Congenital Anomaly Register & Information Service for Wales

caris review 2011

including data 1998 – 2010
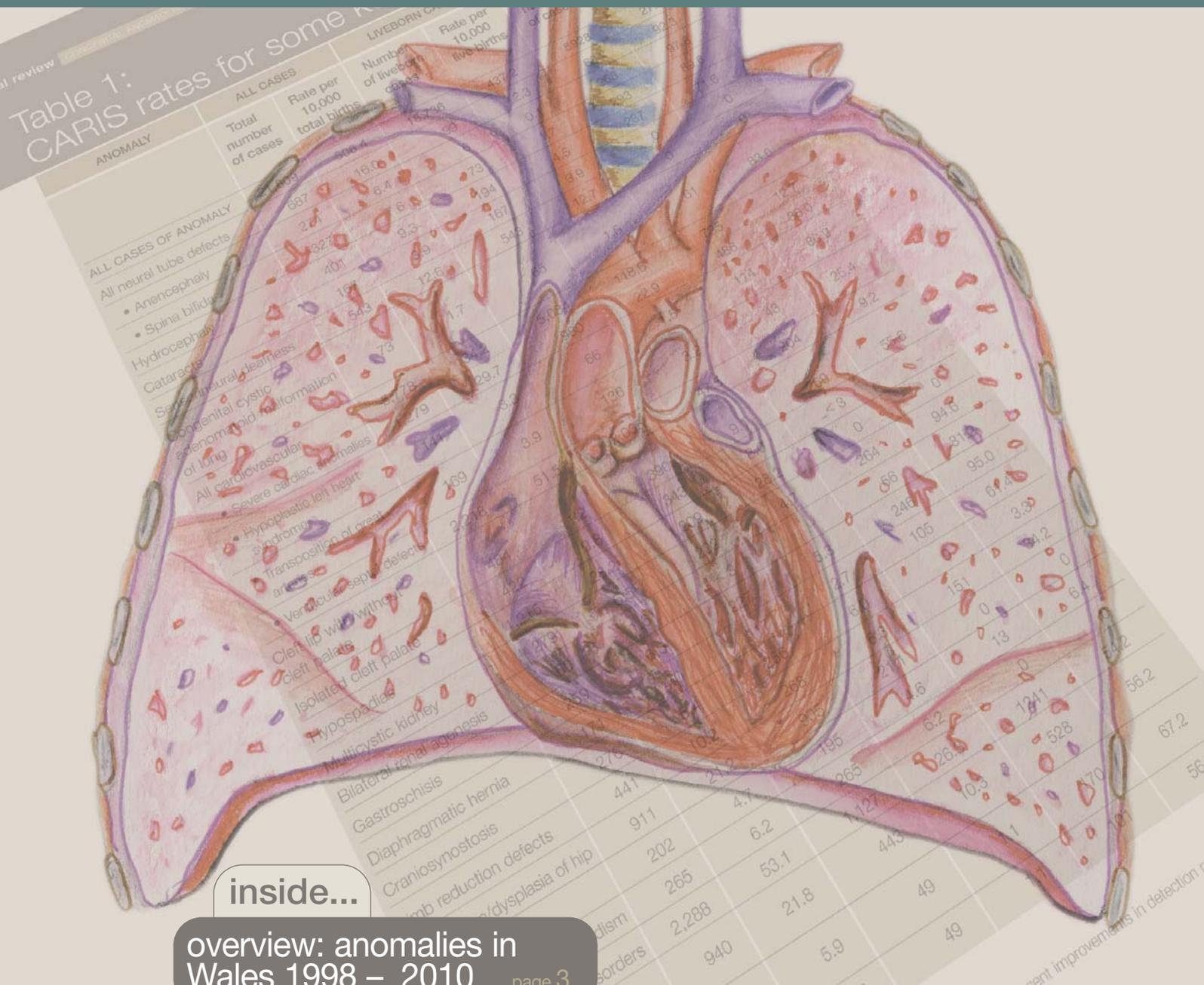
GIG CYMRU NHS WALES

Iechyd Cyhoeddus Cymru
Public Health Wales

Contents

Foreword

Welcome to the 2011 CARIS review.

Based on data reported for pregnancies ending from 1998 to 2010, the review is intended primarily to inform health professionals with an interest in congenital anomalies. It should also be of value to public health professionals, health boards, the Welsh Government and interested lay individuals.

In addition to the annual overview of congenital anomalies in Wales and a summary of CARIS activity over the last year, this year we are focusing on anomalies of the respiratory system and the cardiac outflow vessels.

Once again we would like to thank all contributing health professionals for their ongoing support.

We are very grateful to the following people for their contributions to this report:

- Tracy Price, Bethan Patterson, Hugo Cosh, Rhian Hughes and other members of the Public Health Wales Observatory Analytical Team for data analyses;

- Bethan Thomson for illustrations.

We always welcome feedback on our reports and our work in general. Please get in touch if you have any questions or suggestions.

Margery Morgan, Lead Clinician
Judith Greenacre, Director of Information
David Tucker, Manager

The CARIS team. We are (left to right) Helen Jenkins, David Tucker, Margery Morgan, Judith Greenacre and Val Vye.

Introduction

CARIS, the Congenital Anomaly Register and Information Service for Wales, aims to provide reliable data on congenital anomalies in Wales.

These data are used to assess:

• Patterns of anomalies;

• Possible clusters of birth defects and their causes;

• Antenatal screening and healthcare interventions; and

• Health service provision for affected babies and children.

CARIS is part of Public Health Wales within the NHS in Wales. It is based at Singleton Hospital, Swansea.

As part of an agreement between Public Health Wales and the Welsh Government, CARIS produces a review every year which includes:

• An overview of congenital anomalies in Wales;

• A summary of CARIS activity during the previous year; and

• Two special reports with a more detailed focus on specific anomalies.

This year the review covers data from 1998 – 2010, activity over the year 2010 and special reports with a detailed focus on anomalies of:

• The respiratory system; and

• The cardiac outflow vessels.

Respiratory system anomalies are also being featured in our 2011 annual meetings.

Appendix A includes a list of the special reports published by CARIS in previous reviews.

More detailed information and data tables are available from the CARIS websites www.wales.nhs.uk/caris (internet) and www.howis.wales.nhs.uk/caris (intranet).
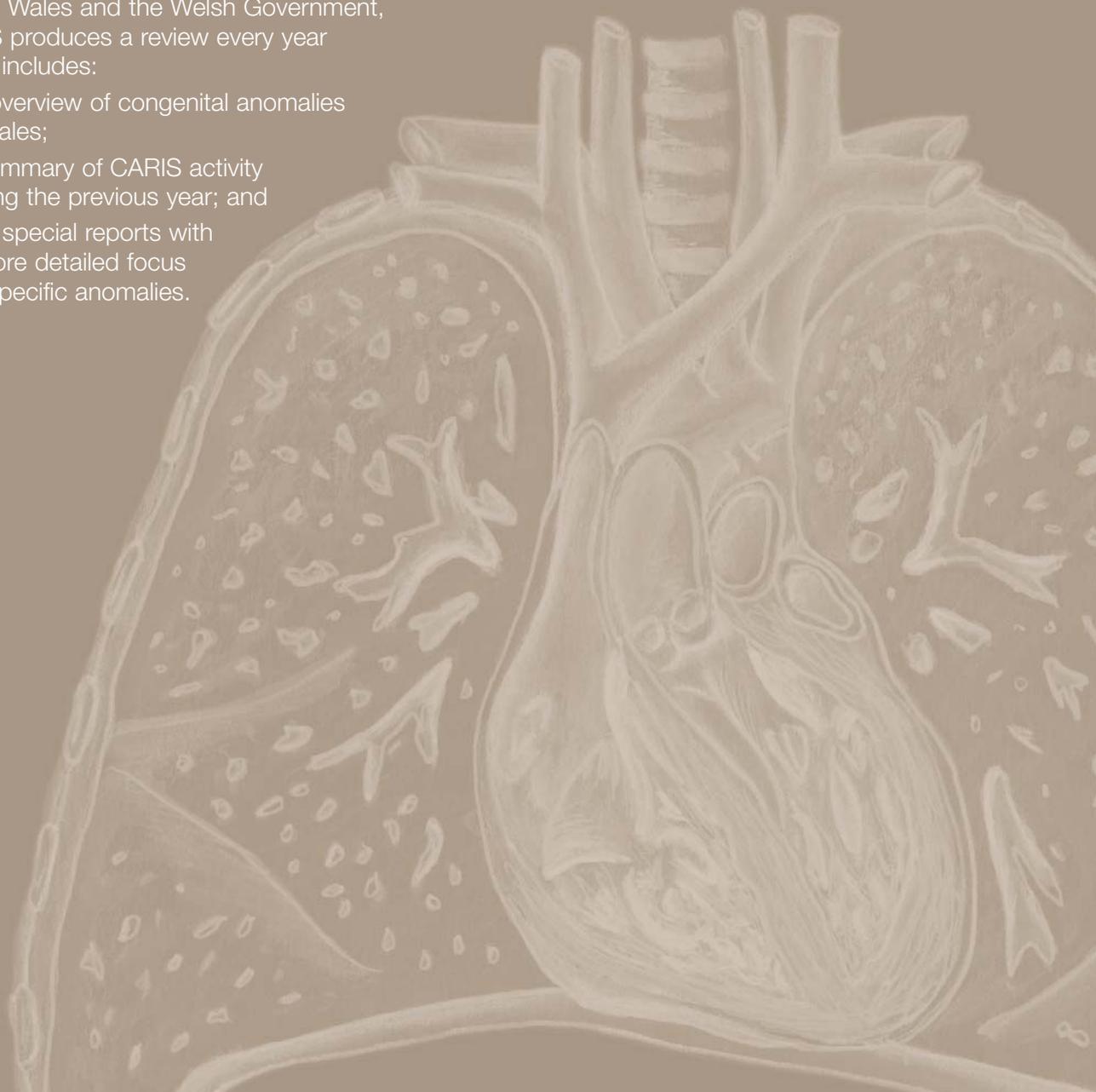
Overview of congenital anomalies in Wales 1998 – 2010

Between 1998 and 2010 there were 21,809 cases of congenital anomalies (18,736 live born) against a background of 430,689 total births in Wales.

