PREGNANCY AND GLOMERULAR DISEASE

Michelle Hladunewich, MD

Associate Professor, University of Toronto

Director, Divisions of Nephrology & Obstetric Medicine

Sunnybrook Health Sciences Centre

Clinical Director of Research, Toronto GN Registry

TORONTO Glomerulonephritis REGISTRY

Disclosers

- Developed a web page with the support of Baxter for the management of pregnant women on HD

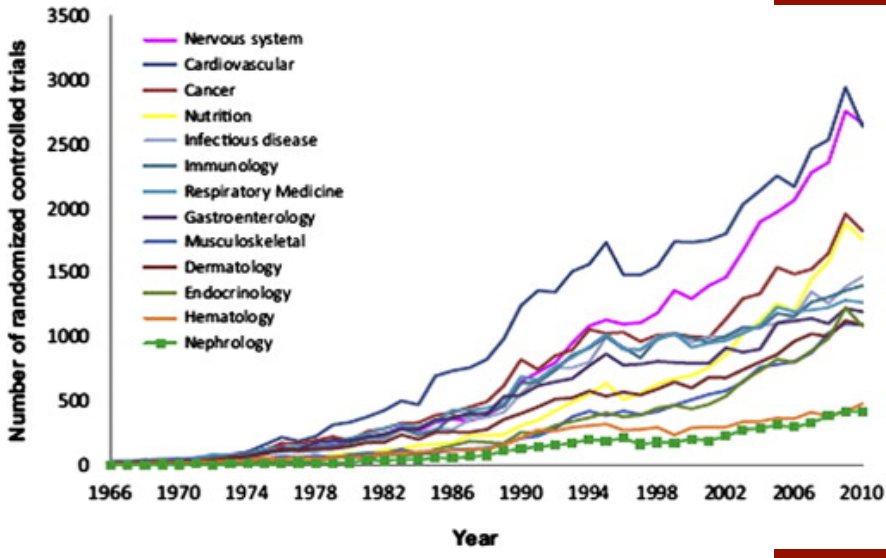
TORONTO
Glomerulonephritis
REGISTRY

Pregnancy and Glomerular Disease

CASES >>> *Evidence*

Pregnancy and Kidney Disease (PreKID) Clinic

- Collaborative approach – MFM & nephrologist at 2 sites
- Patients Counseled – >1500
- Number of Pregnancies 65%
- 75 new patients consulted at clinic undergo pregnancy annually

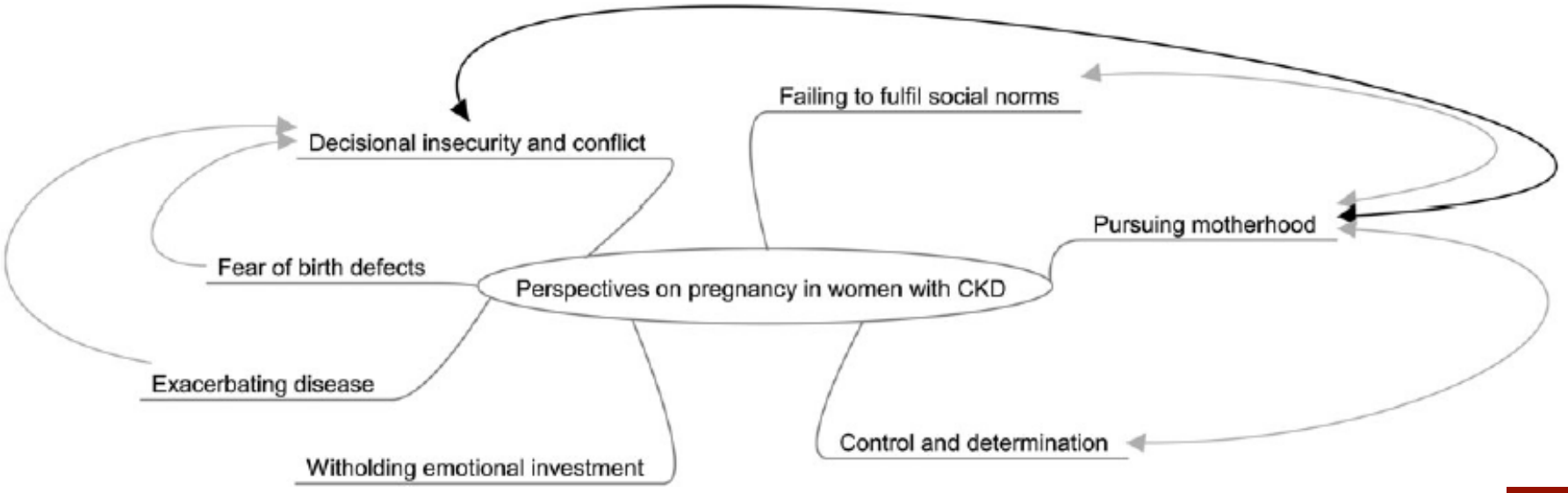


Advances in Chronic Kidney Disease
Volume 19, Issue 1 , Pages 40-46 2012

TORONTO Glomerulonephritis REGISTRY

Pregnancy and Glomerular Disease

- For most women, a child is a life goal and women with CKD are not an exception



- Aggressive counseling against pregnancy results in feelings of traumatization

Tong et al NDT 2015

TORONTO Glomerulonephritis REGISTRY

Pregnancy and Glomerular Disease

"You know, you can't always live in the anxiety of the future."

"So I'm just a little bit worried now, my Cr what if it does go higher. And I'm not pregnant now, and now I'm old. Who knows if its sets me back another 2 years or 3 years I can't even afford it any more."

"If I wait, what if I am not be able to have a healthy pregnancy… I was actually quite scared, I was really going crazy, I was thinking one of the goals in to have a child, to have a family, to raise this child."

TORONTO Glomerulonephritis REGISTRY

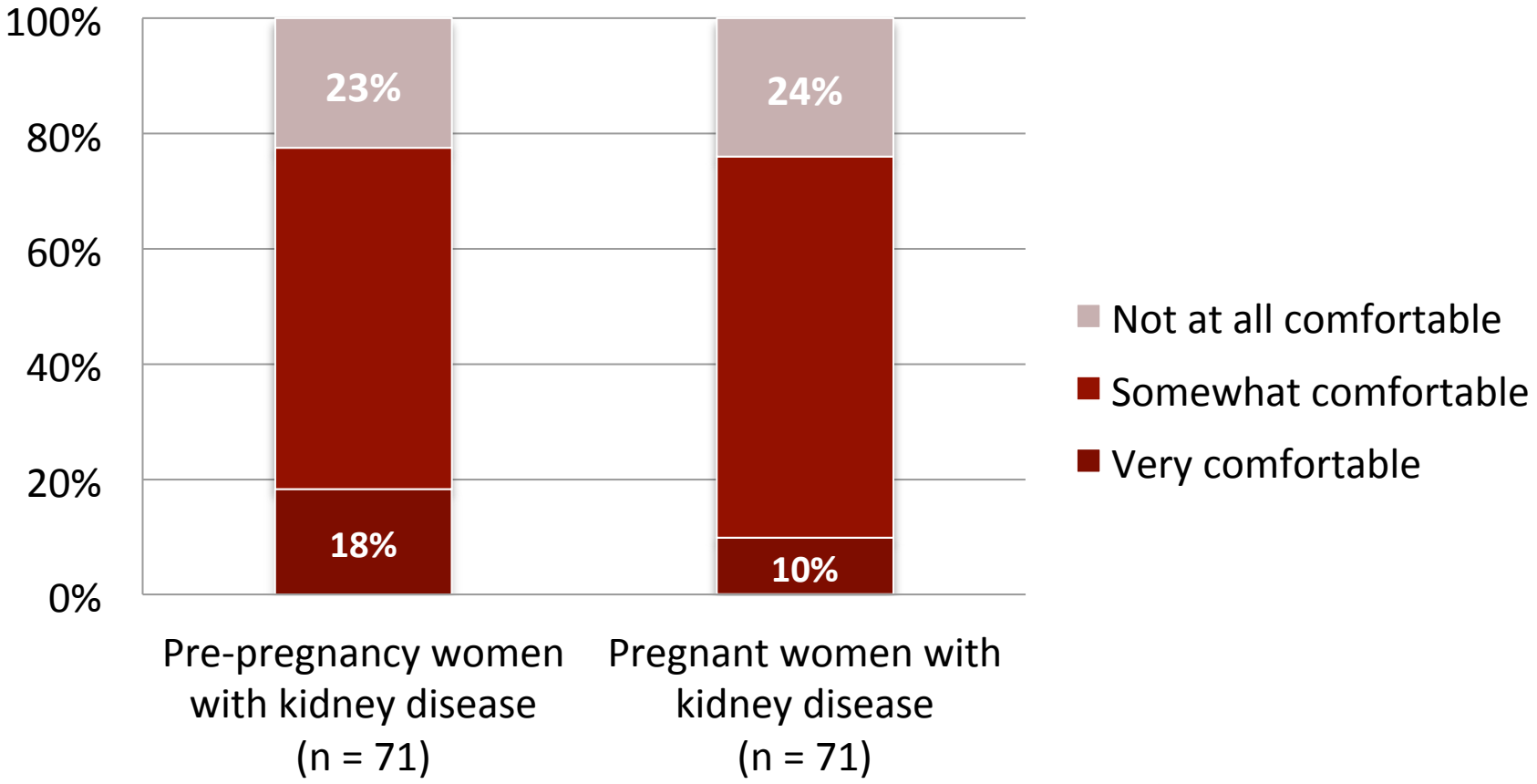
Beanlands, Cattran and Hladunewich KFOC

Pregnancy and Glomerular Disease

- CKD is an often progressive journey
- Nephrologist's role to assist with family planning at all stages of CKD
  - Identify "safest window of opportunity"
  - Discussing and even encouraging pregnancy in earlier stage CKD
  - Providing options in ESRD including on dialysis and after transplantation

TORONTO Glomerulonephritis REGISTRY

Pregnancy and Kidney Disease



TORONTO Glomerulonephritis REGISTRY

Overall Objectives

- **Principles of Pregnancy Risk Assessment and Counseling**
  - Risk of Loss of Kidney Function
  - Risk of Adverse Pregnancy Outcomes
    Preeclampsia, Poor fetal growth, Pre-term Delivery
  - Risk of Flare or Worsening Proteinuria
- **Disease Specific Outcomes**
- **Optimization/Management Strategies**

TORONTO Glomerulonephritis REGISTRY

RISK ASSESSMENT AND COUNSELING IN CKD

TORONTO
Glomerulonephritis
REGISTRY

RISK OF DETERIORATION IN KIDNEY FUNCTION

TORONTO
Glomerulonephritis
REGISTRY

Risk of Deterioration in Kidney Function

	Serum Creatinine	Creatinine Clearance	CKD Stage
Mild Renal Insufficiency	<125 umol/L (1.4 mg/dl)	>70 ml/min	Stage 1 & 2
Moderate Renal Insufficiency	125-220 umol/L (1.4-2.4 mg/dl)	40-70 ml/min	Stage 2 & 3
Severe Renal Insufficiency	>220 umol/L (2.4 mg/dl)	<40 ml/min	Stage 3 & 4

TORONTO Glomerulonephritis REGISTRY

Risk of Deterioration in Kidney Function

Piccoli et al JASN 2015

- Comparison of 504 pregnancies in women with CKD shifted stage or progressed to ESRD (Turin and Cagliari)

	Stage 1	Stage 2	Stage 3	Stage 4-5
N	28/370	1/87	2/37	2/10
%	7.6	12.6	16.2	20

TORONTO Glomerulonephritis REGISTRY

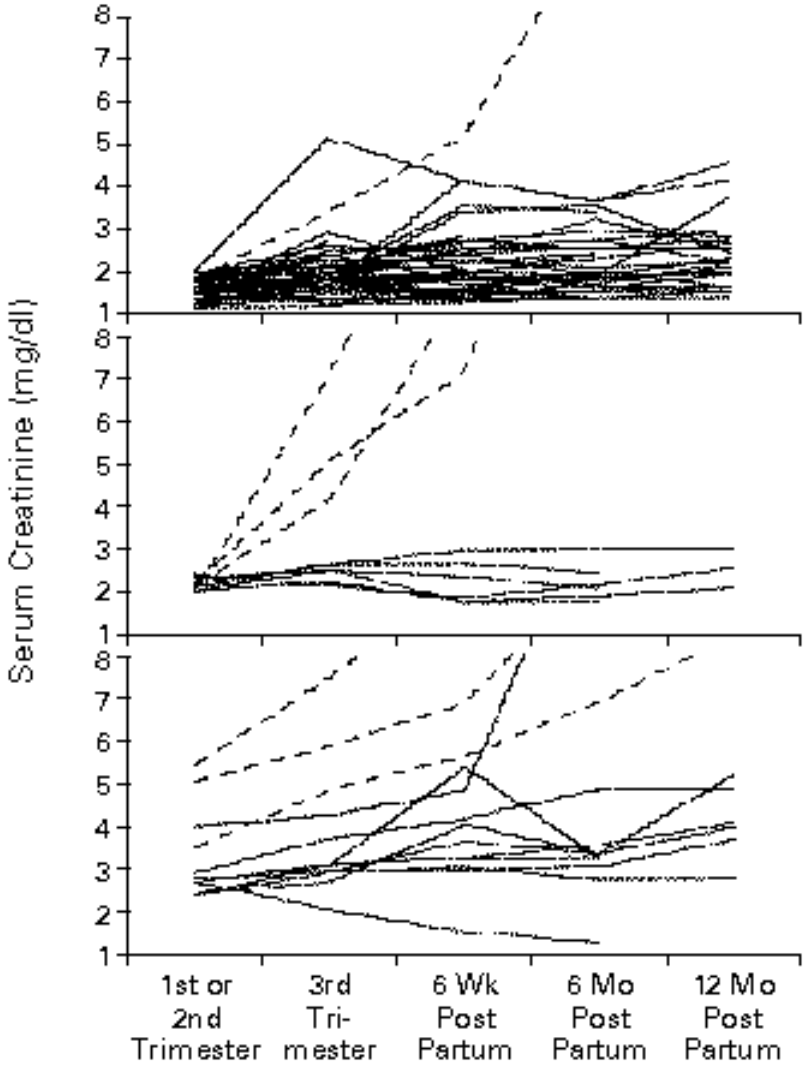
Risk of Deterioration in Kidney Function

