A Systematic Review on Materno-Foetal Outcomes in Pregnant Women with IgA Nephropathy: A Case of “Late-Maternal” Preeclampsia?

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Abstract: Background: IgA nephropathy is the most common primary glomerulonephritis in pregnancy and shares with other immunologic diseases and kidney diseases a relationship with adverse maternal outcomes, whose entity and pattern is only partially quantified. Recent studies provide new information and a systematic review regarded progression of kidney disease. The discussion of the outcomes with respect to low-risk pregnancies may help to perfect the estimation of the risks, and to identify specific research needs. Methods: A search strategy was built on Medline, EMBASE and the Cochrane review for the period January 2000–April 2017, aimed at retrieving both case series (defined as with at least 6 pregnancies in women with IgA nephropathy) and case reports, to look into rare occurrences. All papers, with or without control groups, were selected if they reported on at least one pregnancy outcome, or on long-term kidney function. Search strategy, paper selection and data extraction were done in duplicate (PROSPERO N 42016042623). Meta-analysis of case series was performed with Metanalyst Beta 3.13. Case reports were analysed narratively. Results: The search retrieved 556 papers, of which 27 were included (13 series and 14 case-reports). The case series report on 581 women with 729 pregnancies. The analysis was performed in comparison to the available control groups: 562 non-pregnant controls were available for the analysis of progression of kidney disease. As for pregnancy related outcomes (preeclampsia (PE), pregnancy induced hypertension (PIH), preterm birth, small babies), we meta-analyzed the data with respect to the only series of low-risk pregnancies (1418 pregnancies). When compared with women who never got pregnant after diagnosis of IgA nephropathy, in the present meta-analysis pregnancy in women with IgA nephropathy was not associated with a higher risk of progression of kidney disease, possibly due to the overall preserved kidney function at baseline: end-stage kidney disease (OR 0.68; CI 0.28–1.65). Conversely, the incidence of adverse pregnancy-related outcomes was increased compared to low-risk controls: PE and PIH were more than ten-fold increased (OR 11.80; CI 7.53–18.48 and OR 10.39; CI 5.45–19.80), while the increase in risk of preterm birth and “low birth weight babies” was less marked (OR 3.37; CI 1.91–5.95 and OR 2.36; CI 1.52–3.66), a discrepancy suggesting the occurrence of “late” or “maternal” PE, that may affect less severely foetal growth or shorten gestation. In conclusion, in the present meta-analysis IgA nephropathy was not associated with an increased progression of kidney disease. The more than ten-fold increased risk of PIH and PE, in combination with a doubled
risk of small babies, suggests the occurrence of “late” or “maternal” PE, usually less affecting early foetal growth. This finding may be of help in defining control policies, while further research is needed to guide clinical management.

**Keywords:** IgA nephropathy; pregnancy; preeclampsia; proteinuria; preterm delivery; systematic review

1. Introduction

IgA nephropathy is probably the most common primary glomerular nephritis worldwide; its higher incidence in young people makes it highly relevant in pregnancy [1].

The present term of IgA nephropathy encompasses two previously defined diseases, usually known by their eponyms: Berger’s disease, in which the IgA deposition is limited to the kidney, and Henoch-Shönlein, in which IgA nephropathy is a part of a systemic vasculitis that could involve the skin and the gastro-intestinal tract, with asymmetric acute osteoarthritis [2,3]. The recognition of family clustering of the two diseases, and the identical renal pathology led to gather both diseases under a unifying definition [4–6]. IgA nephropathy may present with a wide spectrum of clinical presentations, from mild, recurrent and remittent microhematuria to boosts of macrohematuria and nephritic syndrome, or a severe and rapidly progressive disease [1,4,7,8]. Hypertension and proteinuria are considered as negative outcome predictors, even if only mild. Their negative effect on outcome is observed even in the absence of reduced renal function, which is a likewise (albeit tautological) acknowledged progression marker itself. Other histological markers of disease progression and risk are still subject of debate [7–14]. The risk of progression to end stage renal disease (ESRD) has been differently evaluated. However, this risk is not negligible over the entire life span as progression to ERSD is reported from rare to frequent, depending on morphological, clinical and laboratory characteristics, and treatment. For these reasons, IgA nephropathy is usually considered as a disease that may remit, but that is never completely cured [14–18].

The acknowledgement of the importance of early renal disease in pregnancy is particularly relevant for IgA nephropathy, due to its relatively high prevalence in young age, slow progression, with frequent preservation of the kidney function at least for long periods, making normal kidney function common in affected patients in childbearing age, and heterogeneous presentation, that may impair early diagnosis [19–22].

As will be further discussed in detail, a systematic review, encompassing a wide time span, was recently focused on the progression of chronic kidney disease in patients with IgA nephropathy who had been pregnant [23]. To try to further add to the knowledge in this important field, we considered several recent publications, not available at the time of the first review, and we focused a second systematic review on the effect of IgA nephropathy on pregnancy and of pregnancy on the progression of IgA nephropathy, on the new millennium, on the account of the changes in disease management and maternofetal care occurring over time, and we attempted for the first time a meta-analytical comparison with a low-risk population, in order to better quantify the risk of the various adverse pregnancy outcomes, as a further support for counseling.

2. Methods

2.1. Eligibility Criteria

The eligibility criteria were broad, because of the expected retrieval of heterogeneous designs and definitions. Consequently, we included all published studies that dealt with IgA nephropathy in pregnancy and that reported on at least one pregnancy-related outcome, or on long-term kidney function. We included all study designs, i.e., prospective or retrospective cohort studies, case-control studies, trial-based analyses, and case reports. Reviews, whether or not systematic, were also gathered.
to check for papers eventually escaped from our wide search strategy. The search was not limited to papers which provided a control group, but information on all control groups were gathered.

Studies were divided into those regarding more than 5 or less than 6 cases (defined as case series and cases reports, respectively).

The review was prospectively registered on PROSPERO International prospective register of systematic reviews (N 42016042623).

The review was performed according to the Meta-analysis of observational studies in epidemiology (MOOSE) criteria.

2.2. Search Strategy

We searched MEDLINE, PubMed, Embase and the Cochrane Review database from January 2000 to April 30th 2017 using a combination of MeSH terms and keywords related to IgA nephropathy and pregnancy, including: pregnancy, pregnant, gestation* and IgA nephropathy, Henoch* or Shoenlein*, Berger*. We also checked the reference lists of relevant articles and citations of included studies.

We did not limit our search to any language, but we limited it to the period starting from 2000, allowing for the considerable changes in management of the disease and in maternofetal follow-up that occurred in the new millennium, in order to implement the clinical decision rules presently recommended by the very few guidelines or consensus statements dealing with glomerular diseases in pregnancy [24–26].

All articles identified were screened for eligibility on the basis of the content only: all papers reporting on any form of IgA nephropathy in pregnancy and reporting on any outcome were selected. The search was performed by G.B.P. and I.A.K., after which I.A.K. and R.A. did a first screening of the papers. The final selection was agreed between G.B.P. and I.A.K., any discrepancy was resolved by discussion.

2.3. Data Extraction and Quality Assessment

Two reviewers (I.A.K. and G.B.P.) extracted study and population characteristics and outcomes. A third reviewer (G.C.) double-checked the accuracy of data entered from each study in case of discrepancies. All definitions of IgA nephropathy, pre-eclampsia (PE), pregnancy induced hypertension (PIH), small babies, small for gestational age babies (SGA) or other pregnancy related outcomes were gathered.

Due to the lack of randomized controlled trials (RCTs), and to the limited number and type of control groups, no formal analysis of risk of bias was performed. No selection for quality was performed. However, the studies were critically analyzed and the completeness of the data was considered as an indirect marker of quality.

The case series were compared with the controls available, regarding progression of chronic kidney disease (CKD), and with the only low risk population available, regarding the various pregnancy outcomes. Odds ratios and confidence intervals were calculated (OR, CI). The case reports were described narratively.

