Interpregnancy interval and obstetrical complications

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INTRODUCTION — The time interval between one pregnancy and the next may affect the risk of pregnancy complications. Both short and long interpregnancy intervals have been associated with adverse outcome, but the bulk of adverse effects have been associated with short intervals [1-3]. Whether the interpregnancy interval is a significant independent biological risk factor for adverse pregnancy events is important because women have some control over the spacing of their pregnancies and thus could potentially reduce their risk of adverse outcomes. Avoidance of short intervals can be achieved through postpartum provision of contraception, but avoidance of long interpregnancy intervals is more problematic since a desired pregnancy may be precluded by subfertility, availability of a partner, economic issues, or illness [4].

Determining whether any particular factor has a clinically significant influence on pregnancy is complex. Many variables are known to influence pregnancy outcome and a single factor, such as interpregnancy interval, cannot be studied without accounting for myriad potential confounders. There are many reasons for the associations described in this topic, and causality should not be assumed. Some examples:

- If the interval between births is measured and the second birth is preterm, the interbirth interval will be shorter than for a term birth and associated with higher neonatal mortality due to prematurity [5].
- After a stillbirth or neonatal death, women often wish to conceive again with minimal delay. If the causative factors for the fetal or neonatal death recur, an association between short interpregnancy interval and perinatal mortality would be observed.
- Breastfeeding both improves infant survival and lengthens the interval between pregnancies due to lactational amenorrhea, thus confounding the relationship between longer interpregnancy interval and improved pregnancy outcome. However, breastfeeding may also deplete the mother, thereby worsening pregnancy outcome.
- Socioeconomic factors and maternal health issues may affect both timing of pregnancy and outcome of pregnancy. In some cases, closer birth spacing is the unintended result of lack of correct and consistent use of contraception, and in others, it is an intentional response to later initiation of childbearing [6].
- The type of pregnancy event needs to be considered. Miscarriages and stillbirth may deplete the mother less than a live born term infant who is breastfed.

This topic will review available data and guidelines on interpregnancy interval, as well as controversies regarding the significance of interpregnancy interval in the determination of obstetrical outcomes.

NOMENCLATURE — The interval between pregnancies can be described in various ways:

- **Interpregnancy interval or birth to pregnancy interval** – Interpregnancy interval (IPI), also referred to as birth to pregnancy (BTP) interval, is defined as the spacing between a live birth and the beginning of the following pregnancy.
- **Interdelivery interval or birth to birth interval** – Interdelivery interval (IDI), or birth to birth (BTB) interval, is defined by the period between consecutive live births. The calculation of the BTB interval can be the same for two women even though one woman conceives only twice during the interval and the other conceives multiple times since BTB ignores abortions and fetal deaths.
- **Inter-outcome interval** – Inter-outcome interval (IOI) is defined as the interval between one pregnancy outcome and the next, regardless of pregnancy outcome. Because all pregnancies are evaluated, IOI provides better risk assessment for stillbirth or a spontaneous or induced abortion [7].

DEFINITION OF SHORT AND LONG IPI — The definitions for short and long interpregnancy interval (IPI) have not been standardized. A short IPI has been defined as less than 3, 6, 9, 12, or 18 months. An IPI less than 6 months is most often associated with adverse outcomes, but some studies have reported correlations with adverse outcome for IPI less than 3 months or IPI less than 18 months [3,8-11].

A long IPI is usually defined as an IPI more than 60 months.

PREVALENCE AND DEMOGRAPHICS — According to a 2015 report by the Centers for Disease Control and Prevention that included birth certificate data from 36 states, about 30 percent of American women had a short IPI defined as less than 18 months [12]. Approximately 50 percent had an IPI of 18 to 59 months and 20 percent had an IPI ≥60 months.

Short IPI was associated with young maternal age: More than two-thirds of teenagers aged 15 to 19 had short IPI; the next-highest percentage was among women aged 20 to 29 (35 percent).

Long IPI was most common for older women. Among women aged 30 to 44, 30 percent had a long IPI. Women with less than a bachelor's degree were about twice as likely to have a long IPI compared with women with a bachelor's degree or higher (23 versus 13 percent). Non-US born Hispanic women had the highest percentage of long IPI of all race and ethnicity groups (30 percent), followed by non-Hispanic black women (24 percent), US-born Hispanic women (22 percent), and non-Hispanic white women (16 percent). Unmarried women had a higher percentage of long IPI compared with married women (24 versus 19 percent).

