November 2015 Literature Alert

1.
Am J Obstet Gynecol. 2015 Oct;213(4):449.e1-449.e41. doi: 10.1016/j.ajog.2015.08.032.
Racial/ethnic standards for fetal growth: the NICHD Fetal Growth Studies.
Buck Louis GM, Grewal J, Albert PS, Sciscione A, Wing DA, Grobman WA, Newman RB, Wapner R, D'Alton ME, Skupski D, Nageotte MP, Ranzini AC, Owen J, Chien EK, Craigo S, Hediger ML, Kim S, Zhang C, Grantz KL.

Abstract
OBJECTIVE:
Fetal growth is associated with long-term health yet no appropriate standards exist for the early identification of undergrown or overgrown fetuses. We sought to develop contemporary fetal growth standards for 4 self-identified US racial/ethnic groups.
STUDY DESIGN:
We recruited for prospective follow-up 2334 healthy women with low-risk, singleton pregnancies from 12 community and perinatal centers from July 2009 through January 2013. The cohort comprised: 614 (26%) non-Hispanic whites, 611 (26%) non-Hispanic blacks, 649 (28%) Hispanics, and 460 (20%) Asians. Women were screened at 8w0d to 13w6d for maternal health status associated with presumably normal fetal growth (aged 18-40 years; body mass index 19.0-29.9 kg/m(2); healthy lifestyles and living conditions; low-risk medical and obstetrical history); 92% of recruited women completed the protocol. Women were randomized among 4 ultrasonography schedules for longitudinal fetal measurement using the Voluson E8 (GE Healthcare, Milwaukee, WI). In-person interviews and anthropometric assessments were conducted at each visit; medical records were abstracted. The fetuses of 1737 (74%) women continued to be low risk (uncomplicated pregnancy, absent anomalies) at birth, and their measurements were included in the standards. Racial/ethnic-specific fetal growth curves were estimated using linear mixed models with cubic splines. Estimated fetal weight (EFW) and biometric parameter percentiles (5th, 50th, 95th) were determined for each gestational week and comparisons made by race/ethnicity, with and without adjustment for maternal and sociodemographic factors.
RESULTS:
EFW differed significantly by race/ethnicity >20 weeks. Specifically at 39 weeks, the 5th, 50th, and 95th percentiles were 2790, 3505, and 4402 g for white; 2633, 3336, and 4226 g for Hispanic; 2621, 3270, and 4078 g for Asian; and 2622, 3260, and 4053 g for black women (adjusted global P < .001). For individual parameters, racial/ethnic differences by order of detection were: humerus and femur lengths (10 weeks), abdominal circumference (16 weeks),

head circumference (21 weeks), and biparietal diameter (27 weeks). The study-derived standard based solely on the white group erroneously classifies as much as 15% of non-white fetuses as growth restricted (EFW <5th percentile).
CONCLUSION:
Significant differences in fetal growth were found among the 4 groups. Racial/ethnic-specific standards improve the precision in evaluating fetal growth.
Published by Elsevier Inc.
KEYWORDS:
birthweight; epidemiology; estimated fetal growth; fetal growth; pregnancy
PMID: 26410205 [PubMed - in process] PMCID: PMC4584427 [Available on 2016-10-01]

2.
Am J Obstet Gynecol. 2015 Oct;213(4):551.e1-5. doi: 10.1016/j.ajog.2015.07.049. Epub 2015 Aug 7.
Dichorionic twin ultrasound surveillance: sonography every 4 weeks significantly underperforms sonography every 2 weeks: results of the Prospective Multicenter ESPRiT Study.
Corcoran S, Breathnach F, Burke G, McAuliffe F, Geary M, Daly S, Higgins J, Hunter A, Morrison JJ, Higgins S, Mahony R, Dicker P, Tully E, Malone FD.

Abstract
OBJECTIVE:
A 2-week ultrasound scanning schedule for monochorionic twins is endorsed widely. There is a lack of robust data to inform a schedule for the surveillance of dichorionic gestations. We aimed to determine how ultrasound scanning that is performed at 2- or 4-week intervals (or every 4 weeks before 32 weeks' gestation and every 2 weeks thereafter) may impact the prenatal detection of fetal growth restriction (FGR) and ultimately influence timing of delivery.
STUDY DESIGN:
In a consecutive cohort of 789 dichorionic twin pregnancies that were recruited prospectively for the multicenter Evaluation of Sonographic Predictors of Restricted Growth in Twins study, ultrasound determination of fetal growth and interrogation of umbilical and middle cerebral artery Doppler scans were performed every 2 weeks from 24 weeks' gestation until delivery. Complete delivery and perinatal outcome data were recorded for all pregnancies. Where delivery was prompted by FGR, abnormal umbilical artery Doppler examination or poor biophysical profile and in the absence of ruptured membranes, onset of labor, preeclampsia, or antepartum hemorrhage, the delivery was considered "ultrasound-indicated." For ultrasound-indicated deliveries, detection probabilities for FGR/abnormal umbilical artery Doppler scans/poor biophysical were determined according to the interval between examinations, by the suppression if alternate examination data.
RESULTS:
Among 789 dichorionic twin pregnancies, 66 pairs (8%) had an "ultrasound indicated" delivery. Detection of FGR was reduced from 88-69%, and detection of abnormal umbilical artery Doppler was reduced from 82-62% when a 4-week ultrasound schedule was simulated. Both of these reductions reached statistical significance. There was a nonsignificant trend toward a

