Outcome of fetal echogenic bowel: a systematic review and meta-analysis

Short title: Outcome of fetal echogenic bowel

Manuscript word: 4414
Table count: 2
Figure count: 3

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Keywords: Echogenic bowel, outcome, cystic fibrosis, fetal infection

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/pd.5638

Conflict of interest statement: All the authors have no conflicts of interest to disclose

Funding: No funding was obtained for this study.
Ethical statement: not required because this study is a systematic review

What's already known about this topic? EB has been associated with a variety of adverse perinatal outcomes. The large majority of previously published studies includes cases at high risk of aneuploidy or presenting with co-existing anomalies, thus making it difficult to extrapolate an objective evidence to guide perinatal counselling.

What does this study add? Fetuses with EB are at increased risk of adverse perinatal outcome, highlighting the need for a thorough antenatal management and post-natal follow-up. Detailed ultrasound assessment should be performed in order to look for additional markers of aneuploidies and invasive procedures offered in case of associated markers or abnormal screening test. Maternal serological assessment for congenital infection and cystic fibrosis should be performed in order to stratify the risk of anomalies. Longitudinal assessment is warranted in order to detect associated anomalies

Data availability statement: n/a

ABSTRACT

The main aim of this systematic review was to explore the outcome of fetuses with isolated echogenic bowel (EB) on antenatal ultrasound.

Inclusion criteria were singleton pregnancies with isolated EB no associated major structural anomalies at the time of diagnosis. The outcomes observed were: chromosomal anomalies, cystic fibrosis, associated structural anomalies detected only at follow-up scans and at birth, regression during pregnancy, congenital infections, intra-uterine (IUD), neonatal (NND) and perinatal (PND) death.

Twenty-five studies (12971 fetuses) were included. Chromosomal anomalies occurred in 3.3% of the fetuses, mainly Trisomy 21 and aneuploidies involving the sex chromosomes. Cystic fibrosis occurred in 2.2%. Congenital infections affected 2.2%, mainly congenital CMV infection. The majority of fetuses with EB experienced regression or disappearance of the EB at follow-up scans. Associated anomalies were detected at a follow-up scan in 1.8%. Associated anomalies were detected at birth and missed at ultrasound in 2.1% of cases. IUD occurred in 3.2% of cases while the corresponding figures for NND and PND were 0.4% and 3.1%.

Fetuses with EB are at increased risk of adverse perinatal outcome, highlighting the need for a thorough antenatal management and post-natal follow-up. Assessment during pregnancy and after birth should be performed in order to look for signs of fetal aneuploidy, congenital infections and associated structural anomalies.

INTRODUCTION

Fetal echogenic bowel (EB) is among the most common ultrasound markers detected on second trimester ultrasound with a reported incidence of 2 to 18 per 1000 pregnancies. EB is defined as bowel of similar or greater echogenicity than surrounding bone, although some authors have relied on comparisons with fetal liver or lung [1]. Assessment of EB is subjective, making its detection prone to significant inter-observer variability, although a grading system based upon the degree of similarity with the surrounding bone was initially proposed by Slotnick et al.[2]

EB has been associated with a variety of adverse perinatal outcomes including chromosomal anomalies, cystic fibrosis, congenital infections, fetal growth restriction (FGR) and structural malformations, mainly involving the gastrointestinal tract. Despite this, the actual burden of adverse outcome in fetuses with EB has yet to be quantified. The large majority of previously published

studies includes cases at high risk of aneuploidy or presenting with co-existing anomalies, thus making it difficult to extrapolate an objective evidence to guide perinatal counselling [1,3-4].

The aim of this systematic review was to quantify the possible adverse perinatal outcome in fetuses with a prenatal diagnosis of isolated EB on ultrasound.

