



Advanced Reproductive Aging: Pregnancy Risks & Management Strategies

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Educational Objectives

- Counsel women on the decrease in fertility with reproductive aging.
- Understand the fertility treatments available to help women of advanced reproductive age (ARA) conceive.
- Recognize the obstetrical risks faced by the “elderly gravida”.

This just in...



Amal Clooney, 39
George Clooney, 55

Expecting twins
summer 2017!

Advanced Reproductive Age: Why?

- Increased access to contraception
- Improved education
- More women in workforce
- Longer life expectancy
- Progress of assisted reproductive technologies (ART)
- Increased cost of childcare and college

OB-GYN Says Janet Jackson Pregnant At Age 50 Is Rare

Janet Jackson's Pregnancy at Age 50 Has Doctor Sending Urgent Message to Women Who Think They Can Wait



Is 50 the new 40 for motherhood?

EXCLUSIVE: Janet Jackson Pregnant at 50: What a Fertility Specialist Says She Should and Shouldn't Worry About

Advanced Reproductive Aging: *Point/Counterpoint*

- Reproductive aging and **fertility**:
 - *Why not?*
 - What are the chances of a successful pregnancy?
 - How can fertility treatment help couples achieve success?
- Reproductive aging and **obstetrical outcomes**:
 - *Why? (Why now?)*
 - What are the risks?
 - How can we best care for the “elderly gravida”?

PREGNANT AT 45: The REI Perspective *Why not?*

So you want to be an elderly primigravida...

- What are the chances of a successful pregnancy?
 - Reproductive biology
 - Fertility rates
- How can fertility treatment help couples achieve success?
 - Superovulation with oral/injectable medications
 - IVF
 - Donor Oocyte

Aneuploidy and Pregnancy Loss

- 50% of pregnancy loss is due to aneuploidy
- Risk of miscarriage directly related to maternal age:

	20-30 years	35 years	40 years	45 years
Risk of miscarriage	9-17%	20%	40%	80%

- Increased risk of monosomy/trisomies with advanced maternal age:
 - Trisomy 21: 1/1000 age ≤ 30 yrs → 1/30 age 45 yrs

ASRM. Eval and Treatment of RPL. Fertil Steril 2012; 98:1103

Reproductive Aging: Everything else

The ovary is not the only reproductive organ that ages

- Uterus:
 - Fibroids
 - Polyps
 - Adenomyosis
- Fallopian tubes
 - Scarring from infection, endometriosis
- Cancer, cardiovascular disease, accidents/injuries

Assessment of the ARA patient

Age 35-40

- Fertility evaluation after 6 months of trying to conceive
- * In the absence of an abnormality, like irregular menstrual cycles or a history concerning for pelvic adhesive disease. If abnormalities → immediate eval

Age >40

- Immediate evaluation

Evaluation

- Ovarian reserve testing
- Tubal patency
- Uterine evaluation
- Semen analysis

Advanced Paternal Age

- Age > 50 years
- Abnormal sperm parameters
- Chromosomal errors
- Sexual dysfunction

ACOG Comm Opinion #589 (2014)

Fertility Treatment

- Primary goal in treating age-related fertility decline is superovulation, or the release of more than 1 oocyte
- Goal = singleton pregnancy
- Can be sometimes be achieved with oral medications (clomid, letrozole)
- More effective with injectable gonadotropins

A randomized clinical trial to determine optimal infertility treatment in older couples: the Forty and Over Treatment Trial (FORT-T)

- 154 couples, female 38-42yo, trying to conceive ≥ 6 months
- Randomized to one of three treatments:
 - 1) Clomiphene/IUI x 2 cycles, then IVF
 - 2) FSH/IUI x 2 cycles, then IVF
 - 3) Immediate IVF

	CC/IUI	FSH/IUI	IVF
Clinical Pregnancy after 2 Cycles	21.6%	17.3%	49.0%
Live Birth after 2 Cycles	15.7%	13.5%	31.4%

- 46% livebirth; 84% from IVF treatment

Goldman Fertil Steril 2014; 101:1574

IVF – National SART Data 2014

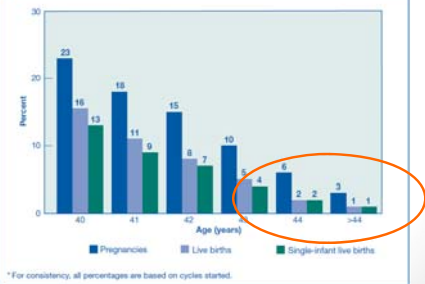
Figure 14
Percentages of ART Cycles Using Fresh Nondonor Eggs or Embryos That Resulted in Pregnancies, Live Births, and Single-Infant Live Births, by Age of Woman,* 2014

Age (years)	Pregnancies (%)	Live births (%)	Single-infant live births (%)
<24	45	35	25
24-25	48	38	28
26-27	45	35	25
28-29	45	35	25
30-31	45	35	25
32-33	42	32	22
34-35	38	28	18
36-37	32	22	12
38-39	25	15	8
40-41	18	10	5
42-43	10	5	2
44-45	5	2	1

* For consistency, all percentages are based on cycles started.

