

Optimal obstetric care for women aged 40 and older

➔ As the trend toward delayed childbearing continues, ObGyns will encounter more pregnancies among patients of advanced maternal age. Here, a guide for assessing risks and managing pregnancy and delivery.

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ON THE WEB

🔊 Dr. Barton discusses obstetric care for women aged 45 and older, at obgmanagement.com

CASE Preterm labor in an older woman

G.S. is a 41-year-old G1P0 with a several-year history of infertility and a medical history of chronic hypertension. She undergoes in vitro fertilization (IVF) using her own oocytes, with transfer of two embryos. Early ultrasonography (US) confirms a diamniotic/dichorionic twin gestation. She undergoes chorionic villus sampling (CVS) during the first trimester, with normal fetal karyotypes noted.

For her chronic hypertension, the patient is treated with oral labetalol 200 mg twice daily, beginning in the first trimester. Results of a baseline comprehensive metabolic profile

and complete blood count, and electrocardiogram are normal. Baseline 24-hour urine study results reveal no significant proteinuria and a normal creatinine clearance.

At 18 weeks' gestation, US results show normal growth and amniotic fluid volume for each fetus, with no anomalies detected. Because of a gradual increase in the patient's blood pressure, her labetalol dose is increased to 400 mg orally thrice daily. Her urine protein output remains negative on dipstick, and US every 4 weeks until 28 weeks' gestation continues to show normal fetal growth and amniotic fluid volume.

At 33 weeks' gestation, the patient presents with regular uterine activity. Nonstress tests for both fetuses are reactive. She is given a 1-L intravenous (IV) fluid bolus of lactated Ringers solution, as well as subcutaneous terbutaline sulfate every 15 minutes for four doses, without resolution of the uterine contractions. Her pulse has increased to 120 bpm.

How do you manage this patient's care?

Nine times as many women aged 35 and older gave birth to their first child in 2012 than did women of the same age 40 years ago, according to the most recent data from the National Center for Health Statistics.¹ The rate of first births for women aged 40 to 44 remained essentially stable during the 1970s and early 1980s but



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increased more than fourfold from 1985 through 2012—from 0.5 to 2.3 per 1,000 women.¹ Clearly, more women are delaying child-bearing to a later age by personal choice for reasons such as completion of education and career advancement.²

The path to late motherhood is not without thorns, however. Heightened risks associated with increasing maternal age include:

- fetal aneuploidy
- fetal malformation
- gestational diabetes
- chronic and gestational hypertension
- antepartum hemorrhage
- placenta previa
- prelabor rupture of membranes
- preterm labor.^{3,4}

Women with advanced age at conception also are more likely to have a multifetal gestation because of the need for assisted reproduction and are more likely to require cesarean delivery⁵ as a result of abnormal placentation, fetal malpresentation, an abnormal pattern of labor, or increased use of oxytocin in labor. In addition, they are more likely to experience rupture of the sphincter, postpartum hemorrhage, and thromboembolism.³ Advanced maternal age also is associated with a higher risk of stillbirth throughout gestation, with the peak risk period reported to occur at 37 to 41 weeks.⁶

Maternal age-related risks of autosomal

trisomies (especially Down syndrome) are well understood and have been quantified for singleton and twin gestations. **TABLE 1** shows the risks at term for singleton and twin gestations for at least one chromosomally abnormal fetus by maternal age (40–46 years) and race.⁷

Preconception considerations

Aging and fertility

These combined result of aging of the ovary and uterus and an escalating risk of underlying medical comorbidities has a detrimental effect on fertility.⁸ Although assisted reproductive technologies are helpful, they cannot guarantee a live birth or completely compensate for an age-related decline in fertility.⁹

Many IVF programs refuse infertility treatment to women over age 43 or 44 who want to use their own oocytes. The reason: low pregnancy rates. The use of donor oocytes, however, increases the risks of gestational hypertension and preeclampsia. And if assisted reproductive technologies are needed, the risk for multifetal pregnancy increases.