METHODS

Protocol, eligibility criteria, information sources and search

This review was performed according to a priori designed protocol recommended for systematic reviews and meta-analysis.[5] Medline, Embase, Cinahl and Clinicaltrials.gov databases were searched electronically in January 2019, utilizing combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for "echogenic" or "hyperechoic "or "bowel" and "outcome". The search and selection criteria were restricted to English language. Reference lists of relevant articles and reviews were hand searched for additional reports. PRISMA and MOOSE guidelines were followed[6-7]. The study was registered with the PROSPERO database.

Study selection, data collection and data items

The inclusion criteria were pregnancies with an ultrasound evidence of isolated EB, defined as an increased echogenicity or brightness of the fetal bowel located primarily in the lower fetal abdomen and pelvis.

The outcomes observed were:

- Chromosomal anomalies
- Cystic fibrosis
- Associated structural anomalies detected only at follow-up scans
- Associated anomalies diagnosed only at birth and missed at prenatal ultrasound
- Regression and persistence of the EB during pregnancy
- Fetal infections
- Growth restriction, defined as birthweight $<10^{th}$ percentile
- Intra-uterine death (IUD), defined as the loss of the fetus ≥20 weeks
- Neonatal death (NND): defined as the death of the new-born within 28 days from birth
- Perinatal death (PND), defined as the sum of IUD and NND within 28 days from birth

Furthermore, we planned to perform sub-group analyses according to type (focal vs diffuse), grade and gestational age at diagnosis of EB.

Only studies reporting the incidence of these outcomes in singleton pregnancies with isolated EB were considered eligible for analysis.

Studies reporting non-isolated cases or the incidence of EB in a specific sub-group of anomalies were excluded. Studies included exclusively pregnancies at high risk for aneuploidies or those reporting the occurrence of EB in cases with peculiar anomalies were also excluded on the basis that they are likely not to reflect the natural history of the disease. Autopsy-based studies without information on prenatal imaging were also excluded on the basis that fetuses undergoing termination of pregnancy are more likely to show associated major structural and chromosomal anomalies. Finally, studies published before 2000 were also excluded, because we felt that advances

in prenatal imaging techniques and improvements in the diagnosis and definition of this ultrasound finding make them less relevant.

Only full-text articles were considered eligible for inclusion; case reports and conference abstracts, and case series with <3 cases, irrespective of whether the anomaly was isolated or not, were also excluded from the main analyses to avoid publication bias.

Two authors (ADA, DB) reviewed all abstracts independently. Agreement regarding potential relevance or inconsistencies was reached by consensus or resolved by discussion with a third reviewer (FDA). Full text copies of those papers were obtained, and the same reviewers independently extracted relevant data regarding study characteristics and pregnancy outcome. If more than one study was published on the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations.

Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale (NOS) for cohort studies[8]. According to NOS, each study is judged on three broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment of the outcome of interest. Assessment of the selection of a study includes the evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and the demonstration that the outcome of interest was not present at start of study. Assessment of the comparability of the study includes the evaluation of the comparability of cohorts based on the design or analysis. Finally, the ascertainment of the outcome of interest includes the evaluation of the type of the assessment of the outcome of interest, length and adequacy of follow-up. According to NOS a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability[8].

Statistical analysis

We used meta-analyses of proportions to combine data and reported pooled proportions (PP). Funnel plots displaying the outcome rate from individual studies versus their precision (1 per SE) were carried out with an exploratory aim. Tests for funnel plot asymmetry were not used when the

total number of publications included for each outcome was <10. In this case, the power of the tests is too low to distinguish chance from real asymmetry [9-12].

Between-study heterogeneity was explored using the I^2 statistic, which represents the percentage of between-study variation that is due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, whereas I2 values ≥50% indicate a substantial level of heterogeneity. A random effect model was used to compute the pooled data analysis. All proportion meta-analyses were carried out by using StatsDirect version 2.7.9 (StatsDirect, Ltd, Altrincham, Cheshire, United Kingdom).

