Anorectal malformations and pregnancy-related disorders: a registry-based case–control study in 17 European regions

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Objective To identify pregnancy-related risk factors for different manifestations of congenital anorectal malformations (ARMs).

Design A population-based case–control study.


Population The study population consisted of 1417 cases with ARM, including 648 cases of isolated ARM, 601 cases of ARM with additional congenital anomalies, and 168 cases of ARM-VACTERL (vertebral, anal, cardiac, tracheo-esophageal, renal, and limb defects), along with 13 371 controls with recognised syndromes or chromosomal abnormalities.

Methods Multiple logistic regression analyses were used to calculate adjusted odds ratios (ORs) for potential risk factors for ARM, such as fertility treatment, multiple pregnancy, primiparity, maternal illnesses during pregnancy, and pregnancy-related complications.

Main outcome measures Adjusted ORs for pregnancy-related risk factors for ARM.

Results The ARM cases were more likely to be firstborn than the controls (OR 1.6, 95% CI 1.4–1.8). Fertility treatment and being one of twins or triplets seemed to increase the risk of ARM in cases with associated with ARM when additional congenital anomalies were present (OR 3.9, 95% CI 1.3–11.6; OR 3.4, 95% CI 1.6–7.1, respectively), whereas maternal epilepsy during pregnancy resulted in a five-fold elevated risk of all manifestations of ARM (OR 5.1, 95% CI 1.7–15.6).

Conclusions This large European study identified maternal epilepsy, fertility treatment, multiple pregnancy, primiparity, pre-eclampsia, and maternal fever during pregnancy as potential risk factors primarily for complex manifestations of ARM with additional congenital anomalies and VACTERL.

Keywords Anal atresia, birth defects, aetiology, maternal, pregnancy, VACTERL.

**Introduction**

Congenital anorectal malformations (ARMs) are the most frequently occurring birth defects of the digestive system, affecting between two and six births per 10 000 births worldwide.\(^1\) ARM is characterised by a narrowing of the anorectal canal or anal atresia with or without fistula to neighbouring organs. Surgical procedures are often required at a very early age, but may not restore function completely, accounting for substantial physical and social morbidity among patients and their families. ARM can occur in isolation, but additional anomalies are present in approximately 50% of cases, especially components of the VACTERL (vertebral, anal, cardiac, tracheo-oesophageal, renal, and limb) association.\(^2\,^3\)

Although the diversity in phenotypes and the presence of associated malformations indicate causal heterogeneity, most aetiological studies analyse all ARM types collectively. These studies have shown contradictory results for associations between ARM and parental lifestyle factors, such as alcohol intake and smoking.\(^4\,^7\) Several studies have been undertaken to investigate other aetiological parameters for ARM, and suggesting such risk factors as maternal pre-pregnancy overweight or obesity,\(^6\,^8\,^9\) pre-existing and/or gestational diabetes,\(^10\,^11\) prolonged time to pregnancy,\(^6\) and use of assisted reproductive techniques.\(^12\,^14\) In addition, indications exist for a role of maternal fever during pregnancy,\(^6\,^15\) maternal drug use (anti-asthmatic drugs,\(^16\) thyroid medication,\(^17\) and the benzodiazepine lorazepam\(^18\)), folic acid supplementation,\(^19\) and parental occupational hazards.\(^6\,^20\) The scientific evidence for the aforementioned potential risk factors for ARM is still growing, but most studies lack power to perform subanalyses on different manifestations of ARM. For these analyses, large population-based case–control studies are most appropriate.

The European Surveillance of Congenital Anomalies (EUROCAT) is a network of population-based congenital anomaly registries in Europe covering more than 1.7 million births per year, collecting data on congenital anomalies for public health, preventive, and epidemiological purposes.\(^21\) The EUROCAT database enabled us to conduct a case–control study for ARM in a large study sample, using information from multiple sources from 17 EUROCAT registries to study potential pregnancy-related risk factors for ARM, and especially for subgroups with different manifestations of ARM.