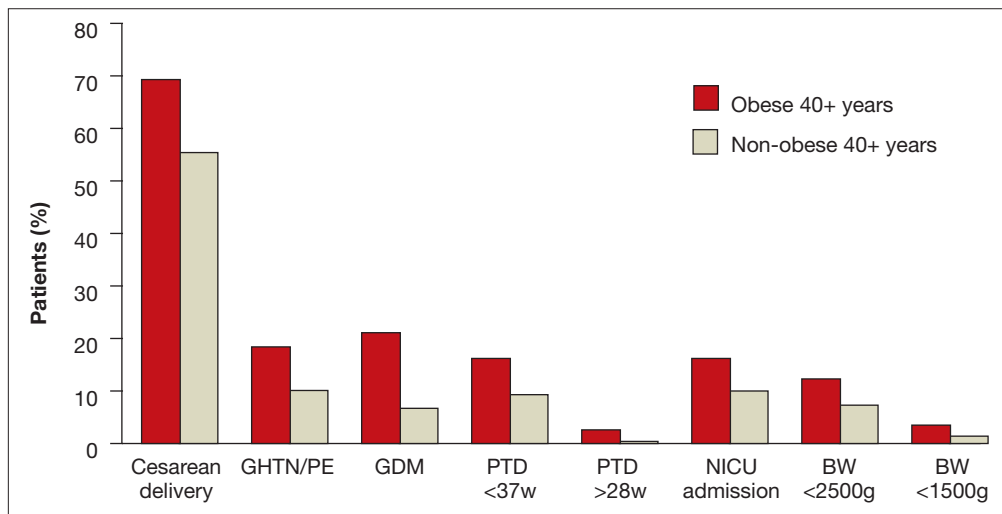
Women of advanced maternal age are likely to have an older spouse or partner. There is no clearly accepted definition of advanced paternal age, but it is most often defined as an age of 40 years or older at the

TABLE 1 Calculated risk at term for a chromosomal abnormality among infants of women aged 40 to 46 years

Maternal age (yrs)	Down syndrome					All chromosomal abnormalities				
	Singleton	White twins		Black twins		Singleton	White twins		Black twins	
		One or both	Both affected	One or both	Both affected		One or both	Both affected	One or both	Both affected
40	1/106	1/56	1/1,002	1/56	1/973	1/66	1/35	1/595	1/35	1/579
41	1/82	1/44	1/675	1/46	1/377	1/53	1/28	1/416	1/30	1/238
42	1/63	1/33	1/557	1/34	1/452	1/42	1/22	1/349	1/23	1/287
43	1/49	1/27	1/319	1/26	1/410	1/33	1/18	1/203	1/18	1/257
44	1/38	1/20	1/381	1/23	1/120	1/26	1/14	1/234	1/16	1/80
45	1/30	1/16	1/348	1/16	1/269	1/21	1/11	1/210	1/11	1/168
46	1/23	1/12	1/284	1/12	1/160	1/16	1/8	1/161	1/9	1/199

Source: Meyers et al.⁷

Pregnancy outcomes in obese vs nonobese older women



This chart highlights significant differences in pregnancy outcomes for obese versus nonobese women aged 40 years and older, tracking cesarean delivery, gestational hypertension and preeclampsia (GHTN/PE), gestational diabetes (GDM), preterm delivery (PTD) before 37 weeks, PTD before 28 weeks, NICU admission, birth weight (BW) below 2,500 g, and BW below 1,500 g. Source: Barton JR, et al.¹¹



Obese women of advanced maternal age had higher rates of cesarean delivery, gestational hypertension, preeclampsia, gestational diabetes, and preterm delivery

time of conception. Advanced paternal age has been associated with a higher risk for autism spectrum disorder and schizophrenia, as well as mutations in the FGFR2 and FGFR3 genes that result in skeletal dysplasias and craniosynostosis syndromes.¹⁰

Medical conditions are more common

Women of advanced maternal age have an increased rate of such prepregnancy chronic medical complications as diabetes, chronic hypertension, obesity, and renal and cardiac disease. Therefore, it is best to optimize control of these chronic illnesses prior to conception to minimize the risks of miscarriage, fetal anomalies, and gestational hypertension and preeclampsia.