Patterns and clusters of anomalies

- The gross [1] rate of congenital anomalies reported is 5.1 per cent.
- The rate of congenital anomalies in live born babies is 4.4 per cent.
- 86 per cent of cases are live born and 97 per cent of these survive to the end of their first year. Survival is reduced with increasing complexity of anomalies.
- Congenital anomaly rates in Wales are often apparently higher than for other areas of Europe or Britain.
- Variations in rates are again seen around Wales (Figure 1). In part this is due to differences in reporting and CARIS continues to keep the situation under review.
- Some specific anomalies continue to be monitored because of previously high rates in Wales. These include gastroschisis, isolated cleft palate and sirenomelia. Further data collected since last year have not identified any change to previous patterns for these anomalies.
- Factors that affect anomaly rates include maternal risk factors such as age and smoking. There is also an association with socioeconomic deprivation, particularly for non chromosomal anomalies.
- Heart and circulatory defects are the largest single group reported, followed by anomalies of the urinary tract, limbs and musculoskeletal system.
- For anomalies detected up to the first birthday, approximately one third of cases are detected antenatally, one third within the first week after the end of pregnancy and the remaining third later in infancy.

- Further study of anomalies of the cardiac outflow tract this year has identified:
  - a gradual fall in numbers and rates of cases of transposition of the great arteries;
  - a gradual rise in numbers and rates of cases of Fallots tetralogy.

The reasons for these changes are not clear and CARIS intends to review this further over the next year.

Interventions and services for anomalies

- Rates of antenatal detection continue to improve in Wales, particularly for heart defects (Table 1 on page 4 and Figure 16 on page 15).
- Further study of congenital cystic adenomatoid malformation of the lung (CCAM) suggests that approximately 16 per cent of cases in Wales may be lost to postnatal follow up. CCAM may lead to malignancy in later life and the level of loss to follow up therefore merits further review.

Figure 1: Gross case rate per 10,000 total births; Wales local authorities

Compared with Wales
- Significantly higher
- Comparable
- Significantly lower

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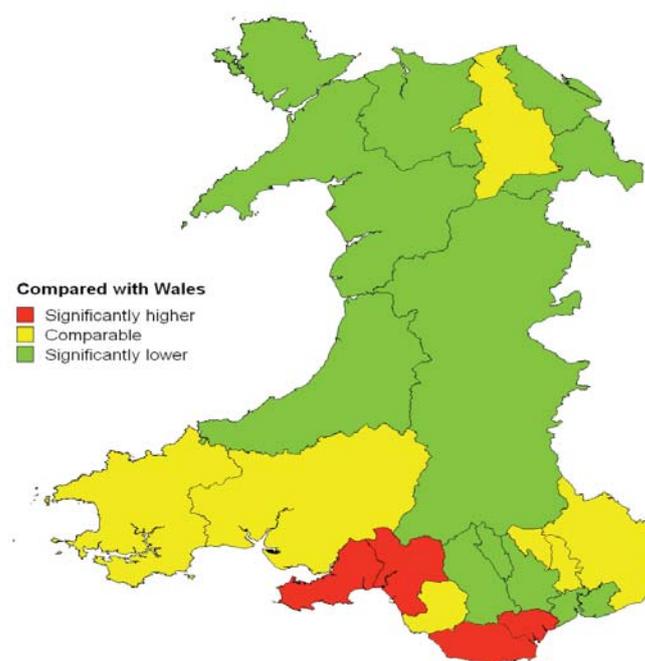
1 The gross rate includes all cases of anomaly recorded as miscarriages, terminations of pregnancy, live and still born babies as a proportion of all live and still born babies.

Table 1:
CARIS rates for some key anomalies (1998-2010)

ANOMALY	ALL CASES		LIVEBORN CASES		ANTENATAL DETECTION*	
	Total number of cases	Rate per 10,000 total births	Number of liveborn cases	Rate per 10,000 live births	Total number of cases	% cases: defect suspected antenatally
ALL CASES OF ANOMALY	21,809	506.4	18,736	437.2	5928	27.2
All neural tube defects	687	16.0	99	2.3	634	92.3
• Anencephaly	274	6.4	6	0.1	268	97.8
• Spina bifida	327	7.6	73	1.7	293	89.6
Hydrocephaly	401	9.3	194	4.5	287	71.6
Cataracts	167	3.9	167	3.9	0	0
Sensorineural deafness	543	12.6	543	12.7	0	0
Congenital cystic adenomatoid malformation of lung	73	1.7	65	1.5	61	83.6
All cardiovascular	5,778	134.2	5,084	118.6	735	12.7
• Severe cardiac anomalies	1,279	29.7	980	22.9	486	38.0
• Hypoplastic left heart syndrome	141	3.3	66	1.5	114	80.9
• Transposition of great arteries	169	3.9	136	3.2	43	25.4
• Ventricular septal defects	2,218	51.5	2,035	47.5	204	9.2
Cleft lip with/without cleft palate	484	11.2	390	9.1	269	55.6
Isolated cleft palate	422	9.8	343	8.0	≤ 3	–
Hypospadias	1,215	28.2	1,209	28.2	0	0
Multicystic kidney	279	6.5	202	4.7	264	94.6
Bilateral renal agenesis	69	1.6	≤ 3	–	56	81.2
Gastroschisis	259	6.0	227	5.3	246	95.0
Diaphragmatic hernia	171	4.0	117	2.7	105	61.4
Craniosynostosis	276	6.4	256	6.0	9	3.3
Limb reduction defects	441	10.2	268	6.3	151	34.2
Dislocation/dysplasia of hip	911	21.2	905	21.1	0	0
Cystic fibrosis	202	4.7	195	4.6	13	6.4
Congenital hypothyroidism	265	6.2	265	6.2	0	0
All chromosomal disorders	2,288	53.1	1,127	26.3	1241	54.2
• Trisomy 21 (Down syndrome)	940	21.8	443	10.3	528	56.2
• Trisomy 18 (Edwards syndrome)	253	5.9	49	1.1	170	67.2
• 45 X (Turner syndrome)	179	4.2	49	1.1	101	56.4

* Represents overall detection rates 1998-2010. This may not fully reflect recent improvements in detection rates.

CARIS activity 2010

CARIS held its annual meetings in 2010 at Ysbyty Glan Clwyd, Rhyl and Prince Charles Hospital, Merthyr Tydfil. The focus was on eye anomalies. More than 150 people attended these meetings.

CARIS continued to contribute to the British Isles Network of Congenital Anomaly Registers (BINOCAR). This included developing proposals for a surveillance system for congenital anomalies across the United Kingdom.

CARIS was involved in discussions at the EUROCAT Registry Leaders meeting in Dublin in June 2010 to plan a EUROMEDICAT study that will look at the association between drugs taken in pregnancy and congenital anomalies. The study start date is 2011.

The CARIS manager, David Tucker, attended the EUROCAT coding committee in Ferrara, Italy to make recommendations on the congenital anomaly component of eleventh version of the International Class of Diseases (ICD). He also contributed to the further development of coding guidance for member registries.

Publications and presentations

Obesity and risk of congenital anomalies.
Pinto A, Tucker D, Morgan M.
Poster presented at Welsh Obstetric and Gynaecological Society meeting, October 2010.

Chronic conditions due to birth defects in Wales.
Greenacre J. Poster presented at Welsh Confederation Conference: Embracing the challenges – changing conditions. November 2010.

Congenital abnormalities: Data needed to establish causes.
Draper ES, Rankin J, Tonks A, Boyd P, Wellesley D, Tucker D, Budd J.
BINOCAR Management Committee (2009), *BMJ*, Vol 339, pp 3428.

Congenital anomaly associated with stillbirth.
Morgan M, Tucker FD, Mohan S.
Presentation made at the International Clearing House of Birth Defects, Surveillance and Research (ICBDSR) 37th Annual Meeting, Buenos Aires, November 2010.

Outcome of fetuses with Turner syndrome: a 10 year, congenital anomaly register based study.
Iyer NP, Tucker FD, Roberts SH, Moselhi M, Morgan M, Matthes JWA.
Poster presentation at the International Clearing House of Birth Defects, Surveillance and Research (ICBDSR) 37th Annual Meeting, Buenos Aires, November 2010.