reduction in the recording of oligohydramnios with a 4-week interval between examinations.
CONCLUSION:
This study suggests that the ultrasound surveillance program of every 2 weeks that is recommended currently for monochorionic twins should be extended to dichorionic gestations.

KEYWORDS:
dichorionic; twins; ultrasound scanning
PMID: 26259909 [PubMed - in process]

3.
N Engl J Med. 2015 Oct 15;373(16):1507-18. doi: 10.1056/NEJMoa1504909.
Neonatal Glycemia and Neurodevelopmental Outcomes at 2 Years.
McKinlay CJ, Alsweiler JM, Ansell JM, Anstice NS, Chase JG, Gamble GD, Harris DL, Jacobs RJ, Jiang Y, Paudel N, Signal M, Thompson B, Wouldes TA, Yu TY, Harding JE; CHYLD Study Group. Collaborators (49)

Abstract
BACKGROUND:
Neonatal hypoglycemia is common and can cause neurologic impairment, but evidence supporting thresholds for intervention is limited.
METHODS:
We performed a prospective cohort study involving 528 neonates with a gestational age of at least 35 weeks who were considered to be at risk for hypoglycemia; all were treated to maintain a blood glucose concentration of at least 47 mg per deciliter (2.6 mmol per liter). We intermittently measured blood glucose for up to 7 days. We continuously monitored interstitial glucose concentrations, which were masked to clinical staff. Assessment at 2 years included Bayley Scales of Infant Development III and tests of executive and visual function.
RESULTS:
Of 614 children, 528 were eligible, and 404 (77% of eligible children) were assessed; 216 children (53%) had neonatal hypoglycemia (blood glucose concentration, <47 mg per deciliter). Hypoglycemia, when treated to maintain a blood glucose concentration of at least 47 mg per deciliter, was not associated with an increased risk of the primary outcomes of neurosensory impairment (risk ratio, 0.95; 95% confidence interval [CI], 0.75 to 1.20; P=0.67) and processing difficulty, defined as an executive-function score or motion coherence threshold that was more than 1.5 SD from the mean (risk ratio, 0.92; 95% CI, 0.56 to 1.51; P=0.74). Risks were not increased among children with unrecognized hypoglycemia (a low interstitial glucose concentration only). The lowest blood glucose concentration, number of hypoglycemic episodes and events, and negative interstitial increment (area above the interstitial glucose concentration curve and below 47 mg per deciliter) also did not predict the outcome.
CONCLUSIONS:
In this cohort, neonatal hypoglycemia was not associated with an adverse neurologic outcome when treatment was provided to maintain a blood glucose concentration of at least 47 mg per deciliter. (Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human

Development and others.).
Comment in
Neonatal Hypoglycemia Studies--Is There a Sweet Story of Success Yet? [N Engl J Med. 2015]
PMID: 26465984 [PubMed - indexed for MEDLINE]

4.
J Pediatr. 2015 Oct;167(4):834-839.e3. doi: 10.1016/j.jpeds.2015.06.067. Epub 2015 Aug 5.
Antenatal Magnesium and Cerebral Palsy in Preterm Infants.
Hirtz DG, Weiner SJ, Bulas D, DiPietro M, Seibert J, Rouse DJ, Mercer BM, Varner MW, Reddy UM, Iams JD, Wapner RJ, Sorokin Y, Thorp JM Jr, Ramin SM, Malone FD, Carpenter MW, O'Sullivan MJ, Peaceman AM, Hankins GD, Dudley D, Caritis SN; Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network.
Collaborators (104)

