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Scoping Review of the Prenatal Diagnosis of Agenesis of the Corpus Callosum

Abstract

Objective: To map and summarize the literature related to the prenatal diagnosis of agenesis of the corpus callosum (ACC) to inform nursing practice.

Data Sources: We searched MEDLINE, CINAHL, PyschINFO, and Academic Search Complete using strings of curated terms to cover the broad ACC nomenclature. Documents were published in English between 2009 and June 1, 2020. We also hand searched the reference lists of included documents.

Study Selection: We screened 582 abstracts and retrieved the full texts of primary research articles, reviews, discussion papers, and peer-reviewed book chapters if the abstracts specifically mentioned ACC and the prenatal period. We excluded case reports, conference and poster abstracts, papers on broader anomalies, and animal studies. We reviewed 84 full-text documents and identified 61 for inclusion.

Data Extraction: We charted the data through an iterative process under headings for location, article type, study design, participant age, ACC type, recruitment, method, tools/assessments, results, key recommendations, gestational age at diagnosis, termination of pregnancy rate, the definition of isolated ACC and our notes of critique of the document.

Data Synthesis: We constructed a narrative synthesis from thematically arranged data. In the included documents, ACC was diagnosed between 17 and 38 weeks gestation and was frequently described as heterogeneous due to different causes, presentations, and outcomes. Whether the ACC was isolated as the only anomaly or present with other anomalies was considered the key factor for prenatal counselling. However, the definition of isolated ACC was inconsistent.

Conclusion: The inconsistent nomenclature and definitions of an isolated presentation of ACC increases the ambiguity within the prenatal diagnosis and must be considered when the outcome and diagnostic efficacy studies are interpreted. There is an absence of research on parents' experiences of prenatal diagnoses of ACC to inform holistic nursing interventions and the provision of psychosocial support.

Keywords

Agenesis of corpus callosum, scoping review, prenatal diagnosis, congenital abnormalities, nursing, midwifery

Précis statement

Inconsistent terminology heightens the ambiguity within a prenatal diagnosis of agenesis of the corpus callosum, and limited evidence exists with which to guide nursing practice.

Three callouts

1. Although agenesis of the corpus callosum is the most prevalent cerebral congenital anomaly, there is a paucity of evidence to inform nursing interventions.
2. The only psychosocial intervention recommended for parents who received prenatal diagnoses of agenesis of the corpus callosum was the referral to parent support groups.
3. Nurses require awareness of the ambiguity within the prenatal diagnosis of agenesis of the corpus callosum to provide holistic support to parents.

Agenesis of the corpus callosum (ACC) is a congenital malformation characterized by the incomplete development of the corpus callosum (CC) (Raybaud, 2010). ACC was the most prevalent cerebral anomaly identified within an epidemiological study with a sample of 4927 cases across 29 European countries (Morris et al., 2019). The rate of the prenatal diagnosis of ACC has increased as prenatal screening technology and knowledge have advanced (Ballardini et al., 2018; Morris, et al., 2019). However, ACC remains difficult to identify before 17 weeks gestation (Vasudevan et al., 2012). As a result, the anomaly is diagnosed within the second or third trimesters (Syngelaki et al., 2019).

The CC is the largest of the brain commissures, the white matter structures that connect the left and right hemispheres (Raybaud, 2010). The CC tract of approximately 190 million myelinated axon fibers coordinates cognitive, motor, and sensory information (Edwards et al., 2014). Pioneering axons cross the interhemispheric fissure to begin the formation of the CC at 13 weeks gestation; this crossing continues until a shaped structure is present at around 20 weeks (Edwards et al., 2014). The typical CC continues to undergo developmental change during childhood and adolescence (Edwards et al., 2014). A congenitally absent or atypical CC will not self-correct with development, and no treatment is available for the anomaly.

The CC develops through a complex sequence of steps from the formation of neurons to the guidance of the axons across the midline of the brain, and interruptions in these processes may occur at many different stages. A disruption within neurogenesis, neuronal migration and specification, telencephalon midline patterning, or axon guidance may result in a developmental malformation of the CC (Edwards et al., 2014). Interhemispheric remodeling deficits may account for the presentation of complete ACC with Probst bundles, the axons of the CC that did not cross the interhemispheric fissure (Gobius et al., 2016).

The number of developmental processes that can be interrupted reflects the many etiologies and presentations of ACC. ACC can present as the only or main anomaly, which is often referred to as isolated ACC. A congenital malformation of the CC may also occur alongside other anomalies or as a consistent or inconsistent feature of syndromes caused by Mendelian disorders, copy number variations in the genome, and syndromes without identified genetic causes (Edwards et al., 2014). Prenatal environmental insults such as fetal alcohol spectrum disorders are also implicated in the etiology of ACC (Edwards et al., 2014).

For this review, the umbrella term ACC was used to represent the range of phenotypes for which the CC is underdeveloped or not visualized, whether this occurred alongside other anomalies, as a non-isolated finding, or in the absence of other anomalies as an isolated diagnosis. The ACC nomenclature varies within the literature inclusive of and not limited to terms such as agenesis, dysgenesis, dysplasia, hypoplasia, isolated, primary, complex and syndromic (see Figure 1). In our review, the term ACC did not include other anomalies such as an enlargement or lipoma of the CC.

An absent or underdeveloped CC is not lethal, but knowledge of the specific effect of the anomaly remains limited. ACC was associated with a neuropsychological syndrome characterized by difficulty with complex processing, reduction in the speed of cognitive processing, and diminished interhemispheric sensory-motor communication with greater complexity of tasks (Brown and Paul, 2019). These core features were said to manifest as a range of emotional, learning, and social challenges as determined from the body of neuropsychological studies on individuals with primary ACC, in which the lack of identified syndromes and other major anomalies suggested the deficits were primarily related to ACC (Brown and Paul, 2019). The studies reviewed often had small or convenience sampled cohorts which presents as a limitation.

In light of the many different causes and outcomes, ACC presents as an anatomical feature of an underlying condition rather than a specific entity (Raybaud, 2010). However, ACC may be the first or only anomaly identified during the prenatal period without an identified etiology, which complicates prognostic counseling. The outcomes for children range from typical development to severe disability (Yeh et al., 2018) and include neonatal or infant death when associated with other anomalies (Oh et al., 2019). The many causes, presentations, and outcomes related to ACC have led to the anomaly being described as heterogeneous (Alby et al., 2016).

The prenatal diagnosis of ACC is likely to cause significant distress for parents. The unexpected news of any congenital anomaly has caused shock and at times, trauma (Hodgson and McClaren, 2018). Women who received a later gestation diagnosis or a diagnosis associated with ambiguity experienced higher psychological distress within a sample of 180 women were received a range of congenital anomalies (Kaasen et al., 2010). Within a further study, diagnostic ambiguity led to higher-intensity emotional responses among women, including anger, sadness, anxiety, and distress (Fonseca et al., 2013).

Antenatal distress and anxiety are considered potential risk factors that affect women's health after birth (Grigoriadis et al., 2018) and child brain structure and function (Adamson et al., 2018). Mental health concerns among women in the antenatal and postnatal periods increased the likelihood of suboptimal neurodevelopmental outcomes for school-aged children (Kingston & Tough, 2014). The consideration of the risk of distress and anxiety to the woman and child highlights the ethical and clinical responsibilities of perinatal care providers to implement evidence-informed strategies to reduce the risk associated with prenatal diagnosis. As a heterogeneous, and therefore ambiguous diagnosis made in later gestation, ACC warrants specific attention.

Several authors have provided overviews of ACC (Leombroni et al., 2018; Palmer & Mowat, 2014; Santo et al., 2012; Vasudeven et al., 2012), but these overviews are limited in terms of search and reporting strategies, and they do not address nursing practice. Despite a search of MEDLINE, Academic Search Premier, CINAHL Plus, PsychINFO, Cochrane Library, and the Joanna Briggs Institute databases, we did not locate any prior, structured reviews on the prenatal diagnosis of ACC that could inform nursing practice.

---- CALL OUT 1 ----- Therefore, the objective of our scoping review was to map and summarize the literature related to the prenatal diagnosis of ACC to inform nursing practice.