RESULTS

General characteristics

1028 articles were identified, 49 were assessed with respect to their eligibility for inclusion (Table S1) and 25 studies were included in the systematic review (Table 1, Figure 1)[1,13-36]. These 25 studies included 12971 fetuses with EB on ultrasound; of those 2832 (21.8%, 95% CI 21.1-22.6) were isolated, defined as EB with no associated major structural anomalies at the time of diagnosis.

The results of the quality assessment of the included studies using Newcastle-Ottawa Scale (NOS) are presented in Table 2. Most of the included studies showed an overall good score regarding the selection and comparability of the study groups, and for ascertainment of the outcome of interest. The main weaknesses of these studies were their retrospective design, small sample size, different gestational ages at scan and lack of stratification according to the grade of EB. Furthermore, not all the included studies were matched case-control series, thus making it possible for other co-factors to affect the robustness of the results.

Synthesis of the results

Chromosomal anomalies and genetic syndromes

Eighteen studies[13,14,16-22,24,25,28-30,33-36] (1530 fetuses) explored the incidence of chromosomal anomalies in fetuses with a prenatal diagnosis of isolated EB. Overall, chromosomal anomalies occurred in 3.3% (95% CI 2.4-4.2; 50/1530) of the fetuses with isolated EB. The most common chromosomal anomaly detected in fetuses with isolated EB was Trisomy 21 (PP: 2.4%, 95% CI 1.2-4.0; 39/1530) and aneuploidies involving the sex chromosomes (PP: 0.7, 95% CI 0.3-1.2; 6/1237), while the occurrence of Trisomy 18 and 13 was 0.4% (95% CI 0.01-0.8; 1/1237) and 0% (0-0.6; 0/1237), respectively (Table 3).

Cystic fibrosis occurred in 2.2% (95% CI 1.0-3.7; 30/1474) of the fetuses with isolated EB, while other genetic syndromes were diagnosed in 0.4% (95% CI 0.1-0.8; 1/1237) (Table 3.)

Congenital infections

Nine studies[13,15,16,19-22,30,34-35] (1206 fetuses) explored the incidence of congenital infections in fetuses with a prenatal diagnosis of isolated EB. Overall 2.2% (95% CI 1.0-3.7; 25/1206) of the fetuses with isolated EB had a serological or virologic confirmation of congenital infection. CMV was the most common congenital infection in fetuses with isolated EB (PP: 1.4, 95% 0.6-2.4; 10/805), while the incidence of Toxoplasma and Parvovirus B19 infections was 0.6% (95% CI 0.2-1.2; 3/860) and 0.9% (95% CI 0.2-1.9; 5/694), respectively. There were no cases of Varicella, HSV or Syphilis infection while congenital Rubella was diagnosed in 0.3% 95% CI 0.04-0.9; 1/694) of the cases included in the present systematic review (Table 3).

Anomalies at follow-up and mortality

The majority (72.3%, 95% CI 57.6-84.9; 213/294) of fetuses experienced regression or disappearance of the EB at follow-up scans, while in 27.7% (95% CI 15.1-42.4; 81/294) of cases EB persisted throughout the pregnancy. Associated anomalies were detected at a follow-up scan in 1.8% (0.01-6.4; 19/579) of fetuses with isolated EB at the time of diagnosis, while FGR complicated 12.6% (95% CI 6.1-21.1; 145/1025) of these pregnancies. Associated anomalies were detected at birth and missed at antenatal ultrasound in 2.1% (95% CI 0.8-3.8; 22/1260) of cases, mainly consisting of gastro-intestinal anomalies (Table 3).

Finally, 15 studies (1278 fetuses) explored the risk of mortality in fetuses with isolated EB. IUD occurred in 3.2% (95% CI 1.6-5.2; 41/1278) of cases, mainly due to severe FGR. Conversely, once excluded cases affected by structural or chromosomal anomalies, genetic syndromes, infections and major anomalies, the incidence of IUD was 1.2% (95% CI 0.6-2.0; 12/944). Finally, NND and PND occurred in 0.4% (95% CI 0.1-0.9; 2/1220) and 3.1% (95% CI 1.5-5.3; 34/1120), respectively.

