9

Timing and mode of delivery

A Pels, P von Dadelszen, S Engelbrecht, H Ryan, M Bellad, A Lalonde, LA Magee

SYNOPSIS

The phrase 'planned childbirth on the best day in the best way' alludes to the fact that there is a myriad of considerations regarding timing (and mode of) childbirth in women with a hypertensive disorder of pregnancy, particularly pre-eclampsia[1]. Complicating this decision-making are inaccurate determination of gestational age, difficulty identifying those women who are at particular risk of an adverse outcome if pregnancy is prolonged, and the fact that 'severe' pre-eclampsia has been variably defined by international organisations and, yet, all list 'severe' pre-eclampsia as an indication for interventionist management, i.e. delivery.

Nevertheless, the past decade has seen publication of a significant body of work that informs our decisions about timing of delivery in women with a hypertensive disorder of pregnancy, particularly pre-eclampsia. Childbirth is recommended for women with pre-eclampsia or gestational hypertension at term for maternal benefit, although expectant care is recommended for women with any hypertensive disorder of pregnancy at late preterm gestational ages to reduce neonatal respiratory morbidity (associated with labour induction and Caesarean delivery). Small trials suggest that expectant care of women with pre-eclampsia from fetal viability to 33^{+6} weeks reduces neonatal morbidity, but the magnitude of maternal risk has not been fully quantified. To date, there are no trials to inform management of women with chronic hypertension.

Mode of delivery is usually determined by obstetric indications; however, if there is evidence of fetal compromise at a gestational age remote from term, women with a hypertensive disease of pregnancy may benefit from delivery by Caesarean. It is particularly important for women with a hypertensive disease of pregnancy to have the third stage of labour actively managed, particularly in the presence of thrombocytopaenia or coagulopathy. Ergometrine maleate should not be administered to women with any hypertensive disorder of pregnancy given its potential to precipitate severe hypertension.

TIMING OF DELIVERY

Optimising the timing of delivery involves striking a balance between the benefits and risks of pregnancy prolongation compared with those of induction or elective Caesarean delivery. Birth of the baby is always in the best interest of the woman. For her, pregnancy prolongation has no direct benefit, but for the baby, the benefits may be large at gestational ages remote from term. This can be a heart-wrenching decision for families and their care providers.

> "I remember asking one of the doctors to please be honest with me and to tell me how soon they thought I would deliver . . . would it be three weeks or three days? I will never forget that doctor as she pulled up a chair next to my bed and held my hand as I cried when she told me that I would probably only make it three days. I was 28 weeks along."
>
> Melissa M

Assessing gestational age

Accurate knowledge of gestational age is critical to decisions about timing of childbirth, diagnosis of intrauterine growth retardation (IUGR) and decisions about whether to administer antenatal corticosteroids for fetal lung maturity. This is of particular importance in low-resource settings where care for preterm infants may be limited to specialised health care facilities not easily accessible to all women.

The most accurate estimation of gestational age can be achieved by ultrasonographic examination in the first trimester. However, ultrasound is not always available in under-resourced settings and, when it is, many women do not present for their first antenatal care visit until the second trimester or later, when ultrasonographic examination is less accurate.

In the absence of an early ultrasonographic assessment of gestational age, it is advisable to use multiple methods. In addition to ultrasonographic assessment in the second trimester (or later), providers may estimate gestational age using last menstrual period (LMP) or clinical examination (abdominal palpation before 24 weeks' gestational age and symphysis–fundal height (SFH) after 24 weeks' gestational age). All of these are less accurate than first trimester ultrasonographic examination[2] (Table 9.1). For example, gestational age estimates were within 7 days when assessed by LMP (65%) or SFH (75%) in a prospective, population-based study in Pakistan[3]. Accuracy was improved by an algorithm that took LMP-based dating only when ultrasound-based values were not available[2]. Memory aids have been developed to assist women in remembering their LMP, such as those relating dates to festivals in Pakistan. In addition, job aids and algorithms have been developed to assist providers in accurately estimating gestational age.

INTERVENTIONIST VERSUS EXPECTANT CARE

When considering timing of delivery, the decision must be made between delivery (i.e., interventionist

Table 9.1 Comparison of methods to estimate gestational age

Method	*Accuracy*	*Limitations*
Ultrasonographic examination (US)	±5 days if first trimester ±7 days after first trimester	Controversial whether all women should undergo routine US screening in the first trimester May be less accurate if fetal malformation, severe IUGR, or maternal obesity If a single late examination is performed, it cannot reliably distinguish between a pregnancy that is misdated and younger than expected, and a pregnancy that is complicated by fetal growth restriction
Last menstrual period (LMP)	±14 days	May be inaccurate if the woman is not sure of the date of her LMP or does not have regular 28-day cycles There is lower accuracy in settings with low literacy Inaccurate assumption of the date of ovulation may be due to early pregnancy bleeding, implantation bleeding, non-ovulatory menstrual cycles, or use of hormonal contraceptives in the preceding 3 months
Symphysis–fundal height (SFH)	±3 weeks	Many factors interfere with accurate assessment, such as leiomyoma, obesity, other factors affecting uterine size or the ability to palpate the uterus (e.g., retroverted position), fetal anomalies affecting fetal size (e.g., hydrocephalus), IUGR, racial differences in SFH growth rates Inter- and intra-observer error Dating based on a single measurement is not recommended and might easily be inaccurate

IUGR, intrauterine fetal growth restriction

care) and pregnancy prolongation (i.e., expectant care).

- *Interventionist care* (also known as 'active management', 'aggressive management', or 'early delivery'): Childbirth by either induction of labour or Caesarean delivery after antenatal corticosteroids have been given to improve fetal lung maturation, which in practice, is after 24–48 hours.
- *Expectant care*: Administration of corticosteroids to improve fetal lung maturation, stabilisation of the woman's condition and then, if possible, delay of childbirth.

The goal of expectant management is to achieve fetal maturation *in utero*, thereby preventing or minimising complications associated with prematurity; there are no maternal benefits to expectant management. A decision to proceed with expectant management follows a period of maternal and fetal observation, assessment and maternal stabilisation. The latter may involve control of maternal blood pressure, magnesium sulphate for eclampsia prophylaxis (among women with pre-eclampsia), and corticosteroids to accelerate fetal pulmonary maturation if delivery is anticipated within the next 7 days and current gestational age is $\leq 34^{+6}$ weeks[4].

Expectant management with inpatient monitoring of maternal and fetal status may improve perinatal outcomes, but women should be chosen carefully and provided with counselling on the likelihood of perinatal survival and the risks of maternal complications. Ideally, candidates for expectant management are women who have been appropriately counselled, have made an informed choice for expectant management, have a viable fetus that is less than $37^{+0/7}$ weeks' gestational age, and have no contraindications (see below) to expectant management.

Although lists have been published of indications for delivery in pre-eclampsia, criteria will vary based on gestational age. These women have indictions for delivery that are consistent with expert opinion and study protocols[5,6]:

- Eclampsia or another serious maternal complications associated with pre-eclampsia[5]
- Severe end-organ complications
- Uncontrolled severe maternal hypertension
- Intrauterine fetal demise
- Fetal compromise that would be an indication for delivery in general obstetric practice (e.g., reversed end-diastolic flow in the umbilical artery)[7]
- Term gestational age.

There appears to be some agreement that risks of expectant management, regardless of gestational age, outweigh any potential benefits in the setting of severe pre-eclampsia, as defined in this book and by SOGC, the Canadian Society of Obstetrics and Gynaecology[8,9]. A pragmatic schema for consideration, and local modification, summarising the place, timing and mode of delivery is presented in Table 9.2[10].