Method

Although a range of review methods are available to researchers, the scoping review method is a structure for a systematic exploration of what is known to clarify concepts and highlight gaps within the literature and to provide a foundation for clinical practice and future research (The Joanna Briggs Institute, 2015). We determined the scoping review method to be well suited to our intent to map the evidence on ACC. The methods for this review were guided by Arksey and O'Malley (2005) and The Joanna Briggs Institute (2015) and are reported in accordance with the PRISMA-ScR checklist (Tricco et al., 2018).

We developed an a priori search strategy and review protocol, although the review was not registered. A university librarian assisted with the selection of search terms and the databases. Individual database searches allowed the adaptation of search terms to suit keywords and database subject headings (Table 1). The first search occurred on the 18th of April 2019, with parameters set to English and published from 2009. We updated the results with a second and third search on the 6th of November 2019, and the 1st of June 2020 using the same terms and databases with the date parameter set from the prior search month. We exported the search results to Endnote (Web of Science Group, 2018) and reviewed the abstracts against the inclusion criteria.

We included primary research articles, reviews, discussion papers, and peer-reviewed book chapters that were primarily focused on ACC and that specifically discussed prenatal diagnosis. We excluded case reports because of the potential for reporting bias, conference or poster abstracts because of incomplete information, documents that were generally focused on prenatal anomalies, and animal studies. If the results of a longitudinal study were reported in a series of documents, we only included the most recent publication of the series.

We retrieved the full text documents that met the inclusion criteria based upon the abstract and reviewed them further against the criteria. We hand-searched the reference lists of all the included documents for any other documents. We charted the data from the included documents into Excel as the process of data extraction (Arksey & O'Malley, 2005). The initial extracted data included the location of the first author and participants, article type, study design, participant age and ACC type, recruitment, method, tools/assessments, results, key recommendations, limitations, and notes. Charting was an iterative process, and based on our increased familiarity with the data, we added the following headings: gestational age at diagnosis, termination of pregnancy rate, and definition of isolated ACC for all studies. The first author (PS) produced a narrative synthesis of the data for further development through a circular process of discussions, drafts, and edits among our author team.

Results

Sixty-one documents met the inclusion criteria (see Figure 2). Through the structured work to scope the literature, we retrieved studies with a variety of objectives, methods, and findings. The majority of the documents focused on neuroanatomy, the diagnosis of ACC, and the outcomes associated with a prenatal diagnosis of ACC. The included documents were summarised in an evidence table available online as a supplementary file (Table S2). We present the findings relevant to inform nursing practice about the prenatal diagnosis of ACC within the themes of *Prenatal Diagnosis*, *Neuroanatomy*, *Additional Anomalies and Causes of ACC*, *Neurodevelopment After a Prenatal Diagnosis*, and *Recommendations for Care*. Before presenting these themes, the first and most significant theme of this scoping review was the *Ambiguous ACC Terminology* related to the terminology used within the ACC literature.

Ambiguous ACC Terminology

We identified ambiguity within the terminology of ACC. A range of terms described atypicalities of the CC, including agenesis, hypoplasia, hypogenesis, dysplasia, hyperplasia, malformation, and dysgenesis. These terms overlapped, such as dsygenesis defined as a partial absence and known as hypogenesis (Alby et al., 2016), and partial ACC diagnosed when a segment of the CC was missing (Shen et al., 2015), see Figure 1. The terms were also used to describe conflicting presentations, exemplified by the use of dysgenesis to refer to the absence of at least one part of the structure (Turkyilmaz et al., 2019) and also used to refer to a CC that was entirely present, but malformed (Santirocco et al., 2019).

Within most of the studies, the authors described the distinction between an isolated and non-isolated presentation of ACC as the most important determinant for prenatal counseling. However, the inclusions and exclusions within the definition of an isolated diagnosis varied. A common definition used to describe isolated ACC was when the CC anomaly occurred without other identified anomalies. The determination of what counted as an additional anomaly was inconsistent, and therefore the definition of an isolated diagnosis was inconsistent.

Some authors explained that dilation of the lateral ventricles was not an additional anomaly and was included within the definition of isolated ACC (Ballardini et al., 2018; Bell et al., 2015; Cignini et al., 2010; de Wit et al., 2017; Griffiths et al., 2017; Kim et al., 2017; Li et al., 2012; Masmejan et al., 2019; Szabo, et al., 2011; Yeh et al., 2018). This definition was not universal as some researchers defined dilated ventricles as an additional finding (Ghi et al., 2010; Jarre et al., 2017; Ozyuncu et al., 2014). In other studies, ventricular dilation over 15mm (D'Antonio et al., 2016; Mangione et al., 2011; Santirocco et al., 2019) or over 20mm

(Folliot-Le Doussal et al., 2018) were excluded from the isolated ACC definition.

Dilation of the lateral ventricles was termed ventriculomegaly, colpocephaly, and as colpocephalic ventriculomegaly. Ventriculomegaly and colpocephaly, when defined, did differ, although it appeared that often one of the two was adopted to refer to any dilation of the lateral ventricles. While most authors that did offer a definition considered ventriculomegaly to be a dilation over 10mm, Noguchi, et al. (2014) defined this to be a measurement over 12mm. Asymmetric dilation of the ventricles, where one lateral ventricle was significantly larger than the other was described within a particular triad presentation of ACC; asymmetric ventriculomegaly, interhemispheric cyst and callosal dysgenesis (Oh et al., 2019; Oh et al., 2012).

Other neuroanatomical differences that commonly occur alongside ACC and the dilation of the ventricles include changes to the cavum septum pellucidum (CSP), a raised third ventricle, a rounded hippocampus, changes to the other commissures and the lack of a clearly defined cingulate gyrus (Raybaud et al., 2010). These anomalies were inconsistently included or excluded within the definition of an isolated diagnosis, at times mentioned but more often implied through the results, while for many studies, the interpretation of these anomalies remained unclear. Interhemispheric cysts were a further neuroanatomical finding both included within the isolated definition (de Wit et al., 2017; Folliot-Le Doussal et al., 2018; Masmejan et al., 2019) and reported as an additional anomaly (Bell et al., 2015; Santirocco et al., 2019; Yeh et al., 2018).

Beyond the variances within the interpretation of the other neuroanatomical differences that present commonly with ACC, the presence of a genetic finding was both excluded from the isolated diagnosis (Bell et al., 2015; Cignini et al., 2010; D'Antonio et al., 2016; des Portes et al., 2018; de Wit et al., 2017; Folliot-Le Doussal et al., 2018; Li et al., 2012; Mangione et al., 2011; Sotiriadis & Makrydimas, 2012), included (Alby et al., 2016), and not stated. Several authors did not specifically define an isolated diagnosis of ACC, and the inclusions were only implied through the discussion of cases (Contro et al., 2015; Ghi et al., 2010; Leombroni et al., 2018; Santirocco et al., 2019; Turkyilmaz et al., 2019). According to the authors of one study, the typical changes in cortical folding suggests that ACC cannot be considered isolated in the pure sense of the word (Tarui et al., 2018).

The Prenatal Diagnosis

The prevalence of ACC, from 2.05 to 3.3 per 10,000 live births, drew from congenital malformation registries and a retrospective survey. Over the study period from 1981–2015, Ballardini et al. (2018) calculated the prevalence of ACC in Emilio-Romagna, Italy, to be 2.49 in 10,000, as determined by a population-based registry and referenced from 1,023,784 live births. The prevalence rose to 3.3 in 10,000, when calculated from 1996, the time when records of terminations began to be collected. Stoll et al., (2019) calculated the prevalence of ACC within and around Strasbourg, France, to be 2.56 per 10,000, drawing from 387,067 consecutive pregnancies through their 11 hospital network. Szabo et al. (2011) sent questionaries to pediatricians in the south-eastern region of Hungary for a retrospective survey of children born with ACC from records between 1992 and 2006. Based on the reference of 185,486 live births, there were 38 children born with ACC, 2.05 per 10,000 live births.

