

Ascertaining Birth Defects: Findings From a National Children's Study Workshop

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Workshop Objectives

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To Outline Feasible Protocols For:

- Ascertaining birth defects in a systematic and reliable manner across facilities; and
- Pilot studies



Possible Examinations by Lifestage

	Prenatal	Birth	1yr	2–5 yr	6 yr	14 yr
Maternal Blood	✓					
2D Fetal U/S	✓					
Fetal Echo	S*					
Family History	✓	✓	✓	✓	✓	✓
Patient History		✓	✓	✓	✓	✓
Physical Exam		✓	✓	✓	✓	✓
Photos		✓	✓	✓	✓	✓
Pulse Oximetry		✓				
Cytogenetics		S				
Placental Pathology		S				
2D Echocardiogram		✓				✓
ECG					✓	
MRI/MRA						S

*S = select individuals

Special Considerations – Prenatal

Exams	Timing (weeks GA)	Issues
2D U/S	11–14, 18–23, 30+/-2 weeks	QC
3D U/S	18–23	Training/QC
MRI	When anomaly suspected	Training/QC
Maternal blood sampling	Preconception, 11–14, 15–20	None

Possible Pilots

- MRI – in small subgroup @ 30 +/- 2 WGA to determine if MRI will increase ascertainment of birth defects above U/S alone; must be performed in tertiary center
 - Goal = determine feasibility of fetal MRI for entire cohort



Additional Recommendations

- All specimens banked, including: paternal semen specimens, cord blood, etc.
- U/S must be performed in an accredited practice
- Maternal blood specimen rationale: increase sensitivity of targeted U/S; may also indicate IUGR and fetal death
- Sensitivity of some biochemical markers is better before 11 WGA or after 15 WGA

Prevalence of Major Congenital Malformations (per 1,000 examined)*

System	Embryo	PVF	SBF	Newborn
CNS	23	12	49	1
CVS	15	96	15	7
Alimentary	12	76	10	5
Musculoskeletal	18	53	13	5

*Dimmick JE, Kalousek DK. *Developmental Pathology of the Embryo and Fetus*. 1987 (pg 67)
PVF <20 wks GA

Special Considerations – Fetal Deaths

Exams	Location	Issues
External Exam/Anthropometry	Center	Site, GA, Condition
Internal Exam	Center	Site, GA, Condition
Imaging	Center	Site, GA, Condition
Digital Photography	Field	None
Chromosomal Analysis	Center	Site, Condition

Possible Protocols

- Standard postmortem (PM) examination to ascertain structural and/or chromosomal anomalies
 - Modifications for GA, condition of fetus, consent, and options for limited exam
- PM exam as part of a comprehensive and standard protocol to determine conditions associated with fetal losses (spontaneous and induced), infant, and child death
 - Existing standard protocols modified for the National Children's Study
- Standard protocol for placental examination in all pregnancies

Possible Pilots

- Feasibility of postmortem in 12–20 week
- Feasibility of MRI to ascertain structural anomalies in cases of autopsy refusal
- Use of 3D photography for non-macerated, intact fetuses
- Prevalence of confined placental mosaicism in normal, growth restricted, and congenital anomalies (sample)

Special Considerations – Heart Defects

Exams	Timing	Issues
Family and Patient History, Exam	Every visit	None
Fetal Echo	18–22 weeks	Site, Costly, False +/-
2D Echo	Birth, 14 yrs	Site, Costly, False +/-
Pulse Oximetry	24–36 hours	False negatives
ECG	6 yrs	Equipment, interpretation

Possible Protocols

- Prenatal period (18–22 wks):
 - Echo: stick volume or equivalent
 - Referral to center in absence of reassuring scan
- Newborn period (24–36 hrs):
 - H&P, Echo (including coronaries), Pulse ox
- 6 yrs old:
 - H&P, ECG
- 14 yrs old:
 - H&P, Echo (a restricted one: mass and volume)



Possible Pilots

- Neonatal and 14 y/o Echo: Coronary artery screening
- Fetal echocardiogram at 18–22 wks: fetal echo vs. fetal screen (extended, heart screening exam)

Special Considerations – Other Defects

Exams	Timing	Issues
Dysmorphologic exam	1–3 days, every 5–7 yrs	
Standardization Med history	Prenatal, 1–3 days	
Standardization 2D photos of face	1 and 3 yrs	

Recommendations for Protocols

- Training for structured dysmorphologic exam
 - Develop standard tool
 - Identify trainer and small number of trainees
 - QC
 - Accuracy in comparison to expert
 - Inter- and intra-observer reliability and reproducibility
- Centralized training of all Study personnel



Recommendations for Sub-Study Protocols

- Indicators: ≥ 1 major, ≥ 3 minor malformations
- Referral to dysmorphologist for assessment of additional investigations