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Maternal-foetal outcomes in pregnant women with glomerulonephritides. Are all glomerulonephritides alike in pregnancy?

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ABSTRACT

In spite of the interest for chronic renal diseases (CKD) in pregnancy data on specific diseases is fragmentary; while recent studies analysed the most common glomerulonephritides (GN), none was addressed at GN as a group. The aim of our study was to analyse the main pregnancy-related outcomes in GN patients in a large multicentre cohort.

Patients with a diagnosis of GN were selected from the TOCOS cohort (TOCOS: TOrino Cagliari Observational Study): out of 714 singleton deliveries GN was the diagnosis in 126; lupus GN and IgA nephropathy accounted for 37 and 33 cases; 1418 low-risk singleton deliveries followed-up in the same Centers served as controls (non diabetic, non nephropathic, non obese women, without any other known chronic illness; pregnancies after ovodonation or in vitro fertilisation were excluded, if declared). Multiple regression analysis considered: pre-term (<37 weeks), early preterm delivery (<34 weeks), small for gestational age baby (SGA) and the development of hypertension, proteinuria and preeclampsia (PE) limiting this outcome to the cases without hypertension and proteinuria at baseline.

The population consisted mainly of early CKD stages (stage 1: 61.9%; hypertension 27.8%; proteinuria <0.5 g/day: 55.7%). Age and parity were not different in cases and low-risk controls (age: 31.20 ± 5.5 vs 31.24 ± 5.5 years, primiparous 56.3% vs 57.5%). The incidence of preterm and early preterm delivery was higher in GN versus controls and increased commensurately with CKD stage. In the multivariate analysis, CKD stage was significantly associated with early preterm delivery and development-doubling of proteinuria (odds ratio (OR) around 3 in both), while the OR for baseline hypertension did not reach statistical significance. While the risk pattern did not differ in lupus and non-lupus GN, a significantly higher OR of PE was observed in IgA nephropathy (OR 28.09 versus other GN); risk for pre-term delivery was not increased (OR 0.27 (0.06–1.11)), thereby suggesting "late-maternal" PE.

In conclusion, within the limits of heterogeneity and small numbers, our analysis identifies proteinuria as the most reliable risk marker for adverse pregnancy outcomes and suggests a specific association between IgA nephropathy and late-maternal PE.

1. Introduction

Growing attention to the complex interactions between chronic renal diseases (CKD) and pregnancy have led to an increased number of studies of pregnancy-related outcomes in various stages of CKD, as well as studies of renal replacement therapy [1–3].

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There is now widespread agreement on the following points: the incidence of adverse pregnancy outcomes increases across CKD stages, but successful pregnancy is possible in patients on dialysis, provided that a high dialysis dose is delivered; the presence of proteinuria and hypertension at baseline are major modulators of the outcomes; there is no increase in malformations in CKD patients, and the risks for neonates are mainly linked to preterm and, especially, early preterm delivery [4–9].

Of the glomerular diseases (GN), Lupus nephropathy and IgA nephropathy, which occur more frequently, have been the most studied [10–17]. Less is known however about the differences in outcomes between the various GN, and with respect to the overall population, an issue that is potentially of great importance as this information is needed to tailor clinical practice and optimize resources.

Lupus nephropathy and IgA nephropathy theoretically represent the two extremes of the severity spectrum of GN in pregnancy. However, several points still need to be clarified, among them, the differences and similarities with other GN which occur less frequently and for this reason have seldom been studied [18–23].

We wished therefore to gather and study data that would enable us to further clarify these issues, and undertook an analysis based on the TOCOS cohort, a large multicentre database, presently encompassing 1019 pregnancies prospectively observed since 2000, with 714 singleton deliveries, 126 of which in women with different forms of GN. The analysis was focused on these cases, with particular attention to the two most common diagnoses: IgA nephropathy and lupus nephropathy, with the related antiphospholipid syndrome [9,24]. The data will also be discussed in relation to the statistics on 1418 low-risk control singleton deliveries followed-up in the same Centers in the same period (non diabetic, non nephropathic, non obese women, without any other known chronic illness; pregnancies after ovodonation or in vitro fertilisation were excluded, if declared).