Abstract
OBJECTIVE:
To evaluate the relationship of maternal antenatal magnesium sulfate (MgSO4) with neonatal cranial ultrasound abnormalities and cerebral palsy (CP).
STUDY DESIGN:
In a randomized trial of MgSO4 or placebo in women at high risk of preterm delivery, up to 3 cranial ultrasounds were obtained in the neonatal period. Images were reviewed by at least 2 pediatric radiologists masked to treatment and other clinical conditions. Diagnoses were predefined for intraventricular hemorrhage, periventricular leukomalacia, intracerebral echolucency or echodensity, and ventriculomegaly. CP was diagnosed at 2 years of age by standardized neurologic examination.
RESULTS:
Intraventricular hemorrhage, periventricular leukomalacia, intracerebral echolucency or echodensity, and ventriculomegaly were all strongly associated with an increased risk of CP. MgSO4 administration did not affect the risk of cranial ultrasound abnormality observed at 35 weeks postmenstrual age or later. However, for the 82% of infants born at <32 weeks gestation, MgSO4 was associated with a reduction in risk of echolucency or echodensity. The reduction in risk for echolucency explained 21% of the effect of MgSO4 on CP (P = .04), and for echodensity explained 20% of the effect (P = .02).
CONCLUSIONS:
MgSO4 given prior to preterm delivery was associated with decreased risk of developing echodensities and echolucencies at <32 weeks gestation. However, this effect can only partially explain the effect of MgSO4 on CP at 2 years of age.
TRIAL REGISTRATION:
ClinicalTrials.gov: NCT00014989.
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PMID: 26254839 [PubMed - in process] PMCID: PMC4587284 [Available on 2016-10-01]

5.
Fetal Diagn Ther. 2015 Oct 23. [Epub ahead of print]
Clinical Potential of Effective Noninvasive Exclusion of KEL1-Positive Fetuses in KEL1-Negative Pregnant Women.
Böhmova J, Vodicka R, Lubusky M, Holuskova I, Studnickova M, Kratochvilova R, Krejcirikova E, Janikova M, Durdová V, Dolezalová T, Filipová H, Dusek L, Dhaifalah I, Vomackova K, Kacerovsky M, Prochazka M, Vrtel R.

Abstract
BACKGROUND:
The clinical importance of assessing the fetal KEL genotype is to exclude 'K'-positive fetuses (genotype KEL1/KEL2) in 'K'-alloimmunized pregnant women (genotype KEL2/KEL2). Noninvasive assessment of the fetal KEL genotype is not yet available in the Czech Republic.
OBJECTIVE:
The aim of this study was to assess the fetal KEL1/KEL2 genotype from cell-free fetal DNA in the plasma of KEL2/KEL2 pregnant women.
METHODS:
The fetal genotype was assessed by minisequencing (a dilution series including control samples). A total of 138 pregnant women (between the 8th and 23rd gestational week) were tested by minisequencing. The fetal genotype was further verified by analysis of a buccal swab from the newborn.
RESULTS:
Minisequencing proved to be a reliable method. In 2.2% (3/138) of the examined women, plasma sample testing failed; 94.8% (128/135) had the KEL2/KEL2 genotype, and a total of 3.1% of fetuses (4/128) had the KEL1/KEL2 genotype. Sensitivity and specificity reached 100% ($p < 0.0001$).
CONCLUSION:
Minisequencing is a reliable method for the assessment of the fetal KEL1 allele from the plasma of KEL2/KEL2 pregnant women.

PMID: 26492079 [PubMed - as supplied by publisher]

6.
J Neonatal Perinatal Med. 2015 Oct 24;8(3):179-87. doi: 10.3233/NPM-15814098.
Born early and born poor: An eco-bio-developmental model for poverty and preterm birth.
Brumberg HL, Shah SI.

Abstract
Poverty is associated with adverse long-term cognitive outcomes in children. Poverty is also linked with preterm delivery which, in turn, is associated with adverse cognitive outcomes. However, the extent of the effect of poverty on preterm delivery, as well as proposed mechanisms by which they occur, have not been well described. Further, the impact of poverty

on preterm school readiness has not been reviewed. As the childhood poverty level continues to increase in the U.S., we examine the evidence around physiological, neurological, cognitive and learning outcomes associated with prematurity in the context of poverty. We use the evidence gathered to suggest an Eco-Bio-Developmental model, emphasizing poverty as a toxic stress which predisposes preterm birth and which, via epigenetic forces, can continue into the next generation. Continued postnatal social disadvantage for these developmentally high-risk preterm infants is strongly linked with poor neurodevelopmental outcomes, decreased school readiness, and decreased educational attainment which can perpetuate the poverty cycle. We suggest social remedies aimed at decreasing the impact of poverty on mothers, fathers, and children which may be effective in reducing the burden of preterm birth.
KEYWORDS:
Stress; neurodevelopment; poverty; prematurity
PMID: 26485551 [PubMed - in process]

7.
Prenat Diagn. 2015 Oct;35(10):1010-7. doi: 10.1002/pd.4675. Epub 2015 Sep 11.
Exome sequencing for prenatal diagnosis of fetuses with sonographic abnormalities.
Drury S, Williams H, Trump N, Boustred C; GOSGene, Lench N, Scott RH, Chitty LS.

