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Advanced Maternal Age

Family Medicine Obstetrics Grand Rounds

September 20, 2018

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Department of Family Medicine

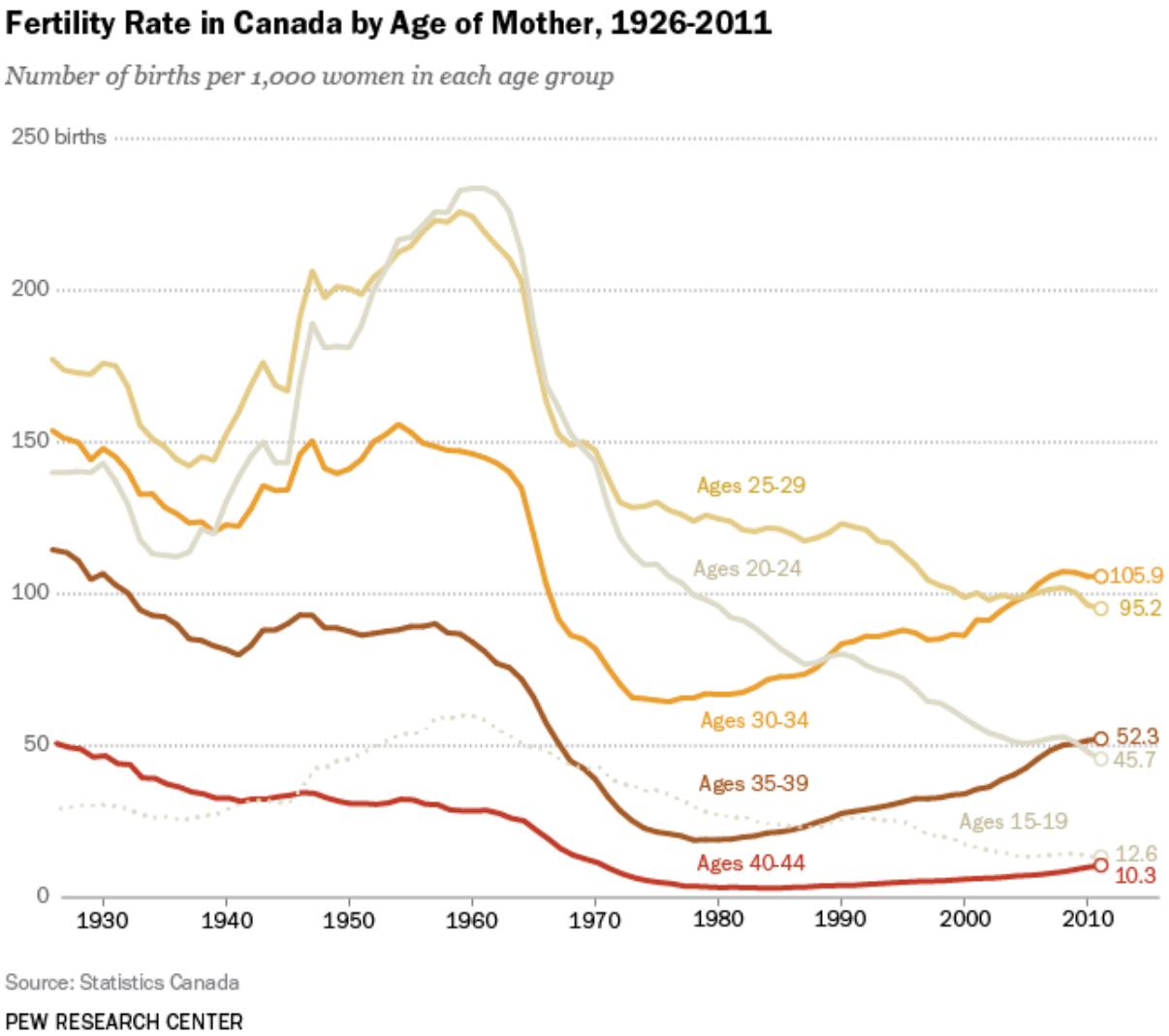
Conflicts of Interest

- I do not have an affiliation (financial or otherwise) with any for-profit or not-for-profit organizations.

Objectives

- What is advanced maternal age (AMA)?
- How should we counsel women who are AMA?
- What are associated risks?
- How should we manage women who are AMA?

Why is this important?



Source: Statistics Canada, 2010

Fertility

Women's Age vs Fertility

- Age 15-19: 14.2%
- Age 20-24: 51.2%
- Age 25-29: 100.6%
- Age 30-34: 107.0%
- Age 35-39: 50.6%
- Age 40-44: 9.2%
- Age 45-49: 0.4%

Fertility rate = # live births /1000 women

Source: Statistics Canada, 2016

Health Advantages

- Folic acid
- Purposeful approach and readiness
- Higher breastfeeding rates
- Socioeconomic influence

How should we counsel women who are AMA?