Appropriate level of care

The place of care for women with a hypertensive disorder of pregnancy will depend on the woman's disorder and associated complications (if any), her gestational age, and the status of her fetus. Different levels of health care systems have different capacities to support the care of sick women and babies, based on levels of staffing, cadres of providers available, infrastructure and the availability of equipment, medications, or laboratory tests. Women with a hypertensive disorder of pregnancy, particularly non-severe pre-eclampsia, must be managed at a facility that can provide at least basic emergency obstetric and neonatal care (EmONC); women with severe pre-eclampsia, eclampsia, or severe hypertension, whether managed expectantly or with interventionist management, should be managed at facilities that can provide comprehensive EmONC; women with severe complications of a hypertensive disorder of pregnancy (e.g., oliguria that persists for 48 hours after delivery, coagulopathy, haemolysis, HELLP (haemolysis, elevated liver enzymes, low platelet) syndrome, persistent coma after convulsion) should be managed at a tertiary care facility. Recognised standards for basic and comprehensive EmONC have been published by the UNFPA[11].

Women with pre-eclampsia

Women with pre-eclampsia must be recognised as having the potential to develop life-threatening or life-altering complications. This has been emphasised by the Confidential Enquiries into Maternal Death (UK), which have consistently identified the failure to appreciate risk in

Table 9.2 Timing of delivery according to gestational age at presentation with pre-eclampsia (reproduced from Steegers EA *et al.*, *Lancet* 2010 Aug 21;376(9741): 631–44[10] with permission from Elsevier)

	Gestational age at diagnosis				
	20^{+0}– viability	*Viability – 29^{+6}*	*30^{+0}–33^{+6}*	*34^{+0}–36^{+6}*	*≥37^{+0}*
Perinatal prognosis	Survival: 18–50% Intact survival: 2–45%	Survival: 60–95% Intact survival: 15–90%	Survival: 98% Intact survival: 88–96%	Survival: >99% Intact survival: >96%	
Maternal risks (relative to normotensive pregnancy)	Significantly increased	Significantly increased	Significantly increased	Moderately increased	Minimally increased
In utero transfer to tertiary centre	NO as a routine, but centre should be competent with 2nd trimester termination and/or expectant management	YES if stable for transfer	Ideally, but perinatal outcomes unchanged if postpartum transfer	NO, but centre should be competent with expectant management	NO
Expectant management	NO as a routine, but at 22–23 weeks some may attempt to attain perinatal survival	YES rate of adverse maternal outcomes same with expedited delivery; significant perinatal gains		YES acute morbidity and school age issues are associated with late preterm birth	NO post-HYPITAT[38]
Betamethasone for fetal lungs	NO	YES	YES	YES if non-laboured Caesarean	NO
Assessment & surveillance	Minimum standard: on admission, day after admission, every Monday & Thursday until delivery, and on day of delivery; additional testing as indicated by changes in clinical state NOTE: this approach has been associated with >80% reduction in adverse maternal outcomes				
Maternal	Blood: CBC, INR, APTT, fibrinogen, creatinine, electrolytes, uric acid, AST, LDH, bilirubin, albumin, glucose (to R/O AFLP) Urine: dipstick, protein:creatinine ratio; pulse oximetry				
Fetal	Ultrasound: AFI, umbilical artery Doppler, ductus venosus Doppler; NST				
Deciding when to deliver	Women with 'severe pre-eclampsia, as defined in this textbook, should be delivered				Delivery, post-HYPITAT[38]
Route of delivery	Vaginal (misoprostol IOL)	Probable Cesarean, unless IUFD	Vaginal; fetal or uterine status may preclude vaginal delivery		

AFI, amniotic fluid index; AFLP, acute fatty liver of pregnancy; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CBC, complete blood count; INR, international normalised ratio; IOL, induction of labour; IUFD, intrauterine fetal death; LDH, lactate dehydrogenase; NST, non-stress test; PTB, preterm birth; R/O, role of

pre-eclampsia as responsible for potentially avoidable mortality or morbidity. As a result, subspecialty consultation has been advised[12] by telephone if necessary depending on the availability of obstetricians in the practice setting.

The optimal timing of birth for women with pre-eclampsia depends on evolving manifestations of pre-eclampsia in one/more organ systems for the woman and baby (Table 9.2). There is no tool available to guide the clinician in balancing the multitude of factors to consider, including the maternal and perinatal benefits and risks as perceived by the physician and the family, availability of personnel and conditions to monitor the woman and fetus, availability of specialist care for a preterm infant, and the preferences of the family. However, tools are available to identify women at increased risk of maternal complications.

Predicting adverse outcomes

Ideally, clinicians would identify women at particular risk of adverse maternal outcomes and undertake interventionist care. Models have not yet been developed and validated that will allow this to be done with a high degree of accuracy. This is discussed in detail in Chapter 3.

In brief, many individual factors (clinical, laboratory, or ultrasonographic) continue to be identified as related to latency (e.g., angiographic factor profile and shorter admission-delivery intervals[13]) or adverse clinical outcomes (e.g., higher uric acid and more adverse perinatal outcomes[14]). However, systematic study is unusual, particularly examinations of their added value over and above information from history and physical examination, with or without basic laboratory testing.

The Pre-eclampsia Integrated Estimate of RiSk (PIERS) score can identify women with pre-eclampsia who are at increased risk of adverse maternal outcomes in the subsequent 7 days, based on maternal history, symptoms, signs and laboratory parameters within the first 48 hours of hospital assessment with suspected pre-eclampsia. (Efforts to predict adverse outcomes farther into the future have not been successful[15].) The fullPIERS model was developed in well-resourced settings and the miniPIERS model in under-resourced settings, with areas under the receiver operating curves (AUC ROC) of 0.76 (95% CI 0.72–0.80) for fullPIERS[16], and 0.88 (95% CI 0.47–0.80) for miniPIERS[17]. (These models are discussed in detail in Chapter 3.)

If laboratory testing is available, then in addition to the clinical features of gestational age on admission and oxygen saturation, the following laboratory tests should be used as they were predictive of adverse maternal outcome in fullPIERS: platelet count, serum creatinine and alanine aminotransferase (https://piers.cfri.ca/PIERSCalculatorH.aspx)[16]. If laboratory testing is NOT available, then the focus should be on those clinical features that were independently predictive of adverse maternal outcome in the miniPIERS study: parity and gestational age on admission, headache/visual symptoms, chest pain/dyspnoea, systolic blood pressure and proteinuria (dipstick)[17]. An online calculator (cfri.ca/piers) is available for entry of continuous variables (such as gestational age) into the miniPIERS model to provide real-time personalised risks to all women whose caregivers have access to the internet.

Consideration of the severity of pre-eclampsia

The timing of birth literature on pre-eclampsia is heavily focused on the distinction between 'severe' and non-severe pre-eclampsia. Yet, there is little consistency between international guidelines in the definition of 'severe' pre-eclampsia[8,9,18–24].

Chapter 3 discusses the definition of 'severe' pre-eclampsia. In brief, when proteinuria is a mandatory criterion for pre-eclampsia in international guidelines[18–20], 'severe' pre-eclampsia is defined as the development of: (1) pre-eclampsia at <34 weeks[18], (2) one/more features of maternal end-organ dysfunction that is either not defined[18,19] or listed as 'symptoms'[20], (3) heavy proteinuria[18,20], or severe hypertension[18,20], or (4) one/more relevant fetal abnormalities[8,9,18]. When proteinuria is not a mandatory criterion for pre-eclampsia (which can be otherwise defined by hypertension and one/more pre-eclampsia-related maternal symptoms, signs, or abnormal laboratory tests or fetal monitoring abnormalities)[8,9,21–24], 'severe' pre-eclampsia is defined as the development of: (1) pre-eclampsia at <34 weeks[21], (2) proteinuria plus one/more feature(s) that alone would signify pre-eclampsia (cerebral/visual disturbances, pulmonary oedema, platelet count $<100 \times 10^9$/L, renal insufficiency, or elevated liver enzymes)[24], or

(3) one/more features of end-organ dysfunction described as: heavy proteinuria[21], one/more features of HELLP[22,23], new persistent and otherwise unexplained right upper quadrant/epigastric abdominal pain[24], severe hypertension[21,24], or those dysfunctions requiring delivery[8,9].

