Patterns of Change in Uterine Artery Doppler Studies Between 20 and 24 Weeks of Gestation and Pregnancy Outcomes

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OBJECTIVES: To describe changes in mean uterine artery resistance index and bilateral notches between 20 and 24 weeks of gestation in healthy nulliparous women and to relate these changes to pregnancy outcome.

METHODS: A total of 2,189 nulliparous participants in the Screening for Pregnancy Endpoints study had pregnancy outcomes compared between four uterine artery Doppler groups: normal at 20 and 24 weeks of gestation (group 1), normal at 20 weeks and abnormal at 24 weeks (group 2), abnormal at 20 weeks and normal at 24 weeks (group 3), and abnormal at both 20 and 24 weeks (group 4). Abnormal uterine Doppler was defined as 1) mean resistance index greater than the 90th centile; 2) bilateral notches; and 3) a combination of 1, 2, or both. The main outcomes were preeclampsia and small for gestational age (SGA) neonates (less than the 10th customized centile).

RESULTS: Preeclampsia developed in 116 (5.3%) women, and 223 (10.2%) delivered SGA neonates. With abnormal Doppler defined as mean resistance index greater than the 90th centile, the rate of SGA increased across Doppler groups: group 1, 156 (8.4%); group 2, 13 (11%); group 3, 25 (19.5%); and group 4, 29 (35.4%) ($P<.001$). The rate of SGA was higher in group 3 compared with group 1. Preeclampsia differed among groups 1 (85 [4.6%]), 2 (9 [7.6%], 3 (7 [5.5%]), and 4 (15 [18.3%]) ($P<.001$).

CONCLUSION: Pregnancy outcomes in women with abnormal uterine artery Doppler results at either 20 or 24 weeks were intermediate between those with normal or abnormal results at both time points. If overall test performance could be enhanced by the addition of clinical data, biomarkers, or both, we would recommend that 20 weeks is the most appropriate gestation in the second trimester to perform uterine artery Doppler studies. *(Obstet Gynecol 2009;113:332–8)*

LEVEL OF EVIDENCE: II

A large number of studies have investigated the potential of second-trimester uterine artery Doppler studies as a screening tool for preeclampsia and fetal growth restriction.[1–3] Currently, there is no consensus as to what should be the optimum timing for uterine artery Doppler screening if it is performed during the second trimester. High rates of false-positive test results at 20 weeks have led some to delay screening until 23–24 weeks.[4–6] Although screening at 23–24 weeks will detect those with persistent abnormalities or those who develop an abnormal Doppler after 20 weeks, it will fail to detect women who had an abnormal Doppler at 20 weeks but underwent late normalization of the Doppler waveform. Another drawback of performing the uterine Doppler at 24 weeks is that this gestation is too late for interventions to reduce the risk of the most severe cases of preeclampsia.[7,8]

Given these limitations, others have recommended two-stage screening to allow earlier intervention and to overcome the problem of false-positive

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results at 20 weeks.[9,10] Two-stage screening assumes a normal result will be sustained, with the second Doppler study at 24 weeks performed only if the first was abnormal.[9,11,12] This approach will detect both those women with persistent abnormalities and those with late normalization, which has been associated with lower birth weight and increased rates of small for gestational age (SGA) neonates.[11,12] However two-stage screening will fail to detect women with normal uterine Doppler results at 20 weeks who develop abnormal Doppler results by 24 weeks. There are no large, longitudinal studies reporting the clinical importance of the four different patterns of change in uterine artery Doppler waveforms measured at both 20 and 24 weeks (normal at both gestations, normal to abnormal, abnormal to normal, and abnormal at both times). Moreover, no Doppler studies to date have classified SGA using customized centiles, which better identify growth-restricted fetuses with morbidity than do population centiles.[13–15]

We hypothesized that rates of SGA neonates and preeclampsia would increase among women with normal uterine artery Doppler results at 20 and 24 weeks, abnormal Doppler at either time point, and those with abnormal Doppler at both time points. The aims of our study were to describe changes in mean uterine artery resistance index and bilateral notches between 20 and 24 weeks of gestation in healthy nulliparous women and to relate these changes to pregnancy outcome.

