Glenwood Springs Prenatal Report
April 2014

Colorado Department of Public Health and Environment

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Background

In January 2014, Colorado Responds to Children with Special Needs (CRCSN), the state birth defects registry was contacted by staff from Women's Health and A Woman's Place – two clinics located in Glenwood Springs, Colorado. There appeared to be an unusual number of prenatal ultrasounds that were presenting with very rare congenital anomalies. The clinical supervisor, clinic director and maternal and fetal OBGYN, who had reviewed the ultrasounds, were quite concerned.

Colorado Responds to Children with Special Needs (CRCSN) is the birth defects monitoring and prevention Section at the Colorado Department of Public Health and Environment (CDPHE). The program began in 1989 under the guidance of an advisory board of parents, physicians, advocates, and representatives from state agencies. The Section collects information about birth defects among Colorado residents diagnosed before birth and up to age three with one of the conditions eligible for the program. Children meeting these criteria are identified from many sources including hospitals, vital records (birth, death, and fetal death certificates), the Newborn Genetic Screening Program, the Newborn Hearing Screening Program, laboratories, prenatal diagnostic centers, physicians, and genetics, developmental, Medicaid and other specialty clinics. The Section collects record level data on live born and non-live born anomalies as well as stillborn and fetal demise. The section does <u>not</u> access prenatal diagnostic facilities to ascertain cases and does not routinely monitor prenatal ultrasounds.

After several conversations with the Medical Director of the clinics, Garfield County Health Department and Disease Control and Environmental Epidemiology Division (DCEED) Division Director, the decision was made to conduct an epidemiological investigation which involved the following:

- A literature review of the diagnosed case conditions observed on ultrasound
- Medical chart review of all cases to assess potential risk factors and review available ultrasound and laboratory findings
- Geocoding and mapping all of the cases to identify possible geographic clusters, identify drinking water sources (municipal and well), and assess proximity to active oil and gas wells (in consultation with Colorado Oil and Gas Conservation Commission staff)
- Consultation with Centers for Disease Control and Prevention experts in genetics and other Medical Geneticists.
- Preparation of a report of the findings for the clinics.

Methods

The Women's clinics provided CRCSN with the results of all the patients with abnormal ultrasound findings. The information provided included the patient name, address, date of birth, ethnicity, employment status, spouse, gravidity (number of times a woman has been pregnant), parity (number of times a women has given birth ≥20 weeks of gestation), maternal height/weight, expected due date, anomaly diagnosed (observed by ultrasound), laboratory testing conducted and findings.

CRCSN reviewed the National Birth Defects Prevention Study (NBDPS), conducted and published in 2001 by the National Center on Birth Defect and Developmental Disabilities-CDC, which was designed to be used as a model for other studies that might observe rare health conditions (1). Based on this study, CRCSN expanded the medical information collected to include the following potential risk factors: place of conception (city and state), over-the-counter drug use, illicit drug use, prescribed drug use, vitamin supplements/herbals, residence drinking water source, alcohol, tobacco use, and caffeine consumption.

Once the additional information to be collected was finalized in a standard chart abstraction tool, arrangements were made for a CRCSN- trained medical abstractor to visit the clinic and review the medical records of all the patients. The abstractor also worked with clinic staff to collect the additional variables that were added by CRCSN. The variables were entered into a database exclusively designed for this investigation via secure connection to the servers at the Colorado Department of Public Health and Environment. The abstractor also reviewed the data that was provided to CRCSN at the initiation of this investigation.

In response to the possibility of indentifying a cluster of health events, CRCSN felt it was important to geographically define the cohort by the residence of each case. We selected CENTRUS-- a geocoding software tool to derive longitude/latitude. The ability to map the cases would provide the necessary assessment in linking the health outcome to some potential exposure or common risk factor (2).

An extensive current literature review was conducted to identify the risk factors and prevalence of each of the major anomalies diagnosed on ultrasound by the clinic's trained physicians. CRCSN's statistician also provided data on the confirmed (live and non-live born) case numbers for the same malformations observed by the clinics.

Finally, CRCSN consulted with a medical geneticist at the Centers for Disease Control and Prevention (CDC) and the CDPHE oil and gas liaison with the Colorado Oil and Gas Conservation Commission (COGCC) to better understand and describe potential genetic and environmental risk factors.