What further complicates timing of delivery related to the severity of pre-eclampsia is that there are women with non-severe pre-eclampsia who should be delivered (e.g., those at $\geq 37^{+0}$ weeks), and those with 'severe' pre-eclampsia (by all but Canadian guidelines[8,9]) who may reasonably undertake pregnancy prolongation (e.g., heavy proteinuria). This is why the Canadian guidelines have tried to single out as 'severe' pre-eclampsia, a group of women who are particularly 'severe' and require delivery by all guidelines. However, clinicians cannot be faulted for finding all of the 'severe' pre-eclampsia definitions difficult to follow.

What can be said is that the woman with pre-eclampsia who is at least 34 weeks' gestation and who is without symptoms, heavy proteinuria, laboratory evidence of end-organ complications, or fetal compromise has non-severe pre-eclampsia by all international guidelines. Also, the woman with pre-eclampsia with proteinuria and one or more end-organ manifestations of pre-eclampsia has 'severe' pre-eclampsia. The only exception is the Canadian guidelines that have tried to single out a particularly high risk group of women (within the women designated as 'severe' by other guidelines) who are inappropriate for ongoing pregnancy prolongation and should give birth.

Indications for delivery in pre-eclampsia vary with gestational age, and are discussed by gestational age below.

Gestational age $<24^{+0}$ weeks

Expectant management of pre-eclampsia at $<24^{+0}$ weeks (prior to fetal viability in well-resourced settings) is associated with high perinatal mortality (>80%) and maternal complication rates that have varied from 27 to 71% (including one maternal death; >40 studies, >4700 women)[6,25]. Given these risks, experts have recommended extensive counselling, which should include as an option termination of pregnancy regardless of the setting[6]. In under-resourced settings where there are limited neonatal services, this approach could be undertaken at gestational ages at which the fetus is 'non-viable' or unlikely to achieve viability within 1 or 2 weeks[18].

Gestational age 24^{+0}–33^{+6} weeks

Observational studies suggest that approximately 40% of women are eligible for expectant care following an initial period of observation and stabilisation (39 cohort studies, 4650 women)[5]. If women are eligible for expectant management of pre-eclampsia at 24^{+0}–33^{+6} weeks, such an approach may decrease neonatal morbidity, although the magnitude of maternal risk is unclear. Rates of serious maternal complications are very low (median <5%) in uncontrolled observational studies in well-resourced settings[5].

In the relevant Cochrane review (4 trials, 425 women[26]), interventionist care (i.e., antenatal corticosteroids if possible, followed by labour induction or emergency Caesarean delivery) compared with expectant care was associated with earlier birth by an average of 9.91 days (95% CI −16.37 to −3.45) and birth by Caesarean (4 trials, 425 women; RR 1.09, 95% CI 1.01–1.18), as well as more of the following adverse neonatal outcomes: neonatal intensive care admission (2 trials, 125 women; RR 1.35, 95% CI 1.16–1.58) and a longer stay there (2 trials, 125 women; mean difference of 11.14 days, 95% CI 1.57–20.72), respiratory distress syndrome (2 trials, 133 women; RR 2.30, 95% CI 1.39–3.81), ventilation (2 trials, 300 women; RR 1.50, 95% CI 1.11–2.02), neonatal intraventricular haemorrhage (1 trial, 262 women; RR 1.82, 95% CI 1.06–3.14), and necrotising enterocolitis (3 trials, 395 women; RR 2.10, 95% CI 0.93–4.79). The excess of morbidity associated with interventionist (vs. expectant) care occurred despite interventionist care being associated with fewer small for gestational age (SGA) babies (2 trials, 125 women; RR 0.30, 95% CI 0.14–0.65). There was no significant difference in adverse maternal outcomes between interventionist (vs. expectant) care, but the event rates were very low and the trials underpowered to find differences that would be clinically significant.

Subsequent to the most recent update of the Cochrane review discussed above, an additional randomised controlled trial (267 women) has been published that both failed to find neonatal benefit associated with expectant care and demonstrated increased maternal risk[27]. This trial was similar to

others in that women had to qualify for expectant care following a period of stabilisation, and interventionist care was associated with delivery an average of 8.1 days earlier (2.2 days in the prompt delivery group versus 10.3 days for the expectant management group). SGA babies were less common in the intervention (vs. expectant care) group (9.4% vs. 21.7%; RR 0.44, 95% CI 0.24–0.83), as in previous trials. However, interventionist (vs. expectant) care was not associated with more neonatal morbidity (56.4% vs. 55.6%; RR 1.01, 95% CI 0.81–1.26) or maternal morbidity (20.3% vs. 25.2%; RR 0.81, 95% CI 0.52–1.27). In fact, interventionist (vs. expectant) care was associated with fewer women with placental abruption (1.5% vs. 7.6%; RR 0.20, 95% CI 0.04–0.88). What makes the results of this trial different from others is not clear. The trial was carried out in South America in tertiary perinatal units, although others have been carried out in similar units in low- and middle-income countries[28]. However, following treatment of severe hypertension, only some units used oral antihypertensive therapy, something that may have been associated with the excess of placental abruption in expectant care and the failure to demonstrate less neonatal morbidity in babies born an average of 8.1 days later, compared with babies born in the interventionist care group.

In observational studies, expectant care of pre-eclampsia at 24^{+0}–33^{+6} weeks is associated with pregnancy prolongation of approximately 14 days. However, if pre-eclampsia is complicated by HELLP syndrome, only a median of 5 days are gained, and serious maternal morbidity is higher (median 15%). Therefore, brief expectant care would be appropriate if disseminated intravascular coagulation (DIC) is absent[29] and either regional anaesthesia or vaginal birth may be possible if there is temporary improvement of HELLP, something that is observed in more than 50% of women so managed[5].

Pending the results of a definitive randomised controlled trial powered to examine perinatal and maternal benefits and risks, timing of delivery in women with pre-eclampsia at 24^{+0}–33^{+6} weeks must be individualised. It would seem prudent to follow advice to clearly document a care plan that outlines the nature of fetal monitoring, indications for delivery, when corticosteroids should be given, and when discussions should take place with neonatology and obstetric anaesthesia staff[19].

Gestational age 34^{+0}–36^{+6} weeks

At these gestational ages, pregnancy prolongation is not expected to have substantial perinatal survival benefits. However, there may be advantages with regards to reduction in neonatal morbidity (particularly central nervous system[30]) and maternal morbidity. There are two published randomised controlled trials that inform timing of delivery at these late preterm gestational ages.