METHODS

Nulliparous women with singleton pregnancies were recruited to the Screening for Pregnancy Endpoints study between November 2004 and July 2007 in Auckland, New Zealand, and Adelaide, Australia. The Screening for Pregnancy Endpoints study is an international, multicenter, prospective cohort study for the prediction of preeclampsia, fetal growth restriction, and preterm birth. Ethical approval was gained from local ethics committee (New Zealand: study number AKX/02/00/364, Australia: study number REC 1712/5/2008). Exclusion criteria were underlying medical conditions or gynecological history known to be associated with high risk for preeclampsia, SGA, or spontaneous preterm birth, or on treatment that might modify pregnancy outcome. The Screening for Pregnancy Endpoints study participants were interviewed by a research midwife at 15 and 20 weeks of gestation. Ultrasound examinations were performed at 20 weeks of gestation, including fetal anatomy assessment, fetal growth and cervical length measurements, and Doppler studies of the uterine and umbilical arteries. Women then were invited to return for an additional scan at 24 weeks, when fetal measurements and uterine and umbilical Doppler studies were repeated. Participants were followed, and pregnancy outcome data and neonatal measurements were collected by research midwives, usually within 72 hours of birth. Women were included in the current study if uterine artery Doppler data at both 20 and 24 weeks were available and outcome data were known.

Ultrasound examinations were performed in clinical practice by sonographers with Diplomas in Medical Ultrasound from the Australasian Society of Ultrasound in Medicine, in accordance with a standard operating procedures manual. Scans were performed with women in a semirecumbent position. Left and right uterine arteries were examined by placing the transducer 2–3 cm medial to the anterior superior iliac spine directed toward the lateral wall of the uterus and downward toward the pelvis on each side. Color flow pulsed Doppler was used to visualize the uterine artery at the point of apparent crossover with the external iliac artery. The sample volume was placed 1 cm distal to the apparent point of crossover before any branching of the uterine arteries. The angle of insonation was maintained as low as possible and always less than 50°. A minimum of five waveforms was recorded. In-built software calculated the resistance index, and the presence of notches was determined and recorded by the sonographer (present, absent, indeterminate). For analysis, the mean resistance index of the left and right uterine arteries was used. If a notch was reported as indeterminate, it was considered absent. Neither uterine nor umbilical Doppler results were to be reported to the providers of obstetric care unless there was absent end diastolic velocity in the umbilical artery at 24 weeks.

The primary outcome measures were preeclampsia, SGA, preeclampsia or SGA or both with delivery at less than 34 weeks of gestation, and uncomplicated pregnancy. Secondary outcome measures included preeclampsia with an SGA neonate, SGA by population centiles, placental abruption, gestational age at delivery, birth weight, and birth weight centile.

The estimated date of delivery was calculated from a certain last menstrual period (LMP) date. The estimated date of delivery was adjusted only if 1) a scan performed at less than 16 weeks of gestation found a difference of 7 or more days between the scan gestation and that calculated by LMP, or 2) after the 20 week scan was performed, a difference of 10 or more days was found between the scan gestation and that calculated by LMP. If the LMP date was uncertain, scan dates were used to calculate the estimated date of delivery. Small for gestational age was defined as a birth weight less than the 10th centile using customized

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birth weight centiles.[15] Preeclampsia was defined as a systolic blood pressure of 140 mm Hg or higher, a diastolic blood pressure of 90 mm Hg or higher, or both on at least two occasions 4 hours apart after 20 weeks of gestation but before the onset of labor, or, in the postnatal period, either proteinuria 300 mg/24 h or higher, spot urine protein:creatinine ratio 30 mg/mmol or higher, or urine dipstick ++ or higher or evidence of multisystem complications.[16] Uncomplicated pregnancy was defined as all pregnancies without preeclampsia, gestational hypertension, SGA, preterm birth, congenital anomaly, other obstetric complications such as placenta praevia or ante partum hemorrhage, or medical complications such as obstetric cholestasis. To enable comparison with prior literature, SGA by population centiles (birth weight less than the 10th centile adjusted only for sex of the neonate) has been included as a secondary endpoint.[17] Placental abruption was defined as vaginal bleeding with uterine tenderness, fetal compromise, or both or evidence of a retroplacental clot seen at delivery or on ultrasound examination. All data were collected in a central Internet-based database with a U.S. Food and Drug Administration-compliant audit trail. All data have undergone stringent monitoring by checking each individual's data and using a customized software program to detect any further data-entry errors. When suspected data-entry errors were identified by either method of data checking, an electronic query was raised about the data point, which then was answered by the research midwife.