- Retrospective Study
- Moderate to Severe Renal Insufficiency
  - Moderate – 59 pregnancies (125-220 umol/L)
  - Severe – 15 pregnancies (>220 umol/L)
- Pregnancy Related Loss of Kidney Function (during or within 6 weeks postpartum)
  - 43% of all pregnancies
  - 23% progressed to ESRD within 6 months

Jones et al NEJM 335(4): 226, 1996

TORONTO Glomerulonephritis REGISTRY

Risk of Deterioration in Kidney Function



Dashed lines - pregnancy related decline in GFR

Top: Cr <168

Middle: 199-212

Bottom: Cr >220

1/6 progression to ESRD - moderate renal insufficiency

1/3 progression to ESRD - severe renal insufficiency

Jones et al NEJM 1996

TORONTO Glomerulonephritis REGISTRY

Risk of Deterioration in Kidney Function

- "mostly" prospective cohort (1977-2004)
  - 49 women with GFR < 60 ml/min/1.73m^2
  - No diabetes or systemic illness
- Primary Outcome

Imbasciati and Ravani AJKD 2007

  - Rate of GFR loss prior to and after pregnancy

GFR Proteinuria	> 40 ml/min < 1 gm	> 40 ml/min > 1 gm	< 40 ml/min < 1 gm	< 40 ml/min > 1 gm
n=	16	6	12	15
Pre-pregnancy	0.47±0.35	0.35±0.31	0.55±0.38	0.21±0.20
Post-delivery	0.30±0.48	0.33±0.31	0.55±0.39	1.17±1.23

Risk of Deterioration in Kidney Function

Mostly Retrospective

Small & Single Centre

Use serum creatinine to determine baseline renal insufficiency and often lack pre-pregnancy Cr

Combine all renal diseases together

Fail to sort out the impact of pre-pregnancy proteinuria/glomerular-based disease (not all proteinuria is created equally)

Difficult to determine independent impact of hypertension, proteinuria and renal insufficiency

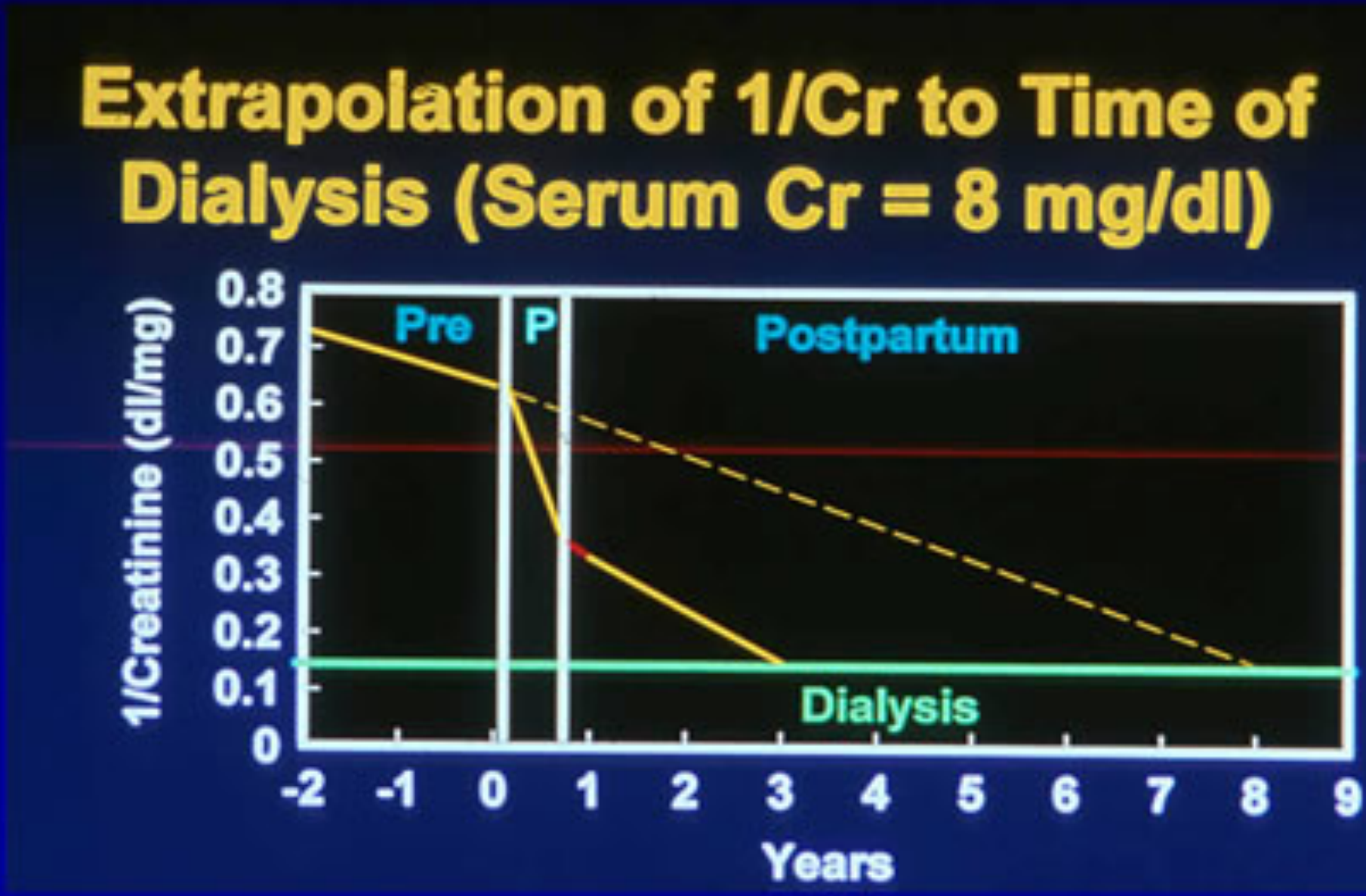
TORONTO Glomerulonephritis REGISTRY

Highest Risk for Progression

- Renal Dysfunction
- Proteinuria
- Hypertension

ADDITIVE

Susan Hou Lecture Series



RISK OF ADVERSE PREGNANCY OUTCOMES

TORONTO
Glomerulonephritis
REGISTRY

Risk of Adverse Pregnancy Outcomes

- Systematic Review and Meta-Analysis
  - 23 studies of 14 included patients with CKD
  - 933 pregnancies
  - Preeclampsia OR 10.36 (95% CI 6.27-17.09)
  - Preterm Delivery OR 5.72 (95% CI 3.26-10.03)
  - SGA OR 4.85 (95% CI 3.03-7.76)
  - C Section OR 2.67 (95%CI 2.01-3.54)
- Heterogeneity was significant
  - Effect modifiers included proteinuria & type of disease

Zhang et al CJASN 2015

TORONTO Glomerulonephritis REGISTRY

Is CKD an Independent Risk Factor for Poor Pregnancy Outcomes ?

Piccoli et al JASN 2015

- Comparison of 504 pregnancies in women with with CKD to 836 low-risk pregnancies (Turin and Cagliari)

Table 4. Comparisons across CKD stages

Characteristic	CKD Stage				*P* Value across Stages
	1 (*n*=370)	2 (*n*=87)	3 (*n*=37)	4–5 (*n*=10)	
Maternal-fetal outcomes					
Cesarean sections	48.4	70.1	78.4	70.0	<0.001
Gestational week	37.6±2.6	35.7±3.2	34.4±2.4	32.6±4.2	<0.001
Preterm delivery (<37 wk)	23.5	50.6	78.4	88.9	<0.001
Early preterm (<34 wk)	7.3	20.7	37.8	44.4	<0.001
Birth weight (g)	2966.5±659	2484±707	2226.3±582	1639±870	<0.001
SGA score (Parazzini)					
<10%	13.3	17.9	18.9	50.0	0.02
<5%	5.1	6.0	5.4	25.0	0.12
Need for NICU	10.3	27.6	44.4	70.0	<0.001
General combined outcome	34.1	63.2	83.8	90.0	<0.001
Severe combined outcome	21.4	44.8	59.5	80.0	<0.001
New-onset hypertension (%)	7.9 (23/290)	17.6 (9/51)	47.1 (8/17)	50.0 (4/8)	<0.001
New-onset or doubling of proteinuria	20.5 (76/370)	37.9 (33/87)	86.5 (32/37)	70.0 (7/10)	<0.001
CKD stage shift or RRT start	7.6 (28/370)	12.6 (1/87)	16.2 (6/37)	20.0 (2/10)	0.12

Risk of Poor Pregnancy Outcome

- Renal Dysfunction
- Proteinuria
- Hypertension

ADDITIVE

RISK OF FLARE OR WORSENING PROTEINURIA

TORONTO
Glomerulonephritis
REGISTRY

Risk of a Flare or Worsening of Proteinuria

- Pregnancy Exacerbated Glomerular Diseases
  - ? MCD, FSGS, MN, IgA
    - Deserves further study
  - Lupus
  - ANCA

TORONTO Glomerulonephritis REGISTRY

DISEASE SPECIFIC OUTCOMES

TORONTO
Glomerulonephritis
REGISTRY

Pregnancy Outcomes of Primary GN

- Systematic Review CJASN in press
  - After 1980
    - Difficult to ascertain pathological diagnosis prior
    - Advances in neonatal care
  - Minimum of 10 women
  - Report live birth weight
- 18 studies, 887 women, 1414 pregnancies
  - Baseline characteristics – not reported or inadequately described
  - Significant heterogeneity
  - Study quality poor

NO POOLING

TORONTO Glomerulonephritis REGISTRY

Pregnancy Outcomes of Primary GN

Table 1. Pregnancy outcomes by primary glomerular disease type

Study, yr	Women (No. of Pregnancies)	Average Age at Pregnancy, yr	Prepregnancy Hypertension (%)	Prepregnancy ↑ Creatinine (%)	Pregnancies with Preeclampsia (%)	↑ BP Postpregnancy	↑ Creatinine Postpregnancy	No. of Infants [Survived Infants (%)]	BW, g	GA, wk
IgA nephropathy										
Surian *et al.* (3)	21 (29)	NA	NA	NA	NA	NA	0 (0)	29 [26 (90)]	NA	NA
Barceló *et al.* (4)	10 (15)	NA	NA	NA	0(0)	NA	0 (0)	15 [14 (93)]	NA	NA
Jungers *et al.* (5)	34 (69)	NA	10 (14)	3 (4)	NA	NA	3 (4)	70 [57 (81)]	3200	NA
Kincaid-Smith and Fairley (6)	65 (102)	NA	NA	NA	NA	16 (16)	NA	102 [74 (73)]	NA	NA
Packham *et al.* (7)	70 (116)	NA	18 (16)	1 (1)	NA	15 (13)[a]	NA	118 [83 (70)]	NA	NA
Nagai *et al.* (8)	17 (19)	29	5 (26)	0 (0)	NA	9 (47)	1 (5)	19[19 (100)]	2937	39
Abe (9)	118 (168)	NA	15 (9)	NA	NA	9 (11)[b]	NA	168 [146 (87)]	NA	NA
Limardo *et al.* (10)	136 (229)	27	27 (20)[c]	0 (0)	17 (9)	34 (31)	13 (9.6)	229 [195 (85)]	3039	NA
Limardo *et al.* (10)	10 (10)	29	4 (40)	10 (100)	NA	NA	NA	10 [8 (80)]	NA	NA
Shimizu *et al.* (11)	29 (29)	31	NA	NA	0 (0)	NA	NA	29 [29 (100)]	2911	38
Waness *et al.* (12)	12 (12)	29	2 (17)	0 (0)	3 (25)	NA	NA	12 [12 (100)]	3100	NA
Liu *et al.* (13)	62 (69)	27	7 (11)	NA	6 (9)	8 (12)	NA	69 [59 (86)]	2972	NA
FSGS										
Surian *et al.* (3)	19 (25)	NA	NA	NA	NA	NA	0 (0)	25 [19 (76)]	NA	NA
Barceló *et al.* (4)	13 (17)	NA	NA	NA	1 (6)	1 (6)	0 (0)	17 [16 (94)]	NA	NA
Kincaid-Smith and Fairley (6)	15 (28)	NA	NA	NA	NA	5 (18)	NA	28 [23 (81)]	NA	NA
Packham *et al.* (15)	21 (31)	NA	5 (24)	NA	NA	NA	4 (13)	31 [17 (55)]	NA	31
MCD										
Abe *et al.* (16)	10 (17)	NA	NA	NA	NA	NA	0 (0)	17 [12 (71)]	NA	NA
Jungers *et al.* (5)	19 (31)	NA	0 (0)	0 (0)	NA	0 (0)	0 (0)	34 [26 (76)]	3300	NA
MN										
Jungers *et al.* (5)	18 (37)	NA	7 (19)	0 (0)	NA	NA	1 (3)	37 [25 (67)]	2900	NA
Packham *et al.* (17)	24 (33)	NA	0 (0)	NA	NA	3 (9)	2 (8)	33 [25 (76)]	NA	NA
GN, disease type not specified										
Malik *et al.* (90)	17 (85)	36	NA	NA	14 (16)	NA	NA	85 [81 (95)]	NA	NA
Abe (91)	12 (15)	28	NA	NA	7 (58)	NA	NA	15 [11 (73)]	2115	NA
Packham *et al.* (92)	91 (168)	NA	20 (12)	0 (0)	NA	11 of 80 without hypertension at baseline	0 (0)	169 [136 (80)]	NA	NA
Abe *et al.* (16)	32 (50)	NA	NA	NA	NA	NA	4 (8)	50 [43 (86)]	NA	NA
Hou *et al.* (93)	12 (12)	NA	6 (50)	12 (100)	NA	3 (25)	9 (75)	12 [11 (92)]	NA	33

CJASN in press

TORONTO Glomerulonephritis REGISTRY

Pregnancy Outcomes in Primary GN

- IgA Nephropathy
  - Live birth rate: 70-100%
    - Worse before 2000
  - Birth weight: 2911-3200 g (n=5)
  - Preeclampsia: 0-25% (n=5)
  - Histology (n=1)
    - Fibrosis and sclerosis associated with worse outcomes

