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Key Words: Ebstein's anomaly, prevalence, antidepressants, psycholeptics, mental illness

Abstract

Objectives: To describe the epidemiology of Ebstein's anomaly in Europe and its association with maternal health and medication exposure during pregnancy.

Design: Descriptive epidemiologic analysis of population-based data

Setting: 15 EUROCAT Congenital Anomaly Registries in 12 European countries: population 5.6 million births 1982-2011.

Participants: Cases included livebirths, fetal deaths from 20 weeks gestation, and terminations of pregnancy for fetal anomaly.

Main outcome measures: Total prevalence per 10,000 births. Odds ratios for exposure to maternal illnesses / medications in the first trimester of pregnancy were calculated by comparing Ebstein's anomaly cases to cardiac and non-cardiac malformed controls, excluding genetic syndromes; adjusted for time period and country.

Results: 264 Ebstein's anomaly cases were recorded; 81% were livebirths, 2% of which were diagnosed after the first year of life. 54% of cases Ebstein's anomaly or a co-existing congenital anomaly was prenatally diagnosed. Total Prevalence rose over time from 0.29 (95%CI 0.20-0.41 to 0.48 (95%CI 0.40-0.57) ($p<0.01$). Nine cases were exposed to maternal mental health conditions/medications (adjOR 2.64, 95%CI 1.33-5.21) compared to cardiac controls. Cases were more likely to be exposed to maternal beta thalassemia (adjOR 10.5, 95%CI 3.13-35.3, n=3) and haemorrhage in early pregnancy (adjOR 1.77, 95%CI 0.93-3.38, n=11) compared to cardiac controls.

Conclusions: The increasing prevalence of Ebstein's anomaly may be related to better and earlier diagnosis. Our data suggest that Ebstein's anomaly is associated with maternal mental health problems generally rather than lithium or benzodiazepines specifically, therefore changing or stopping medications may not be preventative. We find new associations requiring confirmation.

Introduction

Ebstein's anomaly is a rare, congenital cardiac anomaly of the tricuspid valve and right ventricle first described by Wilhelm Ebstein in 1866 (1). Cases were traditionally diagnosed at all ages, with the worst outcomes for neonates who need interventions for cyanotic disease (2). Diagnosis is increasingly happening prenatally; as this anomaly develops throughout fetal life, it can occur in cases who had an apparently structurally normal heart on earlier ultrasonic scan (3). High rates of spontaneous abortion throughout pregnancy have been reported (4).

An association between Ebstein's anomaly and maternal lithium exposure was first reported in the 1970s (5) and led to recommendations still in place today to switch to other antipsychotics in pregnancy where possible (6), but this association has been disputed in more recent literature (7). Associations have also been found with other exposures, including benzodiazepines (8), antihypertensives (9), valproic acid (10), marijuana (11) and organic solvents (11).

A previous study of congenital anomalies associated with selective serotonin reuptake inhibitors use, using some of the same data, found an association with Ebstein's anomaly (12). The purpose of the present study was to test the robustness of this finding by using a larger population and different controls and set it in the context of other mental health-related exposures, and to ascertain other aspects of the epidemiology of Ebstein's anomaly..

Methods

European Surveillance of Congenital Anomalies (EUROCAT) is a network of population-based registries of congenital anomaly in 21 countries of Europe (13). The methods of registry case ascertainment are fully described elsewhere (14). The central database includes standardised data on live born congenital anomaly cases, stillborn cases and fetal deaths after 20 weeks' gestation, and prenatally diagnosed cases resulting in termination of

pregnancy for fetal anomaly. One week survival is also ascertained for liveborn cases (15). All registries record diagnoses made prenatally or at birth, most registries record diagnoses made up to one year of life, and some registries record diagnoses made in later childhood (14).

The 15 EUROCAT congenital anomaly registries in 12 countries (Table 1) which agreed to take part collect data on maternal illness before and during pregnancy and on maternal drug exposure in the first trimester of pregnancy. Most sources of exposure data were prospective to outcome, except in one centre where exposure data are ascertained exclusively by interviewing mothers and clinicians after the congenital anomaly has been diagnosed. Three other registries use maternal interviews to confirm their data (Table 1).

Other variables used in this study were syndrome and malformation diagnoses (coded to International Classification of Diseases versions 9 and 10 with British Paediatric Association extension), family history of congenital anomaly, maternal age and parity, and gestational or postnatal age at diagnosis (15). Denominators including live and stillbirths are available by registry and year.

The total study population was 5,644,312 births covering the years 1982 to 2011. (Table1: Online appendix Table1A). 145,084 babies/fetuses with major congenital anomaly were registered of which 264 were diagnosed as having Ebstein's anomaly (Table 1). All cases were included in the descriptive prevalence study. A case-malformed control study was also carried out comparing cases of Ebstein's anomaly with controls with cardiac and non-cardiac major malformations from the database separately. Excluded from both cases and controls were cases with chromosomal syndromes (11 cases and 20,316 controls), genetic syndromes (2 cases, 2,898 controls), skeletal dysplasia (no cases and 649 controls) and teratogenic syndromes (1 case and 677 controls). Controls with only hip dysplasia (n=5,698 associated with higher gestational age at birth) were also excluded leaving 250 cases and 35,904 controls with cardiac and 78,678 with non-cardiac anomalies for the analysis of

maternal and family exposures (See Figure 1A: online supplement for details of exclusions). Analyses of maternal medication involved 173 EA cases and 26,184 cardiac and 51,024 non-cardiac controls from a population of 3,662,154 births since 1995 (See Figure 1A: online supplement) as medication data were not available for all years (Table1). International Classification of Diseases 9/10 codes for maternal diseases/conditions and Anatomical Therapeutic Chemical codes for medication corresponding to the categories analysed are given in online supplement Table 2A. Maternal diabetes included both pregestational and gestational diabetes due to the potential for undiagnosed pregestational diabetes among those with gestational diabetes (16,17) and the possibility of late development of Ebstein's anomaly (3)

