23 Doppler Velocimetry in Prolonged Pregnancy

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23.1 Introduction

Pregnancies progressing past 42 weeks/294 days are associated with an increase in perinatal morbidity and mortality [1, 2]. The terminologies used to identify these situations include "post-date," "post-term," and "prolonged pregnancy," which are terms sometimes used interchangeably and at other times overlap with differing gestational-age starting points (40, 41, or 42 weeks). A single specific etiology for an increased adverse outcome has not been established with certainty, and multiple factors may be involved. As fetal growth continues, it is possible that the fetal size exceeds the placental ability to provide adequate nutritional and respiratory support.

The prevalence of postdate pregnancy is variable worldwide. European data from 15 different areas drawn predominantly from 2000 found that 0.4–8.1% of deliveries occurred at or beyond 294 [3]. Birth certificate data for the United States from the National Center for Health Statistics covering the years 2010–2017 (just under four million births annually) show pregnancies beyond 294 days occurring for 0.33–0.46% of deliveries [4]. This sub-1% rate is considerably lower than the earlier reported rates of 5–6%. In 2014, the National Center for Health Statistics changed how they calculated gestational age from birth certificate data, switching from the last menstrual period to obstetric estimate [5, 6]. Recent statistics for the United States have shown late preterm delivery (41–0/7 weeks–41-6/7 weeks) rates of just over 6% [4].

The standard testing for fetal evaluation includes non-stress tests (NSTs) and biophysical profiles as markers of fetal health. In postdate pregnancies, amniotic fluid volume is also measured. For over three decades, Doppler velocimetry has been used as an additional tool for fetal evaluation. Doppler provides us with the capability to evaluate hemodynamic changes in both the placenta and fetus. Uterine and umbilical artery Doppler, as a measure of placental resistance, can provide insights into placental perfusion from the maternal and fetal circulations. As compromises in fetal health develop, hemodynamic changes that can occur include hypovolemia and redistribution of fetal blood flow, which are changes potentially detectable through Doppler testing. In this chapter, we will review the information available on Doppler velocimetry in postdate pregnancies. The most common fetal vessels that have been studied and the ones most commonly used for clinical purposes are the umbilical and middle cerebral arteries. Many of the studies include Doppler testing in both vessels. For these reasons,

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studies on these vessels will be covered together in the second section of this chapter. The first section reviews the data on “other vessels,” aorta, pulmonary artery, renal artery, and uterine artery. Studies that performed multi-vessel analysis appear in more than one section.

23.2 Other Vessels

23.2.1 Aortic Blood Flow Doppler

Doppler parameters that have been evaluated in the fetal aorta include velocity (either mean or peak) and blood flow volume. Several of the studies reviewed show a positive association between aortic Doppler results and adverse pregnancy outcomes.

-Battaglia et al. studied 82 pregnancies with Doppler evaluation beginning at 41 weeks. Based on unpublished preliminary data, a mean velocity of 25 cm/s in the thoracic aorta was chosen as the cut-off to separate normal from decreased mean velocity. Pregnancies with low mean thoracic aortic velocities were associated with cesarean delivery for fetal distress, oligohydramnios, meconium-stained amniotic fluid, and abnormal non-stress tests in individual analyses [7].

-Anteby et al. studied 78 pregnancies starting at 41 weeks' gestation. Patients who had fetal distress, defined by the presence of the meconium, abnormal fetal heart rate pattern, or intervention for abnormal fetal heart rate pattern, had a significantly lower mean thoracic aortic velocity [8].

-Olofsson et al. followed 44 patients who delivered after 43 weeks with serial descending aortic testing, which included mean velocity, flow volume, and a pulsatility index (PI) ratio. These three indices were then compared in patients grouped according to four different measures of adverse outcomes: oligohydramnios (maximum amniotic fluid vertical pocket (MVP) $\leq$2 cm), meconium, asphyxia (low Apgar scores or acidosis), or fetal distress (delivery for abnormal fetal heart tones). Of these 12 analyses, the only significant difference was between aortic flow volume and fetal distress. Interestingly, patients delivering with fetal distress had a higher flow volume than did those without [9].

-Weiner et al. published two studies in 1996, which evaluated fetal aortic Doppler in postdate pregnancies [10, 11]. Serial Doppler testing was begun at 41 weeks with measurements of the peak aortic systolic velocity and aortic flow volume. These Doppler indices were compared with pregnancy outcomes of amniotic fluid volume and fetal heart rate testing. The two studies overlap in the periods when patient data were collected; it is not clear whether some patients were included in both studies. In one study of 45 patients, the percentage changes for both aortic Doppler velocity and flow volume were analyzed with the percentage change in amniotic fluid (linear regression) and with fetal heart rate patterns (non-parametric median testing) [10]. A significant decline in both aortic Doppler parameters were noted in association with decreases in amniotic flow volume, while only the aortic flow volume but not the peak velocity correlated with non-reassuring fetal heart rate abnormalities. In the second study, the same 4 parameters (aortic peak velocity, aortic flow volume, amniotic fluid volume, and fetal heart rate pattern) were evaluated in 120 patients. The analysis here used absolute Doppler values instead of percentage change, amniotic fluid index (AFI) $\leq$ 5 instead of percentage change of amniotic fluid, and low fetal heart rate variability on computerized fetal monitoring was used to define an abnormal fetal heart rate pattern.11 Both measures of aortic Doppler were significantly lower in patients with oligohydramnios and decreased fetal heart rate variability. Of the eight statistical analyses in these two studies, seven showed a significant association with lower aortic indices seen with adverse outcomes.

Other studies did not find a positive association between aortic Doppler and clinical outcome in postdate pregnancies.

-Rightmire and Campbell evaluated 35 pregnancies beginning at 42 weeks. The mean Doppler velocity in the thoracic aorta was observed to decrease with gestational age. Although the mean thoracic velocities from fetuses with a compromised outcome were lower than those obtained from fetuses with a normal outcome, this difference was not statistically significant [12].