Results

Maternal Age

A woman who becomes pregnant past the age of 35, is typically considered to be of advanced maternal age. There is an increased risk of chromosome anomalies with advancing maternal age. In this investigation, the range in maternal age for all of the effected cases was between 20 years to 37 years of age, with 9% of the expectant mothers of a higher risk age for pregnancy—greater than or equal to 35 years of age.

Maternal Ethnicity

Studies have found that fewer Hispanic mothers than non-Hispanic white mothers received prenatal care during the first trimester (72.2% vs. 87.4%). Not receiving prenatal care may increase the risk for some birth defects, with rates being highest for Hispanic infants (3). In this investigation, 32% of the clinic's cohort was Hispanic.

Height/Weight/ Pre-pregnancy BMI

Maternal obesity has been considered a risk factor for several adverse birth outcomes such as neural tube defects, birth trauma and late fetal death among other outcomes (4). Obesity is typically determined using a height and weight-based calculation called Body Mass Index (BMI).

IOM Classifications for Pre-Pregnancy BMI and Recommended Weight Gain During Pregnancy.

Pre-pregnancy BMI classification	BMI range	Recommended weight gain during pregnancy (in pounds)
Underweight	<18.5	28-40
Normal weight	18.5-24.9	25-35
Overweight	25.0-29.9	15-25
Obese	>=30.0	11-20

Source: *Weight Gain During Pregnancy: Reexamining the Guidelines*, Institute of Medicine, May 2009.

Colorado mothers categorized as obese prior to pregnancy had higher rates of deliveries of infants with major cardiovascular (24.0 per 1,000 live births vs. 18.0), major musculoskeletal (14.3 vs. 12.2), spina bifida (0.7 vs. 0.3), and overall major congenital anomalies (65.7 vs. 56.0), compared to normal-weight mothers (5).

The range in pre-pregnancy BMI for the cohort is 18.8 to 35.9, and 35% of the women had a pre-pregnancy BMI classification of

overweight or obese. We were unable to find the height of 2 of the cases and therefore could not calculate the BMI.

Expected Date of Confinement

All of the due dates, or expected dates of confinement (EDC), were from January 2014 through September 2014 with the exception of one case with an EDC of 2012-which was excluded from the analysis.

Alcohol, Tobacco and Caffeine

Various congenital anomalies are associated with cigarette smoking and the use of alcohol during pregnancy. These exposures may increase the risk of pregnancy complications such as unexplained stillbirth, fetal alcohol syndrome, preterm labor, neural tube defects and intrauterine growth restriction. There also may be a synergistic effect with combined alcohol use and smoking (6). Caffeine use during pregnancy has been associated with decreased fecundity, spontaneous abortion, and reduced fetal growth (7).

100% of the maternal cohort in this investigation reported no alcohol consumption during their pregnancy, 5% of the cohort reported smoking 2-3 cigarettes per day and 27% of the cohort reported some caffeine use. It should be noted that these were all self-reported activities.

Marijuana and Illicit Drug Use

Associations between illicit drug use and congenital malformations is difficult to determine as illicit drug use is commonly accompanied by other factors that can affect pregnancy outcomes, such as smoking, use of alcohol, and poor prenatal care. Marijuana use during pregnancy has been associated with a neural tube defect, known as anencephaly (8).

There was one case who reported marijuana use during conception and pregnancy.

Vitamin Supplements/ Herbal

Prenatal vitamin supplementation during pregnancy is associated with a decreased risk of poor outcomes (9). However, other types of supplements, such as most herbal preparations and supplements have not been proven to be safe during pregnancy.

Only 9% of cases did not report the use of prenatal vitamins or the information was not noted in the maternal medical record. There were no reported cases of herbal supplement use.

Prescription Drugs - Benefits vs. Risk
FDA Pregnancy Categories

The FDA has established five categories to indicate the potential of a drug to cause birth defects if used during pregnancy. The categories are determined by the reliability of documentation and the risk to benefit ratio. They do not take into account any risks from pharmaceutical agents or their metabolites in breast milk. The categories are (10):

Category A: Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters). No women in this investigation took a Category A drug.

Category B: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

14% of the cohort took one or more of a category B drug during pregnancy

Zofran

Protonix

Azythromycin

Category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

32% of the cohort took one or more of a category C drug during pregnancy.

