**Long-term morbidity of children with specific congenital anomalies**

Protocol for EUROlinkCAT WP4 studies

**Institutions responsible:**

Hospital Lillebaelt, Kolding, Denmark (RSD, Ester Garne)

University of Ulster (UU, Maria Loane)

National Institute for Health and Welfare, Helsinki (THL, Mika Gissler)

Queen Mary University of London (QMUL, Joan Morris)

**The main aim of WP4** is to expand the knowledge on the health and clinical course of children with congenital anomalies up to the first 10 years of life and to evaluate different treatments in prenatal, neonatal and childhood care in Europe in order to optimize diagnosis, treatment and health for these children.

1. **Background and aim**

Every year 130,000 infants are born in Europe with a congenital anomaly (Dolk et al 2010). EUROCAT data for 2011-2015 gives an overall prevalence of livebirths with major congenital anomalies at 1.9% of all births. Congenital anomalies are a leading cause of childhood morbidity and long-term disability. Survival of children with congenital anomalies has improved (Tennant et al 2010), so up-to-date knowledge about childhood morbidity is required in order to counsel parents after a prenatal or postnatal diagnosis of a congenital anomaly. Furthermore, knowledge about morbidity for infants and children with congenital anomalies across the European health care systems will enable comparisons to be made to improve the treatment and outcome for these children.

There are many studies on the outcome of specific congenital anomalies (for example hydrocephaly, spina bifida, congenital cataract, transposition of the great arteries, Tetralogy of Fallot, cleft palate see Annex 2), but the overall morbidity for live born infants with a range of congenital anomalies has not yet been published in a population-based setting. Many of these outcome studies consist of cohorts of live born children referred for surgery, a biased population as not all children may be suitable for surgery (Lumenta et al 1995, Shimokawa et al 2002, Casey et al1997). In addition, many studies have had to recruit newborns over a long time period in order to have a reasonable number of cases for rare anomalies (Shimokawa et al 2002), which limits the validity of the results due to changes in health care practices over time. There is, therefore, a need to improve our knowledge of the overall health of children with congenital anomalies, the clinical course of their disease as well as potential associated complications.

One study from a tertiary neonatal center in the UK showed considerable variation in the length of stay following surgery for gastrointestinal anomalies, both between and within each anomaly subgroup (Shetty 2016). For selected anomalies, variations in all our morbidity measures will be investigated in greater detail and possible explanations for these differences will be explored. Geographical variations will also be examined. Other factors for morbidity will also be investigated, including the timing of surgery and patient level risk factors such as birth weight and gestational age at birth.

Two studies (Derrington et al 2013 in the USA to three years of age and Hung et al 2011 in Taiwan for all ages) demonstrated that socio-economic factors and ethnicity are important influences on the length of inpatient stays in children and adults with Down syndrome. Derrington et al demonstrated that children with Down syndrome who were Hispanic were 40% more likely to be hospitalized (OR=1.4) than non-Hispanic white children and that their stays were almost twice as long, with the main cause being significantly higher rates of respiratory disease. The morbidity of children according to socio-economic factors will therefore also be examined.

Prenatal detection of congenital anomalies has become more common during the last two decades with improvements in ultrasonographic technology and increased accuracy of screening ultrasonography (Peyvandi et al 2016). The increasing prenatal detection rate of congenital anomalies may also reflect the growing number of scans during pregnancy (Mesas Burgos et al 2016). Differences in the detection rates may also be attributable to the quality of ultrasound equipment, the experience of the examiner, the type of anomaly and the gestational age of the fetus at examination (Skari et al 1998). The possibility to detect congenital anomalies before birth allows better planning of the prenatal and postnatal care (Gamba et al 2014). In some rare cases, it also allows prenatal fetal therapy (Grivell et al 2014). However, in many cases, prenatal diagnosis seems not to result in better outcome but has instead predicted a poorer outcome, possibly due to the severity of the cases (Peyvandi et al 2016, Lazar et al 2011). There is also a need to balance between the benefits of a prenatal diagnosis and lower gestational age following an induced birth. For example, elective delivery of fetuses with complex congenital heart disease at early term results in earlier gestational age and lower birth weight, both of which affect morbidity and mortality (Costello et al 2014).

This study will compare the morbidity of prenatally and postnatally diagnosed cases of spina bifida, transposition of great arteries, diaphragmatic hernia and gastroschisis (Annex 1). Since earlier results about the effect of the timing of the diagnosis are limited and conflicting, more research on the subject is needed.

