
Genetic Services Policy Project Final Report

Multiple Congenital Anomalies: A Policy Brief

What are multiple congenital anomalies (MCA)?

- Congenital anomalies (birth defects) are defects existing at or usually before birth.
- Infants with multiple congenital anomalies (MCA) are typically infants with:
 - two or more major malformations (e.g., a neural tube defect, cardiac defect, missing limb), or
 - three or more minor malformations (e.g., syndactyly, a club foot, abnormally formed pinnae).
- Clinical course and prognosis for MCA is highly variable and dependent on the particular anomalies or syndrome present.
- Birth defects are the leading cause of death in infants under age 1 year in the U.S., accounting for over 5,500 infant deaths annually.

Who is affected by MCA?

- Birth defects affect 3% of all newborns in the United States; 1% of newborns have multiple defects or syndromes.
- The most common condition associated with MCA is Down syndrome, which affects 1 out of 800 children and 5,500 births per year in the U.S.
- All racial and ethnic groups are affected, though individuals of low socioeconomic status (SES) may be at higher risk due to environmental or lifestyle factors. In addition, births of infants with MCA may be more common in low SES groups due to lack of access to prenatal care and termination services.
- Anomalies are present in a significant number of pregnancies that end in spontaneous abortion or elective termination.

What are the genetic and non-genetic contributions to MCA?

- Congenital anomalies may result from a number of underlying causes involving both genetic (e.g., single gene or chromosomal abnormalities) and environmental factors (e.g., maternal drug use or illness). Up to 60% of isolated congenital anomalies have no known origin.
- Many cases of MCA are associated with chromosomal abnormalities, including an abnormal number of chromosomes or aneuploidy (e.g., trisomy or monosomy) or abnormal chromosomal structure (e.g., deletions, duplications, etc.). Down syndrome is caused by an extra copy of chromosome 21 and is also known as Trisomy 21.
- Advanced maternal age is a major risk factor for MCA due to aneuploidy. This relates to the increase in chromosomal meiotic errors that occur with age. (Yoon et al, 1996)
- Numerous studies have examined the relationship between environmental pollutants and congenital anomalies, but there is little evidence of clear associations. (Dolk, Vrijheid 2003)

What are the clinical features of MCA?

- Abnormalities vary depending on the underlying cause of MCA. Common abnormalities

include cardiac defects, cleft lip/cleft palate, neural tube defects (NTDs), musculoskeletal defects, abnormalities of the eye, and gastrointestinal or genitourinary defects.

- MCA is often associated with cognitive delay or other neuro-developmental concerns.
- Particular constellations of abnormalities are associated with different syndromes.

What are the psychosocial impacts of MCA?

- MCA is often associated with significant psychosocial impacts on families.
- Couples may experience internal conflicts related to religious and moral values and societal pressure to terminate affected pregnancies.
- Grief may accompany pregnancy termination and may be long lasting, even if parents feel the decision was right. (Korenromp et al, 2007)
- Post-partum depression is more common after the birth of a child with birth defects.

Who provides care for MCA? In what setting?

- Many health care professionals may be involved in evaluating, diagnosing and treating a fetus or child with MCA: primary care providers (obstetrical or pediatric), perinatal specialists, clinical geneticists/dysmorphologists, genetic counselors, and varied pediatric specialists (e.g. cardiologists, urologists, neurologists, surgeons). Nurses, social workers, nutritionists, speech/hearing/physical therapists, and others may also be involved in care.
- Children with complex needs associated with MCA are likely to benefit from comprehensive coordinated care in a medical home setting.
- Public health nurses from local Children with Special Health Care Needs programs may provide home visitation or other services for affected children.

What are standard treatments and therapies for MCA?

- Many pregnancies in which the fetus is identified with MCA through prenatal diagnosis are electively terminated. The termination rates vary depending on the anomalies identified. One decade-long study found termination rates of 28 percent for oral clefts and 62 to 84 percent for chromosomal anomalies.
 - Rates of elective termination are usually higher for more severe conditions.
 - Women who choose to undergo prenatal testing may be more likely to choose to terminate an affected pregnancy than women who opt not to have testing.
- For live-born infants, the prognosis and therapies depend on the nature of the condition.
- Infants with MCA usually need complex medical and surgical management. Care is tailored to clinical need and ranges from palliative care to surgical and nutritional interventions.
- Families are typically referred to health care facilities that specialize in treating children. Multi-disciplinary teams are often needed to address complex needs and coordinate care.
- MCA is often associated with cognitive or sensory impairment that may require early intervention and special education and therapeutic services.
- Increasingly, individuals with conditions such as Down syndrome are living longer, thus requiring services into adolescence and adulthood.

