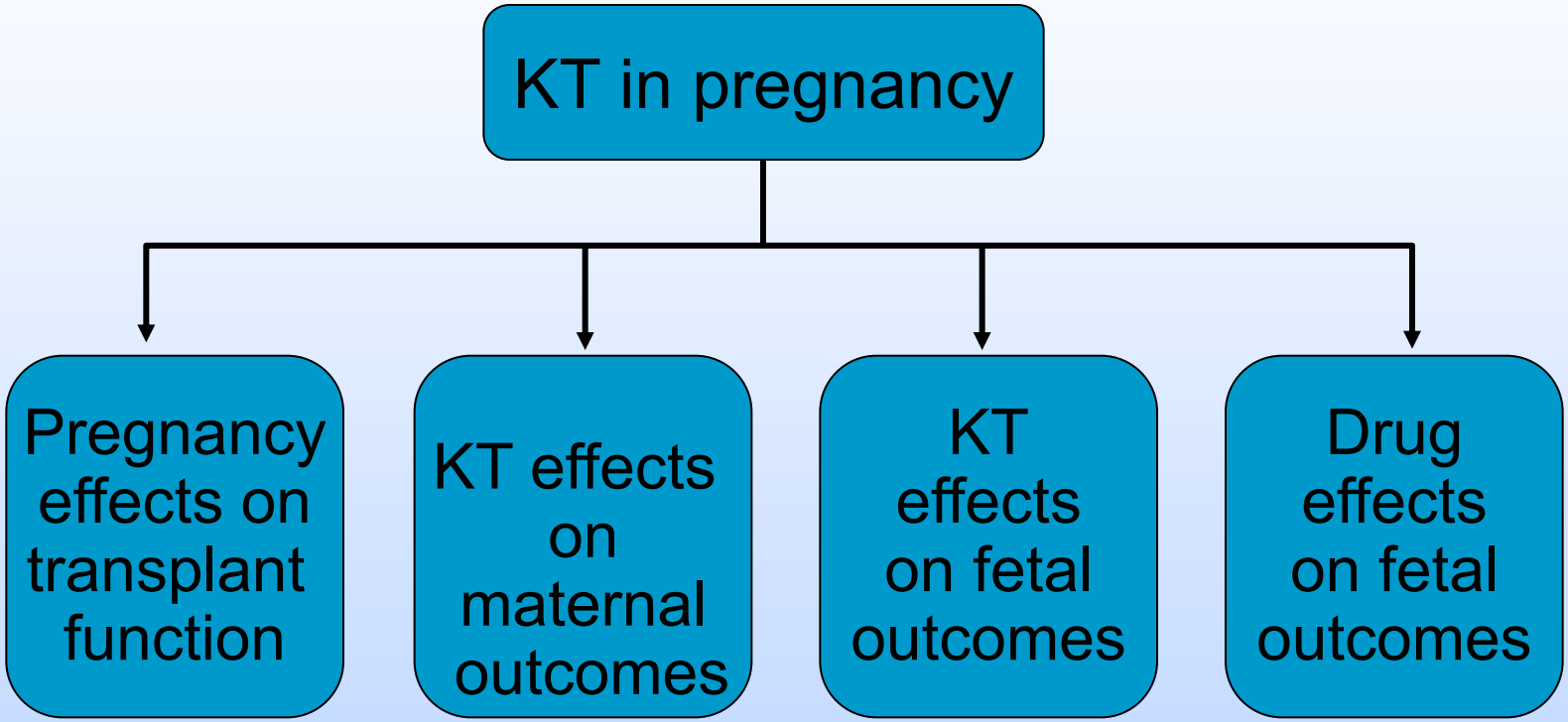
MAYO CLINIC

Pregnancy in Kidney Recipients and Donors

Dr. Vesna D. Garovic

Division of Nephrology and Hypertension
Mayo Clinic Rochester, MN

Kidney Transplant and Pregnancy
The Roadmap



MAYO CLINIC

Physiological Changes of Pregnancy

- Physiological hydronephrosis, which is more prominent on the right side
  - Progesterone-induced ureteral smooth muscle relaxation
  - Ureteral compression 2nd to the enlarging uterus
- GFR increases by up to 50%
  - Elevations in cardiac output
  - ↑renal blood flow
  - Normal pregnancy: ↓Cr by an average of 0.4 mg/dL
  - Cr of 0.9 may indicate underlying renal disease

