Massachusetts General Hospital
Founding Member, Mass General Brigham

IVF and Obstetric Morbidity: A Risk Reduction Opportunity

Malavika Prabhu, MD
Associate Medical Director, Obstetric Quality & Safety
Assistant Professor, Obstetrics & Gynecology, HMS

October 7, 2024

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Disclosures

- **Consulting Fee (e.g., Advisory Board):**
  - BabyList Inc
- **Stock Option Holder (Individual stocks/ Stock Options; diversified mutual funds do not need to be disclosed):**
  - Roon
- **Royalty:**
  - UpToDate, Inc.

Objectives

1) To characterize risks of obstetric morbidity based on IVF interventions

1) To identify patients at risk of obstetric morbidity

1) To target interventions that optimize pregnancy rates while minimizing perinatal complications

Agenda

Perinatal Risks of IVF-conceived Gestations
The typical MFM consult

Dissecting the Risk of Preeclampsia in IVF: An MFM-married-to-an-REI's Perspective
Interventions and counseling matter

Risk Reduction: Pipe dream or reality?
Bidirectional communication to facilitate thoughtful interventions

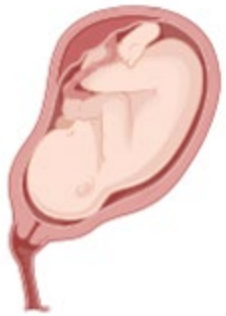
Group Discussion
I hope this is lively!

IVF Risks

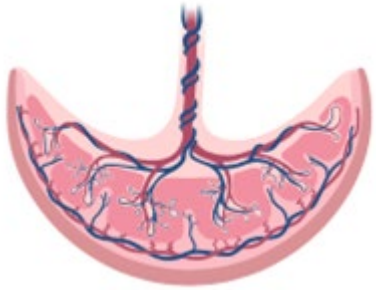
IVF Risks

Society for Maternal-Fetal Medicine Consult Series #60: Management of pregnancies resulting from in vitro fertilization

Hypertension/preeclampsia
Gestational diabetes



Multiple gestation
Small/large for gestational age
Congenital heart disease
Stillbirth



Placenta previa/accreta
Cord abnormalities

IVF Risks and Preeclampsia

Table 1. Clinical Risk Assessment for Preeclampsia[a]

Risk level	Risk factors	Recommendation
High[b]	• History of preeclampsia, especially when accompanied by an adverse outcome • Multifetal gestation • Chronic hypertension • Pregestational type 1 or 2 diabetes • Kidney disease • Autoimmune disease (ie, systemic lupus erythematous, antiphospholipid syndrome) • Combinations of multiple moderate-risk factors	Recommend low-dose aspirin if the patient has ≥1 of these high-risk factors
Moderate[c]	• Nulliparity • Obesity (ie, body mass index >30) • Family history of preeclampsia (ie, mother or sister) • Black persons (due to social, rather than biological, factors)[d] • Lower income[d] • Age 35 years or older • Personal history factors (eg, low birth weight or small for gestational age, previous adverse pregnancy outcome, >10-year pregnancy interval) • In vitro conception	Recommend low-dose aspirin if the patient has ≥2 moderate-risk factors Consider low-dose aspirin if the patient has 1 of these moderate-risk factors
Low	Prior uncomplicated term delivery and absence of risk factors	Do not recommend low-dose aspirin

USPSTF threshold for preeclampsia risk meriting LDASA: at least 8%

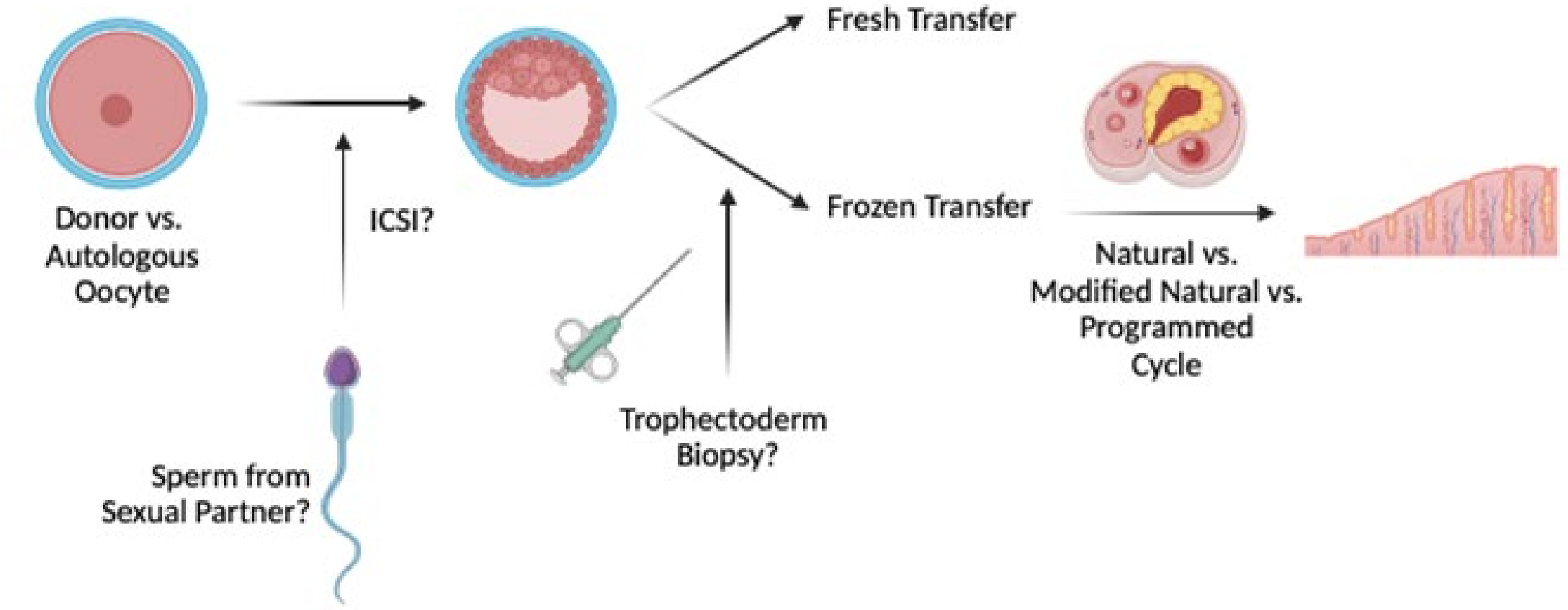
Risk reduction with low dose aspirin: 18%

JAMA 2021;326:1186; Cochrane 2019;CD004659

All IVF is Not The Same

IVF Interventions & Preeclampsia Risk

IVF Interventions: From Gamete to Embryo Transfer

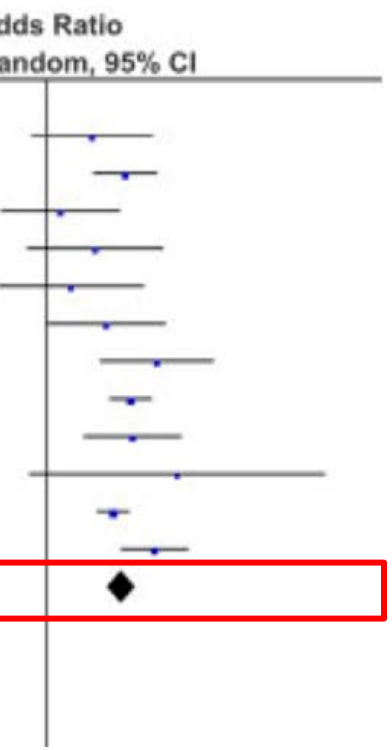


Oocyte: Donor vs Autologous
Risk of Preeclampsia

Study or Subgroup	Oocyte donation (OD) Events	Total	Other methods of ART Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
2.1.1 Singleton, age 18-54							
Stoop et al. 2012	15	147	8	147	2.7%	1.97 [0.81, 4.81]	2012
Malchau et al. 2013	21	215	504	15526	5.8%	3.23 [2.04, 5.11]	2013
van Dorp et al. 2014	8	61	21	192	2.8%	1.23 [0.51, 2.94]	2014
Levron et al. 2014	13	139	6	126	2.3%	2.06 [0.76, 5.60]	2014
Elenis et al. 2015	10	76	6	63	2.1%	1.44 [0.49, 4.21]	2015
Tarlatzi et al. 2016	18	144	8	144	2.9%	2.43 [1.02, 5.78]	2016
Letur et al. 2016	22	169	8	284	3.0%	5.16 [2.24, 11.88]	2016
Nejdet et al. 2016	51	388	1105	26696	7.6%	3.50 [2.59, 4.73]	2016
Rizzo et al. 2016	18	109	16	307	3.7%	3.60 [1.76, 7.34]	2016
Simeone et al. 2016	5	43	1	54	0.6%	6.97 [0.78, 62.13]	2016
Sites et al. 2017	107	912	399	8505	8.4%	2.70 [2.16, 3.38]	2017
Rodriguez-Wallberg et al. 2019	56	259	27	515	5.5%	4.99 [3.06, 8.12]	2019
Subtotal (95% CI)		**2662**		**52559**	**47.5%**	**3.03 [2.46, 3.72]**	
Total events	344		2109				