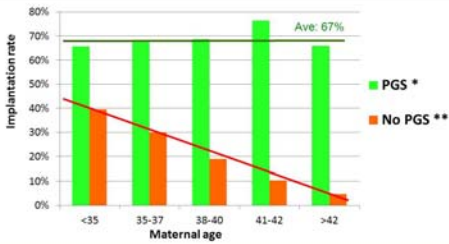
IVF – National SART Data 2014

Figure 15
Percentages of ART Cycles Using Fresh Nondonor Eggs or Embryos That Resulted in Pregnancies, Live Births, and Single-Infant Live Births Among Women Aged 40 or Older, 2014



Solution #1: PGS

- Embryo screening with preimplantation genetic screening allows for the transfer of only euploid embryos
- Implantation rate of 60-70%, reduces miscarriages



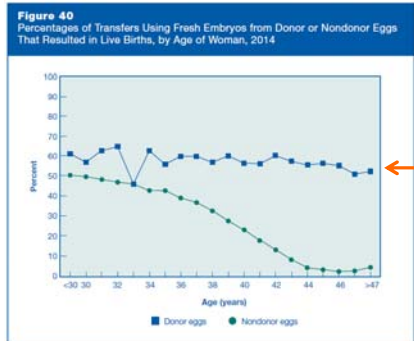
* Harton, Munné et al. (2013) Fertil Steril. And unpublished data to 8/2015. N= 2532 followed up cycles of PGS by aCGH. ** SART 2013

PGS: Chance of no transfer

# of blastocysts	% of patients with normal embryos					
	egg donors	<35 years	35-37 years	38-40 years	41-42 years	>42 years
1-3	86%	85%	72%	60%	58%	24%
4-6	95%	97%	95%	88%	69%	54%
7-10	100%	99%	96%	92%	85%	65%
>7-10	100%	100%	98%	98%	92%	83%

N = 3,571 cycles and 19,356 embryos, up to 8/2013. Ata, Munne et al. (2012) Reprod Biomed Online and unpublished data.

Solution #2: Donor Egg IVF



Donor Egg IVF

- Provides women of ARA with an option that allows them to conceive and carry a pregnancy
- Anonymous vs. Direct Egg Donors
 - Majority of cycles are done with anonymous donors
- Fresh vs. Frozen Oocytes
- Alternatives:
 - 1) Adoption
 - 2) Foster care
 - 3) Choosing to live without children

Oocyte Recipient Screening

- Preconception counseling is *critical* in the Oocyte Recipient
- Preexisting medical conditions:
 - Cardiovascular health: EKG, basic metabolic panel
 - Diabetes screening
 - Cancer screening: pap, mammogram, colonoscopy
- MFM Consultation
- Psychosocial evaluation
 - Adequate supports in place to raise a child to adulthood?

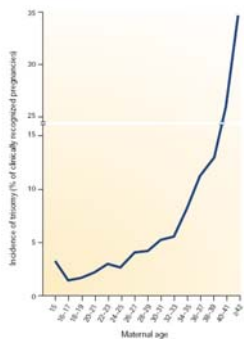
Pregnancy at ARA: Why not?

- Challenges of reproductive aging:
 - Decreased ovarian reserve
 - Disease/injury to other pelvic organs
- Evaluation of the ARA patient trying to conceive
- Fertility treatments that can help:
 - Superovulation
 - IVF +/- Preimplantation Genetic Screening
 - Donor Egg IVF