-Malcus et al. followed 102 pregnancies with testing beginning at or after 42 weeks. Doppler evaluation included the mean velocity and PI for the descending thoracic aorta. Neither of these Doppler measurements were associated with abnormal outcomes of a non-reactive non-stress test or asphyxia, with the latter defined by an umbilical artery pH less than 7.10 or low Apgar scores [13].

-Kauppinen et al. followed 160 pregnancies beginning at 41 weeks. Aortic measurements included the PI ratio, peak systolic velocity, and volume flow. No differences were noted in any of these Doppler parameters between pregnancies with (n = 135) and without (n = 25) a favorable outcome [14].

23.2.2 Pulmonary Artery Doppler

Three of the above studies on aortic Doppler including both studies by Weiner et al. also evaluated the pulmonary artery [10, 11, 14].

-In the first study by Weiner et al., looking at the percentage change for pulmonary artery parameters of peak systolic velocity and flow volume, neither Doppler parameter was associated with the percentage change in amniotic fluid volume. The percentage change in the flow volume was associated with decreased fetal heart rate variability, whereas the percentage change in peak velocity was not [10].

-In the second larger study, neither Doppler parameter was associated with oligohydramnios, but both were associated with decreased fetal heart rate variability [11].

Combining the data from both studies by Weiner et al., none of the four analyses showed an association between pulmonary Doppler testing and amniotic fluid volume, whereas three of the four showed an association with abnormal fetal heart rate.

-Kauppinen et al. did not find a significant difference in pulmonary artery Doppler testing with PI ratio, peak systolic velocity, or volume flow between patients with and without a favorable outcome [14].

23.2.3 Renal Artery Doppler

Amniotic fluid volume begins to decrease in the mid-third trimester, a trend that continues in postdate pregnancies. Several studies have evaluated renal artery hemodynamics in the late term and in postdate pregnancies in conjunction with amniotic fluid volumes, looking for a potential explanation for the declining fluid volumes.

-Arduini and Rizzo followed 97 pregnancies beginning at 42 weeks. The renal artery PI values obtained from these pregnancies were not statistically different from those from a term reference group. When study patients were classified by amniotic fluid volumes (normal, decreased, oligohydramnios), no significant differences in the renal artery PI values were noted between the groups [15].

--Battaglia et al. evaluated 82 pregnancies beginning at 41 weeks with multi-vessel Doppler testing. Statistical Doppler comparisons were made for patients grouped according to normal or decreased mean thoracic aortic velocity. This outcome parameter was chosen for their analyses because in their data it was associated with cesarean delivery for fetal distress, oligohydramnios, meconium-stained amniotic fluid, and abnormal non-stress tests in individual analyses. No differences in the renal artery PI values were noted between pregnancies with normal vs. decreased mean thoracic aortic velocity [7].

-Bar-Hava et al. began serial renal artery Doppler testing at 41 weeks, studying 57 patients. The renal artery resistance index (RI) for pregnancies with oligohydramnios (AFI < 5 cm) was not significantly different from values obtained in patients with normal fluid [16].

In opposition to these negative studies, others did not find a significant difference in renal artery Doppler velocimetry in association with amniotic fluid volume.

-Veille et al. evaluated 50 pregnancies, with Doppler testing beginning at 40 weeks. A significant negative correlation was obtained between oligohydramnios (AFI ≤5 cm, n = 17) and an increased renal artery systolic-to-diastolic ratio (S/D) [17].

-Oz et al. began Doppler testing at 41 weeks, evaluating 147 pregnancies. The renal artery RI was significantly higher in 21 pregnancies with oligohydramnios, defined as an AFI < 5 cm. A low renal artery end-diastolic velocity also increased the risk of oligohydramnios, although on regression analysis only the renal artery RI was associated with oligohydramnios [18].

-The study by Selam evaluated 38 pregnancies beginning at 41 weeks, 10 of which had oligohydramnios (AFI < 5 cm). The renal artery PI was significantly elevated in these patients in comparison to those with normal fluid volume [19].

23.2.4 Uterine Artery Doppler

The placenta is a vital organ for maintaining ongoing fetal health, providing respiratory, nutritive, and excretory functions to the developing fetus. Placental hemodynamic changes, as a potential marker of placental dysfunction, can be evaluated through Doppler of both the maternal (uterine artery) and fetal (umbilical artery) circulations. Studies on uterine artery Doppler have been uniform in their not finding a significant association with complications in postdate pregnancies.

-Battaglia et al. compared the mean Doppler values in 82 pregnancies, with patients grouped according to the mean thoracic aortic velocity. No differences in the uterine artery RI ratios were noted between these two groups [7].

-Olofsson et al. did not find any difference in the uterine artery PIs in 44 patients delivering after 43 weeks in individual statistical analyses for patients with and without the meconium, asphyxia, oligohydramnios, and fetal distress [9].

-Malcus et al. evaluated 102 pregnancies beginning at 42 weeks. A significant association was not found between the uterine artery PI ratio and asphyxia, which was defined by the parameters of umbilical artery pH, Apgar scores, and operative delivery for fetal distress [13].

-Fischer et al. evaluated 75 pregnancies beginning at 41 weeks, grouping pregnancy outcomes as either normal or abnormal based on a composite of multiple clinical parameters. Uterine artery Doppler testing, with waveform analysis by either the RI or S/D, was not significantly different between the normal and abnormal outcome groups [20].

-Zimmerman et al. followed 153 pregnancies beginning at 41 weeks. Clinical outcomes that were evaluated included Apgar scores, umbilical artery pH, neonatal intensive care unit (NICU) admission with asphyxial encephalopathy, postmaturity syndrome, thick meconium, and operative delivery. No differences in the uterine artery RI were noted between pregnancies with and without abnormal outcomes [21].