2.4. Data Synthesis

The PICOS criteria were adapted to this particular situation in which pregnancy is considered the “intervention” as follows:

- **P**—Patients: women with IgA nephropathy in pregnancy;
- **I**—Intervention: in the absence of a true “intervention”, pregnancy was considered as the “intervention”;
- **C**—Comparators: in the case of progression of kidney disease, non-pregnant IgA patients were considered as comparators. In the case of pregnancy outcomes, considered low-risk pregnancies or pregnancies in women not affected by IgA nephropathy (or other kidney diseases);
O—Outcomes: progression of kidney disease; all the materno-fetal outcomes described in the papers (including, but not limited to, PE, PIH, preterm delivery, small babies, SGA).

S—Studies: all studies, regardless of the study design, reporting on pregnancy outcomes or on long-term kidney function in patients with IgA nephropathy.

Statistical analysis was performed using Metanalyst Beta 3.13. Due to the high baseline heterogeneity a random effect model was employed.

Stratification for baseline renal function, hypertension and proteinuria was attempted, but was not possible due to the high heterogeneity of the papers.

The control groups retrieved mainly regarded progression of kidney disease in women with IgA nephropathy who did not get pregnant after diagnosis; these data were used to analyze the effect of pregnancy on kidney function.

For pregnancy-related outcomes, we employed as a control group the only low-risk population available (from the cohort named TOCOS from the Torino Cagliari Observational Study) and meta-analyzed each study with respect to it.

3. Results

3.1. Case Series: Overall Data

The search strategy identified 556 articles, of which 27 met the inclusion criteria: 13 case series, which we attempted to meta-analyze, for the various outcomes, and 14 case reports, discussed narratively (Figure 1) [27–53].

Figure 1. The flow-chart of the retrieved papers.

### Pregnancy in IgA Nephropathy: case series and case reports

- **Records identified through Medline** (n = 343)
- **Records identified through LIRBASE** (n = 211)
- **Records screened** (n = 556)
- **Records excluded** (n = 526)
- **Full-text articles or abstracts only assessed for eligibility** (n = 33)
- **Full-text articles excluded** (n = 46) (abstracts not specified for type of gestational disease = 2, hence included papers without renal measurement = 1, other outcomes = 1)
- **Studies included in qualitative synthesis** (n = 21 + 6 Abstracts only*): Case series = 13 Case reports = 14
- **Studies included in quantitative synthesis** (meta-analysis) (n = 12)

* In 4 cases only the abstract was available (congress proceedings), and in 2 the paper was not retrieved. In all cases the authors and publishers were contacted to obtain further data.
The main characteristics of the case series are reported in Tables 1–4 [27–39].

Overall, the case series included four prospective studies, eight retrospective studies and two matched cohort studies, the latter regarding progression of CKD in women affected by IgA nephropathy, with or without pregnancy (Table 1). Globally, the studies report on 581 women with 729 pregnancies in IgA nephropathy (assuming one pregnancy per woman if not otherwise specified), and on 562 non-pregnant controls distributed over three studies; conversely, normal pregnancies were available in only one study [30].

The studies are heterogeneous for the number of pregnancies (12 to 229), setting of study (seven from Asia, five from Europe, one from the USA and one from Saudi Arabia), and study aims. Six studies provided information on the type and frequency of control policies in pregnancy and during follow-up (Table 2).

3.2. Case Series: Pregnancy Outcomes

Table 3 reports on the main pregnancy-related outcomes reported in the papers. Given the different study designs, the included studies reported on different outcomes: neonatal deaths were reported on by 4 studies, live births were reported on by 8 studies, preterm delivery was reported by 8, and need for admission to neonatal intensive care unit by one study only. All studies reported on preeclampsia (PE) and/or hypertensive disorders of pregnancy. Information on birth weight was available in most studies, but the information was not always contextualized to gestational age, and the information on neonates small for gestational age was available in two studies only.

Overall, the papers describe a population with high incidence of PIH (reported in around 30% of the cases, however, the distinction with preexisting hypertension is usually lacking, and this leads to a possible underestimation of new onset hypertension) and PE (reported in around 15% of the cases), with about 15% incidence of preterm deliveries, usually without exhaustive specification of gestational age (Table 3).

Table 4 reports on baseline kidney function and other maternal outcomes: baseline kidney function (glomerular filtration rate: GFR) was relatively well preserved in most studies but was fully normal in 2 only (GFR was >100 mL/min in 2 studies and <100 mL/min in 7 studies). Mean proteinuria was around 1 g/day. Prevalence of hypertension was not clearly defined at baseline, and the distinction between previous use of angiotensin converting enzyme-inhibitors (ACEi) or Angiotensin II receptor blockers (ARBs) for proteinuria, hypertension or both was not available.

Four of five studies reporting on kidney function over time did not find any difference between cases and non-pregnant controls during follow-up, considering however different outcomes (start of dialysis, doubling of serum creatinine, GFR decrease, new-onset hypertension); the fifth, most recent study, found a correlation between kidney function worsening and the occurrence of adverse pregnancy outcomes [27] (Table 4).

3.3. Case Reports

The main characteristics of the case reports are summarized in Tables 5–7 [40–53].

Keeping in mind the aim to discuss severe or unusual situations, the cases reported on various situations, including new onset-diagnosis of IgA nephropathy in pregnancy, recurrence of IgA nephropathy in a kidney allograft, severe reduction of the kidney function (5 cases); one case reported on three pregnancies in the same woman (one occurring in the pre-dialysis phase, two on dialysis) (Table 5).

Presumably as a consequence of the different selection of the cases compared to that of the series, most of the babies were born preterm (61.5%); maternal complications were common (30%) and more than half of the newborns had low birth weight. Nevertheless, all reported babies had a favorable outcome. Conversely, dialysis was needed in pregnancy in three cases and half of the patients developed hypertension or preeclampsia.
Table 1. IgA nephropathy: Main characteristics of the case series (at least 6 pregnancies).

| Author | Year [Ref] | Years | Country | Study | Objective, as Stated in the Study | Pregnancies (P) | Women (W) |
|--------|------------|-------|---------|-------|----------------------------------|----------------|-----------|
| Park   | 2017 [27]  | 1979–2015 | Korea | Ret   | To assess the relationship between pregnancy and renal prognosis in women with IgAN and to investigate further whether obstetric complications are associated with renal prognosis | 59 W 64 P | 59 W controls (non-pregnant IgA) |
| O'Shaughnessy | 2017 [28] | 1996–2015 | USA | Ret   | To investigate the influence of glomerular disease subtype on pregnancy outcomes | 17 W 18 P | |
| Su     | 2017 [29]  | 2003–2014 | China | Pro   | To assess the effects of pregnancy on kidney disease progression and risk factors for adverse pregnancy outcomes in patients with IgAN | 104 W 116 P 309 W controls (non-pregnant IgA) | |
| Tocos  | 2017 [30]  | 2000–2016 | Italy | Pro   | To evaluate the maternofetal outcomes in different glomerulonephritides | 27 W § 33 P | 1418 P controls (low risk) |
| Liu    | 2014 [31]  | 2003–2012 | China | Matched-cohort | To evaluate the safety of pregnancy in women with IgAN, as well as their risk factors for adverse pregnancy outcomes, as compared to non-pregnant women with IgAN | 62 W 69 P | 62 W controls (non-pregnant IgA) |
| Oh     | 2011 [32]  | 2004–2009 | Korea | Ret   | To investigate whether higher proteinuria at conception predicts a faster decline in maternal renal outcomes and to identify whether proteinuria reduction prior to pregnancy attenuates the deterioration of postnatal maternal outcomes | 52 W | |
| Suetsugu | 2011 (**) [33] | NR | Japan | Ret | To explore the clinical characteristics of predictive factors for hypertension in biopsy-proven IgA nephropathy patients with superimposed preeclampsia | 34 W | |
| Shimizu| 2010 [34]  | 1995–2006 | Japan | Pro   | To evaluate the impact of the CKD staging in patients with IgAN on pregnancy and delivery | 29 W 29 P 45 W controls (non-pregnant IgA) | |
| Waness| 2010 [35]  | 2000–2006 | Saudi Arabia | Pro | To examine the natural history of pregnancies and their impact on renal function in Saudi females affected by IgAN | 12 W 12 P | |
| Limardo| 2010 [36]  | 1974–2003 | Italy | Ret multicenter cohort | To compare the long-term outcome of kidney disease in women with IgAN and preserved kidney function (sCr <1.2 mg/dL) who did and did not become pregnant. Data on 10 pregnant and 12 non pregnant women with sCr >1.2 mg/dL also gathered | 136 W 229 P 87 W controls (non-pregnant IgA) | |
| Donggyu| 2010 (*) [37] | 1987–2008 | Korea | Ret | To clarify the influence of pregnancy on the natural course of IgAN | 25 W 28 P | |
| Ronkainen | 2006 [38] | NR | Finland | Ret | To evaluate renal survival, morbidity, pregnancy complications and factors predicting outcome after childhood IgAN | 10 W 22 P | |
| Ronkainen | 2002 [39] | NR | Finland | Ret | To assess long-term outcome of children with renal involvement at onset of Henoch-Schönlein purpura by comparison with those who have mainly extra-renal symptoms at referral | 14 W 23 P | |