Pregnancy in Patients with Renal Disease

- Physiological increase in protein excretion
  - Increased GFR
  - ↑permeability of the glomerular basement membrane
  - Further exaggerated in patients with proteinuric renal disease, with worsening of proteinuria in 3rd trimester

Pregnancy in Patients with KT

- Pregnancy affects immune system
  - Altered Th1/Th2 balance, with Th2 polarization
    - ↓ Cell-mediated immunity, which could be detrimental to the allogeneic fetus
    - ↑ Production of antibodies
      - ? Auto-antibodies
    - Can improve KT outcomes

MAYO CLINIC

Pregnancy in Kidney Transplant Patients

- Minimal clinical research
- Most data from registries that reflect voluntary participation and reporting
- Restored fertility: 12% of Women of childbearing age
- ↑GFR in women with good RF

MAYO CLINIC

Pregnancy and KT-Guidelines

Nephrol Dial Transplant. 2002;17 Suppl 4:50-5.

European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.10. Pregnancy in renal transplant recipients

MAYO CLINIC

Pre-transplant management

- Rubella vaccine

Post-transplant counseling

- Return of fertility
- Contraception
- Rh compatibility of patient and transplant

Preconception counseling

- Discontinue ACE inhibitors, AII receptor blockers, and change to less cytotoxic immunosuppression
- Hepatitis B and C, herpes simplex, CMV, toxoplasmosis and rubella titers

Monitoring during pregnancy

- Daily BP (by patient)
- Biweekly

  CBC, electrolytes, BUN, Cr, urinalysis, urine culture, cyclosporine or tacrolimus levels

  Office visits monthly until 28 weeks' gestation, then weekly until delivery

Monitoring during pregnancy

- Monthly ultrasound
- Each trimester

  IgM to CMV and toxoplasmosis for seronegative women, 24-hour urine protein and creatinine clearance
- Last trimester

  IgM to herpes simplex for seronegative women, PAP smear; biweekly fetal surveillance

MAYO CLINIC

Monitoring during pregnancy

Peri-partum

- Vaginal delivery recommended
- High-dose steroids during labor (100 mg hydrocortisone)
- Frequent cyclosporine/tacrolimus levels
- Close monitoring of renal function 3 months postpartum

Monitoring during pregnancy

Differential diagnosis of worsening renal function in pregnant transplant recipient

- Preeclampsia
- Acute or chronic rejection
- Cyclosporine toxicity
- Recurrent disease
- TTP/ a HUS
- Obstruction, pyelonephritis
- Prerenal azotemia, nephrotoxic drugs

Hou, 1999

Monitoring during pregnancy

Acute rejection

- Incidence 9-14.5% similar to non-pregnant transplant recipients
- Risk factors: history of rejection, ↑ Cr,

  ↓ levels of cyclosporine, tacrolimus due to ↑ distribution volume
- Treatment: steroids

MAYO CLINIC

Monitoring during pregnancy

Chronic rejection

- Pregnancy-associated hyperfiltration
- EDTA Case-control study: No adverse effect on graft function
- 10-year follow up of 29 Pregnancies and 38 matched controls. Graft survival of 69 % in pregnancy group vs. 100% in control group

Salmela, 1993

Monitoring during pregnancy

- Case control study, 7-year follow up

  18 Women with 25 Pregnancies

  26 Female Controls

  23 Male Controls

- Results:

  Graft survival 78, 69, and 70%, respectively

MAYO CLINIC

First, 1995

Pregnancy in Kidney Transplant Patients

- 3,382 Pregnancies in KT Recipients
- Fetal survival of 75% in women with Cr >1.4 mg/dL and 96% if Cr <1.4 mg/dL

Davison, 1994

MAYO CLINIC

Pregnancy in Kidney Transplant Patients-Infections

Urinary tract infections

- Affect 40% of transplant recipients during pregnancy
- Monthly screening urine cultures
- 2-week treatment for asymptomatic bacteriuria
- ↓ instrumentation during delivery

MAYO CLINIC

Opportunistic and Viral Infections

Cytomegalovirus

- Fetal infections due to both primary infection and reactivation
- 10% of the infected infants: death, mental retardation or microcephaly
- Diagnosis: amniotic fluid culture
- 5-15% late manifestations

MAYO CLINIC

Opportunistic and Viral Infections

Cytomegalovirus

- Titers of anti-CMV IgG and IgM each trimester
- Unclear if treating the mother prevents fetal disease
- Ganciclovir potentially teratogenic