International trends of Down syndrome 1993-2004: Births in relation to maternal age and terminations of pregnancies.
Cocchi G, Gualdi S, Bower C, Halliday J, Jonsson B, Nyrelid A, Mastroiacovo P, Amar E, Bakker M, Correa A, Doray B, Klungsor Melve K, Khoshnood B, Landau D, Mutchinick O, Pierini A, Ritvanen A, Ruddock V, Scarano G, Sibbald B, Sipek A, Tenconi R, Tucker D and Anneren G (2010). Birth Defects Research (Part A), Vol 88, pp474-479.

Additional publications in 2010 using CARIS data

Prenatal screening policies in Europe 2010 (special report), EUROCAT Central Registry. University of Ulster.

Case-control analysis of paternal age and trisomic anomalies.
de Souza E, Morris JK and a EUROCAT Working Group (2010), Arch Dis Child, DOI: 10.1136/adc.2009.176438 (http://adc.bmj.com/content/early/2010/06/28/adc.2009.176438.full.html#ref-list-1

Birth prevalence of congenital heart disease
Dolk H, Loane MA, Abramsky L, de Walle H, Garne E (2010). Epidemiology, Vol 21, No 2, pp 275-277.

Termination of pregnancy for fetal anomaly after 23 weeks of gestation: A European register-based study. Garne E, Khoshnood B, Loane M, Boyd PA, Dolk H (2010). BJOG, Vol 117, No 6, pp 660-666.

Valproic acid monotherapy in pregnancy and major congenital malformations. Jentink J, Loane M, Dolk H, Barisic I, Garne E, Morris J, de Jong-van den Berg L for the EUROCAT Antiepileptic Study Working Group (2010), The New England Journal of Medicine, Vol 362, No 23, pp 2185-2193.

Prevalence of neural tube defects (NTD) in younger mothers in Europe 2000-2008: Analysis of the EUROCAT database – report to Bayer Schiering Pharma. Loane M, Dolk H and a EUROCAT Working group (2010), 30th September 2010, EUROCAT Central Registry, University of Ulster.

Related websites

CARIS is a member of several organisations involved in the study of congenital anomalies. Their website details are:

- British Isles Network of Congenital Anomaly Registers: www.binocar.org.uk

- EUROCAT: www.eurocat.ulster.ac.uk

- International Clearing House of Birth Defects, Surveillance and Research: www.icbdsr.org

Special report: Respiratory anomalies

Introduction

The respiratory tract extends from the mouth and nasal cavity to the alveoli of the lungs. The development of the respiratory tract and its separation from gut structures are important in the development of several respiratory tract anomalies.

This report focuses on:

- Choanal atresia
- Anomalies of the larynx
- Tracheo-eosophageal fistula
- Pulmonary hypoplasia
- Cystic fibrosis
- Congenital cystic adenomatoid malformation of the lung (CCAM)
- Bronco-pulmonary sequestration

Development of the respiratory tract

The development of the respiratory tract of the fetus and child up to the age of eight years is as follows:

### Embryological period 5 to 6 weeks gestation

At about five weeks gestation, the respiratory diverticulum forms as an outgrowth from the embryonic foregut.

The diverticulum elongates to form tracheal and lung buds but also remains in communication with the foregut.

Ingrowth of the oesophagotracheal ridges starts to form the oesophagotracheal septum between the trachea and gut.

Division of trachea and oesophagus by the oesophageal septum is complete by about seven weeks gestation, to form two sets of structures.
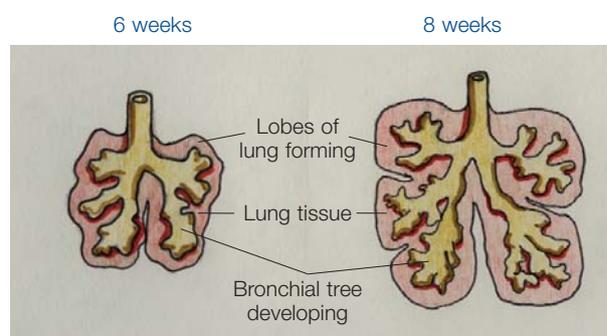
- The laryngotracheal tube (forms larynx, trachea, bronchi and lungs)
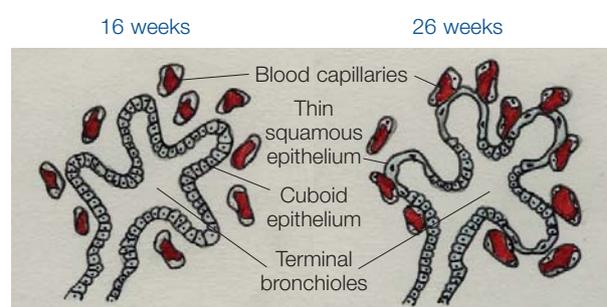- The primordium of oropharynx and oesophagus

5 weeks

6 – 7 weeks
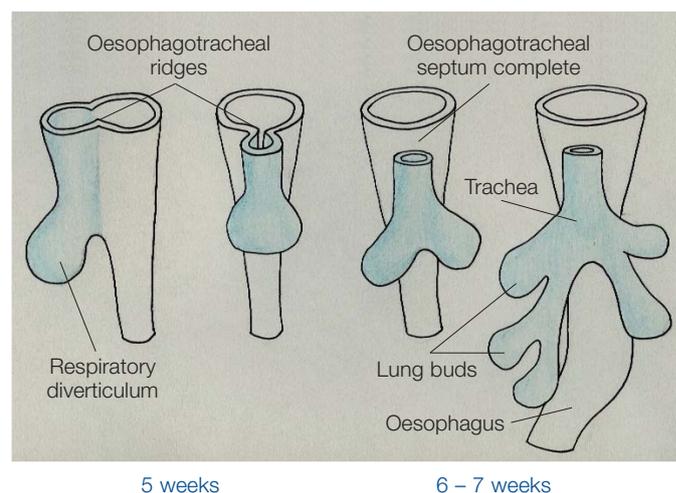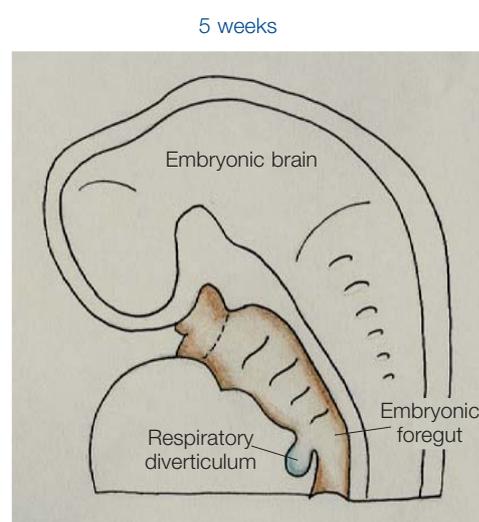
5 weeks

Special report:
Respiratory anomalies

Pseudoglandular period
6 – 16 weeks gestation

- Gross lung structure and bronchial tree develop

6 weeks   8 weeks

Lobes of lung forming
Lung tissue
Bronchial tree developing

Canalicular period
16 – 26 weeks gestation

- Branching of the respiratory bronchioles and vascularisation of the terminal tubules occur

- Pneumocytes can be identified from 20 weeks gestation

16 weeks   26 weeks

Blood capillaries
Thin squamous epithelium
Cuboid epithelium
Terminal bronchioles

Terminal saccular period
27 – 32 weeks gestation

- Blood air barrier established with alveolar surface of lung

- Surfactant produced by pneumocytes to support survival
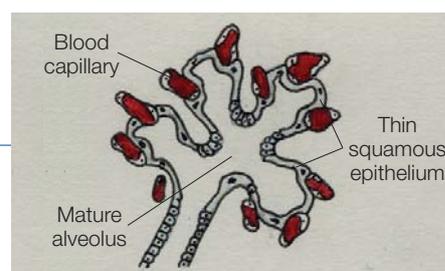
Alveolar period 32 weeks – 8 years

- Alveolar capillary membrane maturing

- Breathing movements occur before birth

- At birth, lung fluid cleared

- Post birth, number of respiratory bronchioles and alveoli increase

Blood capillary
Thin squamous epithelium
Mature alveolus

term fetus

Special report: Respiratory anomalies

Upper respiratory tract anomalies

Choanal atresia

Choanal atresia is a narrowing or blockage of the nasal airways. This occurs when the oronasal membrane that separates the primitive nose and mouth fails to break down to create a passage-way (usually at about 6 weeks gestation). Newborn babies normally breathe through their nose. If the choanal atresia is bilateral then breathing at birth becomes a neonatal emergency as the baby becomes hypoxic. If the baby mouth breathes then feeding can cause difficulties. Choanal atresia can occur alone or with other anomalies as part of the CHARGE syndrome – this is summarised in Box 1.

Box 1: CHARGE syndrome	
Coloboma of iris	
Heart defects (75 – 80% of cases)	
Atresia of choanae	
Restricted growth and development	
Genitourinary anomalies	
Ear defects and associated deafness	
Likely causes:	Most cases sporadic. Possibly autosomal dominant defect of CHD7 gene
Frequency:	Estimates range from 0.1 to 1.2 / 10,000 livebirths [2]
Potential for early detection:	Limited. Detection of polyhydramnios, heart defects or restricted growth may give an indication before birth
Management:	Each condition needs attention. Management is best through a multidisciplinary team
Outlook:	Generally good but likely to need long term management of conditions

Diagnosis of choanal atresia is by inability to pass a catheter along the nose. Treatment is by endoscopic surgery to break down the obstruction.