The retrospective design of the three prevalence studies presents a limitation, and the prevalence is likely an underestimate based upon the challenge to detect ACC through standard screening. The review of a decade of ACC diagnosis demonstrated this challenge to detect ACC, with the finding that mid-gestation ultrasound screening did not identify ACC in 12/43 (26%) of fetuses and for those fetuses, an extra, non-routine ultrasound that occurred for a separate indication led to the ACC diagnosis (Bell et al., 2015). The potential for there to be additional undiagnosed cases of ACC among those who did not undergo a non-routine third-trimester ultrasound is significant, particularly within historical prevalence studies. There was an increased rate of prenatal diagnosis from 1981 to 2015 to the advancements in prenatal screening technology and knowledge (Ballardini et al. 2018).

The earliest gestational age of an ACC diagnosis was 17 weeks for a fetus with non-isolated ACC (Kim et al., 2017). The latest age at identification was 38 weeks (Li et al., 2012) and the termination of pregnancy occurred up to 38 weeks as reported in a study based in Israel (Kidron et al., 2016). ACC was often suspected based on the indirect findings of ventriculomegaly or an absent cavum septum pellucidum (Bayram et al., 2020; des Portes et al., 2018; Kim et al., 2017; Moutard et al., 2012; Sotiriadis & Makrydimas, 2012; Szabo et al., 2011; Vasudevan et al., 2012).

Findings within many studies demonstrated discrepancies between the prenatal and postnatal or post-mortem diagnoses (Bell et al., 2015; Craven, Bradburn, & Griffiths, 2015; Griffiths et al., 2017; Huras et al., 2017; Jarre et al., 2017; Min, A & Zou, L., 2020; Santirocco et al., 2019). This discrepancy may relate to the technology, method of diagnosis, or the experience of the diagnostician (Cignini et al., 2010). Discrepancies may also relate to the timing of the ultrasound or magnetic resonance imaging (MRI) due to the tendency for the lateral ventricles to expand as time progresses (Masmejan et al., 2019), and as some anomalies may only be identified in the late gestation, such as cortical malformations (Griffiths et al., 2017).

Griffiths et al. (2017) reported that termination was offered to 21 parents based upon the ultrasound results alone and that this option was retracted in five cases after fetal MRI (fMRI) refuted the ACC diagnosis. The false-positive diagnosis of ACC by ultrasound was described in three studies where fMRI ruled out the anomaly in 1/11 (Huras et al., 2017), 28/78 (Jarre et al., 2017) and 15/42 (Min, et al. 2020). A further ultrasound accuracy study that utilized post-mortem, fMRI, and postnatal imaging as references, found that 54 postmortems confirmed ACC within 46 fetuses, two fetuses had a typically developed CC, and the final six were inconclusive (Santirocco et al., 2019). Together these studies highlight the potential consequence of a later gestation termination due to the misdiagnosis of ACC.

The search for an earlier diagnosis was undertaken and included the assessment of the visualization of the pericallosal artery (Diaz-Guerrero et al., 2013; Kalayci et al., 2018) and of the midbrain and flax diameters as potential early markers of ACC (Kalayci et al., 2018; Lachmann et al., 2013). However, a premature diagnosis of partial ACC was cautioned given the rate of misdiagnosis and the subsequent psychological burden (Min, et al. 2020).

Neuroanatomy, Additional Anomalies and Causes of ACC.

The authors of two studies sought to assess the presence of the other commissures within samples of fetuses with isolated complete ACC. Cesaretti et al. (2016) grouped 62 fetuses based upon their anterior and hippocampal commissures, while Contro et al. (2015) focused specifically on the hippocampal commissure within 41 fetuses. Within both studies, authors proposed that the variances identified within the other commissures may account for variances within neurodevelopmental outcomes of people with ACC, with the acknowledgment that their studies did not assess outcomes.

The quantified difference within the hippocampus of fetuses who presented with "so called isolated" (p.576) (n=31), non-isolated ACC (n=15) and typically developing controls (n=39) was explored retrospectively (Knezovic et al, 2019). The results showed that the volume of the hippocampus was reduced within both ACC groups in the second and third-trimesters compared to the age-matched controls. The authors' proposed that the growth and elongation of the CC fibres may be influenced by abnormal hippocampal development. Research into the clinical relevance of this finding was recommended.

The presentation of ventriculomegaly within 135 fetuses with ACC reviewed retrospectively, identified that ventriculomegaly was present in 85%, with no statistical difference noted within isolated or non-isolated cases, or between agenesis, hypoplasia or dysplasia groups (Masmejan et al., 2019). Within the 79 fetuses that underwent repeated assessment, the biparietal diameter of the lateral ventricles increased at the mean rate of 2.9mm per week, proportional to head growth (Masmejan et al., 2019). The findings of three studies undertaken to compare mid and late gestational assessments of ACC showed a higher proportion of fetuses had concurrent ventriculomegaly later in the gestational period (de Wit et al., 2017; Masmejan et al., 2019; Paladini et al., 2013). The frequency of ventriculomegaly or colpocephaly led several authors to suggest that the presence of dilated ventricles is unlikely to alter the prognosis when alongside ACC (Bayram et al., 2020; Li et al., 2012; Masmejan et al., 2019; Noguchi et al., 2014). When ventriculomegaly was specifically assessed as a variable there were no significant differences in the neurodevelopment between children with or without ventriculomegaly (Yeh et al., 2018).

The CSP is an interhemispheric space in the developing brain that usually disappears by three months of age, leaving the septum pellucidum (Raybaud, 2010). The presentation of the CSP is dependent on the development of the anterior portion of the CC (Raybaud, 2010), and hence termed a "significant bystander" (p.250) within ACC (Manganaro et al., 2017). However, as discussed, an anomaly of the CSP was another neuroanatomical feature that reported within, and at times out of the isolated diagnosis of ACC. The authors of three studies specifically examined the CSP within fetuses with partial ACC, and concluded that the atypical presentation of the CSP might be considered an indirect sign of partial ACC (Karl et al., 2017; Shen et al., 2015; Zhao, Wang, & Cai, 2019). Griffiths et al., (2009) reflected on their experience and embryology and concluded that displacement or abnormality of the septum pellucidum was typical of ACC, as opposed to an absence, again suggestive of differences in interpretation.

Like the varied interpretation and reports of the CSP and ventriculomegaly, there were varied interpretations of delayed sulcation, the patterns of cortical folding. Delayed sulcation identified in the third-trimester might represent the altered brain development within ACC rather than an additional malformation (Warren et al., 2010). Frequently identified, the differences in cortical folding alongside ACC was also considered to be aberrant rather than delayed (Tarui et al., 2018). No significant differences in the neurodevelopmental outcomes were found when ACC was associated with or without gyration and migration atypicality (Yeh et al., 2018).

Diffusion tensor imaging was used to map the neural connectivity within two studies of 20 fetuses with ACC and control groups (Jakab et al., 2015); Kasprian et al., 2013). Diffusion tensor imaging is a probabilistic and reliable approach to reconstruct neural fibers to track the structural connections within the brain (Tsai, 2018). A marked difference between ACC and typical brains, which included both over-and-under connectivity in varied areas indicated that connectivity in ACC was genetically determined rather than a postnatal experience of compensation (Jakab et al., 2015).

Beyond the blurred understanding of the other common neuroanatomical differences within fetuses with ACC, authors explored many other intracranial and extracranial anomalies. Stoll et al. (2019) found that 73/99 (73.3%) prenatally diagnosed cases of ACC from a population-based registry also had associated anomalies, with the most common being chromosomal conditions, other CNS anomalies, musculoskeletal and congenital heart anomalies. The retrospective records obtained between 1979 and 2007, created a potential bias towards the identification of complex presentations of ACC. Other researchers also identified musculoskeletal anomalies and congenital heart disease as the most common additional anomalies (Balladini, et al, 2018; Bayram et al, 2020).

A study of 2238 consecutive autopsies over three years reported the finding of syndromes within 80% of the 20 fetuses with ACC (Kitova et al., 2014). As an autopsy study, the potential exists for termination rates to be higher among fetuses with more complex presentations, and cannot be considered representative. Nonetheless, a range of syndromes were reported within the studies including and not limited to, trisomy 13, 18 and 21 (Ballardini et al., 2018), trisomy 8 (Cignini et al., 2010), Mowat Wilson (de Wit et al., 2017), Goldenhar and Meckle Gruber syndromes (Oh et al., 2019).

