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Postnatal outcome of fetal cortical malformations: systematic review

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KEYWORDS: fetal cortical malformation; malformation of cortical development; MRI; neurosonography; prenatal diagnosis; ultrasound

CONTRIBUTION

What are the novel findings of this work?
This study demonstrates that one-third of children who were diagnosed antenatally with malformations of cortical development (MCD) had normal or only mild neurodevelopmental delay. However, this conclusion is based on reported outcomes in only 30 cases of fetal MCD and is limited by the inconsistent use of terminology in the published literature.

What are the clinical implications of this work?
The prognosis given to parents after diagnosing fetal MCD is mainly extrapolated from postnatal cohorts. It is possible that the reliance by fetal medicine practitioners on postnatal studies that describe poor neurodevelopmental outcome contributes to the high rate of termination of pregnancy with fetal MCD. There is a need for the evaluation of postnatal neurodevelopment in fetal MCD.

ABSTRACT

Objective *Parental counseling for fetal malformations of cortical development (MCD) is based on data from studies in children and adults undergoing imaging investigation for abnormal neurodevelopment. However, such postnatal findings may not be applicable to prenatally diagnosed cases. The aim of this study was to review the existing data on postnatal neurodevelopmental outcome for fetuses diagnosed with MCD.*

Methods *A literature search was conducted in PubMed, Web of Science and EMBASE for articles published between 2013 and 2023, using standardized keywords to describe fetal cortical malformations. Full-text articles were accessed for the retrieved citations and data on participant characteristics, imaging findings, and pregnancy and neonatal outcomes were extracted. Fetal MCD was defined as either complex or isolated, according to the presence or absence, respectively, of additional brain or extracranial defects.*

Results *Overall, 30 articles including 371 cases of fetal MCD were reviewed. The cases were classified as complex (*n *= 324), isolated (*n *= 21) or unknown (*n *= 26). There were 144 terminations and four stillbirths, with pregnancy outcome unreported in 149 cases. A total of 108 cases had postnatal magnetic resonance imaging or postmortem examination data available. In nine of these cases, a diagnosis of complex fetal MCD was changed to isolated MCD after birth, and one case was found not to have MCD. There were 74 live births, for which postnatal neurodevelopment data were available in only 30 cases. Normal neurodevelopmental outcome was reported in seven (23.3% (95% CI, 9.9–42.2%)) infants, with the remaining 23 exhibiting various levels of neurodevelopmental delay (three mild, seven moderate and 13 severe) from 6 months to 7 years of age.*

Conclusions *Most reviewed cases of fetal MCD were complex in nature and underwent termination of pregnancy. There is a paucity of data on postnatal*

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neurological development in fetuses diagnosed with MCD. The available data suggest antenatal overdiagnosis of case severity in about 5% of cases with known outcome, and either normal neurodevelopment or mild neurodevelopmental delay in approximately one-third of liveborn cases with neurological follow-up. © *2024 The Author(s). Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Central nervous system (CNS) malformations are one of the most frequent congenital anomalies that can be detected during the routine midtrimester anomaly scan[1]. Malformations of cortical development (MCD) comprise a large, heterogeneous group of disorders with disrupted cerebral cortex formation characterized by abnormal cortical structure or the presence of heterotopic gray matter[2]. Abnormal development of the cortex can be identified by ultrasonography and magnetic resonance imaging (MRI)[3]. Typically, a guarded clinical prognosis is given following the diagnosis of fetal MCD because it is associated with neurological impairment, including epilepsy, autism, cerebral palsy and intellectual disability[4,5]. However, this guarded prognosis has been extrapolated from postnatal cohorts in which imaging was only performed when infants or children presented with signs or symptoms suggestive of a neurological disorder. The neurodevelopmental outcome of MCD diagnosed postnatally is invariably poor owing to positive reporting bias, which ignores the possibility that there may be asymptomatic individuals with MCD[6,7]. In addition, prenatal parental counseling for a diagnosis of fetal cortical malformation is further hampered by the paucity of data on the neurodevelopmental outcome of fetal MCD. The aim of this study was to review the current literature on the natural history, pregnancy outcome and neurodevelopmental outcome of fetuses diagnosed with MCD.