In a recent commentary, Shea et al (2016) concluded that linkage of administrative databases with clinical registry data provides a valuable method to describe cost variation across institutions. This was demonstrated in the USA when Pasquali et al (2014) linked The Society of Thoracic Surgeons and Pediatric Health Information Systems Databases and demonstrated that the costs per case for heart operations in children varied considerably between hospitals (up to nine times more expensive in one hospital than another). Differences in length of stay (LOS) and complication rates explained a large proportion of this variation. Dawson et al (2014) found that for Down syndrome the strongest predictor of costs and resource use was whether the infant had severe CHD or not; the presence of other severe anomalies did not have such a strong influence. The morbidity data collected in EUROlinkCAT (particularly information on length of stay and surgery performed) will enable an economic analysis of the costs of hospitalisation for specific congenital anomalies to be evaluated. In addition, the costs for children with and without a prenatal diagnosis will be compared.

For all of the above analyses, data on the children with congenital anomalies will be compared to the same data for control populations where possible. Controls (for some registries) will be all or a selection of live born infants in the same geographical area without congenital anomalies. Controls from the same geographical areas are important as there may be major differences in the rate of admissions in different hospitals and countries across Europe.

In this study, morbidity will be measured by the number of days spent in hospital, occurrence of surgery, days in intensive care units, hours/days on a ventilator and prescriptions of medicine for infections, respiratory illness, diabetes and epilepsy.

**There are four studies included in this WP4 protocol. Their aims are** to evaluate 1) the long-term morbidity of children with specific congenital anomalies (RSD), 2) the impact of risk factors that might explain geographical differences in morbidity (UU), 3) the effect of prenatal diagnosis on morbidity (THL) and 4) the costs of hospitalisations (UU and QMUL)**.** A separate WP4 study will evaluate the use of medications for infections, respiratory illness, diabetes and epilepsy. This protocol will be written later.

1. **Description of data and data sources**

**2.1 Inclusion criteria**

Seventeen EUROCAT registries are included in the study: Finland, Funen (Denmark), England (five registries under BINOCAR), Wales, Northern Netherland, Emilia-Romagna and Tuscany (Italy), Zagreb (Croatia), Valencia Region and Basque Country (Spain), South Portugal, Omni-net (Ukraine), and Reunion (France).

Cases for the study are all live born infants with a major congenital anomaly as defined in EUROCAT (Guide 1.4) born between 1995-2014 or with the first and last year available in both the registry and in the health care databases. For the most recent years follow-up may be less than five years after birth.

Where available, controls will be all or a selection of live born infants born during the same time period as the cases and in the same geographical area without congenital anomalies.

WP2 will develop some data quality indicators to determine inclusion of a registries data in the studies on risk factors and prenatal diagnosis. For example, all registries will be required to have the EUROCAT variable “when discovered” valid for at least 80% of their cases in order for their data to be included in the prenatal study.

**2.2 Data file from the EUROCAT registry**

EUROCAT variables to include are described in Table 1. Each registry will extract a file of all live born congenital anomaly cases, all fetal deaths from 20 weeks of gestation and terminations of pregnancy for fetal anomaly (TOPFA) at any gestational age from the most recent version of EUROCAT Data Management Program (EDMP version 6.10, January 2016). Coding and classification of the congenital anomalies will be based on the coding of anomalies and subgroups in the EUROCAT registry (see Guide 1.4). Each registry should also extract an A6 table showing the number of cases and prevalence per 10,000 births of each anomaly subgroup by each year included using the Reports function in EDMP and send this to UU. The A6 table will be used to crosscheck the number of cases that are linked/ unlinked. As it is usually the most severe cases that result in a TOPFA or a fetal death from 20 weeks of gestation, this will have an impact on morbidity for livebirths when we compare regions across in Europe. Therefore, the numbers of fetal deaths from 20 weeks of gestation and TOPFAs are requested in order to enable statistical analysis to adjust for these when exploring regional differences in Europe.

All live born congenital anomaly cases from the EDMP data file described above will then be linked to health care databases with data on morbidity such as hospital discharge records. The registry or the data provider will produce a short report outlining the number of cases that were linked / unlinked and the reasons for non-linkage. This report should be sent to UU before any data tables are prepared.

**2.3 Health care databases**

The EUROCAT data file will be linked to the local or national databases with hospital episode data using either personal ID number or linked through common variables (date of birth, gestational age, birth weight, sex, maternal age/date of birth). For each child, data will be extracted up to the first 10 years of life or up to the latest available year in the health care databases (2016 or 2017). Variables to include from the hospital episode databases are listed in Table 2 and will be defined for each registry by the Standardisation Committee. Morbidity for this study will be measured by the number of days spent in hospital and the diagnosis for each hospital stay, occurrence of surgery, days in intensive care units and number of days on a ventilator. Variables on maternal socio-economic status, such as maternal education, maternal occupation and estimated level of deprivation from geographic area of residence will also be included.

**2.4 Controls**

Where possible, the controls will be all children in the population, defined as born in the same geographical area and within the same time period as the children recorded in the EUROCAT registry. In some registry areas, only data from a sample of matched control children is available (Table 3). Any child with a diagnosis in the hospital episode databases coded within the WHO ICD10 Q-chapter or with an ICD9 code within 740-759 will be excluded from control group. These children will mainly have minor anomalies or have moved into the area after birth. A few may have major congenital anomalies unknown to the registry. Controls will not be used for the study on prenatal diagnosis.