The etiology of ACC is often difficult to identify. Within a further autopsy study, researchers utilized imaging, karyotyping, chromosomal microarray analysis, and fetopathological examination, and identified an underlying etiology in 46/138 fetuses (33.3%) which included 23 chromosomal abnormalities, 21 Mendelian conditions, and two teratogenic causes, maternal diabetes, and cytomegalovirus infection (Alby et al., 2016). A further maternal infection with *T pallidum* was suspected to be causal in one case (Manfredi et al. 2010). One case of apparently isolated ACC at the prenatal diagnosis was later changed to non-isolated ACC related to fetal alcohol spectrum disorder (Moutard et al., 2012).

Chromosomal microarray led to the determination of an underlying genetic eitiology for 1/8 (12.5) fetuses with ACC (Turkyilmaz et al., 2019) and 2/16 (12.5%) of fetuses with isolated ACC (She et al., 2019). Postnatal exome sequencing identified a monogenic disorder within 2/4 children with intellectual disability with or without other anomalies alongside their ACC (de Wit et al., 2017). While the yield from genetic and genomic testing remains limited in ACC, the future application of whole exome or whole genome sequencing in the prenatal period may provide further diagnostic information (Alby et al., 2016; de Wit et al., 2017; Leombroni et al., 2018; Oh et al., 2019; Palmer & Mowat, 2014).

Neurodevelopment After a Prenatal Diagnosis

Most outcome studies included reports of neurodevelopmental findings with a distinction between an isolated or non-isolated phenotype of ACC. Despite the distinction, both groups presented with a range of outcomes from typical development through to severe disability or neonatal death, see Table S3. Isolated ACC, when drawn from prenatally diagnosed samples, was associated with typical neurodevelopment or mild disability in 71.42% to 100% of participants, and moderate to severe disability in zero to 19.2%. Of note, the figure of 71.42% related to participants with an average or higher IQ rather than the inclusion of mild disability also (D'Antonio et al., 2016). Szabo et al. (2011) reported the neurodevelopmental outcomes of a mixed group of prenatally and postnatally diagnosed children and demonstrated a greater incidence of intellectual disability than the other studies, which may be a consequence of postnatal clinical sampling.

Non-isolated ACC was associated with typical neurodevelopment or mild disability in 39.2% to 66.7% of participants, and moderate to severe disability occurred within between 19.4% and 91.6% of participants. The interpretation of the neurodevelopmental results requires caution due to the differences within the definitions of an isolated or non-isolated diagnosis, along with different categorizations of disability, inclusion criteria, diagnostic procedures, neurodevelopmental assessment, and variances within reporting. The age of the participants within the neurodevelopment outcome studies ranged from infancy to 22 years of age. While a broad age range, the more prevalent earlier assessments may not capture the learning or social difficulties that may present with development (Folliot-Le Doussal et al., 2018). Although assessments of younger children may highlight delays in children who would potentially catch up later (Yeh et al., 2018).

The outcomes varied greatly, even within similar presentations of ACC (Yeh et al., 2018). Potential confounders for development, such as access to early intervention, supported education, maternal mental health, socioeconomic factors, or family history, were not explored within the studies other than within one study where the intelligence of children with ACC was related to maternal IQ (Moutard et al., 2012). As a collective the studies were limited by small sample sizes which included marked reductions in cases from recruitment to reported outcomes due to termination and high loss to follow-up. An exemplar identified 56 cases prenatally, lost 78.5% to follow-up, and a further two underwent termination, leaving only ten fetuses with reported outcomes (Kim et al., 2017).

Recommendations for Care

There were no specific recommendations for nursing practice within the studies. Diagnostic recommendations included the referral to a multidisciplinary expert team (Leombroni et al., 2018; Palmer & Mowat, 2014; Vasudevan et al., 2012). The management protocol of a fetal medicine unit included appointments with the senior sonologist, senior obstetrician, senior neonatologist, and a social worker, with potential appointments with a consultant psychiatrist and a clinical geneticist if indicated (Bell et al., 2015). The tabled protocol, along with a single comment within a review paper by Palmer and Mowat (2014), suggested linking prospective parents with family support organizations. ---- **CALL OUT 2--**

A prenatal management flow chart recommended a detailed neurosonographic assessment within a center with expertise, to offer invasive genetic testing and an fMRI, and included prognostic information related to either isolated or non-isolated diagnoses to guide prenatal counseling, without the provision of a definition of an isolated diagnosis (Leombroni et al., 2018. For non-isolated ACC, Leombroni et al. (2018) reported the prognosis to be determined based upon the other anomalies or any cause identified.

A frequently recommended investigation was fMRI, with suggestions that a further later fMRI may be of value to assess the cortical development (D’Antonio et al., 2016; Griffiths et al., 2017; Leombroni et al., 2018; Manganaro et al., 2017; Tang et al., 2009). A portion of women may decline fMRI due to concerns of safety, claustrophobia, or the consideration that results may not alter their decision making (Bell et al., 2015). Several authors indicated that fMRI occurred after parents declined termination or when parents were unsure. However, the false-positive ultrasound diagnoses highlights the value of fMRI before decision-making. The limitations to the efficacy of diagnostic tests underlined recommendations to ensure that the prospective parents were aware that further anomalies might present after birth (Bell et al., 2015).

Recommended genetic testing included karyotyping and microarray (She et al., 2019) along with potential exome sequencing when a cause was not yet identified (de Wit et al., 2017). Postnatal recommendations included an assessment by a geneticist and a follow-up MRI, along with close ongoing monitoring for neuropsychological disorders (Leombroni et al., 2018). Monitoring past school age and referrals to early intervention were also encouraged (Folliot-Le Doussal et al., 2018; Moutard et al., 2012).

Discussion

The findings from our scoping review revealed ACC as a complex and multidimensional diagnosis that is further complicated by inconsistencies within the nomenclature. While individual research and clinical teams may have a rationale for the terms they use, the inconsistent nomenclature of ACC may complicate the translation of research into evidence based practice for families. Different terms and overlapping definitions complicate literature searches and limit a meta-analysis of the studies. The use of different terms by different clinicians may increase the ambiguity experienced by parents who may interpret a change in terminology as a change in diagnosis or as inconsistent information.

The determination between isolated and non-isolated ACC was often described as a crucial factor for prenatal counseling. Despite the clinical importance of this distinction, we found that there was no universal definition of isolated ACC. This finding is significant as the lack of a clear definition of an isolated diagnosis complicates prognostic determination and the information provided to parents. A clinical team that considers ventriculomegaly or an anomaly of the CSP to be additional findings and hence exclude a diagnosis of isolated ACC is likely to offer different prenatal counseling than clinicians who include these within the definition of an isolated ACC. The differences in prognostic information may affect the amount of distress experienced by the parents or potentially affect their decision making related to the continuation or termination of their pregnancies given the higher incidence of termination related to a non-isolated diagnosis of ACC (Bayram et al., 2020). The lack of a unified definition of an isolated ACC diagnosis must also be considered when interpreting outcome studies and diagnostic efficacy studies.

While nurses and midwives may not be responsible for prognostic or genetic counseling, they may help parents navigate information sources, develop further understanding and support their well-being. Therefore, awareness of the inconsistent terminology is required. For many parents, seeking information about their fetus' anomaly functions as a coping mechanism (Hodgson & McClaren, 2018). Qualitative researchers who explored the experience of a prenatal diagnosis of a range of anomalies found that parents often use the internet to seek this information (Bratt et al., 2015; Hedrick, 2005). The ambiguity within the ACC terminology is likely reflected in the information that parents find. Sources that have been critiqued and clarified by health professionals could be offered to parents (Hedrick, 2005).

The American College of Obstetricians and Gynecologists (2018) recommended that all women undergo screening for perinatal anxiety and depression using a validated measurement scale at least once during their pregnancies. Due to the ambiguity and later in gestation diagnosis of ACC, parents who receive this fetal diagnosis may require additional screening and subsequent linkage to appropriate supports. Routine nurse-led postnatal screening for parents of newborns with a prenatally diagnosed anomaly cared for in the NICU can identify mothers and fathers at risk of traumatic stress and major depression (Cole et al., 2018). While not all newborns with ACC will require NICU care, postnatal mental health screening and psychosocial support may be considered an aspect of holistic care.

