Guidelines for Conducting Birth Defects Surveillance

Chapter 12

Inclusion of Prenatal Diagnoses in Birth Defects Surveillance

Prenatal Diagnosed Defects Workgroup and Other Technical Contributors
Janet D. Cragan, Chair (CDC)
Marlene Anderka (MA)
Jan Byrne (UT)
Mark Canfield (TX)
Marlena Clary (SC)
Tiffany Colarusso (CDC)
Mary Ethen (TX)
Marcia Feldkamp (UT)
Cara Mai (CDC)
Brad McDowell (IA)
Richard Olney (CDC)
Lowell Sever (WA)
Stuart Shapira (CDC)
Brenda Silverman (CDC)
Barbara Warmerdam (CA)

Carter Consulting
Russell Kirby, Editor
Harriett Grissom, Technical Editor

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National Birth Defects Prevention Network, Inc.
Web site: http://www.nbdpn.org
E-mail: nbdpn@nbdpn.org

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12.1 Introduction

The goals of this chapter are 1) to outline the rationale for including ascertainment of prenatally diagnosed defects in birth defects surveillance; 2) to provide a methodological approach for this activity; and 3) to discuss issues that can arise in relation to including these defects. The chapter is intended to help birth defects surveillance programs assess whether and how to include ascertainment of prenatally diagnosed defects in program activities and to offer guidance about how to do so.

While including prenatally diagnosed defects in birth defect surveillance poses some unique challenges, the information in this chapter is meant to augment—not replace—the material in other chapters which describe the basis for conducting birth defects surveillance in general.

12.2 The Rationale for Including Prenatally Diagnosed Defects

The development, advancement, and widespread availability of prenatal screening and diagnostic techniques have made it possible to diagnose a wide variety of structural and genetic abnormalities prior to delivery. The ability to identify such conditions during the first or second trimester of pregnancy can facilitate alternative approaches for managing affected pregnancies, such as delivery and care of the infant at a tertiary center, undertaking therapeutic interventions during gestation (e.g., fetal surgery), or electively terminating the pregnancy. Prenatal diagnosis also has led to increased understanding of the natural history of some abnormalities and has aided correlation of what is observed in the fetus *in utero* with what is seen in the newborn.

Including prenatally diagnosed defects in birth defects surveillance is important for the following reasons:

- *Underestimation of defect prevalence* –When defects are severe or life-threatening, elective termination of the pregnancy may frequently be chosen. The ability to diagnose congenital defects prenatally and to terminate affected pregnancies has implications for the accuracy and completeness of birth defects surveillance data. If surveillance is limited to live births (with or without stillbirths or spontaneous abortions), failure to ascertain electively terminated pregnancies can lead to underestimation of the prevalence of these defects in the population, or in subgroups of the population. It can also limit a program's ability to monitor changes and trends in the prevalence of defects over time and across population subgroups.

- *Targeting prevention efforts* –Identifying pregnancies that have been affected by defects can help to target prevention and education efforts for future pregnancies. An example is promotion of folic acid use among women who have experienced a pregnancy affected with a neural tube defect. Failure to ascertain all of these pregnancies after prenatal diagnosis can lead to missed opportunities for prevention.

- *Evaluation of prevention efforts* – In order to evaluate the effectiveness of prevention efforts, the prevalence of the defect must be assessed accurately. As noted above, failure to ascertain all pregnancies after prenatal diagnosis, including those for which elective termination is chosen, can lead to underestimation of defect prevalence and possible overestimation of the success of prevention efforts.

- *Bias in epidemiologic studies of birth defects* – Unidentified factors associated with both the exposure and the outcome of interest in a study can lead to bias in the results. If factors associated with either prenatal diagnosis of a defect or the choice of elective termination after prenatal diagnosis are also associated with the exposure of interest, then failure to ascertain pregnancies diagnosed prenatally and those electively terminated after prenatal diagnosis can bias a study's findings (Cragan & Khoury, 2000).

12.3 Terminology

Diagnostic Laboratory Test

This is a laboratory test performed on a sample obtained through a prenatal diagnostic procedure (see below) to identify or exclude a defect. These tests also can be performed on samples collected after delivery or in older children or adults. Examples include karyotype, fluorescent *in-situ* hybridization (FISH), and microarray.

Perinatal Surveillance

The term "perinatal surveillance" can be used in clinical practice to refer to any effort made to evaluate fetal well-being. Such efforts can include monitoring fetal heart rate, kick counts, and other measures as well as diagnostic procedures such as prenatal ultrasound. Perinatal surveillance is conducted exclusively in the clinical care of individual patients and should not be confused with the inclusion of prenatally diagnosed defects in public health surveillance for birth defects.

Prenatal Diagnosis

As opposed to prenatal screening, prenatal diagnostic testing is conducted to confirm or rule out the presence of a defect. Examples include the use of amniocentesis to detect or exclude chromosomal abnormalities, or fetal anomaly ultrasound scans to identify or exclude structural malformations. Diagnostic testing can be conducted as a follow-up to positive screening tests, or for simultaneous screening and diagnosis. Birth defect surveillance programs should ascertain prenatal diagnoses of defects regardless of whether prenatal screening was conducted or whether the result of such screening was positive or negative.

However, the sensitivity and specificity of prenatal diagnostic testing, and the certainty of the resulting diagnoses, can vary with different techniques, different defects, and associated factors (see Section 6). Definitive diagnosis can require serial prenatal testing or, in some instances, it must await confirmation after delivery.

Prenatal Diagnostic Procedure

This is a medical procedure conducted on a pregnant woman for the purpose of diagnosing a birth defect in the fetus. In some instances, the procedure itself is sufficient to make a diagnosis or rule it out. For example, an anomaly scan or fetal echo may be conducted to evaluate fetal anatomy. In other instances, the procedure is

performed to obtain a sample for diagnostic laboratory tests that can identify an abnormality. For example, amniocentesis (a medical procedure) is used to obtain a sample of amniotic fluid upon which a karyotype (a cytogenetic laboratory test) is performed to make a diagnosis (e.g., trisomy 18).