**2.5 The linked data**

The linked data file will be stored securely, either within the local registry or within the organisation doing the linkage. The registries will be provided with a set of instructions (syntax script, see section 3 below) to create pre-specified tables and perform analysis on the data and the aggregated tables and analytic results will be transmitted to the Central Results Repository (CRR) at UU. No individual case data will be transmitted to the CRR.

* 1. **Comments on the outcome variables from the health care databases**

The main outcomes for this study are number of days spent in hospital and the diagnosis for the hospital stay, occurrence of surgery, number of days in intensive care units and number of hours/days on a ventilator. Some registries will not have access to all main outcome variables.

* Number of days in hospital will be calculated based on date of admission and date of discharge and, if available, admissions to and number of days in intensive care units will be assessed.
* Number of days on a ventilator will be counted based on procedure codes in the health care databases if available.
* Surgeries will be analysed based on the local coding system used for the procedures. For relevant congenital anomaly subgroups codes for the surgeries performed will be classified into three groups: primary surgery/surgeries for the anomaly, surgery for complications and surgery for other diagnosis. This will programmed into the syntax script for each registry

Non-congenital anomaly diagnoses (main diagnosis or other diagnosis) recorded in the health care databases will be classified into groups to describe why the child was in hospital. This classification based on ICD9 or ICD10 codes will be integrated into the syntax script produced for the analysis. Examples of diagnostic groups are infections, epilepsy/seizures, malnutrition, cancer, diabetes etc.

Each registry/data provider will provide a short report about the validity of the data based on a pre-defined template, that is: Are all hospital contacts for each child included in the health care databases used for the study, or might surgeries have taken place in another region/country? Is morbidity known for children that have moved out of the registry area or out of the country? Could children have been admitted to private hospitals without access to their data?

**3. Local analyses**

A detailed analysis plan will be written by WP4 leaders with support from statisticians from QMUL (month 12) and tested in a few databases before being released to the registries. UU and QMUL will produce common syntax scripts, which will conform to a common data model to ensure that all variables/proxy variables are standardised across all registries (month 18). Registries will use their own registry specific syntax scripts provided on their linked dataset to generate the tables/ results outlined in the analysis plan. A data "dictionary" of every variable in the linked data with its name, description/definition, coding instructions/values (in English) will be created and uploaded to the website. The quality of the data linkage will be investigated and data quality checks will be conducted for unlikely results and outliers across registries (UU) and a report produced.

Analysis will include all cases with congenital anomalies (EUROCAT subgroup al1: all anomalies) and on all relevant EUROCAT subgroups as defined in Guide 1.4 chapter 3.3. For very rare anomalies with very little published information in the literature, morbidity will be analysed if there is a sufficient number of each anomaly in the registries to be able to/allowed to deliver aggregate tables. In addition, power calculations will be performed by QMUL to ensure that the selected anomaly subgroups have sufficient power to derive meaningful conclusions. Cases will be classified as isolated or genetic according to the multiple flowchart programmed in EDMP (Garne 2011) and analyses will be performed in groups of all cases, isolated cases and genetic cases.

Morbidity data will be analysed in two cohorts: all live born infants included in the EUROCAT database and the subset of all long-term survivors defined as alive at one year of age*.* Data on mortality used for WP3 will be used to identify the cohort of longterm survivors (Portugal not in mortality study).

The first study will describe overall morbidity for all cases of major congenital anomalies across Europe compared to the background population or matched controls, and will also describe morbidity for individual subgroups of congenital anomalies and differences between registries/countries. The next two studies (led by UU and THL) will look into risk factors for morbidity and health inequalities in the treatment of congenital anomalies in Europe, and the possible impact of prenatal diagnosis on morbidity (for four anomalies only). The fourth study (led by UU and QMUL) will aim to quantify the relative costs of hospital care for specific anomalies, and investigate whether these costs vary according to the occurrence of prenatal diagnosis.

**4. Data transmission to the Central Results Repository (CRR) and to WP4**

The tables and results created by each registry using the supplied syntax scripts will be submitted in Excel, SPSS or STATA file formats, or other commercially available packages, to UU via the secure project portal (members’ area on the EUROlinkCAT website) (month 22). All data submitted will be aggregated - no individual case data will be sent to UU.

UU will then:

1. Import the tables from each participating registry to the CRR
2. Perform data quality checks
3. Generate extracts of data from the CRR required for this study
4. Send the relevant CRR extracts to the WP4 project leaders via the secure project portal (members’ area on the EUROlinkCAT website) (month 26).