METHODS

Data source and search strategy

This systematic review of the literature on fetal MCD was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and registered with PROSPERO (CRD42024502259). A literature search was performed in PubMed, Web of Science and EMBASE in November 2023 to identify relevant studies using standardized keywords and medical subject heading (MeSH) terms (Table S1). Key search items were 'fetal cortical malformations', 'fetal cortical anomalies', 'cortical development malformations', 'polymicrogyria', 'hemimegalencephaly', 'schizencephaly' and 'lissencephaly'. MeSH terms, keywords and variations of the terms were used. Only human studies including at least three cases of brain abnormality and at least one case of fetal MCD were reviewed. The time frame was restricted to studies published between 2013 and 2023. Relevant studies published in non-English languages were excluded only if an adequate translation could not be produced.

Eligibility criteria

Studies reporting fetuses with a suspected cortical malformation on ultrasound or MRI were included. Cortical malformations may coexist with other CNS or extra-CNS anomalies, and women with such a fetus were also included in our review and analysis. Systematic reviews, cohort studies, case–control studies and case reports were included if they reported on fetuses with any known form of cortical malformation, such as lissencephaly, schizencephaly, polymicrogyria or hemimegalencephaly. We also included any brain lesion that involved the brain cortex, such as tumors. This study was deemed not to require ethics approval or signed patient consent as per the Health Research Authority decision tool.

Study selection and data extraction

Two reviewers (F.F. and N.A.-C.) independently screened all titles and abstracts to select studies eligible for full-text review. Articles thought to potentially address the research question were retrieved and assessed for eligibility. Disagreements were resolved by discussion including a third reviewer (B.T.). Data on participant characteristics, MRI and ultrasound findings, and pregnancy and neonatal outcomes were extracted manually from each study independently by two reviewers and disagreements were resolved by discussion including the third reviewer if needed. Data from the same patients were included only once.

Data synthesis

Cases were classified as isolated, complex or unknown, according to the presence or absence of additional findings. Cases were classified as isolated when the cortical malformation was the only finding. When a genetic or vascular (ischemic or hemorrhagic) anomaly, an infectious cause or another CNS or extra-CNS abnormality was found, the case was classified as complex. The reasons for classification as complex were not mutually exclusive.

Pregnancy outcome and postnatal diagnosis

Pregnancy outcome was extracted when provided by the study authors and was classified as termination of pregnancy (TOP), intrauterine demise or live birth. Data on postnatal diagnosis were collected if neonatal MRI or postmortem analysis was available. Follow-up data of the liveborn cases were collected if provided. Neurological development was deemed normal if no cognitive impairment or delay was recorded. If epilepsy was the only

postnatal diagnosis and it was being successfully managed using medication, neurodevelopment was considered to be normal. If a mild impairment of the motor system was reported without cognitive abnormalities, it was classified as a normal neurodevelopmental outcome. When neurodevelopment was abnormal, it was classified as mild, moderate or severe, according to the study authors' data. Issues limited to behavior and learning without any further impairment were considered to be mild abnormalities. Neurodevelopmental delay not otherwise specified was labeled as a moderate abnormality. When neurodevelopmental delay was defined as global or associated with intractable seizures, cerebral palsy or other system failure (e.g. visual impairment), it was considered severely abnormal. If data on other adverse outcomes were provided, these were also collected. Postnatal deaths were recorded when specified.

RESULTS

The initial literature search yielded a total of 922 studies. After reviewing the title and abstract, 70 articles were retrieved for full-text review. Forty articles were excluded after reading the full text as they did not include any case of fetal MCD or reported fewer than three cases of brain abnormality (Table S2). Therefore, a total of 30 articles including 371 cases of fetal MCD were included in this systematic review (Figure 1, Table 1). All 371 cases were diagnosed on routine antenatal ultrasound and, in at least 239 (64.4%) cases, patients were referred subsequently for MRI.