**Methods**

**EUROCAT**

The EUROCAT database contains standardised data on congenital anomalies recorded by each registry using uniform definitions and coding, which are described elsewhere.\(^22\,^24\) The data used in this study were routinely collected between 1980 and 2008 by 17 EUROCAT registries in 13 countries (Figure 1), including live births, stillbirths from 20 weeks of gestation onwards, and terminations of pregnancy for fetal anomaly following prenatal diagnosis. Major malformations, syndromes, and chromosomal abnormalities were coded according to the International Classification of Diseases (ICD), ninth or tenth revision, whereas specified minor anomalies were excluded according to the EUROCAT classification.\(^23\)

**Case and control definitions**

The study population consisted of 21 606 foetuses or infants with ARM, syndromes, and/or chromosomal abnormalities. Cases were defined as live births, stillbirths, and prenatally diagnosed foetuses with subsequent terminations of pregnancy with all phenotypes of ARM. Foetuses or infants with ARM being part of a recognised syndrome, or the result of a chromosomal abnormality, as well as with exstrophy of the cloaca or bladder, were excluded \((n = 268)\). The syndromes or chromosomal abnormalities excluded \((n = 217; 13\% of ARM cases) mainly comprised trisomy 21 (26\%), sirenomelia (11\%), and trisomy 18 (8\%), as well as many others. We divided the case group into three different manifestations of ARM: isolated ARM (if ARM was the only malformation); ARM and one or more other major congenital anomalies; and ARM cases with the VACTERL association (ARM-VACTERL). Associated anomalies in the latter two manifestations of ARM are shown in Table 1. The VACTERL association includes vertebral defects (only thoracic and lumbar defects), anorectal malformations, cardiac defects (mainly atrial septal defect, ventricular septal defect, and tetralogy of Fallot), tracheo-oesophageal atresia, renal malformations, and radial limb defects. ARM-VACTERL was defined as ARM and at least two of the additional congenital anomalies included in the VACTERL association, which corresponds with the VACTERL definition of the presence of at least three of the associated malformations.\(^25\) Diagnoses of ARM-VACTERL were assigned by the first author (C.W.) based on this definition, and then confirmed by a clinical geneticist (C.M.). Because no healthy controls are included in the EUROCAT registries, by convention the control group included live births, stillbirths, and prenatally diagnosed foetuses with subsequent terminations of pregnancy with recognised syndromes (mostly single gene disorders) or chromosomal anomalies, excluding ARM and VACTERL \((n = 45)\). Frequently occurring syndromes or chromosomal abnormalities among controls were trisomy 21 (54\%), trisomy 18 (8\%), and Turner syndrome (4\%). As some pregnancy-related factors, such as pre-eclampsia and gestational diabetes, are normally not yet diagnosed before
termination of pregnancy, the proportion of terminated pregnancies after prenatal diagnosis in the control group was reduced to the proportion in the case group, for reasons of comparability, by randomly excluding some of these controls (n = 6505).

**Determinant definitions**

In the EUROCAT database, information was recorded after the birth of the child using multiple sources, such as hospital records, birth and death certificates, and postmortem examinations, using uniform definitions and coding.23 A
few registries also incorporated maternal interviews after birth. Several foetus/infant characteristics, including gender, survival (beyond 1 week of age), gestational age (in completed weeks) and birthweight (in grams) were recorded in the database. In addition, information was available on maternal age at delivery, fertility treatment (including hormonal treatment, artificial insemination, in vitro fertilisation (IVF), intracytoplasmic sperm injection (ICSI), and gamete intrafallopian transfer (GIFT)), multiple pregnancy (twins or triplets), parity (no versus one or more previous pregnancies), maternal chronic illnesses, maternal illnesses during first 4 months of pregnancy, and pregnancy complications. The latter three were coded according to ICD9 or ICD10, and we included pre-existing and gestational diabetes mellitus, chronic obstructive lower pulmonary diseases (e.g. asthma and bronchitis), epilepsy, mental disorders (e.g. depressive and anxiety disorders), fever (>38°C) during the first 4 months of pregnancy, and pre-eclampsia, also including eclampsia, as a proxy for placental dysfunction in this study.