Statistical analysis

Total Prevalence of Ebstein's anomaly cases per 10,000 births was calculated as:

$$\frac{\text{Number of Ebstein's anomaly cases (livebirths +fetal deaths+ terminations of pregnancy for fetal anomaly) *10,000}}{\text{Total number of babies (livebirths+stillbirths) in the population}}$$

Prevalence, and proportions by prenatal diagnosis and pregnancy outcome, were calculated for three time periods (Figure 1) and for each country for the years 1992-2011 (Figure 1) when prevalence had stabilised in time.

Odds ratios (OR), with 95% confidence intervals, estimated using logistic regression to analyse risk factors are only presented where there are at least 3 exposed Ebstein's anomaly cases. ORs were adjusted for year of birth, with the data divided into the time periods 1982-1991, 1992-2001 and 2002-2011 and country (pooling data from registries within the same country: Table 1). For analysis of maternal age, maternal age was divided into 3 groups: <25, 25-34 and >34. All cases exposed to maternal diabetes, even if it

occurred later in pregnancy, were excluded from the mental health analysis and vice versa to avoid confounding.

Prior hypotheses for investigation were lithium selective serotonin reuptake inhibitors, other mental health medications, maternal depression and other mental health conditions and maternal diabetes. For other exposures, an exploratory analysis first examined the data to find which maternal diseases/conditions and medication exposures were recorded for at least three Ebstein's anomaly cases, and these exposures were then subject to statistical analysis.

Results

Associated syndromes, malformations and family history

Of the 264 Ebstein's anomaly cases, 11 (4.17%) had chromosomal anomalies (Table 3A, online supplement), less than the 11.9% proportion of chromosomal anomalies among non-Ebstein cardiac anomaly cases. Two cases (0.76%) were diagnosed with other genetic syndromes (Table 3A) compared with 2.35% of other cardiac anomalies. Few cases had any recorded family history (Table 4A, online supplement). Of the 250 non-syndromic Ebstein's anomaly cases, 86 had other cardiac anomalies (34%) including 23 reported as having an ASD only. Twenty EA cases had other right ventricular outflow tract obstruction anomalies (5) - pulmonary valve atresia or stenoses. Nine cases had coarctation of the aorta. Ebstein's anomaly cases were less likely to be associated with non-cardiac anomalies (8.8%, 22 cases) than other cardiac anomaly cases (17.6%) (Table 5A, online supplement). No specific anomaly was associated with Ebstein's anomaly in more than 2 cases.

Prevalence, age at diagnosis, pregnancy outcome and sex ratio

The average total prevalence of Ebstein's anomaly was 0.47 (95%CI 0.41-0.53) per 10,000 births ranging from 0.27 (95%CI 0.20-0.36) in Italy to 0.95 (95%CI 0.53-1.72) in Malta (Table

1). The total prevalence rose significantly from 0.29 (95%CI 0.20-0.41) in the decade 1982-1991 to 0.55 (95%CI 0.46-0.67) in the decade 1992-2001 (trend p<0.01) remaining high at 0.48 (95%CI 0.40-0.57) in the decade 2002-2011 (Figure 1; online appendix Table 6A). The decrease in prevalence between the second and third decades was not statistically significant.

The prevalence of prenatally diagnosed cases (where either Ebstein's anomaly or an associated anomaly were prenatally diagnosed) per 10,000 births rose over time and varied between countries (Figure 2). The proportion of all cases which were prenatally diagnosed rose over time to 54% in the last decade (Figure 2) with 57% of all the isolated Ebstein's anomaly cases prenatally diagnosed in that decade. The proportion of terminations of pregnancy for fetal anomaly rose to 16.7% in the last decade (Figure 3). The prevalence and proportion of terminations of pregnancy for fetal anomaly varied between countries (Figure 3). Termination of pregnancy for fetal anomaly is illegal in both Malta and Ireland. Of the 97 prenatally diagnosed, non-syndromic cases where gestational age at diagnosis was known, 85 (87.6%) were diagnosed at or after 20 weeks' gestation and 44 (45.4%) after 24 weeks gestation. Overall, 16.5% of postnatally diagnosed liveborn cases were diagnosed after the first week of life, not varying substantially between decades. Only 5 cases (2%) were diagnosed after 1 year of life.

16 Ebstein's anomaly cases were stillbirths, 0.03 (95%CI 0.02-0.05) per 10,000 births, Figure 3). 22 EA cases were known to be early neonatal deaths, a rate of 0.04 (95%CI 0.03-0.06) per 10,000 births, Figure 3).

50.8% of 250 non-syndromic cases were male (excluding 3 cases of unknown sex).

Case-malformed control analysis of risk factors

Neither the odds of older or younger maternal age was significantly different from controls (Table 2) but the odds of being a firstborn child, adjusted for maternal age, were significantly lower than that of all controls (Table 2). Cases were non-significantly more likely to have

been from multiple births than non-cardiac controls (Table 2).There was one pair of co-twins concordant for Ebstein's anomaly, a monozygotic pair with twin to twin transfusion. Ebstein's anomaly were non-significantly less likely to have had assisted reproduction than either control group (Table 2).