HYPOTHESES FOR THE RELATIONSHIP BETWEEN IPI AND ADVERSE PREGNANCY OUTCOME — Several hypotheses have been proposed to explain the relationship between interpregnancy interval (IPI) and adverse pregnancy outcome, but none have been proven.

Short IPI — According to the maternal depletion hypothesis [13-15], maternal nutrients (particularly folate) may not be replenished sufficiently between closely-spaced pregnancies, particularly among breastfeeding mothers, and this may lead to adverse pregnancy outcomes.

While maternal depletion may be more prevalent and severe in low income countries due to malnutrition, the maternal depletion hypothesis may also apply to mothers in high income countries [8,16,17]. Ten studies from developed countries have reported low serum levels of folate during the postpartum period [18-21]. In addition, a large prospective cohort study from the Netherlands reported a negative association between short IPI and fetal growth, and that women not using folic acid supplements were at a greater risk of fetal growth restriction after a short IPI [22].

Infectious processes extending from the previous birth to the index pregnancy have also been hypothesized to contribute to the link between short IPI and adverse pregnancy outcomes [23,24]. In particular, inflammation of the genital tract that developed in the previous pregnancy and did not completely resolve may be a link between short IPI and preterm premature rupture of membranes (PPROM) and subsequent preterm birth (PTB) [25].

Other factors that have been suggested to account for an association between short IPI and poor obstetrical and neonatal outcomes include cervical insufficiency, sibling competition for maternal resources, transmission of infection between closely spaced siblings, and incomplete healing of the uterine scar from previous cesarean delivery [18,26].

Long IPI — The physiological regression hypothesis has been proposed to explain the association between long IPI and adverse pregnancy outcome. It asserts that pregnancy causes physiological adaptations of the reproductive system, such as an increase in blood flow to the uterus [8]. When IPI is prolonged beyond a certain point, the subsequent pregnancy can no longer benefit from these temporary beneficial adaptations.

PREGNANCY AND NEWBORN COMPLICATIONS ASSOCIATED WITH IPI — Both short and long interpregnancy intervals (IPI) have been associated with adverse pregnancy outcomes. Meta-analyses, synthesizing data from multiple independent studies, assist in characterizing the effect of IPI on adverse perinatal outcomes. Individual studies differ in their statistical strength and in their ability to account for the effects of confounding factors such as co-morbidities, socioeconomic status, or lifestyle differences.

Several investigators have argued that the apparent association between short IPI and obstetrical complications may simply reflect the prevalence of short IPIs among women predisposed to adverse outcomes based on confounding factors (eg, maternal age, socioeconomic status, lifestyle, and the outcome of the previous pregnancy). In support of this hypothesis, some groups have observed that short IPI was associated with increased risk for adverse outcomes such as PTB in the traditional "between mother analysis," but the risk was substantially attenuated in the "within mother analysis," suggesting that short IPI is a marker for unmeasured confounding factors rather than for a biologic phenomenon underlying the etiology of PTB [27,28]. In contrast, a group using both unconditional and conditional logistic regression models found that short IPI (<6 months) was associated with increased risk for PTB, which suggests that factors besides maternal characteristics may account for the association between short IPI and obstetrical complications [29].

Maternal anemia — The maternal depletion hypothesis predicts a higher rate of maternal anemia after a short IPI [30]. A large study including data from 18 Latin American countries reported a 30 percent increase in risk of maternal anemia after IPI less than 6 months [31], while previous and smaller studies were unable to detect a significant association [32-34].

Whether lack of maternal repletion after a short IPI results in maternal anemia is unclear, as short IPI has also been associated with other possible causes of maternal anemia, such as third trimester bleeding from placental abruption or placenta previa [31,35].

Preterm premature rupture of membranes — About 25 percent of all preterm births are attributed to premature rupture of membranes (PPROM). In two studies, an IPI of 6 to 14 months [32] and an IPI less than 18 months [25] were associated with an increased risk of PPROM in the subsequent pregnancy.