Heterogeneity: Tau² = 0.03; Chi² = 16.03, df = 11 (P = 0.14); I² = 31%

Test for overall effect: Z = 10.52 (P < 0.00001)



Hum Reprod 2022;37:586

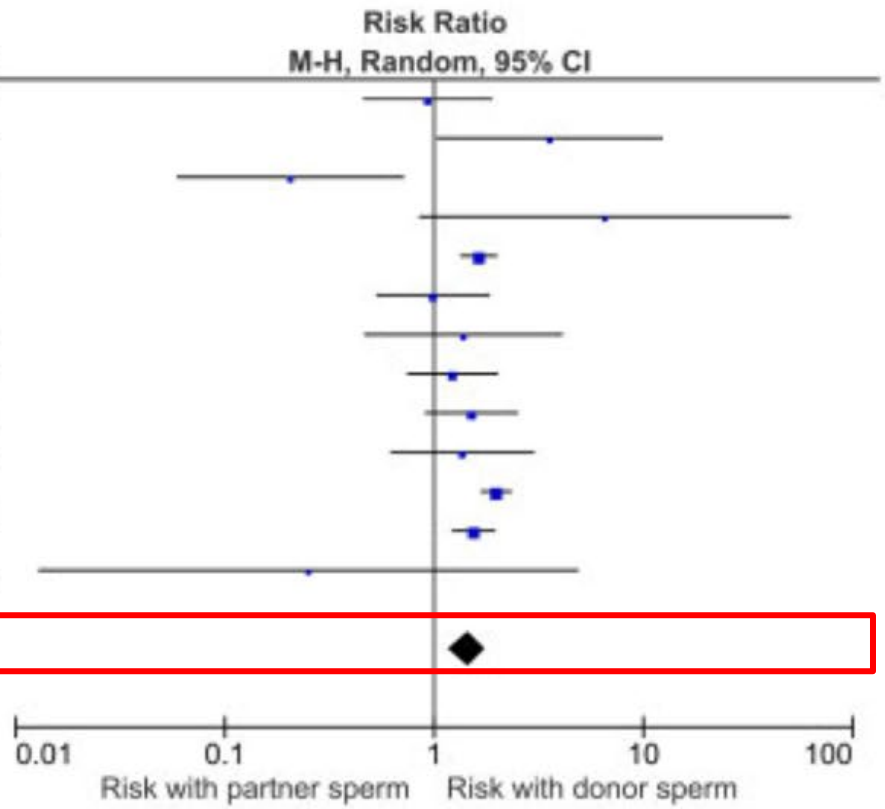
Sperm: Donor vs Sexual Partner

Risk of Hypertensive Disorders of Pregnancy

Study or Subgroup	Donor Sperm Events	Donor Sperm Total	Partner Sperm Events	Partner Sperm Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Varma 1987	7	60	961	7668	6.2%	0.93 [0.46, 1.87]	1987
Smith 1997	9	37	3	44	2.5%	3.57 [1.04, 12.22]	1997
Laivuori 1998	3	73	10	50	2.5%	0.21 [0.06, 0.71]	1998
Salha 1999	7	29	1	27	1.0%	6.52 [0.86, 49.56]	1999
Hoy 1999	131	1552	399	7717	17.6%	1.63 [1.35, 1.97]	1999
Hall 2001	10	45	39	173	7.4%	0.99 [0.53, 1.82]	2001
Gaudoin 2003	3	35	6788	109408	3.1%	1.38 [0.47, 4.08]	2003
Thapar 2007	22	170	40	378	9.7%	1.22 [0.75, 1.99]	2007
Kyrou 2010	48	438	20	275	9.4%	1.51 [0.91, 2.48]	2010
Saavedra-Saavedra 2012	11	164	13	264	5.3%	1.36 [0.63, 2.97]	2012
Malchau 2014	140	1881	8811	233957	18.3%	1.98 [1.68, 2.32]	2014
Adams 2017	65	480	26222	298944	16.5%	1.54 [1.23, 1.94]	2017
Chen 2018	0	173	3	304	0.5%	0.25 [0.01, 4.82]	2018
Total (95% CI)		**5137**		**659209**	**100.0%**	**1.44 [1.17, 1.78]**	
Total events	456		43310				

Heterogeneity: Tau² = 0.05; Chi² = 28.25, df = 12 (P = 0.005); I² = 58%

Test for overall effect: Z = 3.45 (P = 0.0006)

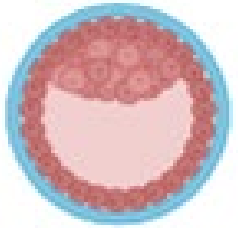


Intracytoplasmic Sperm Injection
Risk of Hypertensive Disorders of Pregnancy

Experimental	Number of studies	ART study size (n)	SC study size (n)	OR; 95% CI	I^2 (%)	*P* value	NNH
Hypertensive Disorders of Pregnancy							
IVF/ICSI singleton	51	268,166	7,728,641	1.70 (1.60–1.80)	80	< 0.01[a]	47.2
IVF singleton	5	41,238	437,723	1.55 (1.23–1.94)	90	< 0.01[a]	85.9
ICSI singleton	9	27,108	446,149	1.52 (1.28–1.80)	75	< 0.01[a]	54.3
IVF/ICSI multiple	41	88,853	120,396	1.34 (1.20–1.50)	76	< 0.01[a]	47.8
IVF multiple	4	13,147	73,297	1.13 (0.98–1.29)	59	0.09	86.3
ICSI multiple	10	9924	77,179	1.11 (0.91–1.36)	77	0.30	12.8
Fresh embryo transfer singleton	16	162,867	4,381,981	1.43 (1.33–1.53)	72	< 0.01[a]	57.4
Frozen embryo transfer singleton	9	41,462	4,090,152	1.74 (1.58–1.92)	55	< 0.01[a]	52.6
Oocyte donation singleton	9	12,461	2,413,466	4.42 (3.00–6.51)	83	< 0.01[a]	16.3
Oocyte donation multiple	2	10,488	59,045	2.62 (2.46–2.79)	0	< 0.01[a]	10.2

BMC Preg Childbirth 2021;21:449

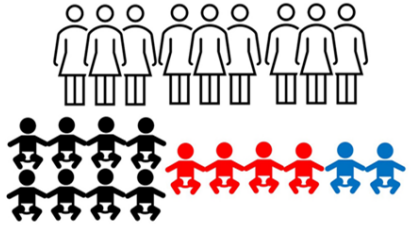
Fresh or Frozen Embryo



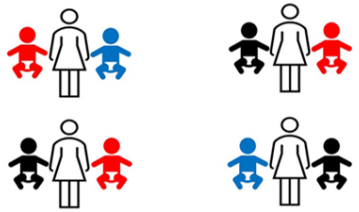
Risk of hypertensive disorders in pregnancy after fresh and frozen embryo transfer in assisted reproduction:
A population-based cohort study with within sibship analysis