TORONTO Glomerulonephritis REGISTRY

Pregnancy Outcomes in Primary GN

- Largest study of 229 pregnancies
  - Cr < 1.2 mg/dl

Table 3. Progressive Models of Kidney Function Decrease Over Time

	Covariates	Coefficient (95% CI)	P
Model 1[a]	Baseline mean CCr (intercept)	96 (93.3 to 98.7)	<0.001
	Overall change (slope)	−1.31 (−1.63 to −0.99)	<0.001
Model 2[b]	Mean CCr, nonpregnancy group	91.7 (88.3 to 95.1)	} <0.001
	Mean CCr, pregnancy group	100.5 (97.2 to 103.8)	
	Slope, nonpregnancy group	−1.13 (−1.62 to −0.64)	} 0.2
	Slope, pregnancy group	−1.56 (−1.95 to −1.16)	
Model 3[b]	Mean CCr, nonpregnancy group	95.6 (91.9 to 99.4)	} 0.001
	Mean CCr, pregnancy group	103.1 (99.4 to 106.7)	
	Slope, nonpregnancy group	−1.08 (−1.59 to −0.56)	} 0.5
	Slope, pregnancy group	−1.30 (−1.76 to −0.84)	
Model 4[b]	Mean CCr, nonpregnancy group	96.4 (92.3 to 100.5)	} 0.001
	Mean CCr, pregnancy group	103.7 (99.2 to 108.2)	
	Slope, nonpregnancy group	−0.62 (−1.15 to 0.08)	} 0.8
	Slope, pregnancy group	−0.70 (−1.23 to 0.17)	

Limardo et al AJKD 2010

Glomerulonephritis REGISTRY

Pregnancy Outcomes in Primary GN

- Excluded Pregnancies
  - Cr > 1.2 mg/dl
  - 8 live births and "other outcomes in keeping with studies of women with more advanced CKD"

	Became Pregnant	Did Not Become Pregnant
No. of patients	10	12
Baseline characteristics		
Age (y)	28.6 ± 4.7	28.3 ± 5.2
SCr (mg/dL)	1.65 ± 0.39	1.60 ± 0.19
CCr (mL/min)	47.2 ± 14.7	49.2 ± 8.4
Proteinuria (g/d)	1.75 (0.48, 2.60)	1.9 (1.43, 3.47)
Hypertension	4	7
Follow-up (y)	5.3 (3-12)	5.0 (4-10)
Outcomes (end of follow-up)		
SCr (mg/dL)	4.68 ± 3.47	4.72 ± 3.40
CCr (mL/min)	24.7 ± 18.6	28.5 ± 22.4
ΔCCr (mL/min/y)	−4.25 ± 4.1	−3.64 ± 4.1
CKD stage 5	4	5
Proteinuria (g/d)	1 (0.2, 2.05)	0.85 (0.28, 2.53)
Hypertension	7	12

Limardo et al AJKD 2010

TORONTO Glomerulonephritis REGISTRY

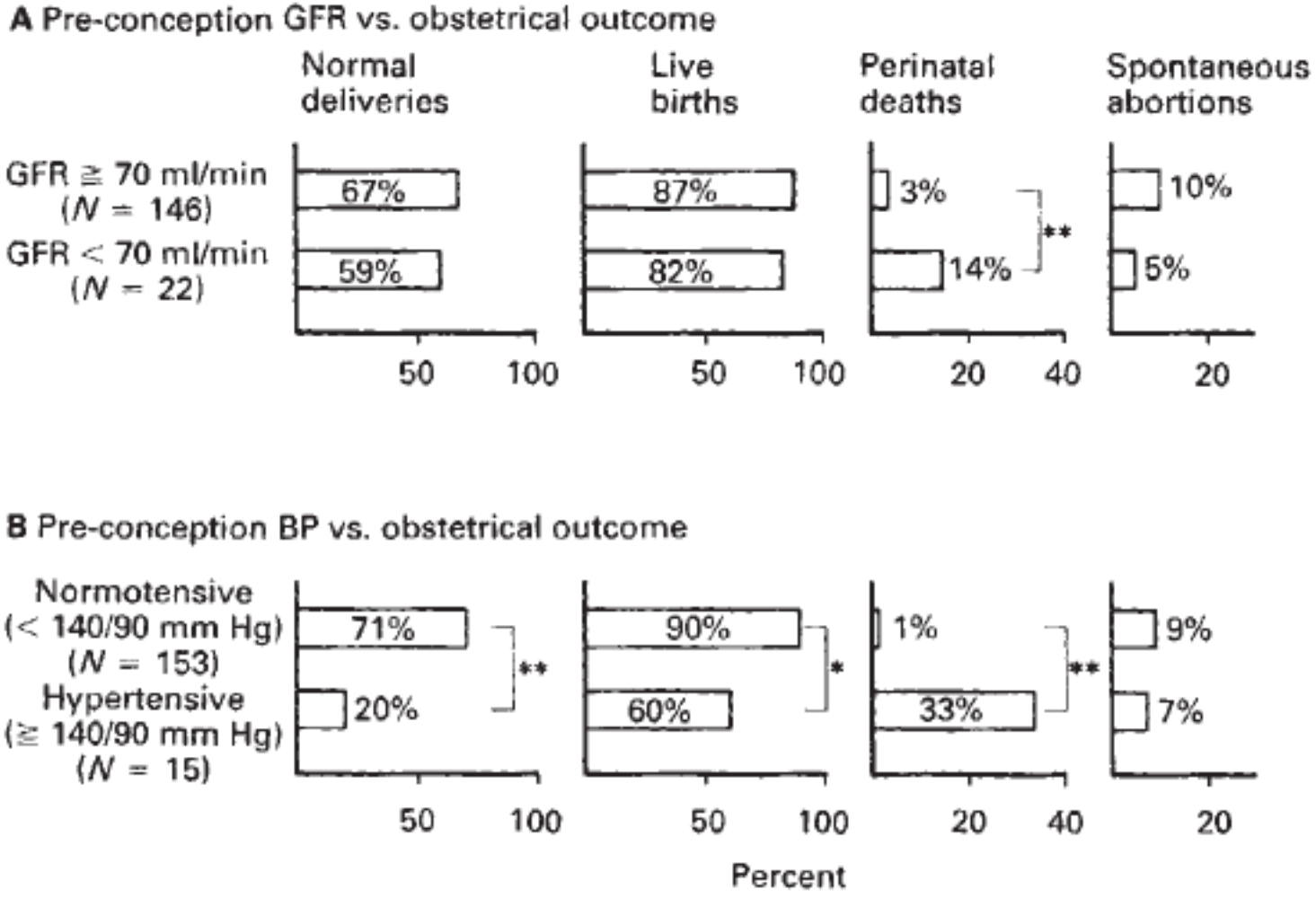
Pregnancy Outcomes in Primary GN

- Pregnancy Outcomes
  - Live Birth Rate: 90%
  - Premature Delivery: 10%
  - Low Birth Weight: 11%
  - Exacerbation of HTN: 21%
  - Preeclampsia: 8.5%
    - Risk Factors proteinuria > 1 g and/or HTN
    - BUT median proteinuria 1 g and only 20% had HTN – WELL COHORT

Limardo et al AJKD 2010

TORONTO Glomerulonephritis REGISTRY

Pregnancy Outcomes in Primary GN

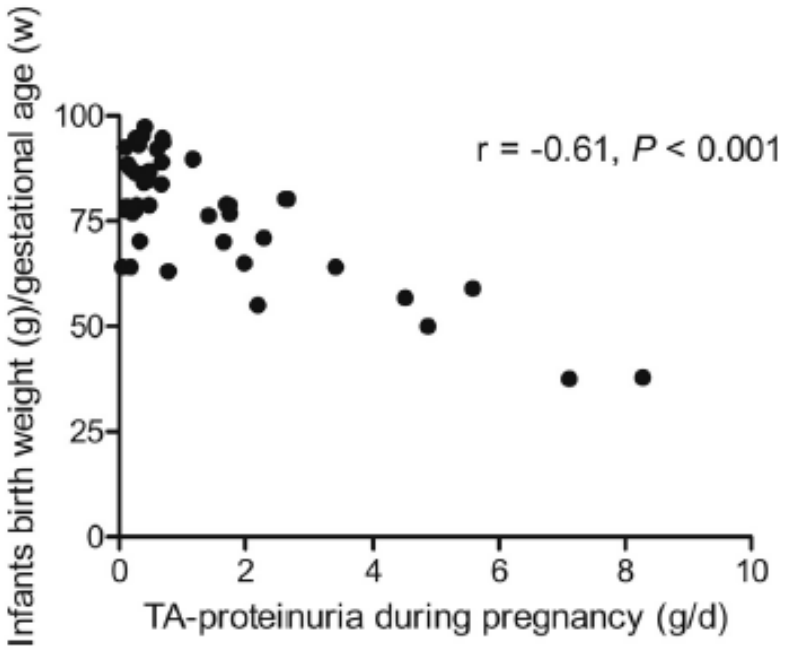


Abe KI 1991

Pregnancy Outcomes in Primary GN

- 62 pregnancies
  - Preserved GFR 102 ± 22 ml/min
  - 57% > 1 g of proteinuria

Variable	Value
Live birth	59 (86)
Preterm delivery	7 (10)
Delivery by cesarean section	42 (61)
Vaginal delivery	17 (25)
Fetal death	10 (15)
Intrauterine death	2 (3)
Embryo damage	3 (4)
Fetal malformation	3 (4)
Spontaneous abortion	1 (2)
Induced abortion	1 (2)
Maternal severe pre-eclampsia	6 (9)
Low birth weight[a,b]	8 (14)
Mean birth weight (g)[b]	2,972 ± 654



Liu et al AJKD 2010

Pregnancy Outcomes in Primary GN

- Small and all published before 1990
  - FSGS (n=4)
    - Live Birth Rate: 54-94%
    - Preterm: 24%
  - MCD (n=2)
    - Live Birth Rate: 71-76%
  - Membranous Nephropathy (n=2)
    - Live Birth Rate: 67-76%
  - Emerging Themes:
    - Low GFR, HTN & proteinuria = worse outcomes

TORONTO Glomerulonephritis REGISTRY

Pregnancy Outcomes in Primary GN

- UNC Contribution Am J Neph 2017

	All (n = 48)	FSGS (n = 17)	IgAN (n = 18)	MN (n = 6)	MCD (n = 7)	p value
Fetal outcomes						
Fetal loss, n	6 (12.5)	2 (11.7)	2 (11.1)	1 (16.7)	1 (14.3)	1.00
Stillbirth at >20 weeks	4 (8.3)	2 (11.7)	0	1 (16.7))	1 (14.3)	0.29
Neonatal death	2 (4.2)	0	2 (11.1)	0	0	0.73
Gestational age, weeks, median (IQR)	37 (31.5–38.5)	36 (29–38)	37.5 (36–39)	38 (28–39)	32 (32–37)	0.39
Premature delivery	23 (47.9)	10 (58.8)	6 (33.3)	2 (33.3)	5 (71.4)	0.24
32–37 weeks gestation	11 (22.9)	5 (29.4)	2 (11.1)	0	4 (57.1)	0.04
Before 32 weeks gestation	12 (25.0)	5 (29.4)	4 (22.2)	2 (33.3)	1 (14.3)	0.83
Reason for premature delivery						0.15
Not premature	25 (52.1)	7 (41.2)	12 (66.7)	4 (66.7)	2 (28.6)	
Spontaneous premature delivery	5 (10.4)	2 (11.8)	1 (5.6)	0	2 (28.6)	
Induced delivery or C-section						
Maternal indication	13 (27.1)	6 (35.3)	5 (27.8)	0	2 (28.6)	
Fetal indication	1 (2.1)	0	0	1 (16.7)	0	
Intrauterine fetal demise	4 (8.3)	2 (11.8)	0	1 (16.7)	1 (14.3)	
Birth weight, g, median (IQR)	2,529 (1,496–3,273)	2,360 (1,118–3,240)	2,627 (2,136–3,315)	2,940 (815–3,317)	1,960 (1,470–2,796)	0.80
IUGR below 10th percentile	6 (12.5)	4 (23.5)	2 (11.1)	0	0	0.50
IUGR below 3rd percentile	2 (4.2)	2 (11.8)	0	0	0	0.59
Apgar scores, median (IQR), min						
1	8 (6–8.5)	7 (5–8)	8 (7–9)	7.5 (7–8)	8 (6–9)	0.60
5	9 (7–9)	9 (7–9)	9 (9–9)	8.5 (8–9)	9 (7–9)	0.51
Maternal outcomes						
Preeclampsia	16 (33.3)	8 (47.1)	6 (33.3)	0	2 (28.6)	0.23
Active GN during pregnancy	35 (72.9)	15 (88.2)	12 (66.7)	4 (66.7)	4 (57.1)	0.29
≥200% increase in proteinuria*	7/18 (38.9)	3/8 (37.5)	2/6 (33.3)	1/2 (50.0)	1/2 (50.0)	1.0
≥150% increase in serum creatinine*	6/22 (27.3)	5/10 (50.0)	1/8 (12.5)	0/2	0/2	0.23
Dialysis during pregnancy	1 (2.1)	1 (5.9)	0	0	0	1.0
ESRD 12 months post-partum	3 (6.3)	1 (5.9)	2 (11.1)	0	0	1.0
ASA	9%	13%	6%	0%	14%	

