Electroencephalography changes following fetal brain injury in intrauterine growth restriction

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Research report

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CONTENTS

LIST OF ABBREVIATIONS

IUGR	Intrauterine growth restriction
EEG	Electroencephalography
SGA	Small for gestational age
AGA	Appropriate for gestational age
GA	Gestational age
RMI	Relative macrocephalic index
AC	Abdominal circumference
EFW	Estimated fetal weight
PI	Pulsatility index
CPR	Cerebroplacental ratio
MCA	Middle cerebral artery
UA	Umbilical artery
CA1	Cornu ammonis 1
FA	Fractional anisotropy
MRI	Magnetic resonance imaging
fMRI	Functional magnetic resonance imaging

ABSTRACT

Intrauterine growth restriction (IUGR) is a pathological condition in which a fetus fails to reach its genetically determined growth potential. IUGR is associated with an increased risk of fetal brain injury and significant neurological morbidities, but the functional manifestations of these neural pathologies are still unclear. Electroencephalography (EEG) can be used to detect abnormalities in neural activity following IUGR-associated brain injury. Current evidence has demonstrated both white and grey matter disruption in IUGR brains, with delayed myelination, decreased neuronal count, impaired dendritic growth and reduced synapse formation. This has resulted in reduced brain volume and abnormal patterns of structural connectivity, and would be expected to translate into EEG abnormalities. Changes in evoked EEG potentials could include reduced amplitudes due to neuronal loss, longer latencies due to myelination deficits in white matter tracts, and polymorphic waveforms due to differential damage to tracts. Heterogeneity in EEG abnormalities is also expected as patterns of brain injury differ between early- and late-onset IUGR. Future studies should test these hypotheses to determine the specific EEG changes seen after growth restriction, and link them with the established pathophysiological mechanisms of IUGR-associated brain injury.

1. INTRODUCTION

Intrauterine growth restriction (IUGR) is a pathological condition in which a fetus fails to reach its genetically determined growth potential. While the causes of IUGR are multifactorial, the most common contributor is placental dysfunction. Placental insufficiency leads to chronic hypoxia, hypoglycaemia, and an altered endocrine balance in the fetus (Dieni & Rees, 2003; Malhotra et al., 2019; Miller et al., 2016). This in turn causes a reduction in fetal growth rate. IUGR is associated with significant perinatal mortality and morbidity, including neurological deficits (Malhotra et al., 2017; Miller et al., 2016; Sharma et al., 2016).

Recent studies have demonstrated that IUGR leads to brain injury and poor neurodevelopmental outcomes (Miller et al., 2016), but there is currently little research into how these neural pathologies manifest functionally, such as in electrophysiological abnormalities. This project is intended to support my supervisor's study of electroencephalography (EEG) changes in IUGR neonates. There are two primary aims. First, a literature review needs to be conducted to guide our hypotheses of how IUGR can lead to changes in neonatal EEG. Second, a preliminary scoping review needs to be performed on the demographic data from our cohort. This will help inform the direction and next steps for the larger project.

2. METHODS

2.1. Literature review

Published studies were accessed through the PubMed database. 65 papers were identified as suitable, but four of them were inaccessible. Relevant citations within the 61 selected papers were followed for a more comprehensive survey of the available literature.

2.2. Preliminary review of data

Data was previously collected by Dr Kimberley Whitehead and her research team. To screen for potentially growth-restricted neonates, the birth weight centile was determined according to sex-specific UK-WHO Neonatal and Infant Close Monitoring Growth Charts (Royal College of Paediatrics and Child Health, 2009). Traditionally, infants with birth weights < 10^{th} centile are classified as small-for-gestational-age (SGA), but the 2016 consensus set a more stringent threshold of < 3^{rd} centile to identify IUGR infants (Gordijn et al., 2016). Out of the 481 neonates in this study, 65 have a birth weight ≤ 9^{th} centile, and 26 have a birth weight ≤ 2^{nd} centile.

In the preliminary demographics data, two parameters are potentially significant: gestational age and head circumference. IUGR fetuses are more likely than their non-growth-restricted counterparts to be delivered preterm (Malhotra et al., 2019), and gestational age at delivery has been shown to be associated with adverse neurodevelopmental outcomes such as low habituation and social-interactive scores (Baschat, 2011). Baschat et al. (2009) also reported that gestational age is the primary determinant for cerebral palsy and an independent risk factor for global neurological delay. Besides, premature birth itself is associated with many clinical complications, so it is important to separate the effects of prematurity from those of growth restriction when evaluating the clinical outcomes of preterm IUGR infants.