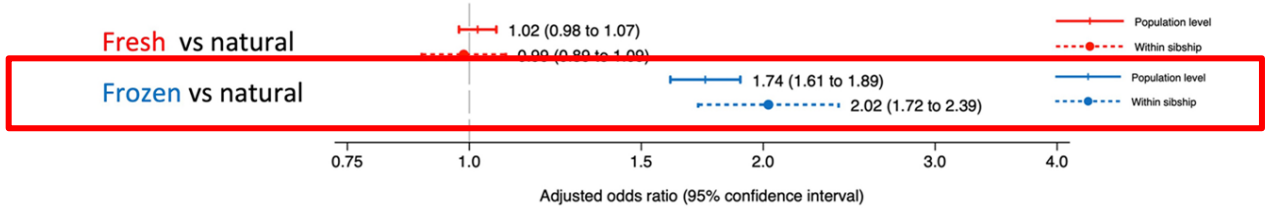
1988–2015 in Denmark, Norway, and Sweden:		**Risk of hypertensive disorders in pregnancy:**	
Natural	4 426 691 pregnancies	Natural	4.3%
Fresh	78 300 pregnancies	Fresh	5.9%
Frozen	18 037 pregnancies	Frozen	7.4%

Population level (n=4 523 028)



Within sibships (n=33 209)

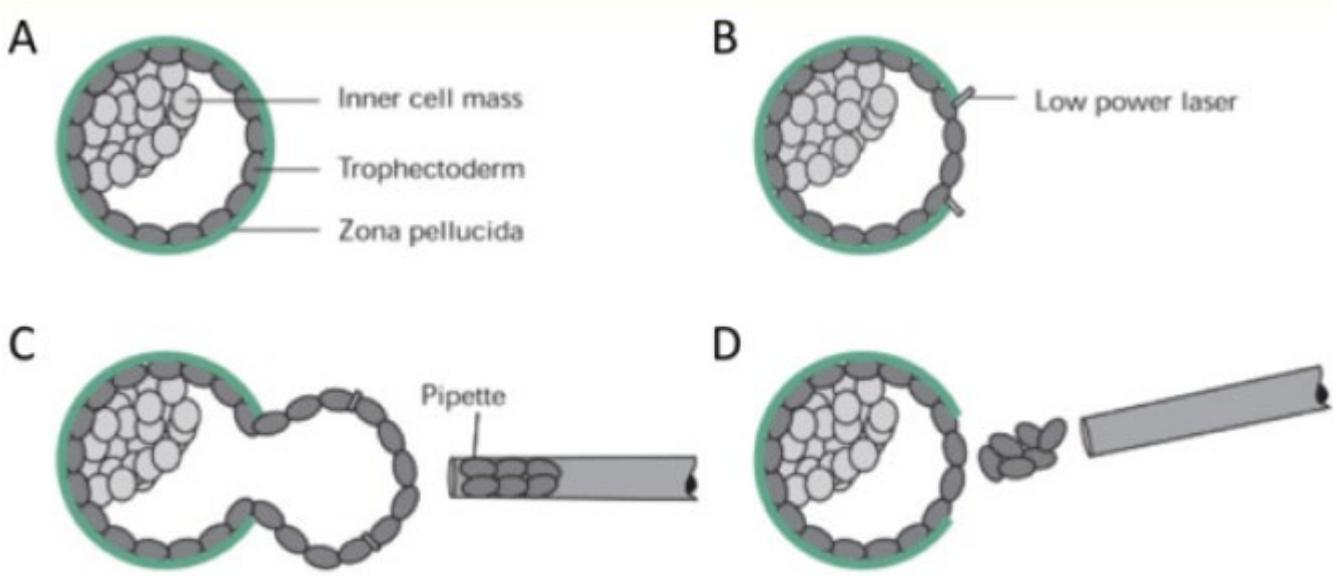


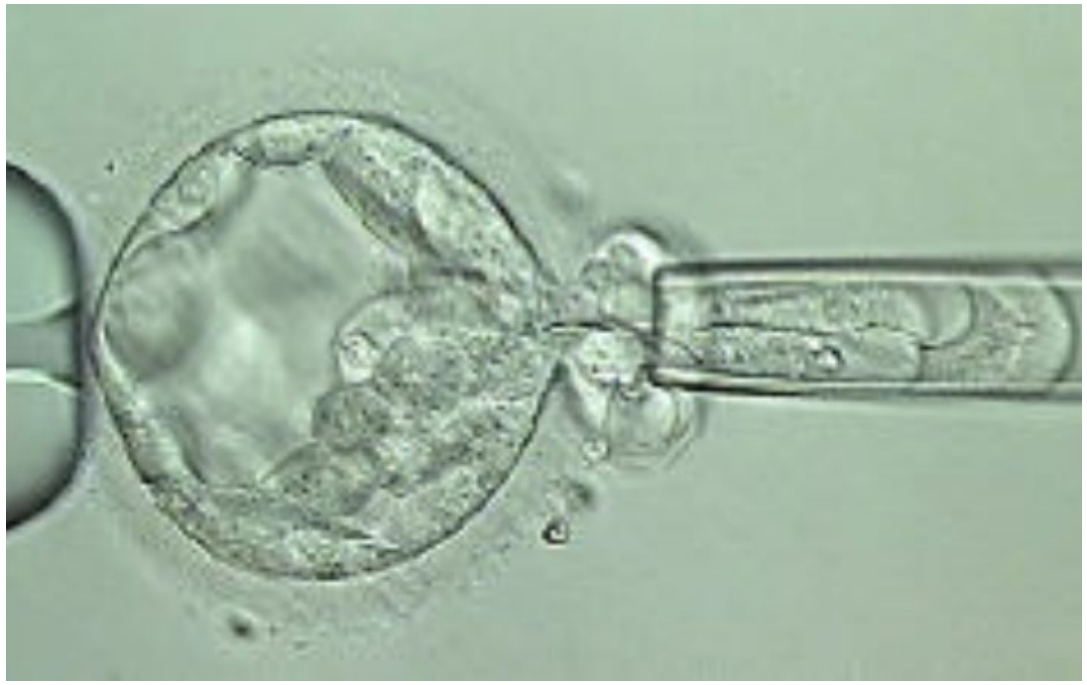


Hypertension 2023;80:e6

Trophectoderm Biopsy

The Future Placenta





Trophectoderm Biopsy
Risk of Hypertensive Disorders of Pregnancy

Cohort studies are small, single center, incompletely account for confounding by indication, transfer type

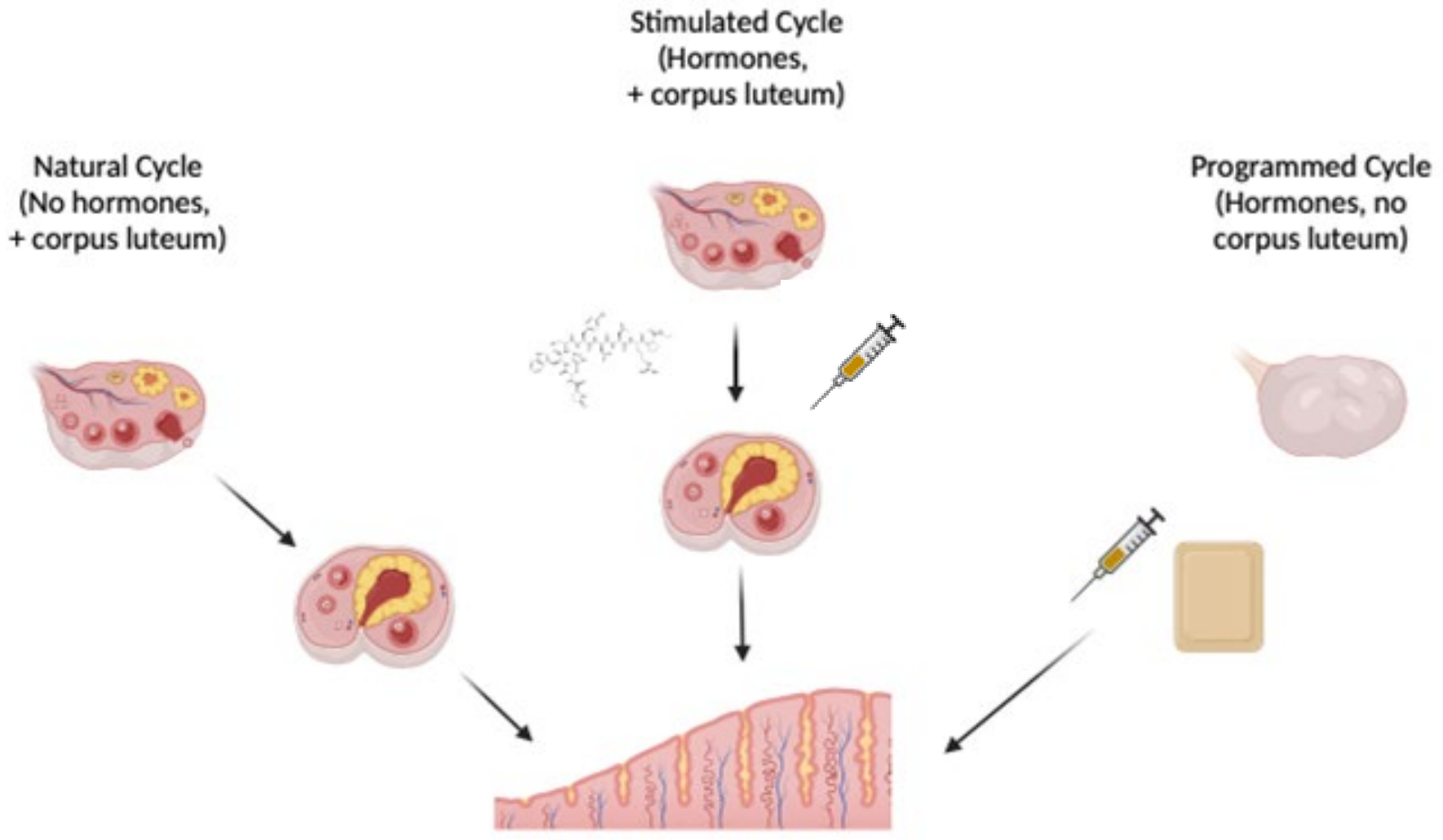
Outcome	IVF (n = 150)	IVF-PGT (n = 155)	aOR[a] (95% CI)	*P* value
Obstetric				
Gestational hypertension	3 (2.2)	3 (1.9)		1.0
Preeclampsia	5 (3.7)	15 (9.3)	2.95 (0.98, 8.92)	.04
Preeclampsia with severe features	3 (2.2)	7 (4.3)	1.59 (0.34, 7.36)	1.0