Abstract
OBJECTIVE:
In the absence of aneuploidy or other pathogenic cytogenetic abnormality, fetuses with increased nuchal translucency (NT ≥ 3.5 mm) and/or other sonographic abnormalities have a greater incidence of genetic syndromes, but defining the underlying pathology can be challenging. Here, we investigate the value of whole exome sequencing in fetuses with sonographic abnormalities but normal microarray analysis.
METHOD:
Whole exome sequencing was performed on DNA extracted from chorionic villi or amniocytes in 24 fetuses with unexplained ultrasound findings. In the first 14 cases sequencing was initially performed on fetal DNA only. For the remaining 10, the trio of fetus, mother and father was sequenced simultaneously.
RESULTS:
In 21% (5/24) cases, exome sequencing provided definitive diagnoses (Milroy disease, hypophosphatasia, achondrogenesis type 2, Freeman-Sheldon syndrome and Baraitser-Winter Syndrome). In a further case, a plausible diagnosis of orofaciodigital syndrome type 6 was made. In two others, a single mutation in an autosomal recessive gene was identified, but incomplete sequencing coverage precluded exclusion of the presence of a second mutation.
CONCLUSION:
Whole exome sequencing improves prenatal diagnosis in euploid fetuses with abnormal ultrasound scans. In order to expedite interpretation of results, trio sequencing should be employed, but interpretation can still be compromised by incomplete coverage of relevant genes. © 2015 John Wiley & Sons, Ltd.

PMID: 26275891 [PubMed - in process]

8.
J Perinatol. 2015 Oct;35(10):885-90. doi: 10.1038/jp.2015.91. Epub 2015 Jul 30.
Changes in infant mortality among extremely preterm infants: US vital statistics data 1990 vs 2000 vs 2010.
Malloy MH.

Abstract
OBJECTIVE:
Infant mortality among extremely preterm infants (22 to 28 weeks gestation) varies considerably by gestational age. The reduction in mortality over a 20-year period, when examined in gestational age week increments, may give a more precise estimate of progress or lack thereof in caring for these infants and provide information to better inform practitioners and parents of the risk of mortality among these small infants. The objective of this analysis is to examine infant mortality (birth to 365 days) by week of gestation for infants 22 to 28 weeks gestation comparing mortality rates, adjusting for maternal and infant birth characteristics, among US births for the years 1990, 2000 and 2010.
STUDY DESIGN:
US vital statistics period-linked birth and infant death certificate files for the years 1990, 2000 and 2010 were used. Maternal and infant characteristics for births at 22 to 28 weeks were abstracted from the files. A trimming procedure was used to remove records that had birth weights that exceeded the interquartile range of birth weights for a given week of gestational age. Infant mortality rates were calculated, and adjusted odds ratios for mortality were generated using logistic regression models.
RESULT:
A total of 15 593 live births, 22 to 28 weeks gestation were available for the year 1990; 17 095 for the year 2000; and 14 721 for the year 2010. Infant mortality rates ranged from 904 per 1000 live births at 22 weeks gestation in 1990, to 835 in 2000, to 866 in 2010. Across all gestational age groups there was an adjusted reduction in the odds ratio for mortality of ~50% from 1990 to the year 2000. However, between 2000 and 2010 there was no significant reduction in infant mortality except at 25 weeks gestation (adjusted odds ratio=0.81, 95% confidence interval=0.70, 0.93).
CONCLUSION:
Despite a significant reduction in infant mortality among extremely preterm infants between the years 1990 and 2000, there has been little progress in reducing mortality between the years 2000 and 2010.
PMID: 26226246 [PubMed - in process]

9.
BJOG. 2015 Oct;122(11):1437-45. doi: 10.1111/1471-0528.13527. Epub 2015 Jul 14.
Maternal group B Streptococcus-related stillbirth: a systematic review.
Nan C, Dangor Z, Cutland CL, Edwards MS, Madhi SA, Cunnington MC.