Previous studies have indicated that the ratio of head circumference to body weight is a more meaningful measure than head circumference alone, as it reflects a

higher risk of neural maldevelopment (Harel et al., 1985; Leitner et al., 2007). Therefore, this ratio (termed ‘relative macrocephalic index’ or RMI in this report) was calculated for all neonates. Data was checked for normality by Shapiro-Wilk tests and visual assessment of distribution graphs. Spearman’s rank-order correlation test was used to determine the strength of association between RMI and PMA. The RMIs of SGA infants were then compared with those of appropriate-for-gestational-age (AGA) controls.

3. RESULTS

3.1. Definition and characteristics of IUGR

IUGR has been poorly defined in the literature thus far, with 11% of clinical studies failing to provide any definition (Fleiss et al., 2019). It is therefore crucial for future studies in this field to establish a meaningful criteria by which an IUGR cohort can be clearly defined.

3.1.1. Neonatal characteristics

The most consistently used characteristic in neonatal diagnosis of IUGR is a birth weight < 10th centile (Fleiss et al., 2019). However, this, along with its antenatal counterpart of fetal size, is inaccurate in itself, since some fetuses may be constitutionally small but healthy, while others that have been pathologically growth-restricted are still above the 10th centile cut-off (Bendix et al., 2020; Gordijn et al., 2018). This statistical definition therefore does not reflect the pathological condition, and many studies fail to make this distinction.

Attempts have been made to determine other neonatal parameters that may indicate IUGR and its adverse outcomes. IUGR infants have been reported to have a smaller head circumference than age-matched AGA controls (Padilla et al., 2010; Tolsa et al., 2004), and a head circumference at birth < 10th centile has been suggested as a contributory variable in defining growth restriction (Beune et al., 2018). However, not all IUGR infants may present with small head circumferences. In symmetric IUGR, both the brain and body are equally growth-restricted, but in asymmetric IUGR, there is preferential perfusion of the brain and therefore relative preservation of brain growth (Fleiss et al., 2019). This brain-sparing effect might initially aim to protect the brain, but it is followed by decompensation and neural injury (Hernandez-Andrade et al., 2012). In fact, brain-sparing is often associated with abnormal neurodevelopment (Figueras et al., 2011), and may reflect advanced IUGR rather than adequate fetal compensation for placental insufficiency. This theory is supported by a previous finding that higher RMI is correlated with more severe clinical outcomes in later gestational ages (Harel et al., 1985). Since

asymmetric IUGR accounts for 70-80% of IUGR cases in high-resource settings (Fleiss et al., 2019), the RMI (also referred to as 'cephalization index' in the literature) is likely to be more useful than absolute head circumference as an IUGR measure in this UK-based study.

3.1.2. Antenatal characteristics

Nevertheless, neonatal parameters alone are insufficient to diagnose IUGR. A recent consensus determined two sets of antenatal measurements for diagnosing early- (< 32 weeks) and late-onset (≥ 32 weeks) IUGR (Gordijn et al., 2016). Since the two time intervals are associated with different underlying causes and clinical consequences (Bendix et al., 2020; Miller et al., 2016), as will be discussed below, they should be studied separately.

Biometric measurements include abdominal circumference (AC) and estimated fetal weight (EFW), while Doppler measurements include pulsatility index (PI) in the umbilical artery and cerebroplacental ratio (CPR; the ratio between the PIs of the fetal middle cerebral artery and the umbilical artery).

Biometric measurements can only evaluate fetal size, which is unhelpful in distinguishing between early-onset IUGR and SGA infants when brain-sparing is not evident. However, Doppler measurements can assess the adequacy of blood supply to the fetus. Since most IUGR cases are caused by placental insufficiency, the umbilical artery (UA) Doppler can be used to detect abnormal placental function (Figueras & Gardosi, 2011; Khalil & Thilaganathan, 2017). An increased UA-PI or the absence or reversal of the end-diastolic flow suggests pathologically reduced placental perfusion, and is highly suggestive of IUGR (Gordijn et al., 2016; Khalil & Thilaganathan, 2017). Furthermore, abnormal UA Doppler has been found to be independently and significantly associated with the adverse perinatal outcomes mentioned above (Unterscheider et al., 2013). However, UA Doppler alone often fails to detect milder placental insufficiencies, which accounts for most late-onset and a few early-onset IUGR cases (Sharma et al., 2016). Therefore, the CPR is more useful for identifying IUGR cases where the only detectable cardiovascular abnormality is a redistribution of cardiac output to the cerebral circulation (Baschat,

2011; Khalil & Thilaganathan, 2017). Gestational age-specific reference ranges for the above Doppler parameters have been recently established (Ciobanu et al., 2019).