Outcomes	PGT singleton pregnancies (n = 214)	IVF/ICSI singleton pregnancies (n = 617)	Odds ratio/mean difference (95% CI)	*P* value[a]
Obstetric outcomes				
Gestational hypertension	11 (5.1)	14 (2.3)	**2.33 (1.04, 5.22)**	**.039**
Preeclampsia	7 (3.3)	12 (1.9)	1.71 (0.66, 4.39)	.269

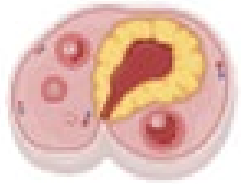
Meta-analyses have conflicting results → Independent risk of trophectoderm biopsy is uncertain

Fertil Steril 2019;112:283; Fertil Steril 2022;117:562; Human Reprod Update 2021;36:340; AJOG 2024;230:199.e5

Transfer Cycle Type



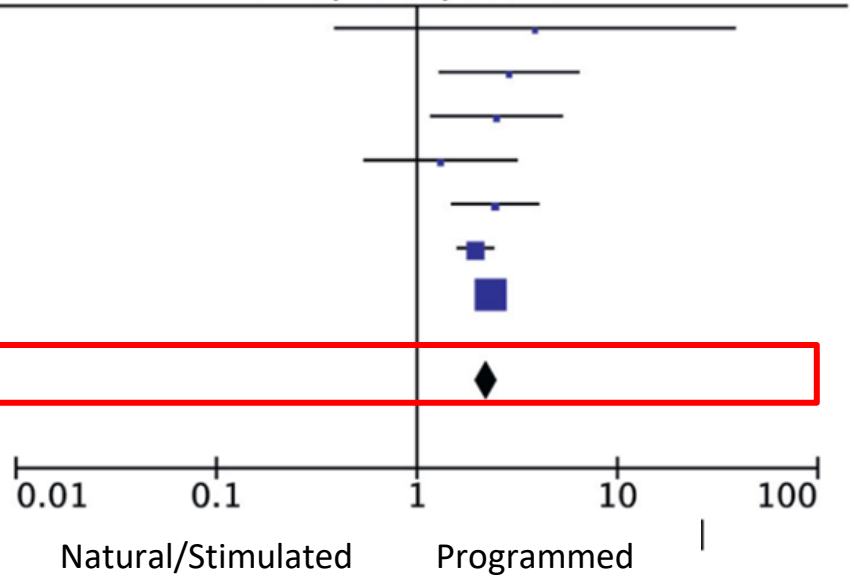
Programmed Transfer
Risk of Preeclampsia



Study or Subgroup	0 CL Events	0 CL Total	1 CL Events	1 CL Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Zaat 2021	3	37	1	45	0.2%	3.88 [0.39, 39.00]
von Versen-Höynck 2019	12	94	14	290	1.7%	2.89 [1.28, 6.48]
Roelens 2020	17	190	12	317	2.4%	2.50 [1.17, 5.35]
Zhang 2021	11	832	9	891	2.5%	1.31 [0.54, 3.18]
Asserhoj 2021	33	357	31	779	5.1%	2.46 [1.48, 4.08]
Ginström Ernstad 2019	118	1446	359	8280	28.2%	1.96 [1.58, 2.43]
Wang, Z 2020	356	4162	393	10211	59.9%	2.34 [2.01, 2.71]
Total (95% CI)		**7118**		**20813**	**100.0%**	**2.23 [1.99, 2.50]**
Total events	550		819			

Heterogeneity: $Chi^2 = 3.96$, $df = 6$ ($P = 0.68$); $I^2 = 0\%$

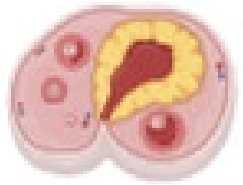
Test for overall effect: $Z = 13.68$ ($P < 0.00001$)



Programmed transfer is associated with term/late preterm preeclampsia, though literature characterizing preeclampsia phenotype (timing, severity) is nascent

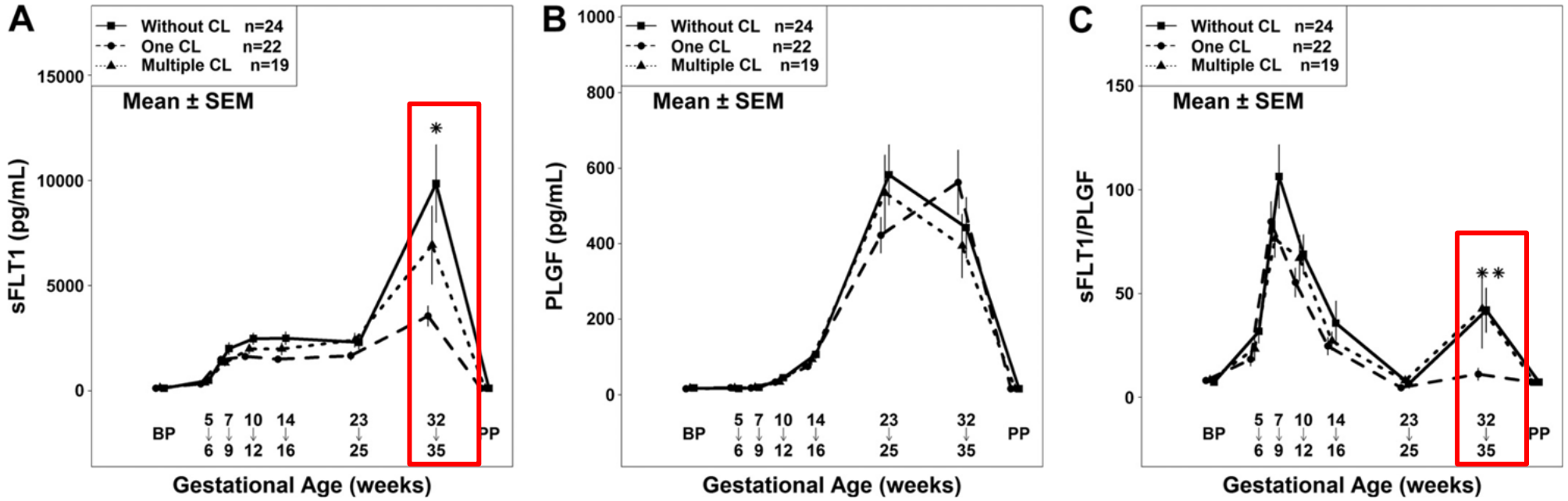
Transfer Cycle Type

Why Does the Corpus Luteum Matter?



