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Pubertal trajectory and the management of menstruation in females with Rett syndrome and Down syndrome

Olivia Annelies Knight
Edith Cowan University

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Pubertal Trajectory and the Management of Menstruation in Females with Rett Syndrome and Down Syndrome.

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Olivia Annelies Knight

**A report submitted in Partial Fulfilment of the Requirements for the Award of
Bachelor of Occupational Therapy, Honours, Faculty of Computing, Health and
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Submitted (October 2010)

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Olivia Annelies Knight

**A report submitted in Partial Fulfilment of the Requirements for the Award of
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ABBREVIATIONS

ARSD-	Australian Rett Syndrome Database; A population-based database established in 1993.
BDR-	Birth Defects Registry
DHEA-	Dehydroepiandrosterone
DHEAS-	Dehydroepiandrosterone Sulphate
3 Beta HSD-	3 beta – hydroxysteroid dehydrogenase
GnRH-	Gonadotrophin-releasing hormone
LH-	Luteinizing Hormone
FSH-	Follicle Stimulating Hormone
GH-	Growth Hormone
MECP2-	Methyl CpG binding protein 2
TD-	Thyroid Dysfunction
T4-	Thyroxine
TSH-	Thyroid Stimulating Hormone
IRTSH-	Isolated Raised Thyroid Stimulating Hormone
TFT-	Thyroid Function Test
DMPA-	Depot Medroxyprogesterone Acetate
OCP-	Oral Contraceptives Pill
MIRENA-	Levonorgestrel Intrauterine System or LNG-IUS
BMD-	Bone Mineral Density

Literature Review

Pubertal Trajectory and the management of Menstruation in Females with Rett Syndrome and Down Syndrome

Olivia Annelies Knight

Pubertal Trajectory and the Management of Menstruation in Females with Rett syndrome and Down syndrome

Abstract

Background: Puberty is a challenging transition for all young women and particularly so for those with an intellectual disability. Individuals with an intellectual disability often experience both cognitive and physical impairment and a wide range of comorbidities. This review explores research into the pubertal trajectory and the management of menstruation in two syndromes within intellectual disability. Rett syndrome which is a severe neurodevelopmental disorder and Down syndrome which is a chromosomal birth disorder.

Aim: The purpose of this review was to identify research exploring pubertal trajectory and menstrual management in females with Rett syndrome and Down syndrome and to identify aspects of these syndromes which may impact puberty for these individuals.

Methods: Databases MEDLINE, CINHALL, Proquest Health and Medical Complete and ISI web of Science/ Knowledge were electronically searched to identify relevant articles from earliest electronic record to 2010. A priori criteria for inclusion of studies were applied first to abstracts and to full texts. Studies were included if they explored reproductive, endocrinological, musculoskeletal systems or puberty in females with Rett syndrome, Down syndrome and Intellectual disability.

Results: Electronic database searches identified 97 relevant articles with predominately cross sectional methodology. Literature identified abnormalities in bone growth and endocrinopathies in Rett syndrome and a high prevalence of thyroid dysfunction in Down syndrome both of which have been documented to affect puberty. Epilepsy was highly prevalent in both syndromes suggesting high incidences of catamenial epilepsy. Menstrual management was affected by a wide variety of factors with no perfect solution presenting.

Conclusion: Literature documented growth retardation, early pubarche and abnormal hormone secretion in Rett syndrome suggesting an underlying endocrine dysfunction. Puberty in Down syndrome is likely to be delayed due to high occurrence of thyroid dysfunction particularly hypothyroidism. Managing menstruation within this population is an area of controversy as many options negatively impact health however reduce distress and discomfort for the individual and the carer. There is a paucity of research into this field and a large proportion of studies carried out have weak methodological quality and use small sample sizes reducing the generalisability.

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PUBERTAL TRAJECTORY AND THE MANAGEMENT OF MENSTRUATION IN FEMALES WITH RETT SYNDROME AND DOWN SYNDROME

Introduction

Puberty describes the transition period between childhood and adulthood in which the ability to reproduce is attained (Terasawa & Fernandez, 2001). In females it is a complex biological process manifested by the development of secondary sex characteristics, accelerated growth, development of genitalia and menarche. The onset and tempo of puberty is regulated by two independently occurring physiological processes: adrenarche and gonadarche (Ellis, 2004; Plant & Barker-Gibb, 2004). Adrenarche occurs when levels of dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulphate (DHEAS) begin to rise due to reduced levels of 3 beta – hydroxysteroid dehydrogenase (3 Beta HSD). This usually occurs between five and seven years of age and plateaus at approximately 20 years of age (Ellis, 2004). Gonadarche occurs between nine and ten years of age and is due to the reactivation of gonadotrophin-releasing hormone (GnRH) resulting in the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH). Together these processes are responsible for the development of ovaries, secondary sex characteristics, an increase in production of sex hormones, widening of hips, menarche and fertility (Ellis, 2004).

This review aims to identify pubertal trajectory and the management of menstruation in two intellectual disability syndromes through exploring research into the reproductive, endocrine and musculoskeletal systems in Rett syndrome and Down syndrome. Rett syndrome is a severe neurodevelopmental disorder representing a severe intellectual disability (Mount, Hastings, Reily, Cass, & Charman, 2001) and Down syndrome is a

chromosomal birth disorder representing a milder intellectual disability which is still often associated with a moderate level of intellectual handicap (Bower et al., 2009; Petterson et al., 2005). Due to the paucity of research into puberty in females with Rett syndrome and Down syndrome literature pertaining to puberty in females with an intellectual disability has been included.

Puberty is a challenging transition for all young women and particularly so for those with an intellectual disability. In addition to cognitive impairment individuals with an intellectual disability often experience physical impairment and a wide range of comorbidities.

Methods

Electronic searches of four databases were used to identify and locate relevant studies for inclusion. Each database was searched from its earliest electronic records (MEDLINE from 1966, CINHALL from 1982, Proquest Health and Medical Complete and ISI web of Science/ knowledge from 1985) to July 2010. Key search terms were Down syndrome, Rett syndrome, intellectual disability, puberty, pubertal trajectory, pubarche, thelarche, menarche, menstruation, contraception, epilepsy, bone dysmorphologies and endocrinopathies. All search terms were truncated, exploded and adjusted to match specific database requirements. Searches were limited to English language and peer reviewed articles. The reference lists of all relevant articles were manually searched to ensure all relevant literature was included. Conference proceedings were not searched however searches of the Australian New Zealand Gynaecology Journal and Journals of Intellectual disability were included.

A priori criteria for inclusion of studies were applied first to abstracts and to full texts in the instance of abstracts not providing sufficient information. Studies were included if they explored reproductive, endocrine, musculoskeletal systems or puberty in females with Rett syndrome, Down syndrome and intellectual disability. Sample sizes and methodology were not limited due to the paucity of research in this field. The level of evidence of articles was based on the National Health and Medical Research Council guidelines (National Health and Medical Research Council, 1999). The data extracted from literature included, the objectives, design, method, participants, participant recruitment method, results and the conclusions.

Results

Due to the broad selection criteria electronic searches of databases identified approximately 1000 articles, once initial exclusion was carried out (n=26) CINHALL, (n=33) MEDLINE, (n=129) Proquest Health and Medical Complete and (n= 46) ISI Web of Knowledge/ Science 96 articles were selected. Descriptions of included studies are presented in table 1. The literature in this field will be presented in five themes: puberty in the normative population, Rett syndrome, Down syndrome, menstrual issues, and methods of menstrual management.

Normative Population

Research conducted in Europe particularly Norway, Denmark and Finland has identified that over the last two centuries the average age of pubertal onset has significantly reduced from 16 to 17 years of age in the 1800's to 13 years by the mid 1900's, (Kaplowitz, 2008), with the rate of decrease stabilising over the last 50 years (Denzer et al., 2007;

Onland-Moret et al., 2005). This decrease has been largely attributed to the improvements in nutrition, hygiene, health status and socioeconomic status (Anderson, Dallal, & Must, 2003). This phenomenon has resulted in a resurgence of interest within this field. Comparisons between studies are limited by factors such as varying methodologies and differing markers of pubertal onset. In 2001 Thomas, Renaud, Benefice, De Meeus and Guegan reviewed studies of the average age of pubertal onset in 67 countries. Findings from this review revealed that the youngest average age of pubertal onset at 12 years of age was reported in 1982 in the Congo and 1984 in Greece (Pentoz-Deponte & Grefen-Peters, 1984). The oldest average age of pubertal onset was 16.1 years and was reported from Senegal (Simondon, Simon, & Simondon, 1997). Australian research, conducted by Morabia and Costanza in 1998 revealed the average age of pubertal onset in Australia was 13 years of age, similar to the findings in Britain, Chile, Belgium, Cuba, Sardinia, Indonesia and Norway (F. Thomas, Renaud, Benefice, De Meeus, & Guegan, 2001). Although findings from this review are important in enabling a description of international variation in relation to average age of pubertal onset, comparison between countries was impacted by variations in methodologies used, the cross-sectional nature of the majority of the research, population sampling methods, and the nearly thirty year span of the research.

Rett syndrome

Rett syndrome is a severe neurodevelopmental disorder resulting in cognitive and physical impairment and almost exclusively affecting females (Mount, et al., 2001). Rett syndrome occurs in 1:9000 and is a leading cause of severe intellectual disability in Australia (Laurvick et al., 2006). Rett syndrome was first described in 1966 by Dr

Andreas Rett, however it was not until 1983 when Hagberg and colleagues reported on a group of females with neurodevelopmental disorders characterised by decelerated head growth and severe mental retardation that Rett syndrome was described in an English publication (Hagberg, Aicardi, Dias, & Ramos, 1983).

Due to the absence of a biological marker an international working group developed clinical criteria that all need to be met for a diagnosis of classical Rett syndrome (Hagberg, Guitieres, Hanefeld, Rett, & Wilson, 1985). However it was recognised that the phenotypic spectrum extended beyond these criteria which resulted in the introduction of the term “atypical Rett syndrome” (Hagberg, Hanefeld, Percy, & Skjeldal, 2002).

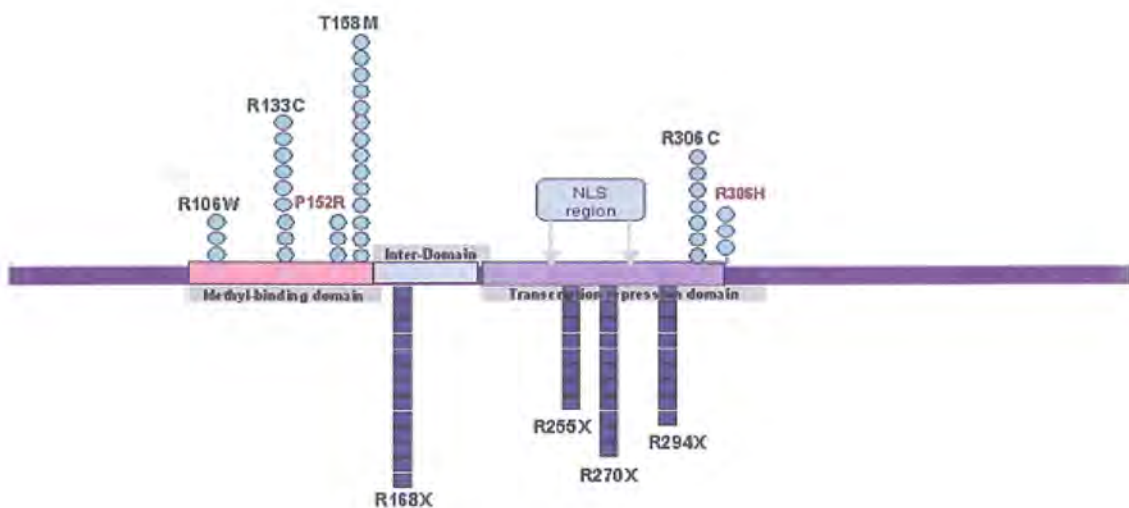
Stages of Rett syndrome

The natural progression of Rett syndrome follows a series of stages (Hagberg, 2002). The first stage is commonly known as early onset stagnation and is described as a period of slowing development. Stage two, developmental regression, is described as an obvious loss of functional abilities. The third stage, the pseudostationary stage, commences when cognitive deterioration ceases, and behavioural characteristics begin to remerge. This stage is complete when the ability to walk is diminished. This final stage, also known as the late motor deterioration, is characterised by the loss of gross motor function and is generally attributed to atrophy, spasticity and dystonic deformities (Hagberg, 2002; Hagberg & Witt Engerstrom, 1986).