Prenatal Screening

Technologies are available to screen pregnancies prenatally for certain types of defects. The intent of prenatal screening is to identify pregnancies that may be at higher risk for a defect and that may call for additional diagnostic testing. An example is measurement of maternal serum markers and fetal nuchal fold thickness in the first trimester to screen for Down syndrome. Because identification of conditions through prenatal screening is always presumptive, an abnormal result does not necessarily indicate the actual presence of a defect. Subsequent diagnostic testing to confirm a provisional diagnosis based on screening is required to establish when the defect is truly present (true positive) and when it is not (false positive). In addition, prenatal screening tests are not necessarily specific to individual defects but may reflect a range of potential abnormalities. Thus, diagnostic testing is required to identify whether a condition actually is present as well as the nature of the condition.

For these reasons, birth defect surveillance programs should focus on ascertainment of prenatal diagnoses of defects, not on abnormal screening results. However, the availability and use of prenatal screening in a population can influence the likelihood that a pregnant woman will subsequently undergo confirmatory prenatal diagnosis.

Prenatal Surveillance

The term “prenatal surveillance” has been used in different contexts to refer to various types of ascertainment such as inclusion of pregnancies electively terminated after prenatal diagnosis in surveillance methods; ascertainment of prenatal diagnoses regardless of the pregnancy outcome (live birth, stillbirth, spontaneous abortion, elective termination); ascertainment of prenatal screening results; or a combination of these. Because the methods utilized by individual programs to include prenatal diagnoses in surveillance data vary with different situations, it is recommended that use of this term be abandoned.

12.4 Prenatal Diagnostic Procedures

Prenatal diagnostic procedures currently available include the following:

- Amniocentesis
  - Insertion of a needle through the mother's abdomen under ultrasound guidance in order to remove a sample of fluid from the amniotic sac.
- Chorionic villus sampling (CVS)
  - Insertion of a needle through the mother's cervix or through the abdomen under ultrasound guidance in order to remove a sample of tissue (villi) from the placenta.
- Cordocentesis or percutaneous umbilical blood sampling (PUBS)
  - Insertion of a needle through the mother's abdomen under ultrasound guidance in order to remove a sample of fetal blood.
- Fetal anomaly ultrasound scan
  - A systematic, detailed, prenatal ultrasound performed in order to evaluate each part of the fetal anatomy, determine the position of the placenta, assess the amount of amniotic fluid, and measure fetal growth.
- Fetal echocardiogram
  - A systematic, detailed, prenatal ultrasound performed in order to evaluate each part of the fetal heart, its function, and rhythm.
- Fetal magnetic resonance imaging (MRI)
  - Magnetic resonance imaging across the mother's abdomen in order to evaluate the fetal anatomy. It often is performed as a follow-up to prenatal ultrasound when there is a need to further clarify fetal structures.

Other commonly used prenatal procedures that do not lead to diagnosis of a defect include the following:

- Maternal serum sampling for determination of the level of alpha-fetoprotein (MSAFP), human chorionic gonadotropin (hCG), unconjugated estradiol, inhibin A, pregnancy-associated plasma protein A (PAPP-A), or other markers.
- Ultrasound performed for purposes of dating, fetal viability, or other indications not related to detection of a structural fetal abnormality. However, in some instances, an ultrasound performed for these purposes can identify a defect.
- Amniocentesis for evaluation of lung maturity or other indications, usually performed in the third trimester or close to the time of delivery.

Because the field of prenatal diagnosis continues to advance and evolve, procedures will change with time as new techniques are developed.

Although programs may be interested in monitoring the use of screening and non-diagnostic procedures to evaluate prenatal services or for other purposes, these procedures are not the primary focus of birth defects surveillance.

12. 5 Pregnancy Outcomes Following Prenatal Diagnosis

In some contexts, the term prenatal diagnosis connotes that a pregnancy was electively terminated following the diagnosis of a defect. However, the outcome of a pregnancy after prenatal diagnosis can vary depending on the nature and severity of the defect, the woman's decisions about pregnancy management, and other factors. Depending on the timing of the diagnosis, a pregnancy diagnosed prenatally with a defect could lead to any of the following outcomes:

- *Live birth* – The decision is made to continue the pregnancy after prenatal diagnosis. This can allow time to consult with neonatal and pediatric specialists, as well as time to plan for the optimal place for delivery of the infant, the appropriate level of newborn care, and the needs of the child and family after discharge from the birth hospital. Also, for some conditions, prenatal diagnosis allows for fetal procedures to be performed that can improve the outcome for the infant at and after birth.

- *Stillbirth* – If the decision is made to continue the pregnancy after prenatal diagnosis and the pregnancy continues beyond 20 weeks gestation, the natural course of the pregnancy could nonetheless result in stillbirth. The cause of the stillbirth could be related to complications from the defect or to other factors unrelated to the prenatal diagnosis.

- *Spontaneous abortion* – If the prenatal diagnosis is made prior to 20 weeks gestation and the decision is made to continue the pregnancy, the natural course of the pregnancy could result in spontaneous abortion. The cause of the pregnancy loss could be related to complications from the defect or to other factors unrelated to the prenatal diagnosis.

- *Elective termination* – The decision is made to end the pregnancy voluntarily. This can occur soon after the diagnosis is made, or weeks to months later, once the processes of gathering information and decision-making are complete.