-Kauppinen et al. performed uterine artery Doppler testing in patients just prior to scheduled delivery after 41 weeks. No difference in the uterine artery PI was noted between the pregnancies with a normal outcome and those with an abnormal outcome defined by umbilical artery pH, Apgar scores, C-section for fetal distress, and NICU admission [14].

-Brar et al. evaluated uterine artery Doppler testing in 26 pregnancies beginning at 41 weeks. These pregnancies were grouped into those with either reassuring or non-reassuring antenatal testing based on NSTs and fluid volume. No significant difference in the mean uterine artery S/D ratios was noted between these groups [22].

-Weiner et al. followed 142 pregnancies beginning at 41 weeks. No significant difference was noted in the uterine artery RI between the normal and abnormal pregnancy outcome groups, with the abnormal group defined by a composite of multiple clinical parameters [23].

-Forouzan and Cohen followed 30 patients with arcuate artery S/D ratios. Adverse outcomes were defined as abnormal intrapartum fetal heart rate patterns requiring cesarean delivery, umbilical artery acidosis or neonatal diagnosis of intrapartum hypoxia requiring NICU care and were seen in 20% of the study group. The mean arcuate artery S/D ratios were not significantly different between the two groups [24].

-Farmakides et al. obtained uterine S/D ratios in 149 pregnancies beginning at 41 weeks. Abnormal pregnancy outcomes were defined by a composite of morbidities, and statistical analysis was performed separately for Doppler testing conducted at 41, 42, and 43 weeks. The mean S/D ratios for the normal and abnormal outcome groups were not significantly different at any of those gestational ages [25].

The vessels reviewed in the section above have been studied for their potential role in the pathophysiology of postdate pregnancies. Decreased fetal cardiac output can be a measure of hypovolemia or a response to a compromised environment. Positive results could provide insights into why adverse outcomes occur and could potentially be useful for ongoing clinical antenatal surveillance.

Are Doppler abnormalities of the aorta and pulmonary artery involved in the adverse outcomes seen in postdate pregnancies? The studies reviewed above do not show a consistent association with postdate pregnancy pathology. The positive results obtained may be suggestive, but, overall, the data neither exclude nor confirm significant Doppler changes in these vessels, which are detectable in postdate pregnancies with adverse outcomes. It would not be unexpected that renal artery hemodynamic alterations would be involved with the decrease in fluid volume noted in postdate pregnancies. In three of the five studies reviewed above, in which renal Doppler was compared between pregnancies grouped according to fluid volume, a positive association was noted. As with the aortic and pulmonary Doppler studies, these results are not conclusive, and it is not clear whether significant Doppler changes are associated with decreased fluid in postdate pregnancies. Uterine artery Doppler studies are more consistent in their findings; placental hemodynamics, as measured from the maternal circulation, are not associated with adverse postdate pregnancy outcomes.

23.3 Umbilical and Middle Cerebral Artery Doppler

Most of the data available on Doppler in postdate pregnancy involve testing in the umbilical and middle cerebral arteries. Umbilical artery Doppler evaluates placental hemodynamics from the fetal perspective, with increased indices indicative of increased resistance and potentially decreased function. Middle cerebral artery Doppler testing showing decreases in resistance is suggestive of a fetal response to a compromised environment, the so-called brain-sparing effect. Taking advantage of these divergent trends, Doppler velocimetry from both vessels can be paired together as the cerebroplacental ratio or CPR (the middle cerebral artery Doppler index/umbilical artery Doppler index). As Doppler evaluations of these two vessels are often used clinically, and are often evaluated together, the data available on their association with adverse outcomes in postdate pregnancy will be covered together.

When evaluating the appropriateness of any test for clinical use, here, Doppler velocimetry, the issues that need to be addressed include:

1. Are Doppler results consistent from study to study, with an accepted cut-off level separating normal from abnormal?
2. Is there an association between abnormal Doppler testing and adverse pregnancy outcomes?
3. Is Doppler testing a good discriminator (sensitivity and specificity) between normal and abnormal pregnancy outcomes, and how does it compare to the antenatal tests currently in use?
4. Does the use of Doppler testing improve outcomes in postdate pregnancies?

These questions will be addressed below.

1. Are Doppler results consistent from study to study, with accepted cut cut-off levels separating normal from abnormal?
   Physiologically, Doppler indices change throughout pregnancy. All of the standard indices used in waveform analysis (PI, RI, S/D) decrease at the end of pregnancy, beginning prior to or at the midpoint of the third trimester [26, 27]. Although week-to-week changes in Doppler indices are small, normalized Doppler results for specific gestational ages are preferable. Multiple nomograms are available to provide normative Doppler data throughout pregnancy. Two recent review articles with similar authorship have highlighted the problems with the normative Doppler data available [27, 28]. For studies that were spe-

cifically conducted to establish normative Doppler data (38 published studies), a high degree of variability in both methodological quality and reported gestational age-specific 5th and 95th percentile values was noted. Even when the comparisons were limited to those studies with the highest methodological quality, significant variation in the Doppler results remained [28]. When the most frequently referenced nomograms were applied to a cohort of 617 intrauterine growth restriction (IUGR) fetuses, wide ranges in the percentage of abnormal tests were obtained: for the umbilical artery, the range of Doppler values above the 95th percentile in the different studies ranged from 2.1 to 24.5%, whereas the range of Doppler values below the 5th percentile was 0.9–23.1% for the middle cerebral artery and 5.5–33.1% for the CPR [27].