Sub-group analyses

Sub-group analyses according to gestational age at diagnosis, grade and type (local vs diffuse) of EB could not be performed in view of the very small number of included cases and even smaller number of events; limitations which might have affected the robustness of the results.

DISCUSSION

Main findings

The findings from this systematic review showed that, in fetuses with EB on ultrasound, chromosomal anomalies occurred in 3.3% of cases, while cystic fibrosis in 2.2%, thus highlighting the need for an accurate stratification of the risk of aneuploidy and CF using NIPT and parental carrier screening respectively. Maternal serological screening is warranted in order to identify pregnancies at higher risk of congenital infections, which can complicate about 2% of fetuses presenting with EB. Thorough ultrasound follow-up during pregnancy is also recommend in order to identify FGR which may co-exist with EB in 12.6% of cases. Finally, accurate post-natal assessment should be performed in order to rule out associated structural anomalies, mainly involving the gastrointestinal tract, which may be present in 2.1% of cases labelled to be affected by isolated EB on prenatal ultrasound.

Comparison with other systematic reviews, strengths and limitations

This is, to our knowledge, the first systematic review exploring the outcomes of fetuses with isolated EB on ultrasound. A recent systematic review exploring the diagnostic accuracy of different ultrasound marker in detecting Trisomy 21 reported a detection rate for Trisomy 21 using EB of 16.7 (95% CI 13.4–20.7) with a false positive rate of 1.1 (95% CI 0.8–1.5). However, this

study included mainly cases at risk of chromosomal anomalies based upon the results of first trimester screening or presenting with multiple ultrasound markers of aneuploidy.

Thorough literature search, number of outcomes observed and inclusion of isolated cases of EB represent the main strengths of the present systematic review. Small sample size of some of the included studies, their retrospective non-randomized design, heterogeneity in outcome assessment and lack of stratification of the analysis according to gestational age at diagnosis, grade and type of EB represent its major limitations.

Implications for clinical practice

EB is a relatively common finding on prenatal, especially during the first and second trimester of pregnancy. The main issue in prenatal cases with EB is to rule out associated structural anomalies which can co-exist with EB in a significant proportion of cases[3]. Assessment of the amniotic fluid should also be performed as EB may be the result of swallowed blood products due to maternal-fetal hemorrhage.

Previous studies had reported a high association between EB and Trisomy 21[1,29]. A recent systematic review exploring the diagnostic accuracy of different soft marker in detecting EB, reported an incidence of about 11.8% of Trisomy 21 in the overall population of fetuses with EB and of 11.5% in those at risk. This relatively high incidence of Trisomy 21 in fetuses with EB is likely to be affected by the inclusion of a large number of cases at high risk of aneuploidy such as advanced maternal age or increased risk form combined screening test[37-38]. In the present systematic review, chromosomal anomalies occurred in 3.3% (95% CI 2.4-4.2) fetuses with isolated EB, while Trisomy 21 in 2.4% (95% CI 1.2-4.0), thus highlighting the need of risk stratification for fetal aneuploidies. Non-invasive prenatal testing (NIPT) is emerging as an alternative to standard invasive testing in women considered to be at high risk for chromosomal anomalies and no associated anomalies on ultrasound. Review of previously published studies suggest that NIPT is highly accurate in detecting common trisomies, with detection rates >99%, 98% and 99% for trisomy 21, 18 and 13 respectively, at a combined false positive rate of 0.13% [39]. In this scenario, NIPT should be reasonably offered to women with isolated fetal EB on ultrasound, especially in those with a previous negative result from combined screening tests, and parents reassured in case

of negative test results. Conversely, invasive tests should be offered in case of EB associated with other ultrasound markers of fetal aneuploidies.