12.6 Utilization of Prenatal Diagnosis and Elective Termination

The medical, ethical, legal, and social issues surrounding the use of prenatal diagnosis and decisions about subsequent pregnancy management are complex. These factors are likely to vary among geographic regions, populations, sub-segments of the same population, and over time (Peller, et al. 2004). Therefore, programs cannot assume that a consistent proportion of pregnant women in their surveillance population who undergo prenatal diagnosis will elect to terminate an affected pregnancy. The factors that most affect diagnosis and management of pregnancies with defects, as well as the need to ascertain those with prenatal diagnoses, are also likely to differ among surveillance programs. The use of prenatal diagnosis and elective termination in a particular population, and among subgroups and geographic areas of the population, thus will need to be assessed over time.

Factors that could affect whether women undergo prenatal diagnosis or elective termination of an affected pregnancy include the following (Velie and Shaw, 1996; Schechtman, et al., 2002):

- Availability of prenatal screening and diagnostic services in their area and the frequency of their use by health care providers
- Presence of indicators of a high-risk pregnancy (e.g. use of assisted reproductive technology, maternal diabetes, advanced maternal age, known teratogen exposure) which can lead to increased scrutiny for complications, including birth defects
- Availability of specialized care for affected pregnancies and newborns in their area
- Availability of elective termination procedures in their area (e.g., rural vs. urban) and to their segment of the population, and the clinical settings in which it is provided
- Financial and insurance status, and the availability of resources for payment for prenatal diagnostic and elective termination services
- Gestational age at which the prenatal diagnosis is made
- Level of knowledge and understanding of the diagnosis and implications for the health of the child
- Beliefs and values regarding pregnancy management options, including elective termination
- Trust and confidence in the medical system and the level of medical care available
- Previous obstetric history

- Social and demographic factors such as age, race, ethnicity, education, religion, cultural factors and traditions, community setting (e.g., rural vs. urban)

- Family situation and the availability of personal support

12.7 Sensitivity and Specificity of Prenatal Diagnoses

The objective of including prenatally diagnosed defects in birth defects surveillance is to ascertain defects that would not have been identified otherwise. Ascertaining prenatally diagnosed defects also makes it possible to assess whether prenatal diagnosis of a defect affects postnatal care and outcome. However, the sensitivity, specificity, and predictive value of abnormal findings on prenatal diagnostic tests, and thus the certainty of the resulting diagnoses, can differ substantially from those for abnormalities identified after delivery. These factors can be affected by:

- Type of prenatal diagnostic procedure
- Nature, clinical significance, and natural course of the defect being evaluated
- Time during gestation when the procedure is performed
- Skill of the technician performing the procedure
- Experience of the physician interpreting the result
- Quality of the equipment
- Maternal factors such as obesity
- Factors related to laboratory testing (e.g., methods, standardization, reference values, interpretation of results)

12.7.1 Defect Prevalence Estimates Most Likely to be Affected by Prenatal Diagnosis and Elective Termination

According to birth defects surveillance programs that ascertain prenatal diagnoses, the prevalence estimates most affected by including pregnancies electively terminated after prenatal diagnosis are usually for those defects which are life threatening or associated with severe clinical outcomes. Using data from 1995–2004, the Metropolitan Atlanta Congenital Defects Program documented that including pregnancies electively terminated after prenatal diagnosis resulted in an increase of greater than 20% in prevalence for defects such as conjoined twins, neural tube defects, chromosomal abnormalities, cystic hygroma, bilateral renal agenesis, abdominal wall defects, atrioventricular septal defect without trisomy 21, and skeletal dysplasias (Cragan and Gilboa, 2009). Data from 1996-1997 analyzed by the Texas Birth Defects Monitoring Program reported an increase of 18% or greater in the prevalence of anencephaly, encephalocele, and trisomy 13 when defects among pregnancies electively terminated prior to 20 weeks gestation following prenatal diagnosis were included (Ethen and Canfield, 2002). The Hawaii Birth Defects Program observed increases in defect prevalence of greater than 40% for anencephaly, spina bifida, encephalocele, and trisomies 13, 18, and 21 when electively terminated pregnancies were included (Forrester, et al., 1998). In South Carolina, Allen, et al. (1996) reported that 51% of pregnancies with neural tube defects were electively terminated after prenatal diagnosis, results similar to the 40% reported by Velie and Shaw (1996) in California.

Women's decisions about the management of affected pregnancies and acceptance of elective termination as a management alternative can change with evolving information and perceptions about the severity and consequences of specific conditions. Therefore, the individual defects most affected by prenatal diagnosis and elective termination may vary over time and among surveillance populations.

12.7.2 Postnatal Verification of Prenatal Diagnoses

Many defects can be identified accurately based solely on prenatal findings. Examples include chromosomal abnormalities, anencephaly, spina bifida, and conjoined twins. Programs should include pregnancies diagnosed prenatally with these defects in their surveillance area even if the final outcome of the pregnancy or the date of the final outcome cannot be documented. Inclusion of these defects is important to estimate defect prevalence accurately.

However, not all defects can be identified accurately based solely on prenatal findings. The positive predictive value of prenatal ultrasound reported for congenital heart defects ranges from 70% to 98%, depending on the type of ultrasound (four chamber view alone, with outflow tract view, fetal echocardiography) and the specific cardiac defect (Forbus, et al., 2004; Gottliebson, et al., 2006; Oggè, et al., 2006; Gelehrter, et al., 2007). An analysis of data from the First and Second Trimester Evaluation of Risk (FaSTER) trial revealed a significant increase in missed diagnoses of cardiac anomalies in obese mothers (Aagaard-Tillery, et al., 2010). While fetal hydronephrosis can be detected by prenatal ultrasound, the optimal timing for evaluation of this condition is unclear. Screening too early in gestation might not detect its development, while some milder forms detected in the second trimester can improve or resolve prior to birth. In addition, the predictive value of prenatal hydronephrosis for the presence of postnatal renal pathology is not clear. While the degree of risk of postnatal pathology increases with the severity of prenatal hydronephrosis, some risk may be present for even mild forms of prenatal hydronephrosis. The optimal postnatal management of these children has not been established (Lee, et al., 2006).