3.1.3. Summary

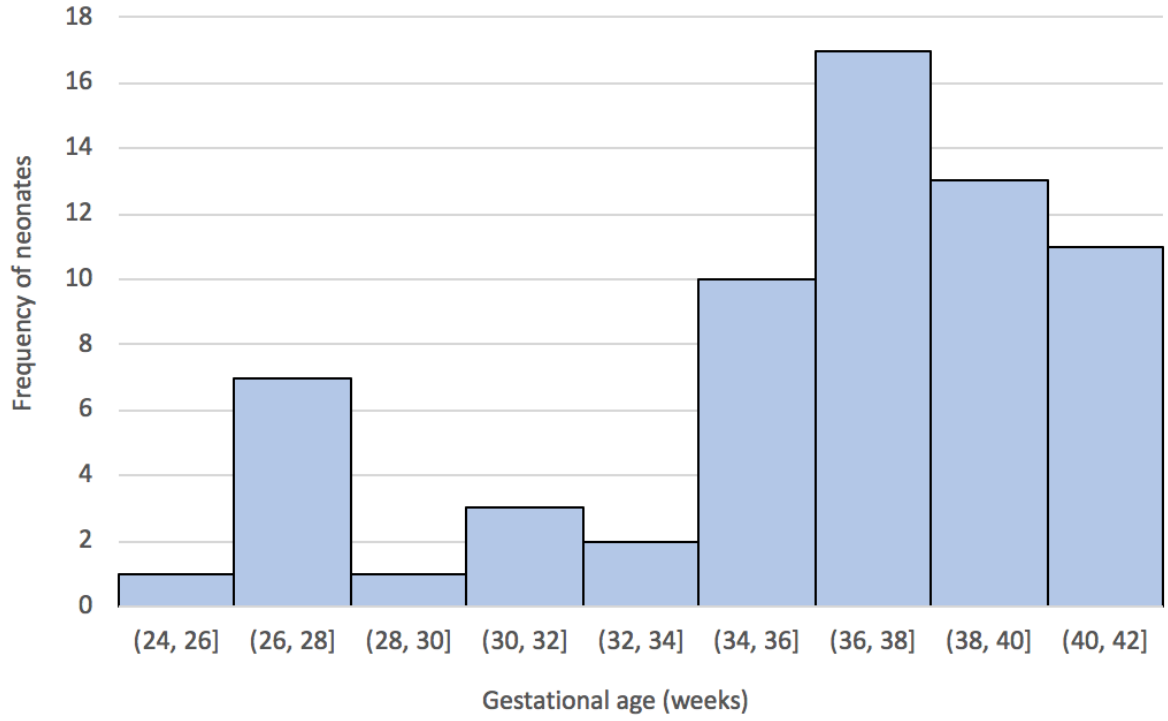
The 2016 consensus definition (Gordijn et al., 2016) is well-supported by current evidence and recommended for my supervisor's research project.

3.2. Demographics data

3.2.1. Gestational age

In our cohort, there is an asymmetric bimodal distribution of gestational ages amongst the SGA neonates (**Fig. 1**). The largest peak is centred around 38 weeks of gestation, indicating that most SGA neonates were delivered at term. However, there is a smaller peak at around 27 weeks of gestation, representing the fetuses that were at risk of severe, possibly fatal, growth restriction and therefore delivered early.