EB has been reported to increase the risk of cystic fibrosis, an autosomal recessive disorder caused by the presence of mutations in both copies of the gene for the cystic fibrosis transmembrane conductance regulator, which is involved in the production of sweat, digestive fluids, and mucus. These mutations are responsible for the production of abnormally thick secretions especially in the lungs, pancreas, liver and kidneys leading to lung infections, poor growth, meconium ileus and infertility.

EB has been reported in about 50% to 80% of fetuses affected with CF[40]. Although the pathophysiology for the occurrence of EB in fetuses with cystic fibrosis has not yet been well established, it seems to be caused by an abnormal consistency of meconium in the small intestine as a result of abnormalities in pancreatic enzyme secretion, leading to diffuse EB, bowel dilatation and calcifications. In the present systematic review, CF was found in 2.2% of fetuses with EB. This highlights the need for assessing parental status for the parental carrier screening for CF in order to stratify the risk for the fetus [41,42].

Congenital infections have also been associated with EB in the published literature[13,19]. Fetuses with congenital infections, especially CMV and Toxoplasmosis, usually present with several anomalies on ultrasound, including FGR, microcephaly, intra-cranial calcifications and placentomegaly. In the present systematic review, congenital infections occurred in 2.2% (95% CI 1.0-3.7) of fetuses with EB; when assessing the type of infection, CMV occurred in 1.4% of cases, while Toxoplasma and Parvovirus B19 infections in 0.6% and 0.9%, respectively. These findings confirm the low risk of infection in fetuses with isolated EB but highlight the need for serological assessment of the mother and for a detailed ultrasound evaluation, including neurosonography, in order to rule out subtle signs of infection.

The findings from this systematic review showed that in about 2% of fetuses with EB, associated anomalies, mainly of the gastrointestinal tract such as bowel obstruction and atresia, were present. On prenatal ultrasound, anomalies of the upper gastro-intestinal tract commonly present during the late second and third trimester of pregnancy with bowel dilatation and polyhydramnios, while those

involving the lower tract can be undetected until birth and usually show signs of bowel dilatation only later on in gestation. The relatively high incidence of undetected gastrointestinal anomalies in fetuses with apparently isolated EB highlights the need for a thorough examination during pregnancy and after birth in order to refer these women to centers with pediatric surgery facilities.

Conclusion

Fetuses with EB are at increased risk of adverse perinatal outcome, highlighting the need for a thorough antenatal management and post-natal follow-up. Detailed ultrasound assessment should be performed in order to look for additional markers of aneuploidies and invasive procedures offered in case of associated markers on ultrasound or abnormal screening test results. Maternal serological assessment for congenital infection and cystic fibrosis should be performed in order to stratify the risk of these anomalies. Finally, longitudinal assessment during pregnancy and after birth is warranted in order to detect FGR and associated anomalies, mainly gastro-intestinal which can be detected only later on in pregnancy or after birth.

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Table 1. General characteristics of the studies included in the systematic review.