Pregnancy outcomes were compared according to uterine artery Doppler results. Abnormal uterine Doppler results were defined as 1) mean resistance index higher than the 90th centile, 2) presence of bilateral notches, and 3) mean resistance index higher than the 90th centile, presence of bilateral notches, or both. For each criterion of abnormal Doppler results, four groups were compared: normal Doppler results at 20 weeks and 24 weeks (group 1), normal Doppler at 20 weeks and abnormal at 24 weeks (group 2), abnormal Doppler at 20 weeks and normal at 24 weeks (group 3), and abnormal Doppler at both 20 and 24 weeks (group 4) (Table 1).

All statistical tests were performed using SAS 9.1 (SAS Institute, Inc., Cary, NC). For main outcome variables, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by fitting a univariable logistic regression model with normal-normal (group 1) as the referent group. Categorical data were compared using χ^2 or Fisher exact test as appropriate. Continuous variables were compared using analysis of variance with post hoc Tukey test for pair-wise comparisons. $P<.05$ was considered significant. Complete data were available for all variables used in the above analyses, and no data were imputed.

Table 1. Uterine Artery Doppler Groups

Group	Characteristic
1	Normal at 20 and 24 wk of gestation
2	Normal at 20 wk of gestation and abnormal at 24 wk
3	Abnormal at 20 wk of gestation and normal at 24 wk
4	Abnormal at both 20 and 24 wk of gestation

RESULTS

Of 2,535 women recruited to the Screening for Pregnancy Endpoints study in Auckland and Adelaide, 2,189 were included in this study (Fig. 1). Women excluded from the study because they did not have a 24-week scan were less likely to be white than those who participated, but the rates of preeclampsia and SGA did not differ. Demographic and pregnancy outcome data for the study population are presented in Table 2. Mean gestational age at the first Screening for Pregnancy Endpoints study scan (20-week scan) was 20.0 (standard deviation [SD] 0.7) weeks and at the second Screening for Pregnancy Endpoints study scan (24-week scan) was 24.3 (SD 0.6) weeks.

Resistance index values reduced between 20 and 24 weeks for the study population (Table 3) and also

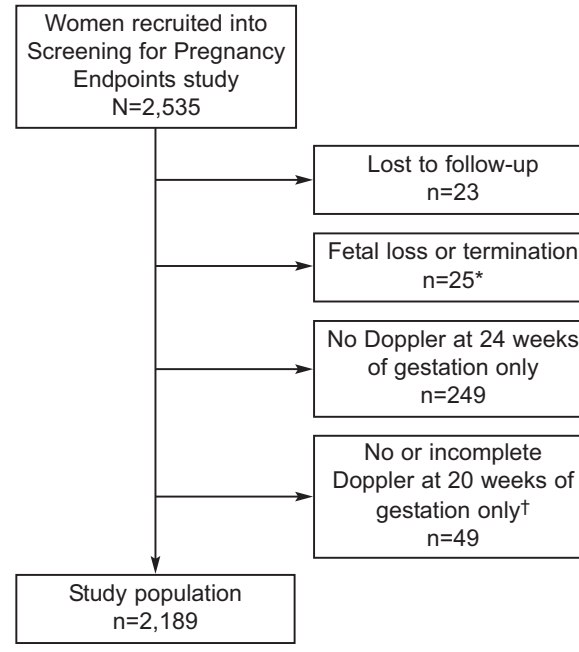

Fig. 1. Recruitment flow chart. *Fetal losses and termination of pregnancy before 24 weeks of gestation. †Five women did not have a 20-week scan, and 44 had incomplete uterine artery Doppler data.

Groom. Uterine Doppler at 20 and 24 Weeks. Obstet Gynecol 2009.