MECP2

In 1999 a breakthrough into Rett syndrome research occurred when Amir and colleagues identified the association with mutations in the *MECP2* gene (Amir et al., 1999) (Figure A). The cytogenic location of *MECP2* is on the long arm of the X chromosome at Xq28 and is subject to X chromosome inactivation. Mutations of the *MECP2* have been estimated to be the cause of 70-80% of clinically defined Rett syndrome (Amir, et al., 1999; Shahbazian, Antalfy, Armstrong, & Zoghbi, 2002). To date more than 200 *MECP2* mutations have been identified with the eight most common representing just over two-thirds of mutations positive (Colvin et al., 2004; Bebbington, 2008). These eight common mutations occur in the form of missense and nonsense mutations, missense mutations are: p.R106W, p.R133C, p.T158M and p.R306C and nonsense mutations are the p.R168X, p.R255X, p.R270X and the p.R294X (Neul, 2008). It has also been identified that C-terminal mutations, early truncations and large deletion account for an additional fifth of mutation positive cases (Young et al., 2008).

Figure A (*MECP2* Gene (Colvin et al., 2003)).



Puberty

There is a paucity of research examining pubertal onset and trajectory in females with Rett syndrome. In 1986 Holm in a cross sectional study of 21 girls with Rett syndrome was the first to examine sexual development. The average age of menarche was found to be 11.2 years. Although research is limited some females with Rett syndrome may experience an earlier than expected pubarche (H. Leonard, Thomson, Glasson, Fyfe, Leonard, Ellaway, et al., 1999). This is supported through families' comments and observations on Rettnet, an internet site which provides families with a child with Rett syndrome the opportunity to seek and share advice and provide support (H. Leonard et al., 2004).

Growth retardation

In recent years considerable research in Rett syndrome has focused on growth retardation. It is well documented that females with Rett syndrome have decelerated head growth and below average body mass index scores; with females with classical Rett syndrome displaying lower BMI scores than those with atypical Rett syndrome (Reilly & Cass, 2001). The lower BMI scores in Rett syndrome are thought to be the result of factors such as feeding difficulties, decreased texture tolerances and disorders of the digestive tract, bowel, oromotor and oesophagus (Oddy et al., 2007; Reilly & Cass, 2001; Thommessen, Kase, & Heiberg, 1992).

Bone Dysmorphologies

Some research in Rett syndrome has focused on bone dysmorphologies. A cross sectional study of 86 girls and women with Rett syndrome reported that 91.3% of cases presented

with one or more orthopaedic conditions, the most common of these being scoliosis (Hennessey & Haas, 1988; H. Leonard, Fyfe, & Msall, 2001). Several studies have examined metacarpal and metatarsal bone length in Rett syndrome cases (Cepollaro et al., 2001; H. Leonard, Thomson, Glasson, Fyfe, Leonard, Ellaway, et al., 1999; Schultz, Glaze, Motil, Hebert, & Percy, 1998). The first study to use metacarpophalangeal pattern profile analysis (MCP) to identify short metatarsals in Rett syndrome was undertaken by Optiz and colleagues in 1987. These findings of short metatarsals in Rett syndrome were later confirmed in population based studies by Leonard and colleagues (1995) and (1999). Leonard et al (1995) reported that 65% of cases (n=11) had short fourth and fifth metacarpal bones, and 57% had short fourth and fifth metatarsals (n=8) (H. Leonard, et al., 1995). Other bone dysmorphologies described in this study were negative ulna variance in 79% (n=11) of cases and advanced bone age in 56% (n=5).

A high prevalence of osteopenia, or reduced bone mass, has also been reported in girls and women with Rett syndrome. The greater risk that females with Rett syndrome have of fractures and reduced bone density (Downs, Bebbington, Woodhead, et al., 2008; Haas, Dixon, Sartoris, & Hennessey, 1997) compared to females in the normative population has been confirmed in population based research. In particular Leonard and colleagues (1999) in a study of 101 females identified significantly lower cortical bone thickness in Rett syndrome (H. Leonard, Thomson, Glasson, Fyfe, Leonard, Bower, et al., 1999). Clearly, girls and women with Rett syndrome are at greater risk of bone related diseases due to compromised bone quality.

Endocrinology in Rett syndrome

The findings of abnormal growth patterns in this population along with the observations of early pubarche have lead to the hypothesis that there is an underlying endocrinological dysfunction in Rett syndrome. This hypothesis is supported by findings from a case study in which reported low levels of prolactin and growth hormone were reported in a girl with Rett syndrome (Percy & Armstrong, 1988). Huppke et al (2001) in a study of 38 females with classical Rett syndrome aimed to determine whether growth hormone deficiency was more prevalent in Rett syndrome. In this sample (n=13) individuals had a height lower than the third percentile, bone age was delayed in four individuals and advanced in three, levels of prolactin, luteinizing hormone (LH), follicle stimulating hormone (FSH) and oestradiol were normal and one and two cases presented with abnormal scores in thyroxine (T4) and thyroid stimulating hormone (TSH), respectively. In addition dehydroepiandrosterone sulphate (DHEAS) levels were low in young females and high in older females suggesting a normal onset of adrenarche. Although this study was limited by the small sample size and missing data, results from this study pointed to signs of an abnormal pattern of hormone secretion, however there was not sufficient evidence to determine if growth hormone played a causative role in the growth abnormalities displayed in Rett syndrome (Huppke, et al., 2001).

Further exploration into growth abnormalities in Rett syndrome have been carried out in mouse model studies. Mice deficient in MeCP2 have a range of neurological and physiological abnormalities which mimic Rett syndrome. Tropea and colleagues (2009) investigated the potential of Insulin-like Growth Factor (IGF-1) when delivered systematically to determine if the synaptic and neuronal immaturities which are

characteristic of Rett syndrome could be overcome and in turn ameliorate Rett like symptoms in a mouse model. This study reported that treatment of IGF-1 increased PSD-95 (postsynaptic scaffold protein responsible for synapse maturation, strength and plasticity), stabilized cortical plasticity and partially restored spine density and synaptic amplitude. These findings strongly suggest that IGF-1 has the potential as a successful pharmacological treatment in Rett syndrome (Tropea, et al., 2009).

Genotype, phenotype

Identification of the *MECP2* mutation as a cause of Rett syndrome has enabled examination of the relationship between genotype and phenotype expression. However, internationally research in this field has been limited in some countries by a lack of population based research and the absence of universal severity scales which would enable comparison between samples. The notable exception is the Australian population-based study which has been recruiting participants through the Australian Rett Syndrome Database. Using cases from this database a 2004 study reported that truncating mutations presented with earlier onset of stereotypical hand movements, greater severity using the Pineda scale (Monros et al., 2001) and lower functional independence scores suggesting that they were causative of a more severe phenotype. Leonards (2003) study comprising of (n=11) Australians, (n=4) Japanese and (n=9) females from the United Kingdom all with R133C mutations used four clinical scales; Pineda, Kerr, Percy and WeeFIM to compare the phenotype in p.R133C to other mutations. This study identified increased hand use and improved ambulation in individual's with p.R133C mutations, a finding which was later supported by Colvin et al (2003), Bebbington (2008) and (Neul, 2008). Bebbington demonstrated that this mutation along with p.R294X resulted in milder

phenotypes, and that p.R270X and p.255X were the most severe phenotypes. It is likely that specific genetic mutations influence aspects of puberty in females with Rett syndrome differently. It can be hypothesized that mutation type will impact on the onset of puberty.

Down syndrome

Down syndrome is a chromosomal birth disorder affecting 1: 1000 live births making it the most prevalent single cause of intellectual disability in Australia (Bower, et al., 2009; Petterson, et al., 2005). Although the exact prevalence is unknown it has been identified that the overall number of Down syndrome conceptions has increased since 1980 from 1.2 / 1000 livebirths to 2.6/1000 livebirths in 2009 (Bower, et al., 2009). This increase can be largely attributed to advances in medical care and increased prenatal screening (Bittles, Bower, Hussain, & Glasson, 2006; Bower, et al., 2009; Sherman, Allen, Bean, & Freeman, 2007). In the past 50 years improvements in medical care have resulted in increased life expectancy of individuals with Down syndrome, increasing from 18 to 60 years of age (Bittles, et al., 2006; Bittles & Glasson, 2004; Weijerman et al., 2008).

Comorbidities in Down syndrome

Down syndrome is associated with numerous birth defects with a variety of comorbidities (S. Leonard, Bower, Petterson, & Leonard, 2000; K. Thomas, Girdler, Leonard, & Downs, 2010). These affect cardiac, respiratory, gastrointestinal, musculoskeletal and endocrine systems. Population based, Western Australian research identified that approximately 20% of children with Down syndrome experienced four or more medical conditions. The most common comorbidity seen in Down syndrome was cardiac disease

with estimates of 46% of Western Australian children with Down syndrome presenting with some form of cardiac disorder (S. Leonard, et al., 2000).

Puberty in Down syndrome

Although still limited, a greater body of research has examined the trajectory of puberty in females with Down syndrome than those with Rett syndrome. However, the majority of this research has focused on age of menarche with very few examining the overall pubertal trajectory. Arnell, Gustafasson, Ivarson and Anneren (1996) in a longitudinal study of males (n=23) and females (n=21) with Down syndrome over the age of ten years, reported that a pubertal growth spurt occurred early but remained lower than in the normative population. The mean age of menarche was 13.2 years (11.8-16.2). Similarly a cross sectional study by Scola, Seigfried and Pueschel (1992) with a sample of girls (n=51) with Down syndrome reported the average age of menarche to be 12.6 years (10-16). Both these studies indicate that pubertal onset occurs at an age similar to that of the normative population (F. Thomas, et al., 2001).

Thyroid Function in Down syndrome

The most prevalent endocrine abnormalities in Down are diabetes and thyroid disease (Gibson et al., 2005; Hawli, Nasrallah, & Fuleihan, 2009). A large proportion of studies exploring thyroid function in Down syndrome have been cross sectional on non-population based samples. In 2006 Gibson commenced a longitudinal study aimed at measuring the prevalence and type of thyroid dysfunction (TD) in children in the United Kingdom (n=122) with Down syndrome ranging in age from 6 to 14 years. A follow up study was able to contact 104 children and young people between four and six years later.

The first assessment revealed 98 euthyroid individuals and of these 83 were retested and four (5%) were found to have hyperthyrotropinaemia (isolated raised thyroid stimulating hormone). Of the 24 children found to have hyperthyrotropinaemia in 2006 14/24 had returned to normal at follow-up. 10/24 (41%) still presented with thyroid abnormalities.

A longitudinal study by Prasher and Gomez of 200 individuals with Down syndrome testing for thyroid dysfunction at one year, five year and ten year reported that at baseline testing, 11% of cases had subclinical hypothyroidism, 10.5% had definite hypothyroidism and 3% were biochemically hypothyroid. At five years follow up (n=104) 19% of individuals were on thyroxin and 28% of individuals had abnormal thyroid function tests. By the final assessment at ten years follow-up, the study group had dropped to 49 and of these 35% were on thyroxin and 37% had abnormal thyroid function tests. These findings confirm the high prevalence and incidence of thyroid dysfunction within Down syndrome, particularly hypothyroidism (Prasher & Gomez, 2007). Hypothyroidism can affect an individual's life in numerous ways such as weight gain and delayed puberty. Delayed puberty is the absence of secondary sex characteristics by the age of thirteen, no signs of menarche by the age of sixteen, and a period of five or more years between the development of secondary sex characteristics and menarche (Shah, 1997).

Weight in Down syndrome

A considerable body of research has described a relationship between Down syndrome and a high body mass index and a lower than normal resting metabolic rate (Melville, Cooper, McGrother, Thorp, & Collacott, 2005). Research in the normative population has supported that there is a positive association between increased BMI scores and earlier onset of puberty, (Buyken, Karaolis-Danckert, & Remer, 2009; Lin-Su, Vogiatzi, & New,

2002). However, although an association has been established, the causative nature of this relationship remains unclear. It is not known whether increased body fat is the cause or the result of decreased age of pubertal onset. Clearly there is a need for further research to be conducted with larger sample sizes and more robust methodologies.

Menstruation

For women with Rett syndrome or Down syndrome multiple factors determine, whether monthly menstruation results in a mild inconvenience or a major health concern (Kaur, Butler, & Trumble, 2003). As no literature has specifically examined issues in relation to these two disorders, literature pertaining to all intellectual disability has been examined in this review. In females with an intellectual disability menstrual management frequently results in many issues and concerns (Kaur, et al., 2003), which can be broadly categorised into self care, menstrual disorders and sexual health (McEvoy, Chang, & Coupey, 2004).

Self Care of menstruation

The onset of menstruation can be a confusing transition for all females, particularly if the individual has not been made aware or educated in these issues (McEvoy, et al., 2004).