Opportunistic and Viral Infections

- Toxoplasmosis: Primary infection → neonatal infection in 25-65% of cases
- Dx: Testing of amniotic fluid and fetal blood. US at 20-24 weeks (ventricular enlargement)
- Th: Sulfadiazine and Pyrimethamine

Opportunistic and Viral Infections

- Toxoplasmosis

  Reactivation is possible in immunosuppressed patients

  Tx should be considered for ↑ titers

- Herpes simplex

  C-section to prevent neonatal infection

  Acyclovir can be safely used

MAYO CLINIC

Opportunistic and Viral Infections

- Hepatitis B

  Vertical transmission (mother →fetus) in 80% of cases during delivery Vaccine + immune globulin is 95% effective in preventing fetal infections

- Hepatitis C

  <7% vertical transmission

Immunosuppression

Prednisone

- Crosses placenta
- Maternal to cord blood ratio 1:10
- Adrenal insufficiency, thymic hypoplasia
- High doses: maternal infections
- Low doses (5-10 mg) safe

Immunosuppression

Azathioprine

- Not converted by immature fetal liver
- No teratogenic effects @ 2 mg/kg/day
- Dose-related myelosuppression in fetus, clinically significant if mother's WBC <7.5x10(9)/L

Immunosuppression

Cyclosporine

- no teratogenic effect
- ~50% of pregnancies associated with IUGR and low birth weight (<2500 gr)
- Hypertension affects 50% of patients on cyclosporine before pregnancy
- Cr >1.5 mg/dL in 25% of pregnant women

Immunosuppression

Tacrolimus

- Increasing number of good quality data
- 70% of pregnancies favorable outcomes
- Preterm delivery 60%
- ∅ IUGR
- Incidence of malformations similar to other regimens

MAYO CLINIC

Immunosuppression

Mycophenolate mofetil (MMF)

- ↑ risk of malformations in animals
- Few reports of structural malformations in offspring of MMF treated pregnant kidney recipients
- Contraindicated, should be stopped 6 weeks before conception is attempted

Immunosuppression

OKT3

- Crosses the placenta
- May cause spontaneous abortions

Polyclonal antibodies

- IgG crosses placenta; effects unknown

Sirolimus

- Relatively contraindicated

MAYO CLINIC

Edith Helma and Wanda Foster
21-year old identical twins from Oklahoma

Figure 9. Identical twins and their children: patients who had children after kidney transplantation. This picture shows donor and recipient of an identical twin pair, taken some years later when both had borne several children. It might be said that the ultimate test of kidney function in both the giver and the taker is the ability to go through pregnancy normally!

The operation on Mrs. E. H. was carried out on May 24, 1956. One gave the kidney to the other who was dying of kidney failure. Now, it is hard to tell which is which.

MAYO CLINIC

Twin sister legacy

- Women with transplants can become pregnant and deliver healthy babies
- Women who donate kidneys have no future fertility concerns

Systemic review and Meta-analysis
50 studies, 4706 pregnancies in 3570 recipients