We found two papers in which authors recommended linking parents with family support organizations (Bell et al., 2015; Palmer & Mowat, 2014). Meaningful insights and non-medical information were sought by parents who received a prenatal diagnosis of a range of anomalies (Bratt et al., 2015). However, we identified the literature related to the prenatal diagnosis of ACC is predominantly focused on the presentation of ACC or neurodevelopmental focused prognosis rather than lived experience and non-medical related information. The link to support groups may provide other meaningful information that cannot be sought from the current available literature. However, peer support groups may potentially attract families who require a greater amount of support and may not be appropriate for or appreciated by all parents (Hodgson & McClaren, 2018). Practice must always remain person-centered and hence, adapted to the needs and wishes of the parents.

The specific effect of mental health screening, linkages with appropriate supports such as perinatal mental health practitioners, and the effect of engagement within patient support groups have not been explored in the context of the prenatal diagnosis of ACC. The paucity of literature related to parents' experiences of receiving a prenatal diagnosis of ACC and evidence to inform nursing care highlights the need for further research. We encourage nurses and midwives to maintain awareness of the ambiguity within the prenatal diagnosis of ACC and the potential effect on the experience of the continued or ended pregnancy, postnatal transitions, parenting, and any subsequent pregnancies.

Limitations

Our scoping review had several limitations. A single author undertook the search, article eligibility screening, and charting. Scoping review methodology that guided our systematic exploration and mapping of evidence does not require critical appraisal or weighting of the evidence (Arksey & O'Malley, 2005; Tricco et al., 2018), hence, the weight of the current evidence cannot be inferred. Terms related to nursing practice were excluded during our search as their inclusion would have limited the scope of the results.

Conclusion

ACC is heterogeneous in presentation, etiology, and prognosis. We identified that there are differences in nomenclature and the definition of isolated or non-isolated ACC within the literature which complicate the translation of research findings into evidence based practice. Small sample sizes, various diagnostic procedures, and neurodevelopmental measurements, along with large numbers of termination of pregnancies or participants lost to follow up, limited the interpretation of outcome studies and the meaning offered by a prenatal diagnosis of ACC. Further research is needed to identify the genotypes and phenotypes within ACC and to determine distinct features of an isolated or non-isolated presentation of ACC to assist with prenatal counseling. **----- CALL OUT 3-------**

The ambiguity and timing of the diagnosis in the second and third trimesters means the prenatal identification of ACC presents a risk to parent antenatal mental health and, therefore, a potential confounding risk factor for the neurodevelopmental outcomes of the child. Despite this risk and the prevalence of ACC, there is a gap in the literature that specifically explored the parents' experience of receiving a prenatal diagnosis of ACC or that provided strategies to support prospective or new parents. Nurses and midwives are well-positioned to assess, monitor, and support parents and to drive research that focuses on the psychosocial aspects of the prenatal diagnosis of ACC and its aftermath.

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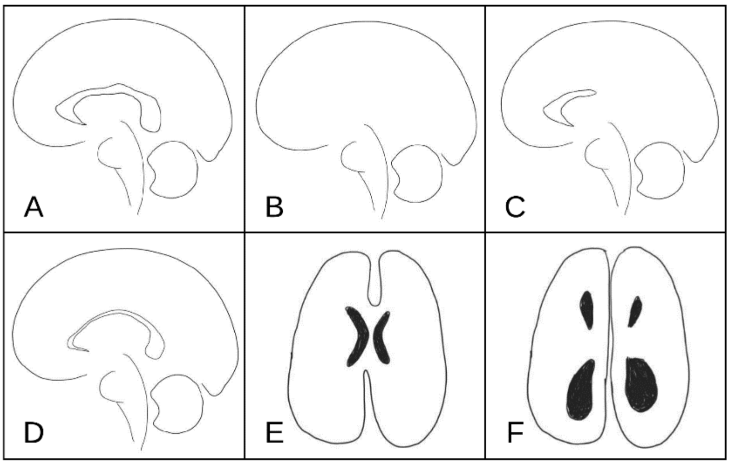
Tables and figures

Table 1. Search strings, databases and the number of abstracts retrieved.

Database	**Search string**	**Search 1**	**Search 2**	**Search 3**
MEDLINE Complete	Corpus callosum OR (MH “Corpus Callosum”) OR (MH “Agenesis of Corpus Callosum”) [Select a Field (optional)] AND (agenesis OR dysgenesis OR hypoplas* OR malform* OR disorder OR hypogenesis) [Select a Field (optional)] AND prenatal or (MH “prenatal diagnosis”) OR antenatal OR pregnan* OR (MH “Pregnancy”) OR fetus OR (MH “Fetus”) OR fetal [Select a Field (optional)]	442	27	42
CINAHL Complete	Corpus callosum OR (MH “Agenesis of Corpus Callosum”) [Select a Field (optional)] AND (agenesis OR dysgenesis OR hypoplas* OR malform* OR disorder OR hypogenesis [Select a Field (optional)] AND prenatal or (MH “prenatal diagnosis”) OR antenatal OR pregnan* OR (MH “Pregnancy”) OR (MH ”Fetus”) OR fetal [Select a Field (optional)]	118	17	6

PsychINFO	Corpus callosum OR DE "Corpus Callosum" [Select a Field (optional)] AND DE "Agenesis" OR agenesis OR dysgenesis OR hypoplas* OR malform* OR disorder OR hypogenesis [Select a Field (optional)] AND prenatal or DE "Prenatal care" OR antenatal OR pregnan* OR DE "Fetus" OR fetal [Select a Field (optional)]	93	1	3
Academic Search Complete	Corpus callosum [Select a Field (optional)] AND agenesis OR dysgenesis OR hypoplas* OR malform* OR disorder OR hypogenesis [Select a Field (optional)] AND prenatal OR antenatal OR pregnan* OR fetus OR fetal [Select a Field (optional)]	249	36	22
Total documents retrieved and exported to Endnote		902	81	73
Additional documents reviewed from hand searching included documents		11		0
Total documents retrieved		1067		

Figure 1. Diagram depicting neuroanatomical atypicality of the corpus callosum



A – D Sagittal view, A: Typical corpus callosum, B: complete agenesis, C: partial agenesis/ dysgenesis/ hypogenesis, D: HCC/ dsygenesis/ hypogenesis, E & F Axial view, E: Lateral ventricles with typical corpus callosum development, F: Dilated lateral ventricles that may occur with ACC.