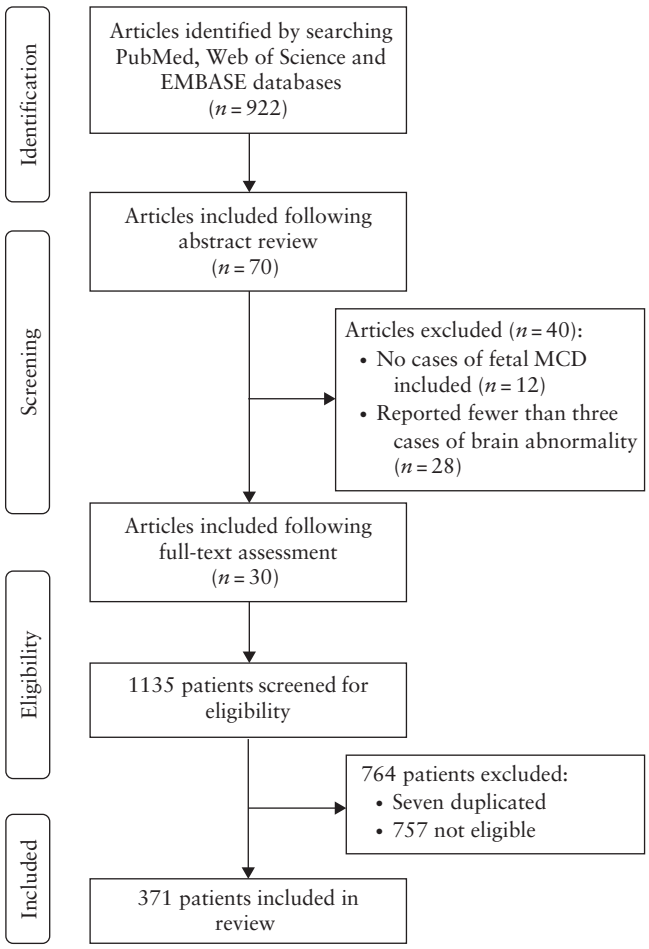

Figure 1 PRISMA flowchart summarizing inclusion of studies and cases in systematic review. MCD, malformation of cortical development.

Classification and pregnancy outcome

The classification and etiology of included cases of fetal MCD are shown in Figure 2. The majority of cortical malformations were complex ($n = 324$ (87.3%)), with non-cortical CNS abnormalities seen in 215 (66.4%) cases and extra-CNS anomalies present in 64 (19.8%) cases. The most common presumed etiology for complex MCD was genetic ($n = 160$ (49.4%)). There were 21 cases of isolated MCD (Table 2). Pregnancy outcome was available for 222 (59.8%) cases (Figure 2). The majority of recorded pregnancy outcomes were terminations ($n = 144$ (64.9%)) or stillbirths ($n = 4$ (1.8%)), with only 74 (33.3%) live births documented.

Confirmation of antenatal diagnosis

In 79 cases, postmortem details were available, of which four had a discrepancy with the antenatal diagnosis. Twenty-nine liveborn cases underwent postnatal MRI, of which six had a significant discrepancy with the prenatal MRI or ultrasound scan. Therefore, in 10/222 (4.5% (95% CI, 2.1–8.1%)) cases with known outcome, there was a significant change in the antenatal diagnosis based on postnatal imaging or postmortem analysis (Table 3). Of these 10 cases, one was found not to have MCD after birth and, in the other nine cases, a diagnosis of a complex MCD was changed to isolated MCD.