Preterm birth — Short IPI has long been recognized as a risk factor for preterm birth (PTB) [8,9,29,36,37]. In a 2006 meta-analysis, an IPI less than 6 months was associated with a 40 percent increase in risk for PTB [1]. Subsequently published studies have confirmed these findings [38-42]. In one, IPIs less than 6 months and 6 to 12 months were associated with an increased risk for PTB (adjusted OR 1.4) [38]. In another, the odds of PTB with IPI less than 6 months was OR 1.58 [39]. When only spontaneous PTBs were considered, women with IPI ≤6 months were at 3.6-fold increased risk for early spontaneous PTB (less than 34 weeks) [42]. Late spontaneous PTB (34 to 36 weeks) was not correlated with short IPI.

Preeclampsia — A long IPI is a well-established risk factor for preeclampsia [2,31]. The risk of new preeclampsia in a subsequent pregnancy following a long IPI is directly proportional to the time elapsed since the previous birth, with an adjusted OR of approximately 1.1 for every additional year [43,44]. Women with an IPI greater than 10 years have a risk for preeclampsia similar to that of a nulliparous woman.

Interestingly, for women with a history of preeclampsia, the risk for preeclampsia in the subsequent pregnancy decreased with IPI length from one to >15 years compared with IPI ≤one year, even after adjusting for maternal age [45].

Placental abruption — In a large United States study, short inter-pregnancy interval of less than six months was associated with increased risk for placental abruption (OR 1.8, 95%CI 1.2-2.7) [46].

Labor dystocia — In a cross-sectional study including nearly 650,000 Michigan births, an IPI of more than 24 months increased the risk of labor dystocia by 50 percent [47]. This study adjusted for multiple factors, including gestational weight gain, smoking, age, race, parity, and infant birth weight. A much smaller study in multiparous Nigerian women did not detect a significant association between long IPI and risk for labor dystocia [48].

Congenital anomalies — Several studies have reported an increased risk of congenital anomalies in births with short or long IPI [49-53]. In a population-based retrospective cohort study, the congenital anomaly rates with IPI 0 to 5 months, 12 to 17 months, and ≥24 months were 2.5, 1.9, and 2.3 percent, respectively; these differences were statistically significant [52]. The association between IPI and congenital anomalies was significant only for folate-independent anomalies, which suggests that folate deficiency from close spacing of pregnancies was not an etiologic factor.

Low birth weight — Several studies have reported an association between short IPI and low birth weight (LBW, birth weight <2500 grams) [1,16,39-41,54,55]. In a 2006 meta-analysis including 10 studies, IPI less than 6 months was associated with a 60 percent increase in risk of LBW when compared with IPI of 18 to 23 months (pooled adjusted OR 1.61, 95% CI 1.39-1.86) [1].

Neonatal morbidity — A population-based retrospective cohort study using Ohio birth records from 2006 to 2011 evaluated the rate of adverse newborn outcomes in almost 400,000 singleton nonanomalous newborns of multiparous mothers with various IPI lengths [56]. The frequency of neonatal morbidity was lowest following IPI of 12 to <24 months (4.1 percent) compared with <6 months (5.7 percent; OR 1.40; 95% CI 1.32–1.49), 6 to <12 months (4.7 percent, OR 1.19; 95% CI 1.13–1.25), 24 to <60 months (4.6 percent, OR 1.12, 95% CI 1.08–1.17) and ≥60 months (5.8 percent, OR 1.34, 95% CI, 1.28–1.40), despite adjustment for confounding factors, including gestational age at birth.

Small for gestational age — Small for gestational age (SGA) is defined as birth weight below the 10th centile for gestational age. Findings from studies of the relationship between IPI and SGA have been inconsistent [3,11,17,39-41,49,57]. Discrepancies may be attributed, in part, to the use of different reference groups or confounding variables. In positive studies, an IPI less than 6 months was generally associated with a 15 to 30 percent increase in risk of SGA compared with longer IPIs [3,17,40,49,58].

Autism and schizophrenia — Both autism and schizophrenia have been associated with short IPI. A large-population survey from California reported that second children born after an IPI less than 12 months versus ≥36 months were 3.39 times more likely to be diagnosed with autism, independent of factors such as LBW, PTB, or previous child with autism [59]. Interestingly, an increased risk of autism was also found for IPIs 12 to 23 months and 24 to 35 months, with odds ratios of 1.86 and 1.26, respectively. In other studies, maternal folate supplementation was associated with a reduced risk of autism among offspring, which supports the hypothesis that maternal depletion plays a role in the association between autism and short IPI [60,61].