Figure 2. PRISMA flow diagram

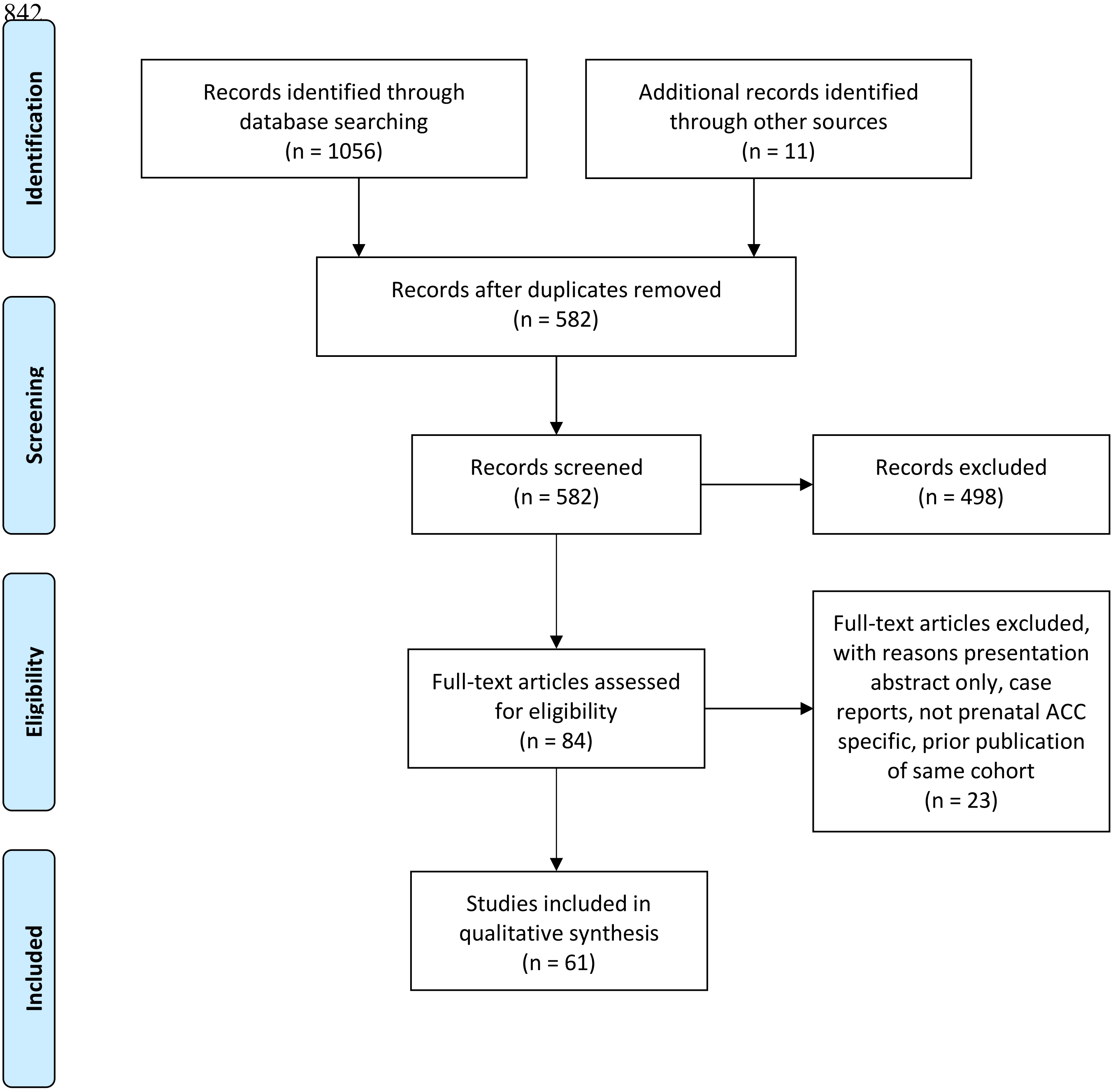


Table S2. Summary of Documents Included in This Scoping Review

Authors and year	**Country**	**Aim**	**Design**	**Sample (*n*)**
Alby et al., 2016	France	Neuropathological review of fetuses with a corpus callosum malformation	Retrospective case series	Fetuses (138): total ACC (53), partial ACC (2), abnormal size of CC (30), dysmorphic CC, including hump shape or cyst (4), malformation associated with cortical maldevelopment (29)
Ballardini et al., 2018	Italy	Prevalence study based on a population congenital malformations registry	Retrospective records review	Review of the Emilia-Romagna Registry on Congenital Malformations to identify ACC or hypoplasia of the CC in a reference population of 1,023,784 live births
Bayram et al., 2020	Turkey	Provide an assessment of fetuses with complete ACC and report outcomes	Retrospective record review and prospective neurodevelopment assessment	Fetuses (109): isolated complete ACC 44), complex complete ACC (65). Neurodevelopmental outcomes reported for 56 of the 60 living cases.
Bell et al., 2015	Australia	Assess diagnostic efficacy of ultrasound and MRI	Retrospective case series	Cases with prenatally diagnosed callosal anomalies that were complex or isolated (43)
Cesaretti et al., 2016	Italy	Describe the forebrain commissures in a sample with apparently isolated ACC	Retrospective case series	Cases of apparently isolated ACC (62)
Cignini et al., 2010	France	Assess the value of a dedicated neurosonographer in diagnosis in	Prospective case series	Cases of isolated cACC (13)

		isolated ACC and report postnatal outcome		
Contro et al., 2015	Italy	Assess the hippocampal commissure in fetuses with isolated cACC	Retrospective case series	Fetuses with isolated cACC (41)
Craven et al., 2015	United Kingdom	Assess diagnostic efficacy of ultrasound	Retrospective case series	Fetuses with ACC (122)
D'Antonio et al., 2016	Italy	Determine the outcomes associated with isolated cACC and isolated pACC	Meta-analysis	Included studies (27) with samples from three to 127 fetuses
de Wit et al., 2017	The Netherlands	Assess the value of single nucleotide polymorphism array and exome sequencing in the prenatal diagnosis of isolated ACC	Retrospective retrieved case series	Fetuses with apparently isolated cACC (25)
des Portes et al., 2018	France	Assess the neurodevelopmental outcomes after prenatal diagnosis of isolated ACC	Prospective longitudinal case series	Fetuses with apparently isolated cACC or pACC (50)
Diaz-Guerrero et al., 2013	Venezuela	Determine the relevance of the pericallosal artery for the early suspicion of ACC	Prospective longitudinal case series	Consecutive high-risk fetuses (150)
Folliot-Le Doussal et al., 2018	France	Assess the long-term neurodevelopmental outcomes after prenatal diagnosis of isolated ACC	Retrospective retrieved case series	Children who had a prenatal diagnosis of isolated ACC (25)
Ghi et al., 2010	Italy	Describe sonographic findings related to CC hypoplasia and pACC	Retrospective case series	Fetuses (19): CC hypoplasia (5) and pACC (14)
Griffiths et al., 2009	United Kingdom	Discuss failed commissuration	Discussion	N/A

Griffiths et al., 2017	United Kingdom	Assess the value of fetal MRI after ultrasound diagnosis of ACC or hypogenesis	Subgroup analysis of larger MERIDIAN study	Fetuses (79): ACC (55) and hypogenesis (24)
Huras et al., 2017	Poland	Assess performance of second trimester ultrasound screening and compare pre and postnatal findings	Prospective observational study	Fetuses screened (3802): cACC (12) and pACC (2)
Jakab et al., 2015	Austria	Assess fibre connectivity and the connectome in fetuses with isolated ACC	Prospective case series	Fetuses with isolated ACC (20)
Jarre et al., 2017	Spain	Assess the value of fetal MRI after ultrasound suspicion of ACC	Retrospective case series	Fetuses with suspected ACC (78): cACC diagnosed (n=33), pACC diagnosed (n=12)
Kalayci et al., 2018	Turkey	Assess the visualization of the pericallosal artery as an early sign of ACC	Retrospective case series	Fetuses before 18 weeks (278), none had ACC
Karl et al., 2017	Germany	Measure the width and length of cavum septum pellucidum in fetuses with pACC and typically developing fetuses	Retrospective case controlled study	Typically developing fetuses (323) and fetuses with pACC (20)
Kasprian et al., 2013	Austria	Assess the feasibility of diffusion tensor imaging to assess connectivity and identify differences in the connectome	Prospective case controlled study	Fetuses with ACC (20): cACC (16), pACC (4), and 20 fetuses with typical development
Kidron et al., 2016	Israel	Evaluate the neuroanatomy and histopathological aspects of fetuses terminated due to ACC	Retrospective case series	Fetuses with ACC or CC hypoplasia (50)
Kim et al., 2017	Korea	Assess neurodevelopment after a prenatal diagnosis of ACC	Retrospective case series	Fetuses (56): isolated ACC (29), non-isolated (27)

Kitova et al., 2014	Tunisia	Examine the associated anomalies through autopsy	Case series	Fetuses (20)
Knezovic et al., 2019	Austria	Assess the size of the hippocampal commissure in fetuses with ACC and typically developing controls	Retrospective case controlled study	Fetuses (85): isolated ACC (31), non-isolated ACC (15), typically developing controls (39)
Lachmann et al., 2013	Germany	Describe ACC presentation in the first trimester	Retrospective case controlled study	Fetuses (515): ACC (15), typically developing controls (500)
Leombroni et al., 2018	Norway	Provide information for the prenatal diagnosis, counselling and management of ACC	Review	Search and included articles not described
Li et al., 2012	United States of America	Assess neurodevelopment after the prenatal diagnosis of ACC in fetuses referred for ventriculomegaly	Prospective case series, subgroup analysis	Fetuses diagnosed with ACC (58): isolated dysgenesis (15), dysgenesis with other anomalies (43)
Manfredi et al., 2010	Italy	Assess the value of MRI in the prenatal diagnosis of ACC with mild ventriculomegaly	Prospective case series	Fetuses (33): typical corpus callosum (20), cACC (8), CC hypogenesis (5)
Manganaro et al., 2017	Italy	Characterize presentations of isolated and non-isolated dysgenesis by MRI	Retrospective case series	Fetuses (104): isolated CC dysgenesis (28), CC dysgenesis with associated anomalies (76)
Mangione et al., 2011	France	Assess the value of ultrasound and MRI in the prenatal diagnosis and document outcomes	Prospective case controlled study	Fetuses with ACC live born (175): followed by (27), and 44 control fetuses with a typical CC
Masmejan et al., 2019	Canada	Assess size of the ventricles in fetuses with anomalies of the CC	Retrospective longitudinal case series	Fetuses (135)