Research on females with an intellectual disability have identified that many do not receive adequate preparation for the onset of puberty (Lin & Barnhart, 2007; McEvoy, et al., 2004). A randomised control study (n=7770) in England explored methods of sexual education finding that in the normative population peer based programmes were valued greater than programmes run by teachers. The main reasons for this were better timing of programmes and a wider variety of content (Forrest, Strange, & Oakley, 2002). It has been reported that females with an intellectual disability often have fewer friendships and

peer relationships suggesting they are less likely to receive sexual education through this avenue (Strully & Strully, 1985). The combination of impaired cognitive ability and lack of education may result in females with Rett syndrome and Down syndrome feeling very confused and distressed during the commencement of menstruation (Quint, 2008).

Factors such as impaired physical mobility and upper limb functioning may also impact on the young women with intellectual disabilities ability to manage self-care during menstruation (Quint, 2008). In females with Down syndrome severity of intellectual and physical impairment varies widely. Physical impairment is likely to be a greater factor in Rett syndrome as both upper and lower limb impairment have been reported in this population. A video analysis study in 2008 explored the gross motor profile in Rett syndrome cases (n=99). Findings were that the majority of girls with Rett syndrome were able to sit independently, approximately 50% were able to walk and a minority were able to independently transfer (Downs, Bebbington, Msall, et al., 2008). The varying severity in both Rett syndrome and Down syndrome indicates that managing the hygiene aspects of menstrual management may be possible for some but not for many individuals within these populations.

Menstrual Disorders

There is a wide variety of disorders associated with menstruation. Common disorders include dysmenorrhoea menorrhagia, polycystic ovary syndrome, pre-menstrual syndrome and catamenial epilepsy (Lin & Barnhart, 2007; Weatherford, 1999). No research into issues relating to menstrual disorders in Rett syndrome has been identified. However research into Down syndrome (n=59) has reported menorrhagia in 30% of females (Mason & Cunningham, 2008). Epilepsy is a highly prevalent disorder in

individuals with an intellectual disability with an estimated population prevalence of 20 %. In samples of girls and women with Rett syndrome (n=53) prevalence estimates have been reported to be as high as 94% (Steffenburg, Hagberg, & Hagberg, 2001). Similarly high rates (81%) were identified in a population based study by Jian and colleagues of females with Rett syndrome (n=275) where the average age of onset was four years of age (Interquartile range IQR 24-90 months) (Jian et al., 2006). A further study by Jian and colleagues reported that among this population higher rates of seizure frequency were more likely in females with lower functional ability and higher clinical severity (Jian et al., 2007). Genotype was identified as a contributing factor with p.R294X, p.R255X and C terminal mutations having lower frequencies of seizures (Jian, et al., 2007). Seizure frequency has also been found to be influenced by age, Jian and colleagues reporting the highest frequency of seizures in the 7-12 year age group. In an earlier non-population-based study, Leonard and colleagues (2001) reported that the prevalence of seizure diagnosis increased from 22.1% in those less than five years of age to 88.9% for individuals over the age of 14 years. Studies exploring epilepsy in Down syndrome have reported lower prevalence (17%) than Rett syndrome but still higher than in the normative population (Johannsen, Christensen, Goldstein, Nielsen, & Mai, 1996; McVicker, Shanks, & McClelland, 1994). This high prevalence of epilepsy within Rett syndrome and Down syndrome indicate that catamenial epilepsy could be a potential problem in the management of menstruation.

Sexual Health

Sexuality is an area of concern for individuals with an intellectual disability and their families (Isler, Tas, Beytut, & ConK, 2009). Research has reported that individuals with an intellectual disability are at a greater risk of contracting sexually transmitted diseases (STDs), having unplanned pregnancies and are three times more likely to be the victim of sexual abuse than the normative population (Nosek, et al., 2001; WHO & UNFPA). These outcomes are thought to be the result of their high dependency levels and the lack of education provided to both the individuals with an intellectual disability, their families and the wider community (Nosek, et al., 2001). Contraception is often used by individuals with an intellectual disability to prevent unplanned pregnancies however contraception does not prevent STDs or abuse. These findings highlight the importance of educating individuals with an intellectual disability and their families about the risks and about methods of reducing these risks.

Managing Menstruation

The methods employed in managing menstruation can be described in three categories: medical suppression; elimination; and, self management (Albanese & Hopper, 2007; Paransky & Zurawin, 2003; Pillai, O'Brian, & Hill, 2009; Quint, 1991). Research examining the management of menstruation in females with an intellectual disability is limited however overall seems to support the conclusion that menstrual suppression is the most common approach (Pillai, et al., 2009). There are a number of methods of menstrual suppression available to females with an intellectual disability. However their prescription is influenced by the complex medical complications seen in this population

(Kaur, et al., 2003). Both medical and surgical methods of suppression are available. Medical interventions include oral contraceptives (OCP), oral progesterone's, depot medroxy progesterone acetate (DMPA) and gonadotrophin releasing hormones (GnRH) (Albanese & Hopper, 2007).

Suppression of menstruation

Research into the use of suppression as a method of menstrual management in Rett syndrome and Down syndrome is very limited. A population based study (n=397) in Brussels explored the use of suppression in females with all levels of intellectual disability aged between 18 and 46 years (mean \pm SD= 33.62 \pm 7.17yrs). It was found that 18% used OCP (n=73), 17.6% used DMPA (n=70), and 40.8% used no form of suppressant (n=162). Comparison with the general population in Brussels highlighted that women with intellectual disability were more likely to use DMPA (17.6 % compared to 2%) (Servais et al., 2002). These findings highlight the difference between menstrual management and contraceptive methods used in females with an intellectual disability to those used in the general population.

Depot medroxy progesterone acetate (DMPA, Depot Provera, Depot-Ralovera)

DMPA is a frequently used suppressant in females with an intellectual disability and is effective as both a suppressant and a contraceptive (Albanese & Hopper, 2007; Dizon, Allen, & Ornstein, 2005; Watson, Lentz, & Cain, 2006). DMPA is a progesterone only drug and is administered quarterly through an intra muscular injection. This drug suppresses menstruation through suppressing pituitary gonadotrophin resulting in anovulation, endometrial atrophy and hypoestrogenemia. DMPA has been associated

with negative health outcomes such as hair loss, cancer and weight gain (Paul, Skegg, & Spears, 1989; Stager & Cromer, 2000; Watson, et al., 2006). Weight gain may be a particular concern for females with Down syndrome as high rates of obesity have been documented within this population (Melville, et al., 2005). However probably the most important factor to consider in the prescription of DMPA to women with Down syndrome and Rett syndrome is its reported association with decreased bone density (Guilbert et al., 2009; Kass-Wolff, 2001; Pongsatha, Elkmahachai, Chaovisitsaree, Suntornlimsiri, & Morakote, 2009; Watson, et al., 2006). Additionally, for some individuals an intramuscular injection may be too traumatising. In these cases oral progesterone is available however the effectiveness of this is reduced due to the high incidence of breakthrough bleeding (Albanese & Hopper, 2007).

Oral Contraceptive Pill

The continuous use of oral contraceptive pills is another frequently used method in females with an intellectual disability (Schrager, 2009). This is a combination of oestrogen and progesterone and is usually taken in the form of nine weeks of continuous use followed by a break on the 10th week. Reported side effects of OCP use are increased risks of venous thrombosis (Vandenbroucke et al., 2001), slightly increased risks of breast cancer and decreased bone density (Hannaford, Kay, Vessey, Painter, & Mant, 1997). A study conducted by Stadel (1981) identified that the risk of venous thrombosis was fourfold in females using the oral contraceptive pill, this study is relatively old and changes to the dosages of oral contraceptives have been made since. A more recent study conducted by the World Health Organization in 1998 identified equally high risks (3-6 times) of thrombosis in OCP users. This study also identified that the risk was greatest

during the first year of use and increased up to but not beyond discontinuation (WHO, 1998). Thrombosis is a particular concern for girls and women with Rett syndrome as many females with Rett syndrome have decreased mobility (Welner, 1999). As in DMPA the use of OCP has been reported to decrease bone density, however this is to a lesser extent than the risks of DMPA and is dependent on the dosage taken (Balasch, 2003). It is unclear as to whether the use of OCP increase the risk of Breast Cancer, one study conducted in USA in 2002 explored this relationship in a sample of (n=4575) females between 35 and 64 years of age, and a control group of (n=4682). This study identified that current use or former use of the OCP was not significantly associated with increased risks of breast cancer (Marchbanks et al., 2002).

MIRENA

In addition to medical suppressants surgical options are available, the most common of which is the levonorgestrel intrauterine system (MIRENA) or LNG-IUS. The LNG-IUS is a 32mm plastic device containing progesterone levonorgestrel that suppresses menstruation through releasing the progesterone levonorgestrel over a five year period (Pillai, et al., 2009). It results in local oestrogen insensitivity which inhibits endometrial proliferation. For females with Rett syndrome the LNG-IUS may need to be inserted under a general anaesthetic which may be traumatising for an individual and consent is needed. Commonly arising issues associated with LNG-IUS are breakthrough bleeding, cysts, bloating and weight gain (Albanese & Hopper, 2007; Freeman & Shulman, 2010).

Research examining menstrual suppression in both females with an intellectual disability and the normative population highlights the numerous side effects associated with each

suppressant. This suggests that there is no ‘perfect option’ and that numerous factors such as medical history and medical comorbidities need to be taken into consideration before any suppressant is prescribed. The association between many of the methods and decreased BMD is an important consideration as adolescents is a period in which bone mass production reaches its peak and females with Rett syndrome (Budden & Gunness, 2003; H. Leonard, Thomson, Glasson, Fyfe, Leonard, Bower, et al., 1999) and Down syndrome (Angelopolulou, Souftas, Sakadamis, & Mandroukas, 1999; Balasch, 2003; Baptista, Varela, & Sardinha, 2005) have already decreased bone densities.

Elimination of menstruation

Elimination of menstruation is available through two surgical operations, endometrial ablation and hysterectomy. Hysterectomy is the removal of all or part of the ovaries, fallopian tubes, uterus and cervix whereas endometrial ablation is the removal of all of the endometrium and part of the myometrium. (Paddison, 2003; Torpy, Lynn, & Glass, 2004). In many countries the sterilization of females with an intellectual disability is an area of great controversy. This is largely due to their inability to provide consent and concern in relation to contravention of human rights. It is well documented that females with an intellectual disability are more likely to be sterilized and at an earlier age than females in the normative population (Servais, et al., 2002; Stansfield, Holland, & Clare, 2007). Stanfield and colleagues (2007) conducted a retrospective case note study of referrals made to the “Official Solicitor’s Office for Sterilization” in England and Wales between 1988-1999. Over the 11 years approval for sterilization was sought through the court for 39 females. In three quarters (n=31) of cases sterilization was deemed to be in the persons best interest. This study also explored the reasons for sterilization. The most

common reason was elimination of the risk of pregnancy (n= 22) and other reasons stated were difficulties managing menstruation (n=3), side effects of suppressants (n=5) and the carer's difficulty in managing the individuals menstruation (n=4).

Sterilization of females with an intellectual disability can be considered either therapeutic or non-therapeutic sterilization. Therapeutic sterilization refers to sterilization carried out to prevent ill health or death whereas non therapeutic sterilization is predominately to prevent pregnancy or reduce issues in the management of menstruation (Brady, 2001)

Australian legislation is strongly against non therapeutic sterilization however this may still be carried out in some females if sterilization is deemed to be in the individuals "best interest" (AHRC, 1997). Servais study conducted in Brussels (n=397) identified that 22.2% of females with an intellectual disability were sterilised (n=88) this is a very high rate when compared to the normative population in Brussels which identified that 7% of females had undergone eliminating surgery (Servais, et al., 2002). This research into sterilization of females with intellectual disability highlights the issues and controversies associated with sterilization in this population. As sterilization is a permanent procedure it should only be carried out as a last resort once all other options have been exhausted (Brady, 2001).

Self Management of menstruation

The literature into the various side effects associated with suppressants suggests that self management is a suitable method in managing menstruation for some individuals, It has been identified that approximately 33% of females with an intellectual disability are able to independently manage menstruation (Rodgers & Lipscombe, 2005). Mason and

Cunningham (2008) in a study of (n=6) young women with Down syndrome and (n=53) mothers of girls with Down syndrome reported that 60% of cases were independent in managing menstruation with no or very limited assistance. There is currently no research exploring self management of menstruation in females with Rett syndrome however the severity of intellectual disability, high levels of dependence and reduced hand functioning of these women suggests that for the vast majority self management may be difficult. Females with Rett syndrome have a high prevalence of incontinence implying that management of hygiene in menstruation may be managed similarly to everyday continence hygiene (H. Leonard, et al., 2001). In order for self management to be successful individuals and their families need to be educated on the topic before puberty commences to reduce the distress the individual experiences.

Discussion

This narrative review found that there are some factors supporting the hypothesis that pubertal trajectory may be abnormal in females with Rett syndrome and Down syndrome and that there are likely to be many issues which need to be taken into consideration when selecting an appropriate method of menstrual management in this population.