Relaxin → maternal vasodilatory changes + optimal decidualization → improved placentation

- Relaxin decreases SVR, increases CO, increases GFR
- Prorenin levels increase → RAAS activation (RAAS suppressed in preeclampsia)
- Lack of CL hormones are (partially) rescued by placental growth factor (PlGF) in early 2nd trimester

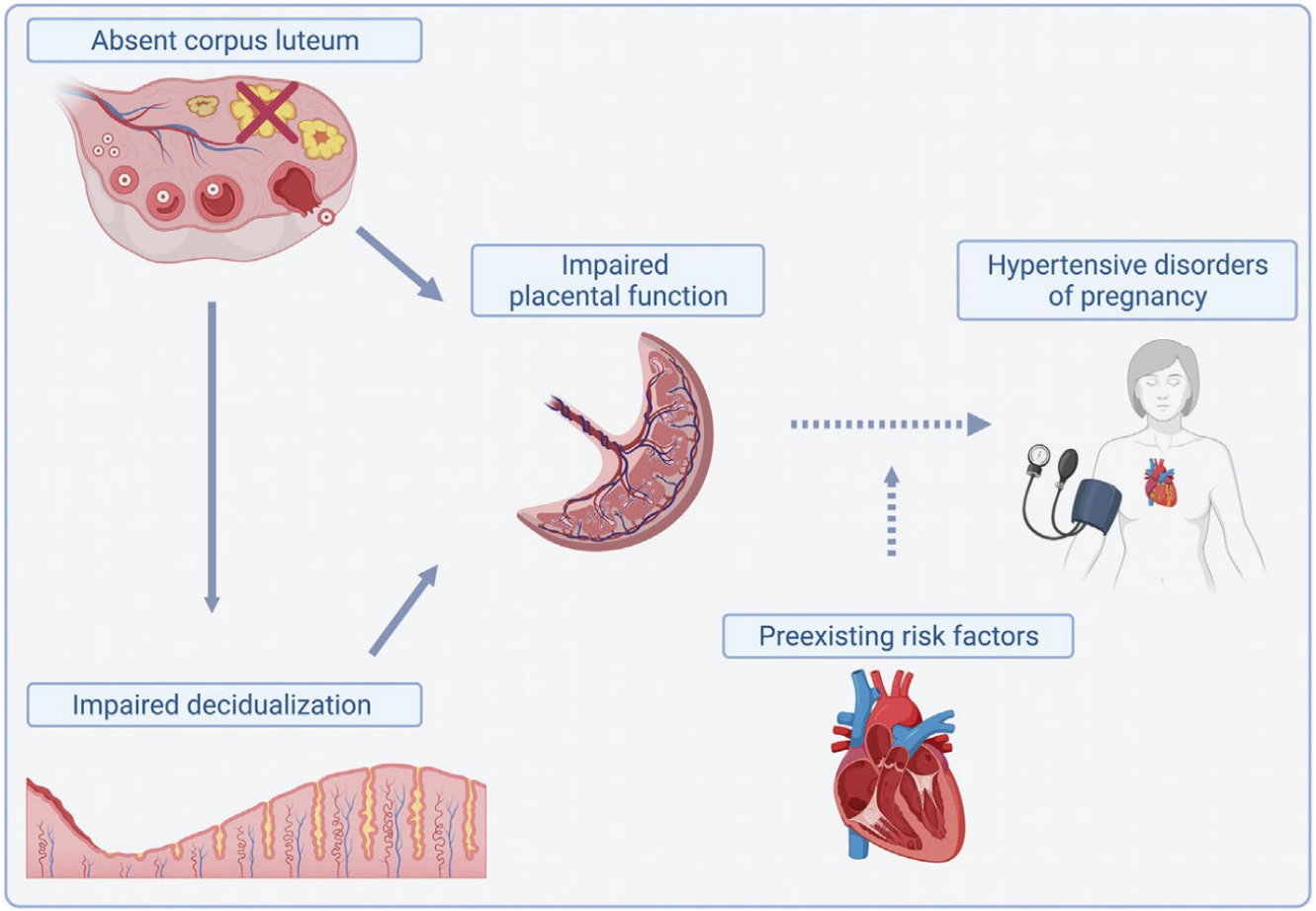


Fertil Steril 2022;118:839; Am J Physiol Endocrinol Metab 2019;317:E677

Transfer Cycle Type
The Corpus Luteum Matters

Association between programmed frozen embryo transfer and hypertensive disorders of pregnancy

Pietro Bortoletto, M.D., M.Sc.,[a,b,c] Malavika Prabhu, M.D.,[c,d] and Valerie L. Baker, M.D.[e]



2-hit hypothesis

More work needed to understand the role of CL secretory hormones

2 Ongoing RCTs to answer the clinical implications of transfer type on HDPs
-NATPRO (US)
-Spanish RCT

REI ↔ OB: A Shared Mental Model To Facilitate Risk Reduction

Tangible Clinical Implications
Hypertensive Disorders of Pregnancy

Nuanced counseling around and selection of IVF interventions in ***at risk patients*** → improved obstetric management of patients with at risk IVF interventions

–Donor gamete (especially reciprocal IVF)

–PGT

–Transfer cycle type

Who is an *at risk patient*, and why does it matter?

- New definition and management of chronic hypertension
- New data on aspirin dosing
- New diagnostics for preeclampsia
- Emerging therapies for preeclampsia

Chronic Hypertension Reimagined
New Definitions, New Treatment

ACOG/SMFM: 140/90

ACC/AHA: 130/80 - stage 1 HTN; 140/90 - stage 2 HTN

- At risk patients may be at risk and not know it
- HTN vs white coat HTN

Stage 1 HTN and obstetric outcomes

- aRR preeclampsia: 2.66 (incidence 15.3% vs 5.4%)
- aOR HDP: 2.54 (incidence 10.9% vs 4.2%)
- Increased risks of preterm birth, variable impact on SGA, NICU admission, GDM

Obstet Gynecol 2018;132:843; AJOG 2021;224:521.e1

Chronic Hypertension Reimagined
The CHAP Trial

Tight BP control (<140/90) vs usual care, in those with mild cHTN <23 weeks' gestation

Table 2. Primary and Safety Outcomes.

Outcome	Imputation Analysis (N=2408)*		Complete-Case Analysis (N=2325)†			
	Adjusted Risk Ratio (95% CI)	P Value	Active Treatment	Control	Risk Ratio (95% CI)	P Value
			no./total no. (%)			
Primary composite outcome	0.82 (0.74–0.92)	<0.001	353/1170 (30.2)	427/1155 (37.0)	0.82 (0.73–0.92)	<0.001
Preeclampsia with severe features	0.80 (0.70–0.92)		272/1170 (23.3)	336/1155 (29.1)	0.80 (0.70–0.92)	
Medically indicated preterm birth at <35 wk	0.73 (0.60–0.89)		143/1170 (12.2)	193/1155 (16.7)	0.73 (0.60–0.89)	
Placental abruption	0.88 (0.49–1.59)		20/1170 (1.7)	22/1155 (1.9)	0.90 (0.49–1.64)	
Fetal or neonatal death at <28 days	0.81 (0.54–1.22)		41/1170 (3.5)	50/1155 (4.3)	0.81 (0.54–1.21)	
Safety outcome						
Small for gestational age						
<10th percentile	1.04 (0.82–1.31)	0.76	128/1146 (11.2)	117/1124 (10.4)	1.07 (0.85–1.36)	0.56
<5th percentile	0.89 (0.62–1.26)	0.51	58/1146 (5.1)	62/1124 (5.5)	0.92 (0.65–1.30)	0.63

162 is the new 81
Is more aspirin better?