Folate deficiency during famine is believed to partially explain the association between prenatal exposure to famine and schizophrenia in offspring [62-64]. A study of the hypothesis that the risk of schizophrenia may be elevated in children conceived following a short IPI when maternal folate stores are still being replenished found that IPIs less than 6 months or 7 to 12 months were associated with an increased risk for developing schizophrenia, with hazard ratios of 2.62 and 1.78, respectively [65].

Fetal, neonatal, or infant death — An association between short IPI and fetal, neonatal, or infant death has been suggested by several studies; however, the reports have not reported consistent findings [3,14,26,36,40,49,66-68]. In positive studies, odds ratios of 1.3 to 3.6 for fetal, neonatal, or infant death after a short IPI have been reported [3,26,36,40,49,67,69]. The inconsistency between reports can be partially explained by differences in parity. One study that found no significant correlation between short IPI and fetal, neonatal, or infant death assessed women only after their first pregnancy [66]. Since high parity can be associated with depletion in maternal nutrient reserves [14,68], women of low parity may be able to recover faster from one pregnancy to the next and thus not experience the adverse effects of a short IPI.

Maternal death — Nested case-control studies from the late 1990s failed to find a significant association between IPI and maternal death [70,71]. However, in a subsequent cross-sectional study of 456,889 parous women in Latin America, maternal death was 2.54 times more likely after an IPI less than 6 months versus 18 to 23 months [2,31].

PREGNANCY COMPLICATIONS ASSOCIATED WITH IOI — In contrast to interpregnancy interval (IPI), which assesses the time between a live birth and the next pregnancy, the inter-outcome interval (IOI) is defined as the interval between any pregnancy outcome and the next pregnancy.

Miscarriage — In 2005, the World Health Organization (WHO) evaluated birth spacing following different pregnancy outcomes; data on birth spacing after an abortion were scarce. Based on a single large-scale study conducted in Latin America (n = 258,108) [72], the WHO recommended that couples wait at least six months after an induced or spontaneous abortion before attempting another pregnancy [7]. Notably, in this study, IOI recordings were based on the mother's recollection, thus were prone to recall bias. Furthermore, the study did not distinguish between induced and spontaneous abortion, obscuring any etiological conclusions.

A 2016 meta-analysis provides evidence for abandoning the WHO recommendation of a six-month minimal IPI following a miscarriage [73]. The authors analyzed 10 studies including the large Latin American study described above [72]. For preterm birth among women with IPI <6 months following a miscarriage, the pooled relative risk was 0.93 (95% CI 0.58-1.48) when compared with an IPI of ≥6 months. When the Latin American study was excluded, the pooled RR was 0.79 (95% CI 0.75-0.83) for the same comparison. Given the methodologic limitations of this study and the consistent but contrary findings from other studies [29,74-79], it appears that the recommended IPI after a spontaneous abortion may as soon as the couple feels ready.

Stillbirth — For each IPI category, rates of stillbirth were highest following preceding stillbirths. Interestingly, they were highest overall for IPIs of 27 to 50 months (9.0 percent) and nearly as high for those of 6 to 14 months (8.8 percent). Short IPI of less than six months after a life birth was associated with increased risk for stillbirth with an adjusted odds ratio of 1.61 (95% CI 1.20-2.18) [80]. In another study by DaVanzo et al, short IPI of less than 15 months after a live birth and after a stillbirth was associated with increased risk for stillbirth with a relative risk of 2.19 and 1.85, respectively [26]. A recent clinical guideline recommended an IPI between 15 to 24 months after a stillbirth [80]. A short IOI (less than 15 months) after a stillbirth has been reported to increase the probability of adverse perinatal complications, such as early neonatal mortality, possibly because of depletion of maternal nutrients [26,81].

Maternal depression or anxiety — In two studies, IOI less than seven months after missed or induced abortion was associated with an increased risk of maternal depression and anxiety [82].

PREGNANCY COMPLICATIONS ASSOCIATED WITH IDI — In contrast to interpregnancy interval (IPI) and inter-outcome interval (IOI), which mark the time between the end of one pregnancy and the beginning of the next pregnancy, the interdelivery interval (IDI) is defined as the period between consecutive live births.