Limitations of this review were the paucity of research into this field which resulted in studies that were cross sectional and longitudinal being used, and studies were not always population based. These factors along with the importance of the subject highlights the need for more studies with population based samples to be carried out.

Conclusion

Although there is a paucity of research examining puberty in Rett syndrome, the identification of decreased bone mineral densities and growth retardation along with the observations of early signs of pubarche strongly suggest an underlying endocrine dysfunction is present in Rett syndrome. These findings imply that the onset of puberty and pubertal trajectory may be different from normal. It is also possible that the wide phenotypic spectrum may influence aspects of puberty as varying levels of severity have been linked to different mutations (Colvin, et al., 2003; Bebbington, 2008).

Research into Down syndrome highlighted the high prevalence of thyroid dysfunction, many of these studies focused on the high incidence of hypothyroidism, suggesting that puberty may be delayed in many females with Down syndrome. The majority of these studies have lacked generalisability due to small sample sizes and weak methodologies (Gibson, et al., 2005; Prasher, 2007).

Research into menstrual issues and management was limited in both the fields of Rett syndrome and Down syndrome resulting in this review including literature pertaining to intellectual disability in general. This research highlighted common issues to be hygiene, sexual health and menstrual disorders particularly catamenial epilepsy. The high prevalence of epilepsy in females with Rett syndrome and to a lesser extent in Down syndrome may have a significant impact on the methods of menstrual management due to increased seizures during menstruation (Jian, et al., 2007; Johannsen, 1996). This is likely to result in the use of menstrual suppressants as a preferred management technique.

Another area of concern in both Rett syndrome and Down syndrome is the increased risk

of sexually transmitted diseases, abuse and unplanned pregnancies. The increased risk of unplanned pregnancies was reported to be a leading factor in the increased rates of sterilization and menstrual suppression in females with an intellectual disability (AHRC, 1997)

Overall the reviewed research highlighted that there are both advantages and disadvantages associated with the use of menstrual suppressants for females with Rett syndrome and Down syndrome. Many of the medical suppressants were found to have serious health consequences such as decreased bone density, venous thrombosis, and slightly increased risks of breast cancer. For individuals with Rett syndrome or Down syndrome the greatest concerns are that of decreased bone density which was found to be caused by OCP but more so by DMPA, this is a concern for females with Rett syndrome and Down syndrome as these individuals have been found to have already decreased bone density. Venous thrombosis is another area of concern particularly in Rett syndrome as many females with Rett syndrome have reduced mobility (Downs, Bebbington, Msall, et al., 2008; Welner, 1999), increased risks of venous thrombosis were found to be associated with the use of OCP (Stadel, 1981; WHO, 1998). Advantages of menstrual suppressants are the elimination of issues relating to managing hygiene and the reduction of seizure activity. The studies into this area highlight that use of suppressants is very individualised and in females with Rett syndrome and Down syndrome aspects such as comorbidities, family medical history and mobility need to be considered before any method is selected. This review also identified high rates of sterilization in females with an intellectual disability in comparison to the normative population, making it an ongoing topic of controversy due to the contravention of human rights. Sterilization may be a

suitable option for some individuals however should only be considered if it is therapeutic (Stansfield, et al., 2007).

Currently very few studies explore pubertal trajectory or menstrual management in females with Rett syndrome and Down syndrome and those that do often use small sample sizes and lack methodological quality. The review identified numerous factors which may impact on the pubertal trajectory within these populations and identified a wide range of factors which may influence the methods of menstrual management used in these females.

References

- AHRC. (1997). *The Sterilization of Girls and Young Women in Australia: Issues and Progress*. Australian Human Rights Commission.
- Albanese, A., & Hopper, N. W. (2007). Suppression of menstruation in adolescents with severe learning disabilities. *Archives of Disease in Childhood*, 92, 629-632.
- Amir, R. E., Van Der Veyver, I. B., Wan, M., Tran, C. Q., Francke, U., & Zoghbi, H. U. (1999). Rett syndrome is caused by mutations in x-linked MECP2 encoding methyl-CpG-binding protein 2. *Nature Genetics*, 23, 185-188.
- Anderson, S., Dallal, G., & Must, A. (2003). Relative Weight and Race Influence Average Age at Menarche: Results from Two Nationally Representative Surveys of US Girls Studied 25 Years Apart. *Journal of the American Academy of Pediatrics*, 111(844-850).
- Angelopolulou, N., Souftas, V., Sakadamis, A., & Mandroukas, K. (1999). Bone mineral density in adults with Down syndrome. *European Radiology*, 9, 648-651.
- Arnell, H., Gustafsson, J., Ivarsson, S. A., & Anneren, G. (1996). Growth and pubertal development in Down Syndrome. *Acta Paediatrics*, 85, 1102-1106.
- Balasch, J. (2003). Sex steroids and bone: current perspectives. *Human Reproduction Update*, 9(3), 207-222.
- Bapista, F., Varela, A., & Sardinha, L. (2005). Bone mineral mass in males and females with and without Down syndrome. *Osteoporos Int*, 16, 380-388.
- Bebbington, A., Anderson, A., Ravine, D., Fyfe, S., Pineda, M., Klerk, N., et al. (2008). Investigating the genotype phenotype relationship in Rett syndrome using an international data set. *Neurology*, 70(868-875).

- Bittles, A., Bower, C., Hussain, R., & Glasson, E. (2006). The four ages of Down syndrome. *European Journal of Public Health*, 17(2), 221-225.
- Bittles, A., & Glasson, E. (2004). Clinical, social and ethical implications of changing life expectancy in Down syndrome. *Developmental Medicine & Child Neurology*, 46, 282-286.
- Bower, C., Rudy, E., Callaghan, A., Quick, J., Cosgrove, P., & Nassar, N. (2009). *Reports of the birth defects registry of Western Australia*.
- Brady, S. (2001). Sterilization of girls and women with intellectual disabilities: Past and present justifications. *Violence Against Women*, 7(4), 432-461.
- Budden, S., S., & Gunness, M., E. (2003). Possible mechanisms of osteopenia in Rett syndrome: Bone histomorphometric studies. *Journal of Child Neurology*, 18, 698-651.
- Buyken, A., Karaolis-Danckert, N., & Remer, T. (2009). Association of prepubertal body composition in healthy girls and boys with the timing of early and late pubertal markers. *The American Journal of Clinical Nutrition*, 89, 221-230.
- Cepollaro, C., Gonnelli, S., Bruni, D., Pacini, S., Martini, S., Franci, M., et al. (2001). Dual x-ray absorptiometry and bone ultrasonography in patients with Rett syndrome. *Calcified Tissue International*, 69, 259-262.
- Colvin, L., Fyfe, S., Leonard, H., Schiavello, S., Ellaway, C., Klerk, N., et al. (2003). Describing the phenotype in Rett syndrome using a population database. *Archives of Disability and Childhood*, 88, 38-43.

- Colvin, L., Leonard, H., Klerk, N., Weaving, L., Davis, M., Williamson, S., et al. (2004). Refining the phenotype of common mutations in Rett syndrome. *Journal of Medical Genetics*, 41, 25-30.
- Denzer, C., Weibel, A., Muche, R., Karges, B., Sorgo, W., & Wabitsch, M. (2007). Pubertal development in obese children and adolescents. *International Journal of Obesity*, 31, 1509-1519.
- Dizon, C., Allen, L., & Ornstein, M. (2005). Menstrual and contraceptive issues among young women with developmental delay: A retrospective review of cases at the hospital for sick children Toronto. *Journal of Pediatric Adolescent Gynecology*, 18, 157-162.
- Downs, J., Bebbington, A., Msall, M., E, McIlroy, O., Fyfe, S., Bahl-Bulsson, N., et al. (2008). Gross motor profile in Rett syndrome as determined by video analysis. *Neuropediatrics*, 39, 1-6.
- Downs, J., Bebbington, A., Woodhead, H., Jacoby, P., Jian, L., Jefferson, A., et al. (2008). Early determinants of fractures in Rett syndrome. *Pediatrics*, 121, 540-546.
- Ellis, B. J. (2004). Timing of pubertal maturation in girls: An intergrated life history approach. *Psychological Bulletin*, 130(6), 920-958.
- Forrest, S., Strange, V., & Oakley, A. (2002). A comparison of students evaluations of a peer delivered sex education programme and teacher led provision. *Sex Education*, 2(3), 195-214.

- Freeman, S., & Shulman, L., P. (2010). Considerations for the use of progestin-only contraceptives. *Journal of The American Academy of Nurse Practitioners*, 22, 81-91.
- Gibson, P., Newton, R., Selby, K., Price, D., Leyland, K., & Addison, G. (2005). Longitudinal study of thyroid function in Down syndrome in the first two decades. *Archives of Disability and Childhood*, 90, 574-578.
- Guilbert, E., Brown, J., Kaunitz, A., Wagner, M., Berube, J., Charbonneau, L., et al. (2009). The use of depot medroxy progesterone acetate in contraception and its potential impact on skeletal health. *Contraception*, 79, 167-177.
- Haas, R., Dixon, S., Sartoris, D., & Hennessay, M. (1997). Osteopenia in Rett syndrome. *The Journal of Pediatrics*, 131(5), 771-773.
- Hagberg, B. (2002). Clinical manifestations and stages of Rett syndrome. *Mental Retardation and Developmental Disorders*, 8, 61-65.
- Hagberg, B., Aicardi, J., Dias, K., & Ramos, O. (1983). A progressive syndrome of autism dementia ataxia and loss of purposeful hand use in girls: Rett's syndrome: Report of 35 cases. *Annal Neurol*, 14(4), 471-479.
- Hagberg, B., Guitieres, F., Hanefeld, F., Rett, A., & Wilson, J. (1985). Rett syndrome: Criteria for inclusion and exclusion. *Brain Dev*, 23(4), 372-373.
- Hagberg, B., Hanefeld, F., Percy, A., & Skjeldal, O. (2002). An update on clinically applicable diagnostic criteria in Rett syndrome. Comments to Rett Syndrome Clinical Criteria Consensus panel Satellite to European Paediatric Neurology Society Meeting Baden, Baden, Germany, 11 September 2001. *Eur.J.Neurol*, 6(5), 293-297.

- Hagberg, B., & Witt Engerstrom, I. (1986). Rett syndrome: A suggested staging system for describing impairment profile with increasing age towards adolescence. *Am.J.Med. Genet. Suppl, 1*, 47-59.
- Hannaford, P., Kay, C., Vessey, M., Painter, R., & Mant, J. (1997). Combined oral contraceptives and liver disease. *Contraception, 55*, 145-151.
- Hawli, Y., Nasrallah, M., & Fuleihan, G. (2009). Endocrine and musculoskeletal abnormalities in patients with Down syndrome. *Endocrinology, 5*, 327-334.
- Hennessey, M., & Haas, R. (1988). The orthopedic management of Rett syndrome. *Journal of Child Neurology, 3*, 43-48.
- Holm, V. A. (1986). Physical growth and development in patients with Rett syndrome. *American Journal of Medical Genetics, 24*, 119-126.
- Huppke, P., Roth, C., Christen, H., Brockmann, K., & Hanefeld, F. (2001). Endocrinological study on growth retardation in Rett syndrome. *Acta Paediatrics, 90*, 1257-1261.
- Isler, A., Tas, F., Beytut, D., & ConK, Z. (2009). Sexuality in adolescents with intellectual disabilities. *Sexuality and Disability, 27*, 27-34.
- Jian, L., Nagarajan, L., de Klerk, N., Ravine, D., Christodoulou, J., & Leonard, H. (2007). Seizures in Rett syndrome: an overview from a one-year calander study. *European Journal of Paediatric Neurology, 11(5)*, 310-317.
- Jian, L., Nagarajan, L., Klerk, N., Ravine, D., Bower, C., Anderson, A., et al. (2006). Predictors of seizure onset in Rett syndrome. *The Journal of Pediatrics, 542-547*.
- Johannsen, P., Christensen, J., Goldstein, H., Nielsen, V., & Mai, J. (1996). Epilepsy in Downs syndrome, prevelance in three age groups. *Seizure, 5*, 121-125.