Nine cases were exposed to mental illness and/or an antidepressant or a psycholeptic medication or both (adjOR 2.80, 95%CI 1.42-5.51, non-cardiac controls, Table 2). The odds ratio was similar when compared to cardiac controls (adjOR 2.64, 95%CI 1.33-5.21) indicating that this effect was specific to Ebstein's anomaly (Table 2). High odds ratios were found for all the subcategories analysed - psycholeptic medications, antidepressants, selective serotonin reuptake inhibitors, diagnosis of anxiety, diagnosis of depression (Table 2). No Ebstein's anomaly case was exposed to lithium, but 5 cardiac and 8 non-cardiac controls were lithium-exposed. Further details of exposures of Ebstein's anomaly cases are given in the footnote of Table 2. Three of the five cases of selective serotonin reuptake inhibitors exposure we found were also in our previous study (12) which covered an overlapping population (28% of the population of this paper).

Ebstein's anomaly was non-significantly associated with diabetes compared to non-cardiac controls and was as likely to be associated with diabetes as other cardiac anomalies (Table 2). Cases were not more likely than controls to have been exposed to non-psychotropic / non-diabetic medications (0.87, 95%CI 0.54-1.39, Table 2).

Cases were more likely to have been exposed to maternal beta thalassemia (adjOR 12.9 (95%CI 3.85-43.0)) based on only 3 cases (Table 2). Haemorrhage in early pregnancy/ threatened abortion was associated with an elevated OR (Table 2).

Discussion

Ebstein's Anomaly and mental health conditions and their medication.

We found that the risk of Ebstein's anomaly rises nearly threefold where the mother is reported to have mental health conditions with medication. Our data suggest that it is not lithium or benzodiazepines specifically which are associated with Ebstein's anomaly as had been previously thought (5,7,8).), or SSRIs specifically as we and others had previously shown (12) but that medicated mental illness in general is a risk factor. We had no data on unmedicated mental illness, and cannot effectively distinguish medication from indication, although the lack of a specific medication effect points to the possibility of the risk being associated with the underlying health condition. Our analyses suggest that switching away from specific medications such as lithium does not protect the fetus. Our data also robustly suggest that these exposures are much more strongly associated with Ebstein's anomaly than cardiac anomalies in general. Recent literature has explored the relationships between congenital cardiac anomalies and both psychiatric conditions and the complex combinations of medications used to control them; other exposures of sufferers may also influence risk or act as confounders (18). We had no systematic data on factors such as smoking, alcohol, or recreational drugs. We excluded those with diabetes from the mental health analyses to avoid confounding due to the association of diabetes and depression(19).

Ebstein's anomaly and other maternal illnesses.

Pregestational diabetes is known to be associated with cardiac and other congenital anomalies (17,20) but has not been specifically investigated with regard to Ebstein's anomaly. Ebstein's anomaly, although it can be detected as early as 14 weeks' gestation, is known to occasionally develop later in pregnancy (3). It has been hypothesized that as women diagnosed with gestational diabetes are more likely to be overweight or obese they may have suffered from undiagnosed type 2 diabetes before pregnancy (17), so we grouped gestational and pregestational disease together, finding a weak association between Ebstein's anomaly and diabetes when compared with non-cardiac controls. This odds ratio is likely to be underestimated due to the inclusion in the control group of other malformations associated with diabetes (17,20). The lack of elevated odds compared to cardiac controls

suggests that Ebstein's anomaly has a similar association to diabetes as cardiac anomalies in general (17,20). Although an association was found between right ventricular outflow tract anomalies and pregestational diabetes in one study, none of the exposed cases in that study had Ebstein's anomaly (17), and 5 exposed cases were not available for analysis in another (20), therefore we conclude that, although diabetes is an important risk factor for congenital cardiac anomalies in general, it is not specifically associated with Ebstein's anomaly.

We were not able to confirm an association between maternal febrile illness, especially genitourinary tract infections, and right ventricular outflow tract obstructions (21) as being specific to Ebstein's anomaly.

Our finding that there is a strong association with beta-thalassemia is new, but it is based on only 3 cases and not hypothesis driven and thus needs confirmation in an independent dataset.

Epidemiology of Ebstein's Anomaly

We estimate a prevalence of Ebstein's anomaly in Europe of 0.47 cases per 10,000 births which is consistent with those in other populations - 0.39 per 10,000 births in Hawaii (1986-1999) (22), 0.52 per 10,000 births in Baltimore (1981-1989) (8), 0.6 per 10,000 in Atlanta (1992-2005) (23) and 0.72 per 10,000 births in Texas (1999-2005) (24). Our cases were drawn from a population of 5.6 million births, more than twice the population of the next largest of these studies (24). The highest European prevalence in our study was found in Malta where the estimate is based on small numbers, but where prevalence of congenital cardiac anomalies is known to be high relative to the rest of Europe (25,26).

The significant increase in prevalence which we found from the 1980s to the 1990s may be due in part to the increase in prenatal diagnosis and in terminations of pregnancy for fetal anomaly as a proportion of cases are lost spontaneously in late pregnancy (3,4). Prenatal and early diagnosis may also lead to better ascertainment of cases which might have been diagnosed later in life in the first study decade, or missed in late fetal and neonatal deaths.

More than half of cases were prenatally diagnosed since the 1990s, mostly after 20 weeks gestation, and often diagnosed after 24 weeks gestation. There is evidence that the majority of cases can be diagnosed by ultrasound as early as 14 weeks gestation (3), and although infrequently Ebstein may develop after 20 weeks {Zimmer}, diagnosis in late pregnancy may reflect the timing of routine congenital anomaly scans throughout Europe (27).