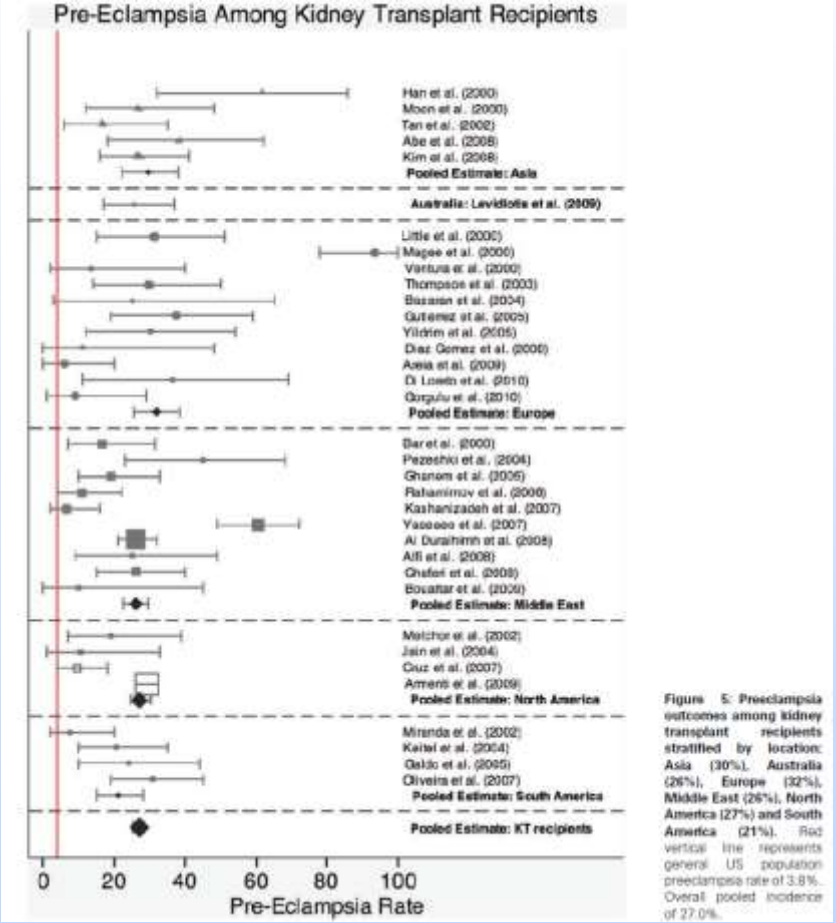


Figure 5: Preeclampsia outcomes among kidney transplant recipients stratified by location: Asia (30%), Australia (26%), Europe (32%), Middle East (26%), North America (27%) and South America (21%). Red vertical line represents general US population preeclampsia rate of 3.8%. Overall pooled incidence of 27.0%.

Deshpande, 2011, AJT

MAYO CLINIC

Meta-analysis results

- Live birth and miscarriage rates similar to general population
- Preeclampsia (27.0%, 95%CI 25.2–28.9)
- Gestational DM (8.0%, 95%CI 6.7–9.4)
- C-section (56.9%, 95%CI 54.9–58.9)
- Preterm (45.6%, 95%CI 43.7–47.5)

- higher than the general population, 3.8%, 3.9%, 31.9% and 12.5%, respectively

National Transplantation Pregnancy Registry –NTPR- 12/2015

Type of Organ Recipient	Live Births	Miscarriages	Stillbirths	Ectopic	Terminations
Kidney	75%	18%	2%	1%	4%
Panc/Kidney	69%	26%	0%	2%	4%
Liver	74%	21%	2%	0.7%	4%
Heart	66%	27%	1%	1%	5%
Lung	55%	31%	0%	2%	12%

But, 30% pregnant KT recipients diagnosed with PE!!!

MAYO CLINIC

Norwegian Transplant Registry

- Retrospective controlled study that was linked to the Medical Birth Registry
- Comparison group: randomly selected women from the Norwegian Medical Birth Registry w/o kidney transplant
- Risk for PE 40 versus 5.9%

