BSPED Statement on the Use of Prenatal Dexamethasone in Congenital Adrenal Hyperplasia

Prenatal dexamethasone has been available since the mid-1980s as an experimental treatment to prevent severe virilisation of a female fetus affected with congenital adrenal hyperplasia (CAH)[1]. Outcome studies are limited but suggest success rates of 80-85% for reducing or preventing virilisation, with low frequency of maternal complications, providing treatment is started early[2]. However, concern has been raised about possible effects in treated children on memory and social interaction[3,4, 5] which emphasises the need for long term follow up and makes it essential to review the costs and benefits fully before making recommendations about dexamethasone treatment.

Women considering treatment need to start taking dexamethasone between 6-7 weeks of pregnancy, as it is at this time that androgens start to exert their effects including virilisation of the external genitalia. Later onset of treatment may be ineffective in minimising virilisation[6]. With the advent of fetal sexing from free fetal DNA in maternal plasma it is possible to identify male fetuses as early as 37 days after conception, which allows treatment to be initiated only in pregnancies with female fetuses. A recent French study reported preventing virilisation in 12 girls treated before 6 weeks and minimising changes in 3 girls treated between 6 and 7 weeks, from early diagnosis due to maternal plasma analysis[7], but New et al have taken this a step further and can now analyse fetal *CYP21A2* mutation status in cell-free DNA, and thereby target only affected female fetuses by 6 weeks of gestation[8]. A wider evidence base of this approach is desirable and ideally the reliability of such an approach should be confirmed by other genetic laboratories. However, it has the potential to become the standard way of offering prenatal diagnosis and treatment, but at present this non-invasive prenatal testing is not routinely available on the National Health Service.

The beneficial effect of treatment on affected females is well established. Virilisation of the external genitalia quantified by Prader Genital Scores has been shown to have been reduced from an average of 3.73 untreated to 1.7 treated, reducing the distress and trauma of genital surgery[9].

Concerns remain, however, about the other possible physical and psychological effects of dexamethasone not only directly on the mother, but also on the developing brain of the treated fetus. Animal studies have suggested that dexamethasone can affect areas of the brain involved in memory and programming, and can cause somatic effects including low birth weight, hypertension and metabolic abnormalities. However, these studies have been generally conducted with higher doses of dexamethasone and species-dependent differences in susceptibility to dexamethasone related health problems are well documented[10]

There have been few robust clinical studies in humans looking at all aspects of physical and neurocognitive outcomes on both mother and child. A meta-analysis in 2010[11] identified only 4 studies, rigorously scrutinised, and concluded the following:

1. Dexamethasone treatment is effective in reducing the degree of virilisation, measured by Prader Genital Score, when started early in pregnancy.2,12,13
2. No evidence of increased risk of stillbirths, miscarriages or fetal malformations in dexamethasone-exposed pregnancies [2,12,13].
3. No differences in fetal or postnatal growth in dexamethasone-exposed or non- exposed groups but data on this insufficient for meta-analysis[13].
4. Increased frequency of self-reported oedema and striae in mothers exposed to dexamethasone, but no significant increase in gestational diabetes, and no glycosuria[2,12,13]
5. Neuropsychological outcome studies suggest no evidence of reduced IQ, but possibly some difficulties with short-term memory, working memory and social anxiety in dexamathasone-exposed children [3,5,4].

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As a consequence of these considerations, and the paucity of long-term outcome data, the BSPED recommends:

1. Prenatal dexamethasone treatment should only be considered at specialist centres that have a multidisciplinary team comprising obstetricians, endocrinologists, paediatric endocrinologists, paediatric urologists, psychologists and clinical geneticists. Detailed information on the current understanding and uncertainties of prenatal treatment must be provided to allow families to make a fully informed decision, and long-term follow up of all treated individuals-mothers, affected offspring and, very importantly, unaffected daughters must be undertaken. When targeted treatment using blood samples from the mother early in pregnancy can be used to determine gender-and, possibly in the future, the *CYP21A2* genotype of the fetus- the number of dexamethasone-exposed, unaffected children will decrease.
2. All individuals who receive dexamethasone treatment in this context should be logged on to a registry (www.i-cah.org) to facilitate future data collection on the short and long term effects of prenatal treatment.