancy is a state of altered hormonal and hemodynamic milieu, with physiological changes such as an increase in glomerular filtration rate (GFR),[1] urine protein excretion,[2] and significant hemodynamic changes including decreased systemic vascular resistance, usually reaching a nadir by 20 weeks' gestation, as well as an increase in blood volume.

These changes lead to a 30-50% increase in cardiac output resulting in a steady increase in renal blood flow, which makes renal biopsy beyond 32 weeks risky.[3] Pregnancy in women with renal disease is associated with significant morbidity and increased mortality for both mother and fetus. This risk is exacerbated both by preexisting renal disease diagnosed before conception and renal disorders that occur for the first-time during pregnancy.[4] It may present in several forms such as nephritic syndrome, which is characterized by hypertension, haematuria with RBC casts, and variable levels of proteinuria (typically, less than 3.5 g/day), or nephrotic syndrome which is characterized by oedema, hyperlipidaemia, hypoalbuminemia, and proteinuria > 3.5 g/day,[5] Hypertensive disorders of pregnancy are the commonest medical complications in pregnancy and remain the most prevalent direct cause of maternal mortality.

The differential diagnosis of hypertensive events during pregnancy includes pre-exciting hypertension, gestational hypertension, or pre-eclampsia,[6] which is characterized by new-onset hypertension and proteinuria after 20 weeks gestation.[7] There are many complexities in managing a pregnancy with co-morbid renal diseases, such as whether the pregnancy is advisable at all, what complications can put mother and fetus at risk, and the long-term impact the pregnancy would have on the underlying renal disease, as well as resultant renal function.[8] Pregnancy outcomes in renal disease are determined by baseline creatinine levels, hypertension, and degree of proteinuria.[9] And advice on termination of pregnancy depends most frequently on the degree of renal impairment and the underlying renal pathology.[10] Treating nephrotic syndrome with corticosteroids might have additional maternal and fetal complications.

Using immunosuppression to treat glomerulonephritis empirically without histology identification as safe options is substantially restricted and may carry significant risk (infection, teratogenicity, infertility, cancer risk).[11] To start disease-modifying therapy, it is imperative to know the exact aetiology of the renal pathology, which often can be known only by performing a renal biopsy. Current guidelines have no consensus on the criteria for indications of renal biopsy or timing to perform a safe renal biopsy during pregnancy, as data is scanty, with teaching in many centers over the last three decades still cautioning against biopsy in pregnancy.

Of the limited series available in the literature, we would like to highlight three: Packham et al. performed renal biopsy in 104 pregnant women. He reported that 80% of the indications were a glomerular disease. He concluded that renal biopsy shouldn't be done as routine.[12] Lindheimer et al. suggested renal biopsy should be performed only when there is a sudden deterioration of renal function or massive nephrotic syndrome of unknown origin before 32 weeks. They also suggested that renal biopsy should not be carried out in the case of proteinuria alone in a normotensive woman with well-preserved renal function.[13] Kuller et al. proposed that renal biopsy should be considered if it offers the opportunity to make a diagnosis other than severe preeclampsia or in patients with pre-existing hypertension and proteinuria in whom it's almost impossible to diagnose superimposed pre-eclampsia. Despite the potential benefits of biopsy, the risk of complications (bleeding, nephrectomy, injury of other organ) remained a major concern in all studies.[14] In view of the limited data available, we undertook this study at our hospital to determine the impact and safety of renal biopsies in pregnant woman (bleeding, nephrectomy) with renal diseases over the last three decades.

MATERIALS AND METHODS

This is a retrospective, descriptive, and analytic study of all pregnant women who underwent renal biopsies at the Division of Nephrology at Tygerberg Hospital in South Africa between 1990-2019.

Patient medical files, demographics, clinical presentations, and diagnostic information were obtained from the renal biopsy folders, our pathology database, the electronic recorded system, and patient records on microfilms. Obtained variables include indication for renal biopsy, the gestion of pregnancy at time of biopsy, post-procedural complications (specifically bleeding requiring blood transfusion and/or further intervention), histopathological results, management, maternal outcome (worsening of renal function or not); and fetal outcome (Normal, stillbirth/neonatal death, premature, and termination of pregnancy). Patients were contacted who are still alive to confirmed termination of pregnancy before or after the biopsy. Data were presented as mean and range for continuous variables and as a frequency for categorical variables, Date been stored with a coding system and protected with a password. Ethical approval was obtained from the Health Research Ethics Committee at the University of Stellenbosch.

RESULTS

We identified 21 women who underwent renal biopsy during pregnancy. Clinical characteristics and outcomes are shown in Table 1. The main indication for renal biopsy was concerns for glomerular diseases (80%, 17 cases), while 10% of women presented with features of unexplained renal failure and 10% with other possible causes such as pre-eclampsia and HIV (two cases each). The median gestation age when the biopsy was performed was 15.6 weeks, ranging from 2–32 weeks. Just over half of patients underwent renal biopsy during the first trimester, only three patients underwent renal biopsy between 29 and 32 weeks of gestation. No biopsies were performed beyond 32 weeks gestation. No patient developed any post-renal biopsy complications, specifically, no significant bleeding needed transfusions or interventions in our patients.