ASPRE trial

- ASA 150 qhs vs placebo, started at 11-14 weeks, in high risk singleton gestations
- "High risk" = Proprietary algorithm using maternal risk factors, uterine artery PIs, mean arterial pressure, PAPP-A, placental growth factor levels → > 1/100 risk of *preterm* preeclampsia

Outcome	Aspirin Group (N = 798)	Placebo Group (N = 822)	Odds Ratio (95% or 99% CI)*
Primary outcome: preterm preeclampsia at <37 wk of gestation — no. (%)	13 (1.6)	35 (4.3)	0.38 (0.20–0.74)
Secondary outcomes according to gestational age			
Adverse outcomes at <34 wk of gestation			
Any — no. (%)	32 (4.0)	53 (6.4)	0.62 (0.34–1.14)
Preeclampsia — no. (%)	3 (0.4)	15 (1.8)	0.18 (0.03–1.03)
Gestational hypertension — no. (%)	2 (0.3)	2 (0.2)	1.02 (0.08–13.49)
Small-for-gestational-age status without preeclampsia — no./total no. (%)†	7/785 (0.9)	14/807 (1.7)	0.53 (0.16–1.77)

NEJM 2017;377:613

162 is the new 81
Is more aspirin better?

ASA 81 vs 162

- Ongoing RCTs, data not yet available
- ASPREO
  - Open label trial of ASA 81 vs 162 if BMI 30+ and one RF (stage 1 HTN, hx preeclampsia, T2DM)
  - ASA 81 vs 162, started at 12-20 weeks, with complicated Bayesian statistics
  - “ASA 162 seems modestly more risk reducing” in this high risk group

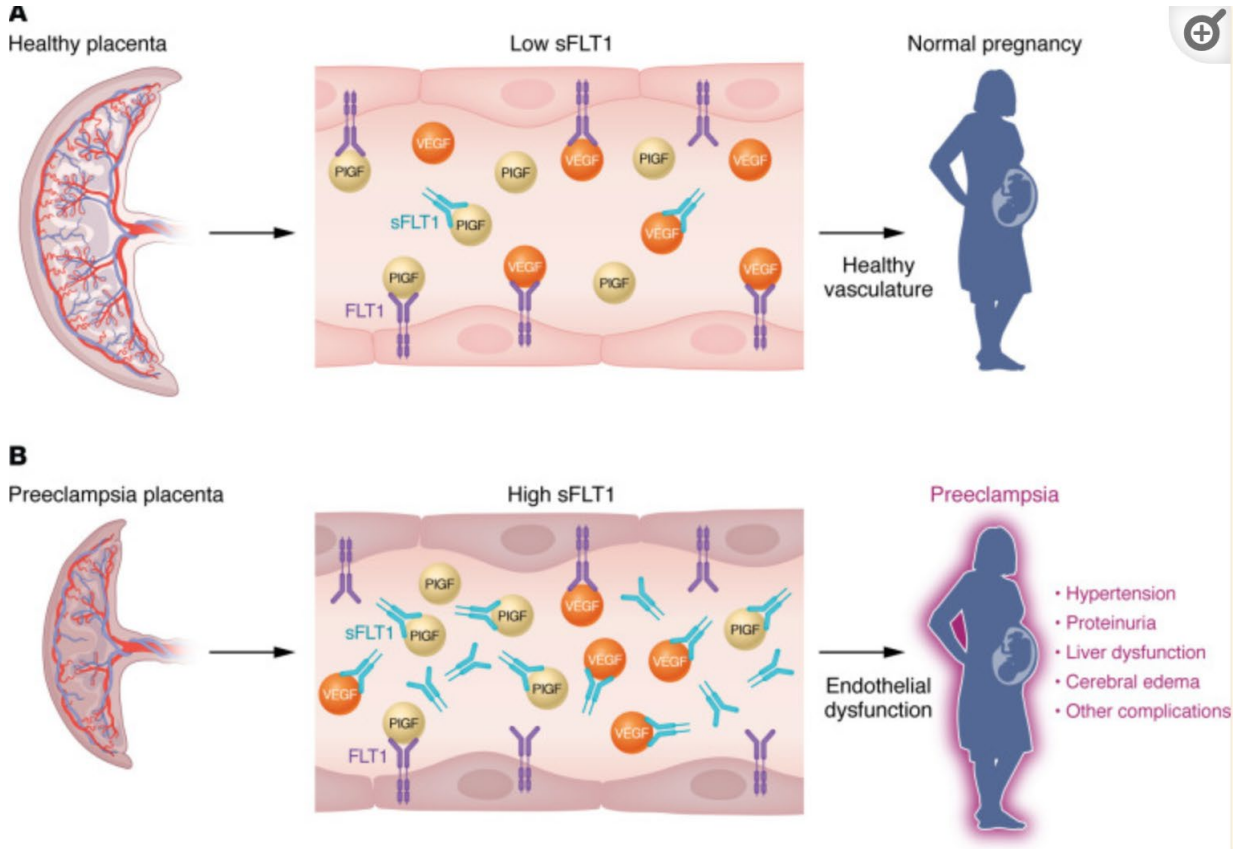
The jury is out

Novel Diagnostics for Preeclampsia

Are we better at finding it?

The sFLT1 (soluble fms-like tyrosine kinase 1) story

- sFLT1: soluble inhibitor of VEGF and PlGF
- sFLT1 allows for vascular homeostasis
- Excess sFLT1 decreases VEGF/PlGF binding → endothelial dysfunction, vascular relaxation inhibited → clinical preeclampsia