Postnatal neurodevelopment

Detailed postnatal follow-up was available in only 38 cases, of which eight were neonatal or infant deaths (Table S3, Figure 3). For the surviving 30 infants (two isolated and 28 complex), postnatal follow-up ranged from 6 months to 7 years. Of the 28 cases of complex MCD, normal neurodevelopment or mild neurodevelopmental delay was reported in seven (23.3% (95% CI, 9.9–42.2%)) and two cases, respectively. Four children diagnosed with complex MCD had medication-controlled epilepsy, of which one had normal neurodevelopment. One of the two cases with isolated MCD was reported to have mild neurodevelopmental delay. In total, 10 (33.3% (95% CI, 17.3–52.8%)) infants were reported as having normal neurodevelopment or mild neurodevelopmental delay at postnatal follow-up. Of two children reported as having normal neurodevelopment, one was found to have hypotonia of the lower limbs at 1 year of age and left upper limb paresis at 2 years of age was found in the other. One child with moderately abnormal

Table 1 Characteristics of studies included in systematic review reporting on fetal malformations of cortical development (MCD)

Study	*Type of study*	*MCD cases* (n)	*Isolated MCD cases* (n)	*Complex MCD cases* (n)
Baffero (2015)[22]	Retrospective cohort	2	0	2
Blumkin (2020)[23]	Case series	3	0	3
Chatron (2019)[24]	Case series	4	0	4
Eyüboğlu (2021)[25]	Retrospective cohort	25	8	17
Fallet-Bianco (2014)[26]	Prospective cohort	26	0	26
Fantasia (2023)[27]	Retrospective cohort	1	0	1
Garcia-Flores (2013)[28]	Retrospective cohort	4	0	4
Goergen (2021)[29]	Retrospective cohort	22	0	22
Goergen (2022)[30]	Retrospective cohort	33	0	33
Griffiths (2018)[31]	Retrospective cohort	11*	—	—
Hagege (2023)[32]	Retrospective cohort	33	0	33
Hawkins-Villarreal (2023)[33]	Retrospective cohort	17	0	17
Kandula (2015)[34]	Prospective cohort	6	0	6
Krajden Haratz (2023)[4]	Retrospective cohort	20	0	20
Kutuk (2015)[35]	Case series	5	1	4
Leibovitz (2018)[36]	Case series	1	0	1
Lihn (2021)[37]	Prospective cohort	9*	—	—
Malinger (2023)[38]	Retrospective cohort	15	0	15
Manganaro (2017)[39]	Retrospective cohort	30	0	30
Maurice (2021)[40]	Retrospective cohort	15	0	15
Montaguti (2021)[41]	Prospective cohort	6*	—	—
Peero (2023)[42]	Retrospective cohort	19	4	15
Pooh (2019)[43]	Retrospective cohort	22	3	19
Righini (2013)[44]	Retrospective cohort	5	0	5
Righini (2016)[45]	Retrospective cohort	8	0	8
Turkyilmaz (2019)[46]	Retrospective cohort	11	0	11
Ulm (2020)[47]	Retrospective cohort	2	0	2
Vinurel (2014)[48]	Retrospective cohort	4	0	4
Williams (2014)[49]	Retrospective cohort	9	3	6
Williams (2017)[50]	Prospective cohort	3	2	1

Only first author is given for each study. *Study did not specify presence or absence of additional anomalies.