**WP4 Analyses and milestones:**

Hospital Lillebaelt:

The WP4 leader and her staff will perform meta-analyses on morbidity outcomes (days in hospital, diagnosis, surgeries, days in intensive care, days on ventilator) based on the data from the 17 registries received from the CRR. Results will be discussed at a subgroup meeting with the involved registries (month 30) and a first draft of the paper will be circulated for comments (month 32). The paper will be submitted before the final report to the EU by month 42.

National Institute for Health and Welfare, Helsinki:

Finland will perform meta-analyses on morbidity outcomes for four congenital anomaly subgroups (spina bifida, transposition of great arteries, diaphragmatic hernia and gastroschisis) and compare the pre and postnatally diagnosed cases. Results will be discussed at a subgroup meeting and a first draft of the paper will be circulated for comments by month 48. The paper will be submitted before the final report to the EU by month 54.

Ulster University:

UU will also perform meta-analyses on the data from the CRR to explore risk factors/geographical differences identified in the analysis of morbidity outcomes above. Results will be discussed at a subgroup meeting (month 40) and a first draft of the paper will be circulated for comments (month 42). The final paper will be submitted by month 47.

Queen Mary University of London:

The PI and statistician at QMUL will work with UU to obtain information on relative costs of surgeries and inpatient stays in the relevant European countries. This will be applied to estimate the costs for specific congenital anomalies (month 36). Results will be discussed at a subgroup meeting (month 43) and a first draft of the paper will be circulated for comments (month 45). The final paper will be submitted by month 50.

**5. Publication of results**

All four studies will be published in high-impact peer-review journals with open access and with authorship according to EUROlinkCAT criteria.

The studies have two deliverables in the Horizon 2020 contract:

D4.1: Report on Hospitalisations and surgery across Europe for the first 5 years of life [month 42]

D4.3: Report on prenatal diagnosis and morbidity [month 54]

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**Table 1**

Variables to extract from the EUROCAT database (EDMP)

|  |  |
| --- | --- |
|  | **EUROCAT core variables and additional variables for WP4 linkage,** **one row of data per case**  |
|  | **EDMP Core variables (shaded in blue)** |
| **Baby and Mother – Variables 1 to 18**  |
| 1 | CENTRE | Centre Number |
| 2 | NUMLOC | Local ID of case |
| 3 | BIRTH\_DATE | Date of Birth |
| 4 | SEX | Sex |
| 5\*\* | NBRBABY | Number of babies delivered |
| 6 | SP\_TWIN  | Specify twin type of birth, like or unlike, zygosity  |
| 7 | NBRMALF | Number of malformed in multiple set |
| 8 | TYPE | Type of birth |
| 9 | CIVREG | Civil registration status |
| 10 | WEIGHT | Birth weight |
| 11 | GESTLENGTH | Length of gestation in completed weeks |
| 12 | SURVIVAL | Survival beyond one week of age |
| 13 | DEATH\_DATE | Date of death |
| 14  | DATEMO  | Date of birth of mother  |
| 15 | AGEMO | Age of mother at delivery |
| 16\* | BMI  | Maternal Body Mass Index  |
| 17  | RESIDMO  | Mother’s residence code  |
| **Diagnosis – Variables 19 to 57**  |
| 19\*\* | WHENDISC  | When discovered |
| 20 | CONDISC | Condition at discovery  |
| 21 | AGEDISC  | If prenatally diagnosed, gestational age at discovery |
| 22 | FIRST PRE | First positive prenatal test |
| 24 | KARYO  | Karyotype of infant/fetus  |
| 25 | SP\_KARYO  | Specify karyotype  |
| 26\* | GENTEST  | Genetic Test  |
| 27\* | SP\_GENTEST  | Specify genetic test  |
| 28 | PM  | Post mortem examination  |
| 29\*\* | SURGERY  | First surgery for malformation performed or planned  |
| 30 | SYNDROME  | Syndrome |
| 31 | SP\_SYNDROME  | Specify Syndrome  |
| 32 | MALFO1  | malformation |
| 33  | SP\_MALFO1  | Specify malformation  |
| 34  | MALFO2  | As MALFO1  |
| 35  | SP\_MALFO2  | Specify malformation  |
| 36  | MALFO3  | As MALFO1  |
| 37  | SP\_MALFO3  | Specify malformation  |
| 38  | MALFO4  | As MALFO1  |
| 39  | SP\_MALFO4  | Specify malformation  |
| 40  | MALFO5  | As MALFO1  |
| 41  | SP\_MALFO5  | Specify malformation  |
| 42 | MALFO6  | As MALFO1  |
| 43  | SP\_MALFO6  | Specify malformation  |
| 44  | MALFO7  | As MALFO1  |
| 45  | SP\_MALFO7  | Specify malformation  |
| 46  | MALFO8  | As MALFO1  |
| 47  | SP\_MALFO8  | Specify malformation  |
| 57# | OMIM  | OMIM code / Type of Mendelian Inheritance  |
| **Exposure and family history – variables 58 to 89** |
| 58\*\* | ASSCONCEPT | Assisted conception (where available) |
| 59##  | OCCUPMO  | Mother’s occupation at time of conception  |
| 60 | ILLBEF1 | Maternal illness before pregnancy 1 |
| 61 | ILLBEF2 | Maternal illness before pregnancy 2 |
| 64 | ILLDUR1 | Maternal illness during pregnancy 1 |
| 65 | ILLDUR2 | Maternal illness during pregnancy 2 |
| 79 | CONSANG | Consanguinity |
| 81 | SIBANOM | Sibs with congenital anomalies |
| 87 | MOANOM | Mothers family with anomalies |
| 89 | FAANOM | Fathers family with anomalies |
| **Sociodemographic – Variables 91 to 94**  |
| 91 | MATEDU | Maternal education  |
| 92  | SOCM  | Socioeconomic status of mother  |
| 93  | SOCF  | Socioeconomic status of father  |
| 94  | MIGRANT  | Migrant status  |
| **EDMP-derived variables** |  |
|  | Byear | Year of birth |
|  | birth\_type | Definitions of stillbirths and spontaneous abortions vary between regions. This variable recodes birth type according to EUROCAT’s specifications: cases with gestational age ≥ 20 weeks are re-coded as “stillbirths” (irrespective of the local definition of stillbirth/spontaneous abortion). |
|  | casestatus | Only cases with casestatus = 1 |
|  | al1-al114 | EUROCAT subgroups: (0 = No, 1 = Yes). Based on EUROCAT coding in Guide 1.4 |
|  | mult\_malf  | Algorithm for case classification into isolated and multiples |

