Clinical Studies on PPARγ Activity in Premature Babies

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Worldwide, three-quarters of a million babies are born extremely preterm (<28 weeks gestation) with devastating outcomes: 20% die in the newborn period, a further 35% develop bronchopulmonary dysplasia (BPD), and 10% suffer from cerebral palsy. Pioglitazone, a Peroxisome Proliferator Activated Receptor Gamma (PPARγ) agonist, may reduce the incidence of BPD and improve neurodevelopment in extreme preterm babies. Pioglitazone exerts an anti-inflammatory action mediated through Nuclear Factor-kappa B repression. PPARγ signalling is underactive in preterm babies as adiponectin remains low during the neonatal period.

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1. Introduction

Prematurity accounts for 11% of all births and is the leading global cause of death and disability under five years of age [1]. Bronchopulmonary dysplasia (BPD), also known as chronic lung disease (defined as supplemental oxygen dependency at 36 weeks postmenstrual age), is seen in around 55% of extremely preterm babies. Around 10,000–15,000 new cases are diagnosed annually in the USA and a further 1250 in the UK. Recurrent respiratory symptoms requiring treatment are common, particularly in those who had BPD, even at school age and in adults, as well as lung function abnormalities and exercise intolerance [2]. Recent evidence suggests that affected individuals are at risk of the premature onset of Chronic Obstructive Pulmonary Disease [3]. Nearly 10% of preterm infants suffer from cerebral palsy, with the risk doubling with BPD (OR: 2.10; 95% CI: 1.57–2.82) [4].

Over 30% of survivors following preterm birth experience neurocognitive and socio-emotional problems from early life lasting into adulthood [5]. Psychiatric disorders are present in around 25% of preterm adolescents [6][7]. Prematurity leads to seventy-five million disability-adjusted life years per annum worldwide.

Improvements in mortality and morbidity in preterm babies have so far been achieved through improvements in intensive care management. There is currently no pharmacological treatment available for preterm infants during the newborn period that aims to prevent BPD and improve neurodevelopmental outcomes. Caffeine, when administered to preterm babies, reduced BPD and improved neurodevelopment, demonstrating that pharmacological treatment for neuroprotection is viable postnatally [8]. The CAP trial found a higher patient survival rate without neurodevelopmental disability (cognitive delay, cerebral palsy, severe hearing loss, or bilateral

blindness) at a corrected age of 18 to 21 months in infants within the caffeine group compared with those in the placebo group (59.8% vs. 53.8%; adjusted OR: 0.77, 95%CI: 0.64–0.93, $p = 0.008$) [8].

2. Adiponectin Concentrations in Premature Babies

Adiponectin is a robust biomarker of PPARγ activity [9]. The existing literature on plasma adiponectin concentrations in preterm newborn babies suggests that PPARγ signalling may be underactive in preterm newborn babies. Kajantie et al. (2004) measured plasma adiponectin concentrations using ELISA in the cord vein of 197 infants [10]. Of them, 122 were born preterm (22 to 32 weeks gestation) and 75 at term (49 from a healthy pregnancy and 26 from a diabetic pregnancy with similar findings, and thus all data from term infants were pooled). At birth, preterm babies have low plasma adiponectin concentrations ($n = 122$; 3.7 ± 10.6 µg/mL) when compared to term babies ($n = 75$; 33.7 ± 13.6 µg/mL) [10]. Mean adiponectin concentrations increased from less than 1 µg/mL at 24 weeks of gestation to approximately 20 µg/mL at term. Preterm females had 57% higher adiponectin concentrations (0 to 146%; $p = 0.05$) than preterm males. Adiponectin levels were lower in preterm infants with recent (<12 h) exposure to maternal betamethasone, but were unrelated to the mode of delivery, preeclampsia, or impaired umbilical artery flow [10].