From 1998 to 2010, 45 cases of choanal atresia were reported to CARIS, giving a gross prevalence in Wales of 1 per 10,000 total births. Laterality was reported in 20 cases with 9 (45%) of these bilateral. Six cases (13%) occured as part of CHARGE syndrome.

Anomalies of the larynx

The larynx can develop various defects including stenosis, subglottic haemangiomata, laryngeal clefts and cysts and vascular anomalies.

Laryngomalacia is the most common cause of congenital stridor. It is caused by the loose folds of the tissues of the larynx including the epiglottis falling inwards on inspiration. Endoscopy is usually done to confirm the diagnosis.

Although this is classified as a congenital structural anomaly, the resultant stridor usually disappears by two years of age.

From 1998 to 2010, 119 cases were reported to CARIS but, as this is a benign resolving condition, reporting may be limited and these cases are unlikely to represent a true rate for Wales.

Congenital subglottic stenosis involves narrowing of the subglottic airway as a result of incomplete recanalisation of the laryngotracheal tube. The most severe form involves complete laryngeal atresia and is often fatal. Milder forms are more common and may not present until the baby develops stridor and breathing difficulties during an upper respiratory infective episode. A history of recurrent croup may suggest the diagnosis. Children with Down syndrome are at increased risk of the defect and males are more commonly affected than females.

Diagnosis may be possible from X-ray and can be confirmed at bronchoscopy.

The outlook for the milder form is generally good as the condition improves or resolves with childhood growth.

A total of 36 cases were reported to CARIS for 1998 to 2010, giving a gross prevalence of 0.8 per 10,000 total births, with a male to female ratio of 1.8 to 1.

2 *Charge syndrome*. Blake KD, Prasad C. 34, 2006, Orphanet Journal of Rare Diseases, Vol. 1. http://www.OJRD.com/content/1/1/34.

Special report: Respiratory anomalies

## Tracheal anomalies

Tracheo-oesophageal fistula (TOF)

The main developmental problem at the level of the trachea is tracheo-oesophageal atresia and or fistula. Failure of normal development of the tracheo-oesophageal septum leads to various degrees of atresia and fistula (Figure 5).

Atresia more commonly affects the oesophagus in this condition. The most common form (85% of cases) involves the upper oesophagus ending in a blind sac and a fistula between the lower oesoghagus and trachea (Figure 5a). Tracheal stenosis or atresia is an uncommon variant but is fatal if air cannot reach the lungs.

The cause of TOF is unclear. Most cases occur sporadically with a recurrence risk of less than 1 per cent in subsequent pregnancies. TOF is associated with other anomalies, particularly chromosomal anomalies. It also occurs as part of VACTERL association (Box 2).

Although associated anomalies may be detected antenatally, diagnosis of TOF is unlikely at the fetal anomaly ultrasound scan (although the stomach may appear small or absent). Polyhydramnios commonly occurs in the third trimester, caused by inability of the fetus to swallow amniotic fluid.
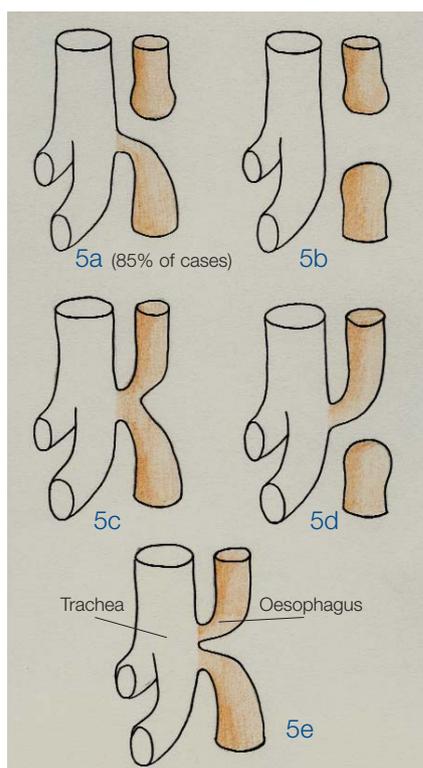
This may precipitate early labour. Immediately after birth, an affected baby produces large amounts of frothy saliva with choking and episodes of cyanosis. Inability to pass a catheter down the oesophagus will confirm the diagnosis. The appearance of gas in the stomach on X-ray will confirm the presence of a fistula.

Management involves nursing upright. Oral feeds are withheld and the oesophageal pouch is aspirated until definitive surgery can take place, once the baby is stable. Associated anomalies will need further management.

With successful surgery, the outlook is generally good.

CARIS received reports of 122 cases of TOF from 1998 to 2010, giving a gross rate of 2.8 per 10,000 total births or 9 cases per year in Wales.

This is comparable to published rates in the literature [3]. Of these 122 cases, 19 (16%) were associated with chromosomal disorders and 16 (13%) occurred as part of VACTERL association. 92 (75%) cases were live born and, of these, 81 survived to the end of the first year of life (88% of live born cases or 66% of all cases reported).

Figure 5: Types of TOF

5a (85% of cases)   5b
5c   5d
Trachea   Oesophagus
5e

Box 2: VACTERL Association	
Vertebral anomalies	
Anorectal anomalies	
Cardiac anomalies	
Tracheo } anomalies, (O)**E**sophageal } particularly atresia / fistula	
Renal and radial anomalies	
Limb anomalies	
Likely causes:	Linked to maternal diabetes and cholesterol lowering drugs
Frequency:	The prevalence at birth has been estimated at between 1 in 6,250 and 1 in 3,333. (Orphanet) [4]
Potential for early detection:	Through antenatal ultrasound detection of structural anomalies
Management:	Through management of associated anomalies
Outlook:	Variable, depending on severity of anomalies

3 Twining, P, McHugo, J and Pilling, D. *Textbook of fetal anomalies*: Churchill Livingstone, 2007

4 www.orphanet.org

Special report: Respiratory anomalies

Lower respiratory tract anomalies

Pulmonary hypoplasia

Pulmonary hypoplasia is defined as an absolute decrease in lung volume and weight for gestational age. The hypoplastic lung usually comprises a bronchial stump and absent or poorly differentiated distal lung tissue.

The hypoplasia can be primary or secondary.

Primary hypoplasia, without any known cause, is very rare. There are no alveoli, meaning that lung development has failed at the pseudoglandular phase (page 7).

Secondary pulmonary hypoplasia

Optimum lung growth in utero requires:

- Normal sized thoracic cavity;
- Normal amniotic fluid volume; and
- Normal fetal breathing movements.

If these requirements are compromised, secondary pulmonary hypoplasia may develop. Box 3 gives examples of situations in which this occurs. The severity of lung deformity varies from mild to severe, according to the nature and extent of the underlying causative factor and the gestational age of onset.

Antenatal diagnosis of mild to moderate degrees of pulmonary hypoplasia is poor. Ultrasonography may show a large heart or signs of the causative condition. Magnetic resonance imaging is useful for assessing lung nature and volume.

The International Classification of Diseases (ICD10) does not differentiate between primary and secondary pulmonary hypoplasia. This, together with the variable extent and causes of pulmonary hypoplasia, means that the true prevalence and survival outcome for the condition are difficult to quantify. For 1998 to 2010, a total of 424 cases were reported to CARIS (9.8 per 10,000 total births) or about 30 to 35 per year in Wales. Of these, 115 were liveborn (27%) and only 24 survived to the end of the first year of life.

Box 3: Causes of secondary pulmonary hypoplasia

Condition causing secondary pulmonary hypoplasia	Mechanism
Diaphragmatic hernia Cystic adenomatoid malformation Lung cysts Pleural effusions Small chest syndromes	Reduction in intrathoracic space
Myotonic atrophy Spinal muscular atrophy Phrenic nerve agenesis Cervical spinal cord lesions	Reduction in fetal breathing movements
Renal anomalies Premature membrane rupture Fetal growth restriction Amniocentesis	Reduction in amniotic fluid volume
Rhesus disease Trisomies 21 and 18 Maternal drugs Anterior abdominal wall defects	Other

Cystic fibrosis – lung complications

Cystic fibrosis is a serious inherited condition that affects many organs of the body and can cause severe lung damage. A defective gene affects the movement of salt in the body. This causes the cells that produce mucus, sweat and digestive juices to produce thick and sticky secretions that block tubes and passageways, especially in the pancreas and lungs. Other problems can include liver disease, diabetes mellitus, osteoporosis and male infertility. This report concentrates on the pulmonary aspects of the disease.

In the past, most people with cystic fibrosis died in their teens. Improved screening and treatments now allow many people with cystic fibrosis to live into middle age and longer.