Diflucan	*Phenergan*
Ventolin	*Glyburide*
Albuterol	*Lexapro*
Zoloft	*Fioricet*
Codiene	*Cymbalta*

Imetrix

Category D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. No women in this investigation took a Category D drug.

Category X: Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from

investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits. No women in this investigation took a Category X drug.

Category N: FDA has not classified the drug. No women in this investigation took a Category N drug.

Over-the- Counter (OTC) Drugs: Some OTC medications are safe to take during pregnancy (1^{st}, 2^{nd} or 3^{rd} trimester dependant), others are not, or their effects on fetal development may not be known.

The majority of the cases did not take any over-the- counter drugs. In this investigation, 27% of the women in the cohort took one of the following safe to use drugs.

Monistat
*Tylenol**
*Ibuprofen**
Claritin

**Not recommended after 32 weeks gestational age*

Place of Residence at Time of Conception/ Distance from Active Oil and Gas Wells

In order to avoid possible exposure misclassification, the clinic staff contacted the mothers to determine where they were residing at the time of conception. This would enable CRCSN to better understand exposures that occurred during the first trimester, when many birth defects occur.

Within the cohort, 40% of the cases were residing in the same location at the time of conception and their ultrasound. The staff was unable to reach the remaining cases for response. We mapped the maternal residences in comparison to active oil and gas well locations, and found that the majority (70%) of the cases lived greater than 15 miles from an active well. The remaining 30% were between 5 to 8 miles from the nearest active well.

Residence Drinking Water Source

Epidemiological studies have suggested that pregnant women exposed to water disinfection by-products (DBPs) containing elevated trihalomethane (THM) concentrations may be at greater risk for adverse pregnancy outcomes, including fetal growth and congenital anomalies, characterized by structural deformities. However, findings of the studies completed to date have been inconsistent (11).

In this investigation, 13% of the cases used local well water as their drinking water source with the remainder of the cohort using municipal water sources. Of the 6

counties in the catchment area, the range in concentration levels of THMs reported by the distribution systems in 2013 was: 7.1 micrograms/liter to 81.4 micrograms/liter.

Prenatal Diagnosis
Fetal Demise

Fetal death refers to the spontaneous intrauterine death of a fetus at any time during pregnancy. Fetal deaths later in pregnancy (at 20 weeks of gestation or more) are also sometimes referred to as stillbirths. Most states report fetal deaths of 20 weeks of gestation or more and/or 350 grams birth weight.

In this cohort, 36% of the cases were either a stillborn, elected termination or spontaneous abortion.

Hydaditiform Mole
A molar pregnancy — also known as hydatidiform mole — is a noncancerous (benign) tumor that develops in the uterus. A molar pregnancy occurs when there is an extra set of paternal chromosomes in a fertilized egg. This error at the time of conception transforms what would normally become the placenta into a growing mass of cysts. In a complete molar pregnancy, there's no embryo or normal placental tissue. In a partial molar pregnancy, there's an abnormal embryo and possibly some normal placental tissue. The embryo begins to develop but is malformed and can't survive (13).

In this cohort, 9% of the cases were identified as a molar pregnancy.

Trisomy 13 – Patau Syndrome
Trisomy 18 and trisomy 13 are the second and third most commonly diagnosed autosomal trisomies in live born infants. These conditions are both associated with a high degree of infant mortality. Trisomy occurs in 1in 10,000 newborns. Among infants with trisomy 13, the estimated probability of survival to 1 month of age was 30.0% (95% CI: 19.3–40.7) and the cumulative survival probability to 1 year of age was 8.6% (95% CI: 4.4–18.9; Fig 1). Median survival time was 7 days (95%CI: 3–15) (13).

In this cohort, 18% of the cases were either a confirmed or suspected Trisomy 13.

Turner’s Syndrome

Turner Syndrome occurs in about 1 in 2,500-3,000 newborn girls worldwide, but it is much more common among pregnancies that do not survive to term (miscarriages and stillbirths). Turner syndrome results when one normal X chromosome is present in a female's cells and the other sex chromosome is missing or structurally altered. The missing genetic material affects development before and after birth (14). The loss or alteration of the X chromosome occurs randomly.

In this cohort, 9 % of the cases were either a confirmed or suspected Turner’s syndrome.