Preconceptual Counseling

- Informed decision-making
  - ↑ pre-existing health conditions
  - ↑ alcohol usage and work hours
  - Age-related subfertility
  - Environmental toxicity exposure
  - Obstetrical and perinatal risks
- Folic acid supplementation

Fertility

SOGC suggests offering fertility evaluations:

- <35: after 1 year of attempted conception in the absence of known cause of infertility
- 35-37: after 6 months
- >37 or those with chronic medical conditions: earlier than 6 months

Assisted Reproductive Technologies

- ART technologies can accelerate the time to conception
  - Do not compensate for natural decline of fertility due to age
- Goals of ART:
  - Increase monthly fecundity
  - Decrease time to conception

ART and AMA

Moaddab et al, 2017

- Population level analysis, 2011 – 2014, 101 494 live births by women ≥ 40 vs < 40 years by ART from CDC data
- Increased risk:
  - Gestational hypertension, gestational diabetes, eclampsia, unplanned hysterectomy, ICU admission

Table 2
Early maternal outcomes, medical, and obstetrics complications for ART pregnancies with regards to maternal age, United States, 2011–2014.*,**

Characteristic		Maternal age < 40	Maternal age 40–44	Maternal age 45–49	Maternal age ≥ 50
Gestational hypertension		8343 (10.5)	2061 (12.7)	724 (15.6)	149 (16.8)
Gestational diabetes		7635 (9.6)	1919 (11.9)	645 (13.9)	119 (13.5)
Eclampsia		423 (0.5)	123 (0.8)	36 (0.8)	11 (1.2)
Chorioamnionitis		1843 (2.3)	336 (2.1)	105 (2.3)	12 (1.4)
Method of delivery	Spontaneous vaginal	28,787 (36.1)	4385 (27.1)	923 (19.9)	173 (19.6)
	Operative vaginal	3241 (4.1)	566 (3.5)	134 (2.9)	18 (2.0)
	Cesarean	47,685 (59.7)	11,218 (69.3)	3577 (77.1)	694 (78.4)
	Unknown	73 (0.1)	17 (0.1)	3 (0.1)	0
Ruptured uterus		30 (0.04)	10 (.06)	2 (0.04)	1 (0.11)
Unplanned hysterectomy		134 (0.2)	71 (0.4)	35 (0.8)	6 (0.7)
ICU admission		362 (0.5)	120 (0.7)	47 (1.0)	9 (1.0)
Maternal transfusion		1065 (1.3)	234 (1.5)	94 (2.0)	18 (2.1)

*Data are reported as number (proportion) and mean ± standard deviation.
**All relationships are significant ($P < 0.001$).

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ART and AMA

Moaddab et al, 2017

- ART in AMA not associated with:
  - Increased risk of chromosomal disorders, anencephaly, Down's syndrome, gastroschisis, neural tube defects, omphalocele, CHD, cyanotic heart defects

What are the risks of being pregnant at an older age?

Maternal Risks

- Exacerbation of pre-existing medical conditions
- Ectopic pregnancy
- Placenta previa
- Breech position
- Caesarean delivery
- Multiples
- Mixed data on placenta abruption

Gestational Diabetes

Age Group	Rate	Risk
<20	1.37%	1 out of 73
20-34	4.11%	1 out of 24
35-39	8.06%	1 out of 12
40+	11.82%	1 out of 8