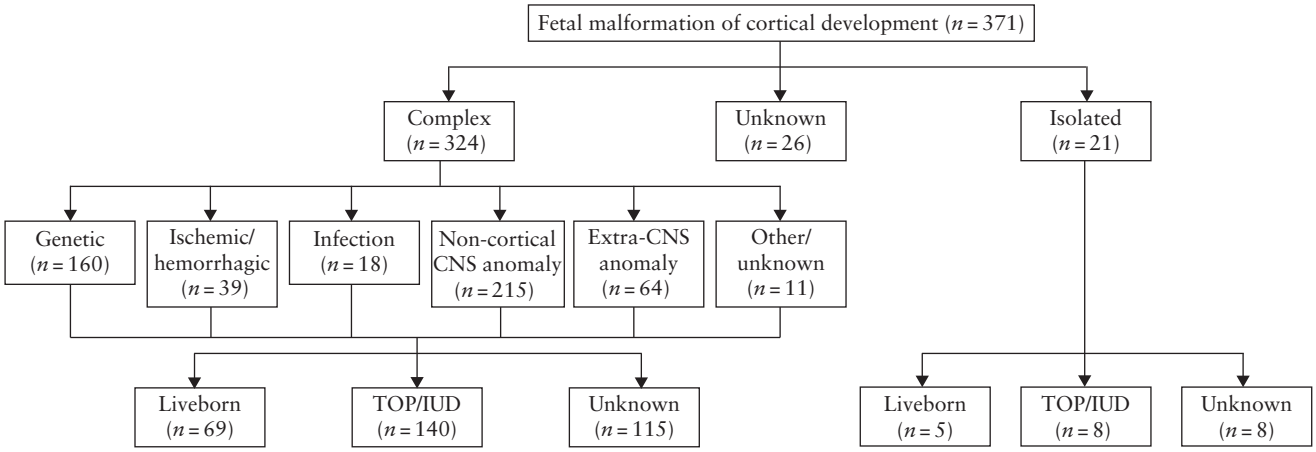

Figure 2 Flowchart summarizing classification and outcome of cases with fetal malformation of cortical development. Reasons for classification as complex were not mutually exclusive. CNS, central nervous system; IUD, intrauterine demise; TOP, termination of pregnancy.

neurodevelopment had mild right-sided weakness at 6 years of age.

A total of 14 children had a confirmed genetic diagnosis, of which three (21.4% (95% CI, 4.6–50.8%)) had normal or mildly abnormal neurodevelopment, two (14.3% (95% CI, 1.7–42.8%)) had moderate neurodevelopmental delay, five (35.7% (95% CI, 12.7–64.8%)) had severe neurodevelopmental delay and four (28.6% (95% CI, 8.4–58.1%)) died.

DISCUSSION

This systematic review found that, in approximately one-third of fetuses diagnosed with MCD, the childhood neurodevelopmental outcome was described as normal or mildly delayed. The veracity of this conclusion is limited by the very high rate of TOP following a diagnosis of fetal MCD, meaning that neurodevelopmental outcome was reported in only a small number of cases. Furthermore, published studies employ inconsistent

Table 2 Characteristics of cases with isolated fetal malformation of cortical development (MCD)

Case[ref]*	*GA at diagnosis (weeks)*	*Prenatal US findings*	*Prenatal MRI findings*	*Pregnancy outcome*	*Postnatal findings*
1[25]	—	Lissencephaly	—	—	—
2[25]	—	Lissencephaly	—	—	—
3[25]	—	Schizencephaly	—	—	—
4[25]	—	Heterotopia	—	—	—
5[25]	—	Heterotopia	—	—	—
6[25]	—	Polymicrogyria	—	—	—
7[25]	—	Polymicrogyria	—	—	—
8[25]	—	Polymicrogyria	—	—	—
9[35]	—	Schizencephaly	Right parietal and left temporal schizencephaly	Liveborn	—
10[43]	—	Focal MCD in bilateral parietal regions	—	TOP	Cobblestone-type focal cortical dysplasia at parietal cortices, leptomeningeal heterotopia
11[43]	—	MCD of whole left hemisphere	—	TOP	Multifocal nodular heterotopia, cortical polymicrogyria in left hemisphere
12[43]	—	MCD, micrognathia, low-set ears, SGA	—	Liveborn	MCD confirmed
13[49]	21	Complex brain malformation	Hemimegalencephaly, complete disruption of transient structures and widespread MCD, central mass-like ventricular layer	TOP	—
14[49]	21	Asymmetric brain, mass lesion	Hemimegalencephaly, widespread MCD, central mass-like ventricular layer	TOP	—
15[49]	23	Hemimegalencephaly	Focal megalencephaly (frontal and ganglionic), MCD, disrupted transient structure, mass-like ventricular layer	Liveborn	MRI confirmed prenatal findings
16[42]	24 + 6	Malformed shallow Sylvian fissures, small frontal lobes, irregular cortical contour, enlarged subarachnoid space	—	Liveborn	Diffuse polymicrogyria
17[42]	26	Flat underdeveloped Sylvian fissures, absence of calcarine and parieto-occipital fissures, small kidneys	—	TOP	Underdeveloped sulcation, cerebellar heterotopia
18[42]	25 + 6	Irregular dilatated right anterior horn, periventricular echogenicity, irregular right frontal cortex, irregular malformed right Sylvian fissure	—	TOP	Right hemisphere: foci of abnormal cortical thickening, loss of normal layering, large neurons; left hemisphere: subcortical heterotopia, focal irregular gyration; facial dysmorphism
19[42]	24 + 4	Atrophic right hemisphere, serrated cortical surface of right frontal lobe, shallow abnormally shaped right Sylvian fissure, dilatated irregular right frontal horn with echogenic periventricular parenchyma	—	TOP	Right frontal and perisylvian polymicrogyria
20[50]	—	Normal	Lissencephaly	IUD	—
21[50]	—	Normal	Lissencephaly, germinolytic cysts	Liveborn	Lissencephaly confirmed on postnatal MRI