Cystic fibrosis occurs most often in white people of northern European ancestry, occurring in about 1 out of 3,000 live births (3.3 per 10,000). The condition is very rare in native Africans and Asians.
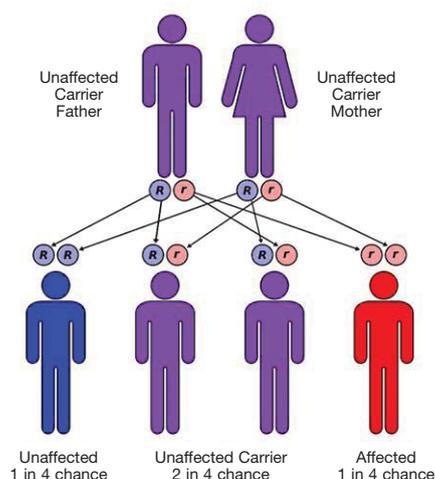
Special report: Respiratory anomalies

The disease follows an autosomal recessive pattern of inheritance.

The affected baby may therefore be the first known in the family. Offspring of two parents carrying the gene have a 1 in 4 chance of being affected. An unaffected sibling of an affected person has a 2 in 3 chance of being a carrier (Figure 7).

Over 2 million people in the UK carry the faulty gene, about 1 in 25 of the population. It is estimated that over 9,000 people in the UK have cystic fibrosis. Based on these figures, we would expect about 10-15 babies in Wales to be born with cystic fibrosis annually.

The CARIS database includes reports of 202 cases of cystic fibrosis for 1998 to 2010, giving a gross rate of 4.7 per 10,000 total births or about 15 cases per year, at the upper end of numbers expected from international prevalence estimates.

Figure 7: Autosomal recessive pattern of inheritance

Unaffected Carrier Father — Unaffected Carrier Mother

Unaffected 1 in 4 chance — Unaffected Carrier 2 in 4 chance — Affected 1 in 4 chance

If there is a family history, antenatal chorionic villus sampling or amniocentesis may be used to establish a diagnosis. Some centres offer pre implantation genetic diagnosis.

The finding of echogenic bowel on antenatal ultrasound may alert to a possible diagnosis. A small study of Welsh data found that for 10 per cent of babies born with cystic fibrosis there was evidence of echogenic bowel on antenatal ultrasound [5].

Every mother in Wales is offered testing for cystic fibrosis for her newborn baby. This is done via a heel prick sample, taken just after birth.

In the absence of previous diagnostic testing, clinical suspicion may be raised by meconium ileus in the neonatal period (see below) or a failure to thrive in infancy with frequent chest infections. There is a high level of sodium and chloride in the sweat which forms the basis for the main non-genetic diagnostic test.

Meconium has a different composition in babies with cystic fibrosis due to pancreatic insufficiency. This can cause problems in the first days of life causing meconium ileus. This shows as bowel obstruction with constipation, vomiting and a distended abdomen. Volvulus and bowel perforation are complications. Conservative treatment with enemas can be successful and surgery is reserved for complicated cases [6]. Of the 195 live born cases of cystic fibrosis reported to CARIS, 37 (19%) developed meconium ileus.

The lungs are almost universally affected in cases of cystic fibrosis. The aims of management are to control infection, preserve lung function and prevent associated complications.

Exercise is encouraged and airway clearance taught to the patient. Supplementary oxygen may be required. Lung transplantation can improve survival and quality of life for those with end stage lung disease.

Much of the morbidity and premature mortality of cystic fibrosis relates to the lung and pancreatic problems. Most units have specialist teams that include physicians, nurses, physiotherapists, dieticians, social workers, psychologists, pharmacists and support staff.

Survival has improved significantly in recent decades with a predicted median age of survival for infants born with cystic fibrosis today in the UK of over 50 years.

5 Cystic fibrosis in Wales: is it worth reporting?, Morgan and Tucker, 2006, International Clearing House meeting, Uppsala, Sweden

6 Oxford Desk Reference Respiratory Medicine, Maskell and Millar, 2009, OUP   http://www.cftrust.org.uk

Special report:
Respiratory anomalies

## Congenital cystic adenomatoid malformation (CCAM)

In this rare condition, lobes of the lung are replaced by non functioning cystic tissue. This can cause a spectrum of problems (Figure 8).

- Fetal CCAMs are almost always unilateral. The condition is thought to resolve in pregnancy in 10 to 20 per cent of cases, though this is difficult to prove without histology.

- Smaller lung lesions may be multiple (Figure 8a) or single (Figure 8b) and can cause respiratory distress in the newborn period or remain asymptomatic until later in childhood when infection, pneumothorax or malignant degeneration may occur.

- A large lung cyst (Figure 8c) can compress the oesophagus and interfere with fetal swallowing of amniotic fluid resulting in polyhydramnios. A consequence of this may also be the absence of fluid in the fetal stomach. If the cyst is large enough to move the mediastinum significantly, the vena cava and heart are likely to be compressed. This can cause hydrops with fetal ascites, pleural and pericardial effusions and skin and scalp oedema.

The reasons why the condition arises are not well understood. It may result from an increase in terminal respiratory structures, probably related to local bronchial atresia or bronchial occlusion. In most cases the prognosis for a fetus with CCAM is very good but larger lesions causing significant complications can be life threatening. The affected tissue is at higher risk of associated malignancies including pulmonary blastoma and rhabdomyosarcoma in infants and bronchioalveolar carcinoma in older children and adults.

The diagnosis is made by antenatal ultrasonographic findings of an echogenic (bright) mass appearing in the chest of the fetus. Other ultrasound findings may include displacement of the heart from its normal position, a flat or everted (pushed downward) diaphragm, or the absence of visible lung tissue.

Figure 8: extent of CCAM

8a

8b

8c
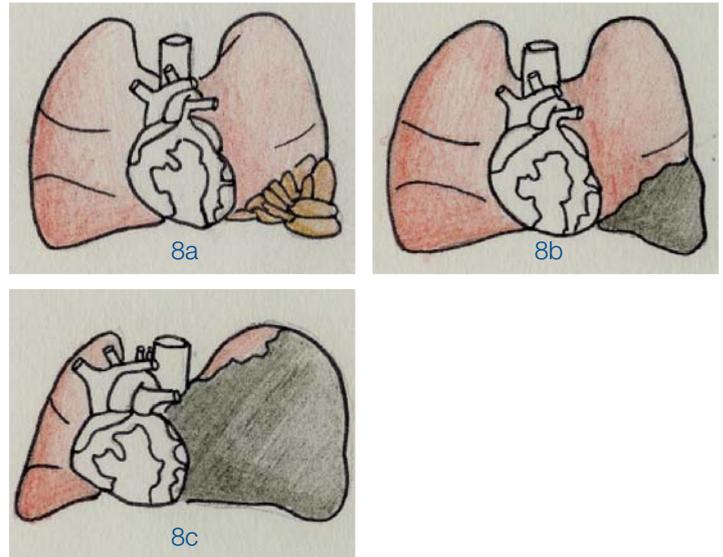
Combined European data for 1998 to 2009 show an overall prevalence of 0.69 per 10,000 total births, suggesting an expected 2 babies with this condition each year in Wales. CARIS data for 1998 to 2010 includes 73 cases or approximately 5 cases a year (a gross rates of 1.7 per 10,000 total births) This is higher than overall European levels but on a par with some of the best reporting individual European registers.

CCAM can be diagnosed on antenatal ultrasound (Figure 9). The condition can be difficult to differentiate from bronchopulmonary sequestration but this is not thought to be essential antenatally. MRI and colour flow Doppler may be useful additional diagnostic procedures.

Monitoring of the cyst volume can be used as a predictor of problems. Some centres have offered fetal surgery for severe cases.