\* New variable In Guide 1.4 from 2013

\*\* Variable compatible over time, but coding has been extended/modified

# Variable name change only

## Guide 1.4 use ISCO-08 classifications

**Table 2**

Variables from the health care databases for cases and controls

|  |
| --- |
| **Variables in health care databases to be linked to congenital anomaly cases**  |
| **The first 16 variables are the same as for mortality study (WP3)** |
|  | L\_CH\_ID | Child unique ID or other unique identifier |
|  | L\_CH\_DATE\_B | Child’s date of birth |
|  | L\_CH\_SEX | Infant’s sex |
|  | L\_CH\_GA\_B | Gestational age at birth |
|  | L\_CH\_BW | Child’s birth weight |
|  | L\_MULT\_BIRTH | Singleton or multiple birth  |
|  | L\_MAT\_CTRY\_B | Maternal country of birth/ place of birth/ country of origin |
|  | L\_MATMAR\_STA | Maternal marital status |
|  | L\_MAT\_EMPL | Mother’s employment status |
|  | L\_MAT\_OCC | Maternal occupation |
|  | L\_MAT\_EDUC | Maternal education |
|  | L\_MATDEPR\_IND | Deprivation index at maternal residence |
|  | L\_MATAGE\_B | Maternal age at infant's birth |
|  | L\_CH\_DATE\_D | Date of death on the death certificate or in the mortality database |
|  | L\_CH\_AGED\_GRa | Categorised age at death |
|  | L\_DATE\_LOST | Date lost to linkage due to emigration, adoption or loss to follow-up |
|  | L\_PARITY | Number of previous pregnancies |
|  | L\_Hosp\_daysY1 | Number of days in hospital year 1 (from birth to 1 year of age) |
|  | L\_Hosp\_daysY2 | Number of days in hospital year 2 |
|  | L\_Hosp\_daysY3 | Number of days in hospital year 3 |
|  | etc | Up to age 10 |
| **For each hospital stay during the first 10 years of ageb** |
|  | L\_DATE\_ADM | Date of admission to hospital |
|  | L\_DATE\_DIS | Date of discharge from hospital |
|  | L\_DIAG\_DIS | Main diagnosis in ICD9 or ICD10 for the hospital stay |
|  | L\_DIAG\_SEC1, DIAG\_SEC2 etc | Other diagnosis for the hospital stay |
|  | L\_DAYS\_ICU | Number of days in intensive care unit during hospital stay (NICU; PICU, ICU) |
|  | L\_DAYS\_VENT | Number of days on ventilator during hospital stay |
|  | L\_SURG\_CODE1, SURG\_CODE2 etc | Codes for surgery performed during hospital stay |
|  |  |  |

aTo be recorded in hours, days or years

b Details about the variables to be agreed with UU (WP2)

**Table 3**

Type of controls planned for the 17 registries according to questionnaire in November 2017

|  |  |
| --- | --- |
| **Registry name** | **Type of controls** |
| Funen, Denmark | Population |
| England, five registries | Matched controls |
| Emilia Romagna, Italy | Population |
| Zagreb, Croatia | Not known yet |
| Tuscany, Italy | Population |
| Northern Netherlands | Population |
| Wales | Population |
| Valencia Region, Spain | Population |
| Finland | Population |
| Omni-Net, Ukraine | No controls |
| South Portugal | Maybe |
| Reunion, France | Not known yet |
| Basque Country, Spain | Population |