Min, A. & Zou, 2020	China	Evaluate the utility of ultrasound and MRI technology for the diagnosis of ACC	Case-series	Fetuses with suspected ACC by ultrasound (42).
Moutard et al., 2012	France	Report the cognitive abilities of children with prenatally diagnosed isolated ACC after long follow-up	Prospective longitudinal case series	Children (17)
Noguchi et al., 2014	Japan	Assess the postnatal outcomes of prenatally diagnosed ACC with ventriculomegaly	Retrospective case series	Children (21): isolated ACC (10), ACC with associated anomalies (11)
Oh et al., 2019	United States of America	Report the neurodevelopmental outcomes for children with asymmetric ventriculomegaly, interhemispheric cyst, and dysgenesis of the corpus callosum	Retrospective case series	Fetuses (15): followed up (n=12)
Oh et al., 2012	United States of America	Present a series of cases with asymmetric ventriculomegaly, a large interhemispheric cyst, and partial or complete agenesis of the corpus callosum	Retrospective case series	Fetuses (20)
Ozyuncu et al., 2014	Turkey	Report prenatal signs of ACC and postnatal outcomes	Retrospective case series	Fetuses (33): cACC (18), pACC (15)
Paladini et al., 2013	Italy	Assess the indirect signs of ACC according to gestational age	Retrospective case series	Fetuses (54): cACC (31), pACC (23)
Palmer & Mowat, 2014	Australia	Guide the clinician in the prenatal and postnatal diagnosis of ACC	Review	Search and included articles not described
Pashaj et al., 2013	Germany	Determine quantitative reference ranges of the fetal CC	Prospective case series	Fetuses of an uncomplicated pregnancy (466)

Raybaud, 2010	Canada	Describe the embryology and disorders of the CC	Topic/ discussion article	N/A
Santirocco et al., 2019	Spain	Assess the accuracy of ultrasound in the prenatal diagnosis of CC alternations	Retrospective case series	Fetuses (86)
Santo et al., 2012	United Kingdom	Answer common questions about the prenatal diagnosis of ACC	Review	Documents published between 1988 and 2012 (26)
She et al., 2019	China	Explore genetic pathogenesis by microarray in isolated ACC	Case series	Fetuses (16)
Shen et al., 2015	France and Israel	Assess the cavum septum pellucidum in the prenatal diagnosis of pACC	Retrospective case series	Fetuses (71)
Shetty et al., 2015	India	Assess the *AKT3* gene in ACC	Case series	Fetuses with ACC (22): prenatal (10), postnatal (12)
Sotiriadis & Makrydimas, 2012	Greece	Review the literature for neurodevelopment after a prenatal diagnosis of ACC	Review	Documents published from 1990 – 2012 (16)
Stoll et al., 2019	France	Assess associated anomalies in cases of ACC in a population sample	Retrospective case series	Cases of ACC (99) in a population sample of 387,067 births
Szabo et al., 2011	Hungary	Describe the prevalence and clinical features of cases with ACC	Retrospective case series	Cases of ACC or CC hypoplasia (38) in a population sample of 185,486 live births
Tang et al., 2009	United States of America	Assess associated anomalies by MRI in prenatally diagnosed ACC and compare to postnatal outcome	Retrospective case series	Fetuses (29)
Tarui et al., 2018	United States of America	Assess the sulcal pattern folding in fetuses with isolated ACC	Case controlled study	Fetuses with isolated ACC (7) and typically developing controls (17)

Tsur et al., 2019	United States of America	Calculate and evaluate clinical ultrasound charts to reduce misdiagnosis of ACC	Retrospective case series	Fetuses (410)
Turkyilmaz et al., 2019	Turkey	Assess efficacy of neurosonography and MRI in the prenatal diagnosis and report outcomes	Retrospective case series	Fetuses (36): cACC (n=17), pACC (n=9) and dysgenesis of the CC (n=10)
Uccella et al., 2019	Italy and Canada	Describe the phenotype of agenesis of corpus callosum (ACC) and interhemispheric cysts associated with malformations of cortical development	Retrospective case series	Patients prenatally diagnosed (36)
Vasudevan et al., 2012	United Kingdom	Review literature of long-term outcomes and discuss	Review	Search and included documents not described
Warren et al., 2010	United Kingdom	Assess the presence of delayed sulcation in fetuses with isolated cACC	Retrospective case controlled study	Fetuses with isolated cACC (20) and aged-matched typically developing controls (20)
Yeh et al., 2018	Republic of Korea	Report neurodevelopment outcomes and associated anomalies after a prenatal diagnosis of CC abnormalities	Retrospective case series	Cases prenatally diagnosed (52)
Yin & Li, 2018	China	Discuss the value of the Omniview technique in the prenatal diagnosis of ACC	Case controlled study	Fetuses with ACC (8) and typically developing fetuses (43)
Zhao et al., 2019	China	Assess the value of prenatal indirect signs to detect pACC	Retrospective case controlled study	Fetuses with pACC (15) and typically developing fetuses (15)

Note. ACC= agenesis of the corpus callosum, CC= corpus callosum, cACC= complete agenesis of the corpus callosum, pACC= partial agenesis of the corpus callosum, MRI= magnetic resonance imaging

Table S2. Neurodevelopmental Outcomes Reported in the Included Documents

Authors and year	**Type of ACC (*n*) per Prenatal Diagnosis**	**Assessment and Age or Length of Follow-up**	**Neurodevelopment and Health Outcomes (*n*)**
Bayram, et al., 2020	Isolated cACC (44) and complex cACC (65	Wechsler Intelligence Scale for Children (4th edition) for children aged 6 and over Standford-Binet Intelligence Scale (4th edition) for children under 6 years of age Ankara Developmental Screening Inventory (4th edition) for children unable to complete Standford-Binet Intelligence Scale Participants age range 6 months to 8 years and 6 months.	Assessed with WISC-IV or SB-IV (n= 29): Normal ND in 48.1% (13/27) Borderline range in 7.4% (2/27) Mild ID in 29.6% (8/27) Moderate ID in 7.4% (2/27) Severe ID in 7.4% (2/27) Assessed with ADSI (n= 29) Normal ND in 58.7% (17/29) Mild DD in 10.3% (3/29) Moderate DD in 17.2% (5/29) Severe DD in 13.7% (4/29) Of the cases with isolated cACC: Normal ND in 79.4% Epilepsy present in 10.1% in complex cACC only Cerebral palsy in 6.4% in complex cACC only TOPFA (36/109), died in utero (2/109), died in postnatal period (11/109).
Cignini et al., 2010	Isolated cACC at prenatal (15)	Binet-Simon Scale revised from Standford Follow up for four years	Isolated cACC postnatally confirmed (13): Regular cognitive and psycho-motor development in 93% (14/15) Hypotonia and mild cognitive delay in 7% (1/15) TOPFA (1/15), lost to follow-up (1/15)
D'Antonio et al., 2016	Isolated cACC (53) and isolated pACC (23)	Meta-analysis of 27 studies	Isolated cACC (53): Normal ND in 76.0% Borderline/ moderate ND in 16.0% Severe ND outcome in 8.1% Isolated pACC (23):

