Pregnancy and Glomerular Disease: A Systematic Review of the Literature with Management Guidelines

METHODS

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [1] and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [2].

Search Strategy

A combination of medical subject heading (MeSH) terms and keywords were used to conduct a systematic search of the following databases: MEDLINE (1946 – February 2016); EMBASE (1980 – February 2016); Cochrane Database of Systematic Reviews (2005 – February 2016) and the Cochrane Central Register of Controlled Trials (1898-February 2016). There were no restrictions on language or other limits on the search strategy.

Eligibility Criteria

We included observational studies published after 1980 that examined the frequency of live births in women with biopsy proven primary glomerular disease (Figure 1 - Appendix). In studies published prior to 1980, it was difficult to ascertain the pathological diagnosis. Furthermore, advances in neonatal intensive care occurring after 1980 significantly improved outcomes irrespective of maternal renal disease (e.g. surfactant use). We were primarily interested in the following 4 conditions: IgA nephropathy, minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS) and membranous nephropathy (MN). Studies were required to include a minimum of 10 women with one of the aforementioned conditions and report the number of live births within the given disease category. Where studies provided data on women in

more than one disease category of interest, results for each disease were included separately. Where two studies reported results based on an overlapping cohort, we selected the most recent study and/or the study with the largest sample size. Where studies did not specify the disease type or the pathological classification was unclear, we included these results as "glomerulonephritis, disease type not specified". Titles, abstracts and full-text studies were reviewed in single, several months apart by one reviewer (AO). To ensure accuracy, a duplicate review of studies was conducted (KB).

Quality Assessment

We evaluated the methodological quality of included studies using the criteria developed by Loney et al [3]. Studies were assessed based on 3 broad areas: 1) how the population was sampled 2) how the outcome was measured and 3) how the results were interpreted. The maximum number of points that could be achieved was 8 points, and studies were deemed to be at low risk of bias if they achieved at least 6 points (Table 1 - Appendix).

Statistical and Qualitative Analysis

The percentage of live births was calculated for each relevant disease category within each study. We refrained from conducting a meta-analysis because there was substantial heterogeneity (I2>70%) and few studies reported baseline data on participants to allow us to explore the sources of heterogeneity. Therefore, we conducted a qualitative, descriptive analysis only.

Data Abstraction

Data were independently abstracted by one reviewer (AO) and reviewed by a second reviewer (KB). Differences were reconciled by discussion or consultation with a third reviewer (MH). The following data

was abstracted: (1) General study characteristics, namely year of publication and study design; (2) Patient characteristics including number of women studied, number of pregnancies and number of infants, mean age, number of pregnancies with hypertension at baseline (pre-pregnancy), number of pregnancies with elevated creatinine at baseline; and (3) Outcome data including number of live births, spontaneous abortions, still births or neonatal deaths, birth weight and gestational age, number of pregnancies with an increase in post-pregnancy blood pressure and creatinine compared to baseline. Study specific definitions for the variables of interest are presented in Table 2 -Appendix where available.