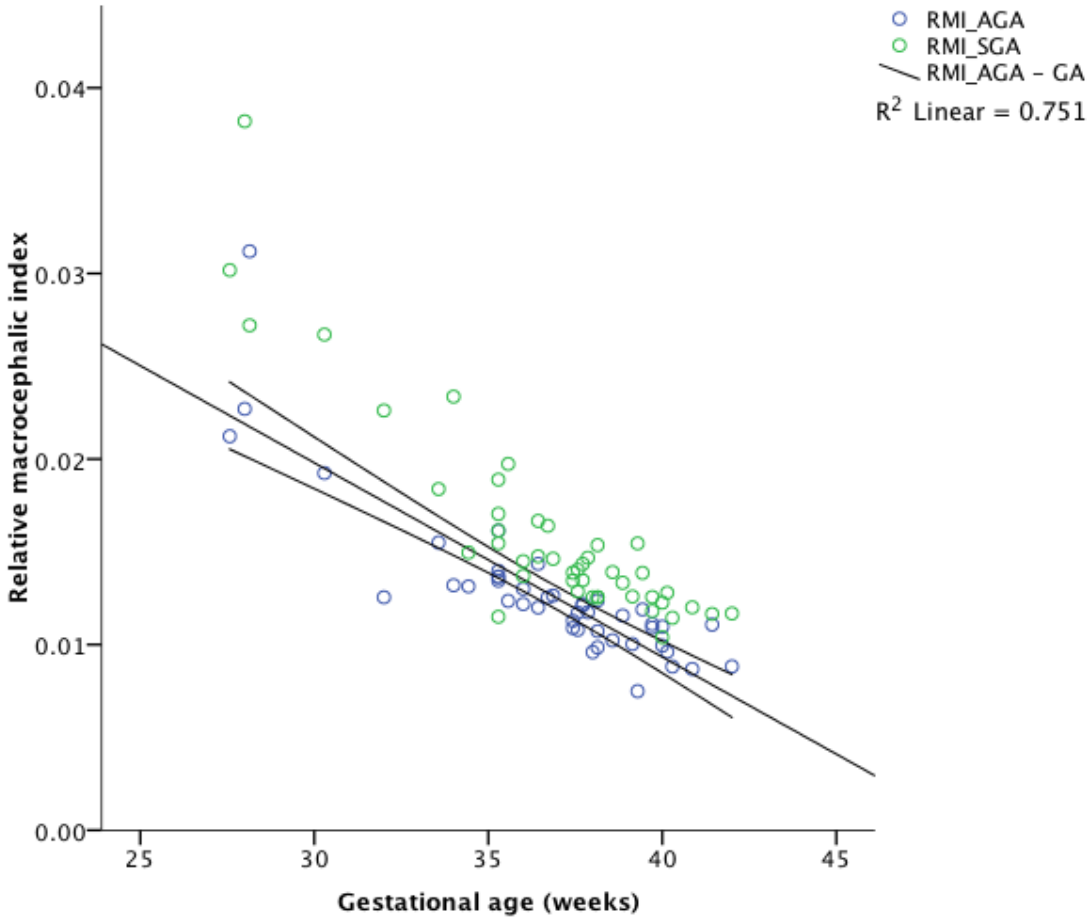
Figure 1. Distribution of gestational ages amongst SGA neonates



3.2.2. Relative macrocephalic index

The RMIs of SGA neonates (RMI_SGA) are found to be consistently higher than those of their AGA counterparts (RMI_AGA) across all gestational ages. A regression line was plotted for RMI_AGA, and most of the SGA neonates fall outside of its 95% confidence interval (**Fig. 2**). Assuming that most of our SGA infants are also IUGR cases, this would support the hypothesis that brain-sparing in IUGR leads to relative macrocephaly. Analysis should be rerun after the IUGR cohort has been defined by antenatal parameters.

Figure 2. Relative macrocephalic index of SGA and AGA neonates across gestational ages.



3.3. Neuropathological mechanisms in IUGR

In normal fetal neurodevelopment, there is a consistent sequence of key events that continue into postnatal life. However, this physiological maturation can become disrupted in IUGR, resulting in both microstructural and macrostructural abnormalities. As gliogenesis, myelinogenesis, synaptogenesis, and dendritic sprouting are actively occurring in the time interval when the fetus may be suffering from growth restriction (de Graaf-Peters & Hadders-Algra, 2006; Semple et al., 2013), these processes are most likely to be impaired.

It is believed that excitotoxicity and neuroinflammation are two of the key mechanisms underpinning neural injury in IUGR (Rees et al., 2011; Wixey et al., 2017). There is evidence to suggest that cerebral hypoxia induces excessive release of excitatory neurotransmitters, particularly glutamate (Longo & Packianathan, 1997; Vannucci, 1990). Animal studies have indicated that the fetal and neonatal brain are more sensitive to glutamate-mediated excitotoxicity than the adult brain, especially in certain neuronal populations such as the hippocampal CA1 pyramidal cells, thus rendering them more susceptible to neuronal damage or death (Dieni & Rees, 2003; Longo & Packianathan, 1997; Mishra & Delivoria-Papadopoulos, 1999). Interestingly, Tauskela et al. (2001) reported that moderate prenatal hypoxia may induce tolerance to subsequent excitotoxic insults, thus implying that the IUGR brain may conversely be less vulnerable to excitotoxic damage than normal controls. The overall role of excitotoxicity in IUGR-associated brain injury is therefore still controversial.