Overall number of women, pregnancies and controls: 581 W 729 P § 562 non pregnant IgA controls 1418 low risk controls

CKD: chronic kidney disease; IgAN: IgA nephropathy; NR: not reported; P: pregnancy; Pro: prospective; Ret: retrospective; sCr: serum creatinine; W: woman. * Abstract only (congress proceeding); (**) paper in Japanese, abstract used. § not mentioned in article, additional information available in original database §§ if number of pregnancies not specified, we assumed 1 pregnancy per woman.
| Author Year [Ref] | Control Policies |
|-------------------|-----------------|
| Su 2017 [29]     | Follow up at least once a month before delivery, and every 1–6 months after delivery, with minimum follow up 12 months postpartum or until dialysis treatment |
| Tocos 2017 [30]  | Follow up at least once monthly if proteinuria, hypertension or kidney function reduction |
| Liu 2014 [31]    | Follow up every ≤1 month; eGFR decline; determination time-averaged MAP and proteinuria every 3 months |
| Shimizu 2010 [34]| BP, proteinuria, blood analysis and eGFR at the baseline at the time of detection of pregnancy; at 16, 22 and 30 weeks of pregnancy; at the time of delivery; and at 3 months and 1, 2 and 3 years after delivery |
| Waness 2010 [35] | Monthly measures of BP, 24 h proteinuria, sCr, CCr; close monitoring and follow up |
| Limardo 2010 [36]| Information gathered at time of biopsy and every 5 year thereafter: Ccr, 24 h proteinuria, body weight, BP, therapy with ACEIs/ARBs or immunosuppressants |
| Donggyu 2010 (*) [37]| sCr followed up max 3 years after delivery |

ACEI: ACE-inhibitor; ARB: angiotensin II-receptor blocker; BP: blood pressure; CCr: creatinine clearance; eGFR: estimated glomerular filtration rate, assessed by MDRD or EPI formula; IgAN: IgA nephropathy; MAP: mean arterial pressure; NR: not reported; sCr: serum creatinine; * Abstract only.

Table 3. IgA Nephropathy: Fetal and pregnancy outcomes in the case series.

| Author Year [Ref] | All Cases Considered | Live Births Only | All Cases | All Cases, or As Stated |
|-------------------|----------------------|------------------|-----------|------------------------|
|                   | P | Abort. Spont. Induced | Still Birth | Live Birth | Neo. Death | Preterm <37 weeks | Early <34 weeks | NICU | PE-HT | Other |
| Park 2017 [27]    | 64 | NR | NR | NR | NR | Preterm: 21 (33%) | Early: 8 (13%) | NR | PE: 13 (20%) | LBW <2500 g: 16 (25%) |
|                   |   |   |   |   |   | LLB: 1500 g: 6 (9%) | SGA <10th: 6 (9%) |   |   |   |
| O'Shaughnessy 2017 [28] | 18 | NA | 0 | 18 (100%) | 2 (11%) | Preterm <37 w: 6 (33%), 5/6 induced/CS on maternal indication | Preterm <32 w: 4 (22%) | NR | PE: 6 (33%) | Median GA: 37.5 week (36–39) |
|                   |   |   |   |   |   | LLB: 2627 g (2136–3315) | IUGR <10th: 2 (11%) |   |   | IUGR<Ind: 0 |
|                   |   |   |   |   |   | Median: 0 | Apgar 1 min: 8 (7–9) |   |   | Apgar 5 min: 9 (8–9) |
| Su 2017 [29]      | 116 | 5 (4%) spont 2 (2%) induc | 18 (16%) | 90 (78%) | 1 (1%) | Preterm: 13 (11%) | NR | GHT: 26/89 (29%) | Severe PE: 12 (10%) | Ptu >3.5 g/day: 19/110 (17%) | CS: 62 (53%) |
|                   |   |   |   |   |   |        | Mean GA: 37.8 week ± 2.4 | Mean BW: 3035 g ± 665 |   |   | Mean BW: 2500 g: 16 (17%) |
|                   |   |   |   |   |   |        | LBW <2500 g: 3 (3%) |   |   | LBW <1500 g: 3 (3%) |
Table 3. Cont.

| Author Year [Ref] | All Cases Considered | Live Births Only | All Cases | All Cases, or As Stated |
|------------------|----------------------|------------------|------------|------------------------|
|                  | P Abort. Spont. Induced | Still Birth | Live Birth | Neo. Death | Preterm <37 weeks Early <34 weeks Extreme <28 weeks | NICU | PE-HT | Other |
| Toces 2017 [30]  | 33 cases NA NA | NA | 33 (100%) | NR | Preterm: 12 (36%) Early: 4 (12%)** Extreme: 1 (3%)** | NR | GHT: 7/24 (29%)*** PE: 4/17 (24%)*** | CS: 9 (27%) LBW: 10 (30%) SGA <10th: 4 (12%)** SGA <5th: 1 (3%)** |
|                  | 1418 controls NA NA | NA | 1418 (100%) | NR | Preterm: 99 (6%) Early: 13 (1%) Extreme: 2 (0.1%) | NR | HT: 66 (5%) PE: 25 (2%) PIU: 25 (2%) | CS: 379 (27%) GA: 39 weeks (25–42) BW: 3232 ± 476 g SGA <10th: 120 (8%) SGA <5th: 45 (3%) |
| Liu 2014 [31]    | 69 8 (12%)§ | 2 (3%) | 59 (86%) | NR | Preterm: 7 (10%) | NR | Severe PE: 6 W (10%) | CS: 42 (67%) LBW: 8/59 (14%) Mean BW: 2972 ± 654 g |
| Oh 2011 [32]     | 52 ‡‡ | NR | NR | NR | Preterm: 8 (15.4%) | 4 (7.7%) | HT: <8 weeks 31 (60%) | CS: 24 (46.2%) LBW 13 (25%) |
| Suetsugu 2011 (**[33]) | 34 NR | NR | NR | NR | 1 (3%) | NR | Superimp. PE: 13 (38.2%) | BW negatively correlated with glomerular sclerosis, sCr and BUN. |
| Shimizu 2010 [34] | 29 0 0 | 29 (100%) | 0 | 0 | Gestation 38.0 ± 2 weeks | NR | No PE | CS: 5 (17.2%) BW: 2911.2 ± 138.7 g LBW: 0 |
| Waness 2010 [35] | 12 0 0 | 12 (100%) | NR | 0 | | NR | HT: 12 (100%) PE: 3 (25%) HELLP: 1 (8.3%) | CS: 2 (HELLP and PE) BW: 3.1 kg LBW: 6 Apgar normal (1’ and 5’) |
| Limardo 2010 [36] | 229 15 spont 13 indu | 5 (2.2%) | 195 (85%) | 1 (0.4%) | Preterm: 20 (10%) | NR | HT: 43/201 (21%) PE: 17 W (13%) | Mean BW: 3039 ± 610 g LBW: 22/195 (11%) |
| Donggyu 2010 (*) [37] | 28 NR | NR | NR | NR | NR | NR | PE: 4 W (of 5 with sCr >2.0 mg/dL) | NR |
| Ronkainen 2006 [38] | 22 At least 2 spont | NR | 20 | NR | Preterm: at least 6 (30%) Extreme: at least 2 (10%) | NR | HT: 10 (46%) Severe PE: 1 W (10%) PIU: 12 (55%) | 6 (30%) of 20 live born infants from mothers with HT and/or proteinuria premature |
| Ronkainen 2002 [39] | 23 NR | NR | NR | NR | NR | NR | HT and/or PIU: 16 (70%) | NR |
| Summary data     | 729 45/685 (9.3%) | 25/473 (5.3%) | 456/528 (86.3%) | 5/426 (1.2%) | Preterm 95/608 (15.6%) Early: 18/135 (13.3%) Extreme: 3/33 (9.1%) | 4/52 (7.7%) | PIH: 98/348 (28.2%) PE: 79/523 (15.1%) | CS: 144/311 (46.3%) LBW: 85/5920 (6.6%) IUGR/SGA <10th: 12/115 (10.4%) |