Acta Obstet et Gynecol Scand 2016

Reasons for increase risk in PE

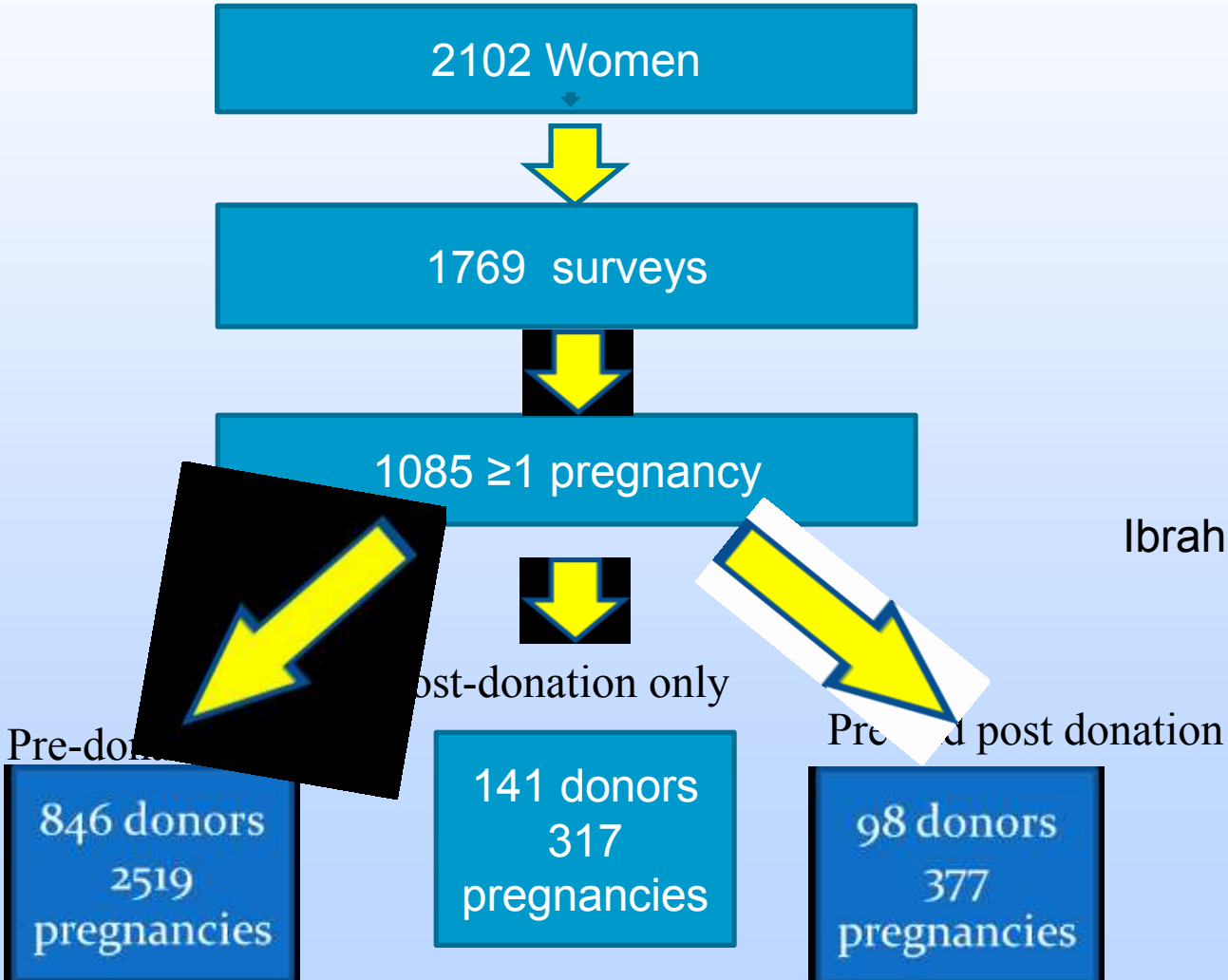
- Pre-existing disease and risk factors
  - HTN and vascular disease
  - Autoimmune connective tissue disorder (SLE/LN)
  - APA/APS
  - DM/Obesity
  - Advanced age
  - Infertility treatments
  - Multiple gestations
- Pre-existing disease may mimic PE
- The role of immunosuppression