Data is from 2006/2007 and 2008/2009. Source: CIHI

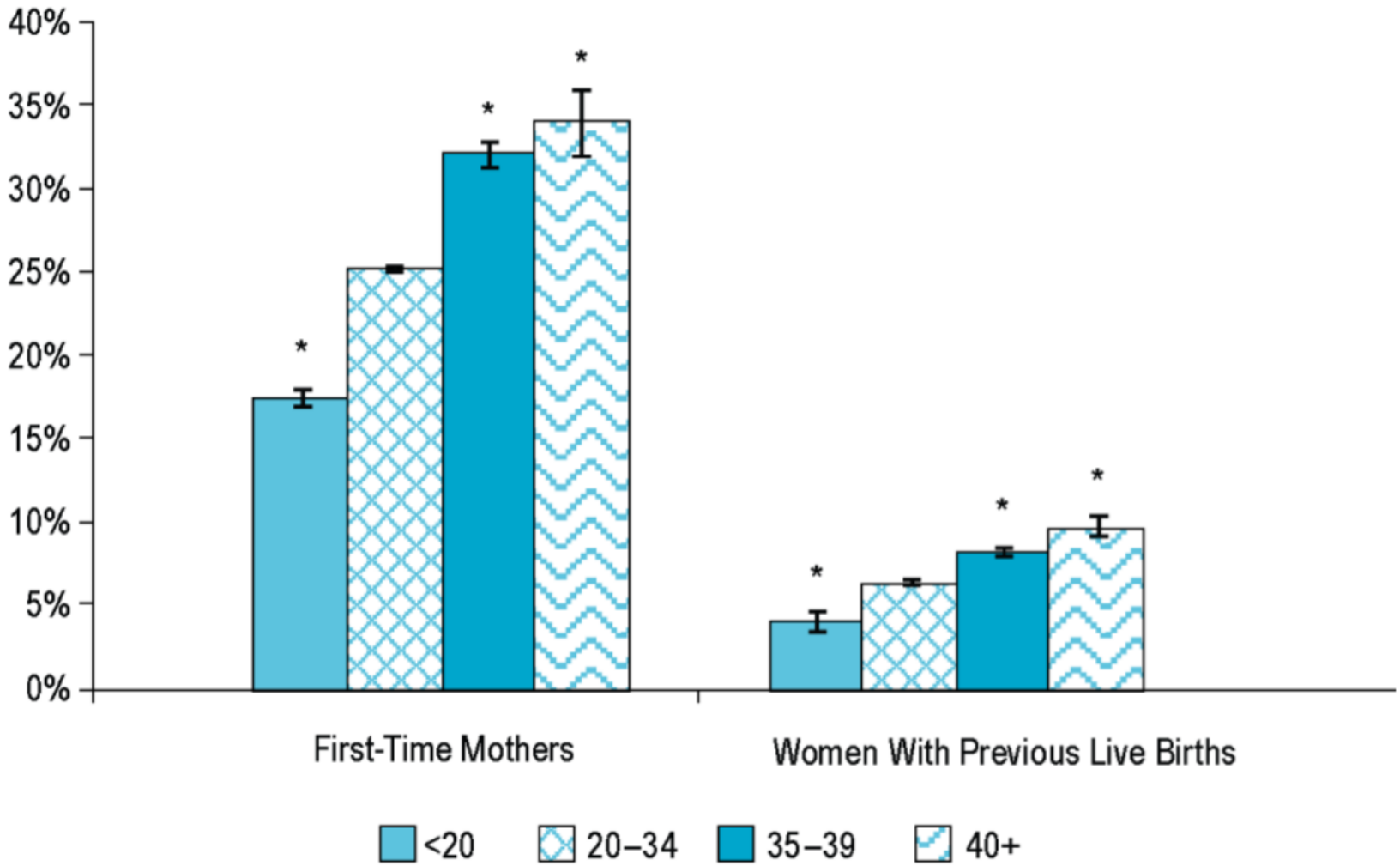
Caesarean delivery

- ≥ 35: 44% higher rates than women 20-34
- ≥ 40: 1 in 3 women have c-sections
- First time mothers ≥ 40: 1 in 2 women have c-sections

Assisted delivery

- Forceps / vacuum extraction rates 28% higher in ≥ 35 than 20-34
- Placental abruption 60% higher in ≥ 40