Preeclampsia. Although daily low-dose (60–81 mg) aspirin has been used to reduce the risk of preeclampsia, current recommendations from the American College of Obstetricians and Gynecologists (ACOG) suggest that this therapy be reserved for women with a medical history of early-onset preeclampsia or those who have had preeclampsia in more than one pregnancy.¹¹

Impact of obesity. We recently examined the influence of age and obesity on pregnancy

outcomes of nulliparous women aged 40 or older at delivery.¹² The study included women aged 20 to 29 years (n = 52,249) and 40 or older (n = 1,231) who delivered singleton infants. Women who reported medical disorders, tobacco use, or conception with assisted reproductive technology were excluded.

In the older age group (≥40 years), obese women had significantly higher rates of cesarean delivery, gestational hypertension, preeclampsia, gestational diabetes, preterm delivery before 37 weeks’ gestation, and preterm delivery before 28 weeks, and their infants had higher rates of admission to the neonatal intensive care unit (NICU), compared with nonobese women (FIGURE).

It would appear, however, that healthy, obese women who delay pregnancy until the age of 40 or later may modify their risk for cesarean delivery, gestational diabetes mellitus, and gestational hypertension and preeclampsia by reducing their body mass index to nonobese levels prior to conception.

In addition to maternal risks for women of advanced maternal age, there are risks to the fetus and neonate, as well as a risk of placental abnormalities. These risks are summarized in TABLE 2, page 33.

TABLE 2 Risks associated with pregnancy in women older than age 40

Placental
<ul style="list-style-type: none"> • Molar or partial molar pregnancy • Fetus or twins with a complete mole • Placenta previa, vasa previa
Fetal/neonatal
<ul style="list-style-type: none"> • Aneuploidy • Selective fetal growth restriction in twin gestation • Twin-twin transfusion syndrome • Preterm birth • Perinatal death
Maternal
Antepartum
<ul style="list-style-type: none"> • Gestational diabetes • Insulin-dependent diabetes • Gestational hypertension and preeclampsia • Cholestasis of pregnancy • Acute fatty liver of pregnancy • Venous thromboembolism • Preterm labor, preterm premature rupture of membranes
Intrapartum
<ul style="list-style-type: none"> • Dysfunctional labor • Malpresentation • Cesarean delivery
Postpartum
<ul style="list-style-type: none"> • Venous thromboembolism • Postpartum hemorrhage

Folic acid supplementation can reduce some risks

The potential benefit of folic acid supplementation to reduce the risk of fetal open neural tube defects is well documented. More recent data suggest that folic acid also is associated with a reduction in the risks of congenital heart defects, abdominal wall defects, cleft lip and palate, and spontaneous abortion. **Supplementation should be initiated at least 3 months prior to conception and continued through the first trimester.**

The first trimester Early pregnancy loss is a risk

Women of advanced maternal age are more likely than younger women to experience

early pregnancy loss. This risk is due to higher rates of fetal aneuploidy as well as declining ovarian and uterine function and a higher rate of ectopic pregnancy.

In the First and Second Trimester Evaluation of Risk (FASTER) trial, in which investigators reported pregnancy outcomes by maternal age for 36,056 pregnancies, the rate of spontaneous abortion after 10 weeks of gestation was 0.8% among women younger than 35 years, compared with 2.2% for women aged 40 or older.⁴

The likelihood of multiple gestation increases

The background risk of multiple births is higher in women of advanced maternal age, compared with younger women. This risk increases further with fertility treatment.

Multiple gestations at any age are associated with increased risks for preterm birth and very-low-birthweight infants. Potential maternal risks are listed in **TABLE 3**, page 34.

To reduce the number of multiple gestations with assisted reproduction, consider elective single embryo transfer, especially if the mother has significant underlying medical complications.

Multiple gestations present difficult management issues in older women. Strategies shown to prevent preterm delivery in singleton gestations, including weekly 17-hydroxyprogesterone injections and cervical cerclage, are not effective in multiple gestations. Moreover, many of these therapies—including bed rest—increase the risk of thromboembolic events in multiple gestations, particularly when the mother is of advanced age.

Maternal adaptations in multiple gestations also may be poorly tolerated by older patients, particularly cardiac changes that markedly increase stroke volume, heart rate, cardiac output, and plasma volume.