Pregnancy Outcomes in Primary GN

- Hope on the Horizon – Cure GN

	Before Diagnosis	After Diagnosis
Number of Pregnancies	612	33
Elective Terminations	4.4% (27/612)	9.1% (3/33)
Kidney Disease Impacted Elective Termination	NA	66.7% (2/3)
Number of Pregnancies excl. Elective Terminations	585	30
Cohort		
MCD (inc. IgM Nephropathy)	10.6% (61/576)	13.3% (4/30)
FSGS	28.1% (162/576)	40.0% (12/30)
MN	25.0% (144/576)	13.3% (4/30)
IgAN (incl. HSP)	35.8% (206/576)	33.3% (10/30)
Increasing Proteinuria	12.5% (67/534)	48.1% (13/27)
Worsening Kidney Function	5.8% (31/538)	35.7% (10/28)
Preeclampsia	7.0% (39/559)	25.9% (7/27)
Eclampsia (Seizures)	0.7% (4/559)	0% (0/27)
HELLP	0.9% (5/547)	3.8% (1/26)
Worsening Blood Pressure	11.7% (65/556)	25.9% (7/27)
Spontaneous Fetal Loss or Still Birth	10.4% (61/585)	14.8% (4/27)
Live Birth	89.1% (521/585)	88.5% (23/26)
Gestational Age of Live Births		
Extremely Preterm (≤27 weeks)	0.4% (2/477)	4.7% (1/21)
Preterm (>27 to <34 weeks)	3.4% (16/477)	9.5% (2/21)
Late Preterm (≥34 to <37 weeks)	7.8% (37/477)	28.6% (6/21)
Full term (37+ weeks)	88.5% (422/477)	57.1% (12/21)

Pregnancy Outcomes in Primary GN

- Hope on the Horizon – Cure GN
- Pregnancies with complications in the before diagnosis group were much sooner to be diagnosed suggesting a mild GN may have already been in place, but not yet diagnosed

	Without Complication		With Complication		GEE
	N	Median (IQR)	N	Median (IQR)	p-value*
Increasing Proteinuria	467	22.9 (12.5-33.2)	67	4.1 (1.3-10.6)	<0.001
Worsening Kidney Function	507	22.2 (11.4-32.2)	31	2.1 (0.8-4.4)	<0.001
Worsening Blood Pressure	491	22.1 (11.2-32.7)	65	9.2 (2.1-22.6)	0.002

*GEE model of square root-transformed pregnancy timing on complication status, unadjusted, accounting for clustering by individual using exchangeable correlation structure

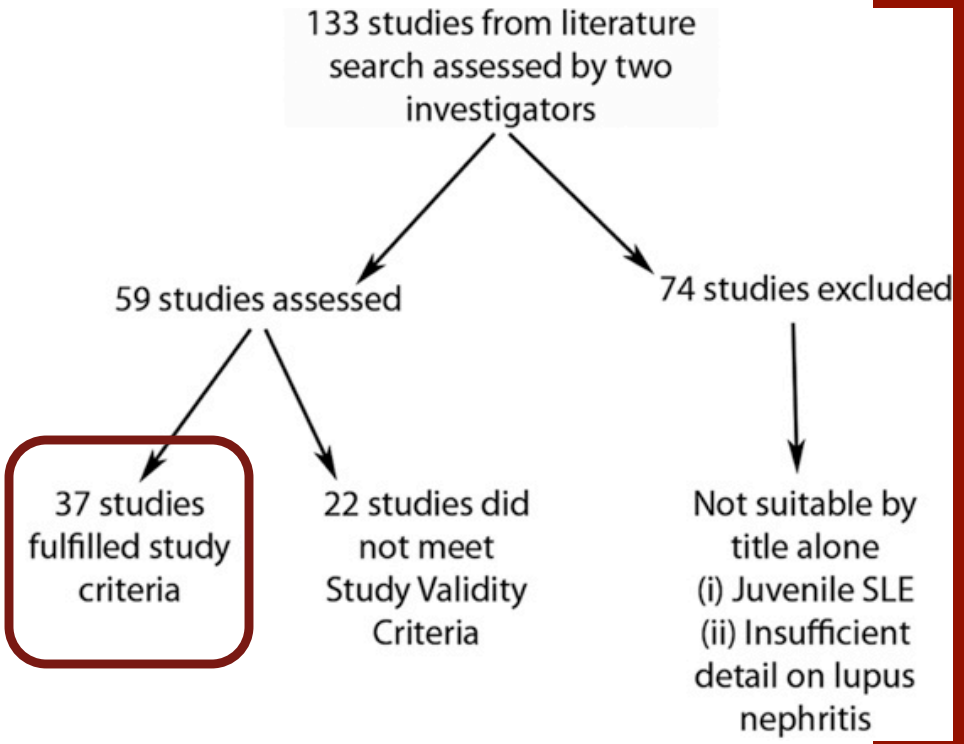
Systemic Lupus Erythematosus & Pregnancy

- Fertility is normal in SLE
- Clinical course in pregnancy is unpredictable; it may improve, exacerbate, or remain unchanged
- Lupus flares can occur during all three trimesters with approximately equal frequency and often in the postpartum period
- Severe morbidity and mortality reported

TORONTO Glomerulonephritis REGISTRY

SYSTEMIC LUPUS ERYTHEMATOUS & PREGNANCY

- Systematic Review & Meta-Analysis
- Pregnancy outcomes in SLE & lupus nephritis
- Studies between 1980-2009
- Purpose:
  - Examine the association of maternal and fetal complications and SLE



1842 patients
2751 pregnancies

Smyth, et al. CJASN (August 2010), 37:754-758.

TORONTO Glomerulonephritis REGISTRY

Systemic Lupus Erythematous & Pregnancy

Maternal Complications	Rate [95% CI]
Overall Unsuccessful pregnancies	23.4% [19.5% to 27.3%]
Lupus flare	25.6% [17.4% to 33.8%]
Hypertension	16.3% [10.3% to 22.3%]
Preeclampsia	7.6% [3.6% to 11.6%]
Severe complications (eclampsia, stroke, maternal death)	1%
Hemodialysis	2 patients
Fetal Complications	
Prematurity	39.4% [32.4% to 46.4%]
Spontaneous abortions	16.0% [12.1% to 19.9%]
IUGR	12.7% [8.8% to 16.7%]
Stillbirth	3.6% [2.0% to 5.2%]
Neonatal Death	2.5% [1.2% to 3.8%]

Smyth, et al. CJASN (August 2010), 37:754-758.

Systemic Lupus Erythematous & Pregnancy
Multivariate Analysis

Maternal Variable	Outcome	P-value
Active Nephritis	Maternal Hypertension Premature Birth	<0.001 <0.020
History of Nephritis	Maternal Hypertension Pre-eclampsia	<0.001 0.017
Positive Anti-phospholipid antibodies	Maternal Hypertension Premature Birth Induced abortion	0.029 0.004 0.016

Smyth, et al. CJASN (August 2010), 37:754-758.

TORONTO Glomerulonephritis REGISTRY

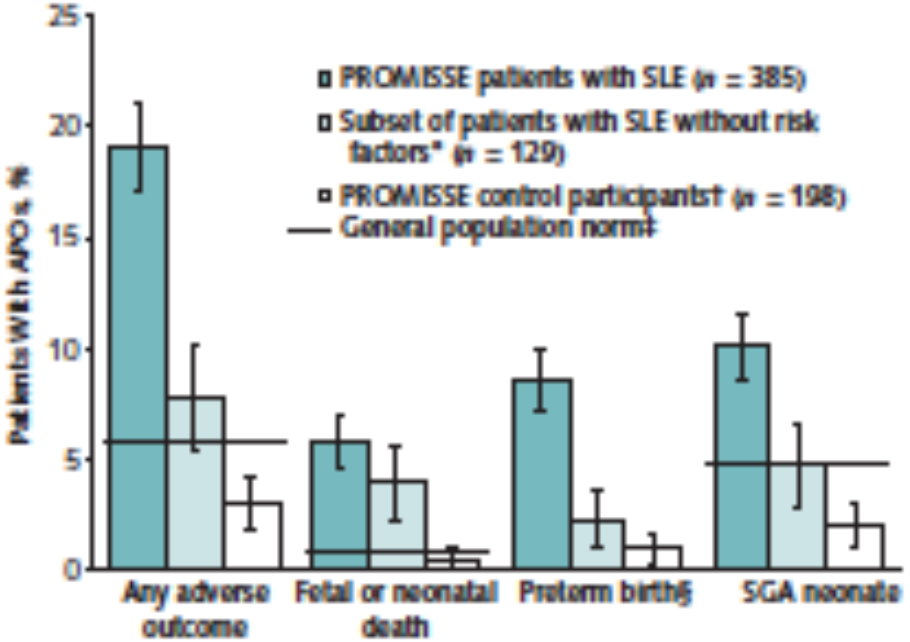
Systemic Lupus Erythematous & Pregnancy

Buyon et al Ann Intern Med 2015

- PROMISSE included 385 women with SLE
  - Excluded
    - U PCR >1000 mg/g
    - Cr>1.2 mg/dL
    - BP > 140/90 mmHg

Adverse Pregnancy Outcomes 19%
Lupus anticoagulant
Antihypertensive Agents
Increased PGA
Platelet count <100
Black or Hispanic

Adverse Pregnancy Outcomes 7.8%
Without Risk Factors



Systemic Lupus Erythematous & Pregnancy

- 71 pregnancies with lupus nephritis

Maternal and fetal complications.

Maternal adverse events	Number (%)
Renal flares	14 (19.7)
Extra renal flares	3 (4.2)
Pre-eclampsia	6 (8.4)
HELLP syndrome	2 (2.8)
Gestational diabetes	6 (8.4)
Severe infections	4 (5.6)
Pregnancies ended in fetal loss	6 (8.4)
Delivery at term	45 (63.4)
Pre-term delivery	20 (28.2)
Fetal adverse events	
Fetal Loss	6 (8.2)
Miscarriages	3 (4.1)
Stillbirths	3 (4.1)
Neonatal deaths	0 (0)
Full term birth	45 (61.6)
Pre-term births	22[a] (30.1)
Small for gestational age	12 (16.4)
Low birth weight <2500 g	20[a] (27.4)
Very low birth weight <1500 g	4 (5.4)
Birth weight g (M±SD)	2753 ± 682

	Odds ratio
Baseline	
SLEDAI	1.184763
Active nephritis	17.73333
Proteinuria g/day	2.746724
Arterial hypertension	18.85714
Previous renal flares	5.25
During pregnancy	
Quarterly change of a single unit in SLEDAI	1.580907
Quarterly increase of proteinuria >1 g per day	14.86718

Moroni et al J Autoimmun 2016

TORONTO Glomerulonephritis REGISTRY

What is Quiescent disease?

- Absence of clinical symptoms
- Laboratory investigations:
  - Normal WBC, PLTs, Hgb
  - Normal or stable C3,C4
  - stable anti-dsDNA

  - Stable renal function
  - Bland urinary sediment
  - Proteinuria <1g/day **OFF RAS**
  - On Hydroxychloroquine

CONSIDER BIOPSY

TORONTO Glomerulonephritis REGISTRY

ANCA Associated Vasculitis

Survey from the Vasculitis Clinical Research Consortium Patient Contact Registry

18 % exacerbated

	Women	
	Pregnancies delivered prior to diagnosis of vasculitis	Pregnancies delivered after diagnosis of vasculitis
No. of pregnancies	496	74
Elective terminations, no.	58	9
Pregnancy loss, no. (%)	98 (22.4)	22 (33.8)*
Miscarriages, no. (%)	93 (94.9)	21 (95.5)
Stillbirths, no. (%)	5 (5.1)	1 (4.5)
Preterm births, no. (%)†	36 (11.1)	10 (23.3)*

Clowse et al Arthritis Care and Research 2013

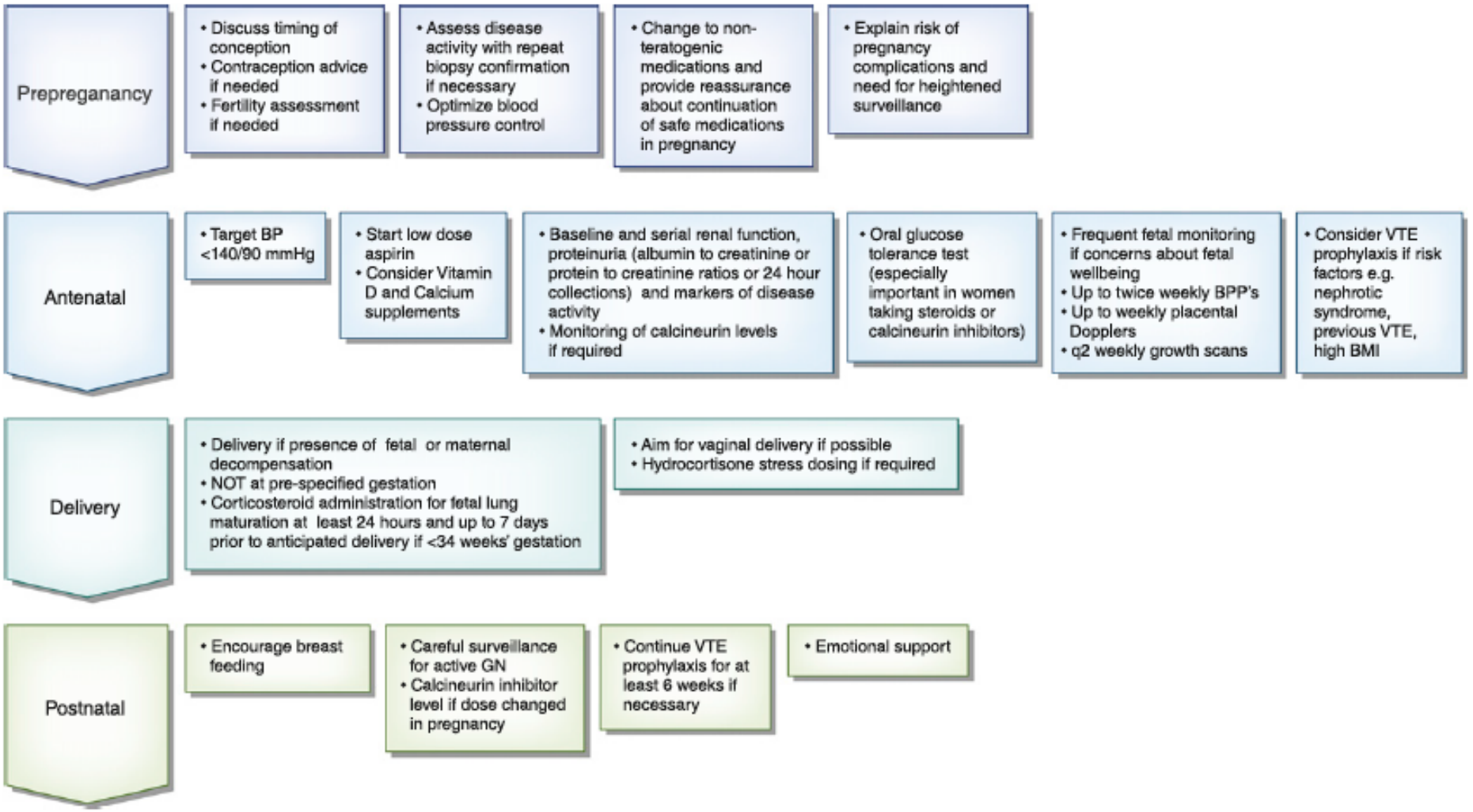
TORONTO Glomerulonephritis REGISTRY

OPTIMIZATION AND MANAGEMENT STRATEGIES

TORONTO
Glomerulonephritis
REGISTRY

Optimization and Management Strategies

CJASN in Press



Treat Proteinuria
Pregnancy Safe Immunosuppression

Prednisone	**B**	**Increased risk of cleft Palate (3/1000 vs 1/1000 in general population)** **Mood/sleep disturbance** **Cushingoid appearance** **Hypertension** **Hyperglycemia/Diabetes Mellitus/Gestational Diabetes** **Osteoporosis** **Avascular necrosis (rare)**
Calcineurin Inhibitors: (monitoring of drug levels recommended during pregnancy) **Cyclosporine (Neoral, Sandimmune)** **Tacrolimus (Prograf)**	**C**	**Use associated with smaller babies** **Hypertension** **Nephrotoxicity/elevated creatinine** **TTP (rare)** **Cyclosporine specific:** **Hirsutism/Hypertrichosis/Gingival hyperplasia** **Tacrolimus specific:** **Alopecia** **Hyperglycemia/Diabetes Mellitus/Gestational Diabetes**
Azathioprine (Imuran)	**D**	**Hepatotoxicity/Elevated bilirubin & ALP**