Rates of assisted vaginal delivery



Data is from 2006/2007 and 2008/2009. Source: CIHI

Placenta Previa

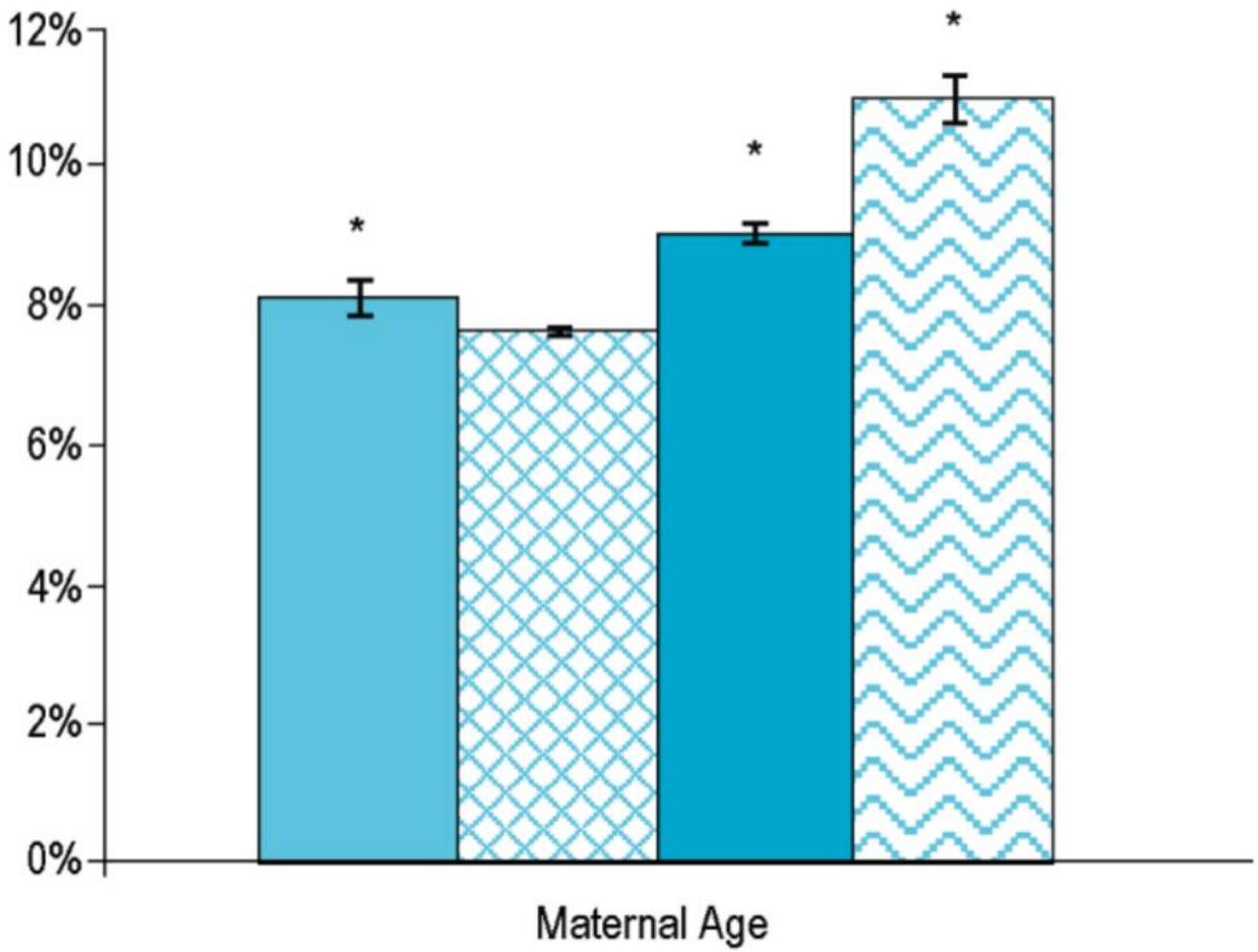
Age Group	Rate	Risk
<20	0.12%	1 out of 833
20-34	0.48%	1 out of 208
35-39	1.03%	1 out of 97
40+	1.55%	1 out of 65

Data is from 2006/2007 and 2008/2009. Source: CIHI

Fetal Risks

- Preterm delivery
- Low birth weight
- SGA
- Increased aneuploidy, non-chromosomal abnormality, and congenital anomaly
- Stillbirth

Preterm Delivery



Data is from 2006/2007 and 2008/2009. Source: CIHI

Aneuploidy

Age Group	Rate	Risk
<20	0.10%	1 out of 1000
20-34	0.10%	1 out of 1000
35-39	0.27%	1 out of 370
40+	0.79%	1 out of 127

Data is from 2006/2007 and 2008/2009. Source: CIHI

Down Syndrome

Rates at 10 weeks GA:

- 1 in 1,064 at age 25
- 1 in 686 at age 30
- 1 in 240 at age 35
- 1 in 53 at age 40
- 1 in 19 at age 45

Rate at term:

- 1 in 1,340 at age 25
- 1 in 939 at age 30
- 1 in 353 at age 35
- 1 in 85 at age 40
- 1 in 35 at age 45

(Haddow, Palomaki et al. 2009)

Stillbirth

Huang et al, 2008

- 24 out of 31 studies: older women more likely to have a stillbirth than younger women
- Risk of stillbirth x 1.2 to 2.23 higher (developed countries)
  - Not due to other known risk factors/confounders i.e. smoking, other medical problems, race, prenatal care, BMI, education level, primiparous status

Stillbirth

Limitations (Huang et al):

- Large variances in:
  - Methodologies of studies
  - Population (low vs high risk)
  - Definition of AMA (>35 vs >40)
  - Inclusion of other risk factors for stillbirth
  - Definition of stillbirth (antepartum vs intrapartum)
- Data from more than 20 years ago
- Lack of risk calculations per year of age

Stillbirth

Jolly et al, 2000

- UK, 1988-1997, 18 hospitals, 358 120 women
  - Controlled for age, BMI, ethnic group, medical issues, primiparous status
  - Stillbirth not defined – ?any GA > 20-28 weeks
- Rates of stillbirth:
  - 18-34: 0.47 % (4.7 / 1000)
  - 35-40 0.61 % (6.1 / 1000)
  - ≥ 40 0.81 % (8.1 / 1000)