Prenatal diagnostic testing also can lead to false positive findings if the abnormality is not confirmed or is not excluded postnatally. For example, the clinical significance of prenatal ultrasound findings suggesting a diagnosis of Dandy-Walker complex of the cerebellum (either a malformation or variant) often must be correlated with postnatal findings (Carroll, et al., 2000; Phillips, et al., 2006; Harper, et al., 2007). There are also instances when chromosomal abnormalities identified prenatally must be verified by a more definitive test. Chorionic villus sampling can reveal chromosomal abnormalities of the placenta, such as mosaicism, that are not present in the fetus (Sifakis, et al., 2010; Ledbetter, et al., 1990). These findings must be confirmed through amniocentesis or postnatal karyotype determination. In addition, even chromosome analysis based on amniocentesis, which is considered highly sensitive and specific for some abnormalities such as trisomy 21, can reveal unexpected or unusual chromosomal arrangements for which the clinical significance is unclear or unknown (Velthut, et al., 2009).

Including these conditions in birth defects surveillance data without post-delivery confirmation could result in misclassification or inflation of prevalence estimates. Therefore, prenatal

diagnoses reported by ascertainment sources should be confirmed through review of postnatal records–including pathology, autopsy, and laboratory records, as well as the results of diagnostic tests in live-born infants–whenever possible.

When postnatal confirmation is not possible, consistent criteria reflecting the certainty of prenatal findings should be applied when including prenatal diagnoses in birth defects surveillance data, regardless of whether the pregnancy outcome is live birth, stillbirth, spontaneous abortion, or elective termination. Review of the prenatal findings by a clinical geneticist or other consultant knowledgeable about birth defects, fetal development, and prenatal diagnosis (e.g., a pediatric cardiologist for heart defects) may be necessary to assess the certainty of prenatal diagnoses. The application of consistent assessment criteria can minimize potential biases in estimates of defect prevalence and facilitate comparison of prevalence estimates across programs.

A suggested list of prenatal diagnoses that can be included in prevalence estimates without a clinician's review of the certainty of the defect descriptions is presented in Appendix 12.2. This list represents the minimum range of defects that programs could ascertain, and it may require revision over time as new diagnostic techniques are developed. Birth defects surveillance programs should focus their efforts on the prenatal diagnosis of defects that are most critical to their goals and objectives; they should also consider their ability to ascertain postnatal confirmation of prenatal diagnoses.

12.7.3 Limitations on the Spectrum of Diagnoses Ascertained Prenatally

By nature, prenatal diagnosis tends to focus on major malformations and genetic abnormalities that are severe or life threatening; prenatal diagnosis also distinguishes characteristics such as limb deficiency that can be identified accurately using available techniques, even when they are nonlethal. However, prenatal diagnostic techniques may not be as sensitive in identifying subtle abnormalities, minor defects, or genetic syndromes that could be diagnosed postnatally (Akgun, et al., 2007). A thorough evaluation of the fetus after delivery for additional abnormalities can yield more complete diagnoses. When pregnancies end in stillbirth or spontaneous abortion, or when elective termination is chosen after diagnosis of a major defect, such evaluation may not be pursued after delivery (Babcook, et al., 2000).

In addition, information about the nature and description of prenatally diagnosed defects depends on the ascertainment source and can be limited. This may be particularly true when the locations for elective termination of pregnancy are different from those sites that perform prenatal diagnosis, or when health records are not available, complete, or fully integrated. Thus, while ascertainment of prenatally diagnosed defects can fill gaps in prevalence estimates for individual defects based on live births and stillbirths, the certainty, sensitivity, specificity, and range of defects identified with this approach will likely differ from those identified among live births. This possible discrepancy has implications not only for the completeness of prevalence estimates within a program, but also for comparisons across programs that ascertain prenatal diagnoses.

12.8 Incorporating Prenatally Diagnosed Defects into Estimates of Birth Defect Prevalence

Underestimation of the prevalence of birth defects by surveillance programs provides a major impetus for incorporating prenatal diagnoses. However, several factors should be considered when including prenatal diagnoses in the estimation of defect prevalence.

Some birth defects surveillance programs include defects among all pregnancy outcomes, including spontaneous abortions. However, many programs ascertain defects only among pregnancies beyond a specified gestational age, often 20 weeks. The decision to terminate an affected pregnancy electively after prenatal diagnosis alters the gestational age at which the pregnancy would otherwise end. Many of these pregnancies would deliver beyond the specified gestational age limit (e.g., 20 weeks) if elective termination was not chosen. Therefore, their inclusion in surveillance data, even when termination occurs before the specified gestational age limit, is critical for complete ascertainment and estimation of the prevalence of defects for which elective pregnancy termination is frequently chosen.

However, some pregnancies that are prenatally diagnosed in the latter first or early second trimester presumably would end in spontaneous abortion prior to the selected gestational age limit (e.g., 20 weeks) if they were not electively terminated. Including these electively terminated pregnancies could result in overestimation of the prevalence among pregnancies beyond the specified gestational age limit (e.g., 20 weeks or greater). Some authors have recommended correcting for the probability of spontaneous abortion at different gestational ages when incorporating prenatal diagnoses of Down syndrome in prevalence estimates (Leoncini, et al., 2010; Carothers, et al., 1999; Krivchenia, Huether, et al., 1993). Attempts also have been made to estimate the risk of spontaneous fetal loss according to gestational age for pregnancies with trisomy 13 or 18 (Morris and Savva, 2008). However, because the potential for fetal loss at different gestational ages can vary depending on the defect, and has not been established for most defects, it is usually impossible to predict what proportion of pregnancies terminated after prenatal diagnosis would otherwise have resulted in spontaneous abortion or stillbirth. It is recommended that pregnancies electively terminated after prenatal diagnosis be included in surveillance data regardless of the gestational age at termination.