Our finding that Ebstein's anomaly is less likely to be part of chromosomal syndromes than other cardiac anomalies is consistent with other studies (8). Less than 1% of our cases were known to have a monogenic or microdeletion syndrome, but this may be partly because specific genetic testing has been infrequently carried out; two cases (both terminations of pregnancy for fetal anomaly) are reported to have thymic agenesis which could indicate an undiagnosed genetic syndrome. In genetic studies of the disease, microdeletions have been found (28) . Although there are reports of familial associations of the disease, these are rare (29) and first degree relatives of Ebstein's anomaly cases are more likely to have other congenital heart defects (30).

The association of Ebstein's anomaly with multiple births is inconsistent in the literature (23,24) and we found only a weak association. It is interesting that, like Correa-Villasenor and co-workers (8) we found a twin pair concordant for Ebstein's anomaly. Monozygotic twins are usually discordant for CHD, with the lesion possibly occurring either as a result of a disturbance in laterality in one twin during separation or as a result of imbalance in placental blood flow (31). Although our twins did have a twin to twin transfusion it is difficult to imagine that such a transfusion caused an identical lesion in both donor and recipient twin; more likely there was a genetic disposition, a teratogenic cause or a combination of both. Correa-Villasenor's twins were reportedly dizygotic and had an older sibling also diagnosed with Ebstein's anomaly. One of the other twins in our data is reported to have had a twin to twin transfusion, but in that case the co-twin was not reported as having a congenital anomaly. One could hypothesise that the higher rate of haemorrhage in early pregnancy/ threatened

abortion in cases than controls, although not reaching statistical significance, may indicate the early loss of co-twins (32).

Our finding that Ebstein's anomaly cases are less likely to be firstborn children support the findings of Correa-Villasenor and co-workers (8), but our data do not support their findings of an association with older maternal age or assisted reproductive therapy.

Strengths and limitations of this study

The strengths of our study are the large population with standardised data on congenital anomaly diagnoses, the inclusion of all pregnancy outcomes (livebirths, stillbirths and terminations of pregnancy), and the prospective nature of most medication recording (blind to anomaly status). The main limitation of our data was probable under ascertainment of exposure status across a range of variables, although this would have been unbiased in the case-malformed control design. We used controls which have the same probability of exposure and of ascertainment of that exposure as the cases (33,33,34), and could therefore judge the specificity of association with Ebstein's anomaly in comparison both with non-cardiac and other cardiac anomalies. However, the disadvantage of the case-malformed control design is that any exposure which is related to the controls will lead to an underestimate of the OR for Ebstein's anomaly – the so called "teratogen non-specificity bias (35) - for example, this could have diluted the OR for diabetes or selective serotonin reuptake inhibitors use where other anomalies are also implicated (12,17,20)). We analysed multiple exposures in our exploratory analyses, and the results should be interpreted taking into account the possibility of chance associations. Since Ebstein's anomaly may sometimes develop later than first trimester (3) later medication exposures may be aetiologically significant, but EUROCAT data includes only first trimester exposures.

Conclusions

Ebstein's anomaly is diagnosed in approximately one in 21,000 babies in Europe. Ebstein's anomaly is associated with a range of maternal health conditions and related medications

and our data support and broaden previous literature. There is a new signal in our data for an association between Ebstein's anomaly and maternal beta-thalassemia which requires further confirmation.

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Table 1: Study population (births) by country and year.

Country	Years included in the study	Years included in medication analysis	Study population 1982-2011: total births	EA: number of cases and prevalence per 10,0000 births (with 95% confidence intervals) 1982-2011	
Denmark (Odense)[M]	1982-2011	1995-2011	159,595	10	0.63 (0.34-1.16)
France (Paris)[M]	1982-1011	2001-2011	994,614	61	0.61 (0.48-0.79)
Netherlands(Northern)[MIP]	1982-2011	1995-2001	506,121	26	0.51 (0.35-0.75)
Switzerland (Vaud)[M]	1989-2011	1997-2001	174,162	13	0.75 (0.43-1.29)
Malta[M]	1986-2010	1996-2011	115,713	11	0.95 (0.53-1.72)
Belgium (Antwerp)[M]	1990-2011	1997-2011	341,573	12	0.35 (0.20-0.62)
Germany (Saxony)[MI]	1987-2011	2000-2011	352,844	12	0.34 (0.19-0.60)
Ukraine[M]	2005-2011	2005-2011	208,772	13	0.62 (0.36-1.07)
Ireland*[M]	1996-2011	1996-2011	232,388	11	0.47 (0.26-0.85)
Italy*[MIX]	1982-2011	1995-2011	1,496,807	40	0.27 (0.20-0.36)
UK (Wales)[M]	1998-2011	1998-2011	466,301	32	0.69 (0.49-0.97)
Spain*[M]	1990-2010	1995-2011	595,422	23	0.39 (0.26-0.58)
Total	**1982-2011**	**1995-2011**	**5,644,312**	**264**	**0.47 (0.41-0.53)**

*Ireland = Cork and Kerry 1996-2010 & SE Ireland 1997-2010
* Italy = Tuscany 1982-2011& Emilia Romagna 1982-2011
*Spain = Basque Country 1990-2010 & Valencia 2007-2010
[M] Medication ascertainment from maternal medical/midwifery notes
[I] Information on medication exposure taken from or confirmed through maternal interviews
[P] Information available on maternal prescriptions
[x] Tuscany has information from maternal interviews only, Emilia Romagna from both interviews and notes.

Table 2: Ebstein's Anomaly: Number, crude odds ratios (OR) and odds ratios adjusted for country and time (adjOR) for maternal characteristics and medication exposures compared to non-cardiac malformed control cases.