In HYPITAT II[31], 703 women with pre-eclampsia (60.2%, *de novo* or superimposed), gestational hypertension (25.9%), or pre-existing hypertension that was deteriorating (13.9%) were randomised to interventionist care (i.e., labour induction or Caesarean birth) or expectant care. Interventionist (vs. expectant) care was associated with possible maternal benefit, but definite perinatal risk. Women assigned to interventionist (vs. expectant) care experienced fewer adverse maternal outcomes (of thromboembolic disease, pulmonary oedema, eclampsia, HELLP syndrome, placental abruption, or maternal death, 1.1% vs. 3.1%; RR 0.36, 95% CI 0.12–1.11) without an increase in Caesarean delivery (30.4% vs. 32.5%; RR 0.94, 95% CI 0.75–1.16). However, interventionist (vs. expectant) care was associated with more admissions to neonatal intensive care (7.4% vs. 3.7%; RR 2.0, 95% CI 1.0–3.8) attributable to neonatal respiratory distress syndrome (5.7% versus 1.7%; RR 3.3, 95% CI 1.4–8.2). These findings did not differ by type of hypertensive disorder of pregnancy.

In a second, smaller randomised controlled trial of 169 women with mild pre-eclampsia without severe features, interventionist (vs. expectant) care was associated with fewer women who progressed to pre-eclampsia with severe features within 72 hours of randomisation (3.2% vs. 41.3%; RR 0.36, 95% CI 0.27–0.47), without an associated increase in Caesarean delivery (44.7% vs. 37.3%; RR not provided, $p = 0.35$) or neonatal intensive care unit admission (21.3% vs. 18.7%; RR not provided, $p = 0.89$)[32]. This trial was not of high quality, having been stopped early for unstated reasons.

In summary, it would appear that interventionist care may decrease the risk of adverse maternal outcome, however defined, among women who are stable and eligible for expectant care. However, the potential for interventionist (vs. expectant) care to increase neonatal respiratory morbidity justifies a

strategy of expectant care at these late preterm gestational ages.

Specific comment must be made about the impact of interventionist (vs. expectant) care on mode of delivery. Caesarean delivery rates have been about 70% in trials comparing one antihypertensive with another near or at term among women with pre-eclampsia who were not delivered immediately[33–37]. Although it has been long-believed that delaying childbirth may allow time for cervical ripening and successful vaginal birth (the preferred mode for all women if possible, including those with HELLP syndrome[29]), neither of the interventionist (vs. expectant) care trials mentioned above associated pregnant prolongation with lower rates of Caesarean delivery. Also, the large HYPITAT trial of women with pre-eclampsia at term (see below) failed to demonstrate this association[38].

Gestational age 37^{+0}–42^{+0} weeks

In the HYPITAT trial (756 women), interventionist (vs. expectant) care was associated with a decrease in progression of maternal disease (31.0% vs. 43.8%; RR 0.71, 95% CI 0.59–0.86); although primarily due to a decrease in severe hypertension (16.4% vs. 27.2%), a similar impact was seen on other serious maternal complications such as HELLP syndrome (1.1% vs. 2.9%)[38]. (Although women were recruited from 36^{+0} weeks, they consisted of only 9.9% of the trial population, so the results of the HYPITAT trial are not considered to be applicable to women at this gestational age.) Interventionist (vs. expectant) care was not associated with an increase in Caesarean birth (RR 0.75, 95% CI 0.55–1.04) or impact on long-term health-related quality of life[39]. Secondary analyses revealed that the benefits of labour induction (with regards to decreasing maternal complications) were even greater among women with an unfavourable cervix within the expectant care group and unrelated to those complications in the interventionist group[40].

Women with gestational hypertension (without pre-eclampsia)

Like those with pre-eclampsia, women with gestational hypertension at 37^{+0}–42^{+0} weeks probably benefit from labour induction by decreasing a composite measure of maternal morbidity[38]. Women with gestational hypertension comprised 65.6% of the relevant HYPITAT trial cohort, and the effect was similar in the gestational hypertension subgroup, although it did not reach statistical significance on its own (RR 0.81, 95% 0.63–1.03). The UK guidelines have interpreted these data as reflecting some uncertainty about whether labour induction is effective for women with gestational hypertension[19]. As discussed above, there was no increase in Caesarean births with labour induction (RR 0.75, 95% CI 0.55–1.04).

Using observational data from a multicentre American database of 3588 women with gestational hypertension at $\geq 36^{+0}$ weeks (1.6% of 228,668 deliveries), labour induction between 38^{+0} and 39^{+6} weeks appeared to offer the best balance between maternal and neonatal complications[41].

Women with pre-existing (chronic) hypertension

There are no randomised controlled trial data that inform timing of delivery in women with pre-existing hypertension.

Using observational data from an American population-based database of 179,669 women with otherwise uncomplicated pre-existing hypertension at 36^{+0}–41^{+6} weeks (half of all women with pre-existing hypertension who represented 1% of all deliveries), labour induction at 38^{+0}–39^{+6} weeks appeared to optimise the trade-off between the risk of adverse fetal (stillbirth) or maternal complications (superimposed pre-eclampsia and abruption) that increase in incidence with gestational age, and the adverse neonatal outcomes (neonatal mortality and morbidity) that decrease in incidence with gestational age[42].

Cost-effectiveness of interventionist management

We were unable to identify data on the cost-effectiveness of interventionist (vs. expectant) care for women with any of the hypertensive disorders of pregnancy before 34^{+0} weeks.

For women with pre-eclampsia or gestational hypertension near term (at 34^{+0}–36^{+6} weeks), we were unable to identify analyses from randomised controlled trials. The relevant analysis identified data from a retrospective controlled study of 4293 pregnant women of whom 1064 developed gestational hypertension or pre-eclampsia; although not recommended by randomised controlled trial

data[31], a policy of labour induction was cost-effective based on neonatal and maternal morbidity; labour induction cost CAD$299 more but was associated with better quality of life[19,43].

For women with pre-eclampsia or gestational hypertension (without pre-eclampsia) at term, labour induction was effective and cost-saving (by CAD$1065 overall) owing to less resource use antepartum[44].

MODE OF DELIVERY

While associated with greater than average rates of Caesarean delivery, the presence of a hypertensive disorder complicating a woman's pregnancy is not an automatic indication for Caesarean delivery. Randomised controlled trial data from India suggest that even women who have experienced antenatal eclampsia at or beyond 34^{+0} weeks of gestation can be considered for induction[45]. However, we do recognise that women with severe pre-eclampsia remote from term with clinical evidence indicative of fetal compromise (e.g., absent or reversed end-diastolic flow by umbilical artery Doppler) may best be delivered by Caesarean section. A randomised controlled trial conducted in India of 200 women with eclampsia identified an almost significant, but clinically important, improvement in adverse neonatal events with a policy of Caesarean delivery (9.90% vs. 19.19%; RR 0.52, 95% CI 0.25–1.05)[45].

Labour induction

Induction of labour in women with severe pre-eclampsia takes more time[46] and is less successful than in women with normotensive pregnancies[47]. However, an unfavourable cervix does not preclude successful induction[48], and neither IUGR nor oligohydramnios are contraindications to induction of labour[49]. Indeed, and against widely held opinion, the HYPITAT trial identified that women with gestational hypertension or mild pre-eclampsia at term who have an unfavourable cervix may benefit *more* from labour induction than other women[40].

For induction of labour, cervical ripening is recommended to increase the chance of successful vaginal delivery, recognising that this statement is supported by data derived from normotensive, rather than hypertensive pregnancies[50]. Cervical ripening could be by either mechanical (e.g., intracervical Foley balloon[51]) or prostaglandin-based (e.g., misoprostol, PGE_2); the use of vaginal PGE_2 is limited owing to both cost and cold chain requirements and may be less effective than oral misoprostol[52,53]. Adding vaginal oestradiol (50 μg) may improve the labour induction properties of vaginal misoprostol[54]. In women with asthma, mechanical approaches to labour induction may be safer and as effective, and do not appear to carry the excess maternal and perinatal morbidity previously associated with this method[55].