*abort: abortions (<24 gestational weeks); W: women; BUN: blood urea nitrogen; BW: birth weight; CS: caesarean section; m: months; NR not reported; HELLP: hemolysis, elevated liver enzymes, low platelets syndrome; HT: hypertension; LBW: low birth weight (<2500 g); NA: not applicable, only included births >20 weeks or only live births; NICU: neonatal intensive care unit; NR: not reported; PE: preeclampsia; P: pregnancies; PIU: proteinuria; sCr: serum creatinine; * Abstract only (**) paper in Japanese, abstract used, † data on 86/116 pregnancies, †† not mentioned in article, additional information available in original database, ††† calculated in W without baseline hypertension and/or proteinuria, § spontaneous abortion: 1 (2%); induced abortion: 1 (2%); embryo damage 3 (4%); fetal malformation 3 (4%), §§ 14 abortions in 80 women, not included in final analyses of the study. Note: if not otherwise clarified, numbers of cases with hypertension, PE and/or PIU were counted separately.
Table 4. IgA Nephropathy. Kidney function and other maternal outcomes in the case series reporting on them.

| Author Year [Ref] | Age (years) | Kidney Function at Baseline | Other Maternal Outcomes and Main Results |
|-------------------|-------------|-----------------------------|-----------------------------------------|
| Park 2017 [27]    | 28 (24–31) (cases) | eGFR: 80.0 (61.0–105.6) | Renal survival rate with gestational complications: 55.3% at 10 y; 46.1% at 20 years |
|                   |             | sCr: 0.90 mg/dL (0.70–1.00) | Renal survival rate without gestational complications: 97.3% at 10 y; 97.3% at 20 years |
|                   |             | PU: 1.09 g/day (0.46–2.02) | Obstetric complications (PE, LBW and/or preterm birth), not pregnancy itself, associated with CKD progress, especially if eGFR <60, preexisting HT and PU >1 g/day (all significant) |
|                   |             | HT: 36 (61%) | |
|                   | 26 (23–32) (controls) | eGFR: 85.0 (64.7–102.0) | Renal survival rate: 80.3% at 10 years, 70.4% at 20 years |
|                   |             | sCr: 0.80 mg/dL (0.70–1.00) | |
|                   |             | PU: 0.87 g/day (0.43–1.60) | |
|                   |             | HT: 33 (56%) | |
| O'Shaughnessy 2017 [28] | 31.3 (23.0–33.8) | eGFR: 72 (61–90) (9/18 P) | ≥200% increase PU (2–12 m postpartum): 2/6 (33.3%) |
|                   |             | sCr: 1.0 mg/dL (0.8–1.2) (9/18 P) | ≥150% increase sCr (2–12 m postpartum): 1/8 (12.5%) |
|                   |             | PUU spot: 1.3 g (0.9–4.1) (8/18 P) | ESRD 1 year postpartum: 2 (11.1%) |
|                   |             | ≥ | Active IgAN during pregnancy: 12 (66.7%). Dialysis during pregnancy: 0 |
| Su 2017 [29]      | 27.2 ± 3.5 (cases) | eGFR: 102.6 ± 23.9 | Persistent HT postpartum: 12/89 (13%). Irreversible PU worsening: 7 (6%) |
|                   |             | PU: 1.04 g/day (0.03–7.25) | PU at pregnancy start or first trimester: risk factor for severe PE and infant loss |
|                   |             | HT: 15 (14%) | ESRD: 4 (4%) |
|                   |             | Follow up: 67 ± 34 months | ESRD/>50% decrease eGFR: 7 (7%) |
|                   | 28.7 ± 6.3 (controls) | eGFR: 94.5 ± 26.7 | Significant decrease kidney function after pregnancy in CKD stage 3–4 only |
|                   |             | PU: 1.29 g/day (0.02–11.78) | |
|                   |             | HT: 52 (17%) | |
|                   |             | Follow up: 65 ± 34 months | |
| Tocos 2017 [30]   | 31.9 ± 5.2 (cases) | eGFR: 89.9 ± 32.7 | Worsening CKD stage during pregnancy: 1/33 (3%) |
|                   |             | sCr: 0.87 mg/dL (0.50–2.88) | Increased risk of PE but not of preterm delivery suggests late maternal PE |
|                   |             | PU ≥ 0.5 g/day: 13 (41%) | |
|                   |             | HT: 9 (27%) | |
|                   | 31.2 ± 5.5 (controls) | HT: none | |
| Liu 2014 [31]     | 27.3 ± 3.6 (cases) | eGFR: 102.3 ± 21.9 | HT after pregnancy 8 (13%); MAP during follow up 86.4 ± 8.6 |
|                   |             | PU: 1.27 (0.06–7.25) g/day | Kidney disease progression: 4 (6%); decrease eGFR >50%; 3 (5%); ESRD: 1 (2%) |
|                   |             | HT: 7 (11%) | Mean change eGFR – 2.5 mL/min (– 8.7 to 0.06) |
|                   |             | PU during follow up: 0.67 g/day (0.10–6.72) | Proteinuria in pregnancy borderline significant for adverse pregnancy outcomes |
|                   | 27.8 ± 4.4 (controls) | eGFR: 103.4 ± 20.8 | MAP during follow up 85.4 ± 7.3; Kidney disease progression: 6 (10%) |
|                   |             | PU: 1.09 (0.06–8.37) g/day | Mean change eGFR – 2.4 — 7.1 to 2.4) mL/min |
|                   |             | HT: 4 (6%) | MAP during follow up 0.68 (0.07–4.30) g/day |
| Oh 2011 [32]      | 30.5 (25.0–39.0) | eGFR: 91.2 (24.1–157.0) mL/min | Median ΔGFR with ≤30% reduction proteinuria prior to conception: 13% |
|                   |             | MAP: 89.6–99.3 mmHg | Median ΔGFR with >30% reduction proteinuria prior to conception: 8.7% |
|                   |             | eGFR after delivery 77.8 (19.8–150.0) | MAP during pregnancy 96.7–102 |
|                   |             | ΔGFR with ≤30% reduction proteinuria prior to conception: 13% | Significant increase sCr (0.8–1.0 mg/dL) and PU (0.7–1.5 g/g) after delivery |
| Suetsugu 2011 (*) [33] | NR | NR | Superimposed PE: preconception SBP, sCr, BUN higher; CCr and eGFR lower |
|                   |             | Delivery: sCr, BUN, uric acid higher; CCr and eGFR lower (significant) | At delivery correlation between BP and histological severity, proteinuria and sCr |
### Table 4. Cont.