Stillbirth

Jacobsson, Ladfors et al, 2004

- Sweden, 1987-2001, 18 hospitals, 909 228 births
  - Compared perinatal death rate between women 20-29 vs women ≥ 40
  - Perinatal birth: stillbirth or newborn up until 28d of age
- Rates of stillbirth:
  - 20-29: 0.6 % (6 / 1000)
  - 40-44 1.08 % (10.8 / 1000)
  - ≥ 45 1.66 % (16.6 / 1000)

Stillbirth

Reddy et al, 2006

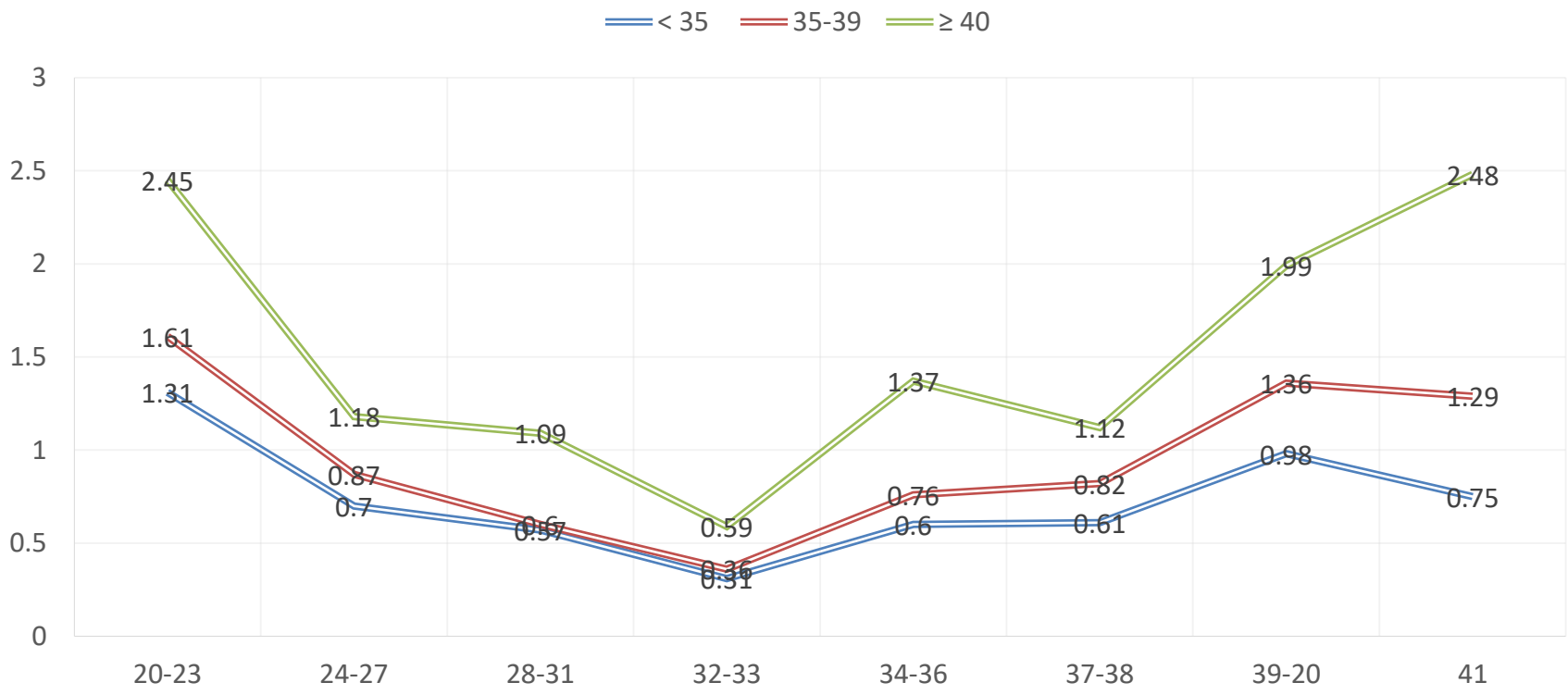
- US, 2001-2002, 5.5 million singleton pregnancies without birth defects
  - Compared stillbirth rates, maternal age, and whether risk was higher for primiparous vs multiparous women

Age groups	Primiparous women	Multiparous women
< 35	3.72	1.29
35-39	6.41	1.99
≥ 40	8.65	3.29

Rates are per 1000 ongoing pregnancies.