Fetal status

When considering the mode of delivery, both the gestational age and the fetal status should be considered. The rate of successful induction of labour with vaginal delivery is 47.5% at 28–32 weeks and 68.8% at 32–34 weeks of gestation. A success rate of 30% can be achieved even when birth weight is <1500 g[48,49]. Conversely, the success of induction at 24–28 weeks of gestation ranges from 6.7% to 10% suggesting that the potential maternal and fetal benefits to be derived by labour induction be carefully considered against the requirements for urgent or emergency delivery[56–58]. When there is increased resistance to diastolic flow in the umbilical artery, the vaginal delivery rate is significantly lower but still greater than 50%[59,60]. Most babies with absent or reversed end-diastolic flow by Doppler velocimetry of the umbilical artery, abnormal biophysical profile scores and abnormal sequential changes in Doppler studies of the fetal arterial and venous systems (e.g., appearance of ductal A waves) are delivered by Caesarean[61–64]. It should be remembered that the biophysical profile appears to be falsely reassuring when pregnancies are complicated by either pre-eclampsia[65] or IUGR[66,67].

In observational studies of women with severe pre-eclampsia, induction of labour (compared with Caesarean delivery) is associated with either similar or lower rates of adverse maternal and fetal outcomes[49,57,68,69]. For example, there was a 52% decrease in the odds for bronchopulmonary dysplasia and shorter duration of ventilator support in the infants born following labour induction compared with those delivered by elective Caesarean section. In addition, there are longer-term considerations relevant to Caesarean delivery, such as the risk of uterine rupture with subsequent pregnancies or morbidity associated with repeat Caesarean deliveries[70].

Potential for bleeding

Women with pre-eclampsia are at risk of thrombocytopaenia and coagulopathy (either antepartum or *de novo* postpartum), and all standard measures including the active management of the third stage of labour[71] should be taken to avoid postpartum haemorrhage. Oxytocin is the uterotonic drug of choice for such active management. Ergometrine (ergonovine maleate) is contraindicated in all forms of hypertensive disorder of pregnancy, particularly pre-eclampsia and gestational hypertension. If oxytocin is not available, safer alternative uterotonic drugs that have significantly fewer side-effects, especially acute elevations in blood pressure, are recommended[19,72–76].

Antenatal corticosteroids

Where delivery is believed to be in the best maternal and/or fetal interest, there are no clinical signs of maternal infection, and gestational age is between 24^{+0} and 34^{+6}, the clinician should offer a single course of antenatal corticosteroids (either IM dexamethasone or IM betamethasone – a total of 24 mg in two divided doses given 12 hours apart)[77]. The beneficial effects of antenatal corticosteroids can be observed within 4 hours of the first dose[77]. A single repeat course of corticosteroids can be considered if iatrogenic preterm birth at $\leq 34^{+6}$ weeks still seems likely within the next 7 days, and at least 7 days have transpired since the initial course of antenatal corticosteroids[78].

BEST PRACTICE POINTS

(Please see Appendix 9.1 for the evaluation of the strength of the recommendation and the quality of the evidence on which they are based.)

Management should be based on the understanding that giving birth is the only cure for pre-eclampsia, and women with gestational hypertension or pre-existing hypertension may develop pre-eclampsia antepartum or postpartum. Mode of delivery is usually driven by the usual obstetric indications, unless there is evidence of substantial fetal compromise or gestational age is <30 weeks. Recommendations for delivery or ongoing pregnancy are outlined in Table 9.2.

Place of delivery

1. All women with a hypertensive disorder of pregnancy of any type require delivery in a centre that can provide EmONC.
2. Women with a hypertensive disorder of pregnancy and serious maternal complications require delivery in a centre capable of providing CEmONC.

Timing of delivery

Women with pre-eclampsia

1. Consultation with an obstetrician is advised in women with pre-eclampsia. (If an obstetrician is not available in under-resourced settings, consultation with at least a physician is recommended.)
2. All women with severe pre-eclampsia or eclampsia should be delivered within 24 hours, regardless of gestational age.*
3. For women with non-severe pre-eclampsia at $<24^{+0}$ weeks' gestation, counselling should include information about delivery within days as an option.
4. For women with non-severe pre-eclampsia at 24^{+0}–33^{+6} weeks' gestation, expectant management should be considered, but only in centres capable of caring for very preterm infants.
5. For women with non-severe pre-eclampsia at 34^{+0}–36^{+6} weeks' gestation, expectant management is advised.
6. For women with pre-eclampsia at $\geq 37^{+0}$ weeks' gestation, delivery within 24 hours is recommended.
7. For women with non-severe pre-eclampsia complicated by HELLP syndrome at 24^{+0}–34^{+6} weeks' gestation, consider delaying delivery long enough to administer antenatal corticosteroids for acceleration of fetal pulmonary maturity as long as there is temporary improvement in maternal laboratory testing.

8. All women with HELLP syndrome at ≥35^{+0} weeks' gestation should be considered for delivery within 24 hours.

*"*Severe*"pre-eclampsia is defined according to Canadian criteria of potentially life-altering complications included within all other definitions of severe pre-eclampsia. There is consensus that these represent indications for delivery: (1) uncontrolled maternal hypertension; (2) maternal end-organ complications of the central nervous, cardiorespiratory, haematological, renal, or hepatic systems; or (3) stillbirth or substantial fetal compromise of abruption with maternal/fetal compromise or reversed ductus venosus A wave. Although these conditions are included in the WHO definition of severe pre-eclampsia, WHO also includes other criteria for severe pre-eclampsia that are not clear indications for delivery: heavy proteinuria, gestational age <34 weeks and evidence of any 'fetal morbidity'.

Women with gestational hypertension (without pre-eclampsia)

1. For women with gestational hypertension at <34^{+0} weeks, expectant management is advised.
2. For women with gestational hypertension at 34^{+0}–36^{+6} weeks', expectant management is advised.
3. For women with gestational hypertension at ≥37^{+0} weeks', childbirth within days should be discussed.

Women with pre-existing hypertension

1. For women with pre-existing hypertension at <34^{+0} weeks, expectant management is advised.
2. For women with pre-existing hypertension at 34^{+0}–36^{+6} weeks, expectant management is advised, even if women require treatment with antihypertensive therapy.
3. For women with uncomplicated pre-existing hypertension who are otherwise well at ≥37^{+0} weeks' gestation, childbirth should be considered at 38^{+0}–39^{+6} weeks' gestation.

Mode of delivery

1. For women with any hypertensive disorder of pregnancy, vaginal delivery should be considered unless a Caesarean delivery is required for the usual obstetric indications.
2. If vaginal delivery is planned and the cervix is unfavourable, then cervical ripening should be used to increase the chance of a successful vaginal delivery.
3. At a gestational age remote from term, women with a hypertensive disorder of pregnancy with evidence of fetal compromise may benefit from delivery by emergent Caesarean.
4. Antihypertensive treatment should be continued throughout labour and delivery to maintain systolic blood pressure at <160 mmHg and diastolic blood pressure at <110 mmHg.
5. The third stage of labour should be actively managed with oxytocin 5 units IV or 10 units IM, particularly in the presence of thrombocytopaenia or coagulopathy.
6. Ergometrine maleate should not be administered to women with any hypertensive disorder of pregnancy, particularly pre-eclampsia or gestational hypertension; alternative oxytocics should be considered.