Statistical analyses
Statistical analyses were performed using the statistical package SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA). We calculated crude odds ratios (ORs) with 95% confidence intervals (95% CIs) for potential risk factors for ARM, namely fertility treatment, multiple pregnancy, primiparity, and the aforementioned maternal illnesses and pregnancy complications. Multiple logistic regression analyses were used to calculate adjusted ORs when at least three cases were exposed. We defined confounding factors as factors that were either causally or accidentally associated with both ARM and the determinant. The reporting registry was selected as an a priori confounding factor, and was included in every model. In addition, maternal age at delivery (divided into ≤35 versus >35 years), year of birth, fertility treatment, multiple pregnancy, primiparity, pre-eclampsia, and maternal epilepsy were considered as potential confounding factors when they were not the primary factor of interest. All factors that changed the ORs in bivariable models were included in the full models, from which they were excluded if the OR did not change more than 10% upon removal. None of the potential confounded factors proved to be true confounding factors, except for maternal age at delivery, primiparity, and year of birth on only a few occasions. Subanalyses were performed for the different manifestations of ARM. Registries were excluded from specific analyses when data on certain determinants were not collected.

Results
A total of 1417 cases and 13,371 controls were eligible for this case–control study. Of the cases, 648 had isolated ARM (46%), 601 had ARM with one or more major congenital anomalies (42%), and 168 were ARM-VACTERL cases (12%). Most ARM cases with associated anomalies had urological (25%), cardiac (17%), skeletal (15%), limb (13%), or genital (13%) anomalies (Table 1). Cases were more often boys than girls, whereas the proportions of control boys and girls were almost equal (Table 2). Approximately 87% of the cases were live-born, 3% were stillborn, and 10% of the pregnancies were terminated after prenatal diagnosis. Survival after 1 week of age was 90% among all live-born ARM cases, 99% among live-born isolated ARM cases, 84% among live-born ARM cases with other anomalies, and 73% among live-born ARM-VACTERL cases. The proportions of mothers whose children were delivered preterm and/or had low birthweights were almost the same for live-born cases and controls. Case mothers were slightly younger than control mothers (28.9 and 32.2 years, respectively), of which a larger proportion were over 35 years of age because of the selection of controls, which included many infants or foetuses with trisomy 21.

Tables 3 and 4 show the associations between ARM and fertility treatment, multiple pregnancy, primiparity, and maternal chronic illnesses, maternal illnesses during the first 4 months of pregnancy, and pregnancy complications. ARM seemed to be weakly associated with fertility treat-
In total, 14 mothers had epilepsy during pregnancy (five cases and nine controls), of whom at least ten mothers reported anti-epileptic drug use during the first 4 months of pregnancy. We did not have information on type and dose of the anti-epileptic drugs. Finally, pre-existing and gestational diabetes, maternal chronic obstructive lower pulmonary diseases (e.g. asthma and bronchitis), and mental disorders (e.g. depressive and anxiety disorders) during the first 4 months of pregnancy were not associated with ARM. Subanalyses including only live births resulted in ORs that were very similar to those in Tables 3 and 4 for all pregnancy-related disorders (data not shown).