Previous studies have demonstrated the presence of activated microglia and reactive astrocytes in the IUGR brain, which can produce proinflammatory cytokines that are toxic to both grey and white matter (Wixey et al., 2017). In these experimental models, the increase in activated glia and astrocytes was found to be associated with neuronal and white matter disruption (Olivier et al., 2007; Pham et al., 2015; Wixey et al., 2019). In addition, Bassan et al. (2010) reported a reduction in the cell size and number of mature cortical astrocytes in asymmetric IUGR. It is therefore possible that IUGR is associated with not only abnormal activation, but also impaired maturation, of astrocytes.

3.3.1. White matter disruption

Regarding white matter disruption, post-mortem studies support the hypothesis that there is reduced myelination in IUGR neonatal brains (Chase et al., 1972), and *in vivo* imaging has confirmed reduced white matter volume and delayed myelination in preterm IUGR neonates, that are more pronounced in infants with brain sparing compared to those with normal MCA Doppler (Ramenghi et al., 2011). Animal studies have demonstrated that there is delayed myelination (Reid et al., 2012) and suggest that this may be due to delayed maturation of oligodendrocytes and

possibly reduced myelin-generating capacity of those that do mature (Nitsos & Rees, 1990; Olivier et al., 2007; Tolcos et al., 2011).

Alterations in myelination were consistently found, but findings differ markedly in the specific details (Eixarch et al., 2012, 2016; Illa et al., 2013; Malhotra et al., 2019; Padilla et al., 2014). Several diffusion tensor imaging studies in animal IUGR models have found decreased fractional anisotropy (FA) and increased sphericity, which suggest reduced myelin content and increased fibre crossing in white matter areas (Eixarch et al., 2012; Illa et al., 2013). In particular, the cortico-striato-thalamic network and the motor network are reported to have reduced FA and reduced integrity, thus implying decreased myelin density (Eixarch et al., 2016). Malhotra et al. (2019) also observed decreased fibre cross-section of specific tracts in the periventricular white matter, hippocampus, and cerebellum, which was confirmed by histological evidence of diffuse fibre disorganisation and hypomyelination. Conversely, increased FA was found in several tracts of human IUGR brains, most notably in the forceps minor of the corpus callosum, which connects the medial and lateral prefrontal regions (Padilla et al., 2014). There have been no reports of FA changes in this region in preterm infants, and therefore any consequent abnormalities can be associated with the effects of IUGR rather than prematurity. Further measurements by the group showed that the change in FA is comprised exclusively of changes in axial diffusivity and not radial diffusivity, suggesting that there is altered fibre organisation rather than increased myelination in these tracts.

While there is evidence that delayed myelination can be restored postnatally (Tolcos et al., 2011), long-term abnormalities in neural structural connectivity patterns will remain (Illa et al., 2013). Overall, there appears to be relative preservation of long integrative myelinated tracts, but a reduced frequency of short tracts (Barbeito-Andrés et al., 2018). Although small-worldness is found to be unchanged (Barbeito-Andrés et al., 2018; Batalle et al., 2012), a fMRI study indicated that functional brain networks may be hyper-connected but sub-optimally organised in IUGR infants (Batalle et al., 2016). This is supported by a diffusion-weighted MRI study in rabbit models, where analysis of global network features suggested that both global and local efficiencies were reduced in IUGR animals

compared to controls (Illa et al., 2018). Nevertheless, connectivity patterns may vary between different networks. There is evidence of increased connectivity in the visual network (occipital pole), but decreased connectivity in the dorsal attention network (frontal pole) and auditory/language network (middle frontal gyrus) (Padilla et al., 2017). This may manifest as differences in EEG patterns between different electrodes.

3.3.2. Neuronal grey matter disruption and synaptic changes

Turning now to grey matter, there is evidence of reduced neuronal count in the cortex (Samuelsen et al., 2007) and cerebellum (Tolcos et al., 2018). Mallard et al. (2000) found a reduction in the total number of CA1 pyramidal cells in the hippocampus and Purkinje cells in the cerebellum. They also observed a reduction in the volume of associated fibre layers in these structures, thus suggesting that there is impaired dendritic growth in the surviving neurons as well.

Evidence of neuronal degeneration has also been reported. Studies have shown increased apoptosis within the mid and deep cortical layers, as well as a loss of normal neuronal integrity in both the cortex and the cerebellum (Alves de Alencar Rocha et al., 2017; Yawno et al., 2019).