Stillbirth

Reddy et al, 2006



Stillbirth

		Absolute Risk (per 1000 ongoing pregnancies)		Relative risk of stillbirth (95th % CI)	
	Maternal age	**<35**	**≥40**	**<35**	**≥40**
GA	**37-41 weeks**	N/A	N/A	1.0	1.88 (1.64-2.16)
	37-38 weeks	0.61	1.12	1.0	1.82 (1.49-2.23)
	39-40 weeks	0.98	1.99	1.0	2.04 (1.64-2.54)
	41 weeks	0.75	2.48	1.0	3.30 (2.24-4.87)

Reddy et al, 2006

Stillbirth

Haavaldsen et al, 2010

- Norway, 1967-2006, 2.1 million pregnancies
  - Compared risk of stillbirth by gestational age among younger and older women

Number of stillbirths per 1000 ongoing pregnancies; data from 1967-2006

	Age 20-24	Age 35-39	Age 40 +
GA 16+0 to 22+6	2.1	4.75	7.07
GA 23+0 to 29+6	2.31	2.53	3.44
GA 30+0 to 37+6	2.51	3.25	5.72
GA 38+0 to 39+6	1.16	1.53	2.93
GA 40+0 to 41+6	1.62	2.59	4.17
GA 42+0 to 43+6	2.82	5.8	12.37

Haavaldsen et al, 2010

Number of stillbirths per 1000 ongoing pregnancies; data from 1967-2006

	Age 20-24	Age 35-39	Age 40 +
GA 16+0 to 22+6	2.1	4.75	7.07
GA 23+0 to 29+6	2.31	2.53	3.44
GA 30+0 to 37+6	2.51	3.25	5.72
GA 38+0 to 39+6	1.16 / **0.65**	1.53 / **1.1**	2.93 / **1.39**
GA 40+0 to 41+6	1.62 / **0.84**	2.59 / **1.91**	4.17 / **1.61**
GA 42+0 to 43+6	2.82 / **1.77**	5.8 / **3.79**	12.37 / **2.64**

Haavaldsen et al, 2010

Stillbirth

Bahtiyar et al, 2008

- Mathematical model showed that the cumulative risk of stillbirth at 38-39 weeks in women aged 40-44 was similar to the risk in women 25-29 at 41-42 weeks

Why does the risk of stillbirth increase in older women?

- ? Increased risk of uteroplacental insufficiency
  - No good evidence!
  - Literature shows no significant difference in rates of IUGR, fetal distress, Caesarean of fetal distress or other clinical markers of aging placenta in women ≥ 35 vs younger women
  - Froen, Gardosi et al, 2004: no difference in IUGR between women ≥ 35 and younger women
  - Seoud, Nassar et al, 2002: 2/3 stillborn babies in women ≥ 40 had no risk factors other than age

Why does the risk of stillbirth increase in older women?

- ? Aging-related health problems
  - Huang et al, 2008: increased risk of stillbirth in women ≥ 35 after accounting for risk factors
- ? Unknown

How should we manage women who are AMA?

Obstetrical Management

- Address pre-existing health concerns
- Manage prenatal complications if and when they present
- Prenatal screening for aneuploidy
- ? Fetal health surveillance
- Induction of labour

Genetic Screening Tests

	eFTS	NIPT	MSS
Components **all screens use maternal age in assessment*	1) PlGF, AFP, PAPP-A, bHCG 2) US for NT	Cell-free fetal (cff) DNA	AFP, uE3, total HCG, inhibin
Gestational age	11 to 13+6	> 9 to 10	15 to 20+6
Detection rate	85-90%	99%	80%
False positive rate	3-6%	< 0.1%	5%
Abnormalities screened for	Trisomy 21, 18	Trisomy 21, 18, 13, X, Y	Trisomy 21, 18, ONTD

NIPT – OHIP coverage:

- Maternal multiple marker screen test positive for aneuploidy
- ≥ 40 years old at EDB
- Previous child with aneuploidy / pregnancy with aneuploidy
- Fetal NT ≥ 3.5 mm

Routine Care

- 1st trimester ultrasound (11-14 wks)
  - Viability, gestational age, # fetuses, chorionicity in multiples, early anatomic assessment, NT
- 2nd trimester ultrasound (18-22 wks)
  - Structural anomalies

Genetic Diagnostic Test

	Amniocentesis	Chorionic Villus Sampling
GA	15-17 weeks	11-13 weeks
Miscarriage Risk	0.25 % (1/400)	1% (1/100)
Fetal anomaly risk	No risk	Limb reduction < 9 weeks Possible hemangioma
% success	>99%	>99%
Time to diagnosis	QI-PCR 2-3 days Microarray 2 weeks Single gene test 2-6 weeks	
Accuracy	Highly accurate for RAD Chromosomal study: 99.9%	98-99%
Post-procedural risks	AF leakage (talipes at 15-16 weeks)	No significant risks