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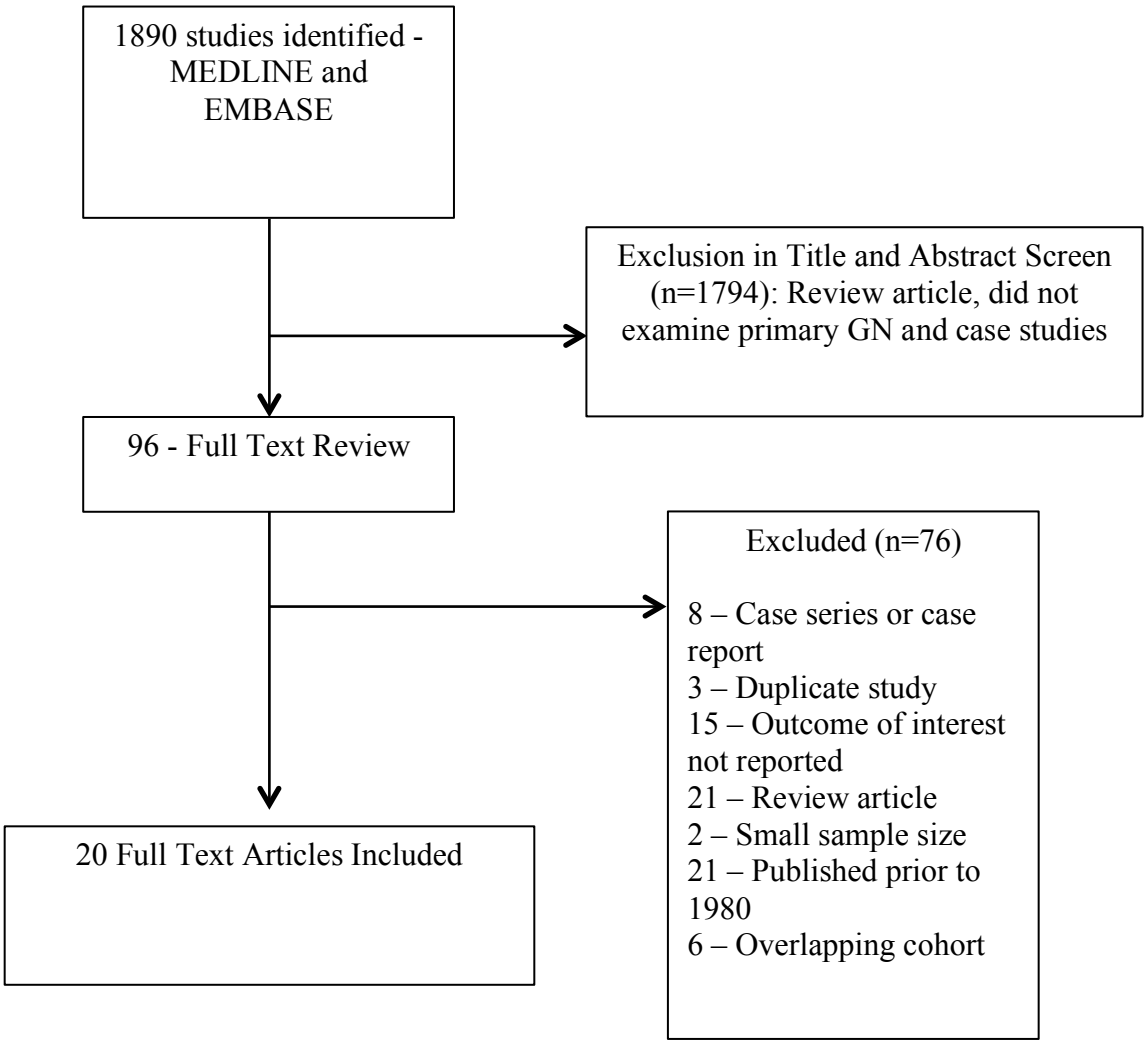
FIGURES

Figure 1: Identification of Included Studies



TABLES

Table 1: Characteristics and Quality of Included Studies

Author, Year	Cohort Name	Disease Type(s)	Risk of Bias Score (out of 8)	Overall Risk of Bias Assessment
Surian, 1984 [4]	Policlinico Hospital	IgA, FSGS	3	High
Abe, 1985 [5]	Keio Hospital	MCD, GN, Disease Type Not Specified	3	High
Hou, 1985 [6]	Multicentre survey, USA	GN, Disease Type Not Specified	3	High
Barcelo, 1986 [7]	Universidad Autonoma, Spain	IgA, FSGS	3	High
Jungers, 1986 [8]	Necker Hospital	IgA, MCD, MN	3	High
Kincaid-Smith, 1987 [9]	University of Melbourne	IgA, FSGS	3	High
Packham, 1987 [10]	Royal Women's Hospital	MN	3	High
Packham, 1988 [11]	Royal Women's Hospital	IgA	3	High
Packham, 1988 [12]	Royal Women's Hospital	FSGS	3	High
Packham, 1988 [13]	Royal Women's Hospital	GN, Disease Type Not Specified	3	High
Nagai, 1989 [14]	Toho University	IgA	3	High
Abe, 1991 [15]	Keio Hospital	IgA	2	High
Abe, 1996 [16]	Keio Hospital	GN, Disease Type Not Specified	3	High
Malik, 2001 [17]	Royal Security Forces Hospital	GN, Disease Type Not Specified	3	High
Limardo, 2010 [18]	Rene e Gravidanza Collaborative Group	IgA	3	High
Shimizu, 2010 [19]	Tokyo Women's Medical University	IgA	3	High
Waness, 2010 [20]	King Abdulaziz University Hospital	IgA	3	High
Liu, 2014 [21]	Peking University First Hospital	IgA	5	High

Glomerulonephritis (GN)

Table 2: Definitions Used in Individual Studies for Baseline Comorbidities and Complications During Pregnancy