*Study in which case was reported. GA, gestational age; IUD, intrauterine demise; MRI, magnetic resonance imaging; SGA, small-for-gestational age; TOP, termination of pregnancy; US, ultrasound.

Table 3 Characteristics of cases with antenatal diagnosis of malformation of cortical development (MCD) that was revised postnatally/postmortem

Case[ref]*	*GA at diagnosis (weeks)*	*Prenatal findings*	*Final postnatal/ postmortem diagnosis*	*Pregnancy outcome*
1[4]	21	Abnormal sulcation, partial ACC, transmantle brain anomaly, irregular lateral ventricular wall	ACC	TOP
2[4]	17	Focal irregular cortex/abnormal sulcation, partial ACC with midline cysts, transmantle brain anomaly, asymmetric hemisphere	Possible hemimegalencephaly	TOP
3[4]	22	Abnormal sulcation, dysgenesis of CC, asymmetric hemispheres	Hemimegalencephaly	TOP
4[43]	—	Unilateral schizencephaly, interhemispheric cyst, CSP defect	Unilateral left schizencephaly	Liveborn
5[43]	—	Cerebral cysts, microcephaly, MCD, cavitation in GE	Microlissencephaly	Liveborn
6[43]	—	MCD, hypogenesis of CC, ventriculomegaly, asymmetrical irregular ventricular wall, vermian hypoplasia, cysts in bilateral GE, upper polydactyly, right unilateral multicystic dysplastic kidney	MCD, polydactyly	Liveborn
7[43]	—	Microcephaly, MCD, cerebellar hypoplasia, flat face, micrognathia, adducted thumbs, SGA	MCD	Liveborn
8[43]	—	Ventriculomegaly, MCD	MCD	Liveborn
9[43]	—	Lissencephaly, ACC, microcephaly, multiple calcifications in brain and placenta, cerebral dysplasia, MCD	Microlissencephaly	Liveborn
10[43]	—	MCD, ventriculomegaly due to cerebral hypoplasia, hypogenesis of CC	Multifocal nodular heterotopia, cobblestone type cerebral dysplasia	TOP

*Study in which case was reported. ACC, agenesis of corpus callosum; CC, corpus callosum; CSP, cavum septi pellucidi; GE, ganglionic eminence; SGA, small-for-gestational age; TOP, termination of pregnancy.