Congenital Diaphragmatic Hernia

A diaphragmatic hernia occurs in 1 out of 2,200 to 5,000 births where there is an abnormal opening in the diaphragm. The opening allows part of the abdominal organs to move into the chest area, which does not allow the lung tissue to develop properly. Maternal factors contributing to the etiology of congenital diaphragmatic hernia (CDH) remain unclear and are considered to be multifactorial—genetic as well as environmental. Maternal pre-gestational diabetes and alcohol use may be significantly associated with occurrence of CDH in infants (15).

In this cohort, 4% of the cases were confirmed or suspected of having Diaphragmatic Hernia

Congenital Cardiovascular Anomalies

Cardiac anomalies are the most common of all birth defects with an occurrence of 1% of all live births and greater when associated as a co-morbidity with other syndromic conditions such as trisomy 21 or stillborn infants (16).

Types of anomalies observed/suspected on ultrasound:

- Ventricular septal defect (VSD)
- Atrial septal defect (ASD)

In this cohort, 9% of the cases had a confirmed or suspected isolated cardiovascular anomaly.

Hydrops Fetalis

Hydrops fetalis occurs in 1 in 2000 newborns. It is considered a prenatal form of cardiac failure. It was traditionally divided into two broad groups: Immune and non-immune hydrops fetalis. The overall prognosis can be variable, dependant on the underlying cause (17).

In this cohort, 4% of the cases were confirmed or suspected Hydrops fetalis.

Cohort Case Status *

At the onset of this investigation the following outcomes had occurred:

- 8 cases had either a fetal demise, stillborn or elective termination-(dilation curettage)
- 2 cases were molar pregnancy
- 3 cases had left the area and were lost to follow-up
- 3 cases had delivered and were receiving medical care

- 6 cases opted to continue their pregnancy

**4% of the cases had a previously affected pregnancy*

Discussion

As cited in the National Birth Defects Prevention Study conducted by eight states with population-based surveillance systems and a study cohort of 11,291 subjects with a birth population of 482,000 the following was concluded (1):

> From an epidemiologic perspective, birth defects are difficult to study. Individual conditions are relatively rare, the fetus is exposed to an array of unknown genetic and environmental factors, the biologic mechanisms that cause birth defects are unknown, and the defects identified at birth represent only the birth prevalence, not the true incidence of the condition.

Overall, we found no predominant risk factor that was common among the majority of women. We also found no common geographic risk factor among the cohort, such as all of the families living within the same street or common area, as some were located in Meeker, Carbondale, Rifle, Glenwood Springs, Snowmass and Silt. The women ranged in age from 20 years of age to 37 years of age with only 9% of the expectant mothers in the high risk age group of 35 years of age and older. The majority of the cohort did not live near and active oil and gas well and none of the drinking water sources presented with any exceeded levels of disinfection by-products (DBPs) containing elevated trihalomethanes (greater than 81.4 micrograms/Liter).

We conclude that there is not one single environmental or genetic or substance-related factor that will explain these rare prenatal outcomes. While individual mothers may have had individual risk factors, no common pattern among all or even most of the mothers emerged. Our recommendation is to define this cohort as a baseline for the two clinics and monitor the outcomes on a yearly basis. We also suggest that the clinics expand their maternal medical data abstractions to include the additional variables we used in this investigation. It is most important to know about the place of conception and alcohol, tobacco and caffeine use as well as marijuana, illicit and prescription drug use.

Limitations

Although we knew that most of these prenatal outcomes were not confirmed by cytogenetic testing, we felt it was important to attempt to identify possible risk factors that may have contributed to the suspected anomaly or fetal demise. We also knew that we would be unable to determine whether the number of suspected cases was significantly elevated, as we do not typically monitor prenatal ultrasounds and had no means to calculate a denominator to determine if this was a higher than normal prevalence for these conditions.

Several additional factors should be considered as well, including the limitations of the ultrasound as a diagnostic tool, inter/intra-observer variability, the timing of the ultrasound during the gestational period and how ultrasound observations prenatally may differ from the final outcome of the pregnancy. However, in this type of investigation, we were unable to account for the potential role these variables may play.

Finally, there were cases within this cohort that differed with regards to both outcomes and types of testing performed. Some were outcomes observed solely on ultrasound without confirmatory testing, others were confirmed through cytogenetic tests, and still others had changes in suspected diagnosis, differing from early in the trimester to later in the same trimester.

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