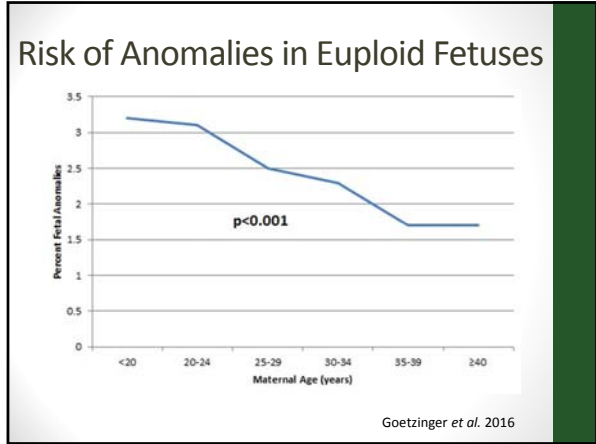
PREGNANT AT 45: The MFM Perspective

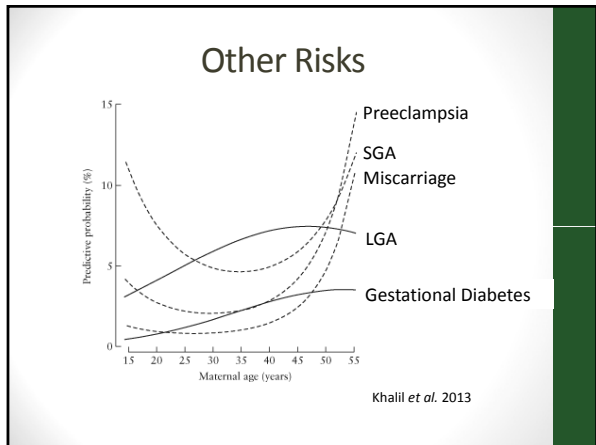
Why?

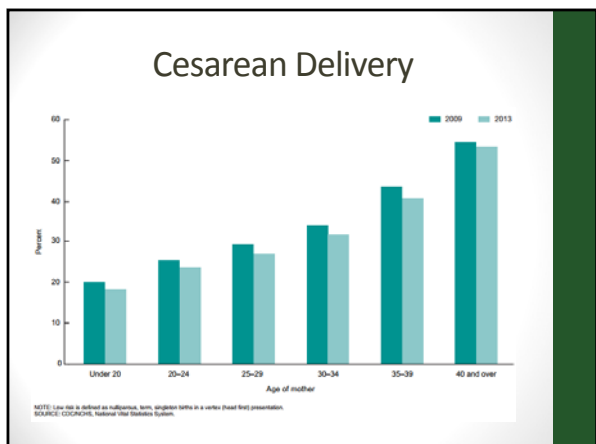
Maternal Age and Aneuploidy



Hassold and Hunt 2001







Cesarean Delivery in Nulliparas

- Age 20-34: 31%
- Age 35-39: 45%
- Age 40-44: 57%
- Age 45-49: 71%
- Age \geq 50: 75%
- 23% prelabor CD
- 34% prelabor CD
- 44% prelabor CD
- 57% prelabor CD
- 67% prelabor CD

Osmundson *et al.* 2016

Intrapartum CD in Nulliparas

- Age 20-34: 10%
- Age 35-39: 17%
- Age 40-44: 22%
- Age 45-49: 33%
- Age \geq 50: 26%

Osmundson *et al.* 2016

Fetal Growth Restriction

- Age 40-44: 1.9 fold increased risk
- Age \geq 45: 2.7 fold increased risk

Odibo *et al.* 2006

Stillbirth

TABLE Risk of antepartum stillbirth based on maternal condition

Condition	Prevalence	Stillbirth risk (per 1,000 births)
All pregnancies		6.4
Chronic hypertension	6%-10%	6-25
Maternal diabetes		
Diet controlled	2.5%-5%	6-10
Insulin	2.4%	6-35
Cholestasis	<0.1%	12-30
Previous stillbirth	0.5-1%	9-20
Advanced maternal age		
35-39 years	15%-18%	11-14
40 years	2%	11-21