The range of genetic screening and testing options has broadened

Options include first-trimester CVS, which provides information about the fetal chromosomal complement but not the presence of a fetal open neural tube defect. The procedure-related



Older pregnant women have an incidence of gestational hypertension and preeclampsia that is 2 to 4 times as high as that of patients younger than 30 years

TABLE 3 Maternal morbidity in multiple gestations

Twins

- Hypertension (2.5 times the risk of a singleton gestation)
- Abruption (3.0 times the risk)
- Anemia (2.5 times the risk)
- Urinary tract infection (1.5 times the risk)

Triplets

- Preeclampsia (risk of 26%–75%) (occurs at earlier gestation)
 - HELLP syndrome (risk of 9%)
- Abruption (20%) (10 times the risk of a singleton gestation)
- Anemia (24%)
- Preterm premature rupture of membranes (24%)
- Gestational diabetes (14%)
- Acute fatty liver (4%) (1 in 10,000 singletons)
- Postpartum hemorrhage (9%)

HELLP = hemolysis, elevated liver enzymes, and low platelets



Older pregnant women have an incidence of gestational hypertension and preeclampsia that is 2 to 4 times as high as that of patients younger than 30 years

rate of fetal loss with CVS is quoted as 1%.

Options for genetic testing in the second trimester include transabdominal amniocentesis. A procedure-related fetal loss rate of 1 in 500 to 1 in 1,600 is quoted for midtrimester amniocentesis.

A relatively new screening option is analysis of cell-free fetal DNA in maternal blood, which can be performed after 10 weeks' gestation in singleton and multiple gestations. This directed analysis measures the relative proportions of chromosomes. The detection rate for fetal Down syndrome using cell-free fetal DNA is greater than 98%, with a false-positive rate of less than 0.5%. However, this screening is unreliable in triplet gestations.

Other screening options include US and biochemical screening to detect fetal aneuploidy and open neural tube defects during the second trimester. These options should be included in counseling of the patient.

Second and third trimesters
Gestational hypertension and preeclampsia are significant risks

Older pregnant women have an incidence of gestational hypertension and preeclampsia 2 to 4 times as high as that of patients younger than 30 years.¹³ The underlying risk for preeclampsia is further increased if

coexisting medical disorders such as diabetes or chronic hypertension are present. Moreover, the risk for preeclampsia increases to 10% to 20% in twin gestations and 25% to 60% in triplet gestations. Le Ray and colleagues reported that, if oocyte donation is used with IVF in women older than age 43, the risk for preeclampsia triples.¹⁴

We previously studied 379 women aged 35 and older who had mild gestational hypertension remote from term, comparing them with their younger adult counterparts in a matched cohort design.¹⁵ Outpatient management produced similar maternal outcomes in both groups, but older women had a statistically insignificant increase in the rate of stillbirth (5 vs 0; $P = .063$).¹⁵

Gestational diabetes risk doubles

The rates of both diabetes mellitus and gestational diabetes increase with advanced maternal age. Data from the FASTER consortium included an adjusted odds ratio of 2.4 for gestational diabetes in women aged 40 or older, compared with a younger control group.⁴ This increased risk may be a consequence of greater maternal habitus as well as declining insulin sensitivity.

Diabetes increases the risks of macrosomia, cesarean birth, and gestational hypertension. Among women with pregestational diabetes, the risks of congenital heart disease and fetal neural tube defects increase threefold. **Because of this increased risk, perinatal screening is indicated for both anomalies in older women.**

Pulmonary complications increase

Another risk facing women of advanced maternal age—particularly those carrying a multiple gestation—is pulmonary edema, owing to the increased cardiac output, heart rate, and blood volume, the decreased systemic vascular resistance, and the physiologic anemia of pregnancy. These risks rise further in women who develop preterm labor that requires therapy and in those who develop gestational hypertension and/or preeclampsia. **Judicious use of IV fluids, particularly those with lower sodium concentrations, can**

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TABLE 4 Evaluation and management of the pregnant woman older than age 40