- Kaplowitz, P., B. (2008). Link between body fat and the timing of puberty. *Pediatrics*, 121, 208-217.
- Kass-Wolff, J., H. (2001). Bone loss in adolescents using depo-provera. *JSPN*, 6(1), 21-31.
- Kaur, H., Butler, J., & Trumble, S. (2003). *Options for Menstrual Management*. Centre for Developmental Disability Health.
- Laurvick, C., L, Klerk, N., Bower, C., Christodoulou, J., Ravine, D., Ellaway, C., et al. (2006). Rett syndrome in Australia: A review of the epidemiology. *The Journal of Pediatrics*, 148, 347-352.
- Leonard, H., Colvin, L., Christodoulou, J., Schiavello, S., Williamson, S., Davis, M., et al. (2003). Patients with the R133C mutation: is their phenotype different from patients with Rett syndrome with other mutations. *Journal of Medical Genetics*, 40, 1-7.
- Leonard, H., Fyfe, S., & Msall, M., E. (2001). Functional status medical impairments and rehabilitation resources in 84 females with Rett syndrome: A snapshot across the world from the parental perspective. *Disability and Rehabilitation*, 23(3/4), 107-117.
- Leonard, H., Slack-Smith, L., Phillips, T., Richardson, S., D'Orsonga, L., & Mulroy, S. (2004). How can the internet help parents of children with rare neurologic disorders. *Journal of Child Neurology*, 19, 902-907.
- Leonard, H., Thomson, M., Bower, C., Fyfe, S., & Constantinou, J. (1995). Skeletal abnormalities in Rett syndrome: Increasing evidence for dysmorphogenetic defects. *American Journal of Medical Genetics*, 58, 282-285.

- Leonard, H., Thomson, M., Glasson, E., Fyfe, S., Leonard, S., Bower, C., et al. (1999). A population based approach to the investigation of osteopenia in Rett syndrome. *Developmental Medicine & Child Neurology*, 41, 323-328.
- Leonard, H., Thomson, M., Glasson, E., Fyfe, S., Leonard, S., Ellaway, C., et al. (1999). Metacarpophalangeal pattern profile and bone age in Rett syndrome: Further radiological clues to the diagnosis. *American Journal of Medical Genetics*, 83, 88-95.
- Leonard, S., Bower, C., Petterson, B., & Leonard, H. (2000). Survival of infants born with with Down syndrome. *Paediatric and Perinatal Epidemiology*, 14, 163-171.
- Lin-Su, K., Vogiatzi, M., & New, M. (2002). Body mass index and age at menarche in an adolescent clinic population. *Clinical Pediatrics*, 41(7), 501-506.
- Lin, K., & Barnhart, K. (2007). The clinical rational for menses free contracteption. *Journal of Women's Health*, 16(8), 1171-1180.
- Marchbanks, P., McDonald, J., Wilson, H., Folger, S., Mandel, M., Daling, J., et al. (2002). Oral contraceptives and the risk of breast cancer. *The New England Journal of Medicine*, 346(26), 2025-2031.
- Mason, L., & Cunningham, C. (2008). An exploration of issues around menstruation for women with Down syndrome and their carers. *Journal of Applied Research in Intellectual Disabilities*, 21, 257-267.
- McEvoy, M., Chang, J., & Coupey, S. (2004). Common menstrual disorders in adolescence. *Nursing Interventions*, 29(1), 41-49.

- McVicker, R., Shanks, O., & McClelland, R. (1994). Prevalence and associated features of epilepsy in adults with Down syndrome. *British Journal of Psychiatry*, 164, 528-532.
- Melville, C., Cooper, S., McGrother, C., Thorp, C., & Collacott, R. (2005). Obesity in adults with Down syndrome: A case-control study. *Journal of Intellectual Disability Research*, 49(2), 125-133.
- Monros, E., Armstrong, J., Aibar, E., Poo, P., Canos, I., & Pineda, M. (2001). Rett syndrome in Spain: Mutation analysis and clinical correlations. *Brain Dev*, 23(1), 251-253.
- Morabia, A., & Costanza, M. (1998). The World Health Organization collaborative study of neoplasia and steroid contraceptives: International variability in ages at menarche, first livebirth and menopause. *Ann J Epidemiol*, 148, 1195-1205.
- Mount, R. H., Hastings, R. P., Reily, S., Cass, S., & Charman, T. (2001). Behavioural and emotional features in Rett syndrome. *Disability and Rehabilitation*, 23(3/4), 129-138.
- National Health and Medical Research Council. (1999). *National statement on ethical conduct in research involving humans*. Canberra: AusInfo, Commonwealth of Australia.
- Neul, J., L. (2008). Specific mutations in Methyl-CpG-Binding Protein 2 confer different severity in Rett syndrome. *Neurology*, 70(16), 1313.
- Nosek, M., A, Foley, C., C, Hughes, R., B, & Howland, C., A. (2001). Vulnerabilities for abuse among women with disabilities. *Sexuality and Disability*, 19(3), 177-189.

- Oddy, W., Webb, K., Baikie, G., Thompson, S., Reilly, S., Fyfe, S., et al. (2007). Feeding experiences and growth status in a Rett syndrome population. *Journal of Pediatric gastroenterology and Nutrition*, 45, 582-590.
- Onland-Moret, N., Peeters, P., Van Gills, C., Clavel-Chapelon, F., Key, T., Tjonneland, A., et al. (2005). Age at menarche in relation to adult height. *American Journal of Epidemiology*, 162(7), 624-632.
- Paddison, K. (2003). Menorrhagia: Endometrial ablation or hysterectomy. *Nursing Standard*, 17, 33-37.
- Paransky, O., & Zurawin, R. (2003). Management of menstrual problems and contraception in adolescents with mental retardation: A medical legal and ethical review with new suggested guildlines. *Journal of Pediatric Adolescent Gynecology*, 16, 223-235.
- Paul, C., Skegg, D., & Spears, G. (1989). Depot medroxy progesterone (Depo-provera) and risk of breast cancer. *British Medical Journal*, 299, 759-762.
- Pentoz-Deponete, A., & Grefen-Peters, S. (1984). Age of the menarche of girls in Thessaloniki, Greece. *Anthropol ANZ*, 42, 219-225.
- Percy, A., & Armstrong, D. (1988). Rett syndrome: A pervasive disorder of growth. *Pediatric Research*, 23, 556.
- Petterson, B., Leonard, H., Bourke, J., Sanders, R., Chalmers, R., Jacoby, P., et al. (2005). Idea intellectual disability exploring answers: A population-based database for intellectual disability in Australia. *Annals of Human Biology*, 32(2), 237-243.

- Pillai, M., O'Brian, K., & Hill, E. (2009). The levonorgestrel intrauterine system (Mirena) for the treatment of menstrual problems in adolescents with medical disorders or physical or learning disabilities. *BJOG*, 117, 216-221.
- Plant, T., & Barker-Gibb, M. (2004). Neurobiological mechanisms of puberty in higher primates. *Human Reproduction Update*, 10(1), 67-77.
- Pongsatha, S., Elkmahachai, M., Chaovitsaree, S., Suntornlimsiri, N., & Morakote, N. (2009). Bone mineral density in women using depot medroxyprogesterone acetate (DMPA) for at least 2 years compared to a control group: A cross sectional study. *Journal Med Assoc Thailand*, 92(10), 1263-1267.
- Prasher, V., & Gomez, G. (2007). Natural history of thyroid dysfunction in adults with Down syndrome - 10 year follow up study.
- Quint, E. (1991). The conservative management of abnormal bleeding in teenagers with developmental disabilities. *Options in Pediatric and Adolescent Gynecology*, 35, 54-56.
- Quint, E. (2008). Menstrual issues in adolescents with physical and developmental disabilities. *Annals of the New York Academy of Sciences*, 230-236.
- Reilly, S., & Cass, H. (2001). Growth and nutrition in Rett syndrome. *Disability and Rehabilitation*, 23(3/4), 118-128.
- Rodgers, J., & Lipscombe, J. (2005). The nature and extent of help given to women with intellectual disabilities to manage menstruation. *Journal of Intellectual & Developmental Research*, 30(1), 45-52.
- Schrager, S. (2009). DMPA's effect on bone mineral density: A particular concern for adolescents. *The Journal of Family Practice*, 58(5), 1-8.

- Schultz, R., Glaze, D., Motil, K., Hebert, D., & Percy, A. (1998). Hand and foot growth failure in Rett syndrome. *Journal of Child Neurology*, 13, 71-74.
- Scola, P. S., Siegfried, M., & Pueschel, M. D. (1992). Menstrual cycles and basal body temperature curves in woman with Down syndrome. *Obstetrics &Gynecology*, 79(1), 91-93.
- Servais, L., Jaques, D., Leach, R., Conod, L., Hoyois, P., Dan, B., et al. (2002). Contraception for women with intellectual disability: prevalence and determinants. *Journal of Intellectual Disability Research*, 46(2), 108-119.
- Shah, N. (1997). Delayed puberty. *Indian Journal of Pediatrics*, 64, 159-164.
- Shahbazian, M., D, Antalfy, B., Armstrong, D., L, & Zoghbi, H. Y. (2002). Insight into Rett syndrome: MeCP2 levels display tissue and cell specific differences and correlate with neuronal maturation. *Human Molecular Genetics*, 11(2), 115-124.
- Sherman, S., Allen, E., Bean, L., & Freeman, S. (2007). Epidemiology of Down syndrome. *Mental Retardation and Developmental Disabilities Research Reviews*, 13(3), 221-227.
- Simondon, K., Simon, I., & Simondon, F. (1997). Nutritional status and age at menarche of Senegalese adolescents. *Annals of Human Biology*, 24, 521-532.
- Stadel, B. (1981). Oral contraceptives and cardiovascular disease. *The New England Journal of Medicine*, 305, 612-618.
- Stager, M., & Cromer, B. (2000). Management of clinical side effects of DMPA. *Journal of Pediatric Adolescent Gynecology*, 13, 147-149.

- Stansfield, A., Holland, A., & Clare, I. (2007). The sterilization of people with intellectual disabilities in England and Wales during the period 1988 to 1999. *Journal of Intellectual Disability Research*, 51(8), 569-579.
- Steffenburg, U., Hagberg, G., & Hagberg, B. (2001). Epilepsy in a representative series of Rett syndrome. *Acta Paediatrics*, 90, 34-39.
- Strully, J., & Strully, C. (1985). Friendships and our children. *Journal of The Association for Persons with Severe Handicaps*, 10, 224-227.
- Terasawa, E., & Fernandez, D. (2001). Neurobiological mechanisms of the onset of puberty in primates. *Endocrine Reviews*, 22, 111-151.
- Thomas, F., Renaud, F., Benefice, E., De Meeus, T., & Guegan, J. (2001). International variability of ages at menarche and menopause: Patterns and main determinants. *Human Biology*, 73(2), 271.
- Thomas, K., Girdler, S., Leonard, H., & Downs, J. (2010). Overview of health issues in school-aged children with Down syndrome. *International Review of Research in Mental Retardation*, 39, 67-106.
- Thommessen, M., Kase, B., & Heiberg, A. (1992). Growth and nutrition in 10 girls with Rett syndrome. *Acta Paediatrics*, 81, 686-690.
- Torpy, J., M, Lynn, C., & Glass, R., M. (2004). Hysterectomy. *The Journal of American Medical Association*, 291(12), 1526.
- Tropea, D., Giacometti, E., Wilson, N., Beard, C., McCurry, C., Fu, D., et al. (2009). Partial reversal of Rett syndrome-like symptoms in MeCP2 mutant mice. *PNAS*, 106(6), 2029-2034.

- Vandenbroucke, J., Rosing, J., Bloemenkamp, K., Middeldorp, S., Helmerhorst, F., Bouma, B., et al. (2001). Oral contraceptives and the risk of venous thrombosis. *The New England Journal of Medicine*, 334(20), 1527-1535.
- Watson, K., Lentz, M., & Cain, K. (2006). Associations between fracture incidence and use of depot medroxyprogesterone acetate and antiepileptic drugs in women with developmental disabilities. *Women's Health Issue*, 16, 346-352.
- Weatherford, K. (1999). Catamenial epilepsy: In search of a clinical entity and its prevalence. *Journal of Neuroscience Nursing*, 31(6), 328-341.
- Weijerman, M., Van Furth, A., Vonk Noodergraaf, A., Van Wouwe, J., Broers, C., & Gemke, R. (2008). Prevalence neonatal characteristics and first year mortality of Down syndrome: A national study. *The Journal of Pediatrics*, 152(1), 15-29.
- Welner, S. (1999). Contraceptive choices for women with disabilities. *Sexuality and Disability*, 17(3), 209-214.
- WHO. (1998). *Cardiovascular disease and steroid hormone contraception: report of a WHO scientific group*. WHO Tech Rep Ser.
- WHO, & UNFPA. *Promoting sexual and reproductive health for persons with disabilities*.
- Young, D., Bebbington, A., Anderson, A., Ravine, D., Ellaway, C., Kulkarni, A., et al. (2008). The diagnosis of autism in a female: Could it be Rett syndrome. *European Journal of Pediatrics*.