An additional consideration for pregnancies that are electively terminated after prenatal diagnosis, or for which the outcome cannot be documented after prenatal diagnosis, is which date to use as the basis for incorporating the prenatal diagnoses into estimates of defect prevalence. Possibilities include the date of the elective termination if known, the date of the last known prenatal visit after prenatal diagnosis of a defect, and the estimated date of delivery (EDD). In general, a program should use the date that most closely corresponds to the date for which pregnancies that end in live birth, stillbirth, or spontaneous abortion are included. For example, if the date of delivery is the basis for including pregnancies without prenatal diagnoses in defect prevalence estimates regardless of the pregnancy outcome (live birth, stillbirth, spontaneous abortion), then the date on which an elective termination is performed after prenatal diagnosis could be used. For a pregnancy in which the outcome cannot be documented after prenatal diagnosis, the date of the last known prenatal visit might be used, assuming that the pregnancy was terminated shortly after

that visit. If the EDD is the basis for including pregnancies without prenatal diagnoses in defect prevalence estimates, then the EDD also should be the basis for including pregnancies with prenatal diagnoses as well. However, selection of the appropriate date can be tricky if a pregnancy is diagnosed prenatally with a defect close to the end of a calendar year, but the EDD or the date of elective termination could fall in the subsequent calendar year. The primary consideration is that programs maintain consistency across years of surveillance in their methods of incorporating pregnancies electively terminated after prenatal diagnosis of a defect, or those in which the pregnancy outcome cannot be documented after prenatal diagnosis.

12.9 Legal and Public Health Authority

It is critical for programs to understand the legal authority and restrictions in their area that shape their access to medical records, including out-patient records; determine the conduct of elective pregnancy termination and the settings in which terminations can be performed; and define the extent of their access to termination records. In general, legislation that supports birth defects surveillance activities should be broad and flexible enough to permit access to all clinical records a program might need, including those related to prenatal diagnosis of defects and subsequent pregnancy termination. Even when inclusion of prenatally diagnosed defects is not an immediate program activity, legislation could be worded to facilitate incorporation of these activities at a later date. Issues related to legislation supporting birth defects surveillance activities in general are discussed in Chapter 2, Legislation.

For some programs, obtaining access to records of prenatal diagnosis and/or elective pregnancy termination may require changes or amendments to existing legislation. Others may find that access is severely restricted or forbidden. However, if the authorizing legislation is sufficiently broad and flexible, obtaining this access may only require changes to agency regulations, not to the underlying legal or public health authority.

Programs should first assess which pregnancy outcomes they are authorized to ascertain. Terminology that refers to collection of data on birth defects among all pregnancy outcomes could enable ascertainment of defects among pregnancies electively terminated after prenatal diagnosis; terminology that restricts data collection to defects only among live births or among live births and stillbirths will exclude these pregnancies. Programs should then assess which data sources (e.g., facilities and clinical records) permit access or which are required to report data under their authority. Terminology that broadly refers to settings where defects are diagnosed, for example, could enable access to records of prenatal diagnoses and prenatal laboratory test results; terminology that restricts data collection solely to hospital records can exclude diagnoses made in out-patient prenatal care settings.

The following provides an example of how wording in the legislation authorizing a birth defects monitoring program can be modified to enable ascertainment of prenatal diagnoses and pregnancies electively terminated after diagnosis.

Initial legislation:

> *"Within 10 days after the date of birth . . . of any child with a congenital deformity or a birth injury which may lead to an incapacity or disability, the hospital wherein such birth occurred shall report such congenital deformity or injury. . . ."*

The legislation was changed to state the following:

> *". . . shall require the reporting of diagnoses made by physicians prenatally, at delivery and up to three years of age as . . . necessary and appropriate for the prevention and early*

> *detection of congenital anomalies or to facilitate epidemiological investigation and health surveillance of the incidence and prevalence of congenital anomalies. . . "*

An additional example shows how wording in legislation authorizing a birth defects monitoring program can enable ascertainment of prenatal diagnoses in pregnancies electively terminated after diagnosis:

> *"The department of health shall establish the . . . birth defects program to . . . collect surveillance information on birth defects and other adverse reproductive outcomes; . . . 'Adverse reproductive outcome' means a birth defect, stillbirth, infant death up to one year of age, or spontaneous or medical termination of pregnancy for a birth defect."*

12. 10 Approaches to Incorporating Prenatal Diagnoses into Birth Defects Surveillance

12.10.1 What to Ascertain

Programs wishing to include prenatally diagnosed defects in their birth defects surveillance must decide how to focus their ascertainment efforts. They may consider ascertaining:

- Pregnancies diagnosed prenatally with a defect before the outcome of the pregnancy has occurred, which could result in live birth, stillbirth, spontaneous abortion, or elective termination
- Pregnancies electively terminated after prenatal diagnosis of a defect
- Or a combination of the two. This will be the most practical and comprehensive approach for most programs

12.10.2 Sources for Case Ascertainment

Chapter 6 of these guidelines, Case Ascertainment Methods, discusses definitions of active and passive case ascertainment, the issues surrounding each, and the content of prenatal medical records as a source of information pertaining to defects diagnosed prenatally, and this material is relevant here.

However, including prenatally diagnosed defects in birth defects surveillance can require expansion of existing case ascertainment sources, addition of new sources, or both. In some settings, it may not be possible to retrieve prenatal care records based on whether a fetal abnormality was identified or on the nature of the abnormality. Therefore, active case-finding methods may be necessary to identify records of pregnancies with prenatally diagnosed defects. Passive reporting of defects by individual providers may be practical only for a limited number of conditions.