Abstract
BACKGROUND:
Limited epidemiological data on the association between maternal rectovaginal group B Streptococcus (GBS) colonisation and stillbirth makes assessment of antenatal interventions for GBS stillbirth difficult.
OBJECTIVES:
To systematically review the existing literature and evaluate the incidence of GBS-related stillbirth by region up to March 2015.
SEARCH STRATEGY:
A systematic review of the published literature was completed using PubMed/MEDLINE, EMBASE, LILACS, and Cochrane Library, with Medical Subject Headings (MeSH) and search terms based upon the Centers for Disease Control and Prevention's (CDC) Active Bacterial Core Surveillance (ABCs) GBS-related stillbirth definition and chorioamnionitis.
SELECTION CRITERIA:
Studies reporting original data on GBS-related stillbirth occurring ≥20 weeks of gestation, with GBS confirmed by autopsy or by culture from the placenta, amniotic fluid, or other normally sterile site samples from the stillborn.
DATA COLLECTION AND ANALYSIS:
Descriptive analyses were performed with the absolute GBS-related stillbirth rates and proportion of stillbirths attributed to GBS calculated per study where possible. Differences in stillbirth definitions did not allow for pooled estimates to be calculated.
MAIN RESULTS:
Seventeen studies reported GBS-related stillbirth rates varying from 0.04 to 0.9 per 1000 births, with the proportion of stillbirths associated with GBS ranging from 0 to 12.1%. Most studies reported data from before the year 2000 and from high-income countries.
CONCLUSIONS:
The sparsely available epidemiological evidence was not reported consistently, emphasising the importance of standardised stillbirth definitions and diagnostic methods to optimally assess the effectiveness of any future antenatal interventions. Timing of stillbirth, GBS serotype, and global diversity were gaps in the current evidence.
TWEETABLE ABSTRACT:
Systematic review finds Group B Streptococcus causes up to 12.1% of stillbirths, but more research is needed.

KEYWORDS:
Group B Streptococcus; guidelines; incidence; perinatal infections; serotype distribution; stillbirth
PMID: 26177561 [PubMed - in process]

10.
BJOG. 2015 Oct;122(11):1467-74. doi: 10.1111/1471-0528.13461. Epub 2015 May 29.
Previous caesarean delivery and the risk of unexplained stillbirth: retrospective cohort study and meta-analysis.
Moraitis AA, Oliver-Williams C, Wood AM, Fleming M, Pell JP, Smith G.

Abstract
OBJECTIVE:
To determine whether caesarean delivery in the first pregnancy is a risk factor for unexplained antepartum stillbirth in a second pregnancy.
DESIGN:
A population-based retrospective cohort study and meta-analysis.
SETTING:
All maternity units in Scotland.
PARTICIPANTS:
A cohort of 128 585 second births, 1999-2008.
METHODS:
Time-to-event analysis and random-effects meta-analysis.
MAIN OUTCOME MEASURE:
Risk of unexplained antepartum stillbirth in a second pregnancy.
RESULTS:
There were 88 stillbirths among 23 688 women with a previous caesarean delivery (2.34 per 10 000 women per week) and 288 stillbirths in 104 897 women who had previously delivered vaginally (1.67 per 10 000 women per week, P = 0.002). When analysed by cause, women with a previous caesarean delivery had an increased risk of unexplained stillbirth (hazard ratio, HR 1.47; 95% confidence interval, 95% CI 1.12-1.94; P = 0.006) and, as previously observed, the excess risk was apparent from 34 weeks of gestation onwards. The risk did not differ in relation to the indication of the caesarean delivery, and was independent of maternal characteristics and previous obstetric complications. We identified three other comparable studies (two in North America and one in Europe), and meta-analysis of these studies showed a statistically significant association between previous caesarean delivery and the risk of antepartum stillbirth in the second pregnancy (pooled HR 1.40; 95% CI 1.10-1.77; P = 0.006).
CONCLUSIONS:
Women who have had a previous caesarean delivery are at increased risk of unexplained stillbirth in the second pregnancy.
TWEETABLE ABSTRACT:
Caesarean first delivery is associated with an increased risk of unexplained stillbirth in the next pregnancy.

KEYWORDS:
Caesarean; second pregnancy; stillbirth; unexplained
PMID: 26033155 [PubMed - in process]

11.
BJOG. 2015 Oct;122(11):1535-41. doi: 10.1111/1471-0528.13015. Epub 2014 Aug 4.
The risk of uterine rupture is not increased with single- compared with double-layer closure: a Swedish cohort study.
Hesselman S, Högberg U, Ekholm-Selling K, Råssjö EB, Jonsson M.

Abstract
OBJECTIVE:
To compare single- with double-layer closure of the uterus for the risk of uterine rupture in women attempting vaginal birth after one prior caesarean delivery.
DESIGN:
Cohort study.
SETTING:
Sweden.
POPULATION:
From a total of 19 604 nulliparous women delivered by caesarean section in the years 2001-2007, 7683 women attempting vaginal birth in their second delivery were analysed.
METHODS:
Data from population-based registers were linked to hospital-based registers that held data from maternity and delivery records. Logistic regression was used to estimate the risk of uterine rupture after single- or double-layer closure of the uterus. Results are presented as odds ratios (ORs) with 95% confidence intervals (95% CIs).
MAIN OUTCOME MEASURE:
Uterine rupture.
RESULTS:
Uterine rupture during labour occurred in 103 (1.3%) women. There was no increased risk of uterine rupture when single- was compared with double-layer closure of the uterus (OR 1.17; 95% CI 0.78-1.76). Maternal factors associated with uterine rupture were: age ≥35 years and height ≤160 cm. Factors from the first delivery associated with uterine rupture in a subsequent delivery were: infection and giving birth to an infant large for gestational age. Risk factors from the second delivery were induction of labour, use of epidural analgesia, and a birthweight of ≥4500 g.
CONCLUSIONS:
There was no significant difference in the rate of uterine rupture when single-layer closure was compared with double -layer closure of the uterus.

