Investigation of a cluster of cases of Gastroschisis in Bridgend County Borough during 2004

Gastroschisis Investigation Group
I should like to thank all the members of the Gastroschisis Investigation Group for their hard work in undertaking this investigation and preparing this report.

Mrs Diane Nutall and Dr Roshan Adappa deserve special thanks for their work in gathering clinical information. I should also like to thank Dr Ciarán Humphreys who has provided the literature review and done much of the report drafting and Dr Mark Temple who chaired the group originally and has worked on the environmental analyses.

Above all, I want to thank the mothers of the babies for being so helpful in providing the group with information. I am sorry that the investigation has not been able to provide the mothers with the answer to the question that they have all asked – “why did this happen to my baby?” Unfortunately it is not always possible to discover any underlying cause for a cluster like this. I hope that they will accept my assurances that we will continue to try and find ways to investigate this condition further in Wales.

I wish all the mothers and their babies well for the future.

Dr Judith Greenacre
Chair, Gastroschisis Investigation Group
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1 Executive Summary

Background information
1) This report describes investigations of a cluster of cases of gastroschisis within Bridgend County Borough. A multi-agency investigation group undertook the work, on behalf of Bridgend Local Health Board.

2) Gastroschisis is a rare congenital anomaly involving a gap in the abdominal wall. The condition appears to be increasing in the developed world and is unusually common among babies born to younger mothers. A number of risk factors for gastroschisis have been identified in previous research studies but the exact cause of the condition remains unknown.

3) The cluster was identified as a result of work undertaken to address concerns expressed both by clinicians in the University Hospital of Wales and by the Welsh Congenital Anomaly Register in early 2004 that they were seeing increasing numbers of cases of gastroschisis in Wales.

4) A cluster is said to occur when more cases of a relatively uncommon condition (such as gastroschisis) occur in an area and / or over a period of time and it is possible that this may not have happened by chance. Most clusters are nevertheless thought to be chance events.

5) Clusters are investigated to try and identify underlying factors that have caused increased numbers of cases of the condition to occur. If specific causes are identified the aim is to institute preventative measures to prevent further cases. Nevertheless, even when an underlying factor is suspected, it is not usually possible to identify the cause with certainty.

Questions addressed
6) The Investigation Group addressed the following questions:
   a) Is there evidence for a cluster of gastroschisis in Bridgend County Borough? If so, is this:
      i) localised to Bridgend County Borough, or
      ii) part of a wider problem?
   b) If there is a problem in Bridgend County Borough, are there any obvious potential causative factors?
   c) Are there any immediate public health actions that need to be taken in relation to any increase in cases in Bridgend County?
   d) Following on from this investigation what recommendations can be made regarding wider investigations into gastroschisis that could reasonably take place in Wales / the United Kingdom.
**Evidence of a cluster**

7) Seven cases of gastroschisis from Bridgend County were identified that were due to be born in 2004, five of whom had mothers’ addresses in the northern part of the county, away from the main centres of population. Normally, up to three cases a year might be expected to occur in the county as a whole. The group considered that this occurrence may not have arisen by chance and should therefore be investigated further. Against this local situation there has also been a noticeable, but more generalised, increase in the condition within Wales and elsewhere in the United Kingdom from 2003 onwards.

**Cluster investigation**

8) An exploratory approach was taken to identify factors that may be responsible for the higher than expected number of cases in Bridgend County Borough. Cases exhibited a number of features previously described in relation to gastroschisis, including young maternal age and low maternal body mass index.

9) Despite detailed interviews with mothers of cases and exploring environmental data no factor was identified that could explain this specific cluster.

**Further action**

10) In the absence of a cause for the cluster, no specific public health action could be recommended to reduce the risk of further cases arising.

11) The investigation showed that a number of mothers of cases had histories of poor nutrition and smoking. **Although this is not considered the cause of this specific cluster**, Bridgend Local Health Board should consider the need for further action to address this issue.

12) This report makes a number of recommendations that are not within the remit of Bridgend Local Health Board. The Investigation Group would ask the LHB to make this report available to other relevant bodies for them to consider further action. The relevant recommendations are as follows:

   a) It was noted that general advice to reduce the risk of congenital anomalies has been issued to doctors and dentists by the Chief Medical Officer for Wales during 2004. Consideration should be given on whether this advice should be disseminated more widely to the general public.

   b) In view of the current difficulties with the NCAS system, ways of strengthening surveillance and monitoring of congenital anomalies in Wales should be considered. In the meantime specific measures to monitor gastroschisis should be put in place.
c) Further work and on the cause of gastroschisis is recommended at an all-Wales and United Kingdom level.

d) Consideration should be given to developing further guidance on the investigation and management of incidents of this type in Wales
2 Introduction

Why this investigation took place

In spring 2004, clinicians at the University Hospital of Wales raised concerns that they were seeing increased numbers of babies with gastroschisis, a congenital defect of the anterior abdominal wall. At the same time, staff at the Welsh Congenital Anomaly Register (CARIS) also noticed a general increase in reported cases for 2003 and 2004, with a noticeable rise in Bridgend County Borough during early 2004. This was discussed in May 2004 by a small group including clinical and academic staff from the University of Wales College of Medicine, The National Public Health Service (including the Local Health Board Public Health Director), The Welsh Assembly Government and CARIS. At that meeting it was agreed that further investigation was required into the potential local cluster of cases of gastroschisis in Bridgend County Borough.

A larger investigation group with a wider membership was convened on behalf of Bridgend Local Health Board, including members of the original group together with local environmental health staff and a member of the environment team of the NPHS (For full membership, see Appendix A). This report covers the work undertaken by this group (referred to in this report as the “investigation group”) up to November 2004.