What costs are associated with MCA?

- There are no overall estimates of costs associated with MCA because the term includes a multitude of different conditions and defects.

- An analysis conducted in 1992 provides an estimate of cost of illness for cerebral palsy and for 17 structural birth defects in the United States. For 1992, the combined estimated cost of the 18 conditions in the United States was \$8 billion. The three conditions with the highest lifetime costs were cerebral palsy, Down syndrome, and spina bifida.
- In 2004, birth defects were responsible for greater than 139,000 hospitalizations with a total cost of \$2.6 billion.

What is the role of genetic services in MCA?

- Overview
 - Genetic services play a role in the detection of MCA in the prenatal and newborn settings (or later), evaluation and diagnosis of the etiology of MCA, and in counseling for reproductive decision-making. Genetic research plays a major role in elucidating the causes of MCA and the development of testing, treatment, and prevention strategies.
 - Despite the availability of prenatal screening and testing services, congenital anomalies are often not identified prior to birth. This may be due to women choosing not to have prenatal screening or testing, lack of access to such testing, or to limitations in the testing technology or users. In one study in Hawaii, less than 16% of congenital anomalies were diagnosed in the prenatal period despite high rates of fetal ultrasound use and moderate use of invasive testing. (Forrester, Mertz 2006) In another study, only 50% of Down syndrome births had the condition identified prenatally. (Benn, Egan et al. 2004)
- Prenatal screening and diagnosis
 - Expert opinion now recommends offering screening and/or invasive testing for Down syndrome and other anomalies in all pregnancies, regardless of maternal age. (ACOG, 2007) Previous guidelines recommended invasive testing primarily in women 35 years of age or older at the time of delivery.
 - Serum screening can identify fetuses at risk for MCA associated with chromosomal aneuploid (e.g., Down syndrome, Trisomy 13 or 18) or open lesions (e.g., spina bifida, omphalocele).
 - A number of different screening methods are available including:
 - Multiple marker maternal serum screening at 15 to 18 weeks gestation (using three or four markers)
 - Integrated serum screening including markers in the first and second trimester
 - First trimester screening with nuchal translucency (an ultrasound technique) and serum markers followed by second trimester serum screening for NTDs
 - Fetal ultrasound (anomalies scan) at 19 to 21 weeks gestation
 - Sensitivity and specificity of different screening protocols vary, but no protocol identifies 100% of affected pregnancies.
 - Fetal MRI, fetal echocardiographs, and amniocentesis with cytogenetic or molecular testing may follow a prenatal screen that demonstrates an increased risk of an affected fetus. A woman or couple can then make more informed decisions about the pregnancy, including continuation of the pregnancy to term or termination.
 - Women over age 35 years, and increasingly younger women, are being offered

- invasive testing as a first line procedure with chorionic villus sampling (CVS) in the first trimester or amniocentesis in the second trimester.
- Pre-implantation genetic diagnosis may also be used with *in vitro* fertilization to identify and deselect embryos with aneuploidy or other genetic/chromosomal abnormalities that may result in MCA.
 - Future trends include the development of non-invasive procedures to obtain fetal cells for prenatal testing, and the increased use of tests such as array-based genomic hybridization/chromosomal microarray analysis (CMA) that can rule out large numbers of disorders in one test.
- Evaluation of the newborn
 - Clinical geneticists, when available, are typically involved in the evaluation of MCA, documenting malformations, signs, and symptoms in order to compare against known syndromes.
 - Several factors must be considered in assessing MCA etiology: maternal health history, prenatal history, family history, and careful and detailed physical examination of the infant.
 - Genetic testing may help to rule out or confirm a suspected single gene disorder or chromosomal abnormality if maternal and pregnancy history are inconclusive.
 - Biochemical studies, molecular testing, karyotype analysis and/or fluorescence *in-situ* hybridization (FISH) testing may help to provide a diagnosis.
 - Identification of a large number of chromosomal abnormalities that were previously undetectable through standard tests may now be detected through CMA. This is likely to increase the number of cases of MCA with an official diagnosis.
 - Genetic counseling
 - Genetic counseling is indicated for pregnant women and couples who are at higher risk for an affected pregnancy based on screening tests or clinical factors or who have an affected pregnancy or child with MCA. Counseling may assist the couple in determining risk for recurrence and providing guidance and support through the diagnostic and follow-up process.

Who uses genetic services for MCA? Where are the gaps?