12.10.2.1 Locations Where Defects Are Diagnosed Prenatally

The locations where defects are diagnosed prenatally can vary widely across states and within a state, region, or other surveillance area. These may or may not be the same sites where pregnancies are electively terminated after a prenatal diagnosis is made.

Settings where defects are diagnosed prenatally can include:

- Hospitals
- Prenatal diagnostic referral centers
- Out-patient prenatal care clinics, including general obstetric, maternal-fetal medicine or high-risk obstetric clinics

- Offices of general obstetricians, family practitioners, perinatologists, maternal-fetal medicine or high-risk obstetric specialists, or midwives
- Subspecialty care clinics, such as genetics clinics or the offices of pediatric cardiology consultants who perform fetal echocardiography

Additional information about prenatally diagnosed defects can be obtained from:

- Cytogenetic laboratories
- Genetic counselors

12.10.2.2 Locations Where Pregnancies are Electively Terminated after Prenatal Diagnosis

The facilities where pregnancies are electively terminated after prenatal diagnosis of a defect can also vary widely across states and within a state, region, or other surveillance area. These may or may not be the same sites where prenatal diagnoses are made.

Settings where pregnancies are electively terminated after prenatal diagnosis can include:

- Hospitals
- Family planning clinics
- Abortion clinics
- Prenatal diagnostic referral centers
- Out-patient prenatal care clinics, including general obstetric, maternal-fetal medicine, or high-risk obstetric clinics
- Offices of general obstetricians, perinatologists, maternal-fetal medicine or high-risk obstetric specialists

The facilities where terminations are performed and how frequently they are performed at any one facility will depend on a number of factors including: the gestational age when the defect is diagnosed and when the decision to terminate is made; the availability of termination services; insurance coverage for these procedures; and legal requirements or restrictions governing their use. In general, mid-second and third trimester terminations after prenatal diagnosis of a defect are performed at specific facilities or in-patient hospitals.

12.10.2.3 Practice and Referral Patterns

A first step in including prenatally diagnosed defects in birth defects surveillance is to understand 1) the settings in the surveillance area where prenatal diagnosis is performed; 2) the circumstances under which patients are referred for confirmation of diagnoses and where they are referred; and 3) where pregnancies with prenatal diagnoses are delivered or electively terminated. The patterns of pregnancy management after prenatal diagnosis can vary widely across states and within a

state, region, or other surveillance area. In some areas, pregnant women may be referred to centers or subspecialists located outside the surveillance area for confirmation of prenatal diagnosis, pregnancy management, or elective termination. In some instances, this may be determined largely by specifications of the insurance coverage, health care system, or other organization of services. In addition, practice and referral patterns could change over time with physician training and experience. Programs should not assume that the ascertainment sources and surveillance methods effective for inclusion of prenatal diagnoses in one area would be equally effective in other areas. Each program must assess these factors for its own area.

For example, some obstetricians may routinely perform amniocenteses during the second trimester but refer patients to a subspecialist for procedures such as chorionic villus sampling or first trimester amniocentesis if they are conducted earlier in pregnancy. Other obstetricians might refer all patients to a perinatologist or maternal-fetal medicine department for amniocentesis. Similarly, some obstetricians may feel comfortable diagnosing certain malformations such as anencephaly or spina bifida by prenatal ultrasound, but prefer to refer suspected cardiac defects to a subspecialist or pediatric cardiologist for conclusive diagnosis by fetal echocardiography. Others might refer all abnormalities detected by prenatal ultrasound to a subspecialist for confirmation.

A notable instance is when termination of an affected pregnancy is performed in one setting, but the pregnancy is delivered in another. For example, a physician may terminate a pregnancy diagnosed prenatally with a defect through amniotic injection of potassium chloride in the out-patient setting, followed by admission to an in-patient hospital for induction of labor and delivery. In this scenario, the pregnancy outcome might be reported as elective termination in the prenatal record but as stillbirth, spontaneous abortion, or fetal death in the delivery record.

12.10.3 The Need to Collect Identifiers

An advantage of focusing solely on ascertainment of prenatal diagnoses among pregnancies that have been electively terminated is that these data can be combined with those from pregnancies ending in live birth and stillbirth without the need to remove duplicates. By definition, live births, stillbirths, and elective terminations are mutually exclusive. This can obviate the need to collect identifying information to link defect reports about the same pregnancy from multiple sources. However, because access to information from settings where elective termination is performed may be limited, and because some sources of termination data do not include personal identifiers, most programs focus on ascertainment of prenatal diagnoses from a variety of sources such as prenatal obstetric records, outpatient diagnostic centers, and delivery hospitals. This requires collecting sufficient identifying information to combine multiple reports about the same pregnancy.

Because pregnancy outcomes (live birth, stillbirth, spontaneous abortion, elective termination) typically occur in settings different from those where prenatal diagnosis is performed, pregnancies with a prenatally diagnosed defect will need to be matched with outcomes ascertained from delivery sites to identify the final outcome of each pregnancy. Linkage with sources of pregnancy outcomes such as vital records will inevitably lead to pregnancies that cannot be linked to an outcome or to a delivery site. The proportion of unlinked pregnancies will depend on the

completeness of the pregnancy outcome sources, whether they include pregnancies that are electively terminated, and whether information is available about women who moved away from the surveillance area before delivery but after an abnormality was diagnosed prenatally.

12.10.4 Steps for Incorporating Prenatally Diagnosed Defects into Birth Defects Surveillance

Program activities essential for including prenatally diagnosed defects in birth defects surveillance include the following:

1. **Identify** the specific program goals and objectives that will be achieved by including prenatally diagnosed defects. This will guide the further development of methods.

2. **Determine** which specific defects are most relevant to those objectives. For example, if a primary objective of including prenatal diagnoses is to evaluate prevention efforts (e.g., the effect of folic acid use), ascertainment of prenatal diagnoses might focus on neural tube defects.