Questions addressed by the group

The investigation group has primarily been concerned with the potential cluster in Bridgend County Borough, rather than wider issues relating to gastroschisis. The questions that the group have addressed are as follows:

1) Is there evidence for a cluster of gastroschisis in Bridgend County Borough? If so, is this:
   a) localised to the county, or
   b) part of a wider problem?
2) If there is a problem in Bridgend, are there any obvious potential causative factors?
3) Are there any immediate public health actions that need to be taken in relation to any increase in cases in Bridgend County Borough?
4) Following on from this investigation what recommendations can be made regarding wider investigations into gastroschisis that could reasonably take place in Wales / the United Kingdom.

A cluster is said to occur when more cases of a relatively uncommon condition (such as gastroschisis) occur in an area and/or over a period of time and it is possible that this may not have happened by chance. Clusters are investigated to rule out any underlying factors that have caused increased numbers of cases of the condition to occur. Most clusters are nevertheless thought to be chance events. Even when an underlying factor is suspected, it is not usually possible to identify the cause with certainty.
**Background information on gastroschisis**

**Clinical condition**
Gastroschisis is a congenital anomaly (birth defect) in which there is a gap in the abdominal wall at the front, separate to the umbilicus\(^1\). The abdominal contents (most often loops of bowel) float freely in the amniotic cavity before birth and are often visible by antenatal ultrasound. Delivery is planned in a specialist unit, with surgery taking place shortly after birth to replace the abdominal contents and to repair the defect. The baby may need to stay on the unit for several weeks. Without treatment this condition is associated with a high (approximately 90%) death rate. With current treatment death rates are in the region of 10%\(^2\).

In 85% of cases, gastroschisis occurs as an isolated condition.\(^2\) If other anomalies are present, intestinal atresia is the most common finding. Occasional cases have been described where the condition is diagnosed antenatally but “disappears” by birth. Such cases have been described associated with subsequent small bowel atresia / stenosis.

**Risk factors**
The cause of gastroschisis is not known, although a number of studies have shown risk factors that are associated with the condition. It is likely that the condition develops as a result of a combination of multiple factors, not all of which have yet been identified.

A review of the literature on risk factors and aetiology of gastroschisis was undertaken in order to inform the investigation. Further details are given in Appendix B. In summary, the following have been considered as risk factors for this condition:

- Young maternal age
- Social disadvantage (low income) – inconsistent
- Aspirin use in pregnancy
- Decongestant use in pregnancy, especially in association with smoking, and other remedies used for colds
- Poor maternal diet / low maternal body-mass index
- Exposure in pregnancy to solvents in hobbies / occupation e.g. auto-mechanics, furniture stripping
- Tobacco, alcohol, and recreational drugs: marijuana, cocaine, and ecstasy use in pregnancy
- Various chemical exposures in animal studies
- There has also been suggestion of association with living near landfill sites

Of all these risk factors young maternal age is the most consistent and striking finding.

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Epidemiology

Gastroschisis is reported to occur in 1 per 10,000 births\(^2\), although rates have been quoted up to 4.9 per 10,000 births in one year (10 cases in 2000 in Eastern Ireland).\(^3\)

Reports of increases in prevalence are recorded from various parts of the developed world.\(^4\) Work is ongoing to establish whether the rise has occurred in all, or selected, maternal age groups.\(^8\) A few reports of possible clusters have been published although in general these have not been described in detail.\(^9\)\(^10\)

Gastroschisis in Wales 1998-2003

Prior to 1998, robust data on congenital anomalies in Wales were not available. A cluster of cases of gastroschisis in Rhondda Cynon Taf in the mid 1990s was noted in relation to health concerns in proximity to a local landfill site.\(^9\) The Welsh Congenital Anomaly Register (CARIS) was established in 1998 as part of NHS Wales, since which time the quality of data on congenital anomalies in Wales has improved. The data used here have been taken from the CARIS database.\(^11\)

Since CARIS began recording data on congenital anomalies in Wales the rates of gastroschisis have been among the highest reported when compared to other areas.\(^12\) Wales is now thought to have a better reporting system than many other countries and this may partly account for higher rates of many congenital anomalies. Wales is also known to have a particularly high proportion of births among younger mothers, which may explain this to some extent. Work is being undertaken by EUROCAT using data on 4.6 million births to assess the extent to which maternal age profile explains geographic variations in gastroschisis.

Table 1 shows the total number of cases reported to CARIS by year in which pregnancy ended, together with the number of liveborn cases that would have presented to fetal medicine and neonatal surgical units. The majority of cases will have undergone

\(^{11}\) Further information available from the CARIS website at http://www.wales.nhs.uk/caris.
surgery in University Hospital of Wales, Cardiff, although babies born to mothers living in mid or north Wales may have been referred to Birmingham or Liverpool for treatment. Reporting of cases treated outside of Wales is often delayed so that numbers of cases from mid and north Wales may increase. In order to overcome this delay CARIS contacted obstetric and paediatric clinicians in north Wales during summer 2004 to ascertain previously unreported cases. So far this has not identified any additional cases for 2003/4.

It can be seen from Table 1 that the all-Wales rate for 2003 was higher than in previous years although this difference was not statistically significant.

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cases reported for year</td>
<td>94</td>
<td>16</td>
<td>19</td>
<td>12</td>
<td>16</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td>Of which Live Born</td>
<td>81</td>
<td>12</td>
<td>15</td>
<td>10</td>
<td>15</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>Gross rate (all cases) per 10000 live &amp; still births (95% C.I.)</td>
<td>4.9 (3.9-5.9)</td>
<td>4.8 (2.4-7.1)</td>
<td>5.9 (3.2-8.5)</td>
<td>3.8 (1.7-6.0)</td>
<td>5.2 (2.7-7.7)</td>
<td>3.3 (1.3-5.4)</td>
<td>6.7 (3.8-9.5)</td>
</tr>
<tr>
<td>Liveborn rate per 10000 livebirths (95% C.I.)</td>
<td>4.3 (3.4-5.2)</td>
<td>3.6 (1.6-5.6)</td>
<td>4.7 (2.3-7.0)</td>
<td>3.2 (1.2-5.2)</td>
<td>4.9 (2.4-7.4)</td>
<td>3.3 (1.3-5.4)</td>
<td>6.1 (3.3-8.8)</td>
</tr>
</tbody>
</table>

Table 2 shows numbers and rates for gastroschisis by Welsh local authority area. Numbers for each local authority are extremely small, even when aggregated over the 6-year period for which data are available (1998-2003). The table shows the average number of cases per year for each authority, together with an estimate of the maximum number that might be expected each year, based on the 6-year rate for that authority. This should be taken as a rough guide only as it does not take account of any national trends in the prevalence of gastroschisis.