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Table 2. Demographics and Pregnancy Outcomes of the Study Population

Demographics	
Maternal age (y)	28.4±5.7
BMI (kg/m^2)	25.2±5.2
Ethnicity	
White	1,924 (87.9)
Maori or Pacific Islander	75 (3.4)
Indian	56 (2.6)
Asian	94 (4.3)
Other	40 (1.8)
Married or in stable relationship	2,022 (92.4)
Smoking history	
Nonsmoker in pregnancy	1,743 (79.6)
Smoked in pregnancy, quit before 15 wk	227 (10.4)
Smoking at 15-wk visit	219 (10.0)
Job situation	
Full-time work	1,545 (70.6)
Part-time work	345 (15.7)
Other	299 (13.7)
Pregnancy outcome	
Uncomplicated pregnancy	1,293 (59)
Preeclampsia	116 (5.3)
SGA by customized centiles	223 (10.2)
Preeclampsia and SGA	26 (1.2)
Preeclampsia or SGA delivered at less than 34 wk	16 (0.7)
SGA by population centiles	206 (9.4)
Placental abruption	12 (0.6)
Gestational age at delivery (wk)	39.9±1.9
Birth weight (g)	3,403±561
Customized birth weight centile	48.2±28.5

SGA, small for gestational age.
Data are mean±standard deviation or n (%).

in women with preeclampsia, SGA, preeclampsia or SGA or both who delivered at less than 34 weeks, and those with uncomplicated pregnancies (data not shown).

A total of 1,861 (85%) women had normal resistance indexes at both 20 and 24 weeks of gestation (group 1), 118 (5.3%) women had normal resistance indexes at 20 weeks that became abnormal by 24 weeks (group 2), 128 (5.8%) women had abnormal resistance indexes at 20 weeks that normalized by 24 weeks (group 3), and the remaining 82 (3.7%) women had abnormal resistance indexes at both 20 and 24 weeks (group 4). The pregnancy outcome according to these groups is shown in Table 4. Women in group 3 had higher rates of SGA (19.5%, OR 2.7, 95% CI 1.6–4.2) and lower mean birth weights, birth weight centiles, and gestation ages at delivery compared with women in group 1. The women in group 4 had the lowest rates of uncomplicated pregnancy (28%) and the highest rates of preeclampsia (18.3%), SGA (35.4%), and preeclampsia or SGA or both with delivery at less than 34 weeks (8.6%). Numbers do not add to 100% because women with pregnancies complicated by conditions other than preeclampsia, SGA, and placental abruption are not included in the tables.

Table 3. Uterine Resistance Index at 20 and 24 Weeks of Gestation in Nulliparous Women

	20-wk Uterine Resistance Index	24-wk Uterine Resistance Index
Minimum	0.30	0.25
10th centile	0.44	0.41
25th centile	0.49	0.45
Median	0.56	0.51
75th centile	0.62	0.57
90th centile	0.69	0.63
Maximum	0.96	0.84

When abnormal uterine artery Doppler was defined as the presence of bilateral notches, group 1 consisted of 1,874 (86%) women, and groups 2, 3, and 4 consisted of 74 (3%), 173 (8%), and 68 (3%) women, respectively. Women in group 3 had higher rates of SGA (17.9%, OR 2.2, 95% CI 1.4–3.3) and lower mean birth weights and birth weight centiles compared with women in group 1 (Table 5). Similar to the abnormal test being defined by a mean resistance index higher than the 90th centile, those in group 4 based on bilateral notches had the lowest rates of uncomplicated pregnancy (44.1%) and the highest rates of preeclampsia (17.9%), SGA (19.1%), and preeclampsia or SGA or both with delivery at less than 34 weeks (8.8%).

The outcomes among groups according to these combined Doppler criteria were consistent with those shown for the other two definitions (data not shown).

DISCUSSION

In this large, prospective cohort study, we report the frequency of occurrence of four different Doppler waveform patterns between 20 and 24 weeks of gestation (normal–normal, normal–abnormal, abnormal–normal, and abnormal–abnormal) and the clinical importance of each. Our data support the hypothesis that rates of SGA increase across the spectrum of normal–normal Doppler results to abnormal–abnormal Doppler results, with normal–abnormal and abnormal–normal being of intermediate risk. Rates of preeclampsia were highest in the abnormal–abnormal group but were not significantly increased in the normal–abnormal or abnormal–normal groups compared with the normal–normal uterine Doppler group.