Most normative Doppler data available do not cover late-term or postdate pregnancies. Published normative data in late pregnancies are limited, but similar concerns on consistency have been raised. D'Antonio et al. noted that prior studies had used a wide range of CPR cut-off values in postdate pregnancy evaluation (CPR 0.81–1.3) [29]. Palacio noted a similar wide range in published gestational age-specific Doppler cut-offs for the umbilical and middle cerebral arteries after 40 weeks. Including their own data, the 95th percentiles for the umbilical artery PI ranged from 1.0 to 1.5 at 41 weeks and 0.9 to 1.5 at 42 weeks, whereas the 5th percentile cut-offs for the MCA-PI ranged from 0.70 to 1.98 at 41 weeks and 0.65 to 1.94 at 42 weeks [30]. A large recent study from the Fetal Medicine Foundation, testing nearly 2400 patients at 41 weeks, has found the 95th percentile for the umbilical artery PI to be 1.05 and the 5th percentiles for the MCA-PI and CPR to be 0.89 and 1.0.25, respectively.

2. Is there an association between abnormal Doppler testing and adverse pregnancy outcomes?

Many of the studies that sought to address this question utilized a similar methodology. Doppler testing, usually on a serial basis, was initiated at a specific gestational age, typically at 41 or 42 weeks. For statistical analysis, the pregnancies were divided into normal and abnormal outcome groups as defined by a preselected list of adverse outcomes that typically included non-reassuring fetal testing, delivery for fetal distress, low Apgar scores, abnormal umbilical blood gas values, NICU admission, and meconium. Most studies compared the mean Doppler values between the normal and abnormal pregnancy outcome groups, whereas some studies compared the percentage abnormal Doppler values between the two outcome groups. Patients with underlying risk factors were usually excluded. These studies are summarized below and are listed in Table 23.1. In many of the studies, no significant difference was noted between the adverse and normal outcome groups.

- Gupta et al. followed 31 pregnancies with biweekly umbilical and middle cerebral artery Doppler testing beginning at 40 weeks. Umbilical artery waveforms were evaluated by S/D ratios, whereas middle cerebral artery waveforms were evaluated by PI ratios. A CPR was also calculated (apparently from the MCA-PI and umbilical artery S/D). Adverse outcomes were noted in 16% of the study population. No significant differences were noted in any of the mean Doppler indices between the abnormal and normal groups [31].
- Guidetti et al. followed 46 pregnancies with umbilical artery S/D ratios starting at 42 weeks. Abnormal outcomes were noted in 42%. No statistically significant difference was noted in the mean umbilical artery S/D ratios between the outcome groups [32].
- Stokes et al. followed 70 pregnancies with umbilical S/D ratios starting at 41 weeks. Abnormal clinical outcomes were seen in 31%. No significant difference in the mean

Table 23.1 Studies comparing the mean Doppler results between pregnancies with normal and adverse outcomes, where an adverse outcome was defined by a composite of outcome measures (unless stated, statistical). Comparisons were made between the mean Doppler values

First author	N GA % abn	Umbilical artery	Middle cerebral artery	CPR
Gupta [31]	31 40 16%	No association S/D	No association PI	No association CPR-PI
Guidetti [32]	46 42W 43%	No association S/D		
Olofsson [9]	44 43W 36%	+ Association PI *PI lower in abn group		
Stokes [33]	70 41W 31%	No association S/D		
Malcus [13]	101 42W 26%	No association PI		
Lebovitz [34]	120 40W 17.5%	No association RI, S/D or PI	No association RI or PI	No association PI
Forouzan [24]	30 41W 20%	No association S/D		
Farmakides [25]	149 41W	No association S/D		
Weiner	142 41W 8.5%	No association RI		
Kauppinen [14]	160 41W 16%	No association PI	No association PI	No association CPR
Rightmire [12]	32 42W 25%	+ Association RI		
Fischer [20]	75 41W 28%	+ Association SD and RI		
Devine [35]	49 41W 20%	No association S/D	Association S/D	+ Association S/D
Maged [36]	100 40W 44%	+ Association PI	Association PI	+ Association PI
Brar [22]	45/ 41W 42%	No association mean S/D and % abnormal S/D	Association S/D	+ Association both mean S/D and % S/D <1 (CPR = internal carotid S/D/ UmbA S/D)
D'Antonio [29]	328 41+W 18%	No association PI	No association PI	No association mean PI, % PI <0.98 or % PI <0.90

Column 2: *N*: number of patients, GA: gestational age at start of Doppler testing, Abn: % of patients with adverse clinical outcomes
Boxes in the table are blank if those Doppler parameters were not evaluated
RI Resistance index, *PI* pulsatility index, *CPR* Cerebroplacental ratio

S/D ratios was detected between the normal and adverse outcome groups [33].

- Malcus et al. followed 101 pregnancies beginning at 42 weeks. Serial umbilical artery waveforms were evaluated by PI ratios, with abnormal outcomes noted in 26%. No difference in the mean PI ratio was noted between the outcome groups [13].
- Lebovitz et al. followed120 pregnancies with an abnormal outcome rate of 17.5%. Both PI and RI ratios were obtained from the umbilical and middle cerebral arteries, with testing beginning at 40 weeks. There were no differences in any of the Doppler parameters studied between the normal and abnormal outcome groups [34].
- Weiner et al. followed 142 pregnancies with serial umbilical artery RI testing beginning at 41 weeks. In 8.5%, an abnormal outcome was obtained. In addition to calculating the mean RI ratios for the normal and abnormal outcome groups, the percentage of cases with an RI ratio above the 95th percentile was also calculated. No significant differences were noted between the groups for either method of Doppler evaluation [23].
- Kauppinen et al. followed 160 women with an abnormal outcome rate of 16%. Doppler testing was limited to a single measurement of umbilical and middle cerebral artery PI ratios that was obtained just prior to elective induction after 41 weeks. No differences were noted between the normal and abnormal groups for either mean PI values for umbilical or middle cerebral arteries or in the calculated CPR [14].
- -Farmakides et al. obtained umbilical S/D ratios in 149 pregnancies beginning at 41 weeks. Abnormal pregnancy outcomes were defined by a composite of morbidities, and abnormal statistical analysis was performed separately for testing conducted at 41, 42, and 43 weeks. The mean S/D ratios for the normal and abnormal outcome groups were evaluated separately for Doppler testing conducted at 41, 42, and 43 weeks, and none of the analyses showed a significant difference [25].