The 2003 CARIS annual report includes a more detailed review of gastroschisis in Wales. The report confirms the association of gastroschisis with younger maternal age, maternal smoking and a history of maternal substance misuse, although it must be stressed that only about 1 in 20 mothers of babies with gastroschisis report using drugs.
Table 2: Confirmed cases of gastroschisis reported to CARIS 1998-2003, for Wales and Local Authorities, showing gross rates and average numbers per year.

<table>
<thead>
<tr>
<th>Area of Wales</th>
<th>Total births (ONS)</th>
<th>Gross CASES (including fetal losses and terminations)</th>
<th>Cases/year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1998-2003</td>
<td>Total</td>
<td>Rate/10000 total births</td>
</tr>
<tr>
<td>Wales</td>
<td>190025</td>
<td>94</td>
<td>4.9</td>
</tr>
<tr>
<td>South East Region</td>
<td>87738</td>
<td>46</td>
<td>5.2</td>
</tr>
<tr>
<td>Blaenau Gwent</td>
<td>4460</td>
<td>3</td>
<td>6.7</td>
</tr>
<tr>
<td>Caerphilly</td>
<td>12247</td>
<td>10</td>
<td>8.2</td>
</tr>
<tr>
<td>Cardiff</td>
<td>22469</td>
<td>10</td>
<td>4.5</td>
</tr>
<tr>
<td>Merthyr Tydfil</td>
<td>3852</td>
<td>1</td>
<td>2.6</td>
</tr>
<tr>
<td>Monmouthshire</td>
<td>5052</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Newport</td>
<td>10123</td>
<td>7</td>
<td>6.9</td>
</tr>
<tr>
<td>Rhondda Cynon Taf</td>
<td>15772</td>
<td>8</td>
<td>5.1</td>
</tr>
<tr>
<td>Torfaen</td>
<td>5958</td>
<td>4</td>
<td>6.7</td>
</tr>
<tr>
<td>Vale of Glamorgan</td>
<td>7805</td>
<td>3</td>
<td>3.8</td>
</tr>
<tr>
<td>Mid &amp; West Region</td>
<td>60035</td>
<td>31</td>
<td>5.2</td>
</tr>
<tr>
<td>Bridgend</td>
<td>8882</td>
<td>7</td>
<td>7.9</td>
</tr>
<tr>
<td>Carmarthenshire</td>
<td>10373</td>
<td>7</td>
<td>6.7</td>
</tr>
<tr>
<td>Ceredigion</td>
<td>3660</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Neath Port Talbot</td>
<td>8268</td>
<td>5</td>
<td>6.0</td>
</tr>
<tr>
<td>Pembrokeshire</td>
<td>7095</td>
<td>5</td>
<td>7.0</td>
</tr>
<tr>
<td>Powys</td>
<td>7281</td>
<td>4</td>
<td>5.5</td>
</tr>
<tr>
<td>Swansea</td>
<td>14476</td>
<td>3</td>
<td>2.1</td>
</tr>
<tr>
<td>North Region</td>
<td>42252</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>Conwy</td>
<td>6479</td>
<td>3</td>
<td>4.6</td>
</tr>
<tr>
<td>Denbighshire</td>
<td>5689</td>
<td>8</td>
<td>14.1</td>
</tr>
<tr>
<td>Flintshire</td>
<td>10036</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Gwynedd</td>
<td>7351</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>Isle of Anglesey</td>
<td>4131</td>
<td>1</td>
<td>2.4</td>
</tr>
<tr>
<td>Wrexham</td>
<td>8566</td>
<td>3</td>
<td>3.5</td>
</tr>
</tbody>
</table>

*Poisson distribution
**calculated from upper 95% CI of gross rate rounded up to nearest whole number

Source: CARIS using data downloaded June 2004 and used in CARIS annual report tables for 2003
3 Establishing whether a cluster of cases has occurred in Bridgend County Borough in 2004

The group considered the evidence for a cluster of gastroschisis in Bridgend County Borough, including whether the rise in cases was localised to Bridgend County Borough or part of a wider problem.

Investigating clusters

Defining what constitutes a cluster is a difficult process.\textsuperscript{14} A cluster is said to occur when an unexpectedly high number of cases of a relatively uncommon condition arise in an area and / or over a period of time. The number is sufficiently large that there is a real possibility that the finding is not simply due to chance.

Clusters are investigated to rule out any underlying factors that have caused increased numbers of cases of the condition to occur. Most clusters are still thought to be chance events and, in spite of large numbers of investigations, it is very unusual to arrive at answers as to why the cluster occurred. Occasionally however, important findings have resulted from cluster investigations.\textsuperscript{15}

The investigation group were aware of pitfalls that have been encountered when investigating possible clusters, including the difficulties defining geographical boundaries. If a geographical boundary is drawn too narrowly this will overestimate the size of the problem, whereas drawing the boundary too widely will underestimate it.

Definition of cases

For the purpose of this investigation, it was agreed that cases in the potential cluster should be defined as:

\textit{Babies / fetuses with gastroschisis whose mothers were normally resident in Bridgend County Borough and who had an expected date for the end of pregnancy during 2004.}


Evidence of cluster in Bridgend County Borough

Local data
A list of cases was compiled using data from the CARIS database and the Fetal Medicine and Neonatal Unit at University Hospital of Wales, Cardiff.