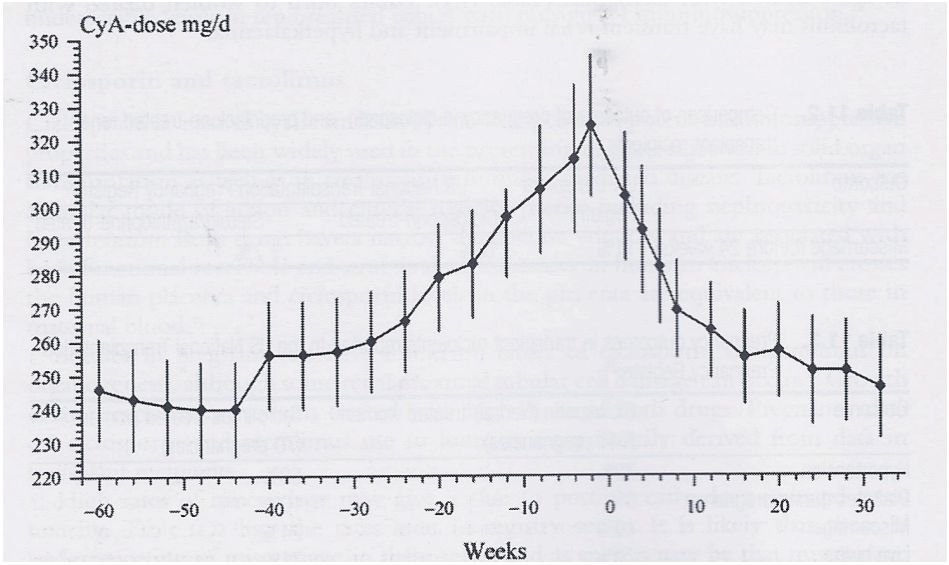
Rituximab (Dose early in pregnancy)
Pulse Methylprednisone
PLEX

TORONTO Glomerulonephritis REGISTRY

CALCINEURIN INHIBITORS

Drug Dosing

- CsA levels go down
  - Increased GFR and metabolism



Davison JM Renal Disease in Pregnancy 2008

- Tacrolimus levels may go up or down
  - Pregnancy may inhibit cytochrome P450 enzymes

Close Follow-up of Levels Target lower Trough

TORONTO Glomerulonephritis REGISTRY

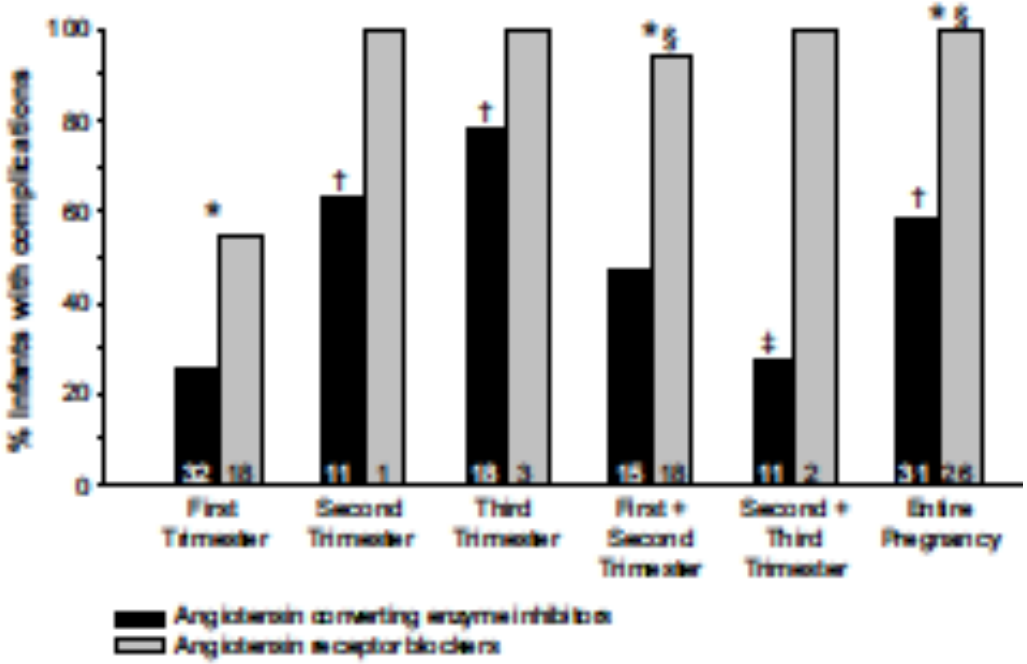
Treat Proteinuria
RAS Blockade

- Second and Third Trimester Exposure
  - oligohydramnios
  - neonatal anuria and renal failure
  - limb contractures
  - craniofacial abnormalities
  - pulmonary hypoplasia
  - patent ductus arteriosus

TORONTO
Glomerulonephritis
REGISTRY

Treat Proteinuria
RAS Blockade

- Systematic Review



Bullo et al Hypertension 2012

TORONTO Glomerulonephritis REGISTRY

Treat Proteinuria

RAS Blockade

First Trimester Exposure

- 465 754 mother infant pairs
  - Kaiser Permanente Northern California
  - Adjusted maternal age, ethnicity, parity and obesity

- 0.9/1000 prevalence of use
- Congenital Heart Defects
  - ACEi vs Normal Control OR 1.54 (0.9-2.62)
  - Other BP Agents vs Normal Control OR 1.52 (1.04-2.21)
  - ACEi or Other BP Agents vs Hypertensive Controls NS

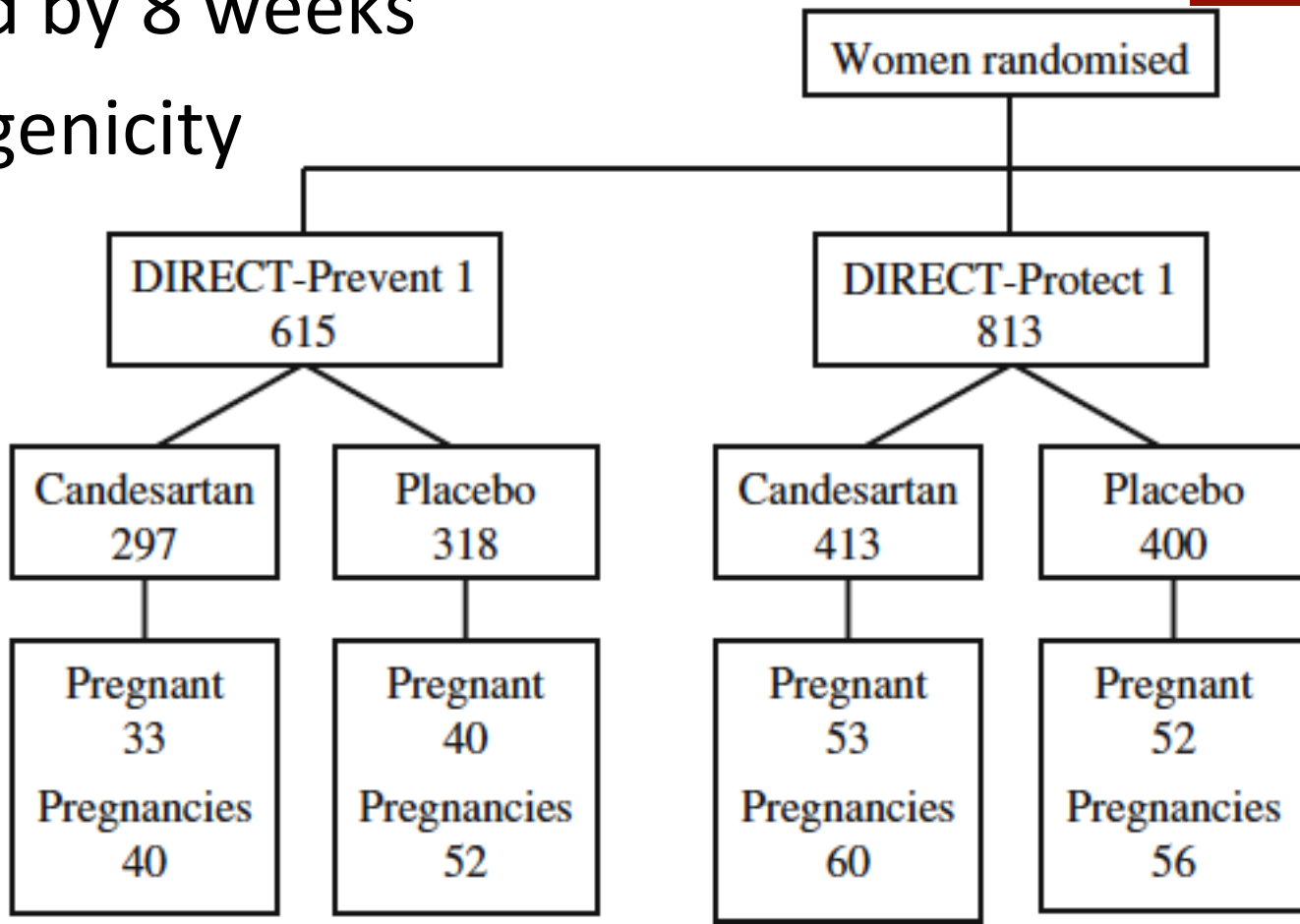
Li et al BMJ 2011

TORONTO Glomerulonephritis REGISTRY

Treat Proteinuria
RAS Blockade

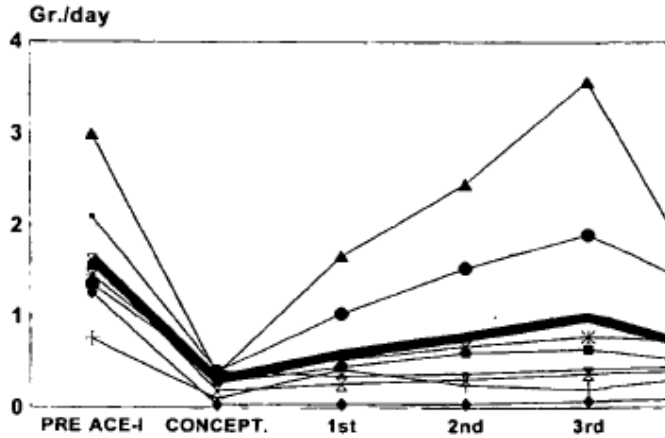
- First Trimester Exposure Direct Studies
  - All stopped by 8 weeks
  - No Teratogenicity

Porta et al
Diabetologica 2011



Treat Proteinuria
RAS Blockade

Hod et al. NDT 1995



- 24 women with diabetic nephropathy
  - 6 months of pre-pregnancy treatment
    - Multiple insulin injections
    - Captopril (37.5-75 mg daily)
  - Pre-Treatment Proteinuria 1292 ± 656 mg/day
  - Post-Treatment Proteinuria 202 ± 141 mg/day
  - Beneficial effect was sustained throughout pregnancy
  - No deterioration in renal function at 2 years postpartum
- Recommendation:
  At least 6 months of ACEI, discontinued at conception

Bar et al Clinical Nephrol 53(6): 437, 2000

TORONTO Glomerulonephritis REGISTRY

Treat Proteinuria
RAS Blockade

Teratogenic

Extreme caution is required in women of child bearing age

Patients that reach ESRD have a decreased life expectancy

Stop at Conception:

Significant Proteinuria without Immunological Options (DM, scarring and IgA)

Regular Cycles

Compliant

TORONTO Glomerulonephritis REGISTRY

Hypertension Management

Methyldopa
- Starting dose 250 BID
- Maximum of 500 QID

Labetolol
- Starting dose 100 BID
- Maximum 200 QID

Nifedipine XL
- Starting dose 30 OD
- Maximum 60 BID

Amlodipine
- 2.5 to 10 mg OD

Hydralazine, thiazides and clonidine also safe

TORONTO
Glomerulonephritis
REGISTRY

CHIPS Trial

ALTHOUGH RENAL PATIENTS EXCLUDED BP CONTROL IS LOGICAL TARGET BP < 140/90 mmHg

- N= 987 (94 sites)
  - Pre-existing or gestational HTN
  - Excluded proteinuria
  - Randomized
    - Less tight control – DBP 100 mmHg
    - Tight Control – DBP 85 mmHg