2. Methods

2.1. Study settings and inclusion criteria

The study analysed data related to all patients with glomerular nephropathies included in the TOCOS database (Torino Cagliari Observational Study). This prospective database includes all pregnant patients diagnosed with CKD before or during pregnancy who were referred to one of the two largest units specializing in the care of pregnant CKD patients in Italy: the Maternal-Foetal Unit of the University Hospital Sant'Anna, Cittá della Salute e della Scienza, Turin, Italy and to the Nephrology Unit of Ospedale Brotzu, Cagliari, Italy.

Both these units have gathered data since January 1, 2000, and in both centers the database was updated until June 2016. At the last update, 1019 pregnancies were included; not considering 40 twin or multiple pregnancies, 63 early pregnancy losses (<24 weeks), 9 intrauterine deaths, 76 on-going pregnancies, 34 pregnancies lost to follow-up and 77 women with an initial diagnosis of preeclampsia, the final selection employed for the analysis consisted in 714 singleton deliveries of live babies. Furthermore, the database includes an additional 1418 low-risk pregnancies gathered in the same setting, to allow for contextualization of results. For more specific characteristics and definitions, we refer readers to earlier studies [9,24].

The choice of considering the outcomes of pregnancy focusing on live-born babies is motivated by the specific referral pattern: in fact, at difference with studies in which the patient population is made up of cases that were known before pregnancy, as in series coming from Nephrology or Immunology Units, the population analysed was referred to our units dedicated to kidney diseases in pregnancy by different sources. Three situations were possible: part of the cases were diagnosed during pregnancy as affected by a glomerular nephropathy; part of the cases did not have a regular nephrology follow-up, either because of clinical remission, or other reasons; the remaining patients were followed in different Nephrology or Immunology Centers and were addressed at different gestational ages to the units in which the study was conducted. Therefore, due to the heterogeneity of the referral pattern, miscarriages, in particular the early ones, could have easily been missed, and were not analysed to avoid introducing a referral bias.

The overall group of glomerular diseases consisted of 145 pregnancies: 126 singleton deliveries were selected for the study after the exclusion of 2 twin births, 4 spontaneous abortions, 5 terminations of pregnancy due to maternal or foetal pathology and 8 ongoing pregnancies. The IgA nephropathy group consisted of 39 pregnancies: 33 singleton deliveries were selected, excluding 1 twin birth, 1 spontaneous abortion, 1 termination of pregnancy due to maternal pathology and 3 ongoing pregnancies.

Lupus nephropathy, which was considered together with the related antiphospholipid syndrome, was the underlying disease in 44 pregnancies: 37 singleton deliveries were selected for the study after the exclusion of 4 miscarriages and 3 ongoing pregnancies.

The most frequent diagnoses, beside IgA and SLE were focal segmental glomerulosclerosis (12 cases); membranous nephropathy: (9 cases); minimal change nephropathy (6 cases). No bioptic diagnosis was available in 23 cases; in 3 the diagnosis was Alport syndrome, while in 6 systemic lupus erthematosus or a collagen disease were present, but a kidney biopsy had not been performed; in 14 a kidney biopsy was planned (7 planned; the biopsy was not performed in 7 because the patient withheld consent). In the absence of a kidney biopsy, the clinical diagnosis of glomerular disease was based on the usual clinical pattern (characterised by proteinuria and/or haematuria unexplained by other renal diseases).

2.2. Definitions employed: CKD stages

CKD was classified according to K-DOQI guidelines. GFR calculation was based on preconception data (CKD-EPI formula), when available within 6 months prior to conception. When preconception data were not available, data at first control in pregnancy were used. In the absence of a validated formula to assess kidney function in pregnancy, the CKD-EPI formula was chosen also in these cases because of its wide use, and in line with previous studies of our group. While we are aware of the fact that this choice possibly leads to underestimation of the severity of the disease, given the physiological decrease of serum creatinine during pregnancy, elsewhere described in detail, such a compromise between a simple and a precise staging was unavoidable due to the frequent diagnosis only in pregnancy or to late referral in particular in patients in remission [9,24].

Proteinuria was assessed on 24-h urine collection; clinical controls followed the usual strict policy followed in our Country [25].

2.3. Obstetric definitions

Hypertension was defined as systolic blood pressure $\geq$140 and/or diastolic blood pressure $\geq$90, or antihypertensive therapy; patients on antihypertensive therapy prior to conception were included even when antihypertensive therapy was discontinued in pregnancy, with the exception of cases in which ACE inhibitors were prescribed only for the control of proteinuria.