Trial of labor after cesarean delivery — A trial of labor after cesarean (TOLAC) has been associated with about a three-fold increase in risk of uterine rupture among women with short IDI up to 18 months [83,84]. The presumed mechanism for the increased risk is incomplete healing of the uterine scar. Importantly, longer IDIs (18 to 24 months) have not been significantly associated with maternal morbidity in women undergoing TOLAC [84,85].

IDIs less than 19 months have also been associated with a decreased rate of TOLAC success in patients who underwent induction, a difference not found in those with spontaneous labor [86].

WHAT IS THE OPTIMAL INTERVAL BETWEEN PREGNANCIES? — The optimal interpregnancy interval (IPI) is unclear, and may depend in part on the outcome of the previous pregnancy.

After a live term birth — After a live term birth, both the World Health Organization (WHO) and the United States Agency for International Development (USAID) recommend an IPI greater than 2

years and less than 5 years [7]. This recommendation is based on accumulating data cited above that an IPI less than 18 months is associated with an increased risk of perinatal and maternal outcomes after a live birth, while an IPI of 18 to 24 months is associated with the lowest relative risk [1,3,11,17,56,87]. The two-year birth to conception interval recommendation by the WHO is in agreement with the United Nations Children's Fund (UNICEF) two-year breastfeeding recommendation, and makes guidelines more easily transmittable to the general public ("2 years" versus "18 months"), even though a recommendation for IPI greater than 18 months may better reflect the data. (See 'Pregnancy and newborn complications associated with IPI' above.)

Advanced maternal age — An IPI of only 12 months is a reasonable approach for women older than 35 years, as it balances the increasing risk of subfertility and infertility with advancing age and the increased risks of pregnancy complications associated with a very short (<6 months) IPI [88,89]. However, the available literature on the interaction between IPI and advanced maternal age is limited and further investigation is warranted.

After a miscarriage or abortion — Guidelines are particularly important for women who have had a spontaneous or induced abortion or a stillbirth since these women may wish to conceive again with minimal delay and it is well established that a spontaneous abortion or a stillbirth increases the risk for a similar poor outcome in the following pregnancy [81,90]. The optimum inter-outcome interval (IOI) for these women has been unclear because of conflicting data [26,72,74,75,81].

In 2005 the WHO recommended a minimum IOI of six months for women after an induced or spontaneous abortion, based on data from a large Latin American study. A 2016 meta-analysis including this and subsequent studies suggests there is no difference in adverse pregnancy outcomes following an IOI <6 months [73]. Given the body of evidence, we suggest counseling couples wishing to conceive after a miscarriage that outcomes may not necessarily be improved by delaying pregnancy. (See 'Miscarriage' above.)

After stillbirth — Patients should be counseled that data are scant and inconclusive regarding the optimal IPI for women after a stillbirth. Two high quality studies of a population of women from Bangladesh showed no significant change in the risk for adverse outcomes with the length of IPI after a stillbirth [26,81]. (See 'Stillbirth' above.) However, until studies from high income countries confirm this assertion, we believe at least a six-month IPI recommendation is appropriate.

After a cesarean delivery — Special considerations may be appropriate following a cesarean delivery. Uterine rupture, which is associated with a trial of labor after cesarean (TOLAC), is a potentially catastrophic outcome, including fetal and maternal mortality, and significantly increases the risks associated with subsequent pregnancies. The American College of Obstetricians and Gynecologists (ACOG) recommend a cautious approach regarding TOLAC following a short interdelivery interval (IDI) [91]. Women considering TOLAC should be informed of the risks associated with short IDI so they may better plan their subsequent pregnancies. We suggest a longer IDI (18 to 24 months), as longer IDIs have not been significantly associated with maternal morbidity in women undergoing TOLAC [84,85]. (See 'Trial of labor after cesarean delivery' above.)

After a preeclampsia — The risk for recurrent preeclampsia is higher for women with an IPI of less than one year versus one to >15 years [45]. We therefore recommend that women with previous preeclampsia wait at least 12 months between pregnancies.

After preterm birth — While data are limited, it may be advisable for women with a history of preterm birth to wait 12 months, and at a minimum of 6 months, before conceiving again [42].