3. **Review** the legal authority, administrative rules, regulations, and restrictions that shape the program's surveillance activities and govern access to records of prenatal diagnoses and elective termination.

4. **Identify** what prenatal diagnostic techniques are utilized in the surveillance area, where they are performed, and by whom. Some may be performed outside the surveillance area, for example, when a pregnant woman is referred to a prenatal diagnostic center in another state, or when laboratory specimens are sent to a national laboratory.

5. **Identify** whether elective terminations are performed after prenatal diagnosis in the surveillance area and, if so, where, by whom, and how frequently. Elective terminations may also be performed outside the surveillance area.

6. **Determine** how, when and where patients are referred for confirmation and management of prenatal diagnoses. This can include general obstetricians, perinatologists, maternal-fetal medicine specialists, and pediatric subspecialists, as well as those who perform elective terminations.

7. **Seek** changes or amendments to authorizing legislation, administrative rules, and regulations to enable access to records of prenatal diagnoses and elective termination, if needed.

8. **Assess** the resources required to add ascertainment of prenatally diagnosed defects to the surveillance program.

9. **Define** what information about prenatal diagnoses and associated pregnancy outcomes is needed.

10. **Establish** procedures for obtaining reports or abstracting records about prenatal diagnoses and associated pregnancy outcomes from case ascertainment sources.

11. **Identify** a clinical geneticist or other consultant knowledgeable about birth defects, fetal development, and prenatal diagnosis to assist with case reviews.

12. **Develop** a plan to assess the success of including prenatally diagnosed defects in birth defects surveillance.

13. **Conduct** a pilot test of the surveillance methods.

14. **Evaluate** the accuracy of the data collected on prenatal diagnoses through additional record review, and assess whether inclusion of prenatal diagnoses meets the program's goals and objectives.

15. **Implement** ascertainment of prenatal diagnoses as an ongoing activity of birth defects surveillance.

16. **Re-evaluate** periodically the accuracy of the data collected on prenatal diagnoses through additional record review, and assess whether inclusion of prenatal diagnoses continues to meet the program's goals and objectives and whether modifications or expansion of this activity is warranted.

17. **Compare** results with those from other birth defect surveillance programs that use similar methods, sensitivity, and specificity, to assess similarities and differences in the contribution of prenatal diagnosis to estimates of the prevalence of specific defects.

12.11 Tips and Hints

- *Include pregnancies electively terminated after prenatal diagnosis regardless of the gestational age at the time of termination.* Even if a program's case definition is limited to pregnancies of a certain gestational age (such as 20 weeks or greater), it is likely that these pregnancies would have continued to deliver beyond the gestational age limit if they had not been terminated.

- *Include pregnancies diagnosed with defects prenatally even when the final pregnancy outcome, date of the outcome, or residence at the time of the outcome cannot be documented.* The most frequent reason for not being able to document the details of a pregnancy outcome may be that the pregnancy has been electively terminated at a facility that is not one of the program's ascertainment sources. Use the most recent address in the prenatal record to determine residence criteria. While a few women may move away from the surveillance area after a defect is diagnosed but before delivery, failure to include all of those without documented residence at delivery could result in underestimation of the prevalence of defects under surveillance.

- *Start small and build activities over time.* Initial activities might include expanding case ascertainment sources at existing surveillance facilities. For example, a program might initiate ascertainment of prenatally diagnosed defects from a participating hospital's out-patient maternal-fetal medicine department, or consider ascertaining prenatal diagnostic test results from laboratories that serve a participating hospital. When expanding to incorporate new case ascertainment sources, begin with prenatal diagnostic centers in tertiary care facilities, as many pregnancies with a suspected prenatal diagnosis will be referred there for confirmation.

- *Engage the services of a clinical geneticist or other consultant knowledgeable about birth defects, fetal development, and prenatal diagnosis to review case information.* Assessment of the certainty of prenatal diagnoses is critical to accurate birth defects prevalence estimates. If the services of a knowledgeable clinician are not available, it is suggested that ascertainment be restricted to the defects listed in Appendix 12.2, which can be included in prevalence estimates without a clinician's review of the defect descriptions. This represents the minimum range of defects that programs could ascertain.

- *Verify prenatal diagnoses through review of prenatal and postnatal records whenever possible.* Simple reporting of prenatal diagnoses by participating facilities usually does not provide sufficient information to identify defects with certainty. Even when review of prenatal diagnostic records is possible, defects may not be described with certainty. For example, a prenatal ultrasound may note the presence of a complex congenital heart defect but may not be able to identify the specific type of defect. Whenever possible, compare prenatal diagnoses with postnatal evaluations to confirm the diagnoses. If reporting by participating facilities is the only method of ascertainment for prenatal diagnoses, perform record reviews for a sample of cases to verify the quality of the diagnoses.

12.12 References

Aagaard-Tillery KM, Porter TF, Malone FD, Nyberg DA, Collins J, Comstock CH, Hankins G, Eddleman K, Dugoff L, Wolfe HM, D'Alton ME. Influence of maternal BMI on genetic sonography in the FaSTER trial. *Prenat Diagn*. 2010;30(1):14-22.

Akgun H, Basbug M, Ozgun MT, Canoz O, Tokat F, Murat N, Ozturk F. Correlation between prenatal ultrasound and fetal autopsy findings in fetal anomalies terminated in the second trimester. *Prenat Diagn*. 2007;27:457-462.

Allen WP, Stevenson RE, Thompson SJ, Dean JH. The impact of prenatal diagnosis on NTD surveillance. *Prenat Diagn*. 1996;16:531-535.

Babcook CJ, Ball RH, Feldkamp ML. Prevalence of aneuploidy and additional anatomic abnormalities in fetuses with open spina bifida: population based study in Utah. *J Ultrasound Med* 2000;19:619-623.