Author	Year	Country	Study period	Type of study	Stratification according to grades of echogenicity	GA at diagnosis	Outcomes observed	Fetuses (n)	Isolated EB (n)
Masini[13]	2018	Italy	2006-2014	Retrospective	Performed	I-II-III trimester	Anomalies, CF, mortality, infections, FGR	154	154
Singer[14]	2018	Israel	2013-2016	Retrospective	NP	25.3±5.6	Anomalies	103	103
Tindley[15]	2017	Canada	2003-2014	Retrospective	NP	II trimester	Mortality, anomalies, infection, FGR	422	346
Ronin[16]	2017	France	2003-2013	Retrospective	Performed	II trimester	Anomalies, CF, mortality, infections, FGR	409	223
Hurt[1]	2015	United Kingdom	2008-2011	Prospective	NP	II trimester	Anomalies, mortality, FGR	83	50
Ahman[17]	2014	Sweden	2008-2011	Prospective	NP	15+0/22+0 weeks	Mortality, anomalies	9	9
Ekin[18]	2014	Turkey	2008-2013	Retrospective	NP	21.2±2.7	Anomalies	281	105
Ameratunga[19]	2012	Australia	2004-2009	Retrospective	NP	19.6 (17-21)	Anomalies, CF, infection, mortality, FGR	63	52
Buiter [20]	2012	Netherlands	2009-2010	Retrospective	Performed	II trimester	Anomalies, infections, mortality	116	48
Mailath-Pokorny[21]	2012	Austria	1998-2011	Retrospective	NP	18 (14–23	Anomalies, mortality, infections, FGR	213	84
Saha[22]	2012	United Kingdom, Germany	2005-2019	Retrospective	NP	II trimester	Mortality, FGR, anomalies	139	99
Goetzinger[23]	2011	USA	1990-2008	Retrospective	NP	18.4±1.8	Mortality, FGR	260	188
Jackson[24]	2010	Australia	2001-2006	Retrospective	NP	NR	Anomalies	35	11
Ruiz[25]	2009	United States	2003-2006	Retrospective	NP	20.3 weeks	Anomalies, mortality	68	48
Aagaard-Tillery[26]	2009	United States	1999-2002	Prospective	Performed	15-23	Anomalies	110	28
Carcopino[27]	2007	France	2003-2005	Prospective	Performed	24 (21-32)	Anomalies, CF	17	11
Aboujaoude[28]	2006	United States	2004-2005	Retrospective	NP	20±3	Anomalies, infection	65	34
Schluter[29]	2005	Australia	1993-2002	Retrospective	NP	15-22 w	Anomalies	265	265
Patel[30]	2004	United Kingdom	1994-2000	Retrospective	NP	II trimester	Anomalies, CF, mortality	109	109
Tan[31]	2003	Singapore	2002-2003	Retrospective	NP	II trimester	Anomalies	70	70
Muller[32]	2002	France	1997-1998	Prospective	NP	II trimester	Anomalies, CF	641	481
Nyberg[33]	2001	United States	1990-1999	Retrospective	NP	mean 16.9 weeks	Anomalies	8830	47

A. Kouatly[34]	2001	United States	1993-2000	Retrospective	NP	18.8±2.0	Anomalies, CF, infections, mortality	318	171
Ghose[35]	2000	United Kingdom	1996-1997	Prospective	NP	16-22 w	Anomalies, FGR, mortality	60	34
Strocker[36]	2000	United States	1992-1997	Prospective	NP	18 (15-23) w	Anomalies, infection, mortality	131	62

Table 2. Quality assessment of the included studies according to Newcastle-Ottawa Scale (NOS) for case-control study. According to NOS, a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Author	Year	Selection	Comparability	Outcome
Masini[13]	2018	★★★	★	★★
Singer[14]	2018	★★	★	★★
Findley[15]	2017	★★	★	★★
Ronin[16]	2017	★★	★	★★
Hurt[1]	2015	★★	★	★★
Ahman[17]	2014	★★	★	★★
Ekin[18]	2014	★★★	★	★★
Ameratunga[19]	2012	★★	★	★★
Buiter [20]	2012	★★	★	★★
Mailath-Pokorny[21]	2012	★★	★	★★
Saha[22]	2012	★★	★	★★
Goetzinger[23]	2011	★★	★	★★
Jackson[24]	2010	★★	★	★★
Ruiz[25]	2009	★★	★	★★
Aagaard-Tillery[26]	2009	★★★	★	★★
Carcopino[27]	2007	★★	★	★★
Aboujaoude[28]	2006	★★	★	★★
Schluter[29]	2005	★★	★	★★
Patel[30]	2004	★★	★	★★
Tan[31]	2003	★★	★	★★
Muller[32]	2002	★★	★	★★
Nyberg[33]	2001	★★	★	★★
Al Kouatly[34]	2001	★★	★	★★
Ghose[35]	2000	★★	★	★★
Strocker[36]	2000	★★	★	★★

Table 3. Pooled proportions for the different outcomes explored in the present systematic review.