Preconception

- Identify risk factors (ie, diabetes, obesity, hypertension, cardiac dysfunction, family history)
- Review outcome of previous pregnancy, if applicable
- Review risks (multiple gestation, birth defects) associated with assisted reproductive technologies if they were needed to achieve pregnancy
- Optimize maternal health
- Begin folic acid supplementation
- Encourage smoking cessation
- If the patient is ≥45 years old:
 - Electrocardiogram
 - Glucose screening (fasting plasma glucose or hemoglobin A1c)
 - Echocardiogram for patients with chronic hypertension

First trimester

- Ultrasonography for dating and to assess fetal number and chorionicity
- Baseline metabolic profile and complete blood count
- Baseline urinalysis
- Continue folic acid supplementation
- Offer first-trimester genetic testing or other genetic screening

Second trimester

- If first-trimester genetic testing is declined, offer second-trimester testing or screening
- Detailed fetal anomaly evaluation by ultrasound
- Fetal echocardiogram if pregnancy was achieved by in vitro fertilization or if it is a monochorionic twin gestation
- Screen for gestational diabetes

Third trimester

- Increased antenatal testing for routine indications, including hypertension, diabetes, and lupus
- Ultrasonography for growth and later ultrasonographic findings of fetal aneuploidy
- Consider delivery by 40 weeks' gestation, given the increased risk of stillbirth after a term gestation

reduce the risk of pulmonary complications.

Women who develop pulmonary edema have an increased risk of peripartum cardiomyopathy.¹⁶

Preterm delivery is more common

Cleary-Goodman and colleagues noted an increased incidence of preterm delivery in women aged 40 and older, compared with women younger than age 35, but no increase in spontaneous preterm labor.⁴ Advanced maternal age appears to be associated with an increased risk of preterm birth largely as a consequence of underlying complications of

fetal growth restriction and maternal disease, including hypertension. Because preterm birth is an important contributor to perinatal morbidity and mortality, **steroids should be administered for fetal lung maturity whenever preterm labor is diagnosed before 34 weeks' gestation.**

Risk of placenta previa is 1.1%

Joseph and colleagues found the risk of placenta previa to be 1.1% in women aged 40 and older, compared with 0.3% in women aged 25 to 29 years.¹⁷ This increased risk likely is a consequence not only of maternal age but increased parity and a history of prior uterine surgery. **If transabdominal US results are suspicious for placenta previa, transvaginal US is indicated for confirmation. Additional US assessment of the cord insertion site to the placenta also should be performed to rule out vasa previa.**

Look for neonatal complications

Ziadeh and colleagues found that, although maternal morbidity was increased in older women, the overall neonatal outcome did not appear to be affected.¹⁸ However, we noted a higher rate of neonatal complications in women aged 40 or older, including higher NICU admission rates and more low-birth-weight infants.¹¹

In addition, Odibo and colleagues found advanced maternal age to be an independent risk factor for intrauterine growth restriction (IUGR).¹⁹ In that study, the odds ratio for IUGR was 3.2 (95% confidence interval [CI], 1.9-5.4) for a maternal age of 40 years or older, compared with a control group. For that reason, **they recommend routine screening for IUGR in all pregnant women of advanced age.**

Stillbirth risk peaks at 37 to 41 weeks

In a review of more than 5.4 million singleton pregnancies without reported congenital anomalies, Reddy and colleagues found an association between advanced maternal age and stillbirth, with a higher risk of stillbirth at 37 to 41 weeks' gestation.⁶ This effect of maternal age persisted despite adjusting for medical disease, parity, and race/ethnicity.

Many women older than age 40 have independent medical or fetal indications for antenatal testing. Some experts have suggested antepartum surveillance starting at 37 weeks for women of advanced maternal age; they argue that the risk of stillbirth at this gestational age is similar in frequency to other high-risk conditions for which testing is performed routinely. However, the National Institute of Child Health and Human Development (NICHD) workshop on antepartum fetal monitoring found insufficient evidence that antenatal testing for the sole indication of advanced maternal age reduces stillbirth or improves perinatal outcomes.²⁰

If increased antenatal testing is indicated for a high-risk condition or electively chosen given advanced age, it should include electronic fetal monitoring as well as amniotic fluid volume assessment. Because the risk of fetal loss sharply increased at 40 weeks' gestation in the study by Reddy and colleagues,⁶ women older than age 40 should be considered for delivery by 40 weeks' gestation in the presence of good dating criteria.