From these sources, initially eight different fetuses were identified that appeared to meet the case definition. At the start of the investigation not all cases had been delivered. In one case a subsequent antenatal ultrasound scan demonstrated no gastroschisis was present. During the course of the investigation, a further case of gastroschisis was identified where the mother was normally resident in Bridgend County Borough, but the expected date of end of pregnancy falls in 2005. Both these cases have been excluded from the current study.

Thus, seven cases of gastroschisis could be identified where the mother was normally resident in Bridgend County Borough and where expected date of delivery was in 2004.

Of the seven cases:
- One fetus did not carry to term
- There were six live born cases.

Table 2 suggests that, based on recent years data, a maximum of no more that three cases of gastroschisis might be expected in Bridgend County Borough in any one year.

Location of cases
Maps were compiled to show the locations of mothers of cases. This demonstrated that 5 of the 6 live-born cases actually lived in the valleys in the north of the county, away from main population centres. However, they did not all live within the same valley, and not all valleys involved have direct road links to each other. The maps have the potential for individual cases to be identified and have therefore not been reproduced in this report.

Timing of cases
More detailed study of the expected dates of delivery of cases indicated that the five liveborn cases that occurred in the North of the county were linked in time as they all had an expected date of delivery (EDD) within a month of each other. The other 2 cases had EDDs within a few weeks of this time period. Literature suggests that the time at which the embryo is most vulnerable to gastroschisis is between the 4th and 6th weeks after conception, and possibly up to the 10th week. From this, it can be estimated that the period during which the embryos in question would have been most sensitive to exposures that might relate to gastroschisis was during the summer of 2003.

It was agreed that the occurrence of these seven cases during 2004 was an important finding that may not have arisen by chance and that further investigation of this event was warranted.
Surveillance data
Surveillance of congenital anomalies in Wales is undertaken by the National Congenital Anomaly System (NCAS), covering England and Wales and run by the Office for National Statistics (ONS). CARIS is not set up to undertake formal surveillance of congenital anomalies but feeds data into the NCAS system. NCAS aims to issue monthly warnings relating to births in the previous quarter, by geographical area, for any anomalies that have higher than expected numbers reported. Any significant rise in reported cases should therefore be reflected in a warning issued by NCAS. To date NCAS has not issued a warning for gastroschisis in Bridgend County Borough in 2004. NCAS have encountered a number of technical difficulties and the system is running with a delay of several months. Surveillance reports have not yet been issued for births in Spring 2004, when most of the cases were born.

Bridgend County Borough cases in the context of the rest of Wales / United Kingdom

Although there was a clearly increased number of cases in Bridgend County Borough, members of the group were aware that numbers of cases for the rest of Wales as a whole were also higher in 2003 and 2004, compared to previous years. It was possible that the apparent cluster was in fact part of a more widespread rise in cases elsewhere in Wales or further afield in other parts of the United Kingdom. It was agreed that the Bridgend County Borough data should be compared to data from elsewhere.

Bridgend County Borough compared to the rest of Wales
Rates of gastroschisis in Wales from 1998 to 2003 are shown in Table 1. These data suggest an increase in rates in 2003, although this is not statistically significant. Rates for 2004 cannot be calculated yet as the full number of cases and the total numbers of births for the year are not known. Figure 1 shows numbers of cases in Wales by year of expected date of delivery for Bridgend County Borough and the rest of Wales. (These data differ from those in Table 1 as they relate to expected rather than actual date of delivery). Figure 1 shows that the number of cases in Wales has continued to rise in 2004. At present however the increase across Wales appears to be generalised, with only Bridgend County Borough showing a dramatic localised increase in numbers this year. CARIS will continue work to describe gastroschisis across Wales in 2004 and 2005, as further data becomes available.
Wales compared to elsewhere in the United Kingdom

The group agreed that it would be useful to establish whether the rise in cases seen across Wales during 2003 and 2004 had occurred elsewhere in the United Kingdom. Data was not yet available from NCAS so, on behalf of the group, CARIS contacted other regional congenital anomaly registers who were members of the British Isles Network of Congenital Anomaly Registers (BINOCAR) and provisional data were obtained for 2003 and early data for 2004 for several other areas. (It is not possible to consider data from the United Kingdom as a whole as several areas of England are not covered by regional registers). BINOCAR members discussed the results at their annual scientific meeting in October 2004. It was agreed that some, but not all regional registers showed an increase in numbers of cases above expected levels in 2003 and 2004 although the rises were not statistically significant. This mirrors the picture in Wales against which the Bridgend County Borough cluster has occurred. BINOCAR has alerted the Chief Medical Officers of these findings and will continue to monitor gastroschisis rates reported by British regional congenital anomaly registers.

Conclusions on evidence for a cluster

- There is epidemiological evidence of a cluster of seven cases of gastroschisis in Bridgend County Borough with pregnancy ending during spring and early summer 2004. Five of these occurred in the north of the county.
• There is evidence of a general rise in cases of gastroschisis in Wales during 2003 and 2004. The rise may be more widespread, affecting other areas of the United Kingdom, but further data is required to confirm this.

4 Factors that might explain the cluster in Bridgend County Borough

The Investigation Group considered possible causes for the cluster. Although many risk factors have been described in relation to gastroschisis, the exact cause is unknown. For this reason, an exploratory approach was taken to try and establish links between cases, or identify factors in the general environment that may be relevant to the cluster in Bridgend County Borough. Factors were chosen on the basis of data availability or because they had been considered in previous investigations into gastroschisis. The fact that the investigation group looked at any particular factor did not therefore mean that it was actively suspected of being the cause of the cluster.

• Information was gathered about individual cases from patient notes and interviews conducted by the clinicians directly involved in the care of cases.
• General information relating to the environment was also sought from a variety of sources.

Clinical interviews

The clinical team responsible for the post-natal care of cases made contact with mothers and undertook interviews.