**Discussion**

In this large European registry-based case–control study, the risk of ARM appeared to be associated with fertility treatment (OR 1.3, 95% CI 0.9–1.8). No association was found between isolated ARM and fertility treatment (OR 0.8, 95% CI 0.4–1.5), but an increased risk was observed for ARM and other congenital anomalies (OR 1.6, 95% CI 1.0–2.4), and possibly for ARM-VACTERL (OR 1.6, 95% CI 0.8–3.3). Comparable odds ratios were found when multiple pregnancies were excluded from the analyses. Among the parents who received fertility treatment, 118 mothers were given hormonal treatment only (21 case and 97 control mothers), 87 mothers were artificially inseminated (ten case and 77 control parents), 14 parents conceived through ICSI (zero case and 14 control parents), and other unspecified techniques were used 38 times. In fact, the only effect observed was for hormonal chronic obstructive lower pulmonary diseases (e.g. asthma and bronchitis), and mental disorders (e.g. depressive and anxiety disorders) during the first 4 months of pregnancy were not associated with ARM. Subanalyses including only live births resulted in ORs that were very similar to those in Tables 3 and 4 for all pregnancy-related disorders (data not shown).
malformations instead of controls with no malformations. Of the infants/foetuses affected, we used controls that had cases. As EUROCAT only collects data on the pregnancies specific risk factors for ARM, especially in ARM-VACTERL, there may have been insufficient to detect moderate effects of mechanisms. Despite the large study sample, the power may have been insufficient to detect moderate effects of specific risk factors for ARM, especially in ARM-VACTERL cases. As EUROCAT only collects data on the pregnancies of the infants/foetuses affected, we used controls that had malformations instead of controls with no malformations.

Table 4. Adjusted associations between different manifestations of anorectal malformations and pregnancy-related disorders (17 EUROCAT registries; 1980–2008)

<table>
<thead>
<tr>
<th>Fertility treatment*</th>
<th>Isolated ARM cases (n = 648)</th>
<th>ARM and other defects (n = 601)</th>
<th>ARM-VACTERL (n = 168)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Adjusted OR (95% CI)</td>
<td>No.</td>
</tr>
<tr>
<td>Fertility treatment*</td>
<td>13</td>
<td>0.8 (0.4–1.5)**</td>
<td>23</td>
</tr>
<tr>
<td>Multiple pregnancy (twins or triplets)</td>
<td>18</td>
<td>1.1 (0.7–1.8)</td>
<td>27</td>
</tr>
<tr>
<td>Primiparity***</td>
<td>213</td>
<td>1.5 (1.3–1.8)</td>
<td>201</td>
</tr>
<tr>
<td>Pre-eclampsia****</td>
<td>3</td>
<td>1.3 (0.4–4.1)</td>
<td>9</td>
</tr>
<tr>
<td>Fever during the first 4 months of pregnancy****</td>
<td>0</td>
<td>–</td>
<td>4</td>
</tr>
<tr>
<td>Diabetes mellitus****</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-existing</td>
<td>3</td>
<td>0.8 (0.3–2.5)</td>
<td>4</td>
</tr>
<tr>
<td>Gestational</td>
<td>1</td>
<td>0.5 (0.1–3.9)</td>
<td>0</td>
</tr>
<tr>
<td>Chronic obstructive lower pulmonary disease****</td>
<td>7</td>
<td>1.4 (0.6–3.0)</td>
<td>7</td>
</tr>
<tr>
<td>Epilepsy during pregnancy****</td>
<td>2</td>
<td>4.5 (1.0–20.8)</td>
<td>2</td>
</tr>
<tr>
<td>Mental disorder during the first 4 months of pregnancy****</td>
<td>2</td>
<td>1.4 (0.3–6.1)</td>
<td>1</td>
</tr>
</tbody>
</table>

The same controls were used as in Table 3. Maternal age at delivery, year of birth, fertility treatment, multiple pregnancy, primiparity, pre-eclampsia, and maternal epilepsy were included as potential confounding factors, but they were excluded from the models if their removal did not change the OR by more than 10%. All factors were adjusted for registry. Crude ORs were presented if less than three cases were exposed.

*Five registries were excluded as data were not available, leaving 460 isolated ARM cases, 470 ARM cases with other defects, 141 ARM-VACTERL cases, and 10,518 controls.
**Adjusted for registry and primiparity.
***One registry was excluded as data were not available, leaving 595 isolated ARM cases, 569 ARM cases with other defects, 161 ARM-VACTERL cases, and 12,774 controls.
****Six registries were excluded as data were not available, leaving 390 isolated ARM cases, 406 ARM cases with other defects, 122 ARM-VACTERL cases, and 8,347 controls.
*****Adjusted for registry and maternal age.
******Adjusted for registry and year of birth.