Appendix 1

Table 1

Key Studies used in Literature Review

Authors	Year	Objective	Methodology	Participant	Database	Main Findings
Laurvick, C; De Klerk, N; Bower, C; Christodoulou, J; Ravine, D; et al	2006	To examine the prevalence, cumulative incidence and survival in an Australian cohort with Rett syndrome	Cross sectional	276 Rett syndrome (RS)	ARSD	1.09:1000 by 12 years of age
Hagberg, B; Witt Engerstrom	1986	To develop a staging system to facilitate the categorisation of disease patterns and profiles from infancy to adolescence in RS	Longitudinal	29 RS Mean=18 Range=13-28	N/A	4 stage system for classical RS developed
Amir, R; Van Der Veyver, I; Wan, M; Tran, C; Francke, U; et al	1999	Determine a cause of Rett syndrome through genetic screening	Cross sectional	21RS	N/A	Systematic gene screening identified MECP2 as cause
Holm, V	1986	Determine linear growth and sexual development in females with RS	Cross sectional	21 RS Mean=9.8	ARSD	Average menarche =11.2
Leonard, H; Slack-Smith, L;Phillips, T; Richardson, S; D'Orsonga, et al	2004	To determine the value of an email listserve for parents of children with RS	Cross sectional	119 RS	Rettnet	81.5% valued Rettnet as a support network

Authors	Year	Objective	Methodology	Participant	Database	Main Findings
Leonard, H; Thomson, M; Glasson, E; Fyfe, S; Leonard, S; et al	1999	To compare bone mass using hand radiographs between females with RS and a control group	Cross sectional Population based	137 RS	ARSD	33.3%had fracture Bone quality compromised
Leonard, H; Thomson, M; Bower, C; Fyfe, S; Constantinou, J	1995	To identify the presence of bone dysmorphologies in females with RS	Cross sectional	19 RS Range=5-37	ARSD	Short metacarpal and metatarsal bones
Leonard, H; Colvin, L; Christodoulou, J; Schiavello, S;	2003	Identify the phenotype of p.R133C in three countries	Cross sectional International comparison	11 from Australia 4 Japan 9 UK RS	ARSD	R133C milder phenotype
Leonard, H; Thomson, M; Glasson, E; Fyfe, S; Leonard, S; et al	1999	Determine bone age in females with RS	Cross sectional Population based	100 RS >20yrs of age	ARSD	Bone age advanced in Rett syndrome
Downs, J; Bebbington, A; Msall, M; Mcllroy, O; Fyfe, et al	2008	Use video analysis to identify gross motor profile in RS	Cross sectional Population based	99 RS	ARSD	p.R133C, p.R294X and p.R225X milder

Authors	Year	Objective	Methodology	Participant	Database	Main Findings
Huppke, P; Roth, C; Christen, H; Brockman, K; Hanefeld, F	2001	Identify if GH plays a causative role in the growth retardation seen in RS	Cross sectional	38 RS	paediatric Department Gottingen	Not sufficient evidence for GH as cause of growth retardation
Colvin, L; Fyfe, S; Leonard, H; Schiavello, S; Ellaway, et al	2003	Describe the variation in phenotype in RS using pineda, Percy, Kerr and WeeFIM	Longitudinal Population based	199 RS	ARSD	Used Percy, Pineda, Kerr and WeeFIM scales
Bebbington, A; Anderson, A; Ravine, D; Fyfe, S; Pineda, M; et al	2008	Examine the genotype phenotype relationships in RS	Cross sectional Population based	272 RS	IntreRett	p.R270X and p.R225X more sever phenotype
Bittles, A; Bower, C; Hussain, R; Glasson, E	2006	Identify four ages of DS, prenatal, childhood and early adulthood, adulthood and senescence	Longitudinal Population based	1332 Down syndrome (DS)	Birth Defects Registry	4 life stages identified
Arnell, H; Gustaffasson, J; Ivarsson, S; Anneren, G	1996	Identify the growth and pubertal development in females with DS	Cross sectional	44 DS Range 10- 24	Health Records Uppsala	Average age of menarche 13.2

Authors	Year	Objective	Methodology	Participant	Database	Main Findings
Scola, P; Siegfried, M; Pueschel, M	1992	Determine average age of menarche in a sample of females with DS	Cross sectional	51 DS Range 10- 27	N/A	Average age of menarche 12.6
Gibson, P; Newton, R; Selby, K, Price, D; Leyland, et al	2006	Identify the pattern of thyroid dysfunction present in DS	Longitudinal Population based	122 DS	Hester Adam Research Centre	Increased prevalence thyroid dysfunction
Prasher, V; Gomez, G	2007	Investigate annual thyroid function tests in females with DS to identify abnormalities	Longitudinal Population based	200	UK	Increased prevalence thyroid dysfunction
Melville, C; Cooper, S; McGrother, C; Thorp, C; Collacott, R	2005	Identify the prevalence of obesity in individuals with DS	Cross sectional Case control study	247	Leicestershire Learning Disability Register	Increased prevalence Obesity
Leonard, S; Bower, C; Pettersen, B; Leonard, H	2000	Evaluate changes in survival from birth in individuals with DS	Longitudinal Population	440	WA birth defects registry	Improvements in survival rates
Forrest, S; Strange, V; Oakley, A	2002	Compare students views on teacher and peer led education programmes	Cross sectional	7770	RCT English Schools	Peer programmes higher valued

Authors	Year	Objective	Methodology	Participant	Database	Main Findings
Mason, L; Cunningham, C	2008	Explore the issues experienced in menstruation in females with DS	Cross sectional	59 53=mothers	N/A	60% independent in managing menstruation
Steffenburg, U; Hagberg, G; Hagberg, B	2001	Identify the prevalence of epilepsy in females with RS	Cross sectional	53	All known RS cases in Sweden	Increased prevalence of Epilepsy
Jian, L; Nagarajan, L; De Klerk, N; Ravine, D; Christodoulou, J; et al	2007	Investigate seizure frequency and its relationship with other factors such as genetics and medication in females with RS	Longitudinal	162	ARSD	Highest in 7-12 year age group
Jian, L; Nagarajan, L; De Klerk, N; Ravine, D; Bower, C; et al	2006	Identify risk factors for seizure onset in Rett syndrome	Longitudinal Population based	275	ARSD	Average age of onset =48 months
Johannsen, P; Christensen, J; Goldstein, H; Neilsen, V; Mai, J	1996	Identify the prevalence of epilepsy in DS in three age groups (14-16 years, 23-29 years and 50-60 years)	Cross sectional	71	Danish register or mental retardation	Increased prevalence

Authors	Year	Objective	Methodology	Participant	Database	Main Findings
Albanese, A; Hopper, N	2007	Provide an account of the various therapeutic suppressant options available to females with ID	Review	N/A	N/A	Wide variety of side effects associated with suppressants
Pillai, M; O'Brian, K; Hill, E	2009	Investigate the experience of females with a disability using LNG-IUS	Longitudinal	14 Range=11-21	GP referral	Found to be therapeutically beneficial
Servais, L; Jaques, D; Leach, R; Conod, L; Hoyois, P; et al	2002	Identify the methods of contraception used in females with ID compared to the normative population	Cross sectional Population based	397 Range 18-46	Government facilities in Brussels	
Dizon, C; Allen, L; Ornstein, M	2005	Define the clinical characteristics of, and management options offered to young women with developmental delay	Retrospective chart review	72 Range 8-17	Toronto Hospital	DMPA most common
Watson, K; Lentz, M; Cain, K	2006	Evaluate any association between osteoporotic fractures and the use of DMPA	Cross sectional Population based	6773 ≥13 years of age		DMPA resulted in increased risk of fractures

Authors	Year	Objective	Methodology	Participant	Database	Main Findings
Angelopoloulou, N; Souftas, V; Sakadamis, A; Mandroukas, K	1999	Elucidate if individuals with DS are likely to experience an increased risk of osteoporosis with advancing age	Cross sectional	22 (9 males 13 females	N/A	Decreased Bone mineral density
Bapista, F; Varela, A; Sardinha, L	2005	Compare bone mineral mass in females and males with DS	Cross sectional	134 Range=14-40	Training centres Lisbon	Decreased Bone mineral density
Guijarro, M; Valero, C; Paule, B; Gonzalez- Macais, J; Riancho, J	2008	Determine the anthropometric and lifestyle factors influencing bone mineral density in DS	Cross sectional	39 Mean=26 78 controls	Marques de Valdealla Hospital	Decreased bone mineral density
Stansfield, A; Holland, A; Clare, I	2007	Identify the number of and reason for sterilization of females with ID	Retrospective case note study	73	Official solicitors office	Increased rates of sterilization

Notes

^a RS stands for Rett syndrome

^b DS stands for Down syndrome

^c ARSD stands for Australian Rett syndrome Database

Journal of Intellectual and Developmental Disability ***(formerly the Australia and New Zealand Journal of Developmental Disabilities)***

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Research Report

Pubertal Trajectory and the Management of Menstruation in Females with Rett Syndrome and Down Syndrome

Olivia Annelies Knight

Pubertal Trajectory and the Management of Menstruation in Females with Rett syndrome and Down syndrome

Background: Growth retardation, low bone mass, osteopenia and bone dysmorphologies have all been identified as clinical features of Rett syndrome, suggesting the presence of an underlying neuroendocrine disorder. Research into Down syndrome has reported high incidences of comorbidities particularly thyroid dysfunction. These findings into Rett syndrome and Down syndrome suggests that pubertal trajectory and other aspects of puberty may be abnormal for these populations. The aim of this study was to determine the pubertal trajectory and methods of menstrual management in females with Rett syndrome and Down syndrome.

Methods This research used data from two sets of surveys. The Rett syndrome component of the study was based on six waves of longitudinal data (1996, 2000, 2002, 2004, 2006 and 2009) collected through the Australian Rett Syndrome Surveys. The Down syndrome data for the current study was based on information collected in the Down Syndrome Needs Opinions and Wishes (NOW) questionnaire 2004. Survival analysis was used in determining the pubertal trajectory using the Kaplan Meier method and life tables to calculate survivor estimates. The relationship of genotype and Body mass index on pubertal trajectory was analysed using Cox Proportional Hazards Method. The menstrual management component of the study was analysed using descriptive statistics and regression.

Results In Rett syndrome the median age to reach Tanners stage two was 11 years, and the median age of menarche was 14years. The duration between the two milestones was greatest in individuals who reached Tanners stage two earliest. Body mass index and genotype were found to have an impact, with high BMI resulting in earlier onsets. In Down syndrome the median age to the first sign of puberty and menarche was 12 years of age. In Rett syndrome and Down syndrome the most commonly used suppressant was the oral contraceptive pill. The most frequently experienced issues were increased seizure activity in Rett syndrome and difficulty understanding in Down.

Discussion Pubertal trajectory in Rett syndrome was delayed compared to that of the normative population, In Down syndrome the trajectory was very similar to that of the normative population. The use of menstrual suppressants was much greater in females with Rett syndrome and Down syndrome than in the normative population, this is a concern due to the serious health concerns associated with the use of suppressants.

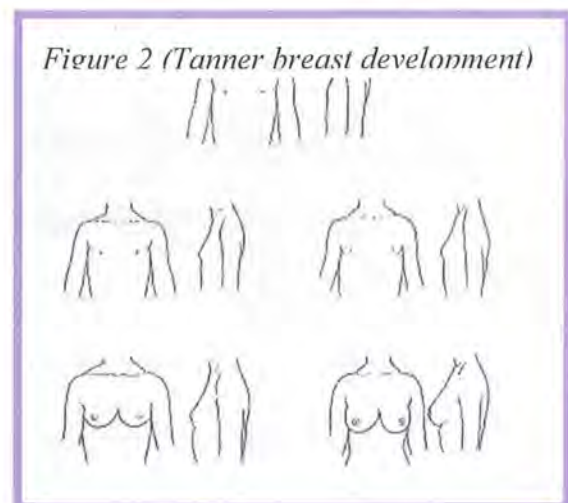
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Pubertal Trajectory and the Management of Menstruation in Females with Rett syndrome and Down syndrome

Puberty is the transitional stage between childhood and adulthood (Terasawa & Fernandez, 2001). In females it is a complex process regulated by adrenarche and gonadarche; two independent processes responsible for the development of ovaries, secondary sex characteristics, increased hormone levels, menstruation and ultimately fertility (Ellis, 2004; Plant & Barker-Gibb, 2004). The sequential series of physical changes that cumulate in sexual maturity were described by Dr James Tanner. Tanner stage one denotes the prepubescent stage where there is no observable sexual development; stages two through five are the four stages of puberty which can be displayed through a visual scale (see Figure A and B) (Marshall & Tanner, 1969)



(Marshall & Tanner, 1969).



Due to its challenging nature and observations that the average age of onset of puberty is getting younger, pubertal onset has been frequently studied across the world within normative populations (Denzer et al., 2007; Kaplowitz, 2008; Onland-Moret et al., 2005). However, limited research has examined the pubertal trajectory of individuals with an intellectual disability. The cognitive, as well as physical impairments and comorbidities often experienced by girls and women with intellectual disability suggest that puberty may pose

additional challenges for this population. This study aimed to explore the pubertal trajectory and management of menstruation in two syndromes within intellectual disability, Rett syndrome and Down syndrome.