Exploratory interviews were undertaken to identify common exposures or potential causative factors that may explain the high number of cases of gastroschisis. A description of categories of information covered is included in Appendix C. In order to have a reference with which to compare information concerning the cluster cases, clinicians asked for information from mothers of babies with gastroschisis from other parts of Wales and who were not part of the cluster, but who had been in their care during 2004.

It was possible to conduct interviews with four of the five mothers of live born cases in North Bridgend County Borough; the fifth was not contactable. Information was also obtained from the mothers of five reference cases of gastroschisis who lived outside Bridgend County Borough.

Details of responses include personal information and are potentially identifiable. Only a broad summary of the findings from clinical interviews is therefore included in this report.
The group were aware that the interviews took place after delivery of the child, and mothers were being asked to recall events that took place some 8-9 months previously. This time meant that mothers were understandably not always able to remember exact details and dates.

No specific factors were identified from the interviews that connected the individuals or that could have explained the cluster. There were, however, features evident among at least some of the cases that have previously been described as having an association with gastroschisis:

- Lower maternal body mass-index / poor diet
- Smoking
- Cold / flu-like symptoms or taking cold remedies / pain killers.

None of these factors were found to be significantly higher among cases from Bridgend County Borough compared to the reference cases interviewed. It could be that the small numbers involved made it difficult to discern differences between the Bridgend County Borough and the reference cases. At this stage however there is no evidence that these factors were specifically associated with the Bridgend County Borough cluster.

**General physical environment**

The group considered the possibility that a common environmental exposure might be responsible for the cluster. Because no agent in the wider environment has been shown to cause gastroschisis an exploratory approach was taken in an effort to identify factors to which pregnant women may have been exposed that would not be evident from clinical interviews.

It was noted that the summer of 2003 was a particularly hot and dry period. The group considered the possibility that this affected the mothers’ exposure to environmental factors, either through changing their pattern of behaviour or changing the behaviour of substances in the physical environment to which mothers were exposed.

Data was supplied by a number of different agencies relating to aspects of the physical environment during the summer of 2003, including Bridgend County Borough Council, the Environment Agency and Dŵr Cymru. Further details are included in Appendix D.

Data and analyses to date have not identified any environmental factor specific to Bridgend County Borough that might explain the cluster.

[16](http://www.metoffice.com/climate/uk/2003/index.html) (accessed 03.08.04)
Conclusion on factors that might explain the cluster in Bridgend County Borough

- Cases in the Bridgend County Borough cluster exhibited a number of general features previously described in relation to gastroschisis, including young maternal age, low maternal body mass index, and maternal smoking. None of these could explain this specific cluster.

- Despite detailed clinical interviews and review of environmental data, the Investigation Group has not identified either:
  o an obvious cause for the cluster in Bridgend County Borough, or
  o any plausible suggestions to explain the cluster that could be investigated in a formal study in that locality.

5 Wider investigations of gastroschisis

Although no formal study into any local cause for the cluster in Bridgend County Borough can be recommended, there is a need for further research into the causes of gastroschisis, as this condition:

a) has a relatively high prevalence in Wales
b) appears to be increasing in prevalence in Wales (and other parts of the developed world)
c) causes considerable distress for affected babies and their families
d) represents a significant workload for neonatal surgical and other paediatric services for Welsh residents.

Work should be taken forward in Wales involving case identification, monitoring and surveillance, and collection of an enhanced data set that could enable hypothesis formation on the cause of gastroschisis. This could then contribute to formal multi-centre UK wide epidemiological studies. Ideally these studies would involve a large number of organisations within Wales, as well as collaboration with relevant centres outside of Wales. The work should involve academic, clinical, public health and other professionals as appropriate. Proper funding and organisation of this research will be essential.

6 Public health action

As no factor was identified that may have caused the cluster, no specific action was possible to reduce risks and prevent further cases arising. However, issuing general advice on reducing risk for congenital anomalies was considered appropriate.

Following expressions of general concern over higher reported rates of congenital anomalies in Wales, various members of the group were in any case involved in preparing an article outlining various measures that could help reduce the risk of
congenital anomaly. This was not aimed specifically at prevention of gastroschisis but measures that could help reduce the risk factors associated with the condition were included. The article was published by the Chief Medical Officer (CMO) for Wales in August 2004\(^{17}\) and was sent to all doctors in Wales. Information was also sent to the Chief Nursing Officer. There is no evidence that reduction of currently known risk factors for gastroschisis will necessarily lead to a reduction in cases of the condition. However, the Investigation Group considered that, as a precaution, further consideration should be given to disseminating the advice more widely.

7 Other issues arising during the investigation

Communications

Communication with public bodies
During the course of investigations, individual group members were able to brief their respective organisations including Bridgend Local Health Board, Bridgend County Borough Council, the National Assembly for Wales, the National Public Health Service for Wales and Cardiff & Vale NHS Trust.

Communication with the media
Communication with the media was either through the National Public Health Service Public Relations (PR) organisation, or through individual members’ organisations PR representatives.

During the course of the investigation the BBC developed and broadcast a ‘Week In Week Out’ programme on gastroschisis in Wales.\(^{18}\) Various members of the group were involved in production in an individual capacity. Some communication between the group and the BBC took place through the National Public Health Service public relations system. The BBC did not seek an interview with the chair of the Investigation Group.

Retention of blood samples

The potential value of biological samples to investigate agents that may be responsible for any cluster of gastroschisis was recognised at an early stage. It was identified that routine antenatal virology samples taken in early pregnancy could be a valuable resource in this investigation. Efforts were therefore made to ensure that such samples were not destroyed during the course of the investigation.


As no specific factor has been identified that might be causal in the cluster in Bridgend County Borough, testing these bloods to investigate the cluster was not considered to be of value by the group. The opportunity is being taken, outside of this investigation, to explore whether testing of blood samples further could produce results useful in hypothesis formation for a wider all-Wales study. Clinicians are seeking consent for this from patients whose blood samples are being stored.