Novel Diagnostics for Preeclampsia
The PRAECIS Trial

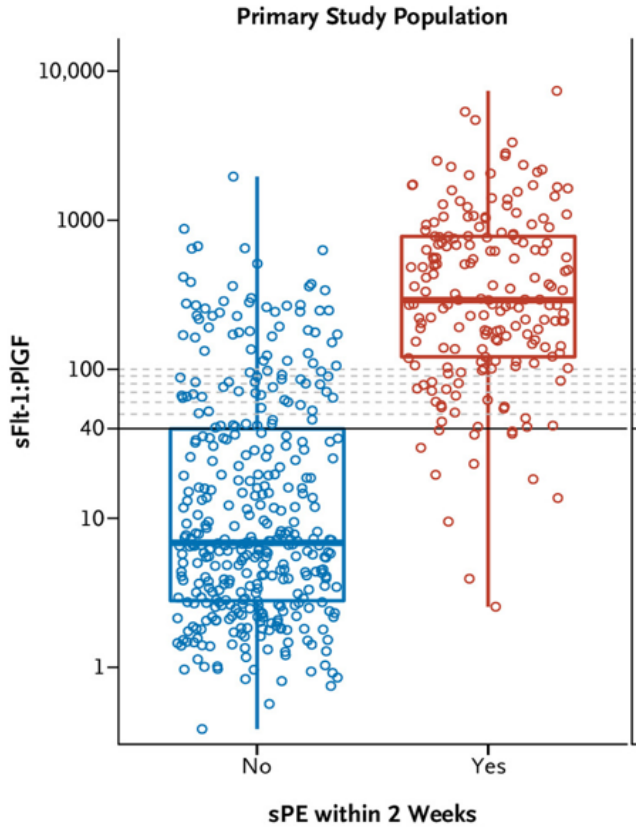
ORIGINAL ARTICLE

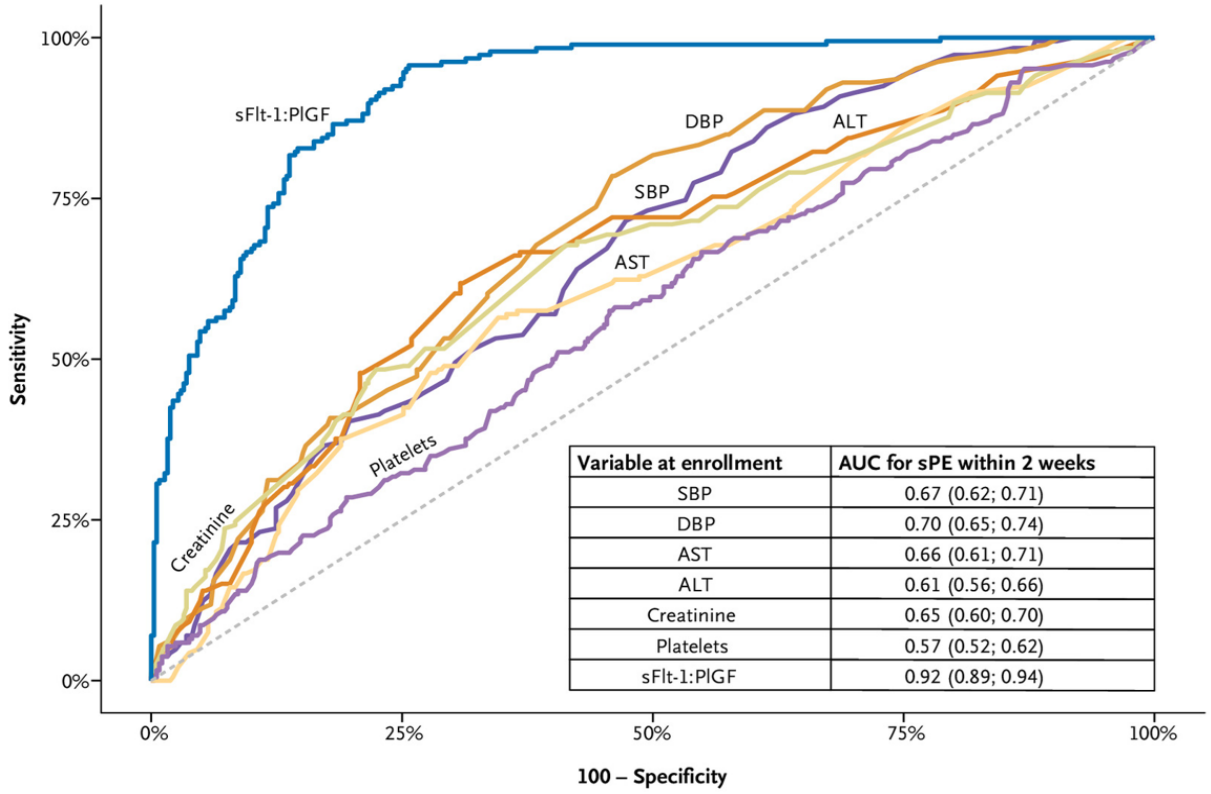
Circulating Angiogenic Factor Levels in Hypertensive Disorders of Pregnancy

- 776 women with singletons 23-35 weeks' hospitalized with hypertensive disorder of pregnancy
- Mean GA 30 weeks, 47% with cHTN, 46% LDASA use, ~25% nulliparous, ~50% White
- Objective: To predict preeclampsia with severe features within 2 weeks of lab draw, after identifying appropriate sFLT1:PlGF cutoff
    - 220 in derivation cohort, 556 in validation cohort

Novel Diagnostics for Preeclampsia

Predicting Preeclampsia





Variable at enrollment	AUC for sPE within 2 weeks
SBP	0.67 (0.62; 0.71)
DBP	0.70 (0.65; 0.74)
AST	0.66 (0.61; 0.71)
ALT	0.61 (0.56; 0.66)
Creatinine	0.65 (0.60; 0.70)
Platelets	0.57 (0.52; 0.62)
sFlt-1:PlGF	0.92 (0.89; 0.94)

All patients: 94% sensitivity, 75% specificity, 65% PPV, NPV 96%

Patients with cHTN: 59% PPV, NPV 94%

12 false negative (2%), 93 false positives (15%)

NEJM Evid 2022:1:12

Novel Diagnostics for Preeclampsia
Predicting Adverse Outcomes

Table 3. Adverse Outcomes Associated with sFlt-1:PlGF Ratios ≥40 at Enrollment.*

Outcome	All (N=556)	sFlt-1:PlGF <40 (n=289)	sFlt-1:PlGF ≥40 (n=267)	Relative Risk (95% CI)
Maternal adverse outcomes				
Composite maternal outcomes	51 (9.2)	8 (2.8)	43 (16.1)	5.8 (2.8–12.2)
ALT (>80 U/l) or AST (>80 U/l)	28 (5.0)	2 (0.7)	26 (9.7)	14.1 (3.4–58.7)
Lowest platelets ≤100,000/μl	10 (1.8)	1 (0.3)	9 (3.4)	9.7 (1.2–76.4)
Highest creatinine ≥1.4 mg/dl	5 (0.9)	2 (0.7)	3 (1.1)	1.6 (0.3–9.6)
Abruption	17 (3.1)	5 (1.7)	12 (4.5)	2.6 (0.9–7.3)
Pulmonary edema	7 (1.3)	2 (0.7)	5 (1.9)	2.7 (0.5–13.8)
Eclamptic seizure	2 (0.4)	0	2 (0.7)	
DIC	2 (0.4)	0	2 (0.7)	
Cerebral hemorrhage/stroke	0	0	0	
Fetal/neonatal adverse outcomes				
Composite fetal outcomes	288 (51.8)	75 (26.0)	213 (79.8)	3.1 (2.5–3.8)
Indicated delivery ≤14 d	236 (42.4)	56 (19.4)	180 (67.4)	3.5 (2.7–4.5)
Birth weight percentile <10	102 (18.4)	23 (8.0)	79 (29.6)	3.7 (2.4–5.7)
Fetal/neonatal death	9 (1.6)	1 (0.3)	8 (3.0)	8.7 (1.1–68.8)

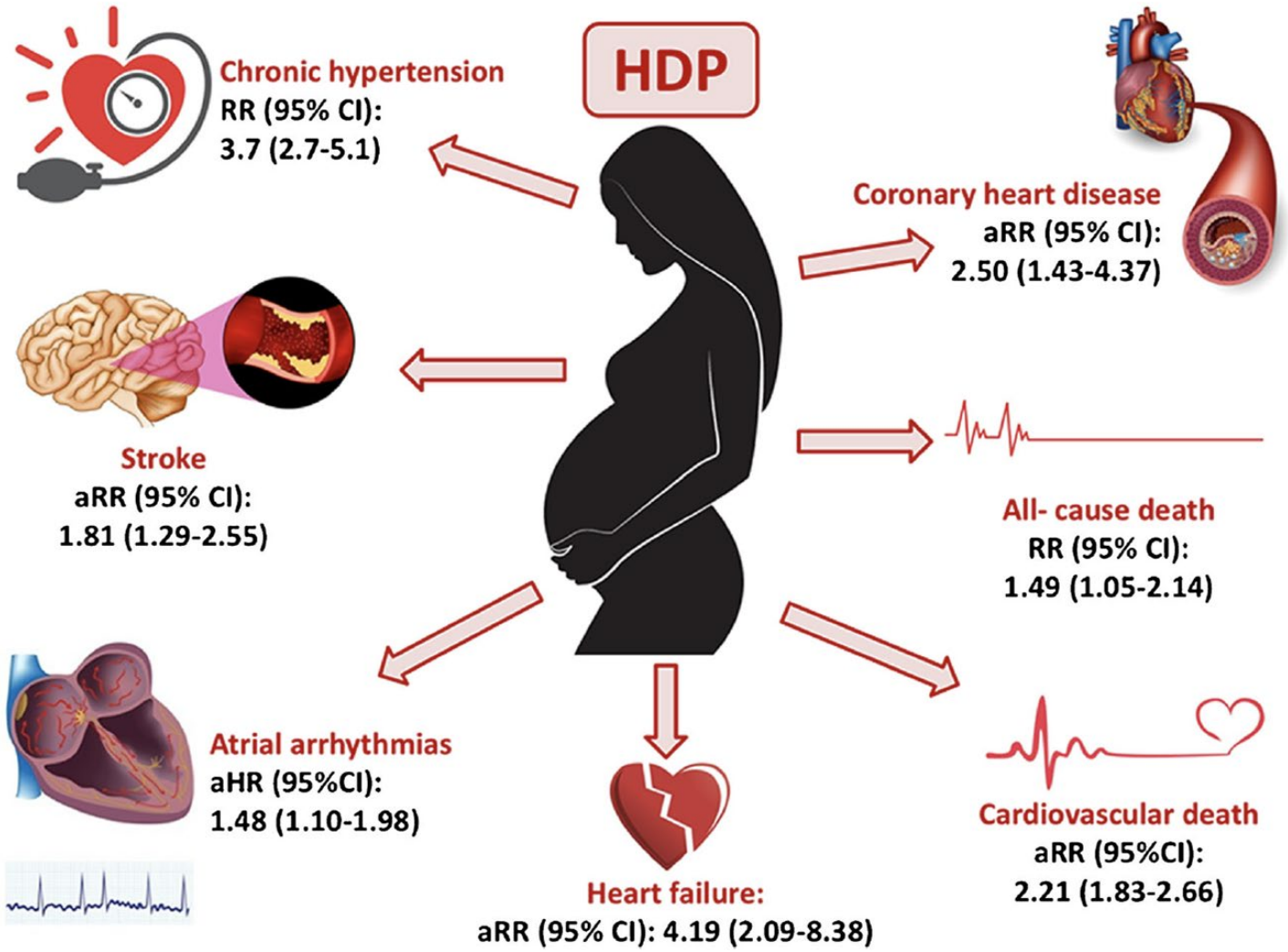
Novel Therapies for Preeclampsia Risk Reduction
Repurposing Old Drugs