- The exact number of women who utilize prenatal screening, diagnostic testing, and/or genetic counseling services during pregnancy is not known, though the majority of pregnant women who receive prenatal care are likely to be offered some level of screening or testing.
- The availability of improved screening techniques (e.g., serum screening and ultrasound) has led to a decrease in the use of invasive procedures. (Benn, Egan, et al. 2004)
- The impact of new guidelines recommending that all pregnant women be offered the option of invasive testing is not yet known, but has the potential to reverse trends and increase utilization of invasive testing and genetic counseling services.
- Factors associated with refusal of prenatal testing have been evaluated. In one study, women who had never had a pregnancy termination, were Spanish-speaking Latina, or who scored high on a religiosity scale were more likely to refuse prenatal screening tests. (Press, Browner 1998) In another study, lower income African American women aged 35 or greater were less likely to utilize prenatal testing, due to greater faith or fatalism and lower perceived value of testing information. Higher income women had increased test use due to lower faith or fatalism and lower perceived procedure-related miscarriage risk. (Learman et al., 2003).

- A study of over 15,000 cases of birth defects in Hawaii found that genetic counseling facilities were utilized in 1,596 (10.6%) of cases. Utilization rates were higher with the presence of multiple major birth defects, chromosomal abnormalities, malformations, certain specific defects (e.g., holoprosencephaly), death of a fetus or infant, and older maternal age. (Forrester, Mertz 2007)

Are high quality genetic services for MCA available and accessible?

- Availability of services
 - Prenatal screening services are available in all areas of the country, but certain procedures are only available in larger centers.
 - First trimester screening involving nuchal translucency is only available in certain medical centers, due to the technical requirements of the procedure.
 - Comprehensive prenatal testing (e.g., amniocentesis) and genetic counseling are often unavailable in smaller communities or rural/frontier areas, which may require travel.
 - California is the only state that has a mandatory state-administered prenatal screening program. All pregnant women must be offered screening and all insurers must cover the screening fee, but women can opt out.
 - Availability of medical genetics consultation for the evaluation of newborns with MCA is limited by:
 - Geographic distribution of providers in larger metropolitan areas, and
 - Relatively small total number of geneticists nationwide.
 - Chromosomal microarray technology for evaluation of MCA is currently available from a limited number of laboratories, including Baylor College of Medicine, Signature Genomics, and Perkin Elmer/Spectral Genomics. However, any physician or authorized provider can order CMA.
- Quality of services
 - Professional standards and guidelines exist for prenatal screening and diagnosis, genetic counseling, and evaluation of newborns with MCA.
 - Prenatal care performance measures have been developed to monitor compliance with some standards (e.g., offering maternal serum screening to women less than 35 years and invasive testing to women 35 years and older). Health plans may use these measures to track individual providers or medical groups. Recent changes in clinical standards will require updating of performance measures.
 - The quality of information provided to parents with an affected pregnancy is of concern to some disability advocates. Anecdotes from parents suggest that many physicians and other health care providers do not provide balanced information about the realities of raising a child with disabilities, focusing primarily on the negative aspects.
- Financial access to services
 - Public and private payers typically support coverage of prenatal screening and/or diagnostic services. Individual health plans, however, may not include prenatal care as a covered benefit or may have limitations on coverage.
 - Newer technologies such as CMA may not be covered, and companies that offer these services may require upfront payment pending insurance decisions.
 - Washington is the only state that mandates Medicaid coverage of prenatal genetic counseling.

What genetic service delivery or policy issues does this case highlight?

- Current clinical policy issues and controversy revolve largely around prenatal screening and diagnosis of congenital anomalies. Trends and policy recommendations advocating earlier prenatal screening in the first trimester are based on the premise that earlier pregnancy terminations are safer. Systems are needed to assure that women and couples are given accurate and balanced information to make informed choices about these pregnancies. Availability of tests such as chromosomal microarrays that can identify large numbers of disorders, some of undetermined significance, will be a challenge for genetic counseling and informed consent processes. Disparities may increase as women who do not have access to early or adequate prenatal care will not receive prenatal testing and will not have the option to terminate affected pregnancies.
- Many disability advocates are concerned about the increased attention on prenatal screening and diagnosis, particularly for non-lethal disorders such as Down syndrome. They argue that the primary purpose of prenatal testing is for the elimination of disabilities, which devalues people living with disabilities. They believe additional resources should be allocated to support people with disabilities as opposed to preventing their births. There are also concerns that pregnant women and couples are not being given balanced information about raising a child with disabilities, leading to uninformed choices.
- Legal issues related to MCA include abortion rights and wrongful birth lawsuits, which hold health care providers liable for failing to diagnose a condition during pregnancy. Abortion regulations have the potential to decrease access to pregnancy termination, particularly in the later stages of pregnancy. Concern about liability for wrongful birth is likely to increase the use of prenatal screening and diagnosis by obstetric providers.
- Other policy issues include coverage and payment for services by private payers, academic and industry policies related to the development, pricing, and marketing of prenatal and other tests, and hospital and health system policies related to pregnancy termination (particularly for those with religious affiliation).