Figure 9: Antenatal ultrasound showing CCAM

Cross section of the thoracic cavity

Placenta

Amniotic cavity

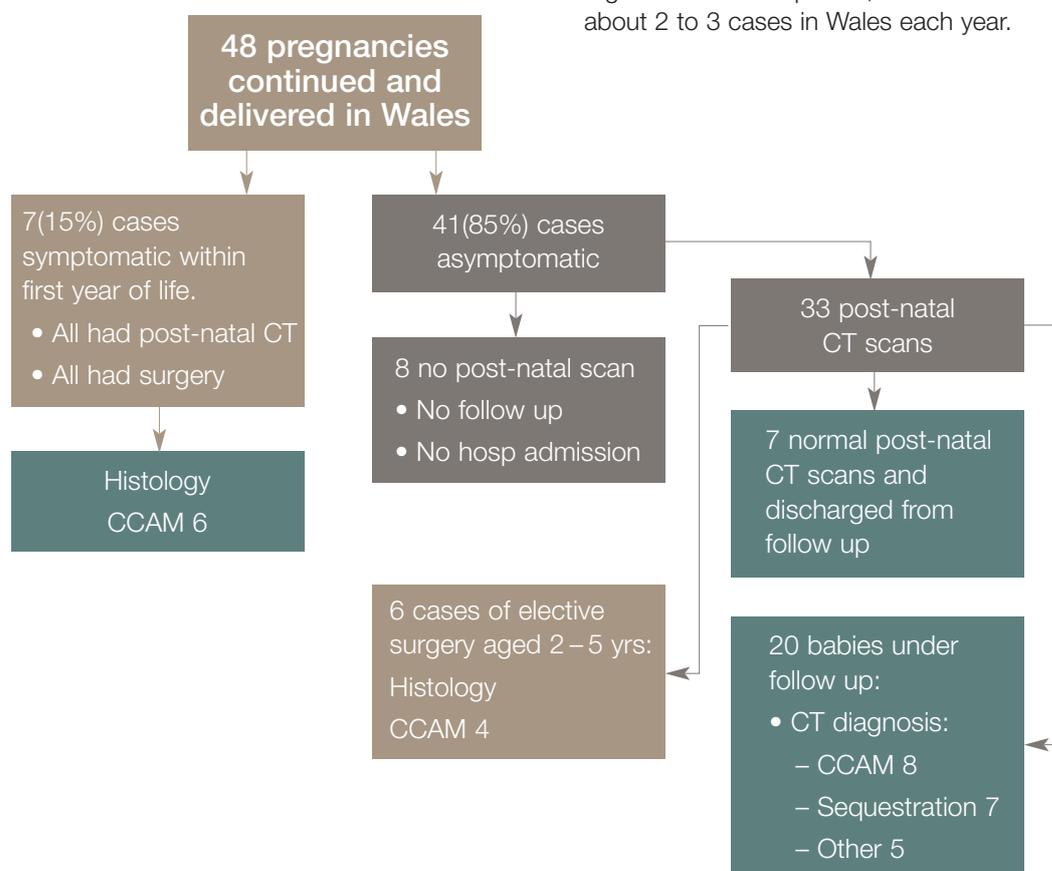Cystic area of lung

4 chamber view of heart

Special report: Respiratory anomalies

Even though there may be some spontaneous resolution, it is important to monitor the baby closely after birth. If there is compromise at birth, resection of the cyst and possibly a lobectomy may be considered at an early stage.

If asymptomatic, further assessment with CT imaging is essential. Because of the risk of malignancy in these cysts, surgical resection of affected tissue may be necessary.

Figure 10 shows the known outcome from a small CARIS study of 48 live born babies who were found to have CCAM antenatally [7]. Of these, 7 were symptomatic within the 1st year of life (15%). The diagnostic status of these babies is shown (Figure 10). Given the risk of future malignancy, the apparent loss of 8 cases (17%) to follow up, merits further consideration.

Broncho pulmonary sequestration

Broncho pulmonary sequestration is a relatively rare condition where part of the lung becomes separated from the bronchial tree during fetal development. It could be caused by a disruption in the blood supply to the area. Seen more commonly in the lower lobes, the condition shows as a bright section of lung on antenatal ultrasound from 18 weeks gestation. Most are on the left side. The portion of lung preserves an arterial supply from the aorta which can be demonstrated with colour flow Doppler ultrasound. There is an association with other anomalies including congenital diaphragmatic hernia.

Resolution may occur to some extent as the pregnancy continues. The prognosis is generally good especially if there has been some resolution. Hydrops suggests a poorer outcome.

Most cases require postnatal removal, though a conservative approach may be possible.

CARIS has reports of 33 cases for 1998 to 2010, a gross rate of 0.8 per 10,000 total births or about 2 to 3 cases in Wales each year.

Figure 10: outcome for cases of CCAM reported to CARIS

7 Outcome of antenatally suspected congenital cystic adenomatoid malformation of the lungs (CCAM) and sequestration of the lungs in Wales, UK: 7 years experience 2000-2006, Gopalkrishnan, Calvert, Morris, Doull and Tucker, ICBDSR annual meeting, Salt Lake City, USA, 2009

Special report:
Anomalies of the cardiac outflow vessels

Introduction

The outflow tract describes the major vessels arising from the heart, from the ventricular outflow valves to the aortic arch and the division of the pulmonary artery into right and left vessels. (Figure 11). This review concentrates on significant anomalies of the aorta and pulmonary arteries, including:

• Transposition of the great arteries;
• Fallot's tetralogy;
• Truncus arteriosus; and
• Coarctation of the aorta.

Figure 11:
Normal heart and
outflow vessels
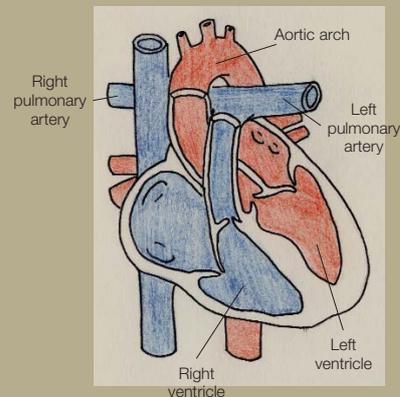
The major human arterial system develops from the 4th week of gestation and is based on the 3rd, 4th and 6th aortic arches, together with the embryonic dorsal aorta (Figure 12). Development is complex and it is not surprising that congenital anomalies arise.

Figure 12: Development of the major arteries
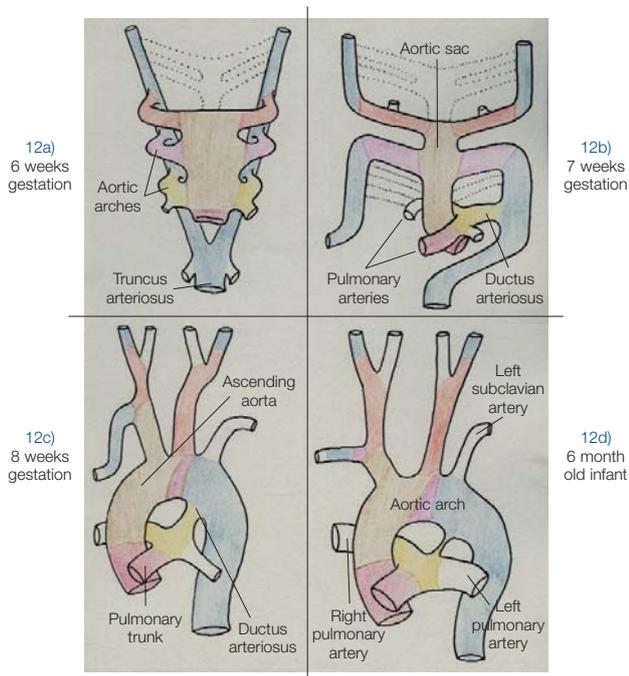
Early detection allows planned delivery and neonatal management in an appropriate centre. This is usually associated with an improved outcome. Antenatal detection of outflow tract anomalies is through the fetal anomaly ultrasound scan at 18 to 20 weeks gestation (Box 4).

The potential for detection was previously low but advances in ultrasound over recent years have made imaging of the outflow tracts possible.

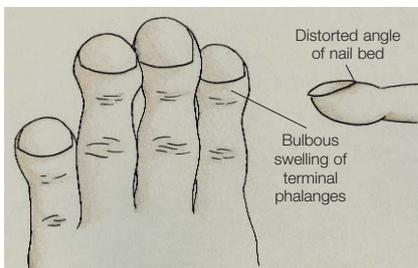**Box 4: Ultrasound Tips to Check Outflow Tracts**

• Pulmonary and aortic valves are seen separately
• Aorta (centre of chest) comes from left ventricle
• Aorta gives rise to aortic arch with characteristic head and neck vessels
• Pulmonary artery arises from right ventricle
• Pulmonary artery branches to the right and left
• Great arteries are similar in size
• Pulmonary valve is anterior and cranial to aortic valve
• Great arteries cross at their origin
• Arch of the aorta is similar in size to pulmonary artery and duct

NICE guidelines for antenatal care (2008)[8] recommend that an assessment of the fetal heart should be part of the routine anomaly scan.

These anomalies are causes of cyanotic congenital heart disease where deoxygenated blood from the right side of the heart enters the left side of the heart and on to the body tissues without first travelling to the lungs for reoxygenation. The lack of brighter red oxygenated blood causes the lips, fingers and toes to appear blue. This 'central' cyanosis is not resolved by giving oxygen to the patient as the blood is bypassing the lungs where gas exchange takes place. Cyanotic congenital heart disease is one of the causes of finger clubbing (Figure 13). Treatment involves finding a way to increase flow of blood from the right side of the heart through the lungs, either as a short term measure (such as atrial balloon septoplasty for transposition of the arterial vessels) or as part of definitive surgical repair of the heart defect.

8 Antenatal care: routine care for the healthy pregnant woman. NICE Guideline 62. March 2008. Available from http://www.nice.org.uk/CG062

Special report: Anomalies of the cardiac outflow vessels

Figure 13: Finger clubbing

Distorted angle of nail bed

Bulbous swelling of terminal phalanges

Transposition of the great arteries

Transposition of the great arteries is the most common cause of cyanotic heart disease in newborn infants and is more common in males. The aorta and pulmonary arteries are 'transposed' with the aorta arising from the right ventricle and the pulmonary artery from the left ventricle, causing two separate circulations of blood (Figure 14). A connection between the two circulations is needed for oxygenated blood to reach the body tissues. This may occur through a ventricular septal defect (25% of cases) or continuation of the patent ductus arteriosus. A balloon septoplasty may be required shortly after birth to create an artificial septal defect until further surgery can be performed. Major correction of the defect involves an arterial switch operation in which the major arteries are reconnected to the correct ventricle.

Without surgery, over half of affected babies die before the age of two. With surgery, outlook has improved and, in the absence of other complications, survival is good, although lifelong follow up is required.

On antenatal ultrasound, the four chamber view is normal so it is essential to review the great arteries.