**Ethics and information sharing**

The investigating team was very conscious that the mothers in question may represent a particularly vulnerable group within the population. Mothers were young and their babies had required surgery immediately after birth, followed by several weeks in hospital. The group was also conscious of the fact that information sought from the mothers of cases was extremely sensitive as it related to personal medical and lifestyle factors. For these reasons, only clinicians who had been involved in the postnatal care of the babies had direct contact with mothers. Names and addressees of cases were not shared with other group members and efforts were made to keep sharing of potentially patient identifiable information to the minimum required to allow the investigation to proceed.

The investigation of the cluster of cases in Bridgend County Borough posed a clinical and public health problem that required addressing. It was not considered by the investigative team to be research. As such ethics committee approval was not considered appropriate. The group did, however, have communications with the Central Office for Regional Ethics Committees (CORECT) based in Cardiff. This included written information of activities and particular reference to patient contact and storage of biological samples; CORECT provided verbal agreement with the approach taken.

**Guidance for future investigations of this type in Wales**

During the course of this investigation the group encountered a variety of issues that are likely to recur in future investigations of this type. These include:

- sharing of potentially patient identifiable data in order to investigate a potential threat to the public health
- the boundary between research with need for ethics approval and clinical / public health investigations
- storage and testing of clinical samples in this context.

The Investigation Group believes that these issues need further exploration and there could be benefit in development of national guidance.
8 Conclusions

1) Gastroschisis is a rare congenital anomaly that is rising in prevalence in the developed world.

2) There is a high reported rate in Wales as compared with many other European regions.

3) There is evidence of a general rise in cases of gastroschisis in Wales during 2003 and 2004. The rise may be more widespread, affecting other areas of the United Kingdom, but further data is required to confirm this.

4) There is epidemiological evidence of a cluster of seven cases of gastroschisis in Bridgend County Borough with pregnancy ending during spring and early summer 2004. Five of these occurred in the north of the county.

5) Cases in the Bridgend County Borough cluster exhibited a number of general features previously described in relation to gastroschisis, including young maternal age, low maternal body mass index, and maternal smoking. None of these could explain this specific cluster.

6) Despite detailed clinical interviews and review of environmental data, the Investigation Group has not identified either
   a) an obvious cause for the cluster in Bridgend County Borough, or
   b) any plausible suggestions to explain the cluster that could be investigated in a formal study in that locality.

7) In the absence of any specific cause having being identified for the cluster, general advice on reducing the risk for congenital anomalies, such as that published by the CMO in 2004, is appropriate rather than specific public health action.

8) The role of CARIS, in particular for establishing background rates of anomalies and coordinating communication with other congenital anomaly registers, was considered important and effective in this investigation. Surveillance / cluster identification is not a function of CARIS and the NCAS system is currently inadequate for timely alerts to rises in numbers of congenital anomalies.

9) Although no formal study into any local cause for the cluster in Bridgend County Borough can be recommended, there is a need for further research into the causes of gastroschisis on an all-Wales and United Kingdom level.

10) Further guidance on investigation and management of clinical / public health incidents of this type may be of benefit in Wales.
9 Recommendations

This report makes a number of recommendations, some of which are not within the remit of Bridgend Local Health Board. The Investigation Group would ask the LHB, after having considered the report, to make it available to other relevant bodies for them to consider appropriate further action.

Specific recommendations

1) There is a need for continued identification of all cases of gastroschisis in Wales. CARIS should continue to work with clinical partners to ensure prompt reporting of cases of gastroschisis both locally and throughout Wales.

2) In view of the current difficulties with the NCAS system, CARIS and the Welsh Assembly Government should discuss ways in which an adequate system for surveillance and monitoring of congenital anomalies can be established. In the meantime specific measures to monitor gastroschisis should be put in place.

3) The Welsh Assembly Government should consider how further research into the causes of gastroschisis in Wales can be taken forward as this condition:
   a) has a relatively high prevalence in Wales
   b) appears to be increasing in prevalence in Wales (and other parts of the developed world)
   c) causes considerable distress for affected babies and their families
   d) represents a significant workload for neonatal surgical and other paediatric services for Welsh residents.

Work should be taken forward in Wales involving case identification, monitoring and surveillance and collection of an enhanced data set that could enable hypothesis formation on the cause of gastroschisis. This could then contribute to formal multi-centre UK wide epidemiological studies. Ideally these studies would involve a large number of organisations within Wales, as well as collaboration with relevant centres outside of Wales. The work should involve academic, clinical, public health and other professionals as appropriate. Proper funding and organisation of this research will be essential.

General recommendations

4) The Welsh Assembly Government should consider whether, in addition to the advice already issued to doctors, advice on measures to reduce the risk of congenital anomalies in general and gastroschisis in particular should be communicated more widely to women in Wales.
5) This investigation identified that a number of mothers of cases had histories of poor nutrition and smoking. Although this is not considered the cause of the cluster, the **Local Health Board** should consider whether further action to address this issue is required.

6) Consideration should be given to developing further guidance on the investigation and management of incidents of this type in Wales. The **Director of the National Public Health Service** will discuss with the **Welsh Assembly Government** how this work can be taken forward with partners.
10 Appendices

Appendix A: Membership of Group

Chair:
(to August 2004)
Dr M Temple Consultant in Environmental Public Health Medicine, National Public Health Service for Wales
(from August 2004)
Dr J Greenacre Consultant in Public Health, NPHS & CARIS

Clinical Team:
Dr R Adappa Specialist Registrar in Paediatric Medicine
Dr M Drayton Consultant Neonatologist, UHW
Mr S Huddart Consultant Paediatric Surgeon, UHW
Mrs D Nutall Senior Nurse, Neonatal Intensive Care, UHW

Other members of the group:
Mr P Cole Senior Environmental Health Officer, Bridgend County Borough Council
Mrs J Donagh Principal Environmental Health Officer, Bridgend County Borough Council
Dr C Humphreys Specialist Registrar in Public Health, NPHS
Dr J Ludlow Consultant in Public Health, Wales Centre for Health & Senior Medical Officer, National Assembly for Wales
Ms S Mayor Lead nurse for Research & Development, Cardiff and Vale NHS Trust
Prof S Palmer Head of Department, Department of Epidemiology, Statistics and Public Health/Director, Chemical Hazards and Poisons Division, Health Protection Agency
Dr N Williams Local Director of Public Health, Bridgend Local Health Board.