| Author Year [Ref] | Age (years) | Kidney Function at Baseline | Other Maternal Outcomes and Main Results |
|-------------------|-------------|-----------------------------|----------------------------------------|
| Shimizu 2010 [34] | 27.3 ± 4.0 (cases) | eGFR mL/min | eGFR 3 year after delivery (mL/min): CKD1: 93.0 ± 1.6, CKD2: 78.2 ± 11.8, CKD3: 58.5 ± 14.4; Overall: baseline 68.9 ± 14.4—three years after 68.5 ± 14.9 |
|                   |             | CKD1: 97.3 ± 9.4 | CKD baseline—3 year after delivery (mg/dL): 1: 0.68–0.64, 2: 0.75–0.72, 3:0.94–0.90. Overall: 0.83 ± 0.20–0.75 ± 0.14 |
|                   |             | CKD2: 74.1 ± 4.5 | PIU baseline—3 year after delivery (g/day): CKD1: 0.19 ± 0.1–0.20 ± 0.28; CKD2: 0.39 ± 0.22–0.48 ± 0.44; CKD3: 0.77 ± 0.31–0.38 ± 0.33 ** |
|                   |             | CKD3: 54.4 ± 11.6 | BP constant in all CKD groups |
|                   | 28.1 ± 5.1 (controls) | eGFR: 70.9 ± 20.7 | eGFR after 3 years (mL/min): 68.6 ± 14.4 |
|                   |             | sCr baseline—3 year after delivery (mg/dL): 1: 0.68–0.64; 2: 0.75–0.72; 3:0.94–0.90. Overall: 0.83 ± 0.20–0.75 ± 0.14 |
|                   |             | PtU baseline—after 3 years (g/day): 0.85 ± 0.65–0.40 ± 0.26 |
|                   |             | No new onset hypertension |
| Waness 2010 [35]  | 28.6        | CCr 88.6 mL/min | In 3rd trimester: BP 163.7/90.3 mmHg |
|                   |             | sCr: 0.99 mg/dL | PIU 2179.2 mg/day |
|                   |             | BP: 128.2/82.1 mmHg | CCr 77.4 mL/min |
|                   |             | PtU: 535.2 mg/day | Cr 84.3 mmol/L |
|                   | 26.72 ± 4.27 (cases) | sCr 0.87 ± 0.15 | After 10 years: 36% on steroids and/or immune-depressors, 63% on ACEIs or ARBs |
|                   |             | CCr 92 ± 17 | Significant CCr decrease (~1–2 mL/min/year) in women with PtU >1 g/day at diagnosis, not modified by number of pregnancies, hypertension, PE |
|                   |             | PIU 1.0 (0–6) g/day | Doubling of sCr in 13 (9.6%); start of dialysis in 3 (3.4%); new-onset HT in 34 (31%) of 109 previously normotensive women |
|                   |             | HT: 27 (20%) | |
| Limardo 2010 [36] | 26.19 ± 5.15 (controls) | sCr 0.86 ± 0.16 | After 10 years: 29% on steroids and/or immune-depressors; 47% on ACEIs or ARBs |
|                   |             | CCr 89 ± 18 | Doubling of sCr in 7 (8%); start of dialysis in 2 (1.5%); new-onset HT in 16 of 77 (21%) previously normotensive women |
|                   |             | PIU 0.5 (0–7.6) g/day | |
|                   |             | HT: 10 (11%) | |
| Donggyu 2010 * [37] | NR | NR | PE in 4 of 5 women with sCr >2.0 mg/dL at delivery |
|                   |             | | ESRD within 2 years in 2/2 W with sCr >2.5 mg/dL in postpartum |
|                   |             | | All women with sCr <2.5 mg/dL in postpartum had stable sCr 3 year after delivery |
| Ronkainen 2006 [38] | NR | NR | ESRD 2.6 year after delivery in a hypertensive woman with slightly impaired renal function before pregnancy § |
| Ronkainen 2002 [39] | NR | NR | HT or PIU in pregnancy: 9 (64.3%), of whom 5 reported poor outcome (not specified); no poor outcome reported in women without HT or PIU in pregnancy |
| Summary data baseline | GFR or CCr >100 mL/min in 2/9 study reporting on this item | PER 1.338 (3.3%) cases vs 22/458 (4.8%) controls, reported on by 3 studies of whom 3 provided a control group § |
|                   | GFR <100 mL/min in 7/9 studies | Significant better renal survival in cases without vs with obstetric complications, and in cases without obstetric complications vs non-pregnant controls |
|                   | PIU ≥0.5 g/day in 6/7; ≤0.5 g/day in 1/7 studies (**) | Summary data progression § |
|                   | Hypertension in 11–61% in 4 studies, in other not clearly defined at baseline | Su: no significant difference in incidence ESRD or eGFR decrease between cases and non-pregnant controls |
|                   | | Liu: no difference between cases and non-pregnant controls over follow-up |
|                   | | Shimizu: no difference in eGFR decrease between pregnancy and non-pregnancy |
|                   | | Limardo: no significant difference in all outcomes (start of dialysis, doubling of serum creatinine, new onset hypertension) |

**BP:** blood pressure; **CCr:** creatinine clearance; **(e)GFR:** (estimated) glomerular filtration rate; **ESRD:** end-stage renal disease; **HT:** hypertension; **MAP:** mean arterial pressure; **NR:** not reported; **P:** pregnancies; **PE:** preeclampsia; **PtU:** proteinuria; **sCr:** serum creatinine. * Abstract only (*) article in Japanese, abstract used. ** discrepant data between the various CKD stages and overall, as for proteinuria: Overall: 0.86 ± 0.80–0.56 ± 0.48. § used in meta-analysis despite of difference in follow-up (1 to 10 years); §§ not mentioned in article, additional information available in original database.
Table 5. IgA Nephropathy. Case reports: baseline data.

| Author Year [Ref] | Country        | Age (years) | sCr-GFR-PtU | Other Data at Referral                      | Main Drugs in Pregnancy             |
|-------------------|----------------|-------------|-------------|---------------------------------------------|--------------------------------------|
| Kaul 2016 * [40]  | India          | NR          | NR          | IgAN new-onset                              | Steroids, fish oil                   |
|                   |                | NR          | NR          | IgAN new-onset                              | Steroids, fish oil                   |
|                   |                | NR          | NR          | IgAN new-onset                              | Steroids, fish oil                   |
| Lim 2016 * [41]   | USA            | NR          | NR          | IgAN (diagnosed several years postpartum)   | NR                                   |
| Su 2015 [42]      | China          | 26          | PtU 1–2+    | HSPN postpartum                             | NR                                   |
| Nagai 2015 [43]   | Japan          | 37          | PtU postpartum|                                             | NR                                   |
| Liang 2015 * [44] | USA            | 32          | PtU 2 g/day | IgAN new-onset                              | NR                                   |
| Zand 2014 [45]    | USA            | 18          | sCr 1.8 mg/dL| IgAN                                         | NR                                   |
| Cornelis 2013 [46]| The Netherlands| 21          | C.Cr 20–25 mL/min| IgAN                                      | Methyldopa, labetalol, EPO, thyroid hormones, oral iron |
| Sun 2015 * [47]   | USA            | 28          | C.Cr 79 mL/min PtU 1.3 g/day | IgAN new-onset | Methyldopa, labetalol, hydralazine, magnesium (31 week), steroid prophylaxis (31 week) |
| Goifrè 2007 [48]  | Italy          | 25          | sCr 2.2 mg/dL PtU 1 g/day | IgAN                                         | ASA, oral iron, vitamins, vaginal dinoprostone gel (36 week) EPO, vit D, calcium carbonate, ritodrin (29 week) EPO, vit D, calcium carbonate, ritodrin (30 week) |
|                   |                | 30          | sCr 8 mg/dL | IgAN                                         |                                       |
|                   |                | 32          | HD          | IgAN                                         |                                       |
| Tanno 2007 [49]   | Japan          | 31          | sCr 0.8 mg/dL| HSPN recurrence in renal allograft          | Methyldopa, amloidpine Immunosuppressors (not clear) |
| Barquero-Romero 2006 [50]| Spain  | 36          | sCr 0.50 mg/dL PtU 1+ | HSPN new-onset | Methylprednisolone |
| Koizumi 2004 [51] | Japan          | 30          | PtU +       | HSPN new-onset                              | Low dose oral steroids for 3 week     |
| Cusi 2003 [52]    | Italy          | 29          | sCr 1.5 mg/dL PtU 1.2 g/day | IgAN                                         | Methyldopa, nifedipine, clonidine, EPO, steroid prophylaxis (26 week) |
| Amir 2002 (*) [53]| Saudi Arabia   | NR          | sCr 2.7 mg/dL PtU 5.4 g/day | IgAN with P-ANCA                            | Cyclophosphamide, prednisone         |
| Summary data      |                | 28.8 (18–37)| sCr <1.0 mg/dL: 2/9 (22.2%) | IgAN: 12 (new-onset: 6) | Antihypertensive agent: 4/10 Immunosuppressors: 4/10 |
|                   |                |             | sCr ≥1.0 mg/dL: 5/9 (55.6%) | HSPN: 4 (new-onset: 3)                      |                                       |
|                   |                |             | C.Cr <90 mL/min: 2/9 (22.2%) |                                       |                                       |
|                   |                |             | C.Cr ≥90 mL/min: 0 |                                       |                                       |
|                   |                |             | PtU ≥ 0.5 g/day: 5/5 (100%) |                                       |                                       |
|                   |                |             | reporting quantitatively |                                       |                                       |