Fetal Health Surveillance

Fretts et al, 2004

- Decision analysis based on unexplained fetal deaths from McGill Obstetrical Neonatal Database
- Prediction: antepartum testing with IOL after a positive test (one antepartum test qweekly, any kind, >37 weeks GA) was the most successful in reducing the number of unexplained stillbirths
  - Also associated with the highest induction rate
- For nulliparous ≥ 35 yo:
  - 863 antepartum tests and 71 additional inductions to prevent 1 unexplained stillbirth

Fetal Health Surveillance

Fox et al, 2013

- Chart review of 1541 women ≥ 35 yo vs. 2928 women <35 yo
  - BPP qweekly at 36 weeks onward and delivery by 41 weeks GA for women ≥ 35 yo
- No statistical difference in the rate of stillbirth
  - ≥35 group had higher IOL rate (18.5% vs 15.8%) with earlier delivery (38.4 vs 38.9 weeks)

Fetal Health Surveillance

Levine et al, 2015

- Retrospective cohort of 276 women ≥ 40 yo exposed (129) vs unexposed (147) to antenatal surveillance
  - Twice weekly NST and fluid assessment at 32 wks
- No significant difference in intervention rates
  - CS rate higher for exposed group (53 vs 39%)… but was not significant when controlling for those with previous CS
  - Induction rate not significantly different
- No significant difference in stillbirths (total # = 3)

Fetal Health Surveillance

Per SOGC CPG No. 197 (Fetal Health Surveillance: Antepartum Consensus Guideline)

- Daily monitoring of FM from 26-32 weeks in all pregnancies with risk factors
  - AMA associated with increased perinatal morbidity / mortality
- <6 distinct movements / 2 hours needs further testing = NST +/- BPP
  - If NST normal (and no risk factors) → continue daily FM count
  - If NST normal + risk factors or suspect IUGR/ oligohydramnios → BPP or fluid assessment / 24 hours
  - If NST abnormal → BPP / fluid asap

Fetal Health Surveillance

- NST
  - Considered when risk factors for adverse perinatal outcome are present
  - If normal NST, fetal movements, and no suspected oligo → not necessary to conduct BPP
- BPP
  - Recommended when risk factors present and evaluation of fetal well-being required

Fetal Health Surveillance

- Umbilical Artery Doppler
  - Should not be used as a screening tool in healthy pregnancies
  - Should be available for assessment of fetal placental circulation with suspected placental insufficiency

Fetal Health Surveillance

- Uterine Artery Doppler

Table 8. Indications for uterine artery Doppler at 17 to 22 weeks

Previous obstetrical history	Previous early onset gestational hypertension
	Placental abruption
	Intrauterine growth restriction
	Stillbirth
Risk factors in current pregnancy	Pre-existing hypertension
	Gestational hypertension
	Pre-existing renal disease
	Longstanding Type I diabetes with vascular complications, nephropathy, retinopathy
	Abnormal maternal serum screening (hCG or AFP > 2.0 MOM)
	Low PAPP-A (consult provincial lab for norms)

Fetal Health Surveillance

Society for Maternal and Fetal Medicine (2012): *Advanced maternal age and the risk of antepartum stillbirth*

"It is currently unclear what the optimal management is for women ≥ 35 years to prevent 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 caesarean section."

Induction of Labour

Walker, Bugg et al, 2016

- RCT, 2012-2015, 600 women ≥ 35 yo, 42 hospitals
  - IOL 39+0 to 39+6 weeks vs. waiting then IOL at 41-42 weeks
  - Induction group: 78% induced
  - Not induced group: 46% spontaneous labour, 49% induced

Induction of Labour

Walker, Bugg et al, 2016

- No difference in Caesarean rates (32-33% both)
- No difference in complication rates for mothers
- No difference in average birth weight, Apgar scores, umbilical cord pH levels, NICU admissions, low blood oxygen, or need for interventions (i.e. tube feeding, O2)
- No stillbirths or deaths in either group

Induction of Labour

Nicholson, Kellar et al 2006

- Chart review, 15 036 low-risk women ≥ 35, 1995-2003, Hospital of the University of Pennsylvania
- 38+5 to 39+6 weeks:
  - Lowest risks of NICU admission, CS, 3rd/4th deg tearing, low 5 min Apgar
- Other risk factors for CS / NICU admission not controlled for

Induction of Labour

RCOG, 2013

- Induction of Labour at Term in Older Mothers (Scientific Impact Paper No. 34)
- UK data, 2009-2010: if all women aged ≥ 40 were induced at 39 weeks instead of 41 weeks, 17 stillbirths could be prevented
  - Inducing 550 women to prevent one stillbirth
  - Induction at 40 weeks would prevent 7 stillbirths