PRIORITIES FOR UNDER-RESOURCED SETTINGS

A challenge with expectant management in low-resource settings is inadequate resources (human and material) to accurately assess gestational age or monitor the woman and fetus intensively. The minimum technology, staffing and infrastructure requirements by level of the health care system (beyond the need for EmONC) are yet to be determined. Also, although many technologies for assessing gestational age, maternal well-being and fetal well-being meet requirements for use in low-resource settings and many have been tested in those settings, there is no clear consensus on cost-effectiveness of their introduction into health systems and potential impact on maternal and perinatal mortality. Ministries of health must consider their budgetary constraints and multiple

priorities when making decisions about introducing new technologies that require capital investments, training interventions and maintenance costs. What is needed at this time is a guide that includes information on how they perform in relation to requirements for low-resource settings: portability, cost, ease of use, ability to record/print images, frequencies, power requirements, battery life, durability, frame rate, screen settings, user interface and ability to communicate with a variety of devices[79]. This will provide ministries of health with guidance for choosing and scaling up use of the technologies.

The authors have suggested priorities for different levels of the health care system in Table 9.3.

WHAT INTERNATIONAL GUIDELINES SAY (APPENDIX 9.2[80])

Abbreviations for Clinical Practice Guidelines: ACOG (American College of Obstetricians and Gynecologists)[24], NICE (National Institutes of Clinical Excellence)[19], NVOG (National Obstetrics and Gynaecology Society, Netherlands)[20], QLD (Queensland, Australia)[22,23], SOGC (Society of Obstetricians and Gynaecologists of Canada)[8,9], SOMANZ (Society of Obstetric Medicine of Australia and New Zealand)[81], WHO (World Health Organization)[18], ESC (European Society of Cardiology)[82], ASH (American Society of Hypertension)[83], AOM (Association of Onario Midwives)[21].

Timing of delivery

Seven international guidelines (NICE, NVOG, ESC, WHO, ACOG, SOGC, SOMANZ) make recommendations regarding timing of delivery.

Recommendations for delivery (and administration of antenatal corticosteroids, if appropriate) focus on women with pre-eclampsia (ACOG, NICE, NVOG, SOGC, WHO, SOMANZ). Uncontrolled severe hypertension is the most widely regarded maternal indication for delivery (and treatment) (NICE, WHO, ACOG, SOMANZ). Expectant care is considered appropriate depending on the type of hypertensive disorder and gestational age, assuming that women and fetuses can be appropriately managed and cared for when delivered.

Table 9.3 Priorities for timing and mode of delivery by level of health care system at which care is delivered

	Antepartum and postpartum	
	Initial priority	*Ultimate goal*
Community		
Primary health care centre (detect, stabilise and refer)	Assess gestational age accurately Use miniPIERS) model (±pulse oximetry to assess risk for individual women with HDPs[14]	mHealth-guided decision-making
Facility		
Secondary-level facility (detect, manage and refer if necessary)	Assess gestational age accurately Monitor maternal well-being with additional testing (blood, urine and pulse oximetry) to derive personalised risk through fullPIERS model (https://piers.cfri.ca/PIERSCalculatorH.aspx)[13]	mHealth-guided decision-making Monitor fetal well-being with NST and ultrasonographic assessment
Tertiary-level (referral) facility (detect and manage definitely)	Assess gestational age accurately Monitor maternal well-being with additional testing (blood, urine and pulse oximetry) to derive personalised risk through fullPIERS model (https://piers.cfri.ca/PIERSCalculatorH.aspx)[13] Monitor fetal well-being with NST and ultrasonographic assessment	mHealth-guided decision-making

NST, non-stress test

There is general consensus that women with pre-eclampsia should be delivered if pre-eclampsia is 'severe' or gestational age is either prior to fetal viability (WHO, ACOG, SOGC, SOMANZ 2014) or term (NICE, WHO, ACOG, SOGC, SOMANZ 2014). Definitions of severe pre-eclampsia vary, but none of the guidelines that have gestational age <34 weeks as a severity criterion indicate that women at <34 weeks with pre-eclampsia must be delivered (WHO, ASH 2008, AOM 2012). It should be noted that of 14 guidelines, only four indicate that 'heavy proteinuria' is a pre-eclampsia severity criterion; if applied strictly, it would mean that women with pre-eclampsia and heavy proteinuria should be delivered (WHO, ASH 2008, NVOG 2011, AOM 2012). There is consensus that women with pre-eclampsia should be considered for expectant management if they are at a gestational age associated with fetal viability and <34 weeks (WHO, NICE, ACOG, SOGC, SOMANZ 2014).

Women with gestational hypertension should be delivered at term (WHO, ACOG, SOGC), although this remains a controversial recommendation, with some guidelines recommending expectant care pending future studies (NICE, SOMANZ 2014).

There is no consistent guidance for women with chronic hypertension.

Mode of delivery

In terms of mode of delivery, the related issues have been addressed by five of the nine clinical practice guidelines (ACOG, AOM, QLD, NICE, SOGC). In pregnancies complicated by pregnancy hypertension, but without fetal compromise, the mode of delivery should be based on the clinical circumstances and usual obstetric indications (N = 4) (ACOG, QLD, NICE, SOGC). If a vaginal delivery is planned, and the cervix is unfavourable, then two guidelines recommend cervical ripening (QLD, SOGC). Active management of the third stage of labour with oxytocin is recommended (N = 2) (AOM, SOGC).

PRIORITIES FOR FUTURE RESEARCH

There is a need for better mechanisms for assessing gestational age in under-resourced settings where there is substantial reliance on inaccurate methods, such as LMP and SFH.

REFERENCES

1. Tuffnell DJ, Jankowicz D, Lindow SW, Lyons G, Mason GC, Russell IF, et al. Outcomes of severe pre-eclampsia/eclampsia in Yorkshire 1999/2003. BJOG 2005;112(7):875–880

2. Traisathit P, Le Cœur S, Mary JY, Kanjanasing A, Lamlertkittikul S, Lallemant M. Gestational age determination and prevention of HIV perinatal transmission. Int J Gynaecol Obstet 2006;92(2): 176–180

3. Jehan I, Zaidi S, Rizvi S, Mobeen N, McClure EM, Munoz B, et al. Dating gestational age by last menstrual period, symphysis-fundal height, and ultrasound in urban Pakistan. Int J Gynaecol Obstet 2010;110(3): 231–234

4. Royal College of Obstetricians & Gynaecologists. Green-top Guideline No. 7: Antenatal corticosteroids to reduce neonatal morbidity and mortality. 2010; Available at: https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_7.pdf. Accessed Oct/28, 2015

5. Magee LA, Yong PJ, Espinosa V, Côté AM, Chen I, von Dadelszen P. Expectant Management of Severe Preeclampsia Remote from Term: A Structured Systematic Review. Hypertens Pregnancy 2009;28(3): 312–347

6. Sibai BM, Barton JR. Expectant management of severe preeclampsia remote from term: patient selection, treatment, and delivery indications. Am J Obstet Gynecol 2007;196(6):514.e1-514.e9

7. Liston R, Sawchuck D, Young D, Society of Obstetrics and Gynaecologists of Canada, British Columbia Perinatal Health Program. Fetal health surveillance: antepartum and intrapartum consensus guideline. J Obstet Gynaecol Can 2007;29(9 Suppl 4):S3–S56

8. Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy: executive summary. J Obstet Gynaecol Can 2014 05;36(5): 416–441

9. Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens 2014 2015/01;4(2):105–145

10. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet 2010 08/21;376(1474–547; 9741):631–644

11. United Nations Population Fund. Featured Publications. 2015; Available at: http://www.unfpa.org/publications. Accessed Oct/28, 2015

12. Reidy J, Russell R. Cmace 2006–2008. Int J Obstet Anesth 2011 Jul;20(3):208–212

13. Gómez-Arriaga PI, Herraiz I, López-Jiménez EA, Gómez-Montes E, Denk B, Galindo A. Uterine artery Doppler and sFlt-1/PlGF ratio: usefulness in diagnosis of pre-eclampsia. Ultrasound Obstet Gynecol 2014; 43(5):525–532