**Appendix to protocol**

**Literature reviews**

**For information for registries – not for ethical applications**

**Annex 1**

**Literature reviews on impact of prenatal diagnosis for liveborn infants with spina bifida, transposition of great arteries, diaphragmatic hernia and gastroschisis**

Institution: THL - Finland

**Spina bifida**

Prenatal detection of spina bifida has become significantly more common and thereby the possibilities to estimate the severity of the cases have increased, which enables planning of the optimal mode of delivery as well as planning and performing immediate and subsequent postnatal care in a specialized unit (Wilson et al). Prenatal myelomeningocele repair by hysterotomy seems to reduce the need for shunting and to improve motor outcomes at 30 months compared to the standard postnatal repair. However, early intervention has also been associated with both maternal and fetal morbidity and potential benefits of prenatal surgery must be balanced against the risks of prematurity and maternal morbidity (Wilson et al). [[1]](#endnote-1)Prenatal diagnosis can be used to plan the mode of delivery, but with myelomeningocele patients the selection between elective cesarean and spontaneous labour does not seem to affect motor function or ambulation status in myelomeningocele patients (vertex presentation) (Lewis et al 2004).

# Wilson RD; SOGC GENETICS COMMITTEE; SPECIAL CONTRIBUTOR. Prenatal screening, diagnosis, and pregnancy man Prenatal screening, diagnosis, and pregnancy management of fetal neural tube defects.agement of fetal neural tube defects.

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**Transposition of great arteries**

Prenatal diagnosis of transposition of the great arteries (TGA) reduces mortality and morbidity (Bonnet et al 1999 and van Velzen et al 2015). Postnatal acidosis and need for intubation has been reported to be more common among the postnatally diagnosed cases,i but many longer-term measures, for example the length of post-op ICU stay, have not differed between the groups. Prenatal diagnosis of TGA has been suggested to be associated with better neurocognitive outcomes, especially executive function (Calderon et al 2012 and Peake et al 2015). Presence of preoperative brain injury has been found to be lower and postnatal microstructural brain development to be better in patients with prenatal diagnosis of TGA. The mechanism behind these findings is likely related to a better hemodynamic state as a result of earlier use of prostaglandin E1 (Peyvandi et al 2016).

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**Congenital diaphragmatic hernia**

In previous studies comparing the outcome of prenatally versus postnatally diagnosed cases of congenital diaphragmatic hernia (CDH), conflicting results have been reported. Prenatal diagnosis has been indicative of more favourable or poorer outcome as well as similar outcome when compared to postnatally diagnosed cases. Fetal therapy has been suggested to improve postnatal survival (Deprest et al 2004).

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**Gastroschisis**

Prenatal diagnosis of gastroschisis does not seem to be associated with either worse disease or a poorer outcome when compared to postnatal diagnosis (Sipes et al 1990). However, there are indications that certain prenatal ultrasound signs (intraabdominal bowel dilatation, polyhydramnios and gastric dilatation) can be used to identify neonates with a higher risk of postnatal complications (D’Antonio et al 2015). Majority of the studies have been conducted on high-income countries with high survival rate of children with gastroschisis. Instead, in low-income countries, such as Uganda where gastroschisis-related mortality rate is over 90%, improving prenatal diagnostics and better prenatal planning of specialized care would inevitably have a favourable effect on prognosis of the children (Wesongo et al 2016).

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**Annex 2**

**Literature reviews on morbidity for selected EUROCAT congenital anomaly subgroups**

Institution: RSD - Hospital Lillebaelt

**Q03: Hydrocephalus**

Congenital hydrocephalus is characterized by an abnormal accumulation of cerebrospinal fluid (CSF) in the brain (1). In the fetus and the infant the main clinical sign is enlargement of the head although in some cases with cerebral ventriculomegaly the head circumference is within normal limits. The CSF may be under pressure causing compression and damage to the brain. The reason for the accumulation of the CSF is an imbalance between production and absorption of the CSF. The most common causes of congenital hydrocephalus are obstruction of the cerebral aqueduct flow, Arnold Chiari malformation or Dandy-Walker malformation (2). As congenital hydrocephalus is rare and because hydrocephalus also may be aquired after perinatal events (tumours, cerebral bleeding, CNS-infections) publications give outcome data on these groups of infants together (3), or include infants with spina bifida (4) or cover a long time period in order to have a reasonable number of cases (5). Further published series only give data on liveborn infants referred for surgery (4, 5, 6). A EUROCAT study including four small registries found high infant mortality (34%). Further half of infants with surgery performed had repeated surgeries within the first 3 years and less than half of survivors at 3 years were normal for age (7). The outcome of adult patients with congenital hydrocephalus suggest that the same fraction grow up to live independent lives (8).