Induction of Labour

Roos et al, 2010

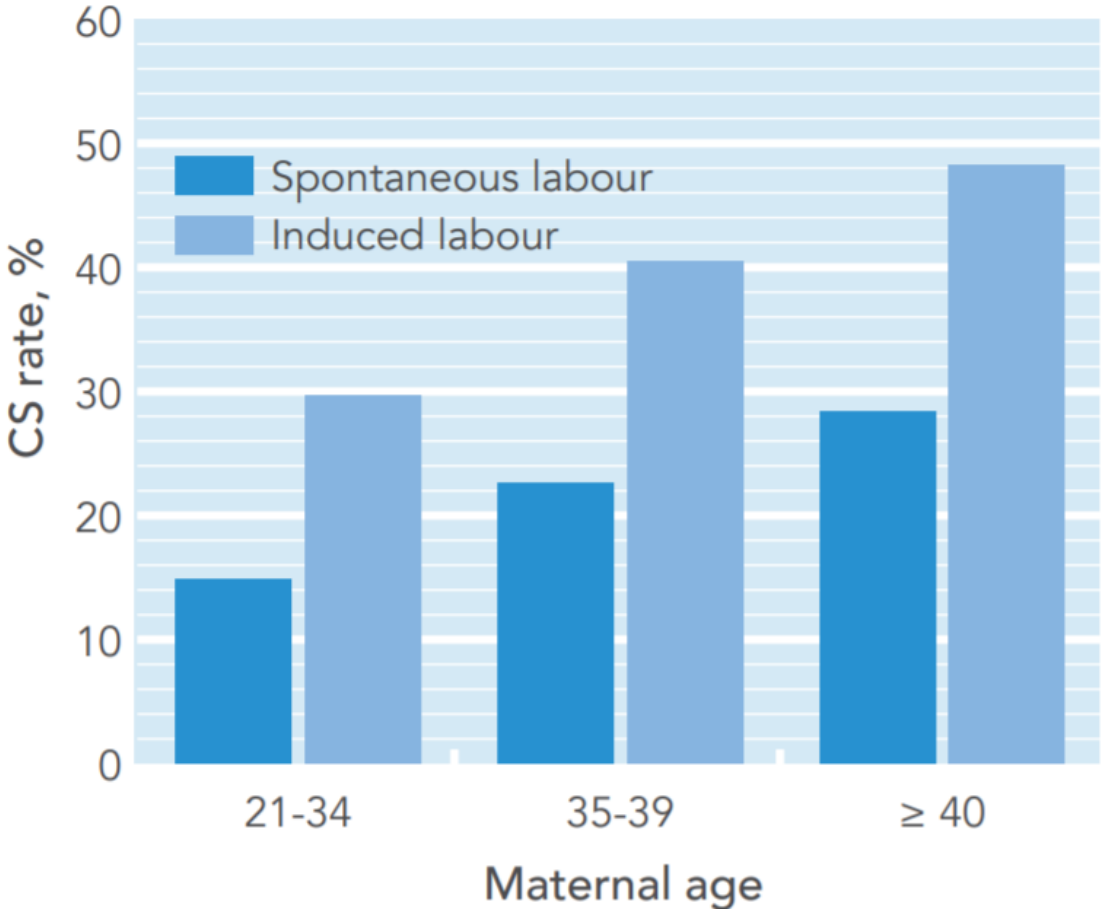
- 1.1 million births, 1992-2002, Swedish Medical Birth Register
- ≥ 35 yo more likely to:
  - Experience postdates pregnancy ≥ 42 weeks (10.4% compared to 7.8% in women 20-24)
  - Failed induction (2x relative risk)

Induction of Labour

Ontario's Better Outcomes and Registry Network (BORN):

- Increasing maternal age significantly associated with a rise in CS rate ($p < 0.0001$)
- Positive association between induction of labour and CS, with rates of CS 15% to 20% higher in primiparas

Induction of Labour



Elective Caesarean

- Not much data
- ACOG: short-term benefits from elective CS may lessen for women who are older or overweight
  - Benefits such as lower risk of hemorrhage, surgical complications, urinary incontinence may decrease with AMA and ↑BMI

Induction of Labour

ACOG: no official recommendations for AMA ≥ 35 yo

RCOG (2013): *Induction of labour at term in older mothers*

> "Risk of stillbirth at 39-40 weeks for all ages is 1/1000… Risk of stillbirth at 39-40 weeks for age ≥ 40 is 2/1000… Women ≥ 40 have a similar stillbirth risk at **39 weeks** to women in their mid-20s at 41 weeks, and the consensus is that IOL should be offered to prevent late stillbirth."

SOGC (2013): *Induction of labour*

> "Given the increased risk of stillbirth in women with advanced maternal age some experts suggest that women ≥ 40 years of age be considered biologically post-term at **39 weeks'** gestation and that delivery be considered at this gestation."

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