KEYWORDS:
Uterine closure; uterine rupture; vaginal birth after caesarean section
PMID: 25088680 [PubMed - in process]

12.
Obstet Gynecol. 2015 Oct;126(4):737-46. doi: 10.1097/AOG.0000000000001029.
Prenatal Testing in the Genomic Age: Clinical Outcomes, Quality of Life, and Costs.
Kaimal AJ, Norton ME, Kuppermann M.

Abstract
OBJECTIVE:
To use a decision-analytic model to assess a comprehensive set of outcomes of prenatal genetic testing strategies among women of varying ages.
METHODS:
We assessed outcomes of six testing strategies incorporating diagnostic testing with chromosomal microarray, multiple marker screening, cell-free DNA screening, and nuchal translucency screening alone, in combination, or in sequence. Clinical outcomes included prenatal detection or birth of a neonate with a significant chromosomal abnormality and diagnostic procedures performed. Other outcomes included maternal quality-adjusted life-years and costs. Sensitivity analyses were conducted to examine the robustness of the findings.
RESULTS:
At all ages assessed, screening strategies starting with multiple marker screening offered the highest detection rate when all chromosomal abnormalities were considered. Incorporating cell-free DNA as an optional secondary screen decreased the number of diagnostic procedures, but also decreased the number of abnormalities diagnosed prenatally, resulting in a similar number of procedures per case diagnosed at age 30 years; the option of secondary cell-free DNA screening becomes more favorable at older ages. Multiple marker screening with optional follow-up diagnostic testing was the most effective (highest quality-adjusted life-years) and least expensive strategy at ages 20-38 years. At age 40 years or older, cell-free DNA screening was optimal with an incremental cost-effectiveness ratio of $73,154 per quality-adjusted life-year.
CONCLUSION:
When considering all detectable chromosome problems as well as patient preferences and baseline risks, multiple marker screening with the option of diagnostic testing for screen-positive results is the optimal strategy for most women. At age 40 years and older, cell-free DNA as a primary screen becomes optimal and is cost-effective.
LEVEL OF EVIDENCE:
II.
PMID: 26348190 [PubMed - in process]

13.
Pediatrics. 2015 Oct;136(4):e906-13. doi: 10.1542/peds.2015-2114.
Bladder Function After Fetal Surgery for Myelomeningocele.
Brock JW 3rd, Carr MC, Adzick NS, Burrows PK, Thomas JC, Thom EA, Howell LJ, Farrell JA, Dabrowiak ME, Farmer DL, Cheng EY, Kropp BP, Caldamone AA, Bulas DI, Tolivaisa S, Baskin LS; MOMS Investigators.

Abstract
BACKGROUND:
A substudy of the Management of Myelomeningocele Study evaluating urological outcomes was conducted.
METHODS:
Pregnant women diagnosed with fetal myelomeningocele were randomly assigned to either prenatal or standard postnatal surgical repair. The substudy included patients randomly assigned after April 18, 2005. The primary outcome was defined in their children as death or the need for clean intermittent catheterization (CIC) by 30 months of age characterized by prespecified criteria. Secondary outcomes included bladder and kidney abnormalities observed by urodynamics and renal/bladder ultrasound at 12 and 30 months, which were analyzed as repeated measures.
RESULTS:
Of the 115 women enrolled in the substudy, the primary outcome occurred in 52% of children in the prenatal surgery group and 66% in the postnatal surgery group (relative risk [RR]: 0.78; 95% confidence interval [CI]: 0.57-1.07). Actual rates of CIC use were 38% and 51% in the prenatal and postnatal surgery groups, respectively (RR: 0.74; 95% CI: 0.48-1.12). Prenatal surgery resulted in less trabeculation (RR: 0.39; 95% CI: 0.19-0.79) and fewer cases of open bladder neck on urodynamics (RR: 0.61; 95% CI: 0.40-0.92) after adjustment by child's gender and lesion level. The difference in trabeculation was confirmed by ultrasound.
CONCLUSIONS:
Prenatal surgery did not significantly reduce the need for CIC by 30 months of age but was associated with less bladder trabeculation and open bladder neck. The implications of these findings are unclear now, but support the need for long-term urologic follow-up of patients with myelomeningocele regardless of type of surgical repair.