- Primary (perinatal) outcome [31.4% vs. 30.7%; aOR 1.03, 95% CI 0.78, 1.36]
- Secondary (maternal) outcome [3.7% vs. 2.0%; aOR 1.74, 95% CI 0.79, 3.84]
- 'less tight' control more frequently developed BP ≥160/110mmHg) (40.4% vs. 27.5%; aOR 1.78, 95% CI 1.35, 2.36)

Magee et al NEJM 2015

TORONTO Glomerulonephritis REGISTRY

Secondary Analysis from the CHIPS Trial

- Methyldopa vs Labetalol was associated with less small babies (<10th centile) and preterm delivery (< 37 weeks)

Table 3. Outcomes according to methyldopa or labetalol therapy post-randomisation before delivery, including women who changed from methyldopa or labetalol to a drug other than these two in their 'postrandomisation' group*

	Antihypertensive therapy postrandomisation–before delivery					
	MD (n = 278)**	LB (n = 452)***	Unadjusted		Adjusted*	
			OR (95% CI)****	P	OR (95% CI)****	P
Primary outcome	79/278 (28.4%)	172/452 (38.1%)	0.65 (0.47–0.89)	0.008	0.67 (0.44 1.02)	0.06
Secondary outcome	7/278 (2.5%)	17/452 (3.8%)	0.66 (0.27–1.62)	0.36	0.66 (0.23–1.88)	0.43
Birthweight <10th centile	41/277 (14.8%)	95/449 (21.2%)	0.65 (0.43–0.97)	0.03	0.60 (0.37–0.97)	0.04
Severe hypertension	91/278 (32.7%)	173/452 (38.3%)	0.79 (0.57–1.08)	0.13	0.67 (0.44–1.03)	0.07
Pre-eclampsia	131/278 (47.1%)	236/450 (52.4%)	0.81 (0.60–1.09)	0.16	0.76 (0.51–1.12)	0.17
Delivery <34 weeks	36/277 (13.0%)	84/451 (18.6%)	0.65 (0.43–1.00)	0.05	0.69 (0.41–1.17)	0.17
Delivery <37 weeks	82/277 (29.6%)	187/451 (41.5%)	0.59 (0.43–0.82)	0.001	0.60 (0.40–0.90)	0.01

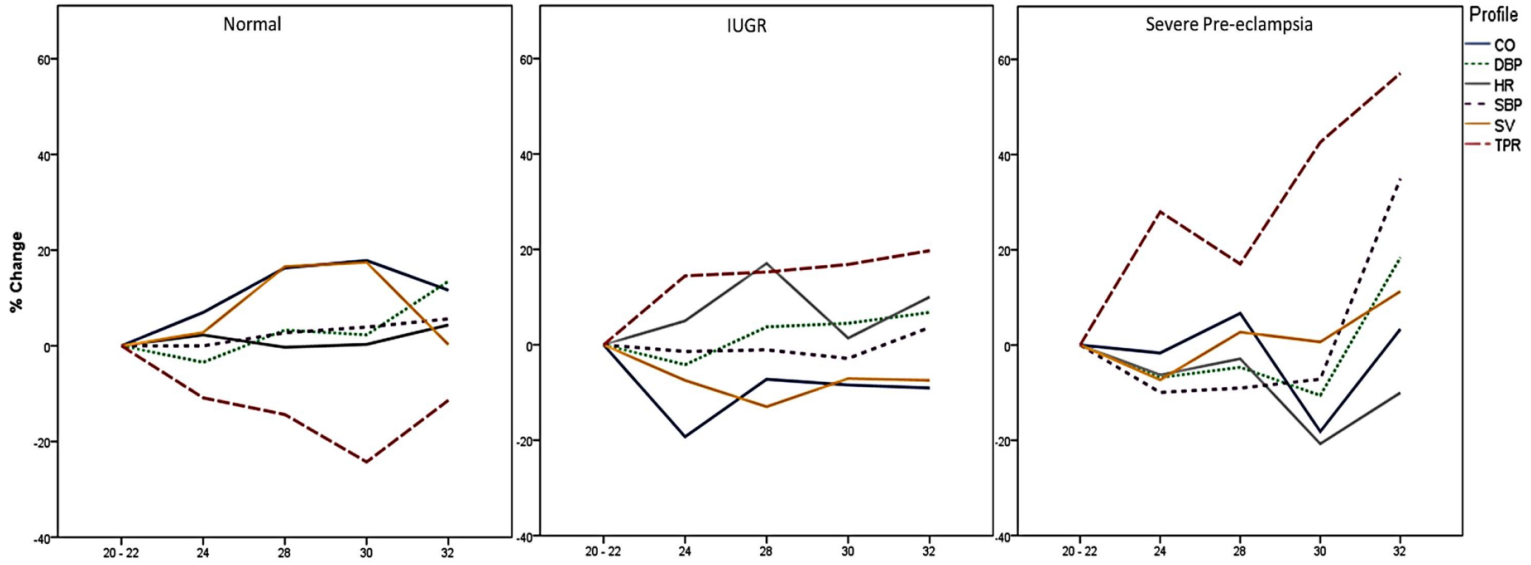
Magee et al. BJOG 2015

TORONTO Glomerulonephritis REGISTRY

Hypertension Management

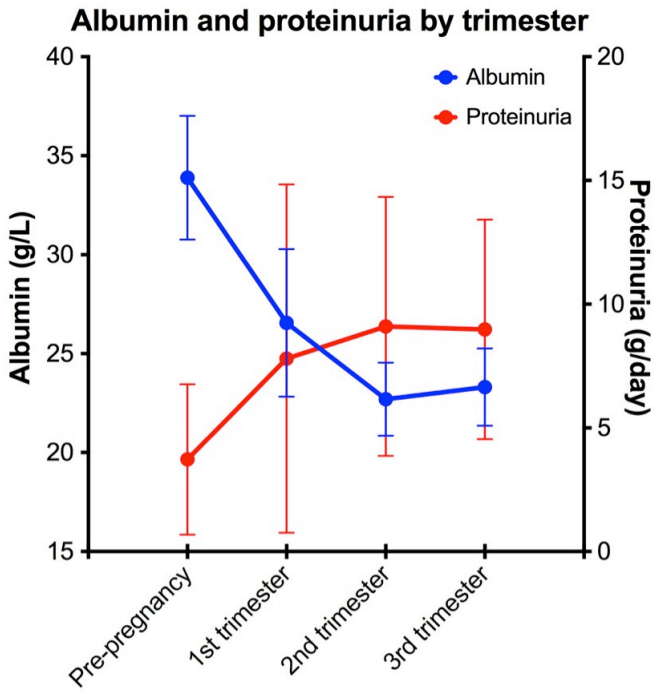
- 1233 eligible women (300 on labetalol and 923 on methyldopa)
- Higher rates of RDS, sepsis and seizure in the infants of mothers prescribed labetalol OR 1.51, 95% CI 1.02-2.22

Xie et al Eur J of Obstet Gyn Reprod Biol 2014



Manage Nephrotic Syndrome

- Management of edema
  - Diuretics
  - Albumin



TORONTO Glomerulonephritis REGISTRY

Pilozzi-Edmonds et al FR-PO579

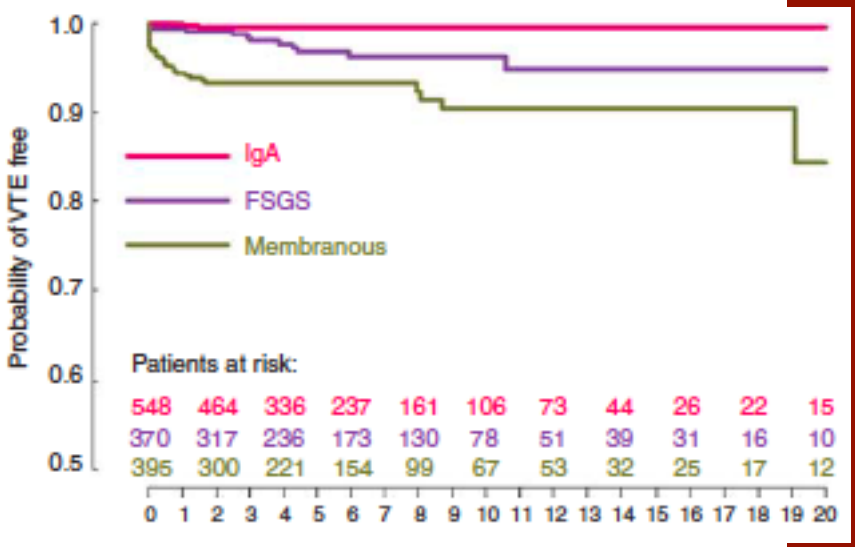
Manage Nephrotic Syndrome

Risk of VTE in Pregnancy

- Population-based cohort study – CIHI data
  - N=3 852 569
- DVT 12.1/10 000
- PE 5.4/10 000
  - Death rates were low

J OB Gyn of Can 2009

Risk of VTE in Nephrotic Syndrome



Barbour et al. KI 2012

Consider VTE prophylaxis

High Grade Proteinuria

Low Albumin

Membranous or Vasculitis

TORONTO Glomerulonephritis REGISTRY

PREVENT PREECLAMPSIA

High-Risk CKD Population

- Renal Insufficiency
- Proteinuria
- Hypertension

Prescribe

- ASA 81 mg daily
- MVI with Folic Acid
- Calcium 1000 mg daily
- Vitamin D 600 IU

recommended to support maternal and fetal bone metabolism

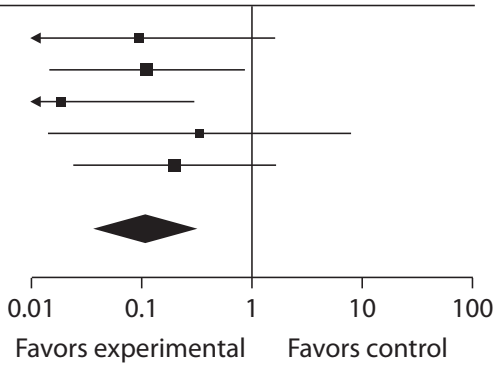
TORONTO Glomerulonephritis REGISTRY

PREVENT PREECLAMPSIA

- ASA prior to 16 weeks reduces only preterm, but not term preeclampsia

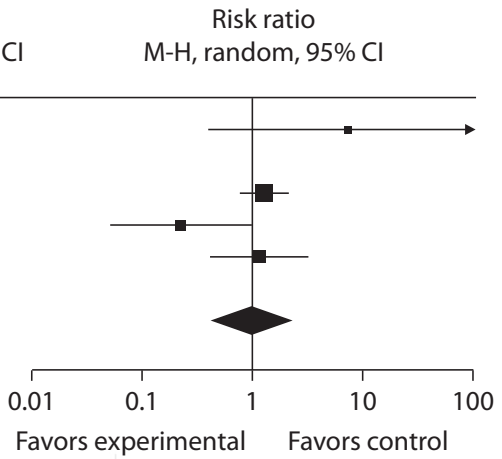
Study or subgroup	ASA events	ASA total	Control events	Control total	Weight %	Risk ratio M-H, random, 95% CI
August, 1994	0	24	5	25	15.2	0.09 (0.01, 1.62)
Bakhti, 2011	1	82	9	82	29.4	0.11 (0.01, 0.86)
Ebrashy, 2005	0	73	23	63	15.9	0.02 (0.00, 0.30)
Vainio, 2002	0	43	1	43	12.2	0.33 (0.01, 7.96)
Villa, 2010	1	61	5	60	27.4	0.20 (0.02, 1.63)
Total (95% CI)		**283**		**273**	**100.0**	**0.11 (0.04, 0.33)**
Total events	2		43			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.79$, d.f. = 4 ($p = 0.59$), $I^2 = 0\%$
Test for overall effect: $Z = 3.92$ ($p < 0.0001$)



Study or subgroup	ASA events	ASA total	Control events	Control total	Weight %	Risk ratio M-H, random, 95% CI
August, 1994	3	24	0	25	7.5	7.28 (0.40, 133.89)
Bakhti, 2011	0	82	0	82		not estimable
Ebrashy, 2005	25	73	17	63	42.8	1.27 (0.76, 2.13)
Vainio, 2002	2	43	9	43	20.4	0.22 (0.05, 0.97)
Villa, 2010	7	61	6	60	29.3	1.15 (0.41, 3.22)
Total (95% CI)		**283**		**273**	**100.0**	**0.98 (0.42, 2.33)**
Total events	37		32			

Heterogeneity: $\tau^2 = 0.38$; $\chi^2 = 6.50$, d.f. = 3 ($p = 0.09$), $I^2 = 54\%$
Test for overall effect: $Z = 0.04$ ($p = 0.97$)



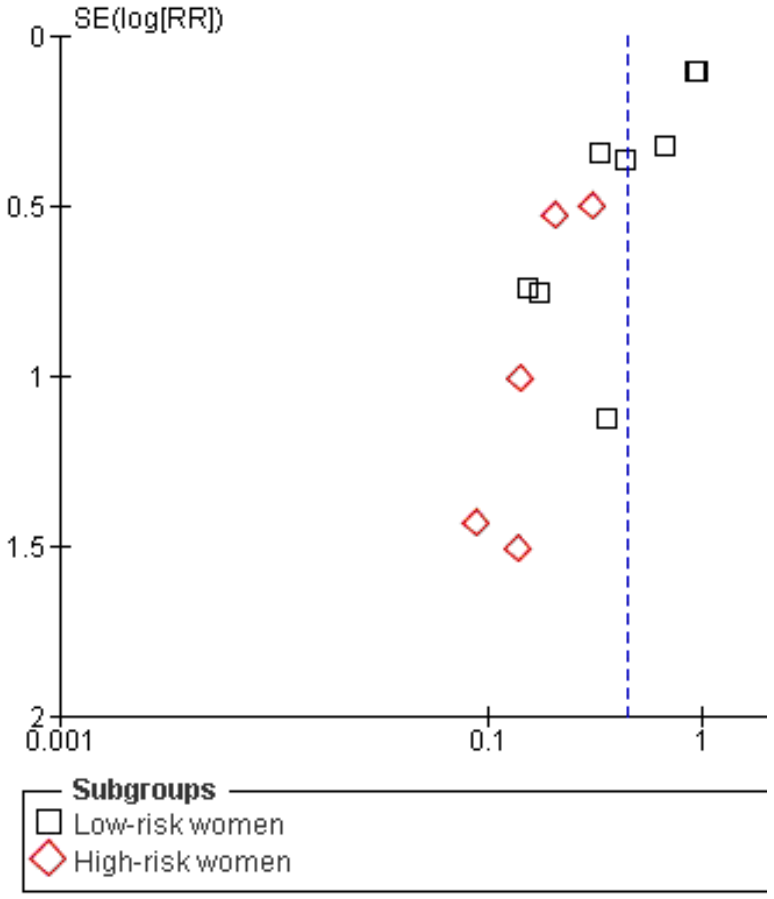
Roberge Fetal Diagn Ther 2012

TORONTO Glomerulonephritis REGISTRY

PREVENT PREECLAMPSIA

Calcium Supplementation

- Overall Risk of Preeclampsia
  - 13 trials (n=15 730)
  - RR 0.45 (0.31-0.65)
- Low Calcium Intake
  - 8 trials (n=10 676)
  - RR 0.36 (0.20-0.65)
- High Risk Women
  - 5 trials (n=587)
  - RR 0.22 (0.12-0.42)