ASA: acetyl salicylic acid; CCr: creatinine clearance; EPO: Erythropoietin; GFR: Glomerular filtration rate; h: hours; HSPN: Henoch-Schönlein purpura nephropathy; IgAN: IgA nephropathy; i.v.: intravenous; methyldopa: alpha-methyldopa; NR: Not reported; PtU: Proteinuria; sCr: serum creatinine; vit: vitamin; w: week. * Abstract only (*) abstract used.
**Table 6. IgA Nephropathy. Case reports: fetal outcomes.**

| Author       | Year | Pts | GW | Parity | Delivery | Indication for Delivery | NICU | APGAR 1–5 min Infant Outcomes | Sex | Weight (g) | Centile * |
|--------------|------|-----|----|--------|----------|--------------------------|------|-----------------------------|-----|------------|----------|
| Kaul          | 2016 * | 3   | NR | NR     | NR       | NR                       | NR   | All live births             | NR  | NR         | NR       |
| Lim           | 2016 * | 1   | NR | NR     | NR       | NR                       | NR   | NR                          | NR  | NR         | NR       |
| Sun           | 2015   | 1   | 40 | Primi  | CS       | NR                       | NR   | NR                          | NR  | NR         | NR       |
| Nagai         | 2015   | 1   | At term | NR       | Vaginal   | None                     | NR   | NR                          | NR  | NR         | NR       |
| Liang         | 2015 * | 1   | 36 + 5 | Gravi 7 Para 1 | P1051 | Vaginal induced | Presumed superimposed PE | NR   | NR                       | F   | NR         | NR       |
| Zand          | 2014   | 1   | 32  | NR     | Vaginal   | None                     | NR   | Healthy                    | M   | 2480       | 25       |
| Cornelis      | 2013   | 1   | 36  | Primi  | Vaginal assisted | Sudden HT | YES | 9 and 10 Wet lung syndrome, NICU non-invasive ventilatory support 1 day. Discharged 8 days later. | M   | 1596       | 46       |
| Hou           | 2013   | 1   | 31  | Gravi 2 Para 0 | CS       | PE, failed induction | NR   | 3 and 8 Normal development 11 years later. | F   | 3150       | 45       |
| Goirfè        | 2007   | 1   | 38  | Gravi 1 Para 0 | Vaginal | None                     | YES | 8 and 9 NICU, discharged 20 days later. | M   | 2190       | 65       |
| Tanno         | 2007   | 1   | 33  | Gravi 2 Para 1 | CS | NR                       | YES | 7 and 8 NICU for RD (ventilatory support for 6 h); discharged 20 days later. | M   | 2500       | 90       |
| Barquero-Romero | 2006 | 1   | 39  | Multi | Vaginal | None                     | NR   | Healthy at 3 m follow up | M   | 3380       | 41       |
| Koizumi       | 2004   | 1   | 40  | Primi  | Vaginal   | None                     | NR   | Healthy                    | M   | 2986       | 11       |
| Cusi          | 2003   | 1   | 31  | NR     | Vaginal   | None                     | NR   | 8 and 9 Healthy             | F   | 1626       | 68       |
| Amir          | 2002 (*) | 1   | NR  | NR     | NR       | NR                       | NR   | NR                          | NR  | NR         | NR       |
| Summary data  |      | 16 (18 cases) | <37 w: 8/13 (61.5%) | Primi: 4/9 (44.4%) | Vaginal: 8/13 (61.5%) | Maternal complications: 3/10 (30%) | All reported cases had favorable outcomes; NICU reported in 4 cases | F: 3/10 (30%) | M: <2500 g: 5/9 (55.6%); <1500 g: 1/9 (11.1%) | AGA: 9/9 (100%) (calculated upon INeS charts) |

AGA: appropriate for gestational age; CS: cesarean; d: days; F: female; Gravi: gravidity; GW: Week of gestation; h: hours; HT: hypertension; LGA: large for gestational age; M: male; m: months; Multi: multipara; NICU: neonatal intensive care unit; NR: not reported; Para/P: parity; PE: preeclampsia; Primi: primipara; Pts: Patients; RD: respiratory distress; w: weeks. * Abstract only (*) abstract used * Centiles calculated according to the INeS charts (reference). If parity or sex are not specified: male sex and primipara considered.
Table 7. IgA Nephropathy. Case reports: maternal outcomes.

| Author Year [Ref] | PE/Other | Maternal Outcomes, as Reported in the Paper |
|-------------------|----------|---------------------------------------------|
| Kaul 2016 * [40]  | NR       | All 3 patients treated with steroids and fish oil, complete remission in all 3 patients |
| Lim 2016 * [41]   | HT and PtU at 22 weeks, presumed PE. No follow up postpartum. | Several years postpartum (age 25) presentation with severe HT and cardiac failure, pulmonary edema, hematuria, proteinuria, small hypo-echoic kidneys on ultrasound. Kidney biopsy: IgAN with severe atrophy and fibrosis |
| Sun 2015 [42]     | None     | 5 days postpartum atypical hemolytic uremic syndrome (AKI, nephrotic syndrome, thrombocytopenia and hemolytic anemia), HD for 5 weeks |
| Nagai 2015 [43]   | 6th month HSP purpura, during pregnancy normal urinalysis | 1 m postpartum HSPN without renal dysfunction, and anti-PL-7 anti-synthetase syndrome with interstitial lung disease and subclinical myopathy |
| Liang 2015 * [44] | HT, proteinuria and hematuria | Normalization BP; persistent PtU and hematuria; biopsy proven IgAN 1.5 years later |
| Zand 2014 [45]    | HT, anemia, atypical hemolytic uremic syndrome, start HD | On HD; living kidney donor transplant 5 months later |
| Cornelis 2013 [46] | 26 week start intensive HD for rapidly progressive deterioration kidney function; sudden HT 35 + 5 weeks | 2 weeks postpartum restart HD; 1 year later living-donor kidney transplant |
| Hou 2013 [47]     | HT, PE 31 weeks | 1 year later deterioration kidney function; 11 years later evaluation for kidney transplant |
| Goifrè 2007 [48]  | Anemia   | Pre HD (CKD in 1st pregnancy) |
|                   | Anemia; start HD end 1st trimester; polyhydramnios 28 weeks | On HD |
|                   | Anemia, polyhydramnios 30 weeks | On HD; 1 year later: kidney transplant |
| Tanno 2007 [49]   | 17 week HT and PtU, microhematuria; worsening of kidney function at 24 weeks and 28 weeks | Postpartum decrease BP and sCr, PtU from 6.0 to 1.0 g/day 6 months postpartum kidney biopsy: HSPN recurrence in renal allograft with additional focal segmental membranous nephropathy with C1q deposition |
| Barquero-Romero 2006 [50] | HSP at 36 weeks, good response to steroid | Healthy at 3 months follow up |
| Koizumi 2004 [51] | Elevated levels CRP and ALT/AST | Normalization of blood analysis and urinalysis |
| Cusi 2003 [52]    | HT, anemia | Persistence of HT and anemia |
| Amir 2002 (*) [53] | 11 week rapidly progressive GN: sCr 2.7 mg/dL, PtU 5.4 g/24 h | Good response to cyclophosphamide and prednisone: sCr 1.4 mg/dL, PtU 0.516 g/day, 18 months after diagnosis no significant clinical problems and stable kidney function |
| Summary data      | PE, 1 Pregnancy induced HT: 6 | Different outcomes of the kidney function also depending upon the disease |