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# Q05: Spina bifida

Spina bifida is a congenital anomaly resulting from failure of fusion of the caudal neural tube. Children born with spina bifida are at risk for hydrocephalus, leg weakness and paralysis, sensory loss, and bladder and bowel incontinence(1).

Treatment of spina bifida is surgery with closure of the spinal canal within the first days after birth. If prenatally diagnosed prenatal surgery is now possible (2). The option to terminate pregnancy or to endure risks associated with prenatal surgery offers several ethical issues (3).

Mann et al. studied the use of Emergency Rooms (ER) and inpatient clinics (IP) for adolescents and young adults with spina bifida and found that persons with SB in the older age group exhibited higher rates of ER use because of endocrine, nervous system, skin, musculoskeletal, genitourinary, and digestive conditions and a higher rate of IP use for skin conditions. Associated hydrocephalus was not significantly associated with ER or IP use overall, but the rate of ER use due to epilepsy was markedly greater in persons with hydrocephalus(4).

Young et al. conducted a secondary analysis of health services utilization data from the Canadian Institute for Health Information. They found that annual rates of outpatient physician visits rates for young and adult patients with spina bifida were approximately 2.9 and 2.2 times higher, respectively, than for their age-matched peers(5).

Wang et al. observed a temporal and geographic trend toward decreasing urological surgery and increasing chronic renal insufficiency rates in spina bifida and a wide variation in urological surgical rates among states in the US (7) and large variations in spina bifida managements.

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**Q120**: **Congenital cataract**

Bilateral congenital cataract is the most common cause of treatable childhood blindness. Nuclear cataract is usually present at birth and is non-progressive, while lamellar cataract usually develops later and is progressive. Prompt surgery has to be performed in cases with dense congenital cataract: if nystagmus has developed, the amblyopia is unfortunately irreversible(1).

Hospitalization: In China 9.2% of the identified Congenital Cataract patients had ≥ 2 hospitalizations due to the necessity of additional surgeries, with a total ratio of boys to girls of 1.75(2).

Surgery: Primary intraocular lens (IOL) implantation is associated with an overall satisfactory visual outcome, especially when surgery is performed before 6 months or after 12 months of age and in bilateral cases. Glaucoma is the main complication associated with poor visual outcome (3).

Surgery complications: 22 % of the patients required re-operation for visual axis obscuration after cataract surgery independent of type of intraocular lens and age, but this rate is affected by the rate of perioperative complications (4) Strabismus occurred more frequently in patients with congenital cataracts (30.3%) than in acquired cases (5), however strabismus surgery were not required in most cases (6). Estimates show that nearly two thirds of operated eyes will develop glaucoma or become glaucoma suspects by 10 years after cataract surgery. (7). Up to 56% of children with surgery for cataract may show amblyopia(8).

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**Q203: Transposition of great arteries**

Prevalence of isolated transposition of the great arteries (TGA) is 2.0 out of 10.000 livebirths(1). In TGA, the ventriculo-arterial connection is discordant, which means that the aorta arises from the morphological right ventricle, and the pulmonary artery arises from the morphological left ventricle(2). Rate of prenatal diagnosis by ultrasound has improved, but is still low in detection rate compared to other severe congenital heart defects(3;4). Approx 27% of cases are diagnosed prenatally, and of these pregnancies 40% are terminated(3).

Hospitalization: One study of the length of hospitalisation after surgery for TGA showed that longer postoperative Intensive care stay and total hospital length of stay is associated with worse cognitive function at age eight years, even when adjusted for perioperative and sociodemographic variables(5). Adult patients with TGA in the United states are four times as often in hospital as the general population with 0.41 hospitalizations per patient-year(6).

Children with TGA diagnosed prenatally have better early complex cognitive skills, particularly executive function, as compared with those diagnosed postnatally, in whom pre-operative acidosis and profound hypoxemia are more common(7). This is partly explained by the higher rate of balloon atrial septostomy in infants with severe hypoxemia.

Surgery: Balloon atrial septostomy (BAS) can be performed soon after birth together with prostaglandin infusion to reduce hypoxemia. BAS has a risk of stroke (8;9) and will prolong later surgery because of the time it takes to repair the aquired atrial septal defect.(8) However BAS is not associated with increased odds for perioperative brain injury during later arterial switch operation (ASO) (10). ASO allows better postoperative survival and outcomes than atrial switch procedures(11). One study showed low mortality and short time complications related to ASO to be 12% in simple ASO and 39% in complex ASO using prospective risk stratification(12).

Morbidity: After ASO rare complications are the need for lung transplantation or Potts shunt due to pulmonary arterial hypertension (PAH)(13;13-15)). Risk factors for unplanned cardiac hospitalisation in young adults with TGA includes associated Ebstein malformation, surgeries other than the primary repair, noncardiac diagnoses, atrial arrhythmias, atrioventricular nodal block, low left ventricular ejection fraction, and smoking(5).