The commonest disorder identified histologically was that of glomerulonephritis, with mesangiocapillary glomerulonephritis (MCGN) being the most common diagnosis (24%), followed by focal segmental glomerulosclerosis (19%). Histopathological results have been useful in guiding patients's management, as six patients required conservative treatment only (blood pressure control and diabetes mellitus (DM) control). These were patients with histopathological features of diabetic nephropathy, immunoglobulin A (IGA) nephropathy, atypical hemolytic uremic syndrome, pre-eclampsia, and end stage renal disease.

Fourteen women required additional immunosuppression in the form of corticosteroids, while one patient diagnosed with Lupus nephritis required both steroids and cyclophosphamide.

We obtained details of follow-up serum creatinine values on all our biopsied patients from three months beyond biopsy onwards. Of the 21 patients, 14 (67%) patients had chronic kidney disease, while seven (33%) patients had normal kidney function. Eleven (53%) of the pregnant women had a normal delivery, while 2 were premature deliveries, and seven (33%) pregnant women underwent termination of pregnancy. One miscarriage was recorded on day 4 post-biopsy, not related to the procedure. Four out of the seven patients who chose termination of pregnancy were diagnosed with mesangiocapillary glomerulonephritis, while the other three patients were diagnosed with end-stage renal disease, atypical hemolytic uremic syndrome, and lupus nephritis, respectively.

DESCUSSION

As with most other single center studies on the topic, we were limited by the small sample size. In our study, the most common indication for renal biopsy was the concern for glomerular disease, accounting for more than 80% of the cases. This is similar to the previous study by Packham et al., where 80% of the indications for renal biopsy were for investigating glomerular disease.[12] Chen et al. report a series of 15 pregnant women from Taiwan biopsied over 10 years. Twelve had nephrotic syndrome, whereas the other three had significant impairment of renal function.[15] Although previous recommendations from Lindheimer et al. indicate that a renal biopsy should be performed in symptomatic nephrotic syndrome or when there is a sudden worsening in renal function without a clear cause before 32 weeks of gestation, there remains a considerable difference in clinical practice.[13]

In the current study, all the renal biopsies were done before 32 weeks. Half of our patients underwent renal biopsy during the first trimester,

Table 1. Clinical characteristics of women who underwent renal biopsy.

	Indication for biopsy	Gestation-age at biopsy (weeks)	Complications of biopsy	Histopathological findings of biopsy	CKD (creatinine > 100 mmol/l after > 18 month of biopsy)	Treatment	Fetal outcome
1	Nephritic/nephrotic	22	No	DM nephropathy	No	Conservative treatment	Normal
2	Nephritic vs Pre-eclampsia	26	No	FSGS	Yes	Conservative treatment + Steroid	Normal
3	Nephritic /nephrotic	12	No	FCGS	Yes	Conservative treatment + Steroid	Normal
4	Unexplained renal failure	31	No	FSGS	Yes	Conservative treatment + Steroid	Normal
5	Nephrotic	10	No	FSGS	Yes	Conservative treatment + Steroid	Normal
6	Unexplained renal failure	32	No	Crescentic GN	Yes	Conservative treatment + Steroid	Normal
7	Nephritic/nephrotc	23	No	End-stage renal disease	Yes	Conservative treatment	Termination
8	Pre-eclampsia	15	No	Atypical HUS	Yes	conservative treatment	Termination
9	Nephrotic	6	No	MCD	No	Conservative treatment + Steroid	Normal
10	Nephritic/nephrotic	6	No	MCGN	Yes	Conservative treatment + Steroid	Termination
11	Nephrotic	6	No	MCGN	Yes	Conservative treatment + Steroid	Normal
12	HIV vs RPGN	6	No	MCGN	No	Conservative treatment + Steroid	Termination
13	Nephritic/nephrotic	11	No	MCGN	Yes	Conservative treatment + Steroid	Termination
14	Nephritic/nephrotic	8	No	MCGN	Yes	Conservative treatment + Steroid	Termination
15	Nephrotic/nephritic	5	No	Interstitial nephritis	Yes	Conservative treatment + Steroid	Normal
16	Nephrotic/nephritic	16	No	Membranous GN	Yes	Conservative treatment	Normal
17	Nephrotic	2	No	Membranous GN	No	Conservative treatment + Steroid	Normal
18	Nephritic	31	No	Pre-eclampsia	No	Conservative treatment	Premature
19	Nephrotic/nephritic	26	No	IGA nephropathy	No	Conservative treatment	Miscarriage
20	Nephrotic/nephritic	8	No	Lupus nephritis	Yes	Steroid + Cyclophosphamide	Termination
21	Nephritic/nephrotic	26	No	Immune complex deposit	No	Conservative treatment + Steroid	Premature