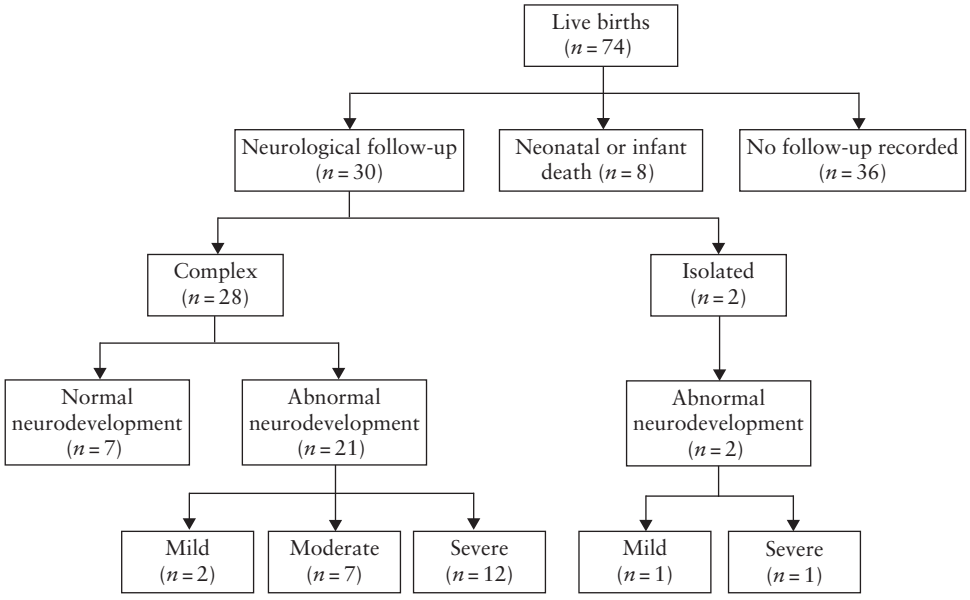

Figure 3 Flowchart summarizing detailed outcome of liveborn cases diagnosed prenatally with malformation of cortical development.

terminology, with presumed etiology and radiological findings used interchangeably to describe and/or classify MCD, limiting the generalizability of our findings.

Classification of fetal MCD

The etiology of cortical maldevelopment may be genetic, infectious, dysgenetic, hemorrhagic or ischemic in nature. The terminology prevalent in the published literature was derived mainly from either the presumed etiology or the findings from prenatal ultrasound/MRI imaging. Despite the distinction between etiological and radiological terminology, these descriptions were used interchangeably and confusingly to describe the very same fetal MCD lesions. The imprecise use of such terminology in the published literature makes data retrieval and classification of fetal MCD especially challenging. Such inconsistent use of terminology for classification, in conjunction with

limitations in antenatal imaging, may have resulted in prenatal overdiagnosis of case severity in about one in 20 cases of fetal MCD. This finding is consistent with the study of Hart *et al.*[8], in which 12% of children who had been diagnosed prenatally with a brain abnormality had a significant change in their diagnosis by 3 years of age. Certain etiologies (such as genetic abnormalities) and radiological findings (such as lissencephaly) have an independent and overwhelming influence on the expected postnatal prognosis. For this reason, there is a consensus regarding postnatal classification for MCD based on radiological findings, but this is not available for fetal MCD[2]. There is an urgent need to formalize a systematic classification for fetal MCD that can be used as the basis for collecting and describing data and predicting postnatal prognosis and outcome.