AKI: acute kidney injury; BP: blood pressure; CRP: C-reactive protein; d: days; GN: glomerulonephritis; HD: hemodialysis; HT: hypertension; HSPN: Henoch-Schönlein purpura nephropathy; IgAN: IgA nephropathy; NR: Not reported; PE: pre eclampsia; PtU: proteinuria; * Abstract only (*) abstract used.
3.4. Meta-Analysis

Kidney Function

Figure 2 reports on ESRD and the start of renal replacement therapy in patients with and without pregnancy. The incidence was low in the five studies reporting on this outcome: 11/330 patients versus 22/458 controls, and there was no significant difference found between the two groups (OR 0.68; CI 0.28–1.65).

**Odds ratio for ESRD or start of renal replacement therapy in pregnant women with IgA nephropathy versus non-pregnant controls with IgA nephropathy.**

![Odds ratio for ESRD or start of renal replacement therapy in pregnant women with IgA nephropathy versus non-pregnant controls with IgA nephropathy.](image)

Figure 2. Odds ratio for end-stage renal disease in patients with IgA nephropathy, with or without pregnancy. Legend: ESRD: end stage renal disease. CI: confidence intervals.

These reassuring data have to be contextualized to patients with good renal function, and it has to be taken into account that time of follow up differed notably between the studies (ranging from 1 to 10 years postpartum), which reduces the clinical value of this comparison (Figure 2).

3.5. Pregnancy Related Outcomes

The risk for adverse pregnancy-related outcomes was higher in IgA patients than in the low-risk cohort (Figure 3).

While the incidence of caesarean sections and the incidence of small for gestational age babies were not significantly different in IgA nephropathy and in the low-risk control group, the odds ratio for preterm delivery, PE and PIH were significantly higher for women with IgA nephropathy (Figure 3).

Odds ratio (OR) for PE and PIH were particularly high: PE: OR 11.80; CI 7.53–18.48, PIH OR 10.39; CI 5.45–19.80. Conversely, the risk of preterm birth was about threefold that of the low-risk population (OR 3.37; CI 1.91–5.95), while the risk of neonates with low birth weight is about twice as high (OR 2.36; CI 1.52–3.66).
Odds ratio of pregnancy related outcomes in IgA nephropathy versus low-risk controls:
PE (a), hypertension* (b), preterm delivery (c), early preterm delivery (d), low birth weight (e), SGA – IUGR (f), caesarean section (g), stillbirth (h).

### a

| Study or Subgroup | IgA | Total | Low-risk | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
|-------------------|-----|-------|----------|-------|--------|---------------------|---------------------|
| Park 2017         | 13  | 64    | 25 1418  | 12.7% | 14.20  | [6.87, 29.36]       |                     |
| O’Shaughnessy 2017| 6   | 18    | 25 1418  | 9.2%  | 27.86  | [9.66, 80.16]       |                     |
| Su 2017           | 12  | 116   | 25 1418  | 12.8% | 6.43   | [3.14, 13.16]       |                     |
| TOCOS 2017        | 4   | 17    | 25 1418  | 8.1%  | 17.14  | [5.22, 56.27]       |                     |
| Liu 2014          | 6   | 62    | 25 1418  | 10.4% | 5.97   | [2.36, 15.13]       |                     |
| Suetsugu 2011     | 13  | 34    | 25 1418  | 11.9% | 34.49  | [15.55, 76.52]      |                     |
| Shimizu 2010      | 0   | 29    | 25 1418  | 2.2%  | 0.93   | [0.06, 15.58]       |                     |
| Wanessa 2010      | 3   | 12    | 25 1418  | 6.9%  | 16.57  | [4.74, 72.74]       |                     |
| Limardo 2010      | 17  | 136   | 25 1418  | 13.6% | 7.96   | [4.18, 15.16]       |                     |
| Dongguy 2010      | 4   | 25    | 25 1418  | 8.5%  | 10.61  | [3.39, 33.19]       |                     |
| Ronkainen 2006    | 1   | 10    | 25 1418  | 3.7%  | 6.19   | [0.76, 50.73]       |                     |
| **Total (95% CI)**| 523 | 15598 | 100.0%   | 11.80 | [7.53, 18.48]       |                     |

**Total events**: 79 275

Heterogeneity: Tau² = 0.28; Chi² = 21.37, df = 10 (P = 0.02); I² = 53%

Test for overall effect: Z = 10.78 (P < 0.00001)

### b

| Study or Subgroup | IgA | Total | Low-risk | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
|-------------------|-----|-------|----------|-------|--------|---------------------|---------------------|
| Su 2017           | 26  | 89    | 66 1418  | 26.9% | 8.45   | [5.03, 14.21]       |                     |
| TOCOS 2017        | 7   | 24    | 66 1418  | 19.7% | 8.43   | [3.38, 21.04]       |                     |
| Wanessa 2010      | 12  | 12    | 66 1418  | 4.5%  | 508.46 | [29.78, 8680.06]    |                     |
| Limardo 2010      | 43  | 201   | 66 1418  | 28.6% | 5.57   | [3.67, 8.47]        |                     |
| Ronkainen 2006    | 10  | 22    | 66 1418  | 20.4% | 17.07  | [7.12, 40.94]       |                     |
| **Total (95% CI)**| 348 | 7090  | 100.0%   | 19.39 | [5.45, 19.80]       |                     |

**Total events**: 98 330

Heterogeneity: Tau² = 0.33; Chi² = 14.14, df = 4 (P = 0.007); I² = 72%

Test for overall effect: Z = 7.11 (P < 0.00001)

### c

| Study or Subgroup | IgA | Total | Low-risk | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
|-------------------|-----|-------|----------|-------|--------|---------------------|---------------------|
| Park 2017         | 21  | 64    | 89 1418  | 12.8% | 7.29   | [4.15, 12.82]       |                     |
| O’Shaughnessy 2017| 6   | 18    | 89 1418  | 10.1% | 7.47   | [2.74, 20.36]       |                     |
| Su 2017           | 13  | 116   | 89 1418  | 12.5% | 1.88   | [1.02, 3.49]        |                     |
| TOCOS 2017        | 12  | 33    | 89 1418  | 11.7% | 8.53   | [4.07, 17.90]       |                     |
| Lu 2014           | 7   | 69    | 89 1418  | 11.3% | 1.69   | [0.75, 3.79]        |                     |
| Oh 2011           | 8   | 52    | 89 1418  | 11.5% | 2.72   | [1.24, 5.94]        |                     |
| Shimizu 2010      | 0   | 29    | 89 1418  | 3.2%  | 0.25   | [0.02, 4.15]        |                     |
| Wanessa 2010      | 0   | 12    | 89 1418  | 3.2%  | 0.59   | [0.03, 10.12]       |                     |
| Limardo 2010      | 20  | 195   | 89 1418  | 13.1% | 1.71   | [1.02, 2.84]        |                     |
| Ronkainen 2006    | 8   | 20    | 89 1418  | 10.6% | 9.96   | [3.97, 24.98]       |                     |
| **Total (95% CI)**| 668 | 14180 | 100.0%   | 3.37  | [1.91, 5.95]        |                     |