**Teratogenicity non-specificity bias may occur when a certain exposure leads to malformations in both cases and controls. To reduce this type of bias, only controls with recognised syndromes or chromosomal abnormalities were included, under the assumption that these abnormalities originated because of genetic defects only. Because these syndromes and chromosomal abnormalities arise before or during conception, it is not likely that pregnancy-related factors influenced their occurrence. Furthermore, previous studies argued that these types of congenital anomalies are suitable and representative sources of controls.26,27 A few potential risk factors, including gestational diabetes mellitus, chronic lower obstructive pulmonary disease and mental disorders, seemed to be under-reported in mothers of both cases and controls, but the figures for most determinants in controls were similar to those found in the general pregnant population.28,29 As a postmortem examination after a stillbirth or for prenatally diagnosed foetuses with subsequent termination of pregnancy was not always performed, some controls may have had ARM. This could have resulted in a dilution of the effects that were found.**
Differential misclassification of exposure status because of poorer recording of exposures for controls compared with cases is unlikely, as information on pregnancy-related factors was obtained from hospital records by the EUROCAT registry, with already-existing data gathered prospectively during pregnancy for most infants in our study, regardless of the type of malformation. Only a few registries used maternal interviews after birth, but pregnancy-related factors, such as fertility treatment, multiple pregnancy, primiparity, pre-eclampsia, and other maternal disorders, are not expected to be prone to recall bias. A limitation of this registry-based study was the lack of information on parental lifestyle factors and of detailed information on certain potential risk factors, such as zygosity in multiple pregnancies, the type of fertility problems of the parents, and specific information on illnesses and drug use. Therefore, residual confounding cannot be excluded. All associations were adjusted for the registry, which is appropriate as small differences are existent between the EUROCAT registries. Although we described some potential biases that are usually associated with observational studies, we expect that these biases only influenced our findings to a minimal extent.

Approximately 54% of the ARM cases without syndromes, chromosomal abnormalities, or cloacal or bladder extrophy had one or more additional congenital anomalies. Among all ARM cases up to 62% had additional congenital anomalies. This is in line with previous studies that reported percentages of between 40 and 70%, usually including syndromes and chromosomal abnormalities. Urological (25%) and cardiac (17%) malformations appeared to be the most prevalent additional malformations, which also confirms other studies. The male/female ratio of 1.8 among ARM cases was higher than previously described ratios of 1.2–1.4. Females more often suffer from mild and unrecognised phenotypes of ARM without clinical symptoms than males. In this registry-based study, the diagnoses of these mild phenotypes of ARM may have been missed or delayed, which could have led to a relatively high male/female ratio.

To our knowledge, this is the first study to perform subanalyses on associations between fertility treatment and different manifestations of ARM. Even after adjustment for multiple pregnancy, we found fertility treatment to be associated with ARM in combination with other defects only, and we found an effect for hormonal treatment without IVF or ICSI in general. In contrast, clomiphene citrate, a hormonal drug for subfertility treatment, was not found to be associated with ARM in a study on the effect of this drug on major birth defects. Other studies showed that assisted reproductive techniques, including IVF and ICSI, increased the risk of several major birth defects, including ARM. However, these studies did not perform subanalyses for different manifestations of ARM. Although contrasting, all of these findings seem to point towards an association between ARM and fertility treatment. This may be caused by epigenetic mechanisms, which were also described for associations between fertility treatment and certain syndromes (e.g. Beckwith–Wiedemann syndrome); however, it may also indicate that the underlying subfertility of the parents is the main risk factor in the aetiology of ARM.