PMID: 26416930 [PubMed - in process] PMCID: PMC4586733 [Available on 2016-10-01]

14.
Eur J Obstet Gynecol Reprod Biol. 2015 Oct;193:34-9. doi: 10.1016/j.ejogrb.2015.06.024. Epub 2015 Jul 9.
Folic acid in pregnant women associated with reduced prevalence of severe congenital heart defects in their children: a national population-based case-control study.
Czeizel AE, Vereczkey A, Szabó I.

Abstract
OBJECTIVE:
Previous Hungarian intervention trials have shown an association between periconceptional folic-acid-containing multivitamin supplementation and significantly reduced risk of congenital heart defects (CHDs). These findings were confirmed in observational multivitamin studies in the USA, and studies in the Netherlands and China regarding folic acid. The objective of this observational population-based study was to estimate the possible preventive effect of folic acid supplementation for different CHDs during their critical period of development.

STUDY DESIGN:
Evaluation of medically recorded use of folic acid (calculated daily average 5.6mg) during the critical period of development of eight types of CHD (verified through autopsy reports or after catheter examination and/or surgical correction) in the population-based Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA), 1980-1996, containing 22,843 cases with congenital abnormalities and 38,151 population controls without any CHDs, including 5395 matched controls of 3567 live-born cases with various CHDs. A conditional logistic regression model was used to estimate the relative risk/protection [odds ratio (OR) with 95% confidence intervals (CI)] of folic acid in the mothers of cases with various types of CHD and their matched controls.
RESULTS:
There was a significant decrease in the prevalence of cases with ventricular septal defect (OR 0.57, 95% CI 0.45-0.73), tetralogy of Fallot (OR 0.53, 95% CI 0.17-0.94), d-transposition of great arteries (OR 0.47, 95% CI 0.26-0.86) and atrial septal defect secundum (OR 0.63, 95% CI 0.40-0.98) in infants born to mothers who had taken high doses of folic acid during the critical period of CHD development.
CONCLUSIONS:
The risk of development of certain types of CHD was significantly reduced in pregnant women who were supplemented with folic acid. Thus, CHDs should be included as a secondary assessment in neural-tube-defect preventive programs.

KEYWORDS:
Congenital heart defect; Folic acid; Population-based case–control study; Tetralogy of Fallot; Ventricular septal defect; d-Transposition of great arteries
PMID: 26225846 [PubMed - in process]

15.
JAMA. 2015 Oct 20;314(15):1588-98. doi: 10.1001/jama.2015.12505.
Association Between Preeclampsia and Congenital Heart Defects.
Auger N, Fraser WD, Healy-Profitós J, Arbour L.

Abstract
IMPORTANCE:
The risk of congenital heart defects in infants of women who had preeclampsia during pregnancy is poorly understood, despite shared angiogenic pathways in both conditions.
OBJECTIVE:
To determine the prevalence of congenital heart defects in offspring of women with preeclampsia.
DESIGN, SETTING, AND PARTICIPANTS:
Population-level analysis of live births before discharge, 1989-2012, was conducted for the entire province of Quebec, comprising a quarter of Canada's population. All women who delivered an infant with or without heart defects in any Quebec hospital were included (N = 1,942,072 neonates).

EXPOSURES:
Preeclampsia or eclampsia with onset before or after 34 weeks of gestation.
MAIN OUTCOMES AND MEASURES:
Presence of any critical or noncritical congenital heart defect detected in infants at birth, comparing prevalence in those exposed and not exposed to preeclampsia.
RESULTS:
The absolute prevalence of congenital heart defects was higher for infants of women with preeclampsia than those without it. Infants of women with preeclampsia had no increased prevalence of critical heart defects but did have an increased prevalence of noncritical heart defects compared with infants of nonpreeclamptic women. [table: see text]. Among specific defects, prevalence was greatest for septal defects. Compared with infants of women with late-onset preeclampsia, those with early onset (<34 weeks) had greater prevalence of critical heart defects (364.4/100,000 [20/5488]; prevalence ratio, 2.78; 95% CI, 1.71-4.50; prevalence difference, 249.6/100,000; 95%CI, 89.7-409.6) and noncritical heart defects (7306.9/100,000 [401/5488]; prevalence ratio, 5.55; 95%CI, 4.98-6.19; prevalence difference, 6089.2/100,000; 95%CI, 5350.0-6828.3).
CONCLUSIONS AND RELEVANCE:
In this population-based study, preeclampsia was significantly associated with noncritical heart defects in offspring, and preeclampsia before 34 weeks was associated with critical heart defects. However, the absolute risk of congenital heart defects was low.
PMID: 26501535 [PubMed - indexed for MEDLINE]

16.
Ultrasound Obstet Gynecol. 2015 Oct;46(4):391-7. doi: 10.1002/uog.14915.
Ultrasound screening for fetal growth restriction at 36 vs 32 weeks' gestation: a randomized trial (ROUTE).
Roma E, Arnau A, Berdala R, Bergos C, Montesinos J, Figueras F.