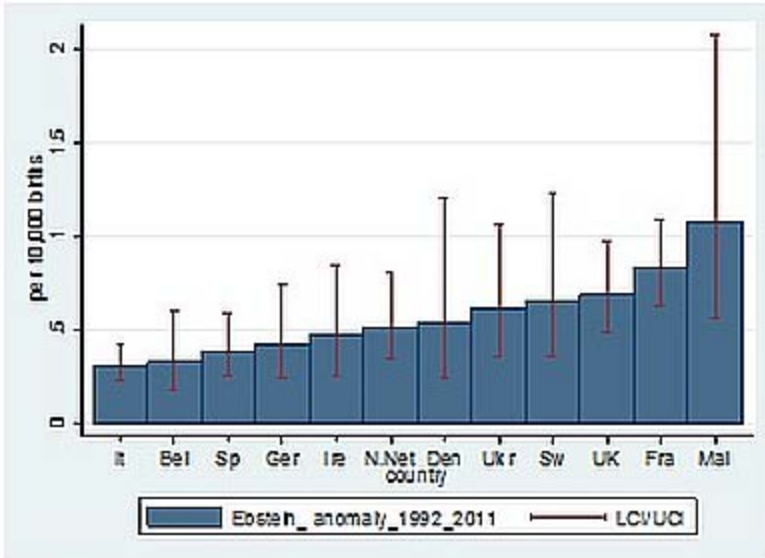
Exposure			Non-cardiac controls			Cardiac controls	
	Cases exposed	Controls exposed	OR (95%CI)	Adjusted for country and time	Controls exposed	OR (95%CI)	Adjusted for country and time
Maternal reproductive history							
Firstborn*	69	24,660	**0.72 (0.54-0.96)**	**0.70 (0.52-0.95)**	11,255	0.76 (0.57-1.02)	**0.74 (0.56-0.99)**
Maternal age <25	52	15,165	1.10 (0.80-1.51)	1.14 (0.82-1.58)	6,388	1.18 (0.86-1.62)	1.24 (0.89-1.73)
Maternal age >34	45	14,078	1.02 (0.73-1.42)	1.03 (0.74-1.45)	6,932	0.94 (0.67-1.32)	0.95 (0.68-1.33)
ART **	4	1,862	0.65 (0.24-1.75)	0.61 (0.23-1.66)	885	0.65 (0.24-1.74)	0.58 (0.22-1.58)
Multiple birth	14	3,084	1.51 (0.88-2.59)	1.48(0.86-2.55)	1,746	1.18 (0.69-2.03)	1.17 (0.68-2.02)
Mental Health [XD]							
Mental illness or medication [XD***]	9	962	**3.04(1.56-5.94)**	**2.80 (1.42-5.51)**	497	**2.65 (1.35-5.18)**	**2.64 (1.33-5.21)**
Depression [XD]	4	330	**3.89 (1.44-10.5)**	**3.52 (1.19-8.91)**	203	**2.84 (1.05-7.71)**	2.70 (0.98-7.43)
Anxiety [XD]	3	56	**17.2(5.34-55.3)**	**15.4(4.72-49.9)**	34	**12.7 (3.89-41.8)**	**13.8 (4.15-45.8)**
Psycholeptic (N05) [m XD]	4	266	**4.56 (1.68-12.4)**	**4.50 (1.64-12.3)**	122	**5.02 (1.84-13.8)**	**4.95 (1.79-13.7)**
Antidepressants (N06A) [m XD]	7	359	**6.02 (2.80-12.9)**	**6.00 (2.76-13.0)**	186	**5.86 (2.71-12.7)**	**6.04 (2.75-13.2)**
SSRIs (N06AB) [m XD]	4	234	**5.19 (1.91-14.1)**	**5.24 (1.91-14.4)**	116	**5.29 (1.93-14.5)**	**5.35 (1.93-14.9)**
SSRI excluding other antidepressants [m XD]	4	234	**5.27 (1.94-14.3)**	**5.39 (1.96-14.8)**	116	**5.37 (1.96-14.7)**	**5.49 (1.97-15.3)**
Antidepressants excluding Psycholeptics [m XD]	5	303	**5.13 (2.09-12.6)**	**5.32 (2.14-13.2)**	159	4.97 (2.01-12.3)	5.22 (2.08-13.1)
Mental illness excluding psycholeptics [m XD]	5	601	**2.57 (1.05-6.29)**	**2.50 (1.01-6.16)**	341	2.29 (0.93-5.61)	2.14 (0.87-5.29)
Non mental health / non-diabetic medications [m]	23	7,923	0.88 (0.57-1.37)	0.87 (0.54-1.40)	3,937	0.90 (0.58-1.40)	0.89 (0.56-1.43)
Disease/condition							
Diabetes [XP]	6	1,285	1.52 (0.67-3.42)	1.51 (0.67-3.40)	1,063	0.82 (0.37-1.86)	0.87 (0.38-1.96)
Beta thalassemia [XP XD]	3	114	**8.65 (2.73-27.4)**	**12.9 (3.85-43.0)**	65	**6.81 (2.13-21.8)**	**10.5 (3.13-35.3)**
Haemorrhage in early pregnancy [XP XD]	11	1,602	**2.29 (1.25-4.21)**	1.77 (0.92-3.38)	771	**2.14 (1.16-3.93)**	1.77 (0.93-3.38)
Maternal infection							
Genitourinary infection [XP XD]	3	799	1.22 (0.39-3.83)	1.02(0.32-3.24)	394	1.11 (0.36-3.49)	1.03 (0.33-3.28)
Antibiotics (J01) [m XP XD]	6	1,277	1.47 (0.65-3.33)	1.68 (0.73-3.87)	632	1.50 (0.66-3.40)	1.80 (0.78-4.15)