Pravastatin
- Biologic plausibility: restores angiogenic balance
- Small studies suggest benefit
- Increasing safety data (hydrophilic)
- Large scale RCT by MFMU ongoing

Calcium
- WHO recommends 1500mg/d with low dietary calcium intake
- 500mg daily noninferior to 1500mg daily
- Meta-analyses find 50% risk reduction

Others
- Metformin: restores angiogenic balance (↓sFLT1)
  - Conflicting secondary analyses
- Esomeprazole: decreased endothelial dysfunction
  - RCT in Australia
- Sildenafil: stopped due to neonatal pHTN concern
- Immunomodulators / RNA-interference

Long-term Cardiovascular Risk of Preeclampsia



Curr Treat Options Cardiovasc Med 2018;19:56

What Can We Do Differently?
Better Bidirectional Information Transfer

MFM Preconception Consultation
–clearly denote risk factors for HDP → **at-risk patient**
–reach out to REI with specific concerns (the warm handoff)

REI Consultation/Early Obstetric Care
–clearly denote interventions pursued for ongoing pregnancy → **at-risk interventions**

Tradeoffs are real: Optimize transparent counselling, even when options to accomplish pregnancy and livebirth are limited

Clinical Practice
A Hypothetical Scenario

36 yo G3P0111, prior 35w vaginal birth after preeclampsia with severe features and fetal growth restriction, now with chronic HTN on low-dose labetalol, and difficulty conceiving but ovulatory

REIs, OBs, MFMs in the room, what would you do? How would you counsel this patient?

THANK YOU!!!


Mass General Brigham

Oocyte: Donor IVF vs Autologous Spontaneous Conception
Risk of Preeclampsia

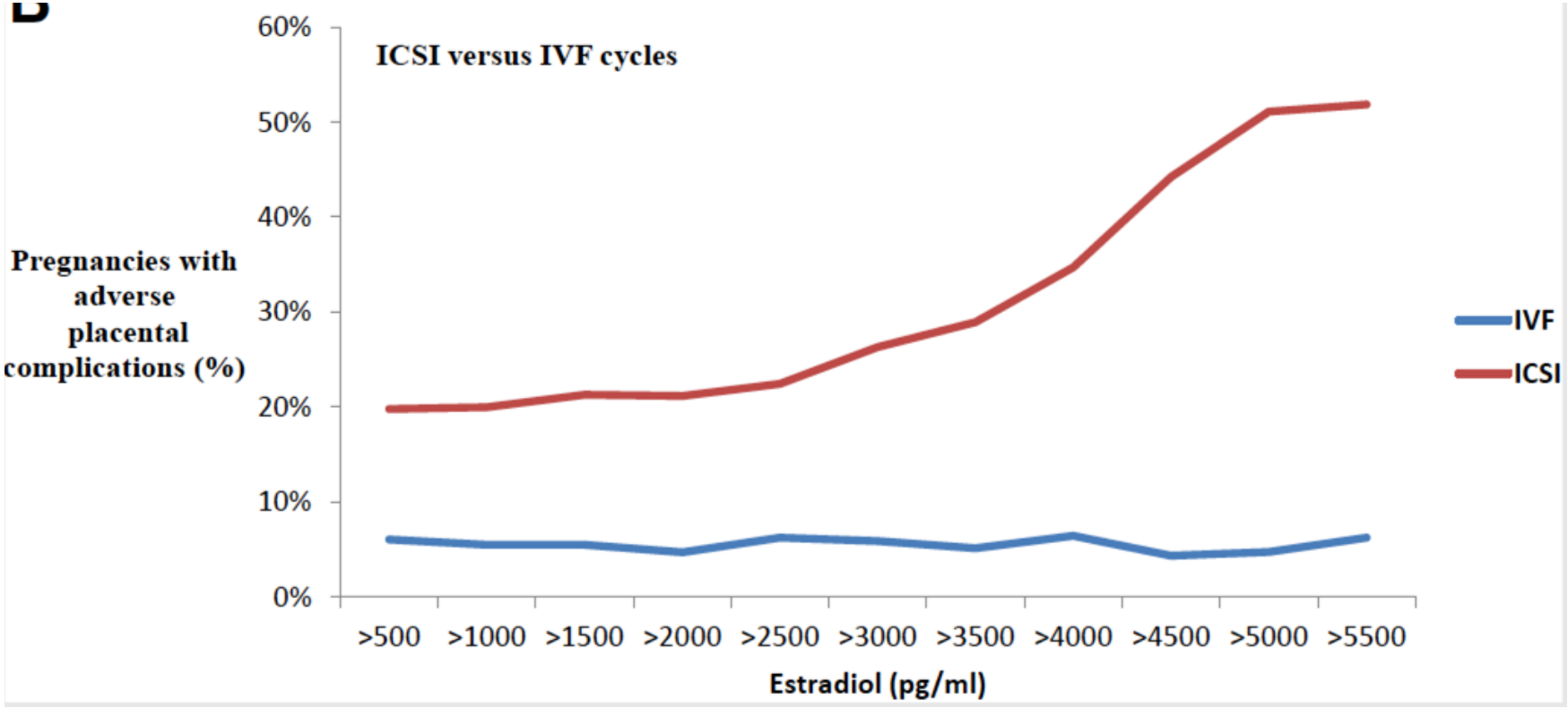
Experimental	Number of studies	ART study size (n)	SC study size (n)	OR; 95% CI	I^2 (%)	*P* value	NNH (n)
Hypertensive Disorders of Pregnancy							
IVF/ICSI singleton	51	268,166	7,728,641	1.70 (1.60–1.80)	80	< 0.01[a]	47.2
IVF singleton	5	41,238	437,723	1.55 (1.23–1.94)	90	< 0.01[a]	85.9
ICSI singleton	9	27,108	446,149	1.52 (1.28–1.80)	75	< 0.01[a]	54.3
IVF/ICSI multiple	41	88,853	120,396	1.34 (1.20–1.50)	76	< 0.01[a]	47.8
IVF multiple	4	13,147	73,297	1.13 (0.98–1.29)	59	0.09	86.3
ICSI multiple	10	9924	77,179	1.11 (0.91–1.36)	77	0.30	12.8
Fresh embryo transfer singleton	16	162,867	4,381,981	1.43 (1.33–1.53)	72	< 0.01[a]	57.4
Frozen embryo transfer singleton	9	41,462	4,090,152	1.74 (1.58–1.92)	55	< 0.01[a]	52.6
Oocyte donation singleton	9	12,461	2,413,466	4.42 (3.00–6.51)	83	< 0.01[a]	16.3
Oocyte donation multiple	2	10,488	59,045	2.62 (2.46–2.79)	0	< 0.01[a]	10.2

Oocyte: Donor vs Autologous
Risk of Preeclampsia

Table II **Prevalence of PE and severe PE in oocyte donation, IVF and natural pregnancies.**

Prevalence % (95% CI)	Subgroups	Subgroups	IVF OD	NC and non-IVF	IVF
PE	All ages	Singleton	10.7 (6.6–15.5)	2.0 (1.0–3.1)	4.1 (2.7–5.6)
		Multiple	27.8 (23.6–32.2)	7.5 (7.2–7.8)	9.7 (6.2–13.9)
	Age >40	Singleton	17.4 (13.3–22.0)	1.3 (0.2–2.9)	1.3 (0.2–2.9)
		Multiple	17.9 (13.5–23.1)	3.6 (3.5–3.7)	3.6 (3.5–3.7)
	Overall		15.7 (11.3–20.6)	3.1 (2.1–4.2)	5.3 (4.0–6.8)

Intracytoplasmic Sperm Injection
Adverse Placental Outcomes



Fertil Steril 2016;106:363