References

(1999) "Evaluation of the newborn with single or multiple congenital anomalies: a clinical guideline." American College of Medical Genetics Foundation Clinical Guidelines Project, sponsored by New York State Department of Health, 1999. <http://www.health.state.ny.us/nysdoh/dpprd/index.htm>

American College of Obstetricians and Gynecologists (ACOG). Screening for fetal chromosomal abnormalities. ACOG Practice Bulletin #77, January 2007.

Asch A. Prenatal diagnosis and selective abortion: a challenge to practice and policy. *American Journal of Public Health* 1999;89(11):1649-57.

Ball R, Caughey A, Malone F, et al. First and second trimester evaluation of risk for Down syndrome. *Obstet Gynecol* 2007;110:10-17.

Bauer P. What's lost in prenatal testing: why encourage testing for Down syndrome. *Washington Post*, January 14, 2007. Accessed on August 23, 2007 from <http://www.washingtonpost.com/wp-dyn/content/article/2007/01/12/AR2007011201954.html>

Benn P, Egan J, Fang M, Smith-Bindmann R. Changes in the utilization of prenatal diagnosis. *Obstetrics and Gynecology* 103:1255-1260 (2004)

California Expanded AFP (XAFP) Screening program www.dhs.ca.gov/pcfh/gdb/html/PS/PS.htm (accessed 3/12/07 and 7/31/07)

Campbell K, Grosse S, Chattopadhyay S. Prenatal diagnosis of chromosomal abnormalities and neural tube defects evidence statement: screening and testing. In: Campbell KT, Lanza A, Dixon R, Chattopadhyay S, Molnari N, Finch R, editors. *A Purchaser's Guide to Clinical Preventive Services: Moving Science into Coverage*. Washington DC: National Business Group on Health. 2006.

Centers for Disease Control and Prevention (CDC). Economic costs of birth defects and cerebral palsy—United States, 1992. *MMWR* 1995; 44(37): 694-9.

CDC. Hospital stays, hospital charges, and in-hospital deaths among infants with selected birth defects—United States, 2003. *MMWR* 2007; 56(02):25-9.

CDC. Improved national prevalence estimates for 18 major birth defects—United States, 1999-2001. *MMWR* 2006;54(51&52):1301-5.

Correa-Villasenor A, Cragan J, et al. (). "The Metropolitan Atlanta Congenital Defects Program: 35 years of birthdefects surveillance at the Centers for Disease Control and Prevention." *Birth Defects Res A Clin Mol Teratol* 2003; 67(9):617-24.

Dolk H, Vrijheid M. The impact of environmental pollution on congenital anomalies. *British Medical Bulletin* 2003;68(1):25-45.

Ewigman BG, Crane JP, et al. Effect of prenatal ultrasound screening on perinatal outcome. RADIUS Study Group. *N Engl J Med* 1993; 329(12): 821-7.

Forrester MB, Merz RD. Genetic counseling utilization by families with offspring affected by birth defects, Hawaii, 1986-2003. *Am J Med Genet A* 2007;143(10):1045-52.

Forrester MB, Merz RD. Use of prenatal diagnostic procedures in pregnancies affected with birth defects, Hawaii, 1986-2002. *Birth Defects Research (Part A)* 2006;76:778-80.