Outcomes	Studies (n)	Fetuses (n/N)	Raw proportions (95% CI)	I^2 (%)	Pooled proportions (95% CI)
	Chromosomal anomalies				
Chromosomal anomalies (overall)	18	50/1530	3.27 (2.4-4.3)	45.2	3.25 (2.4-4.2)
Trisomy 21	18	39/1530	2.55 (1.8-3.5)	63.4	2.38 (1.2-4.0)
Trisomy 18	16	1/1237	0.08 (0.001-0.4)	0	0.35 (0.01-0.8)
Trisomy 13	16	0/1237	0 (0-0.3)	0	0 (0-0.6)
Anomalies of sexual chromosomes	16	6/1237	0.49 (0.2-1.1)	0	0.66 (0.3-1.2)
Deletions	16	0/1237	0 (0-0.3)	0	0 (0-0.6)
Duplications	16	1/1237	0.08 (0.001-0.4)	0	0.35 (0.01-0.8)
Inversions	16	0/1237	0 (0-0.3)	0	0 (0-0.6)
Translocations	16	0/1237	0 (0-0.3)	0	0 (0-0.6)
Others	16	2/1237	0.16 (0.02-0.6)	0	0.44 (0.1-0.9)
	Genetic syndromes				
Cystic fibrosis	13	30/1474	2.04 (1.4-2.9)	0	2.17 (1.5-3.0)
Genetic syndromes	16	1/1237	0.01 (0.001-0.05)	0	0.36 (0.1-0.8)
	Congenital infections				
Infections (overall)	9	25/1206	2.07 (1.3-3.0)	56.4	2.18 (1.0-3.7)
CMV	8	10/805	1.24 (0.6-2.3)	17.1	1.39 (0.6-2.4)
Toxoplasmosis	8	3/860	0.35 (0.1-1.0)	0	0.58 (0.2-1.2)
Parvovirus B19	7	5/694	0.72 (0.2-1.7)	25.1	0.86 (0.2-1.9)
Varicella	7	0/694	0 (0-0.5)	0	0 (0-0.7)
Rubella	7	1/694	0.14 (0.01-0.8)	0	0.33 (0.04-0.9)
HSV	7	0/694	0 (0-0.5)	0	0 (0-0.7)
Syphilis	7	0/694	0 (0-0.5)	0	0 (0-0.7)
	Follow-up in pregnancy and after birth				
Regression of EB on US	3	213/294	72.45 (67.0-77.5)	83.7	72.34 (57.6-84.9)
Persistence of EB on US	3	81/294	27.55 (22.5-33.0)	83.7	27.66 (15.1-42.4)
Anomalies at follow-up US	6	19/579	3.28 (2.0-5.1)	86.1	1.78 (0.01-6.4)
• GI anomalies	6	3/579	0.52 (0.1-1.5)1260	0	0.76 (0.2-1.6)
• Extra GI anomalies	6	16/579	2.76 (1.6-4.4)	86.7	1.42 (0.01-5.8)
Anomalies at birth	15	22/1260	1.75 (1.1-2.6)	68.6	2.08 (0.8-3.8)
• GI anomalies	13	11/1158	0.95 (0.5-1.7)	53.9	1.10 (0.4-2.3)
Extra GI anomalies	13	4/1158	0.35 (0.1-0.9)		0.49 (0.2-1.0)
FGR/SGA	8	145/1025	14.15 (12.1-16.4)	91.9	12.64 (6.1-21.1)
	Mortality				
IUD	15	41/1278	3.21 (2.3-4.3)	65.6	3.17 (1.6-5.2)
NND	14	2/1120	0.18 (0.02-0.6)	0	0.40 (0.1-0.9)
PND	14	34/1120	3.04 (2.1-4.2)	65.6	3.11 (1.5-5.3)
	Adverse perinatal outcome				
Isolated EB at diagnosis					
Isolated EB at birth