Some clinicians also would consider delivery by 39 weeks' gestation with good dating criteria if the Bishop score is favorable.

Risks of labor and delivery

Multiple variables contribute to a higher cesarean delivery rate

The risk of cesarean delivery increases with advancing maternal age.^{5,11} This increased risk is a consequence of multiple variables, including the rate of previous cesarean delivery, malpresentation, underlying complications such as preeclampsia and diabetes, and a higher prevalence of dysfunctional labor.²¹ Further, Vaughn and colleagues noted that the cesarean delivery rate increases in direct proportion to age, with a rate of 54.4% in women older than age 40.⁵

As Cohen pointed out in a commentary accompanying a study of dysfunctional labor in women of advancing age, "the notion of a premium baby (ie, that the fetus of a woman with a reduced likelihood of having another

pregnancy is somehow more deserving of being spared the rigours of labour than the fetus of a young woman) may play a role" in the high rate of cesarean delivery.^{21,22}

Postpartum hemorrhage risk may be lower in older women

Advanced maternal age is assumed to be a risk factor for postpartum hemorrhage.²³ The increased risk was thought to be related to the increased incidence of multiple underlying factors, such as cesarean delivery, multiple gestation, and hypertensive disorders of pregnancy.

However, in a retrospective cohort study, Lao and colleagues found that advanced maternal age (≥ 35 years) served only as a surrogate factor for postpartum hemorrhage due to associated risk factors, obstetric complications, and interventions.²⁴ After multivariate analysis, aging was associated with a *decreased* rate of postpartum hemorrhage, which declined progressively from ages 25 to 40 years and older, compared with women aged 20 to 24.²⁴

Nevertheless, **medical interventions should be readily available at the time of delivery for treatment of uterine atony, especially with multiple gestation and grand multiparity.**

CASE Resolved

The patient is admitted to the hospital, where she is given IV magnesium sulfate (6-g load followed by an infusion of 3 g/hr) and betamethasone for fetal lung maturity enhancement. She continues to receive IV fluids as well (125 mL/hr lactated Ringers solution). Uterine activity abates.

IV magnesium sulfate is continued for 36 hours, but urine protein output is not monitored. Her heart rate ranges from 105 to 115 bpm, and blood pressure from 130/80 mm Hg to 138/88 mm Hg. Forty-eight hours after admission, she reports a gradual onset of tightness of the chest and breathlessness. She is agitated, with a pulse of 130 bpm, 30 respirations/min, and room air pulse oximetry of 90%. Rales are noted upon auscultation of both lungs. A radiograph of



Some experts have suggested antepartum surveillance starting at 37 weeks for women of advanced maternal age


the chest demonstrates bilateral air-space disease consistent with pulmonary edema. IV furosemide and oxygen (by mask) are provided, with some respiratory improvement.

The patient then reports leakage of amniotic fluid, and preterm rupture of membranes is confirmed on examination. Because steroids for fetal lung maturity have been administered, and given improvement in her pulmonary edema and a footling breech presentation for Twin A, cesarean delivery is performed.

The patient's immediate postoperative course is uncomplicated. On postoperative day 2, however, she develops recurrent pulmonary edema, as confirmed by physical examination and chest radiograph. She also reports headache, and her blood pressure rises to 164/114 mm Hg—findings consistent with postpartum preeclampsia. Magnesium sulfate and antihypertensive therapy are initiated, along with IV furosemide and oxygen, which improves her respiratory status.

An echocardiogram to rule out peripartum dilated cardiomyopathy finds no evidence of a dilated left ventricle, and the calculated left ventricular ejection fraction (55%) is normal.

After diuresis and improvement in her blood pressure, she is discharged home. By the time of her follow-up office visit 7 days later, her blood pressure has normalized on labetalol therapy.

For an overview of evaluation and management of pregnant women aged 40 or older, see TABLE 4, page 36 

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