Although all the above studies failed to detect a significant difference in Doppler testing between the normal and abnormal pregnancy outcome groups, several studies utilizing the same format did find significant differences.

-Rightmire and Campbell followed 32 patients with serial umbilical artery Doppler testing beginning at 42 weeks. A “less-than-acceptable outcome” was noted in 25%. The mean umbilical artery RI was higher in the adverse outcome group when compared to that seen in the normal outcome group [12].

-Fischer et al. followed 75 pregnancies with twice-a-week umbilical artery Doppler testing. Both S/D and RI ratios were obtained beginning at 41 weeks. Abnormal outcomes were noted in 28. The differences in the mean Doppler indices between the two groups were small but statistically significant with higher indices in the abnormal group [20].

-Devine et al. followed 49 women with serial S/D ratios of the umbilical and middle cerebral arteries beginning at 41 weeks. An abnormal pregnancy outcome was noted in 20%. Although the umbilical artery S/D ratio was not different between the two groups, the MCA S/D ratio and the CPR were significantly lower in the adverse outcome group. It should be noted that this study was unusual, in that patients with underlying high risk factors were not excluded and made up one-third of the overall study group. A higher prevalence of chronic hypertension was present in the adverse outcome group [35].

-Maged et al. followed 100 pregnancies with serial umbilical and middle cerebral artery PI ratios beginning at 40 weeks. A total of 44% of the group had an abnormal outcome. Significant differences were noted in both umbilical and middle cerebral artery PI ratios and the calculated CPR between the normal and abnormal groups. Of the three parameters, the CPR was the best to discriminate between the normal and abnormal groups [36].

-Olofsson et al. began serial Doppler testing at 42 weeks with umbilical artery PI levels. Analyses were conducted on 44 patients who delivered after 43 weeks. Adverse outcomes were noted in 16 of the patients. Although a significant difference in the Doppler testing was noted between patients with and without adverse outcomes, it was the adverse outcome group that had lower umbilical artery PIs. In separate analyses for individual adverse outcomes, significant differences were noted between patients delivering with and without the meconium and fetal distress but not oligohydramnios or asphyxia. Again, lower umbilical artery PIs were noted in association with adverse outcomes. The reason for the finding of lower umbilical artery PIs in association with adverse outcomes was unknown, and the authors hypothesized the possibility of placental vasodilation in response to fetal hypoxia [9].

A similar methodology of comparing the Doppler values between normal and abnormal pregnancy outcomes, but with a more limited list of abnormal outcomes, was utilized in the following studies:

-Brar et al. followed 45 patients beginning at 41 weeks, with the criteria for abnormal pregnancy outcomes limited to non-reassuring fetal heart rate testing and low amniotic fluid volume. These abnormalities were noted in 42% of the study population. Along with umbilical artery testing, the internal carotid artery was also evaluated as a measure of lowered intracranial resistance/brain-sparing effect. Both the mean and percentage abnormal Doppler values were evaluated, with abnormal S/D cut-offs being set at 3.0 for the umbilical artery and at 1.0 for the CPR calculated from the internal carotid artery–umbilical artery ratios. No differences in either the mean or percentage abnormal umbilical artery Doppler indices were noted between the normal and abnormal outcome groups. Distinct from the negative umbilical artery results, both internal carotid artery S/D ratios and the calculated CPR were significantly different, with mean values for both being significantly lower in the abnormal outcome group. In addition, using a CPR cut-off <1.0, the percentage of the abnormal CPR ratios was significantly higher in the adverse outcome group [22].

-D'Antonio et al. followed 320 women with serial testing beginning at 41 weeks. Adverse outcomes included only abnormal umbilical artery blood gas at delivery or operative intervention for non-reassuring ST segment analysis in labor. One or both abnormal outcomes were seen in 18% of the study population. Doppler calculations included umbilical and middle cerebral artery PI ratios and a calculated CPR. No significant difference between the outcome groups was noted. The percentage of abnormal CPR ratios was also calculated for each outcome group. Two different cut-off values were used for this calculation: 0.9, which was the 5th percentile from a published nomogram K, and 0.98, which was the 5th percentile for this study. The percentage of abnormal cases was not statistically significant between the two study groups. A power analysis showed that this study was significantly underpowered to determine whether the detected differences were significant [29].

-Forouzan and Cohen followed 30 patients with umbilical artery S/D ratios beginning at 41 weeks. Adverse outcomes were defined as abnormal intrapartum fetal heart rate patterns requiring cesarean delivery, umbilical artery acidosis, or neonatal diagnosis of intrapartum hypoxia requiring NICU care and were seen in 20% of the study group. The mean umbilical artery S/D ratios were not significantly different between the two groups [24].

The above studies compared Doppler testing between pregnancies classified as normal or abnormal based on a composite of clinical findings. Different approaches were used in other studies to evaluate the association between Doppler testing and adverse pregnancy outcomes in postdate pregnancies. These studies are summarized below and are listed in Table 23.2.