Cochrane Review 2010

TORONTO Glomerulonephritis REGISTRY

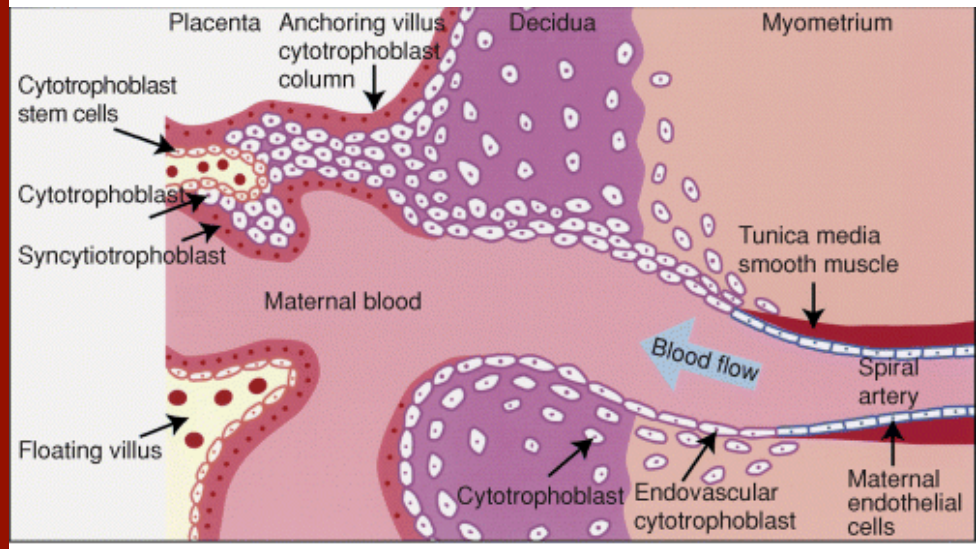
Diagnose Preeclampsia

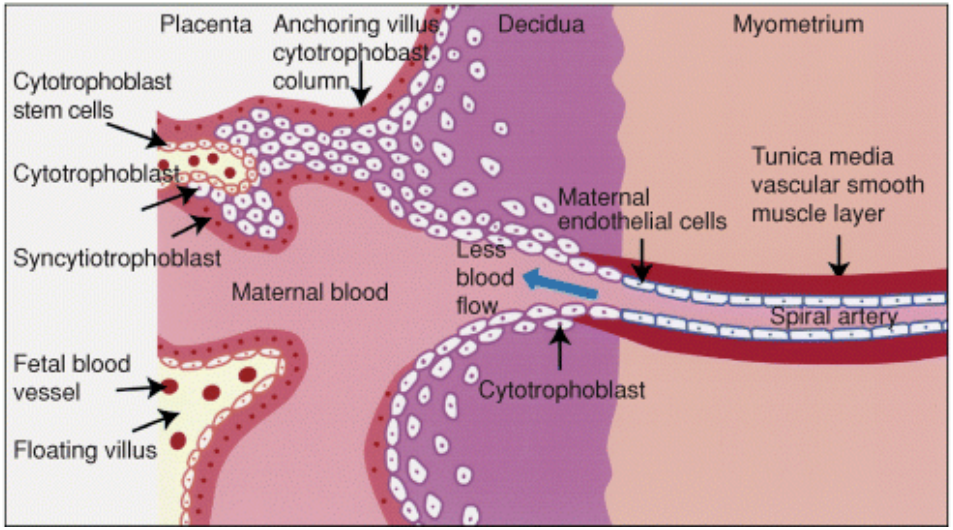
- Urinalysis
- Serology
- Renal biopsy
  - <32 Weeks
    - Based on Expert Opinion
  - Systematic Review
    - 4/197 or 2% major complication rate
      - median of 25 weeks gestation
    - 5% minor complication rate
  - NOT HOW YOU WANT TO DIAGNOSE PREECLAMPSIA

Piccolli et al BJOG 2013

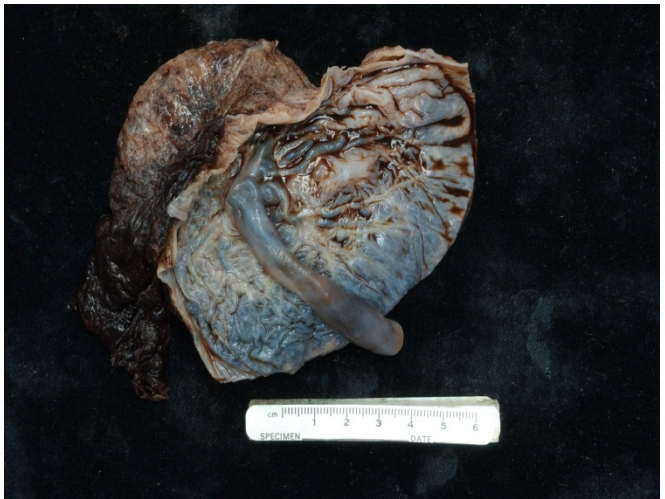
TORONTO Glomerulonephritis REGISTRY

Diagnose Preeclampsia





Alternative splicing of Flt1 ⇨ sFlt1
serum levels of sFlt1 5x higher
unbound VEGF & PlGF are reduced



Antiangiogenic Factors

- Prognosis Study Zeisler NEJM 2016
  - Developmental Cohort (n=500)
  - Validation Cohort (n=550)
  - Predictive Value of sFlt-1/PLGF ratio - < 24 in women suspected of having preeclampsia RULE OUT
- Low PlGF predictive of delivery within 14 days in women with HTN and CKD Bramham KI 2016
- Roche sFlt-1/PlGF Ratio Test (Elecsys®)
  - Electrochemiluminescence
  - Available in the UK, Europe, Canada, Australia, Asia and parts of Latin America

TORONTO Glomerulonephritis REGISTRY

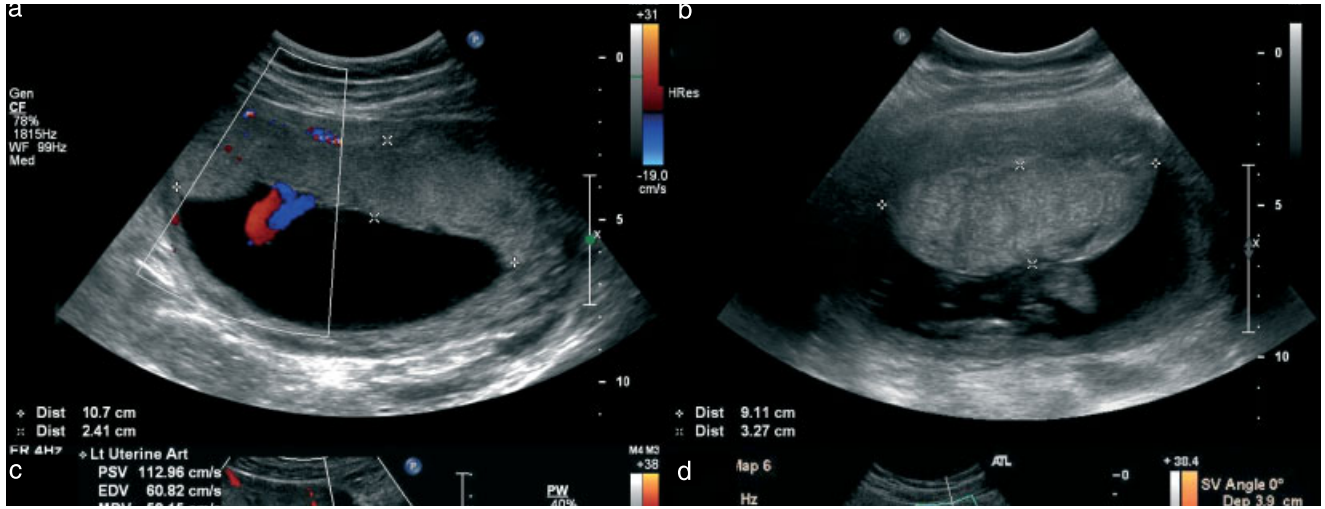
Diagnose Preeclampsia
Clinical Indicators of Abnormal Placentation

First Trimester Screen – 11 to 13 weeks gestation		
PAPP-A	Activate inulin-like growth factors that facilitate placental growth	↓
Maternal Serum Screen – 15 to 20 weeks gestation		
AFP	Fetal liver is the source so its presence in a normal fetus suggests breach in the placental villi	↑
HGC	Excessive secretion by an abnormal syncytiotrophoblast (beware as cleared by kidneys)	↑
DIA	Excessive secretion by an abnormal trophoblast	↑

MSH Placenta Clinic – Dr. John Kingdom
http://www.mountsinai.on.ca/care/placenta-clinic

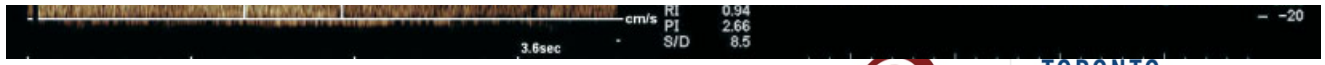
TORONTO Glomerulonephritis REGISTRY

Diagnose Preeclampsia
Clinical Indicators of Abnormal Placentation



Abnormal placenta's might include length<10cm, thickness>4cm, heterogeneous appearance, echogenic cystic areas or even appear "jelly-like"

