Pregnancy in IgA Nephropathy: An Effect on Renal Outcome?

Chee Kay Cheung^{a, b} Jonathan Barratt^{a, b}

^aDepartment of Infection, Immunity and Inflammation, University of Leicester, Leicester, UK; ^bJohn Walls Renal Unit, University Hospitals of Leicester NHS Trust, Leicester, UK

With IgA nephropathy being the commonest primary glomerulonephritis worldwide and having a peak incidence between the 2nd and 3rd decades of life, pregnancy is a major concern for many with this condition [1]. The association between chronic kidney disease and a higher risk of adverse maternal and fetal outcomes, including pre-eclampsia, accelerated decline in renal function, intrauterine growth retardation, preterm delivery and fetal death, is well recognised [2]. What remains unclear is whether IgA nephropathy confers the same or its own disease-specific degree of risk compared to patients with equivalent levels of kidney function impairment due to other causes.

In this edition of the *American Journal of Nephrology*, Wang et al. [3] report a systematic review and meta-analysis of the renal and pregnancy outcomes of women with IgA nephropathy. They include 9 cohort or case-control studies, all requiring a control group consisting of non-pregnant patients with IgAN matched for age and renal function for inclusion. Importantly, 8 out of the 9 studies included were conducted in Asia (2 in China, 4 in Japan and 2 in South Korea), with the remaining study performed in Italy. In both the pregnancy and non-pregnancy groups, there were a total of 145 combined renal out-

come events (doubling of serum creatinine, 50% decline in eGFR or end-stage kidney disease) in the 1,198 patients studied. The main finding was that there was no significant difference between the 2 groups in combined renal outcome events (11.6% in the pregnant group and 12.5% in the non-pregnant group). Subgroup analyses demonstrated that there was no difference when the pregnancy and non-pregnancy groups were analysed according to the sample size of the study, length of follow-up, baseline age, serum creatinine or proteinuria, although the numbers studied in these groups were small and likely to be underpowered to detect any difference. During follow-up, no difference was found in the rate of change of eGFR between the 2 groups. Although higher rates of adverse pregnancy outcomes (preterm delivery, pre-eclampsia or low birth weight) were found in patients with IgAN who had impaired kidney function pre-pregnancy compared to the general Chinese population, these risks were lower in IgAN than those reported with CKD of other causes (including lupus nephritis or diabetic nephropathy).

The results of this study are consistent with existing data and provide reassurance that pregnancy does not appear to confer a specific risk for decline in renal function in IgAN with CKD stages 1–2 [4]. However, as with all

meta-analyses, the strength of these findings relies on the methodological quality of the studies included, which the authors rate as being very low. Four out of the 9 studies included fewer than 50 pregnancies. The earliest study was conducted in 1991, 27 years before the most recent included study. Standards of nephrology and obstetric care have changed significantly over this time period. Five out of 9 studies did not include complete basic demographic and clinical data at baseline, including age at pregnancy, proteinuria, serum creatinine or blood pressure. Out of the 543 pregnant patients with IgAN included in this meta-analysis, only 70 had an eGFR lower than 60 mL/min/1.73 m² at the start of their pregnancy, emphasising the need for more data in this group of patients (i.e., CKD stage 3 or lower) so that the risk in patients with IgAN with more impaired kidney function can be more accurately determined. Only 5 out of the 9 studies were prospective, 2 were retrospective and the nature of the remaining 2 could not be determined, raising concerns regarding potential reporting bias. The 9 studies were conducted in 4 different countries, each with different healthcare systems, screening policies (and therefore detection rates) for IgAN, and socio-economic factors, all of which could potentially confound the findings. Furthermore, IgAN is a highly heterogeneous disease being more common in Asia with a different gender distribution compared to the United States and Europe and a greater likelihood of progressing to end-stage kidney disease [5]. There is also growing evidence to suggest that the levels of IgA1 hinge-region glycosylation, believed to be a central pathogenic feature of this condition, are different in people from Asia compared to Caucasians. All of these

factors potentially limit the generalisability of the findings and grouping studies from heterogeneous populations together runs the risk of masking more subtle findings that may be present within individual groups.

The authors rightly emphasise that the link between CKD and poorer maternal and fetal outcomes is well described, and that using data derived from all causes of glomerular disease and indeed non-glomerular causes of CKD as the basis for pre-conception counselling in IgAN potentially overemphasises the maternal and fetal risks for women with IgAN. The risks in IgAN are certainly lower than in other glomerular diseases such as vasculitis and lupus nephritis, where the natural history of these diseases, and the requirement for immunosuppressive treatments to prevent relapse is very different [6]. What is needed going forward are data from large multi-centre prospective registry studies, with standardised baseline and outcome measures and robust follow-up, to provide high-quality data that will enable clinicians and patients to better discuss the impact of IgAN on the success of a pregnancy. Such studies are underway and include the CureGN study and the UK Rare Renal Diseases Registry [7, 8]. Both are already providing fascinating insights that should go some way to allowing us to accurately describe the natural history of pregnancy in IgAN.

Disclosure Statement

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References

- 1 Penfold RS, Prendecki M, McAdoo S, Tam FW: Primary IgA nephropathy: current challenges and future prospects. *Int J Nephrol Renovasc Dis* 2018;11:137–148.
- 2 Nevis IF, Reitsma A, Dominic A, McDonald S, Thabane L, Akl EA, Hladunewich M, Akbari A, Joseph G, Sia W, Iansavichus AV, Garg AX: Pregnancy outcomes in women with chronic kidney disease: a systematic review. *Clin J Am Soc Nephrol* 2011;6:2587–2598.
- 3 Wang F, Lu JD, Zhu Y, Wang TT, Xue J: Renal outcomes of pregnant patients with immunoglobulin A nephropathy: a systematic review and meta-analysis. *Am J Nephrol* 2019;49:214–224.
- 4 Su X, Lv J, Liu Y, Wang J, Ma X, Shi S, Liu L, Zhang H: Pregnancy and kidney outcomes in patients with IgA nephropathy: a cohort study. *Am J Kidney Dis* 2017;70:262–269.
- 5 Cheung CK, Barratt J: Is IgA nephropathy a single disease? Tomino Y, (ed): *Pathogenesis and treatment in IgA nephropathy: an international comparison*. Japan: Springer, 2016, pp 3–17.
- 6 Blom K, Odutayo A, Bramham K, Hladunewich MA: Pregnancy and glomerular disease: a systematic review of the literature with management guidelines. *Clin J Am Soc Nephrol* 2017;12:1862–1872.
- 7 Oliverio AL, Zee J, Mariani LH, Reynolds ML, O'Shaughnessy M, Hendren EM, Alachkar N, Herreshoff E, Rizk DV, Nester CM, Steinke J, Twombly KE, Hladunewich MA: Renal complications in pregnancy preceding glomerulonephropathy diagnosis. *KI Reports*, In Press.
- 8 Selvaskandan H, Dillon M, Barratt J: IgA nephropathy: driving innovation with a rare renal disease registry. *J Kidney Care* 2017;2: 205–211.