- Forrester MB, Merz RD, Yoon PW. Impact of Prenatal Diagnosis and Elective Termination on the Prevalence of Selected Birth Defects in Hawaii. *Am J Epidemiol* 1998;148(12):1206-1211.
- Gessner BD. Reasons for trisomy 13 and 18 births despite availability of prenatal diagnosis and pregnancy termination. *Early Hum Dev* 2003;73(1-2):53-60.
- Grody WW. Ethical issues raised by genetic testing with oligonucleotide microarrays. *Mol Biotechnol* 2003;23(2):127-38.
- Johnson K, Posner S, Biermann J, et al. Recommendations to improve preconception health and health care—United States. A report of the CDC/ATSDR Preconception Care Workgroup and Select Panel on Preconception Care. *MMWR Recomm Rep* 2006; 55(RR-6):1-23.
- Kalter H, Warkany J.. Congenital malformations (second of two parts). *N Engl J Med* 1983;308(9): 491-7.
- Kalter H, Warkany J. Medical progress. Congenital malformations: etiologic factors and their role in prevention (first of two parts). *N Engl J Med* 1983;308(8): 424-31.
- Korenromp M, Page-Christiaens G, van den Bout J, et al. A prospective study of parental coping 4 months after termination of pregnancy for fetal anomalies. *Prenatal Diagnosis* 2007; 27(8):709-16.
- Khoshnood B, De Vigan C, Vodovar V, et al. Advances in medical technology and creation of disparities: the case of Down syndrome. *Am J Public Health* 2006;96:2139-2144.
- Learman, L.A., Kuppermann, M., Gates, E., Nease R.F., Gildengorin, V. and Washington, A.E. (2003) Social and familial context of prenatal genetic testing decisions: are there racial/ethnic differences? *American Journal of Medical Genetics*, 119C, 19– 26.
- Malone FD, Canick JA, Ball RH, et al. First-trimester or second-trimester screening, or both, for Down's syndrome. *NEJM* 2005; 353(19):2068-70.
- March of Dimes. Birth Defects: Quick References and Fact Sheets. Pregnancy and Newborn Health Education Center. 2002. Retrieved February 26, 2006, from http://www.marchofdimes.com/printableArticles/4439_1206.asp.
- Mathews TJ, Menacker F, et al. Infant Mortality Statistics from the 2001 Period Linked Birth/Infant Death Data Set. *National Vital Statistics Report* 2003;52(2): 1-27.
- Ming JE, Geiger E, James AC, et al. Rapid detection of submicroscopic chromosomal rearrangements in children with multiple congenital anomalies using high density oligonucleotide arrays. *Hum Mutat* 2006; 27(5):467-73.
- Menten B, Maas N, Thienpont B, et al. Emerging patterns of cryptic chromosomal imbalance in patients with idiopathic mental retardation and multiple congenital anomalies: a new series of 140 patients and review of published reports. *J Med Genet* 2006; 43(8):625-33.
- National Down Syndrome Congress Press Release January 23, 2007. NDSC, Atlanta, Georgia. www.ndscenter.org
- Obido A, Stamilio D, Nelson D, et al. Cost effectiveness analysis of prenatal screening strategies for Down syndrome. *Obstet Gynecol* 2005; 106(3):562-8.
- Prescott K, Wilkie A. Genetic aspects of birth defects: new understandings of old problems. *Arch Dis Child Fetal Neonatal Ed* 2007; 92:F308-314.
- Press N, Browner CH. Characteristics of women who refuse an offer of prenatal diagnosis: data from the California maternal serum alpha fetoprotein blood test experience. *Am J Med Genet* 1998; 78:433-45.
- Russo CA, Elixhauser A. Hospitalization for birth defects, 2004. *Healthcare Cost and*

Utilization Project Statistical Brief #24. January 2007.

Sahoo T, Cheung SW, Ward P, Darilek S, et al. Prenatal diagnosis of chromosomal abnormalities using array-based comparative genomic hybridization. *Genetics in Medicine* 2006; 8(11):719-27.

Sekhobo JP, and Druschel CM. An evaluation of congenital malformations surveillance in New York State: an application of Centers for Disease Control and Prevention (CDC) guidelines for evaluating surveillance systems." *Public Health Rep* 2001; 116(4): 296-305.

Shaffer LG, Bejjani BA. Medical applications of array CGH and the transformation of clinical cytogenetics. *Cytogenetic and Genome Research* 2006;115:303-9.

Shuster E. Microarray genetic screening: a prenatal roadblock for life? *Lancet* 2007; 369:526-29.

Sowards KA. What is the leading cause of infant mortality? A note on the interpretation of official statistics. *Am J Public Health* 1999; 89(11): 1752-4.

Trust for America's Health. Birth defects tracking and prevention: too many states are not making the grade. Issue Report, February 2002

Weil E. A wrongful birth? *N Y Times Mag*, March 12, 2006:48-53.

Wilcox LS, Marks JS, eds. From data to action: CDC's public health surveillance for women, infants, and children. Atlanta, U.S. Dept. of Health & Human Services, Public Health Service, Centers for Disease Control and Prevention, 1993.

Yoon P, Freeman S, Sherman L, et al. Advanced maternal age and the risk of Down syndrome characterized by the meiotic stage of chromosomal error: a population based study. *Am J Hum Genet* 1996; 58(3): 628-33.

This work is supported in part by Projects # U35MC02601 and # U35MC02602 from the Maternal and Child Health Bureau (Title V, Social Security Act), #11223, Health Resources and Services Administration, Department of Health and Human Services.