Neurodevelopmental outcome of fetal MCD

This study found that, in the limited number of liveborn pregnancies for which long-term outcome data were available, about one-third of children who had a diagnosis of fetal MCD had normal neurodevelopment or mild neurodevelopmental delay. This finding is inconsistent with the postnatal literature, which invariably reports a high rate of intractable seizures, neurological deficits and severe neurodevelopmental deficits in adults diagnosed with MCD[9–12]. On the other hand, 21% of such infants died in the first days or months after birth, and around 65% of those surviving had a moderate or severe neurodevelopmental delay. The rate of TOP in this study was over 60%, probably reflecting the guarded prognosis provided to parents by clinicians citing the available postnatal literature. However, brain imaging in adult life is usually performed only when concerning neurological signs and symptoms arise. As such, the discovery of MCD is inevitably linked to the reasons for undertaking specialist imaging. In contrast, asymptomatic adults with MCD lesions are likely to remain undetected and, as a consequence, unreported. In a prospective study of 16 400 healthy children and adult volunteers (1 year to 94 years of age) undergoing MRI, 3.7% had an incidental brain finding that was deemed to require specialist neurological follow-up[13]. Although MCD constituted a small proportion of the cohort, other studies also report cases in which MCD have been found incidentally in asymptomatic adults[14,15].

It is entirely plausible that there are many asymptomatic children and adults who have as-yet undiagnosed MCD, resulting in positive reporting bias in those in whom a diagnosis has been made as a consequence of neurological signs or symptoms. CNS development is a multi-step process that continues after birth[2,9,16]. Neuronal plasticity is an accepted phenomenon that implies that the developing brain has the capacity to recover from maldevelopment or injury. One of the proposed mechanisms is neuron overproduction during fetal life to support brain-injury repair, which is more likely to occur in fetal than in adult life[17]. Furthermore, children who undergo focal cortical resection or extensive hemispherectomy often regain the ability to walk and speak, demonstrating that the child's brain can reorganize after an extended injury[17]. One could therefore postulate that plasticity-dependent repair may occur in fetuses and/or children born with MCD, resulting in adults with asymptomatic MCD lesions who are not represented in the postnatal literature.

Strengths and limitations

Heterogeneity among the included retrospective studies precluded formal meta-analysis. The studies also used inconsistent nomenclature for classifying defects, limiting our ability to designate outcomes according to either etiology or radiological findings. Out of 30 studies representing the published literature, only 13 reported on postnatal follow-up in a total of 38 cases of fetal MCD, with only 30 cases surviving into infancy with neurodevelopmental data provided. Given that more than 60% of fetal MCD cases with pregnancy outcome reported underwent TOP, there is a possibility that the most severe cases of fetal MCD were terminated before birth, presenting prognostic bias in the postnatal follow-up. Furthermore, neurodevelopmental assessment in these children was typically reported informally and performed at early ages, when the evaluation of certain language, motor and cognitive milestones or autism may be limited[18]. Epilepsy is a neurological condition that affects up to 2% of the population worldwide[19] and that may or may not present together with neurodevelopmental delay. Nevertheless, according to the World Health Organization, up to 70% of people with epilepsy could live a seizure-free life with adequate medication, which can lead to a normal life[20]. For the purposes of this study, children with a diagnosis of epilepsy that was being successfully managed with medication were classified as having normal neurodevelopment if epilepsy was the only reported postnatal issue at follow-up. It was not possible to ascertain whether these children may have subsequently developed overt disability.

The strengths of this study include its rigorous PRISMA-compliant nature. Moreover, the added value of fetal MRI has been demonstrated only in the last decade[21]; therefore, only studies published during the past 10 years were included.

Conclusions

This study demonstrates that approximately one-third of children who were diagnosed antenatally with MCD had normal neurodevelopment or only mild neurodevelopmental delay. This conclusion is based on reported outcomes in 30 cases of fetal MCD and is limited by the confusing and inconsistent terminology used to describe fetal MCD, as well as limited postnatal follow-up and lack of formal neurodevelopmental assessment. It is probable that the reliance by fetal medicine practitioners on postnatal studies, which describe poor neurodevelopmental outcomes of MCD and are subject to positive reporting bias, contributed to the high rate of TOP in this cohort of women. There is an urgent need for evaluation

of postnatal neurodevelopment in fetal MCD in order to support clinicians and counsel parents appropriately.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Search strategy

Table S2 Excluded studies and reason for exclusion

Table S3 Characteristics of liveborn cases with fetal malformation of cortical development (MCD)