-Zimmerman et al. followed 153 pregnancies with serial middle cerebral and umbilical artery RI testing beginning at 41 weeks. Pregnancy outcomes were divided into asphyxial and non-asphyxial complications, which were noted in 25 and 20%, respectively. Statistical analysis involved comparing the range of RI ratios obtained from both abnormal groups with the range of values obtained from pregnancies with normal outcomes. Two normal outcome groups were used: the normal outcome group from this

Table 23.2 Studies evaluating Doppler velocimetry in postdate pregnancies by methods other than comparison of Doppler values within normal and adverse pregnancy outcome groups, where an adverse outcome was defined by a composite of morbidities

First author	N GA	Clinical outcomes (% adverse outcomes)	Umbilical artery	Middle cerebral artery	CPR
Lam [37]	118 40w	Evaluation of individual outcomes of a thick meconium (22%), SGA (8.3%) and AFI < 3 Doppler testing categorized as <10th, >10th–<90th and >90th	<u>+ Association PI >0.97 (90%)</u> – SGA <u>No association PI >0.97 (90%)</u> – Low AFI – Thick meconium	<u>+ Association PI <0.84 (10%)</u> – Thick meconium <u>No association PI <0.84 (10%)</u> – SGA – Low AFI	<u>+ Association PI < 1.09 (10%)</u> – SGA <u>No association PI < 1.09 (10%)</u> – Low AFI – Thick meconium
Selam [19]	38 41w	AFI < 5 cm (26%)	No association mean PI	+ Association mean PI	+ Association mean PI
Bar-Hava [16]	57 41w	AFI < 5 (26%)	No association mean RI	No association mean RI	No association mean RI
Veille [17]	50 40w	AFI < 5 (34%)	No association mean S/D		
Battaglia [7]	82 41w	Patients grouped by normal or decreased peak fetal thoracic aorta velocities (28%)	No association mean RI	No association mean RI	
Anteby [8]	78 41w	Evaluation of individual outcomes of moderate-to-thick meconium (21%), moderate/severe persistent intrapartum heart rate abnormalities (42%), and operative delivery for fetal heart rate abnormalities (19%)	<u>+ Association S/D</u> – Operative delivery <u>No association PI</u> – Operative delivery – Meconium – FHR abnormalities <u>No association S/D</u> – Meconium – FHR abnormalities	<u>+ Association PI</u> – FHR abnormalities <u>No association S/D</u> – FHR abnormalities – Meconium – Operative delivery <u>No association PI</u> – Meconium – Operative delivery	<u>+ Association (not specified if S/D or PI)</u> – Operative delivery <u>No association (not specified if S/D or PI)</u> – Meconium – FHR abnormalities
Pearce [38]	534 42w	Cohen kappa statistic for absent/reverse end-diastolic flow in the umbilical artery and fetal distress in the first stage of labor (2.1%)	+ Association		

Zimmerman [21]	153 41w	Asphyxial (25%) and non-asphyxial (20%) complications	<u>No association RI</u> All Doppler ratios from both abnormal outcome groups within the 5th–95th percentiles from the normal group	<u>No association RI</u> All Doppler ratios from both abnormal outcome groups within the 5th–95th percentiles from the normal group	
Olofsson [9]	34 42w	Evaluation of individual outcomes of oligohydramnios, fetal distress, asphyxia, and meconium (overall 36% with adverse clinical outcomes)	<u>No association PI</u> – Oligohydramnios – Asphyxia <u>+ Association PI</u> – Meconium – Fetal distress (PI lower with these abnormal outcomes)		
Figueras [39]	56 41w	Stepwise linear regression with Doppler indices and umbilical artery blood gas values at birth	<u>No association PI</u> – Umbilical artery blood gas results	<u>+ Association PI</u> – Proximal MCA with umbilical artery pO_2 – Distal umbilical artery PI with umbilical artery pH	<u>No association PI</u> – Umbilical artery blood gas results
Ropacka-Lesiak [40]	148/ 40w	Patients grouped by normal/abnormal Doppler results evaluated for clinical outcomes of emergency cesarean section (15.5%), abnormal fetal heart rate patterns (39%), and adverse neonatal outcomes (27%)	Abnormal cut-off values and statistical significance for RI and PI not specified Likelihood ratios for adverse neonatal outcomes and abnormal fetal heart rate patterns, 2.3–3.1	Abnormal cut-off values and statistical significance for RI and PI not specified Likelihood ratios for abnormal fetal heart rate patterns and adverse neonatal outcomes, 1.3–2.6	+ Association – CPR-RI < 1.1 associated with a variety wide variety of adverse outcomes, emergency cesarean section, abnormal fetal heart rate pattern, IUGR, umbilical cord blood gas analysis, and adverse neonatal outcomes

Column 2: *N*: study size, GA: gestational age at start of Doppler testing. Blank spaces indicate that the Doppler parameters were not evaluated
PI pulsatility index, *RI* resistance index, *CPR* cerebroplacental ratio

study and a separate term reference group. All of the Doppler RI values from both the asphyxial and non-asphyxial complications fell within the 5th–95th percentiles for both normal outcome groups [21].

-Battaglia et al. chose fetal thoracic aortic velocities for their outcome measure instead of specific clinical morbidities. This parameter was chosen as it was the only ultrasound parameter that was associated with clinical outcome, with abnormal velocities being seen in 29% of the study group. Serial Doppler testing was conducted in 82 patients with umbilical artery RI and middle cerebral artery PI values beginning at 41 weeks. No significant difference was noted for either umbilical or middle cerebral artery Doppler indices between the normal and abnormal thoracic aortic velocity groups [7].

-Anteby et al. analyzed Doppler results for individual outcome parameters rather than a composite abnormal outcome group. Serial umbilical and middle cerebral artery Doppler testing was conducted on 78 pregnancies starting at 41 weeks, with statistical evaluation performed on 3 outcome measures: moderate-to-thick meconium (21%), moderate-to-severe persistent intrapartum heart rate abnormalities (42%) and heart rate abnormalities requiring operative delivery (9%). The mean Doppler indices (umbilical artery S/D and PI, middle cerebral artery S/D and PI, CPR S/D and PI) and the mean S/D and PI ratios for both the umbilical and middle cerebral arteries were compared with the presence or absence of each of the three outcome measures individually. Of these 12 analyses, the only statistically significant differences found were for the mean umbilical artery S/D ratios for the presence or absence of intervention for abnormal fetal heart rates and for the mean MCA-PI for the presence or absence of abnormal fetal heart rate patterns. Separate from the statistical analysis involving the individual fetal heart rate, the mean CPR was associated with the intervention for fetal heart rate abnormalities. Not stated in the study, but presumed by its absence, is that the CPR was not associated with the other two outcome measures. It was also not stated whether this significant association was for the CPR-S/D, CPR-PI, or both [8].