Carothers AD, Hecht CA, Hook EB. International variation in reported livebirth prevalence rates of Down syndrome, adjusted for maternal age. *J Med Genet*. 1999;36:386-393.

Carroll SGM, Porter H, Abdel-Fattah S, Kyle PM, Soothill PW. Correlation of prenatal ultrasound diagnosis and pathologic findings in fetal brain abnormalities. *Ultrasound Obstet Gynecol*. 2000;16:149-153.

Cragan JD, Gilboa SM. Including prenatal diagnoses in birth defects monitoring: experience of the Metropolitan Atlanta Congenital Defects Program. *Birth Defects Research (Part A).* 2009;85(1):20-29.

Cragan JD, Khoury MJ. Effect of prenatal diagnosis on epidemiologic studies of birth defects. *Epidemiology*. 2000;11:695-699.

Ethen MK, Canfield MA. Impact of including elective pregnancy terminations before 20 weeks gestation on birth defect rates. *Teratology* 2002;66:S32-S35.

Forbus GA, Atz AM, Shirali GS. Implications and limitations of an abnormal fetal echocardiogram. *Am J Cardiol*. 2004;94:688-689.

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;148:1206-1211.

Gelehrter S, Owens ST, Russell MW, van der Velde ME, Gomes-Fifer C. Accuracy of the fetal echocardiogram in double-outlet right ventricle. *Congenit Heart Dis*. 2007;2:32-37.

Gottliebson WM, Border WL, Franklin CM, Meyer RA, Michelfelder ED. Accuracy of fetal echocardiography: a cardiac segment-specific analysis. *Ultrasound Obstet Gynecol*. 2006;28:15-21.

Harper T, Fordham LA, Wolfe HM. The fetal Dandy-Walker complex: associated anomalies, perinatal outcome and postnatal imaging. *Fetal Diagn Ther*. 2007;22:277-281.

Krivchenia E, Huether CA, Edmonds LD, May DS, Guckenberger S. Comparative epidemiology of Down syndrome in two United States populations, 1970-1989. *Am J Epidemiol*. 1993;137:815-828.

Ledbetter DH, Martin AO, Verlinsky Y, Pergament E, Jackson L, Yang-Feng T, Schonberg SA, Gilbert F, Zachary JM, Barr M, Copeland KL, DiMaio MS, Fine B, Rosinsky B, Schuette J, de la Cruz FF, Desnick RJ, Elias S, Golbus MS, Goldberg JD, Lubs HA, Mahoney MJ, Rhoads GG, Simpson JL, Schlesselman SE. Cytogenetic results of chorionic villus sampling: high success rate and diagnostic accuracy in the United States collaborative study. *Am J Obstet Gynecol*. 1990;162:495-501.

Lee RS, Cendron M, Kinnamon DD, Nguyen HT. Antenatal hydronephrosis as a predictor of postnatal outcome: a meta-analysis. *Pediatrics*. 2006;118: 586-593.

Leoncini E, Botto LD, Cocchi G, Annerén G, Bower C, Halliday J, Amar E, Bakker MK, Bianca S, Tapia MAC, Castilla EE, Csáky-Szunyogh M, Dastgiri S, Feldkamp ML, Gatt M, Hirahara F, Landau D, Lowry RB, Marengo L, McDonnell R, Mathew TM, Morgan M, Mutchinick OM, Pierini A, Poetzsch S, Ritvanen A, Scarano G, Siffel C, Sípek A, Szabova E, Tagliabue G, Vollset SE, Wertelecki W, Zhuchenko L, Mastroiacovo P. How valid are the rates of Down syndrome internationally? Findings from the International Clearinghouse for Birth Defects Surveillance and Research. *Am J Med Genet Part A*. 2010;152A:1670-1680.

Lumley MA, Zamerowski ST, Jackson L, Dukes K, Sullivan L. Psychosocial correlates of pregnant women's attitudes toward prenatal maternal serum screening and invasive diagnostic testing: Beyond traditional risk status. *Genet Test.* 2006;10:131-138.

Morris JK, Savva GM. The risk of fetal loss following a prenatal diagnosis of trisomy 13 or trisomy 18. *Am J Med Genet Part A*. 2008;146A:827-832.

Oggè G, Gaglioti P, Maccanti S, Faggiano F, Todros T, and the Gruppo Piemontese for Prenatal Screening of Congenital Heart Disease. Prenatal screening for congenital heart disease with four-chamber and outflow-tract views: a multicenter study. *Ultrasound Obstet Gynecol*. 2006;28:779-784.

Peller AJ, Westgate M-N, Holmes LB. Trends in congenital malformations, 1974-1999: effect of prenatal diagnosis and elective termination. *Obstet Gynecol.* 2004;104:957-964.

Phillips JJ, Mahony BS, Siebert JR, Lalani T, Fligner CL, Kapur RP. Dandy-Walker malformation complex: correlation between ultrasonagraphic diagnosis and postmortem neuropathology. *Obstet Gynecol*. 2006;107:685-693.

Schechtman KB, Gray DL, Baty JD, Rothman SM. Decision-making for termination of pregnancies with fetal anomalies: analysis of 53,000 pregnancies. *Obstet Gynecol*. 2002;99:216-222.

Sifakes S, Staboulidou I, Maiz N, Velissariou V, Nicolaides KH. Outcome of pregnancies with trisomy 2 cells in chorionic villi. *Prenat Diagn*. 2010;30:329-332.

Velie EM, Shaw GM. Impact of prenatal diagnosis and elective termination on prevalence and risk estimates of neural tube defects in California, 1989-1991. *Am J Epidemiol*. 1996;144:473-479.

Velthut A, Peters M., Roovere T, Kilusk G., Horelli-Kuitumem M, Sois M, Salumets A. Fetal trisomy 13 and 21 mosaicism diagnosed at amniocentesis: a case report. *Prenat Diagn*. 2009;29: 995-997.