We found an over-representation of ARM with additional congenital anomalies and ARM-VACTERL among multiple pregnancies, whereas few other researchers found increased numbers of heterogeneous groups of gastrointestinal atresias, including ARM, in multiple pregnancies. Doyle et al. showed the proportion of chromosomal abnormalities to be lower in multiple pregnancies, which could correspond with a decreased number of multiple pregnancies among our controls. As more recent studies did not confirm this result, it is debatable whether our ORs for multiple pregnancies were overestimated. Primiparity was associated with all manifestations of ARM, and pre-eclampsia was associated with ARM and additional congenital anomalies only, although the risk estimates for primiparity may be slightly inflated as firstborns are relatively uncommon among controls with trisomy 21. Interestingly, multiple pregnancy, primiparity, and pre-eclampsia are all factors that may reflect situations in which the placenta insufficiently supplies the foetus with nutrients and hormones. Therefore, we hypothesise that placental insufficiency in early pregnancy partly explains the associations found, especially those for ARM occurring in combination with other congenital anomalies. Similar results have been found for hypospadias, a frequently occurring congenital malformation among boys. Although the rates of low birthweight among cases and controls were almost equal, these were high compared with controls without malformations. Low birthweight may also be a consequence of placental insufficiency, which strengthens our placental insufficiency hypothesis. Another biological mechanism underlying the associations between ARM and multiple pregnancy and primiparity may be a disturbed androgen–oestrogen balance, as endogenous levels of free oestradiol are increased in first and multiple pregnancies. Free oestradiol levels also increase with an increasing body mass index of the mother, and maternal overweight and obesity have consistently been identified as risk factors for ARM.

Although adverse effects of maternal epilepsy and/or anti-epileptic drug use on birth defects have already been shown, we found a five times increased risk of ARM in infants/foetuses of mothers with epilepsy during pregnancy. Unfortunately, we were not able to study associations between ARM and the different types and doses of anti-epileptic drugs, as no information on these was available. It
is unclear whether congenital anomalies result from the teratogenic effects of anti-epileptic drugs alone, or are partly the result of the underlying epilepsy itself. Previously, a reduced risk of ARM was shown after periconceptional folic acid supplementation.\(^\text{19}\) This may explain the association between ARM and maternal epilepsy during pregnancy, as treatment with most anti-epileptic drugs was associated with reduced folate serum levels.\(^\text{43}\) In agreement with our previous studies on parental risk factors for ARM,\(^\text{4,15}\) maternal fever during the first 4 months of pregnancy was found to be associated with ARM, mainly in infants/foetuses with additional congenital anomalies. A recent meta-analysis reported an increased risk of ARM for maternal pre-existing or gestational diabetes mellitus,\(^\text{41}\) but we could not confirm these findings, possibly because of the under-reporting of pre-existing or gestational diabetes among cases and controls, and because of the small numbers in the case groups.

**Conclusion**

This is the first study emphasising the importance of performing subanalyses on different manifestations of ARM. Our findings suggest the involvement of multiple pregnancy, primiparity, and pre-eclampsia, factors that are possibly related to placental insufficiency or a disturbed androgen–estrogen balance, as well as fertility treatment, maternal epilepsy, and fever during the first 4 months of pregnancy in the aetiology of ARM. These pregnancy-related disorders mainly seem to play a role in complex phenotypes of ARM, in which additional congenital anomalies are present. Only maternal epilepsy and primiparity were found to be involved in the occurrence of isolated ARM. Although these factors increased the risk of ARM 1.5–5.0 times, the absolute risks of having a child with ARM were relatively low, ranging between 0.05 and 0.26% for each potential risk factor. In addition to relative and absolute risks, however, these findings also provide clues about the pathophysiological mechanisms involved in the aetiology of ARM, which may in turn guide further research, preventive strategies, and health care for ARM patients in the future.

**Disclosure of interests**

All authors reported no conflicts of interest related to this research.

**Contribution to authorship**

CW, IR, NR, and HW initiated and coordinated the study, drafted the protocol, and contributed to the interpretation of the data. CW, IB, and CM classified the cases and controls. CW conducted statistical analyses and drafted the article. MB, MA, IB, JB, SB, FB, EC, RG, NL, AL, CD, BM, CM, VN, MO, AQ, JR, NZ contributed data to the study from their registries, and checked the accuracy and validity of the data. All authors made substantial intellectual contributions to the conception, design, and interpretation of the data, revised the article critically, and approved the final version for publication.

**Details of ethics approval**

Not required.

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**References**

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