-Lam et al. analyzed individual outcome measures with umbilical and middle cerebral artery Doppler testing that were classified as ≤10th, 10th–90th, and > 90th. The pregnancy outcomes evaluated included the presence or absence of a thick meconium (22%), AFI ≤ 3 cm and small for gestational age (SGA) (8.3%). Pregnancies with an umbilical artery PI above the 90th percentile were associated with the presence of a thick meconium and SGA fetus. Pregnancies with the middle cerebral artery PI below the 10th percentile were associated only with a thick meconium, whereas the CPR ratio below the 10th percentile was associated only with SGA [37].

-In a large study, Pearce and McParland evaluated umbilical artery Doppler testing with fetal distress in labor. Serial testing was conducted in 534 pregnancies beginning at 42 weeks. A Cohen kappa statistic was calculated from sensitivity and predictive values. Absent end-diastolic umbilical artery flow was associated with fetal distress in the first stage of labor, with a value of 0.91 (values above 0.8 are consistent with a strong correlation). Although specific data were not provided, the addition of umbilical artery Doppler results where end-diastolic flow was present did not improve the evaluation. It should be noted that both absent end-diastolic flow and fetal distress in the first stage of labor were infrequent at 2.1% each [38].

- Figueras et al. performed stepwise linear regression for Doppler indices with umbilical artery blood gas testing at birth. The Doppler indices evaluated included separate PI ratios for the proximal and distal segments of the middle cerebral artery, the umbilical artery PI, and a calculated CPR. Doppler testing began at 41 weeks, and 56 patients that were delivered within 48 hours of their final Doppler evaluation were analyzed. Significant correlations were only noted for the proximal MCA and umbilical artery pO_2 and a weak correlation for the distal MCA and umbilical artery pH [39].

-Ropacka-Lesiak et al. analyzed pregnancy outcomes in patients grouped by Doppler results rather than by pregnancy outcomes. A total of 144 women had umbilical and middle cerebral artery Doppler PI and RI testing conducted between 40 and 42 weeks. Although listed as a low-risk group, 47% of the pregnancy showed a brain-sparing effect, defined as a CPR-RI <1.1. The brain-sparing group showed a significantly worse outcome in a wide variety of clinical parameters including abnormal fetal heart rate patterns (62.3% versus 19.0%), emergency cesarean sections (24.6% versus 7.6%), lower birth weight and Apgar scores and worse umbilical artery blood gas testing. The clinical outcome for pregnancies grouped by the individual umbilical and middle cerebral artery values rather than the CPR was not provided [40].

-Studies by Selam, Veille et al., and Bar-Hava et al. limited their statistical evaluation to a single outcome: amniotic fluid volume [16, 17, 19]. Oligohydramnios (AFI < 5) was found in 26%, 34%, and 26% of the pregnancies studied, respectively. In each study, the frequency of low fluid volume was 26%. The mean umbilical artery indices between normal and oligohydramnios pregnancies were not significantly different in any of the three studies. In the study by Selam, the MCA Doppler indices and calculated CPR were significantly lower in the oligohydramnios group, a finding that was not found by Bar-Hava et al. and not studied by Veille et al.

3. Is Doppler testing a good discriminator between normal and abnormal pregnancy outcomes (sensitivity/specificity), and how does it compare to the antenatal tests currently in use? Most of the studies reviewed above compare the results of Doppler testing between pregnancies with normal and abnormal outcomes. Although useful in evaluating the association between Doppler testing and clinical outcome, this type of analysis does not provide information on the ability of Doppler testing to discriminate between normal and abnormal outcomes. Sensitivity and specificity calculations are provided in some of the studies and, when available, are summarized in Table 23.3. Included in this table is information from the study by El-Sokkary et al. [41] Umbilical and middle cerebral artery Doppler testing was conducted in 100 hospitalized patients, finding a significant difference between all Doppler indices that did and did not need NICU admission. This study was not reviewed in the above sections as half of the pregnancies were evaluated prior to 40 weeks and a separate analysis was not provided for the 50 patients tested at 41 weeks. Sensitivity and specificity calculations were provided for the patients tested at 41 weeks and are included in Table 23.3.

The studies summarized in Table 23.3 show significant variability in their sensitivities and specificities for adverse outcomes. Combining the studies, Doppler evaluations for the umbilical and middle cerebral arteries and the calculated CPR all have similar averaged specificities of approximately 75%. Averaged sensitivities for the umbilical and middle cerebral arteries are just under 50%, whereas the sensitivity for the CPR is higher at approximately 75%. Although it has been suggested that the calculated CPR may be the best Doppler index for risk assessment, comparative evaluations should be made cautiously. These studies utilize varying methodologies in terms of the various aspects of Doppler testing and evaluation and differ in terms of which pregnancy outcomes were evaluated. Most of the studies in this table found a positive association between Doppler testing and adverse pregnancy outcomes. Studies in which no such association was found are less likely to provide sensitivity and specificity information, and thus they are underrepresented in this table. The low likelihood ratios in most of the studies suggest that the predicted increase in abnormal outcomes with abnormal Doppler testing is at best a modest one.