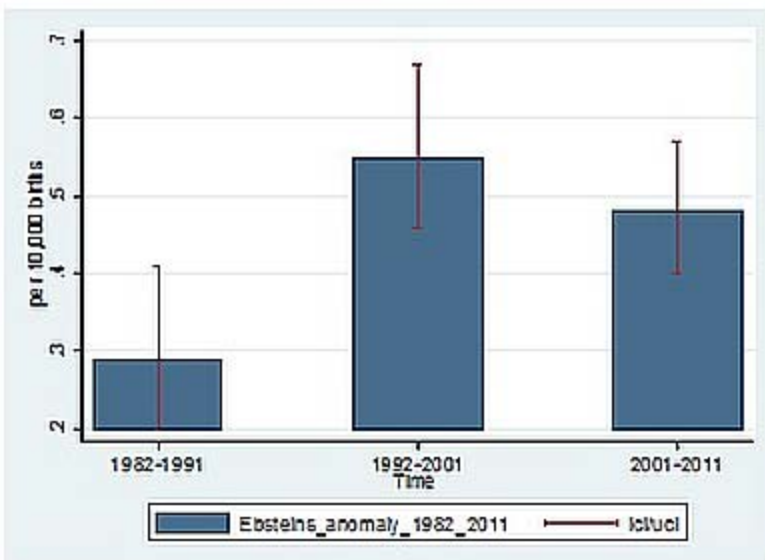
[m] Analysis restricted to years with medication data available (Table 1)
*Cases and controls where the total number of previous pregnancies was unknown were excluded (47 (18.8%) cases 16,958 (21.6%) controls. OR adjusted for country and time were also adjusted for maternal age.
** 1992-2011only
***There were no cases with recorded exposure to maternal mental illness who were not exposed to psycholeptic or antidepressant medications. 3 of the 9 cases with medications had no diagnosis recorded, including one who took an antipsychotic. 2 cases exposed to psycholeptics, both exposed to a benzodiazepine derivative (anxiolytics), were also exposed to a Selective Serotonin Reuptake Inhibitor (SSRI). There were 2 cases exposed to SSRIs only. One mother, who took both a benzodiazepine derivatives and an SSRI, was also using beta-blockers and drinking more than 5 units of alcohol per day. The other 8 had no relevant medical history, were not known to have used assisted reproductive therapies (ART) and all were singleton births.

[XP] Excluding cases and controls exposed to mental health issues (0 cases, 18 cardiac, 40 non-cardiac controls). Two pregestational, three gestational.

[XD] Excluding cases and controls exposed to diabetes (0 cases, 18 cardiac, 40 non-cardiac controls)

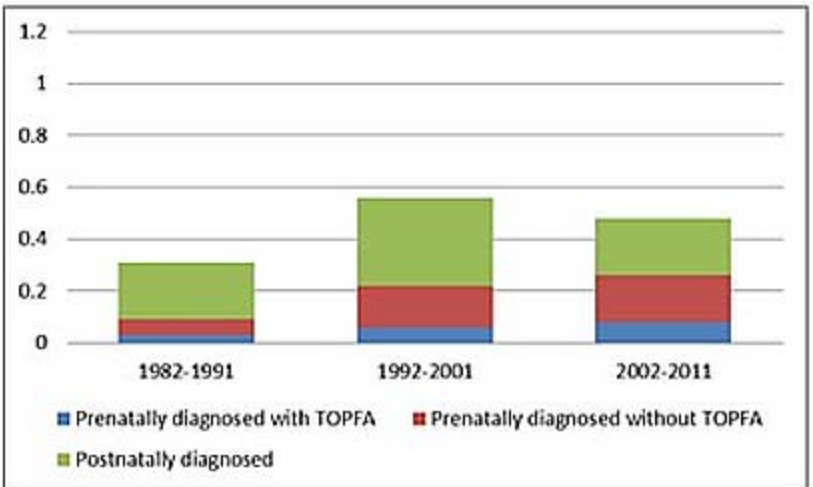
Figure 1: Ebstein's anomaly: Prevalence per 10,000 births over time and by country with 95% confidence intervals

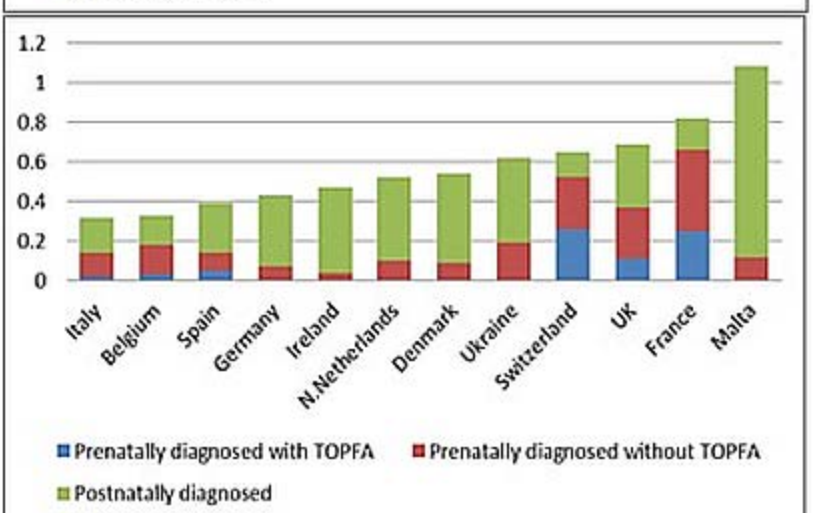




NB. Only data from the second two decades when diagnosis / ascertainment may have improved are shown by country