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Table 4. Abnormal Doppler=Resistance Index More Than 90th Centile—Pregnancy Outcomes According to Uterine Doppler Group

	Uterine Doppler Groups—Mean Resistance Index Higher Than the 90th Centile				
Outcome	Group 1 (n=1,861)	Group 2 (n=118)	Group 3 (n=128)	Group 4 (n=82)	*P*
Uncomplicated pregnancy	1,142 (61.3), 1.0	61 (51.7), 0.7 (0.5–1.0)	67 (52.3), 0.7 (0.5–1.0)	23 (28.0), 0.2 (0.1–0.4)	<.001
Preeclampsia	85 (4.6), 1.0	9 (7.6), 1.7 (0.8–3.3)	7 (5.5), 1.2 (0.5–2.5)	15 (18.3), 4.7 (2.5–8.3)	<.001
SGA	156 (8.4), 1.0	13 (11.0), 1.4 (0.7–2.4)	25 (19.5), 2.7 (1.6–4.2)	29 (35.4), 6.0 (3.7–9.6)	<.001
Preeclampsia and/or SGA, delivered at less than 34 wk	5 (0.3), 1.0	2 (1.7), 6.4 (0.9–30.0)	2 (1.6), 5.9 (0.8–27.6)	7 (8.6), 34.7 (10.8–119.4)	<.001
Preeclampsia and SGA	12 (0.6)	3 (2.5)	4 (3.1)	7 (8.5)	<.001
SGA population centiles	142 (7.6)	15 (12.7)	22 (17.2)	27 (32.9)	<.001
Abruption	6 (0.3)	1 (0.9)	1 (0.8)	4 (4.9)	<.001
Gestation at delivery (wk)	39.6±1.9	39.7±1.7	39.4±2.1*	38.0±2.9*	<.001
Birth weight (g)	3,448±530	3,331±548	3,234±599*	2,770±725*	<.001
Birth weight percentile	50.4±28.2	40.7±26.9*	38.3±28.2*	23.7±22.7*	<.001

SGA, small for gestational age.
Data are n (%), odds ratio (95% confidence interval), or mean±standard deviation.
*$P<0.05$ for post hoc Tukey comparison with group 1.

Rates of SGA (by customized and by population centiles) were increased two-fold in the group with late normalization of the uterine artery Doppler waveform (abnormal–normal), and mean birth weight was reduced correspondingly, regardless of which criterion was used to define an abnormal Doppler study. Consistent with our findings, a reduction in mean birth weight by 200–300 g and a higher rate of SGA has been reported previously with late normalization.[11,12] These findings suggest that reduced uteroplacental perfusion at 20 weeks or earlier may affect fetal development at a critical stage, subsequently resulting in impaired fetal growth despite restoration of normal uterine blood flow by 24 weeks. Alternatively, our data are consistent with hypotheses from the 1980s that suggested that early impairment of uteroplacental perfusion may lead to subsequent villous vascular damage that later results in the development of SGA.[18]

In contrast, the odds of SGA were not increased in the normal–abnormal group, suggesting that the pathological processes responsible for the recently reduced uteroplacental perfusion indices at 24 weeks are not associated with later SGA.

As has been described previously, the rate of preeclampsia was increased several fold in the group with abnormal uterine Doppler studies at both timepoints.[11] In the late-normalization group, preeclampsia was not significantly increased, consistent with findings from two earlier studies.[11,12] Similarly, the

Table 5. Abnormal Doppler=Presence of Bilateral Notches—Pregnancy Outcomes According to Uterine Doppler Group