Animal studies in the hippocampus (Dieni & Rees, 2003) and cerebellum (Rees & Harding, 1988) have demonstrated reduced dendritic length of hippocampal CA1 neurons and cerebellar granule cells, which is accompanied by reduced branching density of CA1 apical dendrites and granule cell dendrites. This may be the cause of the decreased number of synapses and widened synaptic clefts found in IUGR brains (Bisignano & Rees, 1988; Liu et al., 2011). Synapse formation and maturation may also be impaired due to reduced proliferation of presynaptic nerve terminals (Piorkowska et al., 2014). This effect is more pronounced in symmetrical IUGR and with more severe growth restriction.

The above neuropathologies are reflected by a reduction in grey matter volume, involving the cerebral cortex (Tolsa et al., 2004) and hippocampus (Gilchrist et al., 2018; Lodygensky et al., 2010), as well as the amygdala, basal ganglia, thalami,

insula, angular gyrus, left occipital and parietal lobes, and right perirolandic area (Padilla et al., 2014). However, it is still unclear as to whether decreased brain volume is mainly associated with the degree of prematurity or the severity of IUGR (Morsing et al., 2018).

3.3.3. Heterogeneity in IUGR brain injury

It has been hypothesised that aberrant cortical connections resulting from white matter disruption causes cortical neuronal injury, either by neuronal deafferentation or by direct damage to neuronal axons and somas (Rees et al., 2011). While early- and late-onset IUGR both present with combined white and grey matter injury, early-onset IUGR appears to be associated with neuroinflammation and more widespread white matter injury, and late-onset IUGR with increased levels of apoptosis within the cortex but limited neuronal loss overall (Alves de Alencar Rocha et al., 2017). Therefore, there may be heterogeneity in EEG abnormalities of the IUGR cohort.

3.4. EEG hypotheses

The current literature on EEG abnormalities in IUGR neonates is very limited and contradictory. Previous EEG studies using power spectral analysis had found that both preterm and term-born IUGR neonates display increased delta power and reduced power of faster frequency bands, which reflects immature electrophysiological patterns (Ozdemir et al., 2009; Yerushalmy-Feler et al., 2014). In contrast, more recent studies have demonstrated reduced delta power instead, with increased power of alpha, beta, and theta frequency bands (Castro Conde et al., 2019; Cohen et al., 2018). This appears to suggest that the IUGR brain is relatively mature compared to the AGA brain. However, Cohen et al. (2018) may have confounded results, as EEG data was collected from either hemisphere and from a variable number of sleep cycles. Furthermore, Castro Conde et al. (2019) concurs that visual analysis of EEG traces revealed features suggestive of dysmaturity: an increased percentage of discontinuous EEG, asynchrony, interhemispheric asymmetry, and bursts with delta-brushes, longer interburst-interval duration, and more transients per hour. Discrepancies between EEG

findings may have arisen due to methodological differences, such as the timing of EEG recordings, but there are not enough existing studies to determine any specific associations between methodology and result. From the collective evidence thus far, we hypothesise that the above-mentioned features of dysmature EEG patterns will be found in our IUGR cohort. This would reflect the impairment of normal neurodevelopmental processes, which had resulted in structural and functional immaturity of individual neurons and myelinated tracts.

In terms of changes in evoked EEG potentials, we expect to see reduced amplitudes due to neuronal loss, as well as longer latencies due to myelination deficits in white matter tracts (Eggermont, 1988). As there is likely to be differential damage to tracts, polymorphic waveforms may also be observed.

4. DISCUSSION

The major problem in this field is the inconsistent, and sometimes inaccurate, definitions of IUGR across the literature. While attempts have been made in this literature review to select studies that have carefully defined IUGR, there are sometimes no equivalent findings. This is an issue that should be addressed in all future IUGR studies.

Furthermore, previous studies are often descriptive rather than hypothesis-based, and sometimes lack clearly defined cut-offs for investigated parameters such as head growth (Baschat, 2011). This undermines the generalisability of study results, and increases the challenges in understanding the pathophysiological mechanisms that underlie this condition.

There is still a lack of consistent evidence regarding neonatal EEG patterns after IUGR. Considerably more work needs to be done to confirm the specific EEG changes seen after growth restriction, and link them with the established pathophysiological mechanisms of IUGR brain injury. My supervisor's project will address these knowledge gaps, and the findings from her study should help to improve understanding on electrophysiological changes in the IUGR brain and inform potential therapeutic interventions in the future.

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