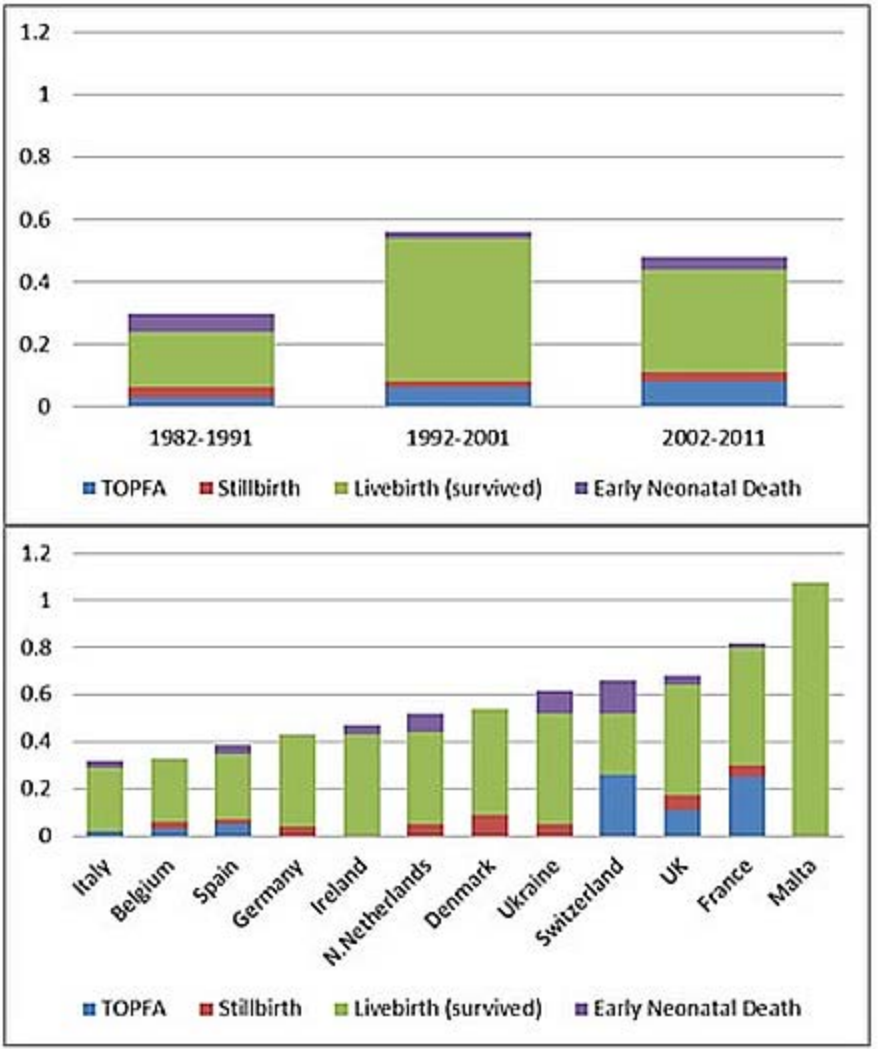
Figure 2: Ebstein's anomaly: Prevalence per 10,000 births by time, country and prenatal diagnosis





NB. Only data from the second two decades when diagnosis / ascertainment may have improved are shown by country

Figure 3: Ebstein's anomaly; Prevalence per 10,000 births, by time, country and pregnancy outcome



NB. Only data from the second two decades when diagnosis / ascertainment may have improved are shown by country

Online appendix

Table 1A: Study population (births) by country and year.

Country	Years included	1982-1991	1992-2001	2002-2011	Total births in study years 1982-2011	Years included in medication analysis	Total births in medication study years 1995-2011
Denmark (Odense)	1982-2011	49,475	5,7936	52,184	159,595	1995-2011	92,211
France (Paris)	1982-1011	365,807	361,464	267,343	994,614	2001-2011	293,767
Netherlands(Northern)	1982-2011	124,583	196,761	184,777	506,121	1995-2001	323,728
Switzerland (Vaud)	1989-2011	23,120	76,232	74,810	174,162	1997-2001	112,156
Malta	1986-2010	32,491	47,238	35,984	115,713	1996-2011	63,051
Belgium (Antwerp)	1990-2011	8,428	135,969	197,176	341,573	1997-2011	286,751
Germany (Saxony)	1987-2011	72,877	106,958	173,009	352,844	2000-2011	209,956
Ukraine	2005-2011			208,772	208,772	2005-2011	208,772
Ireland*	1996-2011		74,817	157,571	232,388	1996-2011	232,388
Italy*	1982-2011	315,353	507,186	674,268	1,496,807	1995-2011	1,031,189
UK (Wales)	1998-2011		128,106	338195	466,301	1998-2011	466,301
Spain*	1990-2010	32,729	163,572	399,121	595,422	1995-2011	341,884
Total	1982-2011	1,024,863	1,856,239	2,763,210	5,644,312	1995-2011	3,662,154

Ireland = Cork and Kerry 1996-2010 & SE Ireland 1997-2010
* Italy = Tuscany 1982-2011 & Emilia Romagna 1982-2011
*Spain = Basque Country 1990-2010 & Valencia 2007-2010

Table 2A: ICD9 /10 codes and Drug (ACT) codes used in the analysis

Disease / Condition / Anomaly	ICD10	ICD9	ACT
Ebstein's anomaly	Q22.5	746.2	
Beta-thalassemia	D561	282.4	
Haemorrhage in pregnancy	O20*	640*	
Genitourinary infection in pregnancy	O23*	646.6	
Depression	F32/33	311*	
Anxiety	F41*	300*	
Mental illness	F*	29*/30*/31*	
Diabetes	E10*/11*/12*/13*/14*	249*250*	
Gestational Diabetes	0244/9	6480/8	
Antibiotics			J01*
Psycholeptics			N05*
Antidepressants			N06A*
SSRI			N06AB*

Table 3A: Genetic and teratogenic syndromes diagnosed in Ebstein's Anomaly cases who were excluded from the case malformed control study.