Abbreviations: CKD: Chronic Kidney Disease, RPGN: Rapidly progressive glomerulonephritis, DM: Diabetes Mellitus, FSGC: Focal segmental glomerulosclerosis, MCGN: Mesangio-capillary glomerulonephritis, HUS: Haemolytic uremic syndrome, MCD: Minimal change disease, IGA: Immunoglobulin A

a third of patients during the second trimester, and only three patients in the third trimester before 32 weeks. Day et al. considered performing renal biopsy in the first trimester in those with structurally normal kidneys and active urinary sediment, nephrotic syndrome, unexplained Chronic Kidney Disease (CKD), and those with evidence of renal impairment and proteinuria in the context of systemic disease or positive autoimmune serology.[16] He also suggested that pre-eclampsia and any physiological rise in proteinuria should be first excluded in the second trimester, and renal biopsy should be reserved for those with unexplained nephrotic range proteinuria, progressive CKD, and renal disease in the presence of active systemic disease.[17] Kuller et al. suggested performing a renal biopsy in pregnancy as late as 32 weeks if indicated[14] We feel a diagnosis at an early stage of pregnancy is of benefit to guide treatment and allow an informed discussion of the risk-to-benefit ratio of continuation of pregnancy. We remain concerned about the risk of complications in biopsies performed beyond 32 weeks gestation.

The complication rate of renal biopsy in a pregnant population is well described, ,albeit only in small studies. Initial reports of renal biopsy in pregnancy described a high complication rate, with Schewitz et al. describing gross haematuria in 16.7% and 4.4% developing peri-renal hematomas (as well as one maternal death in total, 90 patients had biopsied), compared to 6.2% gross haematuria and 0.9% per-renal hematoma in 450 female non-pregnant patients.[18] This high rate of complications is similar to a study conducted by Kuller et al., who studied 18 pregnant women. He found that seven had renal hematomas, and in two cases patients required blood transfusion.[14]

Other studies found that complications after renal biopsies appeared similar to those in non-pregnant patients. McCartney et al. had observed gross haematuria in only 3.5% of 400 renal biopsies from pregnant and puerperal patients.[19] Experiences from most other centers were similar to those of McCartney: despite earlier warnings, complications after renal biopsies appeared not different from those in non-pregnant patients.[12, 13] In our series of 21 biopsies, no patient experienced significant complications post-biopsy. A likely explanation would be advances in the biopsy technique under guided ultrasound and the use of smaller and technologically more advanced needles.

In our study, we have made a definitive diagnosis in all of our 21 pregnant women, five were diagnosed with mesangiocapillary glomerulonephritis, four with focal segment glomerulosclerosis, and two patients had membranous nephropathy. Only one case of each of the following conditions was observed: atypical hemolytic uremic syndrome (HUS), immune complex deposition, rapidly progressive glomerulonephritis (RPGN), minimal change disease, DM nephropathy, IGA nephropathy, lupus nephritis, interstitial nephritis, pre-eclampsia, and end-stage renal disease.

Histopathological results were useful in guiding patient management; patients with diabetic nephropathy, IGA nephropathy, or atypical HUS required only conservative treatment. While two patients with active nephritis and focal segment glomerulosclerosis required additional immunosuppression treatment. In eight patients with histological and biochemical evidence that pointed to progression in renal failure with the risk of the mother developing end stage kidney disease during pregnancy, termination of pregnancy was offered. Four of the five patients with mesangiocapillary glomerulonephritis chose termination of pregnancy. In addition, the patients with end-stage renal disease, atypical hemolytic uremic syndrome, and lupus nephritis also opted for termination of pregnancy. Of much importance during follow-up was the fact that at 18 months post-biopsy, two thirds of the patients had persistent established CKD.

CONCLUSIONS

In our limited experience, pregnancy per se did not increase the risks of renal biopsy. We can but speculate if this is due to technological advances in ultrasound imaging or improved biopsy needle quality over the years.

We consider it important to establish an appropriate histopathological diagnosis of renal disease in pregnant patients with overt nephrotic-range proteinuria once pre-eclampsia has been ruled out, as well as in patients with nephritis and progressive decline in renal function, and in those with acute unexplained renal failure, before 32 weeks gestation. The timing of the initiation of the appropriate treatment may well determine the outcome of renal disease in pregnancy. Different histological types of glomerular diseases have an entirely different treatment and prognosis regardless

of the impact of pregnancy and offer us good guidance in selecting the appropriate treatment. In addition, renal biopsy in early pregnancy provides baseline histology for comparison should deterioration in renal function occur later in pregnancy and offers the opportunity to counsel patients regarding the choice of termination of pregnancy if continuation may possibly lead to the progression to end stage kidney disease during the pregnancy.

On the other hand, the antenatal progress of women with mild or moderate proteinuria and/or asymptomatic microscopic haematuria who are normotensive and have well preserved renal function can be monitored frequently without intervention, and we suggest more extensive assessment of their disease deferred to the postpartum period if there is no progressive deterioration in renal function. Furthermore, we would not recommend the routine use of biopsy to distinguish between pre-eclampsia and primary renal disease, as it is usually possible clinically by observing the rate of progression of proteinuria and hypertension, which is typical.

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