14. Urato AC, Bond B, Craigo SD, Norwitz ER, Paulus JK, Strohsnitter WC. Admission uric acid levels and length of expectant management in preterm preeclampsia. J Perinatol 2012;32(10):757–762

15. Ganzevoort W, Rep A, de Vries JIP, Bonsel GJ, Wolf H, PETRA-investigators. Prediction of maternal complications and adverse infant outcome at admission for temporizing management of early-onset severe hypertensive disorders of pregnancy. Am J Obstet Gynecol 2006;195(2):495–503

16. von Dadelszen P, Payne B, Li J, Ansermino JM, Broughton Pipkin F, Cote AM, et al. Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model. Lancet 2011 Jan 15;377(9761):219–227

17. Payne BA, Hutcheon JA, Ansermino JM, Hall DR, Bhutta ZA, Bhutta SZ, et al. A risk prediction model for the assessment and triage of women with hypertensive disorders of pregnancy in low-resourced settings: the miniPIERS (Pre-eclampsia Integrated Estimate of RiSk) multi-country prospective cohort study. PLoS Med 2014 01;11(1):e1001589

18. World Health Organization. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. 2011

19. National Collaborating Centre for Women's and Children's Health (UK). CG107: Hypertension in pregnancy: The management of hypertensive disorders during pregnancy. NICE: Guidance 2010 Aug

20. Nederlandse Vereniging voor Obstetrie en Gynaecologie. Hypertensieve aandoeningen in de zwangerschap. 2011

21. Salehi P, Association of Ontario Midwives HDP CPG, Working Group. Hypertensive disorders of pregnancy (Clinical Practice Guideline 15). 2012; Available: http://www aom on ca/Health_Care_Professionals/Clinical_Practice_Guidelines/

22. Queensland Maternity and Neonatal Clinical,Guidelines Program. Hypertensive disorders of pregnancy. 2013; MN10.13-V4-R15

23. Queensland Maternity and Neonatal Clinical, Guidelines Program. Supplement: hypertensive disorders of pregnancy. 2013;MN10.15.V4-R15

24. American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013 Nov;122(5):1122–1131

25. Ganzevoort W, Sibai BM. Temporising versus interventionist management (preterm and at term). Best Pract Res Clin Obstet Gynaecol 2011;25(4): 463–476

26. Churchill D, Duley L, Thornton JG, Jones L. Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation. Cochrane Database Syst Rev 2013 Jul 26;7:CD003106

27. Vigil-De Gracia P, Reyes Tejada O, Calle Miñaca A, Tellez G, Chon VY, Herrarte E, et al. Expectant management of severe preeclampsia remote from term: the MEXPRE Latin Study, a randomized, multicenter clinical trial. Am J Obstet Gynecol 2013;209(5): 425.e1-e8

28. Odendaal HJ, Pattinson RC, Bam R, Grove D, Kotze TJ. Aggressive or Expectant Management for Patients With Severe Preeclampsia Between 28–34 Weeks' Gestation: A Randomized Controlled Trial. Obstet Gynecol 1990;76(6):1070–1075

29. Aloizos S, Seretis C, Liakos N, Aravosita P, Mystakelli C, Kanna E, et al. HELLP syndrome: Understanding and management of a pregnancy-specific disease. J Obstet Gynaecol 2013;33(4):331–337

30. Adams-Chapman I. Neurodevelopmental outcome of the late preterm infant. Clin Perinatol 2006;33(4): 947

31. Broekhuijsen K, van Baaren G, van Pampus MG, Ganzevoort W, Sikkema JM, Woiski MD, et al. Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (HYPITAT-II): an open-label, randomised controlled trial. Lancet 2015;385(9986): 2492–2501

32. Owens MY, Thigpen B, Parrish MR, Keiser SD, Sawardecker S, Wallace K, et al. Management of preeclampsia when diagnosed between 34–37 weeks gestation: deliver now or deliberate until 37 weeks? J Miss State Med Assoc 2014;55(7):208

33. Gul A, Aslan H, Cebeci A, Polat I, Ulusoy S, Ceylan Y. Maternal and Fetal Outcomes in HELLP Syndrome Complicated with Acute Renal Failure. Ren Fail 2004; 26(5):557–562

34. Sagen N, Haram K, Nilsen ST. Serum Urate as a Predictor of Fetal Outcome in Severe Pre-Eclampsia. Acta Obstet Gynecol Scand 1984;63(1):71–75

35. Varma TR. Serum uric acid levels as an index of fetal prognosis in pregnancies complicated by pre-existing hypertension and pre-eclampsia of pregnancy. Int J Gynaecol Obstet 1982;20(5):401–408

36. Hjertberg R, Faxelius G, Lagercrantz H. Neonatal adaptation in hypertensive pregnancy--a study of labetalol vs hydralazine treatment. J Perinat Med 1993; 21(1):69

37. Montan S, Anandakumar C, Arulkumaran S, Ingemarsson I, Ratnam S. Randomised controlled trial of methyldopa and isradipine in preeclampsia--effects on uteroplacental and fetal hemodynamics. J Perinat Med 1996;24(2):177

38. Koopmans CM, Bijlenga D, Groen H, Vijgen SM, Aarnoudse JG, Bekedam DJ, et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. Lancet 2009;374(9694): 979–988

39. Bijlenga D, Koopmans CM, Birnie E, Mol BJ, van der Post JA, Bloemenkamp KW, et al. Health-Related Quality of Life after Induction of Labor versus Expectant Monitoring in Gestational Hypertension or Preeclampsia at Term. Hypertens Pregnancy 2011;30(3): 260–274

40. Tajik P, van der Tuuk K, Koopmans C, Groen H, van Pampus M, van der Berg P, et al. Should cervical favourability play a role in the decision for labour induction in gestational hypertension or mild pre-eclampsia at term? An exploratory analysis of the HYPITAT trial. BJOG 2012;119(9):1123–1130

41. Cruz MO, Gao W, Hibbard JU. What is the optimal time for delivery in women with gestational hypertension? Am J Obstet Gynecol 2012;207(3): 214.e1-e6

42. Hutcheon JA, Lisonkova S, Magee LA, von Dadelszen P, Woo HL, Liu S, et al. Optimal timing of delivery in pregnancies with pre-existing hypertension. BJOG 2011;118(1):49–54

43. Habli M, Levine RJ, Qian C, Sibai B. Neonatal outcomes in pregnancies with preeclampsia or gestational hypertension and in normotensive pregnancies that delivered at 35, 36, or 37 weeks of gestation. Am J Obstet Gynecol 2007 10;197(4): 406.e1-406.e7

44. Vijgen S, Koopmans C, Opmeer B, Groen H, Bijlenga D, Aarnoudse J, et al. An economic analysis of induction of labour and expectant monitoring in women with gestational hypertension or pre-eclampsia at term (HYPITAT trial). BJOG 2010;117(13):1577–1585

45. Seal SL, Ghosh D, Kamilya G, Mukherji J, Hazra A, Garain P. Does route of delivery affect maternal and perinatal outcome in women with eclampsia? A randomized controlled pilot study. Am J Obstet Gynecol 2012;206(6):484.e1-484.e7

46. Griffiths AN, Hikary N, Suzer AR. Induction to delivery time interval in patients with and without preeclampsia: a retrospective analysis. Acta Obstet Gynecol Scand 2002;81(9):867–869

47. Xenakis EM-, Piper JM, Field N, Conway D, Langer O. Preeclampsia: Is induction of labor more successful? Obstet Gynecol 1997;89(4):600–603