**Total events**: 95 890

Heterogeneity: Tau² = 0.58; Chi² = 41.14, df = 9 (P < 0.00001); I² = 78%

Test for overall effect: Z = 4.18 (P < 0.00001)

### d

| Study or Subgroup | IgA | Total | Low-risk | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
|-------------------|-----|-------|----------|-------|--------|---------------------|---------------------|
| Park 2017         | 8   | 64    | 13 1418  | 39.8% | 15.44  | [6.15, 38.76]       |                     |
| O’Shaughnessy 2017| 4   | 18    | 13 1418  | 22.0% | 30.88  | [9.95, 106.51]      |                     |
| TOCOS 2017        | 4   | 33    | 13 1418  | 24.3% | 14.91  | [4.58, 48.49]       |                     |
| Ronkainen 2006    | 2   | 20    | 13 1418  | 13.9% | 12.01  | [2.52, 57.12]       |                     |
| **Total (95% CI)**| 135 | 5672  | 100.0%   | 17.22 | [9.63, 30.79]       |                     |

**Total events**: 18 52

Heterogeneity: Tau² = 0.00; Chi² = 1.18, df = 3 (P = 0.76); I² = 0%

Test for overall effect: Z = 9.60 (P < 0.00001)

**Figure 3. Cont.**
Figure 3. Odds ratio for different pregnancy related outcomes. SGA: small for gestational age. IUGR: intrauterine growth restriction. PE: preeclampsia. CI: confidence intervals.

4. Discussion

This systematic review identified 13 cases series and 14 case reports, reporting on pregnancy-related outcomes in IgA nephropathy [27–53]. This is, at the best of our knowledge, the largest number of papers meta-analyzed or narratively discussed on IgA nephropathy in pregnancy, with particular attention to the risk of adverse pregnancy-related outcomes. In this regard, our review may add information to a previous recent systematic review, which included papers published since the start of Medline, and
was mainly focused on the progression of kidney disease in patients with IgA nephropathy with and without pregnancy [23]. The review, that selected 4 papers with a control group, providing data of 273 patients with IgA nephropathy and of 241 patients with IgA nephropathy who did not become pregnant, supported a lack of disadvantage on the progression of nephropathy for IgA nephropathy patients with well-preserved function that became pregnant.

The main novelty of the present review is to give more insight into the risk of pregnancy-related outcomes, that were already reported as frequent by the previous study, but that are meta-analyzed for the first time with respect to a low-risk population; in this context, limiting the analysis to the studies published since 2000 may allow for a better contextualization in the present panorama (Figure 3).

The pattern of pregnancy-related outcomes is complex and the behavior of the risks may offer some interesting insights into the pathogenesis of pregnancy complications in IgA nephropathy. In fact, the meta-analysis identifies a particularly high risk of PE and PIH in women with IgA nephropathy, with an over ten-fold increase, within wide but consistent confidence intervals (Figure 3). In spite of these high odds ratios, the significantly increased risk of preterm birth was only about triple compared to the low-risk population and the incidence of newborns with low birth weight is only doubled, while no difference was found in the incidence of both caesarean sections and of small for gestational age babies (Figure 3). This finding suggests that the very high risk for hypertensive disorders of pregnancy is not accompanied by a correspondent increase of preterm babies, and of babies whose growth has been severely impaired, as it occurs in the “placental” early forms of preeclampsia, and therefore suggests that the related event occurs later, corresponding with the so-called “late” form of PE [54–58]. Such a form of PE is usually milder, and is often associated with maternal diseases, and indeed some authors distinguish between “maternal” and “placental” preeclampsia, the latter characterized by a primary defect of placentation, and frequently associated with intrauterine growth restriction. Conversely, the maternal form is more often of late onset, frequently, even if not always, less severe, and is associated with a lower risk of newborns that are small for gestational age, a pattern that may be consistent with the observations gathered in the present review [54–59].

With respect to disease progression, the lack of negative effect of pregnancy, at least in populations with relatively preserved kidney function, reported in the previous meta-analysis, is confirmed by our analysis, performed with a different, selection of the papers, and with the chance of adding several recent studies on this issue (Figure 2) [23]. In most of the studies retrieved by both reviews kidney function was normal or well-preserved before pregnancy and, in this context, the progression of the kidney disease does not appear to be affected by pregnancy. However, most studies fail to give information both on women with severe CKD and the duration of the observation time is not always clear. Furthermore, even if relatively long, the median follow-up period of 10 years described by Limardo, and of 4.5 years by Liu, could still be too short to draw conclusions, given the slow progression of early IgA nephropathy [31,36]. The interesting new suggestion that progression of kidney disease is limited to the cases who display adverse pregnancy outcomes should be confirmed in further studies [27].

The case reports, as expected, focus on exceptional events, and are probably affected by reporting and publishing biases. Despite these limits, they may underline that positive pregnancy outcomes are possible, even in severe advanced chronic kidney disease [40–53] (Tables 5–7).

The major strength of this study is that it provides an updated systematic review in one of the most common nephropathies observed in young patients all over the world, gathering over 700 pregnancy published in the new millennium, and attempting, for the first time, a risk assessment with regard to the overall population. The integration with case reports, a further novel aspect of this review, underlines that a positive outcome is possible even in women with severe CKD, who are usually excluded from the larger case series.

The main limitations of this review are linked to the heterogeneity of the studies in terms of populations, definitions and outcomes, as well as duration of follow-up. Heterogeneity is a common problem in systematic reviews on CKD pregnancies, which limits the value of the meta-analysis,
and calls for a common language, a still unmet goal [60–62]. Furthermore, due to lack of data on low-risk populations, we employed the only available one, from a multicenter Italian study; the approach of choosing a reference population for a wider meta-analysis is not new, and was for example employed by Deshpande and coworkers in the pivotal analysis on pregnancy after kidney or after liver transplantation, which plotted the data against the reference USA population [63,64]. Such a choice is an obvious compromise, and the lack of matched populations limits the precision of the comparison; however, the differences with the low-risk populations are highly significant, and their pattern is consistent, thus allowing at least posing new hypotheses and indications for future research.

Within these limits, we hope that our findings may be of interest for counseling and for tailoring clinical surveillance for clinicians working in obstetrics and in nephrology.

Our study may also indicate uncovered fields for future research. First of all, more data is needed to better define the risk of adverse pregnancy outcomes, particularly so in case of kidney function decrease. Secondly, given the impossibility to clinically distinguish an increase in proteinuria and hypertension related to the IgA nephropathy from that related to preeclampsia, there is need for precise description of these cases, with stratification for previous hypertension, and univocal definitions of superimposed PE. In this regard, IgA nephropathy may represent a field for the systematic use of old and new biomarkers of PE and kidney disease [63–68].

5. Conclusions

Patients with IgA nephropathy and severe CKD should be informed about the paucity of data allowing a precise quantification of the risks. In patients with preserved kidney function, that represent the majority of those reported, the risk of progression of kidney disease is low, and may be limited to the cases who display adverse pregnancy related events. Conversely the risk of developing PE and PIH is very high compared to the low-risk population (OR > 10). The pattern of these hypertensive disorders of pregnancy, associated with a significant but milder increase in preterm delivery but not of small for gestational age babies, suggests the presence of late onset PE, in its “maternal” form, thought to affect fetal growth less severely than ‘placental’ early PE. This hypothesis, needing confirmation on a larger scale, may prove of interest in interpreting the increase in hypertensive disorders of pregnancy observed in chronic kidney disease.

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