MANAGEMENT OF PREGNANCIES — Educating women regarding the risks at extreme interpregnancy intervals (IPI) and better management of these pregnancies may improve perinatal and maternal outcomes. Established guidelines are lacking for prenatal care for women with a short or long IPI. The specific risks of short and long IPIs should be taken into account when managing these pregnancies (table 1).

Ultrasound may be used to detect fetal anomalies possibly associated with short IPI [49,50] and to evaluate fetal growth, given the association of short IPI with small for gestational (SGA) and low birth weight (LBW) [3,8]. The optimal timing of a single examination to screen for fetal anomalies is 18 to 20 weeks of gestation. (See "Routine prenatal ultrasonography as a screening tool".) Ultrasound examination for diagnosis of fetal growth restriction is performed if clinically indicated because of uterine size that is small for dates and in women at high risk for impaired fetal growth because of factors in addition to short IPI. (See "Fetal growth restriction: Diagnosis".)

We inform women considering trial of labor after cesarean (TOLAC) after a short interdelivery interval (IDI) of the increased risks for failure [86] and uterine rupture [84,85,92].

Based on the folate depletion hypothesis, we feel it is reasonable to recommend additional folate supplementation to women with short IPI, although this has not been studied. Iron deficiency anemias should certainly be corrected.

SUMMARY AND RECOMMENDATIONS

- The interval between pregnancies can be described in various ways (see 'Nomenclature' above):
  - Interpregnancy interval (IPI) is the spacing between a live birth and the beginning of the following pregnancy.
  - Interdelivery interval (IDI) is the period between consecutive live births.
  - Inter-outcome interval (IOI) is defined as the interval between one pregnancy outcome and the next, regardless of pregnancy outcome.
- The definitions for short and long IPI have not been standardized. An IPI less than 6 months is a common definition of a short IPI because this interval is most often associated with adverse outcomes. A long IPI is usually defined as more than 60 months between pregnancies. (See 'Definition of short and long IPI' above.)
- Both short and long IPIs have been associated with adverse outcome, but the bulk of adverse effects have been associated with short intervals (table 1). It is unclear whether the apparent association between IPI and obstetrical complications is due to unmeasured confounding factors or a true causal biologic phenomenon. (See 'Pregnancy and newborn complications associated with IPI' above.)
- After a term live birth:
  - We suggest women <35 years of age wait at least two years but less than five years before conceiving again (**Grade 2C**). This is in agreement with recommendations from the World Health Organization and the United States Agency for International Development. (See 'What is the optimal interval between pregnancies?' above.)

- For women ≥35 years of age, we suggest women wait 12 months before conceiving again (**Grade 2C**). This balance the increasing risk of subfertility and infertility with advancing age and the increased risks of pregnancy complications associated with a very short (<6 months) IPI. (See 'What is the optimal interval between pregnancies?' above.)

- Contemporary data suggest that after spontaneous abortion there is no need to wait six months to conceive. (**Grade 2C**). (See 'What is the optimal interval between pregnancies?' above.)

- After a stillbirth, we suggest women wait 15 months before conceiving again (**Grade 2C**). (See 'After stillbirth' above.)

- After a cesarean delivery, we suggest women wait 12 months before conceiving again (**Grade 2C**). (See 'After a cesarean delivery' above.)

- After previous preeclampsia or previous preterm birth, we suggest women wait 12 months before conceiving again (**Grade 2C**). (See 'What is the optimal interval between pregnancies?' above.)

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Topic 6767 Version 21.0

GRAPHICS

Summary of pregnancy outcomes associated with short and long interpregnancy intervals

	Short interpregnancy interval (variously defined)	Long interpregnancy interval (at least 24 months)
Low birth weight	↑	
Small for gestational age	↑ or ↔	
Preterm premature rupture of membranes	↑	
Preterm birth	↑	
Congenital anomalies	↑	↑
Autism	↑	
Schizophrenia	↑	
Labor dystocia		↑
Fetal, neonatal, or infant death	↑	
Maternal anemia	↑ or ↔	
Preeclampsia	↑	↑
Maternal death	↑ or ↔	
Miscarriage	↓ or ↔	
Stillbirth	↑	
Uterine rupture at TOLAC	↑	

TOLAC: trial of labor after cesarean delivery.

Graphic 89410 Version 2.0

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