Study, Year	Pre-Pregnancy HTN	Increased Pre-Pregnancy Creatinine	Increased Post-Pregnancy BP	Increased Post-Pregnancy Creatinine	Preeclampsia
IgA Nephropathy					
Surian, 1984 [4]	Not Available	Not Available	Not Available	≥50% increase in serum creatinine compared to "initial values"	Not Available
Barcelo, 1986 [7]	Not Available	Not Available	Not Available	≥50% increase in serum creatinine compared to "initial values"	No Definition
Jungers, 1986 [8]	BP ≥150/90 mmHg	Serum creatinine ≥1.3 mg/dL	Not Available	No Definition. *However, raw data was provided by authors. For the purposes of this review, we used a definition of ≥50% increase in serum creatinine at 6 months* postpartum	Not Available
Kindcaid-Smith, 1987 [9]	Not Available	Not Available	Increase ≥15 mmHg DBP at 6 months postpartum	Not Available	Not Available
Packham, 1988 [11]	DBP ≥95 mmHg or need for anti-HTN agents	Serum creatinine >1.24 mg/dL	DBP ≥90 mmHg or increase ≥15 mmHg DBP at 6 months postpartum	Not Available	Not Available
Nagai, 1989 [14]	No Definition	No Definition	BP ≥140/90 mmHg	No Definition	Not Available
Abe, 1991 [15]	BP ≥140/90 mmHg or need for anti-HTN agents	Not Available	No Definition	Not Available	Not Available
Limardo, 2010 [18]	No Definition	Serum Creatinine <1.2 mg/dL	BP ≥140/90 mmHg or need for anti-HTN agents	No Definition. *However data provided for those*	New-onset HTN and proteinuria ≥20 weeks

				that doubled serum creatinine	gestation in women without baseline HTN and proteinuria <300 mg/day
Limardo, 2010 [18]	No Definition	Serum Creatinine >1.2 mg/dL	Not Available	Not Available	Not Available
Shimizu, 2010 [19]	Not Available	Not Available	Not Available	Not Available	No Definition
Waness, 2010 [20]	No Definition	No Definition	Not Available	Not Available	HTN, severe edema and heavy proteinuria
Liu, 2014 [21]	No Definition	Not Available	No Definition	Not Available	Severe HTN (≥160/110 mmHg), severe proteinuria (>5 g/day) and additional symptoms (headache, abdominal pain etc.)
Focal Segmental Glomerulosclerosis (FSGS)					
Surian, 1984 [4]	Not Available	Not Available	Not Available	≥50% increase in serum creatinine compared to "initial values"	Not Available
Barcelo, 1986 [7]	Not Available	Not Available	Increase of ≥20 mmHg DBP at 3-6 months postpartum	≥50% increase in serum creatinine compared to "initial values"	No Definition
Kindcaid-Smith, 1987 [9]	Not Available	Not Available	Increase ≥15 mmHg DBP at 6 months postpartum	Not Available	Not Available
Packham, 1988 [12]	DBP ≥95 mmHg or need for anti-HTN agents	Not Available	Not Available	≥50% increase in serum creatinine at 6 months postpartum	Not Available
Minimal Change Disease					
Abe, 1985 [5]	Not Available	Not Available	Not Available	No Definition	Not Available
Jungers, 1986 [8]	BP ≥150/90 mmHg	Serum creatinine ≥1.3 mg/dL	No Definition. *However, postpartum BP ≥150/90 mmHg was considered increased, and all participants had normal pre-pregnancy BP*	No Definition. *However, postpartum creatinine ≥1.5 mg/dL considered increased, and all participants had normal pre-pregnancy creatinine*	Not Available

Membranous Nephropathy					
Jungers, 1986 [8]	BP ≥150/90 mmHg	Serum creatinine ≥1.3 mg/dL	Not Available	No Definition. *However, postpartum creatinine ≥1.5 mg/dL considered increased, and all participants had normal pre-pregnancy creatinine*	Not Available
Packham, 1987 [10]	DBP ≥90 mmHg	Not Available	Increase ≥15 mmHg DBP at 6 months postpartum	≥50% increase in serum creatinine at 6 months postpartum	Not Available
GN, Disease Type Not Specified					
Malik, 2001 [17]	Not Available	Not Available	Not Available	Not Available	Development of reversible HTN
Abe, 1996 [16]	Not Available	Not Available	Not Available	Not Available	Diagnosed by attending physician using clinical criteria from the American College of Obstetricians and Gynecologists
Packham, 1988 [13]	DBP ≥95 mmHg or need for anti-HTN agents	Serum creatinine ≥1.24 mg/dL	DBP >90 mmHg at 6 months postpartum	≥50% increase in serum creatinine at 6 months postpartum	Not Available
Abe, 1985 [5]	Not Available	Not Available	Not Available	No Definition	Not Available
Hou, 1985 [6]	BP ≥140/90 mmHg	Serum creatinine ≥1.4 mg/dL	BP ≥140/90 mmHg if not hypertensive at conception or the use of anti-HTN agents. If hypertensive at conception, SBP increase ≥30 mmHg or DBP increase ≥15 mmHg	Serum creatinine increased ≥1.0 mg/dL at ≥3 months postpartum	Not Available

Blood pressure (BP), systolic blood pressure (SBP), diastolic blood pressure (DBP), hypertension (HTN). Definition was not available if no outcome data was provided (see Table 1, main manuscript) whereas no definition indicates that although outcome data was provided, the authors failed to define the variable.