Figure 14: Transposition of the Great Arteries

Pulmonary artery transposed to left ventricle

Aorta transposed to right ventricle
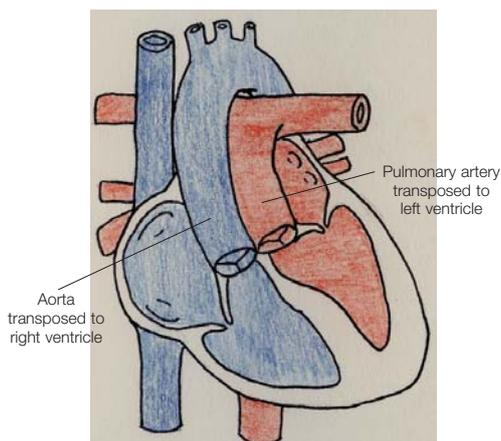
These arise parallel to each other and do not cross over at their origin. The aortic arch forms a wide arch instead of the tight hooked arch seen normally.

Most undiagnosed babies become cyanosed soon after birth. If unrecognised, increasing distress and collapse will occur as the ductus arteriosus closes.

From 1998 to 2010, 169 cases of transposition were reported to CARIS with a male to female ratio of 2.3 to 1. This gives a gross rate of 3.9 per 10,000 total births or about 12 cases per year in Wales. Within this overall figure, there has been a gradual decline in numbers and rates of the condition in recent years (Figure 15). The reasons for the decline are not clear but are unlikely to be due to lower rates of reporting as the same trend is not seen for cardiac anomalies overall.

Of the 169 cases, 136 (80%) were live born (3.2 per 10,000 live births). CARIS has collected inpatient data from 2005 through which 72 cases can be identified as undergoing surgical repair of the defect. Of these, 70 children have survived to the age of at least two years (97% of surgical cases).

Figure 15

Transposition of the great arteries, Wales: 1998 – 2010

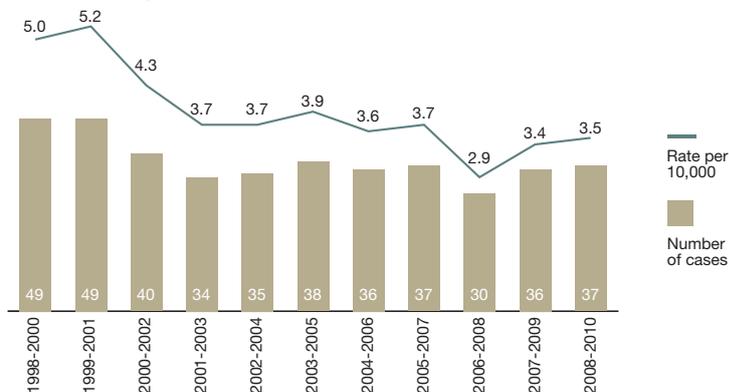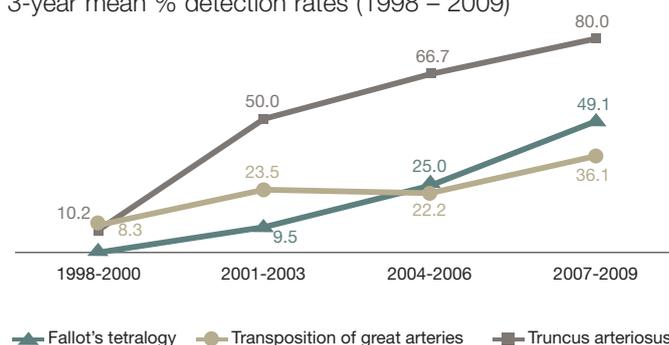3-year rolling counts and rates per 10,000 live and still births

	Rate	Number of cases
1998-2000	5.0	49
1999-2001	5.2	49
2000-2002	4.3	40
2001-2003	3.7	34
2002-2004	3.7	35
2003-2005	3.9	38
2004-2006	3.6	36
2005-2007	3.7	37
2006-2008	2.9	30
2007-2009	3.4	36
2008-2010	3.5	37

Rate per 10,000

Number of cases

Figure 16

Antenatal detection rates of outflow tract anomalies in Wales

3-year mean % detection rates (1998 – 2009)

	1998-2000	2001-2003	2004-2006	2007-2009
Fallot's tetralogy		9.5		49.1
Transposition of great arteries	8.3	23.5	22.2	36.1
Truncus arteriosus	10.2	50.0	66.7	80.0

Also shown: 25.0 (2004-2006)

◆ Fallot's tetralogy   ● Transposition of great arteries   ■ Truncus arteriosus

Special report:
Anomalies of the cardiac outflow vessels

Fallot's tetralogy

Fallot's tetralogy is a form of cyanotic congenital heart disease and involves four significant heart defects (Figure 17):

- Anterior deviation (over-riding) of the aorta;
- Ventricular septal defect (VSD);
- Pulmonary stenosis; and
- Right ventricular hypertrophy.

The pulmonary stenosis limits blood flow to the lungs, causing a build up of oxygen depleted blood on the right side of the heart. Right ventricular pressure rises to shunt the deoxygenated blood through the VSD and the over-riding aorta to the left side of the heart, without it passing through the lungs. Right ventricular hypertrophy develops as the right ventricle works to push an increased volume of blood through the stenotic pulmonary valve.

At birth, cyanosis is rare as babies usually have a patent ductus arteriosus that improves pulmonary blood flow. As the ductus closes, cyanosis and a loud harsh murmur develop. Once suspected, the elements of Fallot's can be identified postnatally through echocardiography. Cardiac catheterisation may be required to study pulmonary blood flow.

Figure 17: Fallot's tetralogy

Overriding aorta
Ventricular septal defect
Pulmonary stenosis
Right ventricular hypertrophy
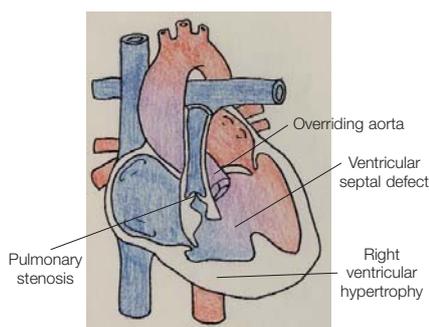
Fallot's is associated with other anomalies including omphalocoele, diaphragmatic hernia and chromosomal defects. The cause of the condition is unknown but has been associated with various maternal risk factors, including:

- Diabetes;
- Maternal age 40+years;
- Alcoholism in the mother;
- Poor nutrition during pregnancy; and
- Rubella or other viral illnesses during pregnancy[9].

There is a high incidence of chromosomal disorders in children with Fallot's tetralogy, such as Down syndrome and DiGeorge syndrome (a condition that causes heart defects, low calcium levels and immune deficiency).

Once diagnosed, initial management focuses on maintaining adequate blood oxygenation. Surgical correction is usually undertaken at about six months of age although earlier intervention may be required if oxygen levels are low. Survival rates for children with Fallot's tetralogy have improved dramatically in recent decades. In the absence of additional risk factors, over 95% of infants successfully undergo surgery in the first year of life and long term cardiac function is excellent. Later complications may include leaking or re-stenosing of the pulmonary valve, both of which may require further surgery.
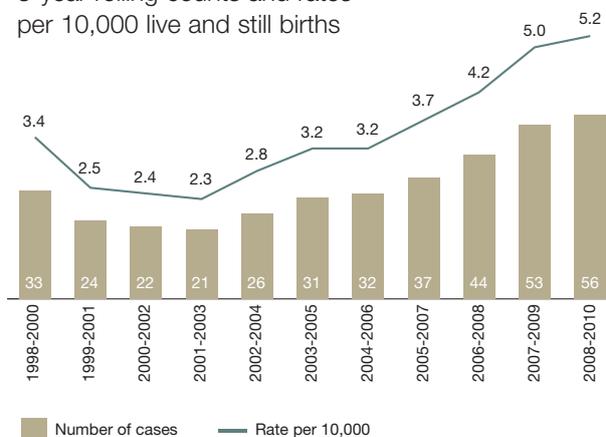
For the years 1998 to 2010, 157 cases of Fallot's tetralogy were reported to CARIS, a gross rate of 3.6 per 10,000 total births or about 12 cases per year in Wales. Of these, 149 (95%) were live born.

The prevalence of Fallot's tetralogy has gradually risen in Wales over the past decade (Figure 18). This rise may be associated with a rise in the prevalence of some maternal risk factors but the situation merits further consideration.

Overall, one third of cases (51) were detected antenatally. Of the live born cases, 149 (95%) have survived at least to the age of two.

Figure 18

Fallot's tetralogy, Wales: 1998 – 2010
3-year rolling counts and rates
per 10,000 live and still births

Period	Number of cases	Rate per 10,000
1998-2000	33	3.4
1999-2001	24	2.5
2000-2002	22	2.4
2001-2003	21	2.3
2002-2004	26	2.8
2003-2005	31	3.2
2004-2006	32	3.2
2005-2007	37	3.7
2006-2008	44	4.2
2007-2009	53	5.0
2008-2010	56	5.2

Number of cases   Rate per 10,000

9 Zipes DP, Libby P, Bonow RO, Braunwald E, eds. *Braunwald's heart disease: A textbook of cardiovascular medicine*, 8th ed. St. Louis, Mo; WB Saunders; 2007

Special report:
Anomalies of the cardiac outflow vessels

Truncus arteriosus

Instead of separate pulmonary arteries and aorta, in this anomaly a single large arterial trunk arises from the two heart ventricles. The anomaly is often associated with a large ventricular septal defect which allows oxygenated and deoxygenated blood to mix in what is effectively a single ventricle (Figure 19). As a result, the flow of blood to the lungs is increased, causing pulmonary congestion and potentially life-threatening pulmonary hypertension. A number of types of the defect have been identified, depending on the anatomy of the trunk.