Rett syndrome is a severe neurodevelopmental disorder that almost exclusively affects females (Mount, Hastings, Reily, Cass, & Charman, 2001). It is a leading cause of severe intellectual disability affecting 1:9000 female births (Laurvick et al., 2006). In 1999, breakthrough research by Amir and colleagues identified mutations in the *MECP2* gene as the cause of Rett syndrome (Amir et al., 1999). However more than 200 *MECP2* mutations have now been described with the eight most common being; p.R106W, p.R133C, p.T158M, p.R306C, p.R168X, p.R255X, p.R270X and the p.R294X (Neul, 2008).

To date only one study by Holm (1986) has examined the average age of menarche in (n = 21) girls with Rett syndrome, reporting the average age on onset to be 11.2 years. However, early pubarche has also been reported (H. Leonard, Thomson, Glasson, Fyfe, Leonard, Ellaway, et al., 1999). This finding, along with population based studies that have documented growth retardation, low bone mass, osteopenia and bone dysmorphologies as clinical features of Rett syndrome suggests the possibility of an underlying neuroendocrine disorder in Rett syndrome (Huppke, Roth, Christen, Brockmann, & Hanefeld, 2001; H. Leonard, Thomson, Bower, Fyfe, & Constantinou, 1995; H. Leonard, Thomson, Glasson, Fyfe, Leonard, Bower, et al., 1999; H. Leonard, Thomson, Glasson, Fyfe, Leonard, Ellaway, et al., 1999).

Down syndrome is a chromosomal birth disorder affecting 1: 1000 live births and is the most common cause of intellectual disability in Australia (Bower et al., 2009; S. Leonard, Bower, Petterson, & Leonard, 2000; Petterson et al., 2005). Although still limited, there has been more research examining the trajectory of puberty in females with Down syndrome than in

Rett syndrome. One study of ($n = 21$) females with Down syndrome identified the mean age of menarche to be 13.2 years, range (11.8, 16.2) (Arnell, Gustafsson, Ivarsson, & Anneren, 1996) a similar study reported the age of menarche in a sample of 51 girls with Down syndrome to be 12.6 years, range (10, 16) (Scola, Siegfried, & Pueschel, 1992). Although more research has been conducted in this population it has involved small sample sizes and did not use population based samples. Research into Down syndrome has documented a wide range of comorbidities with thyroid dysfunction being among the most common (Gibson et al., 2005; Hawli, Nasrallah, & Fuleihan, 2009). Thyroid dysfunction particularly hypothyroidism has been reported to greatly impact pubertal timing suggesting that individuals with Down syndrome may experience abnormal pubertal trajectory (Prasher & Gomez, 2007).

Methods Rett syndrome

This research used data from two sets of surveys, longitudinal Rett syndrome surveys and the Down syndrome 2004 survey. The Rett syndrome component of the study was based on six waves of quantitative data collected through follow-up questionnaires administered in 1996, 2000, 2002, 2004, 2006 and 2009 to parents of girls and women with Rett syndrome recruited through the Australian Rett Syndrome Database (ARSD) (H Leonard, C Bower, & D English, 1997). The ARSD is a population based database of clinically or genetically diagnosed Rett syndrome cases living in Australia and born since 1976. The database was established in 1993 and cases have been sourced through the Australian Paediatric Surveillance Unit, the parent group, the Rett Syndrome Association of Australia and referring doctors (H. Leonard, C. Bower, & D. English, 1997). The current study included confirmed female cases whose parents or carers and had answered the puberty section of at least one of the six waves of questionnaires.

Data Management and Analysis

All data was de-identified and stored electronically on Filemaker Pro databases (FileMaker, 2010). Further to cleaning and coding, data was then exported to STATA for analysis (STATA, 2010). Data analysis examined both the pubertal trajectory and menstrual management of eligible cases. Pubertal trajectory was divided into three stages: the trajectory to Tanner stage two, trajectory to menarche and the trajectory between Tanner stage two and the onset of menarche. In examining issues relating to menstrual management issues pertaining to puberty and menstrual management were described and the frequency of menstrual suppression through medical and surgical techniques described.

Pubertal Trajectory

Tanner stage two was accepted as the first sign of puberty (Marshall & Tanner, 1969). At each wave parents were asked to score their daughter's level of breast development and pubic hair development based on a visual representation of the Tanner stages (Figure 1 and 2). Where stage two was not documented and the individual had progressed from stage one to stage three between waves, a mid-point between the two time points was imputed. Age at menarche was measured by parent's response to the question, "At what age did your daughter commence menstruation?" In cases where several ages were reported for menarche the first recording was taken. If an individual had not reached menstruation at one survey and the following survey stated they had reached menarche and no age was provided the midpoint between the two time points was imputed.

The effect of Body Mass Index (BMI) and mutation type on all three trajectories was investigated. BMI z scores were calculated using Centres for Disease Control (CDC) norms (Kuczmarski & Flegal, 2000; Ogden et al., 2002). For individuals with a gastrostomy (n = 63) only BMI scores prior to the gastrostomy were used. BMI z scores were categorised into

underweight (<-1.99), normal ($-1.99-1.99$) and overweight (>1.99) (Kuczmarski & Flegal, 2000). Mutation group was classified as C-terminal deletion, early truncation, p.R106W, p.R133C, p.R168X, p.R255X, p.R270X, p.R294X, p.R306C, T158M, large deletions, and others. Cases where the results of genetic testing had not been provided or were negative were grouped separately.

Survival analysis was used to analyse the pubertal trajectory of cases. (Klein & Moeschberger). Survival time was taken as the age at which the event occurred and in those that were censored survival time was calculated as the age at the most recent questionnaire. In analysing the trajectory from Tanner stage two to menarche survival time was calculated as the length of time between Tanner stage two and the onset of menarche, and in those censored it was calculated as the time from Tanner stage two to the age at the most recent questionnaire. The Kaplan Meier method and life tables were used to calculate the survival estimates (Hosmer, Lemeshow, & May, 2008). The relationships between BMI and mutation on the trajectories were investigated using Cox proportional hazards method (Allison; Klein & Moeschberger).

Menstrual Management

Management of menstruation was described in relation to three key areas: issues experienced in menstruation; medications taken to manage menstruation; and the use of surgery in managing menstruation. Cases for this analysis were only included if they had reached menarche. The following factors were examined: age, functional ability, presence of epilepsy, BMI and mutation type. BMI, mutation and age at most recent questionnaire were calculated the same way as they were in the analysis of pubertal trajectory. Functional ability was measured by a total WeeFIM score (Msall et al., 1994). The Wee FIM is a standardised assessment composed of 18 items in six domains which has been reported to have excellent

test-re-test and inter-rater reliability and high criterion validity (Msall et al., 1996). The presence of epilepsy was collected in the medical conditions section of each questionnaire by parental response to the question, “Has your daughter ever been diagnosed with epilepsy?” Descriptive statistics and regression were used to describe the frequencies of use and types of menstrual suppressants and issues experienced and to make comparisons with specific factors. To add further detail to the descriptive statistics individual quotations from the open questions in the puberty section of the questionnaire were included.

Methods Down syndrome

The Down syndrome data for the current study was based on information collected in the Down Syndrome Needs Opinions and Wishes (NOW) questionnaire administered in 2004. The questionnaire was sent to 500 families of children and young people with Down syndrome aged up to 25 years, who were sourced through the Intellectual Disability Exploring Answers Database (Bourke et al., 2008). Individuals were included in the current study if they were female and their families had answered the puberty section of the questionnaire. Participants were only included if they were over the age of 12 as this was a specification on the questionnaire.

Data Management and Analysis

All data were de-identified and electronically stored at the Telethon Institute for Child Health Research. Data were cleaned and coded in Filemaker Pro and exported to STATA for analysis (FileMaker, 2010; STATA, 2010). Analysis of the pubertal trajectory in females with Down syndrome was divided into two sections; the trajectory to the first sign of puberty and the trajectory to menarche. Issues relating to menstrual management were examined in relation to the use of menstrual suppressants and the issues experienced in puberty.

Pubertal Trajectory

The age at the first sign of puberty was taken from parent's response to the question, "Has your child begun to display signs of puberty? (Growth of pubic or hair breast budding)".

Parents responding positively to this question were asked to indicate the age of their child when they first noticed these changes. This age was then taken as the failure point for the trajectory to the first sign of puberty. Age at menarche, in years and months, was obtained from response to the question, "Has your daughter started having menstrual periods; how old been your daughter when she started her periods?" Survival analysis was used to analyse the trajectory to both the commencement of puberty and menarche. In both trajectories survival time was calculated as the length of time from birth to the event, in individuals who were censored the survival time was the age the individual was at the 2004 questionnaire. Kaplan Meier method and life tables were used to determine survival estimates; both trajectories were analysed against BMI z scores using Cox proportional hazards method.

Menstrual Management

Description of menstrual management was carried out as for Rett syndrome. The use of menstrual suppressants and issues experienced in puberty were investigated in relation to age, total WeeFIM scores, BMI z-scores, and presence of thyroid condition through regression.

Descriptive statistics were again used to describe the frequencies of use and types of menstrual suppressants and issues experienced and to make comparisons with specific factors. Where relevant, quotations pertaining to the issues in puberty and the suppressants used were included.

Results Rett syndrome

Trajectories to Tanner stage two in cases with Rett syndrome

This sample comprised of ($n = 221$) individuals and on average cases were under analysis for 9.98 years, range (2.81, 27.54). A quarter of cases had reached Tanner stage two by 9.14 years, half by age 11, and three quarters by the age of 12.65 years (see Figure 4 and Table 2). The most common age to reach Tanner stage two was between 11 and 12 years of age. The youngest age at which Tanner stage two occurred was between five and six years of age ($n = 2$), nine individuals reached between six and seven years and 12% reached the event by the age of eight. The latest age for the onset of Tanner stage two was 21 years of age (see table 1). Weight was identified as a contributing factor (see Figure 5), with individuals classed as overweight reaching Tanner stage two at an earlier time than those classed as underweight (Hazard Ratio(HR) = 4.109, 95% Confidence Interval (CI = 1.94, 8.72). Mutation type was also found to effect the age at which Tanner stage two was reached with females with C-terminal mutations, (HR = 1.56 , 95% CI = 0.81, 2.99) and p.R106W, (HR = 1.6 , 95% CI = 0.62, 4.11) reaching this stage at an earlier age in comparison to the baseline (mutation negative). Subjects with mutations p.R133C, (HR = 0.70, 95%, CI = 0.35, 1.4) and p.R168X, (HR = 0.64, 95% CI = 0.32, 1.26) were found to reach at a later age (see Figure 6 and table 3).

Trajectory to menarche in cases with Rett syndrome

320 cases were included in the survival analysis of trajectory to menarche with the most common age for commencement of menarche occurring between 11 and 12 years and the median age to the event was 14 years of age. The youngest onset of menarche was between eight and nine years of age and the latest onset of menarche was 23 years of age (see Figure 7 and Table 4),. Individuals with lower BMI reached menarche at a significantly later age than

those categorised as overweight (HR = 4.348, 95% CI = 1.69, 11.17) (see Figure 8). In comparison to the baseline (mutation negative) earlier age of onset of menarche was associated with individuals with C-terminal mutations, (HR = 2.15, 95% CI = 1.22, 3.80) early truncation, (HR = 2.18, 95% CI = 1.03, 4.61) mutation p.R294X, (HR = 1.01, 95% CI = 0.52, 1.94) and p.T158M., (HR = 1.13, 95% CI = 0.61, 2.07). Later age of onset was associated with individuals with the mutation p.R168X, (HR = 0.60, 95% CI = 0.3, 1.23) p.R255X, (HR = 0.64, 95% CI = 0.3, 1.35) and p.R133C, (HR = 1.37, 95% CI = 0.71, 2.64) (see Figure 9 and table 5).

Trajectory between Tanner stage two and menarche in cases with Rett syndrome

Survival analysis between Tanner stage two and menarche (n = 150) (see Figure 10 and Table 6) identified the average time under analysis to be 2.97 years, with a range of 0.001-12.06 years. A quarter of cases had progressed between these two stages in 1.7 years, 50% in 3.4 years and 75% in 7.6 years. The most common duration between the two events was 3 years (n = 73). Pictorial representation in the form of two-way scatter plots revealed a longer progression period between the two events in cases who reached Tanner stage two at an earlier age (see Figure 13). Individuals who were of normal weight (HR = 1.26, 95% CI = 0.74, 2.15) or overweight (HR = 1.27, 95% CI = 0.43, 3.76) progressed between these two stages more rapidly compared with those who were underweight (see Figure 11). Individuals with mutations p.R306C (HR = 2.86, 95% CI = 0.82, 9.93) and p.R294X, (HR = 1.9, 95% CI = 0.78, 4.9) had a shorter period of time between the two events, and p.T158M, (HR = 0.50, 95% CI = 0.18, 1.4), p.R270X, (HR = 0.48, 95% CI = 0.16, 1.41) and p.R255X, (HR = 0.7, 95% CI = 0.24, 2.11) had a longer period of time than those with the baseline mutation (mutation negative) (see Figure 12 and table 7).