Hansen-Pupp et al. (2015) analysed adiponectin concentrations in cord blood at birth and peripheral blood at 72 h, on day 7, and then weekly until the postmenstrual age of 40 weeks in 52 preterm babies born at 26 ± 1.9 weeks gestational age [11]. The mean adiponectin concentration increased from 6.8 ± 4.4 µg/mL at 72 h to 37.4 ± 22.2 µg/mL at three weeks. The mean adiponectin concentration during days 3 to 21 (21.4 ± 12 µg/mL) correlated with gestational age at birth ($r = 0.46$, $p = 0.001$), birth weight ($r = 0.71$, $p = 0.001$), and birth weight Standard Deviation Score (SDS) ($r = 0.42$, $p = 0.003$). Furthermore, the mean adiponectin concentration during days 3 to 21 correlated with weight SDS, length SDS, and head circumference SDS at 35 weeks corrected gestational age (r = 0.62, 0.65, and 0.62, respectively; all $p = 0.001$). Peak concentrations at 3 weeks of age ($n = 52$; 37.4 ± 22.2 µg/mL) did not correlate with gestational age, but positively correlated with catch-up growth (β = 0.021, CI:0.001–0.041, $p = 0.04$) [11].

3. PPARγ Signalling in Brain Imaging Genetics Studies

In a candidate gene study of thirteen genes from seventy-two preterm infants, Single Nucleotide Polymorphisms (SNPs) in the genes FADS2 and ARVCF were significantly associated with fractional anisotropy (FA) in white matter extracted using Tract Based Spatial Statistics (TBSS). FADS2 is involved in lipid metabolism, including PPARγ signalling [12]. A pathway-based genome-wide imaging genomics analysis was carried out on the same cohort, using the Pathways sparse Reduced Rank Regression (sRRR) machine learning approach with genome-wide SNP (Single Nucleotide Polymorphism) genotyping and a reduced version of the same TBSS phenotype. This showed that the PPARγ signalling pathway was the top ranked pathway in the model, which included adjustment for both gestational age and post menstrual age [13].

A SNP-based genome-wide imaging genomics analysis was carried on a large independent cohort of 271 preterm infants, using the sRRR method with genome-wide SNP genotyping and a probabilistic tractography phenotype incorporating FA. This detected an association between SNPs in the PPARγ gene, and the imaging phenotype was fully adjusted for gestational age, post menstrual age, and ancestry [14].

Meirhaeghe et al. (2007) genotyped two independent cross-sectional studies from Northern Ireland (n = 382 and 620) for the Pro12Ala polymorphism of PPARγ2 [15]. In combined populations, the PPARγ2 Ala12 allele was associated (p = 0.03) with lower birth weight, primarily caused by shorter gestational duration (p = 0.04). The frequency of Ala12 allele carriers was higher (p = 0.027) in the group of individuals born before term (35%, n = 60) than in the group of individuals born at term (22%, n = 942). The odds ratios (95% CI) of preterm birth for Ala12 allele carriers were 1.9 (1.1–3.4), p = 0.022, and 4.2 (1.9–9.7), p = 0.0006 (adjusted for sex, maternal age, and study), when considering 37 or 35 weeks of pregnancy as a threshold for preterm birth, respectively.

The association between PPARγ2 Pro12Ala polymorphisms and neurodevelopment at 18–24 months of age was assessed in two groups of European infants (155 born before 33 weeks of gestation and 180 born later than 36 weeks of gestation) [16]. The Ala allele of the Pro12Ala polymorphism was noted in 25% of the preterm infants and 20% of the term infants. The Ala allele of PPARγ2 was significantly associated with adverse cognitive (p = 0.019), language (p = 0.03), and motor development (p = 0.036) at 18 to 24 months of age after taking into consideration the duration of ventilation, gender, and index of multiple deprivation scores, but without correction for potential shared ancestry. There was no association between the PPARγ2 Pro12Ala polymorphism and neurodevelopment in term infants.

4. Clinical Trials of PPARγ Agonists in Preterm Babies

No clinical trials have been conducted using PPARγ agonists in preterm babies. Pioglitazone has been trialled in children and adults for its neuroprotective action and has been found to be safe. Improvements in behaviour were demonstrated in 4 to 12-year-old children (n = 44; 30 mg once daily) with Autistic Spectral Disorders after 10 weeks of treatment with pioglitazone [17]. The occurrence of adverse events was mild and transient, and none warranted medical intervention or alteration of the treatment regimen. Vomiting (4% vs. 3% in controls) and headache (3% vs. 3% in controls) were the most frequent side-effects reported in the pioglitazone group (n = 22).

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