Truncus arteriosus is linked with various other anomalies including chromosomal defects, DiGeorge syndrome, renal agenesis and pulmonary hypoplasia.

Antenatal ultrasound detection has previously been difficult as the four chamber view of the heart may be normal. Detection has improved in recent years with advances in antenatal ultrasound imaging of the outflow tract (Figure 16). Postnatally, symptoms usually appear at 2 to 3 weeks of age with breathlessness and signs of heart failure.

Complete surgical repair is needed to close the septal defect and to separate the pulmonary arteries from the arterial trunk. This usually provides good results although further surgery may be required as the child grows. Heart failure and pulmonary hypertension are recognised complications. If untreated, death usually occurs during infancy.

Figure 19: Truncus arteriosus
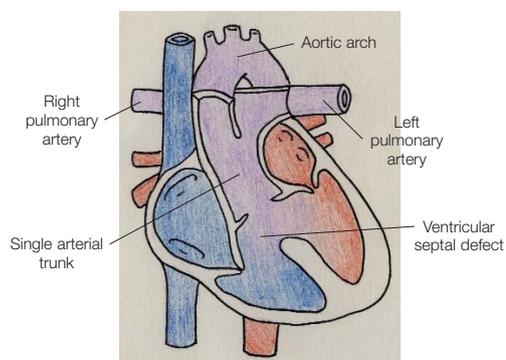
CARIS has had 52 cases reported from 1998 to 2010, giving a gross prevalence of 1.2 per 10,000 total births, or about 4 per year in Wales. Of these, 31 (60%) were live born and 29 (56%) were associated with other anomalies.

Coarctation of the aorta

Coarctation involves a narrowing of the aorta. The defect can occur anywhere along the aorta but is commonly situated just after the subclavian artery at the level of the ductus arteriosus (Figure 20 and Figure 12d on page 14). The head and arms have a normal blood supply but the blood supply to the lower half of the body will be compromised.

Figure 20: Coarctation of the aorta
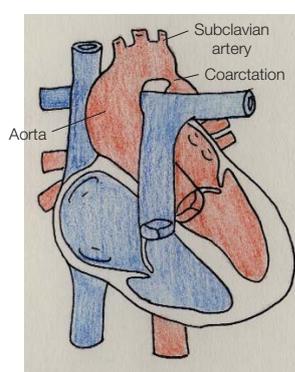
Evidence of coarctation depends on the severity of narrowing. Antenatal ultrasound features include a smaller left ventricle compared with the right and a smaller aorta and aortic arch.

Severe coarctation of the aorta usually gives rise to clinical signs shortly after birth including pale skin, irritability, heavy sweating and difficulty breathing. At birth the closure of the ductus arteriosus results in abrupt obstruction to flow in the aorta and the baby can present with severe respiratory distress. If left untreated, severe coarctation may lead to heart failure and death.
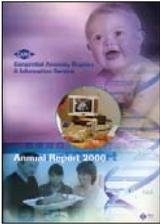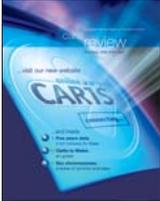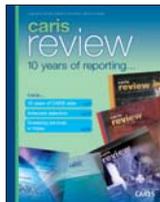
Presentation later in childhood or as an adult usually suggests a less severe anomaly. Common later findings include high blood pressure in the arm, a discrepancy between the pulse and blood pressure in the upper and lower limbs, shortness of breath, headache, muscle weakness or cramps and nosebleeds.

The cause of coarctation is not understood. It occurs twice as often in males and is often associated with other heart defects including a bicuspid aortic valve, valve stenosis, septal defects and a patent ductus arteriosus. About 10 to 15 per cent of girls and women with Turner's syndrome also have coarctation.

CARIS has received reports of 261 cases of coarctation from 1998 to 2010. This gives a gross prevalence rate of 6.1 per 10,000 total births or about 19 cases in Wales each year. Of these, 239 (92%) were live born and 116 (44%) were associated with other anomalies.

Appendix A:
Previous CARIS reports

Subject of special reports	Report year	Data
Neural tube defects Gastroschisis	1999	1998
Cleft lip & palate Down syndrome update	2000	1998-1999
Antenatal detection Limb reduction defects	2001	1998-2000
Congenital heart disease Trisomies 13 & 18	2002	1998-2001
Update on clefts Sex chromosome anomalies	2003	1998-2002
Urinary tract anomalies Update on gastroschisis	2004	1998-2003
Congenital causes of intestinal obstruction Congenital defects of the diaphragm and abdominal wall	2005	1998-2004
Neural tube defects Disorders of the central nervous system	2006	1998-2005
Congenital anomalies – causes and mechanisms Risk factors for congenital anomalies	2007	1998-2006
Antenatal detection Screening services in Wales	2008	1998-2007
Skeletal anomalies NHS fetal anomaly screening programme	2009	1998-2008
Eye anomalies Facial anomalies	2010	1998-2009

Appendix B:
Champions and co-ordinators

CARIS co-ordinators

Welsh delivery units have a co-ordinator, experienced in advising about reporting to CARIS. They can supply warning cards, forms and help with filling these in. They can retrieve notes to record the best data about the mother and baby. In many units the initial warning card is sent to the co-ordinator before being sent to the CARIS office so that the co-ordinator is aware of the suspicion of an anomaly.

CARIS champions

All units have an obstetrician and paediatrician with a particular interest in congenital anomalies. They have kindly agreed to act as champions for CARIS, keeping the profile high in the unit. They also are available if there are local reporting problems.

Hospital	CARIS champion in paediatrics	CARIS champion in obstetrics	CARIS co-ordinators
Bronglais	John Williams	Angela Hamon	Jo Mylum/Helen James
Glangwili	Gwyneth Owen	Roopam Goel	Anya Evans
Neath Port Talbot/ Princess of Wales	Katherine Creese	Sushama Hemmadi	Elaine Griffiths & Diane Evans
Nevill Hall	Tom Williams	Delyth Rich	Tim Watkins
Powys	(to be confirmed)	(not applicable)	Val Hester & Sue Tudor (Welshpool) Carole Stanley & Pat Mason (Newtown)
Prince Charles	David Deekollu	Jonathan Rogers	Kindry Dennett
Royal Glamorgan	Jay Natarajan	Jonathan Pembridge	Nicola Ralph
Royal Gwent	Vera Antao	Anju Kumar	Tim Watkins
Singleton	Geraint Morris	Marsham Moselhi	Helen Jenkins / Valerie Vye
UHW	Jenny Calvert	Christine Connor	Danielle Richards
Withybush	Devasettihalli Appana	Chris Overton	Amanda Taylor / Camilla Cooke
Wrexham	Praveen Jauhari	Bid Kumar	Sue Yorwerth
Ysbyty Glan Clwyd	Ian Barnard	Maggie Armstrong	Jenny Roberts
Ysbyty Gwynedd	Mair Parry	David Gatongi	Jackie Stockton & Jane Williams

Appendix C:
Ways to report to CARIS

Warning cards/e-alerts

Warning cards can be used to let CARIS know about results of an anomaly scan or other concerns in the antenatal period. This lets CARIS know of potential cases to follow-up. This year web-based reporting has been developed to make this quicker and easier.

The e-alert can be found on the CARIS website or at http://nww2.nphs.wales.nhs.uk:8080/CARIS WarningCard.nsf/WarningCardForm?OpenForm

The e-alert or warning card can be used when there is an antenatal suspicion of an anomaly or to alert postnatally. This may be a particularly useful way for staff to notify the register of cases when time is pressing.

CARIS is keen to hear of any possible cases:

- to contribute to the evaluation of antenatal screening; and
- to improve the number of confirmed cases subsequently identified.

Reporting forms

This represents all the clinical data collected by CARIS on any baby or fetus. It is normally completed once the pregnancy has ended and there is reasonable evidence of at least one congenital anomaly.

Specialist sources

Information from specialist sources usually involves detailed diagnostic data and is extremely useful to CARIS, both in improving the quality of information on known cases and discovering new ones.

Useful sources include:

- PEDW – (Patient Episode Database Wales) – records inpatient activity including any paediatric surgery;
- NCCHD – (National Community Child Health Database) – all children born in Wales should be recorded;
- Paediatric cardiology databases,
  – University Hospital of Wales
  – Alder Hey Hospital, Liverpool;
- New born blood test results;
- Cytogenetics; and
- SHIRE medical genetics register.

Reporting support

The CARIS staff offer support to units to facilitate data collection.

First reporting source to CARIS (2008 – 2010)

Ophthamology 1%
Pathology 3%
New born blood test results 1%
Paediatrics 7%
NCCHD 5%
PEDW 29%
Midwives/ CARIS co-ordinators 22%
Cytogenetics 6%
SHIRE 2%
Radiology 15%
Cardiology 9%
CARIS staff 1%

n = 3,969