	Uterine Doppler Groups—Bilateral Notches				
Outcome	Group 1 (n=1,874)	Group 2 (n=74)	Group 3 (n=173)	Group 4 (n=68)	*P*
Uncomplicated pregnancy	1,133 (60.5), 1.0	39 (52.7), 0.7 (0.5–1.1)	91 (52.6), 0.7 (0.5–1.0)	30 (44.1), 0.5 (0.3–0.8)	.007
Preeclampsia	87 (4.6), 1.0	4 (5.4), 1.2 (0.4–2.9)	13 (7.5), 1.7 (0.9–3.0)	12 (17.9), 4.4 (2.2–8.2)	<.001
SGA	168 (9.0), 1.0	11 (14.9), 1.8 (0.9–3.3)	31 (17.9), 2.2 (1.4–3.3)	13 (19.1), 2.4 (1.2–4.4)	<.001
Preeclampsia and/or SGA, delivered at less than 34 wk	7 (0.4), 1.0	1 (1.4), 3.7 (0.2–20.9)	2 (1.2), 3.1 (0.5–13.0)	6 (8.8), 25.8 (8.1–79.9)	<.001
Preeclampsia and SGA	15 (0.8)	3 (4.1)	4 (2.3)	4 (5.9)	<.001
SGA population centiles	154 (8.2)	10 (13.5)	30 (17.3)	12 (17.6)	<.001
Abruption	8 (0.4)	0 (0.0)	2 (1.2)	2 (2.9)	.03
Gestation at delivery (wk)	39.6±1.9	39.5±2.0	39.5±1.9	38.4±2.9	.001
Birth weight (g)	3,437±540	3,277±632	3,264±606*	2,966±693*	<.001
Birth weight percentile	49.6±28.2	41.1±29.3	41.4±29.9*	33.0±24.4*	<.001

SGA, small for gestational age.
Data are n (%), odds ratio (95% confidence interval), or mean±standard deviation.
* $P<.05$ for post hoc Tukey comparison with group 1.

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rate of preeclampsia in the normal–abnormal group was not elevated. Given the low prevalence of preeclampsia in our cohort, larger studies are required to either confirm our findings or to detect small increases in preeclampsia in the normal–abnormal Doppler group.

The Screening for Pregnancy Endpoints study is a prospective, multicenter screening study with stringent data validation and outcome data available for more than 99% of participants. Because the 24-week scan was not a compulsory component of the study design, 9.3% of the study population did not have this scan. There were no significant differences in the rates of preeclampsia or SGA between those who did and those who did not have scans at 24 weeks of gestation. We consider that this is unlikely to have introduced important bias into the results.

Our study allows assessment of the effect of the gestation at screening, 20 or 24 weeks, on the number of cases of preeclampsia and SGA detected or missed. To illustrate this using the criterion of mean resistance index higher than the 90th centile, if a single scan is performed at 20 weeks, an abnormal test would be a composite of the abnormal–normal and abnormal–abnormal groups, which is 64% of all abnormal tests. A similar proportion (61%) of abnormal Doppler tests (a composite of normal–abnormal and abnormal–abnormal) would be detected if the scan was performed only at 24 weeks of gestation. A single scan at 20 weeks or 24 weeks (abnormal test defined as a mean resistance index higher than the 90th centile) would have missed 5.8% and 11.2% of SGA fetuses and 7.8% and 6.0% of women with preeclampsia, respectively. Given these data, if a single screening scan is to be performed in the second trimester, a scan at 20 weeks may be the best option because this fits with the timing of an anomaly scan, will detect a similar number of cases as a single scan at 24 weeks of gestation, and allows earlier intervention.[7,8] Previous second-trimester uterine artery Doppler studies have reported that sensitivity and positive predictive values for preeclampsia and SGA are too low, particularly in nulliparous women with low disease prevalence, to recommend routine Doppler screening from a clinical or health-economics perspective.[3,19] Recent data suggest the combination of clinical and biomarker data with Doppler data may improve performance as a screening test.[5,20,21] Although we are not advocating routine 20-week uterine artery Doppler studies, if overall test performance could be enhanced by the addition of clinical data, biomarkers, or both, we would recommend that 20 weeks is the most appropriate gestation in the second trimester to perform uterine artery Doppler studies.

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3. MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines for meta-analyses and systematic reviews of observational studies
4. STARD (Standards for Reporting of Diagnostic Accuracy) standards for reporting studies of diagnostic accuracy
4. STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for the reporting of observational studies

Investigators who are planning, conducting, or reporting randomized trials, meta-analyses of randomized trials, meta-analyses of observational studies, studies of diagnostic accuracy, or observational studies should be thoroughly familiar with these sets of standards and follow these guidelines in articles submitted for publication.

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Summaries of the guidelines may also be obtained by contacting the Editorial Office (Phone: 202-314-2317; Fax: 202-479-0830; E-mail: obgyn@greenjournal.org).

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