Procter et al US Ob Gyn 34:274-282, 2009

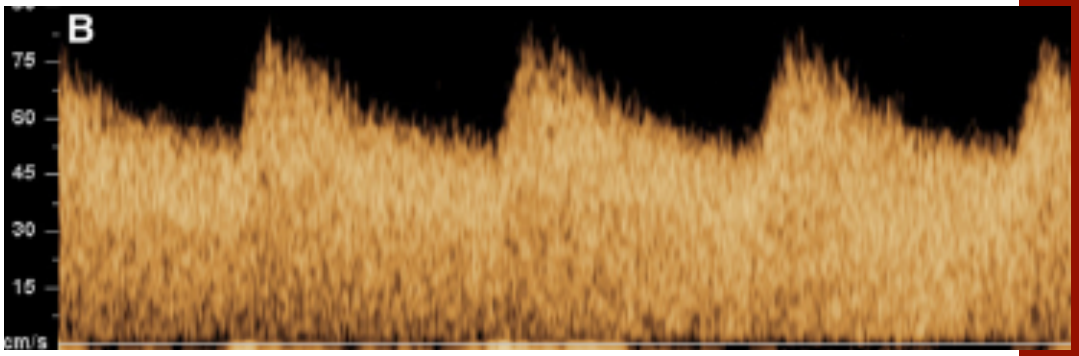


TORONTO Glomerulonephritis REGISTRY

Diagnose Preeclampsia
Clinical Indicators of Abnormal Placentation

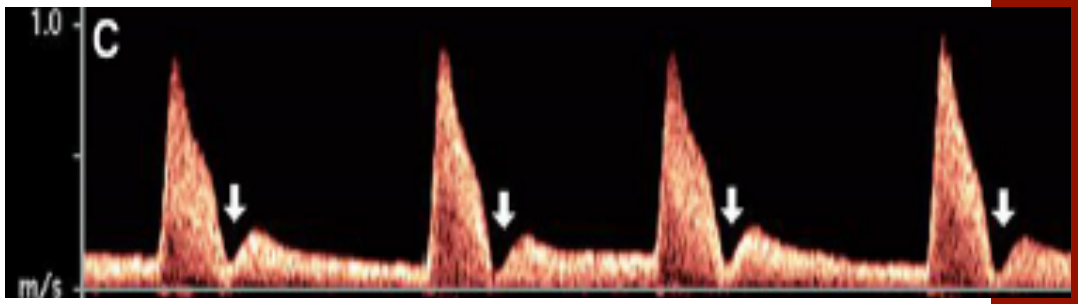
Uterine Artery Doppler

Normal



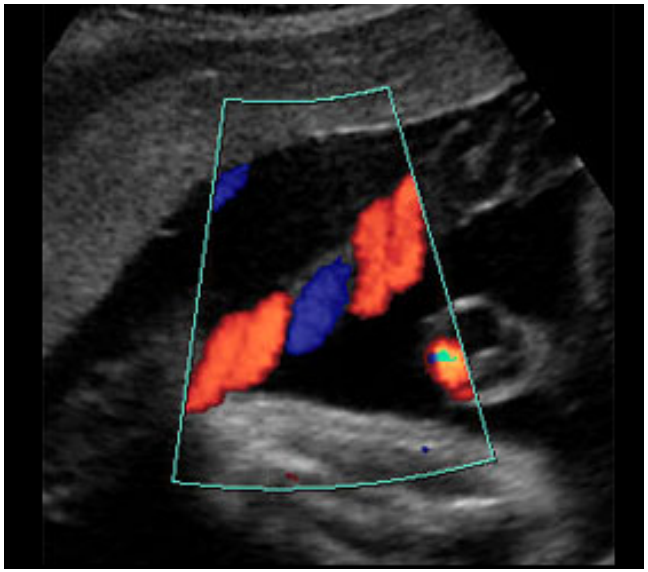
Abnormal

Presence of bilateral UA notching or Pulsatility index >1.45



Diagnose Preeclampsia
Clinical Indicators of Abnormal Placentation

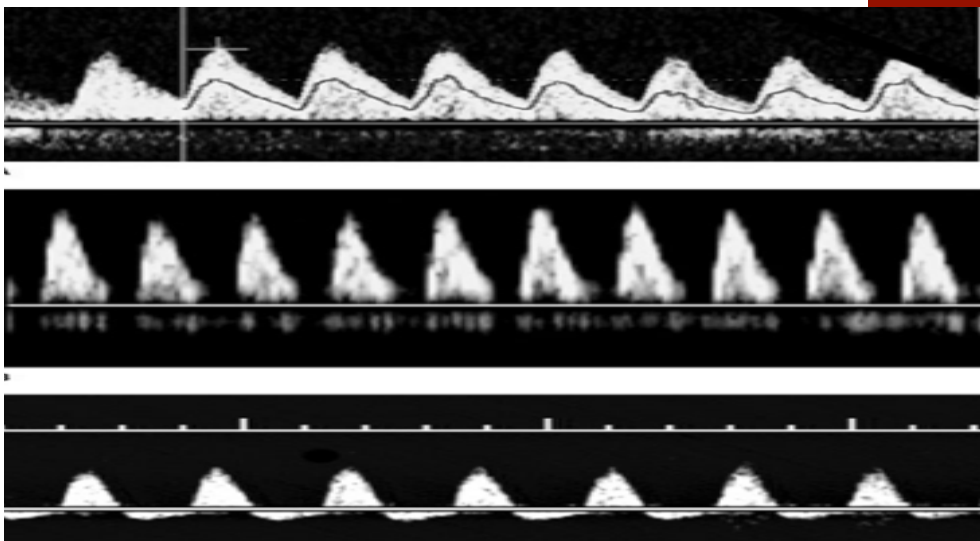
Umbilical Artery Doppler



Normal

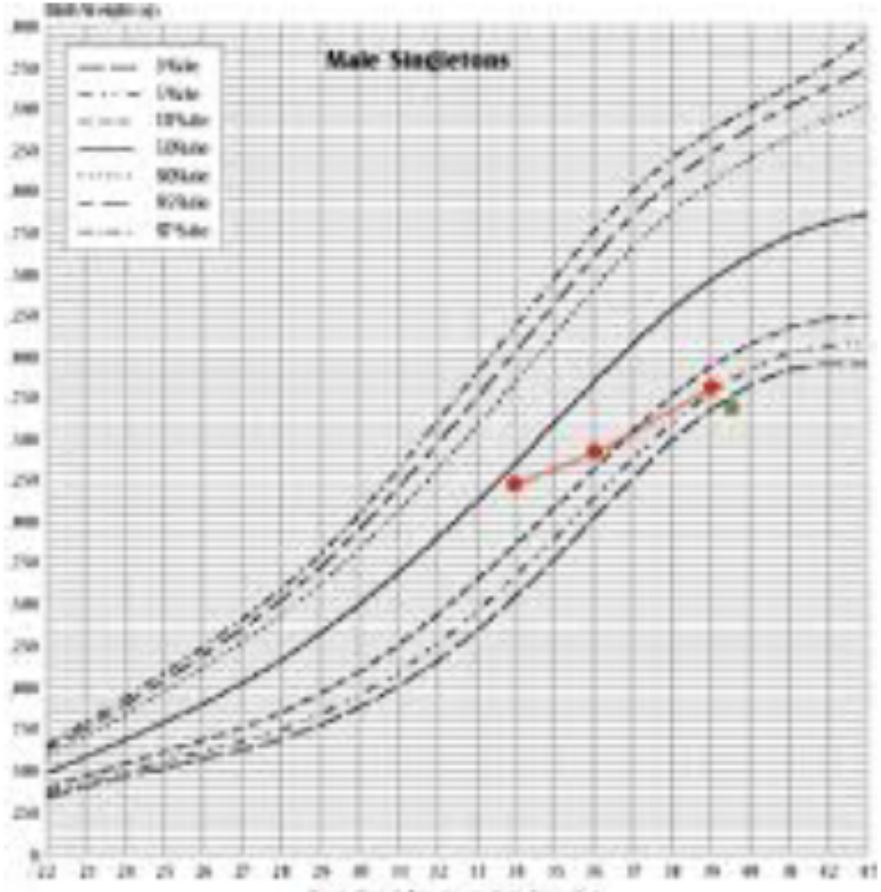
Absent EDF

Reverse EDF



Diagnose Preeclampsia
Clinical Indicators of Abnormal Placentation

- Dropping fetal growth percentile



TORONTO
Glomerulonephritis
REGISTRY

Post Partum Care
Drugs and Breastfeeding

Immunosuppression

- Prednisone
- Imuran
- Cyclosporin
  - Up to 2% of the maternal weight adjusted dose
- Tacrolimus
  - 0.5% of the maternal weight adjusted dose
  - <0.2% of the paediatric dose – MOTHER RISK
  - 0.23% of the maternal weight adjusted dose CJASN 2013

Anti-Hypertensives

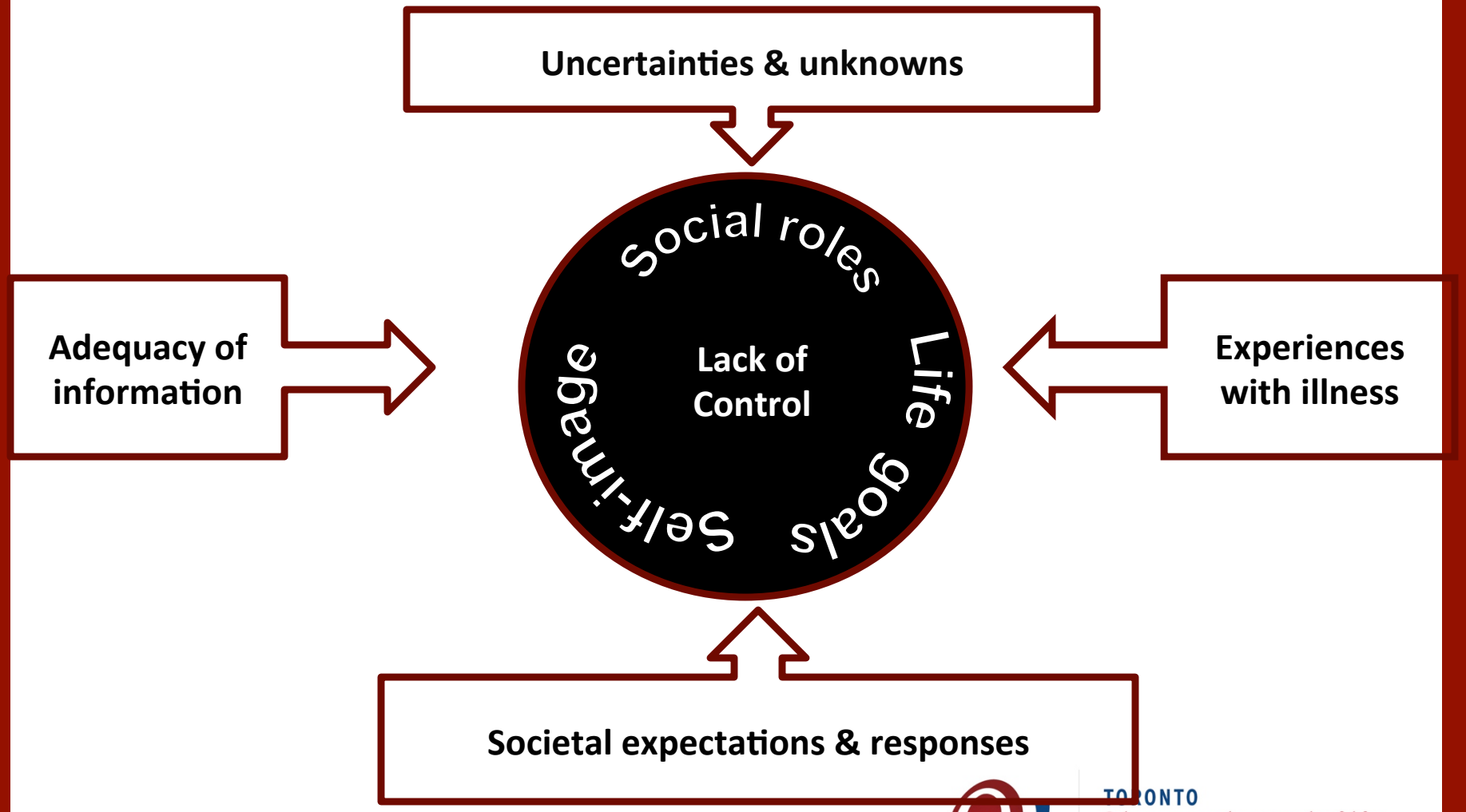
Methyldopa

Lowest Milk/Plasma Ratios

- Labetalol
- Nifedipine
- Captopril
- **Enalapril**
- Quinalapril

TORONTO Glomerulonephritis REGISTRY

Emotional Support



TORONTO Glomerulonephritis REGISTRY

Beanlands, Cattran and Hladunewich KFOC

Pre-Pregnancy Consultation Helps

- 179 women
  - 90% found the clinic informative
  - 92% stated it helped them decide to pursue a pregnancy

Emotional response	9	4	5

- I found this quite stressful and frightening
- The risks scared me so much
- It made me feel safe

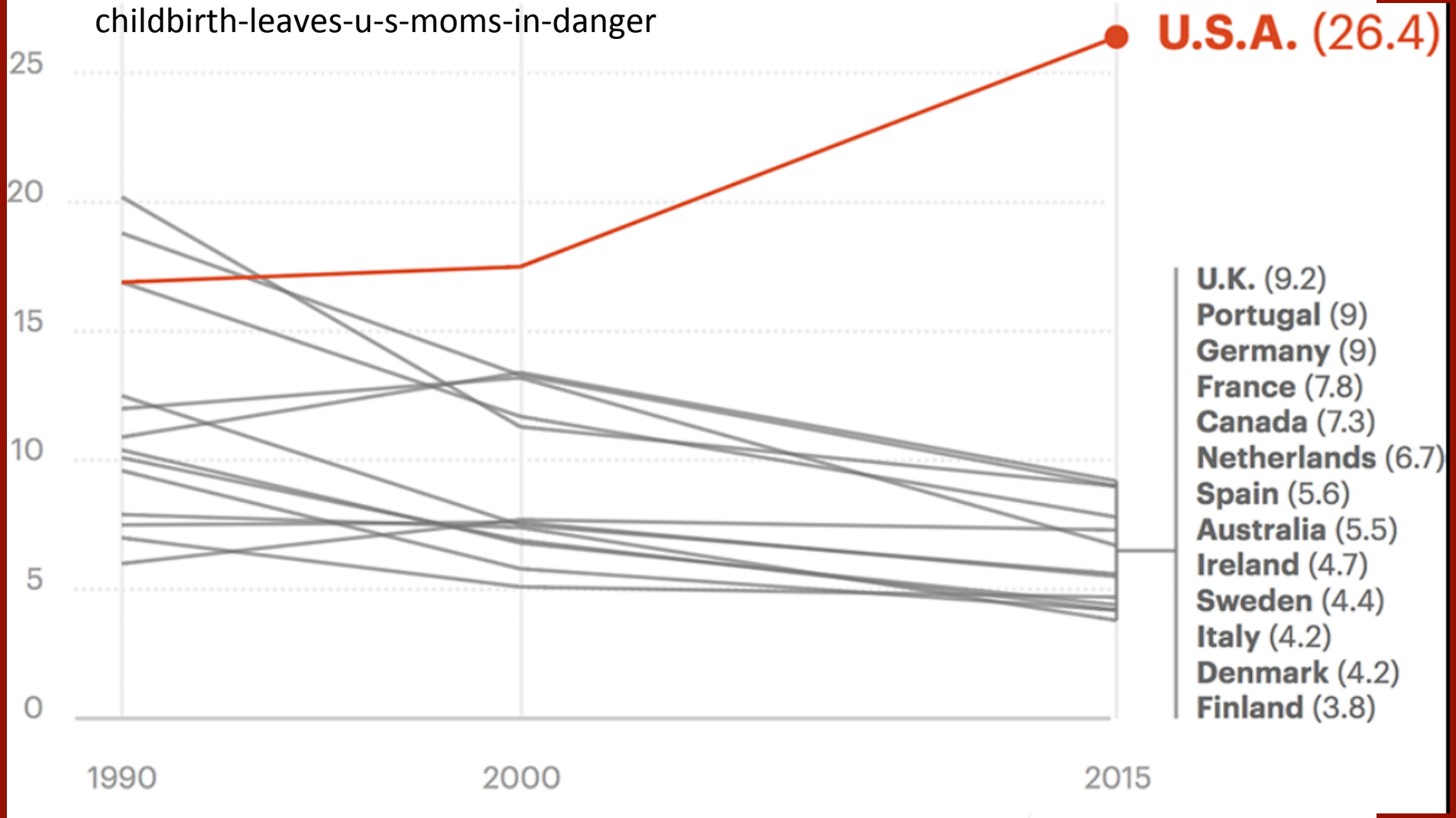
Counseling and preparation requires a significant investment of time and patience

Wiles et al BMC Nephrology 2015

TORONTO Glomerulonephritis REGISTRY

You have to do better

http://www.npr.org/2017/05/12/527806002/focus-on-infants-during-childbirth-leaves-u-s-moms-in-danger



Summary Statements

- Planning Pregnancy – Active Process
  - Educate all young women with kidney disease as to the risks of unplanned pregnancy
  - Treat the Disease Before Conception and during Pregnancy
  - Identify “Windows of Opportunity” along the CKD Continuum as Early is Better than Late
  - Multicenter efforts to refine our advice and management are desperately needed

Cure GN, Neptune,
UKCAN Pregnancy Registry

TORONTO Glomerulonephritis REGISTRY