48. Regenstein AC, Laros J,R K., Wakeley A, Kitterman JA, Tooley WH. Mode of delivery in pregnancies complicated by preeclampsia with very low birth weight infants. J Perinatol 1995;15(1):2–6

49. Alexander JM, Bloom SL, McIntire DD, Leveno KJ. Severe preeclampsia and the very low birth weight infant: is induction of labor harmful? Obstet Gynecol 1999;93(4):485–488

50. Crane J. SOGC Clinical Practice Guideline, No. 107: Induction of Labour at term. 2001; Available at: http://sogc.org/wp-content/uploads/2013/01/gui107ECPG0108.pdf. Accessed Oct/28, 2015

51. Mozurkewich EL, Chilimigras JL, Berman DR, Perni UC, Romero VC, King VJ, et al. Methods of induction of labour: a systematic review. BMC Pregnancy Childbirth 2011;11(1):84

52. Alfirevic Z, Aflaifel N, Weeks A. Oral misoprostol for induction of labour. Cochrane Database Syst Rev 2014; 6:CD001338

53. Alfirevic Z, Keeney E, Dowswell T, Welton NJ, Dias S, Jones LV, et al. Labour induction with prostaglandins: a systematic review and network meta-analysis. BMJ 2015;350(feb05 10):h217-h217

54. Dasgupta E, Singh G. Vaginal Misoprostol vs Vaginal Misoprostol With Estradiol for Labor Induction: A Prospective Double Blind Study. J Obstet Gynaecol India 2012;62(1):47–51

55. McMaster K, Sanchez-Ramos L, Kaunitz AM. Evaluation of a Transcervical Foley Catheter as a Source of Infection: A Systematic Review and Meta-analysis. Obstet Gynecol 2015;126(3):539–551

56. Alanis MC, Robinson CJ, Hulsey TC, Ebeling M, Johnson DD. Early-onset severe preeclampsia: induction of labor vs elective cesarean delivery and neonatal outcomes. Am J Obstet Gynecol 2008 9;199(3):262.e1-262.e6

57. Blackwell SC, Redman ME, Tomlinson M, Jr JBL, Tuynman M, Gonik B, et al. Labor induction for the preterm severe pre-eclamptic patient: is it worth the effort? J Matern Fetal Med 2001;10(5):305–311

58. Baschat AA, Galan HL, Bhide A, Berg C, Kush ML, Oepkes D, et al. Doppler and biophysical assessment in growth restricted fetuses: distribution of test results. Ultrasound Obstet Gynecol 2006;27(1):41–47

59. Li H, Gudmundsson S, Olofsson P. Prospect for vaginal delivery of growth restricted fetuses with abnormal umbilical artery blood flow. Acta Obstet Gynecol Scand 2003;82(9):828–833

60. Skinner J, Greene RA, Gardeil F, Stuart B, Turner MJ. Does increased resistance on umbilical artery Doppler preclude a trial of labour? Eur J Obstet Gynecol Reprod Biol 1998;79(1):35–38

61. Weiss E, Ulrich S, Berle P. Condition at birth of infants with previously absent or reverse umbilical artery end-diastolic flow velocities. Arch Gynecol Obstet 1992; 252(1):37–43

62. Hiett AK, Brown HL, Britton KA. Outcome of infants delivered between 24 and 28 weeks' gestation in women with severe pre-eclampsia. J Matern Fetal Med 2001;10(5):301–304

63. Wallace EM, Baker LS. Effect of antenatal betamethasone administration on placental vascular resistance. Lancet 1999;353(9162):1404–1407

64. Turan OM, Turan S, Berg C, Gembruch U, Nicolaides KH, Harman CR, et al. Duration of persistent abnormal ductus venosus flow and its impact on perinatal outcome in fetal growth restriction. Ultrasound Obstet Gynecol 2011;38(3):295–302

65. Payne BA, Kyle PM, Lim K, Lisonkova S, Magee LA, Pullar B, et al. An assessment of predictive value of the biophysical profile in women with preeclampsia using data from the fullPIERS database. Pregnancy Hypertens 2013;3(3):166–171

66. Shalev E, Zalel Y, Weiner E. A comparison of the nonstress test, oxytocin challenge test, Doppler velocimetry and biophysical profile in predicting umbilical vein pH in growth-retarded fetuses. Int J Gynaecol Obstet 1993;43(1):15–19

67. Kaur S, Picconi JL, Chadha R, Kruger M, Mari G. Biophysical profile in the treatment of intrauterine growth-restricted fetuses who weigh <1000 g. Am J Obstet Gynecol 2008;199(3):264.e1-264.e4

68. Nassar AH, Adra AM, Chakhtoura N, Gómez-Marín O, Beydoun S. Severe preeclampsia remote from term: Labor induction or elective cesarean delivery? Am J Obstet Gynecol 1998;179(5):1210–1213

69. Coppage KH, Polzin WJ. Severe preeclampsia and delivery outcomes: Is immediate cesarean delivery beneficial? Am J Obstet Gynecol 2002;186(5):921–923

70. Liu S, Liston RM, Joseph KS, Heaman M, Sauve R, Kramer MS, et al. Maternal mortality and severe morbidity associated with low-risk planned cesarean delivery versus planned vaginal delivery at term. Can Med Assoc J 2007;176(4):455–460

71. Schuurmans N, MacKinnon C, Lane C, Etches D. Prevention and Management of Postpartum Haemorrhage. 2000; Available at: http://sogc.org/wp-content/uploads/2013/01/88E-CPG-April2000.pdf. Accessed Oct/28, 2015

72. Leung S, Ng P, Wong W, Cheung T. A randomised trial of carbetocin versus syntometrine in the management of the third stage of labour. BJOG 2006; 113(12):1459–1464

73. Ergonovine Maleate Injection USP. Therapeutic Category: Oxytocic. Product Information Insert. March 2009

74. Leduc D, Senikas V, Lalonde AB, Ballerman C, Biringer A, Delaney M, et al. Active management of the third stage of labour: prevention and treatment of postpartum hemorrhage. J Obstet Gynaecol Can 2009; 31(10):980–993

75. Mitchell GG, Elbourne DR. The Salford Third Stage Trial. Oxytocin plus ergometrine versus oxytocin alone in the active management of the third stage of labor. Online J Curr Clin Trials 1993;No. 83: 2305–2332

76. National Collaborating Centre for Women's and Children's Health (UK). CG55: Intrapartum care: care of healthy women and their babies during childbirth. 2014

77. Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2006(3): CD004454

78. Peltoniemi OM, Kari MA, Hallman M. Repeated antenatal corticosteroid treatment: a systematic review and meta-analysis. Acta Obstet Gynecol Scand 2011; 90(7):719

79. World Health Organization, Regional Office for the Western Pacific. 2.1 Essential Medical Equipment, 2.3.3.1 (2) Diagnostic imaging equipment. District Health Facilities: Guidelines for development and operations Manila, Philippines: WHO Regional Office for the Western Pacific; 1998. p. 145

80. Gillon TE, Pels A, von Dadelszen P, MacDonell K, Magee LA. Hypertensive disorders of pregnancy: a

systematic review of international clinical practice guidelines. PLoS One 2014;9(12):e113715

81. Lowe SA, Bowyer L, Lust K, McMahon LP, Morton MR, North RA, et al. The SOMANZ guideline for the management of hypertensive disorders of pregnancy. Sydney: SOMANZ; 2014

82. Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart J, et al. Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J 2011;32(24):3147–3197

83. Lindheimer MD, Taler SJ, Cunningham FG. Hypertension in pregnancy. J Am Soc Hypertens 2010; 4(2):68–78