Case	Diagnosis	Karyotype
1	Additional marker autosomes	Unknown
2	Other loss of autosomal material	Unknown
3	Down syndrome	47,XY,+21
4	Down syndrome	Unknown
5	Turner syndrome	Unknown
6	Partial trisomy	46,XY,der(20)t(2;20)
6	Down syndrome	47, XY, +21
8	Down syndrome	Unknown
9	Down syndrome	47, XX + 21
10	Down syndrome	47,XX,+21
11	Down syndrome	47,XX+21
12	Prader-Willi syndrome	unknown
13	Pena Shokeir syndrome	unknown
14	Maternal cytomegalovirus	-

Table 3A: Number of Ebstein's anomaly cases with relevant family history

Family History	No. of EA cases	Remarks
Co-twin with EA	2 (I twin pair)	Twin to twin transfusion
EA	1	Cousin (not in our data)
Pena Shokeir syndrome	1 (case 13)	Sibling without EA
Congenital Cardiac anomaly	2	First degree relatives
Congenital Cardiac anomaly	9	Second degree relatives
Chromosomal anomaly	1	Co-twin without EA

Table 5A

Table 5A: Non-CHD congenital anomalies seen in non-syndromic Ebstein's anomaly cases

Congenital anomaly	Multiple anomalies*, no. and (%) of EA cases	Multiple anomalies*, no. and (%) of non-EA CHD cases
Any non-CHD anomaly	22(8.8)	6326 (18)
Eye	3 (1.2)	347 (1.0)
Nervous system	4 (1.6)	1,113 (3.1)
Hydrocephalus	1 (0.4)	299 (0.8)
Microcephaly	1 (0.4)	215 (0.6)
Oro-facial clefts	3 (1.2)	593 (1.7)
Cleft lip with or without palate	2 (0.8)	323 (0.9)
Cleft palate	1 (0.4)	270 (0.8)
Ear face and neck	3 (0.8)	326 (0.9)
Respiratory	3 (1.2)	613 (1.1)
Digestive system	6 (2.4)	1,360 (3.8)
Diaphragmatic hernia	2 (0.8)	189 ((0.5)
Urinary	4 (1.2)	1,345 (3.8)
Congenital hydronephrosis	2 (0.8)	329 (0.9)
Genital	3 (1.2)	593 (1.7)
hypospadias	2 (0.8)	397 (1.1)
Limb	3 (1.2)	1,383 (3.9)
Hip dislocation (non-isolated)	1 (0.4)	157 (0.4)
Polydactyly	2 (0.8)	243 (0.7)
Syndactyly	1 (0.4)	161 (0.5)
Craniosynostosis	1 (0.4)	70 (0.2)

NB Ebstein's anomaly cases may appear more than once in this table if they have more than one other major congenital anomaly

Table 6A: Ebstein's anomaly: Prevalence per 10,000 total births over time and by country 1982-2011

Country	n	1982-1991	n	1992-2001	n	2002-2011	n	1982-2011
Denmark	4	0.81 (0.30-2.15)	5	0.86 (0.36-2.07)	1	0.19 (0.03-1.36)	10	0.63 (0.34-1.16)
France	9	0.25 (0.13-0.47)	24	0.66 (0.45-0.99)	28	1.05 (0.72-1.52)	61	0.61 (0.48-0.79)
Netherlands	6	0.48 (0.22-1.07)	9	0.46 (0.24-0.88)	11	0.60 (0.33-1.07)	26	0.51 (0.35-0.75)
Switzerland	3	1.30 (0.42-4.02)	6	0.79 (0.35-1.75)	4	0.53 (0.20-1.42)	13	0.75 (0.43-1.29)
Malta	2	0.62 (0.15-2.46)	4	0.85 (0.32-2.26)	5	1.39 (0.58-3.34)	11	0.95 (0.53-1.72)
Belgium	1	1.19 (0.17-8.42)	5	0.37 (0.15-0.88)	6	0.30 (0.14-0.68)	12	0.35 (0.20-0.62)
Germany	0	0	3	0.28 (0.09-0.87)	9	0.52 (0.27-1.00)	12	0.34 (0.19-0.60)
Ukraine		-		-	13	0.62 (0.36-1.07)	13	0.62 (0.36-1.07)
Ireland		-	4	0.53 (0.20-1.42)	7	0.44 (0.21-0.93)	11	0.47 (0.26-0.85)
Italy	3	0.10 (0.03-0.29)	22	0.43 (0.29-0.66)	15	0.22 (0.13-0.37)	40	0.27 (0.20-0.36)
Wales			11	0.86 (0.48-1.55)	21	0.62(0.40-0.95)	32	0.69 (0.49-0.97)
Spain	1	0.31 (0.04-2.17)	10	0.61 (0.33-1.14)	12	0.30 (0.17-0.53)	23	0.39 (0.26-0.58)
Total	**29**	**0.29 (0.20-0.41)**	**103**	**0.55 (0.46-0.67)**	**132**	**0.48 (0.40-0.57)**	**264**	**0.47 (0.41-0.53)**

Figure 1A: Flowchart showing data used in each exclusions and numbers included in each group of analyses