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**Q213: Tetralogy of Fallot**

The term tetralogy of Fallot (TOF) refers to a tetrad of: (i) ventricular septal defect with (ii) over-riding of the aorta, (iii) right ventricular outflow obstruction, and (iv) right ventricular hypertrophy and is attributed to Canadian Maude Abbott in 1924, first described by Niels Stenson in 1671(1). TOF consists of a wide variety of diseases with variability in terms of pulmonary artery anatomy, associated abnormalities, and outcomes(1;2) Prevalence is up to 3 per 10,000 livebirths(2). Overall, approximately 85% survive to adulthood(3).

Hospitalization: Adult patients with complex TOF are hospitalized at a rate four to eight times greater than the general US population (P < .001). Risk factors are pulmonary atresia, depressed left ventricular and right ventricular ejection fraction and smoking(4).

The most common primary admission diagnosis is heart failure (HF; 17%), arrhythmias (atrial 10% and ventricular 6%), pneumonia (9%), and device complications (7%). The rates of co-morbidities includes particularly diabetes (4.5% to 8.1%), obesity (2.1% to 6.5%), hypertension, and renal disease(5).

Surgery: Corrective surgery includes closure of the VSD and removal of the right ventricular outflow tract obstruction. Surgery has evolved greatly over time and include either transannular patch, right ventricular outflow tract patch, or no patch, and a right ventricular-pulmonary artery conduit (3). Postoperative complications encountered can be: low cardiac output syndrome, pleural effusion requiring tapping, infection, reoperation for bleeding, pulmonary regurgitation and arrhythmias(6-8) and in the long term there is a higher prevalence of coronary disease and heart failure(4;5;8).

Chronic hemodynamically relevant pulmonary regurgitation (PR) resulting in important right ventricular dilation and ventricular dysfunction is commonly seen after TOF repair, and is treated with pulmonary valve replacement which is the most frequent form of surgical reintervention after initial TOF repair(9-11). A Canadian Outcomes Registry Late After Tetralogy of Fallot Repair (CORRELATE) has been established to follow up patients with TOF, but has not yet published any results(12).

Intensive care: Egbe et al. found the median intensive care unit stay after corrective surgery to be 6 days (range 2-21 days) and the median duration of mechanical ventilation was 19 h (range 0-136 h)(6;7)

Morbidity: Pokorski reported a 36-year follow-up of 490 patients observed for a mean duration of 25 years after surgical repair of TOF and found elevated morbidity manifest by cardiac symptoms, arrhythmias, subsequent heart surgery, and disability. Most surviving patients were actively at work (70.8%), homemakers (20.1%), or retired (6.1%); 3% were unable to work.(13). Arrhythmias occur more frequently in adulthood in TOF patients and increase risk for sudden death(14)

Comorbidity: Tetralogy is often associated with non-cardiac anomalies, chromosomal anomalies and syndromes, examples are Di George syndrome and velocardiofacial syndrome, both of which have 22q11 deletions(15;16)

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**Q35 Cleft palate**

Cleft palate can be part of a syndrome or “non-syndromic clefts”. The subtypes consist of unilateral or central cleft palate, bilateral cleft palate, cleft uvulae, or submucosal cleft palate(1) Classification in relation to the orbita according to Tessier is still modified to etiological derive as a brachial arch defect(1-4)

Hospitalization: 10% of children with cleft palate has at least one hospital-based acute care visit (10.6 %) within 30 days after primary surgery(6). Emergency department visits not resulting in hospital admission where primarily associated with failure to thrive or upper respiratory infections(6). Co-morbidity, diagnosis (cleft lip versus cleft palate with or without cleft lip), and age at initial surgery are the most important factors associated with the highest quartile of cumulative hospital charges(6).

Surgery and length of stay: Outcome measures and regrafting in alveolar bonegrafting research is not clearcut, because of a lack of agreement of what characterizes graft failure and combining imaging with clinical outcomes as well.(7) Following surgery the mean length of stay in hospital is 2 days, but increases with comorbidity and if the hospital is not a paediatric hospital or has a paediatric intensive care unit(8). Complications include airway/respiratory failure (2%), infection, haemorrhage or wound disruption (Less than 1%). Overall mortality rate during postsurgical hospital stay is 0,01%.(8)

Morbidity: Problems with the eustacic tube can results in persistent conductive hearing loss despite treatment with pressure equalizations tubes placement.(5) A standard set of outcome measures has recently been proposed(4) Speech management is relevant after surgery with cleft palate to treat associated persistent speech disorders, but methods defer vastly(9). Quality of life in children and teenagers with cleft palate depends on the complications, the amount of surgeries and implants required, as well of the age, and resilience of the patient. Generally, surgery seems to improve QOL and mastery(10)

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…. To be extended

1. [↑](#endnote-ref-1)