In six of the studies, listed in bold type at the bottom of Table 23.3, sensitivity and specificity calculations were also provided for currently used clinical antenatal tests (BPP, NST, fluid volume). In two of these studies, information for CPR is provided, showing a higher likelihood ratio than both other Doppler indi-

Table 23.3 Predictive ability of Doppler and standard antenatal testing (BPP, fluid volume, and NST in bold) for evaluating adverse pregnancy outcomes

Study	Test	Cut-off	Outcome measure	Sensitivity (%)	Specificity (%)	Likelihood ratio
Anteby [8]	UA-S/D	2.5	Intervention for fetal distress	60	71	2.1
		2.4		80	55	1.8
		2.3		93	48	1.8
Lam [37]	MCA	10th percentile	Thick meconium	34	94	5.7
Ropaka-Lesiak [40]	CPR-RI	1.1	Abnormal FHR in labor	74.1	71.1	2.6
	MCA-RI	Not stated		12.0	91.1	1.3
	MCA-PI	Not stated		56.9	77.8	2.6
	UA-RI	Not stated		32.8	87.8	2.7
	UA-PI	Not stated		27.6	91.1	3.1
Ropaka-Lesiak [40]	CPR-(RI)	1.1	Adverse neonatal outcome	87.8	68.5	2.8
	MCA-RI	Not stated		17.5	92.6	2.3
	MCA-PI	Not stated		65.0	75.0	2.6
	UA-RI	Not stated		40.0	87.0	3.1
	UA-PI	Not stated		27.5	88.0	2.3
El-Sokkary [41]	UA-S/D	2.57	NICU admission	56	45	1.0
	UA-RI	0.62		50	92	6.3
	UA-PI	0.93		40	16	0.5
	MCA-S/D	2.45		48	60	1.2
	MCA-RI	0.67		40	39	0.7
	MCA-PI	0.94		50	40	0.8
	CPR-RI	0.85		80	72	2.9
Gupta [31]	CPR	1.1	Multiple clinical parameters	40	77	1.7
		1.3		80	54	1.7
Forouzan [24]	UA-S/D	3.12	Multiple clinical parameters	83.3	87.5	6.7
Fischer [20]	UA-S/D	2.4	Multiple clinical parameters	57	78	2.6
	NST/AFV	**MVP <2 cm**		**19**	**85**	**1.3**
Pearce [38]	UA	AEDF	Fetal distress in the first stage of labor	91	100	–
	NST	**MVP<3 cm**		**55**	**98**	**27.5**
	AFV			**82**	**99**	**82.0**

Weiner [23]	UA-RI **AFV** **NST**	0.68 **Not stated non-reactive, recurrent FHR decelerations**	Multiple clinical parameters	17 **25** **8**	96 **94** **95**	4.3 **6.3** **1.6**
Zimmerman [21]	UA-RI UA-RI **AFV** **NST/CST**	0.62 0.58 **MVP < 2**	Asphyxial complications	37 53 **16** **8**	75 55 **95** **96**	1.5 1.2 **3.2** **2.0**
Devine [35]	CPR-S/D **AFV** **BPP** **NST**	1.059**AFI < 5 cm** **<6** **Non-reactive**	Multiple clinical parameters	80 **20** **30** **40**	95 **97** **92** **90**	16.0 **6.7** **3.0** **4.0**
Maged [36]	UA-PI MCA-PI CPR-PI **AFV** **BPP**	0.82 1 1.05 **MVP < 2 cm** **≤4**	Multiple clinical parameters	68.2 77.3 75.0 **77.7** **63.6**	76.8 87.5 98.2 **91.1** **89.3**	2.9 6.2 41.7 **8.7** **5.9**

ces and standard antenatal tests [35, 36]. It should be noted that the CPR likelihood ratios in these two studies are higher than those obtained by other studies listed in this table, and, given the limited number of studies evaluated, caution is advised when making comparative evaluations.

4. Does the use of Doppler testing improve outcomes in postdate pregnancies?
   No studies were identified that directly evaluate whether Doppler testing when used clinically in postdate pregnancies improves the clinical outcomes.

23.4 Conclusions

In this chapter, we have reviewed the data on Doppler testing in postdate pregnancies. The one remaining issue to be discussed is should Doppler testing be recommended for clinical evaluation of these pregnancies? Doppler testing is an attractive option for a variety of reasons. In postdate pregnancies, the risk of fetal and neonatal morbidity and mortality is increased. Doppler velocimetry can evaluate two separate aspects of pregnancy health: hemodynamic changes within the placenta as a measure of placental function and fetal hemodynamic alterations as a measure of fetal response to its environment and possible compromised health. The negative consequences of a false-positive test, likely the induction of labor, are limited. Neonatal sequelae of prematurity are obviously not an issue at this gestational age. A 2018 Cochrane Database Review analyzed 30 randomized trials (12,479 pregnancies) that compared routine induction of labor with expectant management for pregnancies at or beyond term. Induction of labor was associated with a decrease in perinatal deaths (relative risk (RR) 0.33), stillbirths (RR 0.33), cesarean section rate (RR 0.92), NICU admission (RR 0.88), and 5-min Apgar less than 7 (RR 0.7). Operative vaginal delivery was increased (RR 1.07) with elective induction [42].

Concerns with the use of Doppler for evaluating postdate pregnancies span a wide range of issues involved with this testing. Starting with the normative Doppler data, prior studies have not provided consistent results, with significant differences noted between studies on normal values. Uniformly accepted cut-off levels are not available. Using the different cut-off levels that are currently available results in a wide range of the percentage of pregnancies that are classified as abnormal. It is also not clear whether there is an association between Doppler testing and adverse pregnancy outcomes. The studies available and the literature utilize a wide range of methodologies, with differences in the initiation and frequency of Doppler testing, which Doppler indices are evaluated, what cut-off values were used for identifying abnormal results, and which pregnancy morbidities were evaluated. As noted in Tables 23.1 and 23.2, an association between Doppler testing and adverse pregnancy outcomes has not been consistently shown; most of the studies did not find a positive association. Finally, studies showing that the use of Doppler on a clinical basis in postdate pregnancies improves outcomes have not been conducted. For these reasons, we cannot recommend the use of Doppler testing in the evaluation of postdate pregnancies. Although there certainly is room for an adequately powered well-designed randomized study to evaluate this issue directly, the prospects of successfully completing such a study is uncertain given evidence suggesting consideration for induction instead of expectant management [42, 43].

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