Abstract
OBJECTIVE:
To compare the utility of routine third-trimester ultrasound examination at 36 weeks' gestation with that at 32 weeks in detecting fetal growth restriction (FGR).
METHODS:
This was an open-label parallel randomized trial (ROUTE study) conducted at a single general hospital serving a geographically well-defined catchment area in Barcelona, Spain, between May 2011 and April 2014. Women with no adverse medical or obstetric history and a singleton pregnancy without fetal abnormalities at routine second-trimester scan were assigned randomly to undergo a scan at 32 weeks' gestation (n = 1272) or at 36 weeks' gestation (n = 1314). Primary outcome measures were detection rates of FGR (customized birth weight < 10(th) centile) and severe FGR (customized birth weight < 3(rd) centile).
RESULTS:
There were no significant differences in perinatal outcome between those who underwent a scan at 32 weeks' gestation and those who underwent a scan at 36 weeks' gestation. Severe

FGR at birth was associated significantly with emergency Cesarean delivery for fetal distress (odds ratio (OR), 3.4 (95% CI, 1.8-6.7)), neonatal admission (OR, 2.23 (95% CI, 1.23-4.05)), hypoglycemia (OR, 9.5 (95% CI, 1.8-49.8)) and hyperbilirubinemia (OR, 9.0 (95% CI, 4.6-17.6)). Despite similar false-positive rates (FPRs) (6.4% vs 8.2%), FGR detection rates were superior at 36 vs 32 weeks' gestation (sensitivity, 38.8% vs 22.5%; P = 0.006), with positive and negative likelihood ratios of 6.1 vs 2.7 and 0.65 vs 0.84, respectively. In cases of severe FGR, FPRs for both scans were also similar (8.5% vs 8.7%), but detection rates were superior at 36 vs 32 weeks' gestation (61.4% vs 32.5%; P = 0.008). Positive and negative likelihood ratios were 7.2 vs 3.7 and 0.4 vs 0.74, respectively.
CONCLUSION:
In low-risk pregnancies, routine ultrasound examination at 36 weeks' gestation was more effective than that at 32 weeks' gestation in detecting FGR and related adverse perinatal and neonatal outcomes.
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KEYWORDS:
fetal development; fetal growth restriction; neonatal complications; placenta; ultrasonography
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17.
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Impact of cerebral redistribution on neurodevelopmental outcome in small-for-gestational-age or growth-restricted babies: a systematic review.
Meher S, Hernandez-Andrade E, Basheer SN, Lees C.

Abstract
OBJECTIVES:
To review systematically the evidence on impact of cerebral redistribution, as assessed by fetal middle cerebral artery (MCA) Doppler, on neurological outcomes in small-for-gestational-age (SGA) or growth-restricted fetuses.
METHODS:
For this systematic review, MEDLINE was searched for all controlled studies reporting neurological outcomes in SGA or growth-restricted babies with cerebral redistribution based on MCA Doppler indices, from inception to September 2013. We used relative risk or odds ratios, with 95% CI, to identify the association of cerebral redistribution with neurological outcomes.
RESULTS:
The search yielded 1180 possible citations, of which nine studies were included in the review, with a total of 1198 fetuses. Definitions of SGA and cerebral redistribution were variable, as was study quality. Data could not be synthesized in meta-analyses because of heterogeneity in outcome reporting. Cerebral redistribution was not associated with increased risk of intraventricular hemorrhage in neonates (five studies; n = 806). When present in preterm fetuses, cerebral redistribution was associated with normal Neonatal Behavioral Assessment Scale (NBAS) scores at 40 weeks (one study; n = 62) but abnormal psychomotor development at 1 year of age on the Bayley scale (one study; n = 172). When present in term SGA fetuses,

cerebral redistribution was associated with increased risk of motor and state organizational problems on NBAS (two studies; n = 158), and lower mean percentile scores in communication and problem solving at 2 years of age on the Ages and Stages Questionnaire (one study; n = 125).
CONCLUSIONS:
SGA fetuses with cerebral redistribution may be at higher risk of neurodevelopmental problems. More data are needed from adequately controlled studies with long-term follow-up before conclusions can be drawn. If these findings are true, there is a need to re-evaluate timing of delivery in the management of SGA fetuses, particularly when cerebral redistribution is found at term gestation.
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KEYWORDS:
MCA; brain sparing; cerebral redistribution; cerebroplacental ratio; middle cerebral artery; neurodevelopment; neurological outcome
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