			Normal ND in 71.4% Borderline/ moderate ND in 14.9% Severe ND outcome in 12.5%
de Wit et al., 2017	Isolated cACC on ulatrsound (25)	Clinical neurodevelopmental assessment (not named) Follow up range 9 – 98 months	Of all 25 cases: Intellectual disability in 28% (7/25) No intellectual disability in 40% (10/25) Lost to follow up (2), TOPFA (6) Of those with no cause identified: Postnatal confirmation of isolated ACC in 12.5% (2/16) Intellectual disability in 18.8% (3/16) No intellectual disability in 43.8 % (7/16)
des Portes et al., 2018	Isolated cACC (25) and pACC (25)	Wechsler Intelligence Scales at 3, 5 and 7 years	IQ > 85 with no learning difficulties in 47% (16/34) IQ > 85 with learning difficulties in 18% (6/34) IQ 70 – 84 with learning disabilities in 29% (10/34) IQ < 70, moderate to severe disability in 6% (2/34) TOPFA (12), death in utero (1), lost to follow up (3)
Folliot-Le Doussal et al., 2018	Isolated cACC (17), isolated pACC (5), isolated HCC (3)	Wechsler Intelligence Scales at 2 – 16 years	Normal ND in 36% (9/25) Mild disabilities in 52% (13/25) cACC (8/13), pACC (2/13), HCC (3/13) Moderate/ severe disabilities in 12% (3/25) cACC (3/3)
Ghi et al., 2010	Isolated and non-isolated pACC (14), HCC (5)	Non-standardised assessment Participants aged between 1 and 10 yo	From live born (10): Normal development in 40% (4/10) Motor motor development delay in 10% (1/10) Severe developmental delay and seizures in 10% (1/10) Mental delay in 10% (1/10) Unclear ND in 20% (2/10) Neonatal death in 10% (1/10) TOPFA (9)
Kim et al., 2017	Isolated ACC (29) & non-isolated ACC	Alberta Infant Motor Score, Activities of Daily Living evaluation and Denver Developmental Screening but not for all	Isolated ACC confirmed after delivery (9): Normal ND in 55.6% (5/9) Mild developmental delay in 22.2% (2/9)

	(27) suspected by ultrasound	children. Follow up until 3 yo	Moderate developmental delay in 22.2% (2/9) Non-isolated ACC confirmed after delivery (3): Cleft lip in 1/3 Holoprosencephaly in 2/3 ACC not confirmed after delivery (3), TOPFA (2), unknown (14), lost to follow up – suspected TOPFA (23), referred back to other clinic (7)
Leombroni et al., 2018			Reported adapted outcomes from the study by D'Antonio et al. (2016)
Li et al., 2012	Callosal dysgenesis with ventriculomegaly Isolated (14) and non-isolated (44)	Some children underwent Bayley Mental Scale (Mental Developmental Index) and Motor Scale (Psychomotor Development Index) at 1, 2 and 3 yo	Postnatally confirmed isolated colossal abnormality (12): Normal ND and mild resolved delays in 67% (8/12) Mild persistent delays in 8% (1/12) Moderate to severe delays in 25% (3/12) Postnatally confirmed non-isolated (31): Normal ND and mild resolved delays in 6.5% (2/31) Mild persistent delays in 19.4% (6/31) Moderate to severe delays in 61.3% (19/31) Neonatal death in 6.5% (2/31) Infants lost to followup 6.5% (2/31) TOPFA (14), lost to follow up prenatally (1)
Mangione et al., 2011	Apparently isolated ACC and isolated HCC (88)	CDI, Ireton's Child Developmental Inventory Follow up 30 – 74 months	Postnatally confirmed isolated ACC (22) and additional anomalies (4): Normal ND in 73.0% (19/26) Borderline ND in 7.7% (2/26) ND delay in 19.2% (5/26) TOPFA (60), excluded as age 14 months at assessment (1), intrauterine death (1)
Moutard et al., 2012	Isolated ACC (17)	Weschler Intelligence Scale for Children & Rey-Osterrieth Complex Figure Test Follow up for 10 years	Completed the follow up period (12): Diagnosed maternal fetal alaochol syndrome (1) Normal range intelligence in 73% (8/11) Borderline intelligence in 27% (3/11) FSIQ median 91 (range 73 – 124)

			Attention disorders in 33% (4/12) Slowness in 58% (7/12) Required rehab programs in 25% (3/12) Difficulties at school in 50% (6/12) Lost to follow up (5)
Noguchi et al., 2014	ACC with ventriculomegaly (21)	Kyodaisiki Developmental Schedule Follow up from 3 months to 8 years	Isolated ACC (9): Normal ND in 40% (4/9) Mild disabilitites in 40% (4/9) Moderate motor impairment in 10% 1/9) ACC with other CNS anomalies (6): Severe disabilities in 6 (100%) Infant death due to X-linked lissencephaly in 33% (2/6) ACC with extra-CNS anomalies (4): Neonatal and infant death in 75% (3/4) Severe disabilities in 25% (1/4) Lost to follow up (2)
Oh et al., 2019	Asymmetric ventriculomegaly, interhemispheric cyst, and callosal dysgenesis (AVID) (15)	Developmental quotient Participants were aged between 2 and 11 yo	Liveborn with AVID Triad (12): Neonatal death in 25% (3/12) Infant death in 8% (1/12) Mild and moderate delays in 17% (2/12) Moderate and severe delays in 17% (2/12) Profound delays in 33% (4/12) All required shunting, many required revisions TOPFA (3)
Szabo et al., 2011	ACC + HCC (38) [included both pre and postnatally diagnosed, clinically sampled cases]	Not specified Participants were aged between 1 and 14 yo	Isolated ACC/HCC (18): Developmental delay in 61% (11/18) Intellectual disability in 39% (7/18) Epilepsy in 50% (9/18) Non-isolated ACC/HCC (15): 93% intellectual disability in 93% (14/15) All had a developmental delay (16/16) Neonatal death due to syndrome (4), Child death (1)

Sotiriadis & Makrydimas, 2012	Isolated ACC (132) [review of cases from 16 studies]	Review of standardized and non-standardised	Normal ND outcome in 71.2% (94/132) Borderline or moderate disability in 13.6% (18/132) Severe disability in 15.2% (22/132)
Turkyilmaz et al., 2019	Prenatal MRI, Isolated and non-isolated: cACC (16), pACC (11), dysgenesis (9)	Ages & Stages Questionnaires, Third Edition Follow up 34 - 45 months	cACC group (10): Normal ND in 70% (7/10) Unclear in 10% (1/10) “Risky” ND in 20% (2/10) Isolated cACC group (8): Normal ND in 87.5% (7/8) Unclear in 12.5% (1/8) pACC group (4): ND delay in 50% (2/4) Normal ND in 25% (1/4) Unclear in 25% (1/4) Dysgenesis group (2): Both had other anomalies, both had a low ND score. TOPFA (18), neonatal death (1)
Uccella et al., 2019	ACC with interhemispheric cysts associated with malformations of cortical development (36) [32/36 diagnosed prenatally – 4 diagnosed postnatally]	Griffith’s Mental Developmental Scales-Extended and Revised for under 5 yo Wechsler scales and Leiter scales for over 5 yo Multidimensional Anxiety Scale for Children, and Children’s Depression Inventory. Participants aged between 7months – 22 yo	Global developmental delay in 66.6% (24/36) Borderline delay in 4.2% (1/36) Reassessment after 5yo (22): Normal cognition in 63.6% (14/22) Borderline cognition in 18% (4/22) Mild intellectual disability in 9% (2/22) Severe intellectual disability in 9% (2/22) Epilepsy diagnosed in 44.4% (16/36) Psychiatric comorbidities in 33.3% (12/36) Aicardi syndrome diagnosed in 16.6% (6/36) Death at 2yo (1)
Vasudevan et al., 2012	ACC		Narrative review of studies published before 2012

Yeh et al., 2018	Isolated ACC + HCC (16) and non-isolated ACC + HCC (33)	The Korean Infant and Child Development Test or Bayley Scales of Infant Development II. Follow up 10-60 months	Of the children that unwent assessment (40): Isolated ACC group (12): Normal development in 58% (7/12) No diagnosis of epilepsy, hearing or visual diasability Non-isolated ACC group (28) Normal development in 39.3% 11/28 Moderate to severe delay in 35.7% Epilepsy in 14.3% (4/28), hearing disability in 14.3% (4/28), visual disability in 3.6% (1/28)

Note. ACC= agenesis of the corpus callosum, cACC= complete agenesis of the corpus callosum, pACC= partial agenesis of the corpus callosum, HCC= hypoplasia of the corpus callosum, TOPFA= termination of pregnancy after fetal anomaly, ND = neurodevelopment, yo = years old.