  - CSA model of PE
  -

MAYO CLINIC

Renal transplant and risk of PE

- Risk of PE may be increased due to pre-existing disease and risk factors
  - Close monitoring and f/u by multispecialty team
- What about kidney donors?
  - Studies in 80's and 90's suggesting no major issues

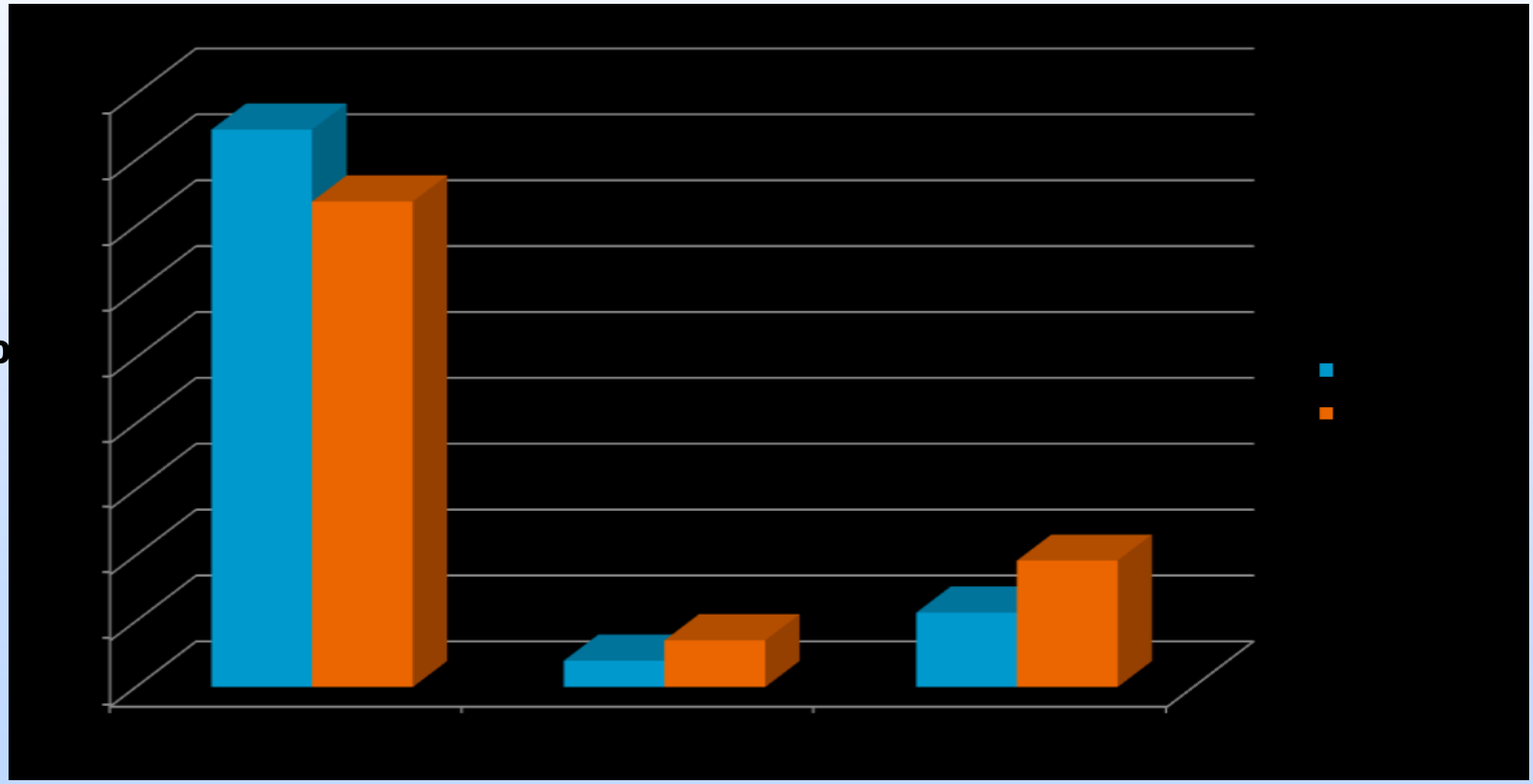
Pregnancy Outcomes after Kidney Donation Survey-based study