Named secretarial staff who undertook minute taking:
Mrs S Brackin National Public Health Service
Ms A Coombes National Public Health Service
Mrs J Jones National Public Health Service
Mrs C Nurton National Public Health Service
Appendix B: Literature regarding known risk factors

Although the cause of gastroschisis is unknown, a number of studies have shown risk factors that are associated with this anomaly. It is likely that multiple factors combine in individuals to result in the condition.

Below is a description of some of the findings of epidemiological studies into the cause of gastroschisis. As the purpose of this literature review was to identify factors that could be attributable to an increased incidence of gastroschisis, the quality of these studies has not been assessed in detail.

Demographics and socioeconomic factors

Young maternal age is consistently associated with gastroschisis, with a median age of 21 years in an England and Wales study (Tan et al., 1996), and a twelve fold increased risk for gastroschisis in women younger than 20 years of age at time of conception when compared with older women (Penman et al., 1995). There is notable geographic variation between countries and within countries for this of this condition (Curry et al., 2000), however what extent of this is due to ascertainment differences is unclear. There is little evidence for racial variation in formal studies (TBDM, 2002).

Social disadvantage may be important, and both poor education and low family income have been associated with gastroschisis (Torfs et al., 1994, Torfs et al., 1996 and Vrijheid et al., 2000 as cited by TBDM, 2002); however this is not consistent (Werler, Sheehan & Mitchell, 2003). How these factors might result in increased risk is not clear; they are likely to be markers for other exposure. The study by Torfs et al. 1994 also found an association with maternal marital status (those married and living with the father at lowest risk), however low maternal education, although not significant on multivariate analysis, was associated with a lower risk of gastroschisis.

Maternal illness

There has been no clear link found between gastroschisis and maternal illness, and in particular a study found no association with fever, upper respiratory tract infection or allergies (Werler, Sheehan & Mitchell, 2003). Similarly a study looking specifically at thyroid disease found no association (Khoury et al., 1989).

Werler, Sheehan & Mitchell (2002) noted the tendency for gastroschisis to cluster, and they consider that this may be related to an infectious disease process (p 28). Although 34% (71) of their cases filled their definition of cluster, there was no difference in illness / medication use between these and other cases. A cluster was defined as three or more cases from the same geographic area occurring within 30 days of each other; no definition for “geographic area” given. Aspirin was cited as being more common in the cluster group, however this was non-significant OR: 1.67 (95% CI: 0.47 – 5.84), p = 0.4 using EpiInfo (6) Statcalc.
Maternal medication

Aspirin intake has been linked to gastroschisis in a number of studies, and a recent meta-analysis found an OR of 2.4 (95% CI: 1.44-3.88) for aspirin use and gastroschisis (Kozer et al., 2002), this study did not include the data from Werler, Shehan & Mitchell (2002) which found a similar OR of 2.7 (95% CI: 1.2-5.9) for aspirin use, and animal studies also suggest a relationship (see Torfs et al., 1996).

Vasoconstricting medications, such as decongestants have been implicated in association with gastroschisis. One case-control study (Werler, Shehan & Mitchell, 2003) looking at vasoconstricting drugs found almost all such drugs taken were decongestants: pseudoephedrine or phenylpropanolamine20, and taking such drugs was associated with a higher risk of gastroschisis (OR: 1.8, 95% CI: 1.2-2.6); this effect was amplified when combined with cigarette smoking, and with a dose response relationship associated with smoking. The study by Torfs et al. (1996) found an increased risk due to these vasoconstricting medications, but this did not achieve statistical significance. Other medications including paracetamol (Werler, Shehan & Mitchell, 2002) and ibuprofen (Torfs et al., 1996) have been linked to gastroschisis but are not consistent with other studies. One study (Torfs et al., 1996) suggested a protective effect from antibiotic use. A case report of gastroschisis associated with carbimazole use has also been reported (Guignon, Mallaret & Jouk, 2003).

Lifestyle issues

1. Diet

Poor diet has been implicated and low α-carotene, low glutathione and high nitrosamines in the diet were found to be statistically significant on multivariate analysis in a hypothesis generating study (Torfs et al., 1998). A related study (Lam, Torfs & Brand, 1999) found gastroschisis to be associated with low body mass index (using self reported height and weight measures). One study has, however, found an association with maternal obesity (Moore et al., 2000 as cited by TBDM, 2002).

A recent animal study in mice has found gastroschisis can occur with the combination of protein zinc deficiency and carbon monoxide exposure in mice, although extrapolation to humans should be undertaken with caution (Singh, 2003).

2. Occupation & Hobbies

Several hobby exposures were significantly associated with gastroschisis in a case control study undertaken by Torfs et al. (1996) including automechanics (OR: 2.51, 95% CI: 1.17-5.39), dyeing (OR: 2.18, 95% CI: 1.08-4.40), furniture stripping (OR: 3.83, 95% CI: 1.34-10.95), and painting (OR: 1.95, 95% CI: 3.25). This study identified exposure to solvents in particular as being associated with gastroschisis and this had dose-response relationship (OR low exposure: 2.83; OR high exposure: 6.29). The fact that the controls in this study were

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20 Two individuals took MDMA (ecstasy), and one took ephedrine.
healthy infants may lead to recall bias in this study. One study has suggested an increased risk in relation to commercial and sales work (Hemminki et al., 1982 as cited by TBDM, 2002).