Adapted from Fretts, et al.⁴

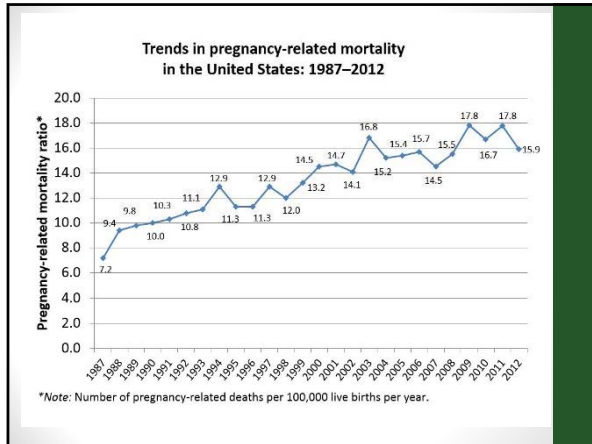
Stillbirth

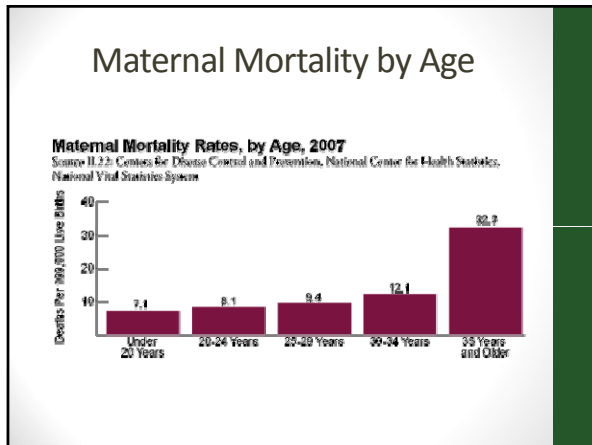
- 1.9 fold increase in risk in women age 35-39
- 2.29-2.4 fold increase in risk in women age ≥ 40
- Risk of stillbirth in women age 40-44 at **38-39 weeks** is similar to risk in women age 25-29 at **41-42 weeks**

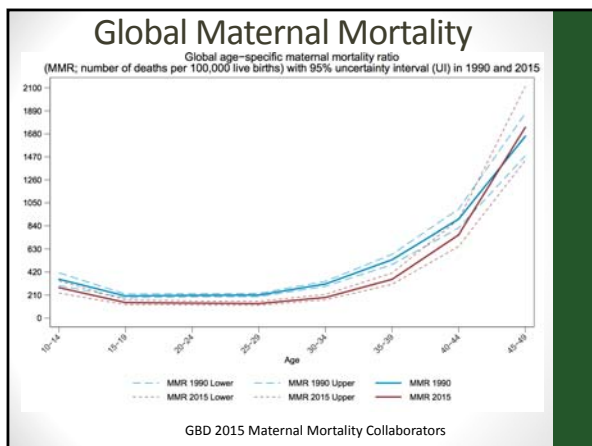
SMFM Guideline:

Advanced Maternal Age and the Risk of Antepartum Stillbirth

“There is insufficient evidence to confirm that antenatal testing for the sole indication of AMA reduces stillbirth or improves perinatal outcomes. The potential benefits of routine antepartum testing needs to be weighed against the potential harm of increased interventions, iatrogenic delivery, labor induction and possibly cesarean section.”







Global Perspective on Maternal Mortality

- Delaying 100,000 adolescent pregnancies until age 20-24 could prevent 70 deaths
- More than 1000 deaths could be prevented if 100,000 pregnancies occurred in 20s vs. ≥ 40 years of age
- High vs. low parity patients in low vs. high-income countries

Nove et al. 2016

Management of AMA ≥ 40

- Preconception counseling
 - Assessment of chronic health conditions
 - Body mass index
 - Lifestyle modifications
- Low-dose aspirin
- Early glucose screening
- Aneuploidy screening options
- Offer level II ultrasound

Management of AMA ≥ 40

- Consider growth ultrasound(s)
- Offer antenatal testing
 - UAB starts nearly all testing at 32 weeks
 - Other institutions start at 36-37 weeks
- Offer delivery at 39-40 weeks
- CD for usual obstetric indications

Ethical Implications

- Parental lifespan
 - Increased risk of mental health disorders in children who experience a loss in childhood
 - Commonly, grandparents raise their grandchildren
- Emotional and physical demands of parenting
 - Mitigated by absence of chronic health conditions, activity level, and nutrition

Ethical Implications

- Increased financial stability
- Potentially less interference with career trajectory
- Maturity and life experience

Concluding Thoughts

- “40 is not the new 20”
- Reproductive mythology is perpetuated by the media
 - Societal changes do not alter biologic realities
 - “Motherhood at age any is never risk free: Older gravidity is always high risk”
 - Combat misperceptions with education and preventative medicine

Sauer Fertil Steril 2015; 103:1136

ASRM Guidelines

- “Providing donor oocytes or embryos to women over 55 years of age, even when they have no underlying medical problems, should be discouraged.”
- Women should undergo testing for cardiovascular and metabolic fitness and a psychosocial evaluation.
- Single embryo transfer is preferred given the increased risk of multiple pregnancy.
- “It is ethically permissible for programs to decline to provide treatment to women of ARA based on concerns over the health and well-being of the patient and offspring.”