Ibrahim, 2009, AJT

MAYO CLINIC

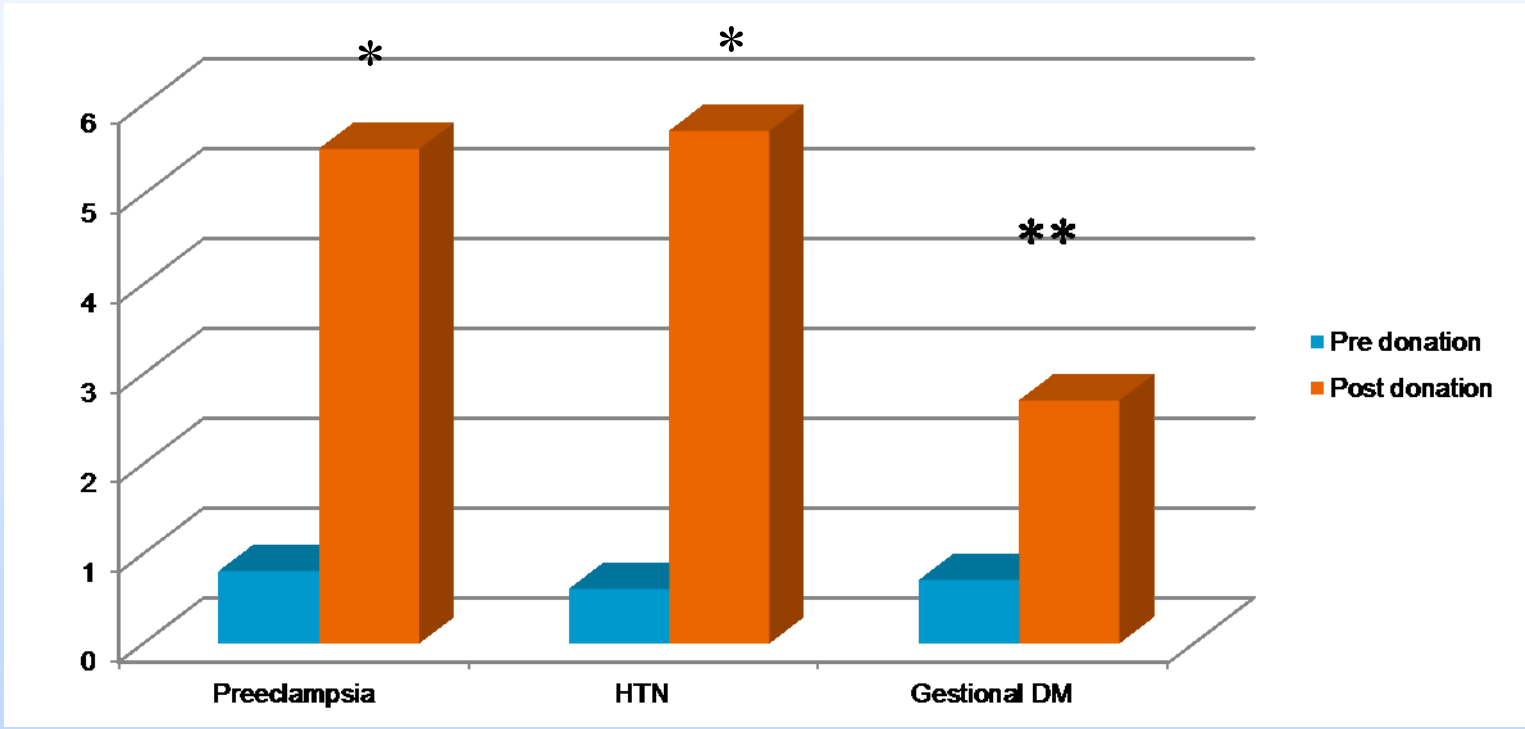
Fetal outcomes post versus pre-donation



*p= 0.004; **p=<0.001

MAYO CLINIC

Maternal outcomes post versus pre-donation



*p<0.001; **p=0.001

Pregnancy Outcomes after Kidney Donation Survey-based study

- Fetal and maternal outcomes and pregnancy outcomes after kidney donation were similar to those reported in the general population, but inferior to pre-donation pregnancy outcomes
  - Incidence of PE vey low pre-donation (0.8%!)
  - Advanced age at time of post-donation pregnancy

A National Survey of Pregnancy Outcomes in Live Kidney Donors

- Medical Birth Registry of Norway (since 1967)
- Renal Registry (records on all kidney transplants done in Norway)
- Identified pregnancies of all kidney donors 1967-2002
  - Controls randomly chosen from birth registry

AJT: 2009; 9:820

MAYO CLINIC

Results

- 326 donors and 726 pregnancies with
  - 106 pregnancies after donation
  - Successful live births:
  - 97.2% after donation
  - 98.7% before donation
  - 98.8% in controls

MAYO CLINIC

Hypertensive pregnancy disorders

	Control n=21511 (%)	Before n = 620 (%)	After n = 106 (%)	p	p
Chronic hypertension	52 (0.2)	1 (0.2)	1 (0.9)	0.28	--
Gestational hypertension	314 (1.5)	11 (1.8)	3 (2.8)	0.26	NS
Preeclampsia	666 (3.1)	16 (2.6)	6 (5.7)	0.22	<0.026

MAYO CLINIC

Interpret with caution

- Small number of events overall
- Studies of women after nephrectomy showed no increase in PE incidence
- The incidence of PE unknown, subject to definition
- Aging mother at time of pregnancy after kidney donation
- No difference in primary analysis

Maternal and Fetal Outcomes of Pregnancies: Living Kidney Donors and Matched Female Non-donors

Table 3. Maternal and Fetal Outcomes of Pregnancies after Cohort Entry in Living Kidney Donors and Matched Nondonors.

Outcome	Pregnancies in Donors (N=131)	Pregnancies in Nondonors (N=788)	Odds Ratio (95% CI)	P Value*
	no. of events (%)			
Primary outcome: gestational hypertension or preeclampsia	15 (11)	38 (5)	2.4 (1.2–5.0)	0.01
Secondary outcomes				
Gestational hypertension†	7 (5)	17 (2)	2.5 (0.9–6.5)	0.06
Preeclampsia	8 (6)	21 (3)	2.4 (1.0–5.6)	0.05
Cesarean section	41 (31)	224 (28)	1.2 (0.7–2.1)	0.44
Postpartum hemorrhage	≤5 (≤4)‡	24 (3)	0.9 (0.3–2.9)	0.91
Preterm birth with gestation of <37 wk	10 (8)	52 (7)	1.2 (0.5–2.5)	0.70
Low birth weight of <2500 g	8 (6)	31 (4)	1.7 (0.7–4.0)	0.21

* P values were derived from random-effects logistic-regression models for binary outcome data, accounting for the correlation structure within matched sets and in women with multiple pregnancies.
† When diagnostic codes for both gestational hypertension and preeclampsia were present in a given pregnancy, the outcome was counted as a diagnosis of preeclampsia.
‡ To comply with privacy regulations for minimizing the chance of identification of a study participant, numbers of participants are suppressed in the case of 5 or fewer participants (reported as ≤5).