3. Smoking and alcohol
Both tobacco and alcohol use have been associated with gastroschisis in a number of studies, however this may be a marker for other exposures. Haddow, Palomaki & Holman (1993) found an increased risk of gastroschisis associated with smoking (OR: 2.1 (95% CI: 0.9-4.8)); there was adjustment for maternal age and month of delivery but not for other factors e.g. socio-economic, other exposures. Werlerm Mitchell & Shapiro (1992) found a relation with heavy alcohol use, as did Torfs et al. (1994), although this was on univariate analysis only. As described above smoking may play a role in combination with vasoconstrictors (Werler, Shehan & Mitchell, 2003).

Torfs et al. (1996) found both smoking and alcohol bingeing to be significantly associated with gastroschisis in univariate analysis, but neither variable were included in the final model multivariate analysis.

4. Recreational drug use
As vasoconstriction is a proposed mechanism in the pathogenesis of gastroschisis recreational drugs that are vasoconstrictive, such as cocaine or ecstasy (MDMA) have been potential candidates in the aetiology of this condition.

Marijuana has been associated with gastroschisis in studies (Torfs et al., 1994, Werler, Sheehan & Mithcell, 2003), however it is considered that this may be a marker for other illicit drugs that mothers may not wish to admit to taking (ibid.).

Cocaine and other drug use have been associated with gastroschisis by Torfs et al. 1994 on univariate analysis, where multiple drug use was found to increase risk; although important in the multivariate model maternal drug use was not statistically significant. Drongowski et al., 1991 as cited by TBDM, 20002 have also found an association; although, in the study by Werler, Sheehan & Mithcell (2003) none of the mothers declared that they had taken cocaine.

Current studies of the aetiology of gastroschisis listed on the UK National Research Registry (NRR, 2004) are focused on recreational drug use. Provisional results suggest strong further evidence for a link between gastroschisis and recreational drug use, although it cannot explain the cause in most in cases (Draper et al., 2004).
Other factors
Landfill sites: One study in Wales has found a higher than expected number of
gastroschisis occurring among residents near a landfill site when compared with those
not near a landfill (Fielder et al., 2000), however the numbers involved were small.
Another study comparing those resident near landfill sites in Britain (Elliott) with those
further from such sites found a slightly increased risk (RR: 1.05, 95% CI: 1.047-1.055);
a European study taking account of proximity to hazard waste sites found an association
which did not reach statistical significance (OR: 3.19, 95% CI: 0.95-10.77) (Dolk et al.,

Exposures to X-rays was found to have a significant association in the Torfs et al.
(1996) study, and there is some support in animal models for this theory (ibid.);
however as dental X-rays were the main reason for exposure it was suggested that this
may be a marker for drugs used in dentistry such as adrenaline or nitrous oxide (ibid.)

Seasonality has been suggested by Goldbaum, Darling & Milham (1990) who found a
higher proportion of births in January, February and March, and suggested that between
May and September there may be exposure to summer viruses, heat or other activities.

Animal studies have suggested association with a wide variety of agents including
scopolamine hydrobromide, triamcinolone acetonide, oestrogen antagonists, 6-
mercapturine, nitrous oxide, methyl mercury, benzopyrene, hydroxyurea, pyrabital,
methyl-parathion, aurothiomalate, concanavalin A, gold thioglucose, N,N’-bis (2-
chloroethyl)-N-nitrosurea, cadmium, cis-platinum, methyl aliclylate, mevinolin,
petroylglutamic acid and streptonigrogrin (Curry et al., 2000).

Genetic effects
There have been many case reports of familial occurrences of gastroschisis, however
studies have not been consistent in demonstrating familial effects (Curry et al., 2000). It
is likely that genetics plays some role in gastroschisis, however no discernable pattern of
inheritance is evident as yet (ibid.).

References
anomalies: an ecologic study in Argentina” Environmental Health Perspectives, vol

gastroschisis” British Journal of Obstetrics and Gynaecology, vol 107, pp 1339-1346.

Dolk H, Vrijheid M, Armstrong B, Abramsky L, Bianchi F, Garne E, Nelen V, Robert


**Virtual references**


Appendix C: Clinical interviews with mothers

The following is a summary of the areas included in interviews with mothers. Paternal factors including lifestyle issues were also included.

- Demographic details
- Factors relating to pregnancy
- Factors relating medical conditions
- Factors relating to medication use in pregnancy
- Smoking, use of alcohol
- Recreational drug use
- Dietary intake
- Occupation, hobbies, places where socialise
- Other environmental exposures including housing conditions, water supply, home heating, local physical environment
- Contact with other mothers of affected individuals
Appendix D: Environmental investigations

Factors examined as part of the exploration of the physical environment in Bridgend County Borough for the summer of 2003.

Information was supplied by Environmental Health Officers of the Borough, officers of the Environment Agency (Wales), and Dŵr Cymru.

In particular:
- the pollution inventories of all the regulated sites within the borough were reviewed and the inventories of large sites, whose environmental ‘foot print’ might affect the borough were looked at in detail.
- Additionally, the site inspectors or equivalent were asked if they were aware of any abnormal operating conditions during the period of concern.
- UK based web sources of data such as the emissions inventory was also reviewed. However, due to the national nature of these sources, no conclusions relating to a local cluster could be drawn.
- Details of water supplies to the area were reviewed.

The only abnormal industrial state reported was that one major plant had been idle for the period due maintenance during the summer break.

There are data suggesting that a UK wide peak in airborne particulates occurred during the time period of interest. Detailed work to establish local levels is being undertaken using data from local monitors. There is no evidence to date that the situation in Bridgend County Borough was different to the UK picture.

Information from Dŵr Cymru confirmed that the area in which most of the cases had occurred shared a common water supply with a very large, unaffected population, and individual cases did not share local reservoirs with each other.