MAYO CLINIC

Garg AX et al. N Engl J Med 2015;372:124-133

Interpret with caution

- Kidney donors tend to be followed closely
- Possible role of hyperfiltration of the single and resultant proteinuria
- But….
- Although PE remains an infrequent complication, the risk seems to be real!!!

MAYO CLINIC

Current approach

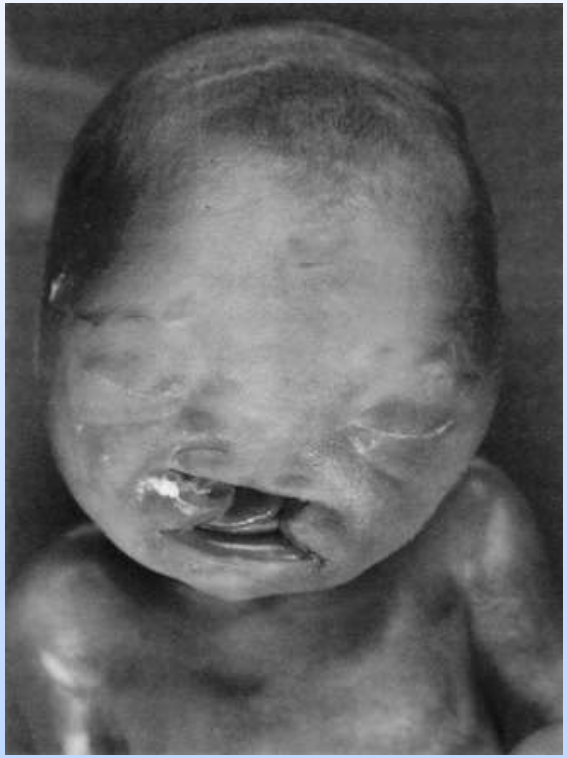
- Evolving field that requires additional, adequately powered studies
- Majority of young patients can expect normal pregnancy after kidney donation
- The PE risk may be elevated, but it seems that it may be related to factors other than kidney donation
- Open discussion with a potential donor, close multispecialty f/u during pregnancy

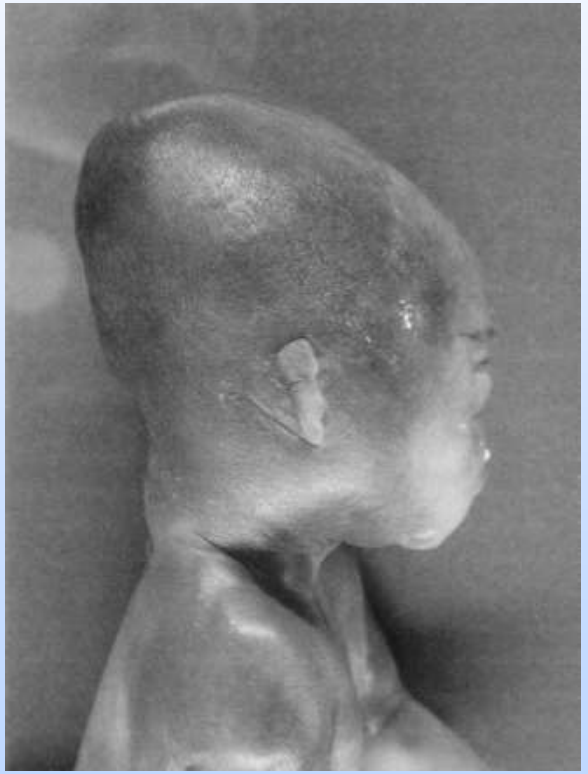
Immunosuppression

- Steroids
- Azathioprine, CSA, tacrolimus
- Cytoxan, mycophenolate contraindicated
- Blood pressure control
  - ACE, ARB contraindicated, renal and skeletal abnormalities
  - Atenolol, IUGR

MAYO CLINIC

Mycophenolate (Cellcept) in Pregnancy





Le Ray et al. Obstet Gynecol, 2004

MAYO CLINIC

Good Prognosis

- >2 years post-transplant, Cr <2.0 mg/dL
- No evidence of acute rejection
- BP normal or easily controlled
- 24-hour urine protein level<500 mg
- Prednisone<15mg/d, azathioprine<2mg and cyclosporine<5mg/kg/d
- Discontinuation od cytotoxic agenta
- Normal allograft ultrasound

MAYO CLINIC