Management of Menstruation in Rett syndrome

One hundred and seventy two cases had reached menarche and were included in the investigation of menstrual management and related issues. Of these 73 (42%) used a form of menstrual suppressant the most common being the oral contraceptive pill (n = 41) (see Figure 14) and secondly, Depot Medroxy progesterone acetate (DMPA) (n = 27). Linear regression revealed that WeeFIM scores were higher though not significantly for patients using a menstrual suppressant, average = 29.16 (\pm 12.11) (Odds Ratio(OR) = -0.01, 95% CI = -0.01, 0.01, p = 0.323) compared to patients not using a suppressant, average = 31.31 (\pm 16.03). Age was also found to impact the use of menstrual suppressants with patients on suppressants being on average 1.3 years older than those not, although this difference was not significant (OR = 0.01, 95% CI = -0.001, 0.03, p = 0.09). Logistic regression identified that females with mutations p.R106W (OR = -0.57, 95% CI = -1.07, -0.07, p = 0.025) and p.R270X (OR = 0.43, 95% CI = 0.08, 0.78, p = 0.017) were significantly more likely to use a menstrual suppressant. Mothers whose daughters were on some form of suppressant commented:

“Our daughter is on the oral "Pill" continuously as her periods distressed her greatly; she seemed to be in great pain and was lethargic for two days at the beginning of her period. Her seizures much are worse at that time”.

“I asked my Dr at one stage about the injection that prevents her periods for 3 or 6 months, but he would not give it to her as I did not have Government approval. So I give her Nurofen for the first 2 days and nights when she seems to have most discomfort.”

“[She] had DMPA injections for at least 2 years. When we heard about the story of a girl with osteo we took her off. [She] has had only three intermittent periods after that then none since a year. Then she had a heavy period this week”

Exploration of these issues experienced in relation to menstruation revealed increased seizure activity to be the most commonly occurring problem (n = 51). Mothers whose daughters experienced problems with seizures during menstruation commented:

“Seizure activity definitely increased at the onset of her periods. Bleeding was very heavy and due to inability to gauge her discomfort we decided to place her on the pill continuously to avoid this problem”.

“Seizures become more frequent with the onset of puberty. I have chosen not to manage menstruation and she is on the pill.”

“Seizure activity definitely increased at the onset of her periods. Bleeding was very heavy and due to inability to gauge her discomfort decided to place her on the pill continuously to avoid this problem. If breakthrough bleeding occurs I allow her to have a period - approximately every 6 months.”

Parents described other common issues associated with menstruation to include pain (n = 48), irregularity (n = 37), and heavy bleeding (n = 27) (see Figure 15). Comparisons between patients experiencing and those not experiencing issues identified that there was no significant association between subjects with issues and WeeFIM scores (OR = -0.00, 95% CI = -0.003, 0.003, p = 0.815), age (OR = -0.01, 95% CI = -0.2, 0.001, p = 0.091), or epilepsy (OR = 0.09, 95% CI = -0.04, 0.22, p = 0.153),

Five of the 172 subjects had undergone surgery to eliminate menstruation; individuals who underwent this surgery were aged 10, 11, 11, 14 and 16. Logistic regression identified that none of the variables had a significant impact on the use of eliminating surgery. One mother whose daughter's had a hysterectomy commented:

“This surgery was undergone solely for her comfort. Mother suffered severe pain, nausea all her reproductive years, when menstruating and didn’t want daughter to suffer similarly”.

Results Down syndrome

Pubertal Trajectory in Down syndrome

The dataset for the trajectory to the first sign of puberty in females over 12 years with Down syndrome comprised 66 individuals. The average time under analysis for individuals in this analysis was 12 years. The median age for puberty and menarche for individuals with Down syndrome was 12 years (see Figure 16 and Table 10). BMI impacted on age at puberty with higher BMI resulting in earlier onset (HR = 1.169, 95% CI = 0.85, 1.61). The trajectory to menarche utilised the same data set (n = 66) and the average time under analysis for the trajectory to menarche was 12.64 years and the median age to the event was 12.3 years (see Figure 17 and Table 11). The most common age at commencement of menarche was between 12 and 13 years of age (n = 23). Analysis for the relationship between BMI and age at menarche identified the risk of menarche to increase as BMI increased (HR = 1.89, 95% CI = 0.90, 1.57).

Menstrual Management in Down syndrome

All females over 12 years who had reached menarche were included in the investigation of menstrual management (n = 60). Of these 14 (23.33%) used a menstrual suppressant. Nearly half (43%) of those using a suppressant had a thyroid condition. Individuals using a menstrual suppressant were on average 1.18 years older than those not using a suppressant. The most commonly used suppressant was the oral contraceptive pill (n = 9) followed by DMPA (n = 2) (see Figure 18). Regression identified that; Wee FIM (OR = -0.01, 95% CI = -0.01, 0.002, p = 0.163); epilepsy (OR = 0.12, 95% CI = -0.59, 0.83, p = 0.735); thyroid

condition (OR = 0.23, 95% CI = -0.04, 0.49, $p = 0.096$), and age (OR = 0.02, 95% CI = -0.01, 0.06, $p = 0.201$) did not have a significant impact on whether or not individuals with Down syndrome used a menstrual suppressant. No parents of daughters with Down syndrome reported that their daughter had undergone surgery to eliminate menstruation. One mother whose daughter had previously used the oral contraceptive pill stated:

“Heavy bleeding was a problem, after 2 years we tried the contraceptive pill with some success but this caused a deep vein thrombosis (DVT) problem at the age of 20 years. As a result we have a lifelong problem and can no longer use the pill. Medication for blood thinning is permanent. We have subsequently had an IUD inserted with tremendous success. A definite improvement in quality of life for a young woman who really finds her period a great inconvenience.”

One mother whose daughter was not using any form of menstrual suppressant stated:

“I don’t believe in children with disabilities having to take medication unless really necessary”

Categorisation of the issues experienced in puberty identified the most common issue to be daughter’s understanding of what was going on ($n = 18$) (See Figure 19). This finding was reflected through numerous mothers’ comments which highlight some of the misunderstandings..

“I thought I had done a good job of explaining ‘the facts of life’ in simple and understandable terms for my daughter however, when her first period arrived I was horrified to realise she thought she was ‘having a baby’ ... so much for my expertise of explaining! We survived of course but I realised how difficult it was to be sure she ‘understood’ what was taking place with ‘details on many issues’.”

“[She] did not understand the appropriate behaviour and was easily persuaded into overt sexual behaviour by other normal teenagers e.g. kissing boys despite education to the contrary. [She] became socially withdrawn during puberty. This may be due to the teasing and rejection by other teens during these years. [She] was very outgoing, happy and accepted by peers prior to puberty”.

“My daughter has to be protected from sexual exploitation as she could be taken advantage of easily. This restricts her independence”

Of the 60 females included in this analysis 90% reported experiencing an issue.

Experiencing an issue was associated with higher BMI z-scores 1.03 (± 0.89) compared to 0.88 (± 0.54). Age was also found to be different with the average age of those experiencing issues being 18.70 (± 3.42) compared to 15.88 (± 2.97) in those with no issues. Regression identified that none of these changes was significant.

Discussion

This study aimed to describe the pubertal trajectory in females with Rett syndrome and Down syndrome. In addition it explored the management of menstruation within these two populations.

It was found that in females with Rett syndrome the median age at which individuals reached Tanner stage two was 11 years. In females with Down syndrome the most common age to Tanner stage two, was one year later than in Rett syndrome with the median age being 12 years. American Research examining the onset of puberty in the normative population has reported the average age of thelarche (onset of breast development) in Caucasians to be 10 years and in African American females it was one year earlier. Onset of pubarche was found to be 10.5 and 9 years of age in Caucasians and African American females, respectively

(Herman-Giddens, 2006). These findings suggest that the onset of puberty may be delayed in females with Rett syndrome and Down syndrome. A wide range was identified in the trajectory to Tanner stage two in Rett syndrome with the earliest onset being five to six years of age and the latest being 21 years of age. Both these findings fall significantly outside the pubertal norms suggesting pubertal trajectory in females with Rett syndrome is abnormal.

The median age to reach menarche in females with Rett syndrome was 14 years of age with the most common age to reach being 11-12 years. These findings are similar to those reported in Holm's 1986 study comprising of 21 females with Rett syndrome, Holm's study documented the average age of menarche in to be 11.2 years, limitations of Holm's study were the small sample size used and as the identification of mutations in the MECP2 gene had not yet been discovered this study was unable to explore the effect of genotype (Holm, 1986). In this sample of females with Rett syndrome the earliest onset of menarche was between eight and nine years of age and the latest was 23 years of age; puberty is classed as delayed if menarche has not been reached by the age of 16 (Shah, 1997). The finding of menarche occurring at 23 years of age further suggests that pubertal trajectory may be abnormal in females with Rett syndrome. In females with Down syndrome the most common age to reach menarche was 12 to 13 years with the median age being 12.3 years. These findings are similar to those of Scola, Seigfried & Pueschel (1992) and Arnell, Gustafsson, Ivarsson & Anneren (1996) studies, which reported the average age of menarche to be 13.2 years, range (11.8-16.2) and 12.6 years, range (10-16), respectively. Findings regarding puberty in the normative sample of Americans were described through the National Health and Nutrition Examination Survey (NHANES) study which identified the average age of menarche to be 12.6 years in Caucasians and 12.1 years in coloured females, both of which are similar to the findings in the current study (Herman-Giddens, 2006).

Examination of the trajectory between Tanner stage two and menarche in females with Rett syndrome revealed that half of the subjects progressed between the two stages in 3.4 years, with the most common duration between the two events being 2-3 years. It was found that those who reached Tanner stage two at an earlier age took a longer period of time to reach menarche. The study of Marti-Henneberg and Vizmanos (Marti-Henneberg & vizmanos, 1997) based on the normative population reported a shorter time frame between the two events with an average age of $1.96 \text{ years} \pm 0.06$. This study also identified that the timing of onset of Tanner stage two influenced the duration between the onset and menarche, with those commencing puberty at an earlier age taking a longer length of time between the two events.

Body weight was found to impact on pubertal trajectory in both females with Rett syndrome and Down syndrome, with higher BMI scores associated with earlier onset of puberty and menarche and a shorter duration between these two stages. These findings concur with previous population based research in the normative population which reported a strong relationship between higher BMI's and earlier onsets of puberty (Anderson, Dallal, & Must, 2003; Lin-Su, Vogiatzi, & New, 2002). Pubertal trajectory in Rett syndrome was analysed in relation to genotype, revealing the greatest impact to be the trajectory between Tanners stage two and menarche. Cases with mutation R270X and R255X were found to take the greatest length of time to progress between these two stages. Australian population based research exploring the genotype phenotype relationship in Rett syndrome have identified that cases with these mutations to have the most severe phenotype (Bebbington et al., 2008; Colvin et al., 2003; Colvin et al., 2004; H. Leonard et al., 2003).

Analysis of menstrual management in females with Rett syndrome and Down syndrome found oral contraceptive pills to be the most frequently used method of menstrual suppressant

followed by DMPA. In females with Rett syndrome the most common issue experienced was increased seizure activity, whereas in Down syndrome it was lack of understanding. Mother's comments in both Rett syndrome and Down syndrome highlighted numerous issues experienced in puberty. Functional ability, BMI, age of epilepsy onset and the presence of a thyroid condition had very little effect on the menstrual suppressants used and issues experienced in both Rett syndrome and Down syndrome. Similar findings were reported in a study conducted in Brussels ($n = 397$) which explored the use of suppression and elimination in females with a mild to profound intellectual disability finding 22.2% of cases were sterilised, 18% used OCP and 17.6% used DMPA (Servais et al., 2002). The identification of lack of understanding which was reported as the most frequently occurring issue in females with Down syndrome is supported in previous research into intellectual disability which identified that this population does not receive adequate education leading up to the onset of puberty (Lin & Barnhart, 2007; McEvoy, Chang, & Coupey, 2004).

In interpreting the findings from this study several limitations should be considered. The data collection method through surveys resulted in the possibility of recall error where parents or carers provided incorrect answers due to memory recall over time. In the Rett syndrome questionnaires parents were asked to document their daughters Tanner stage however were not asked the specific age at which the stage occurred. The main limitation of the study was that in the Down syndrome NOW questionnaire parents were only asked to answer the puberty section if their daughter was over the age of 12, which may have resulted in the loss of valuable information. Although limitations exist, this study has many strengths and provides valuable insight into puberty within these two populations. This study is unique as it describes the trajectory through puberty along with genotype and BMI which has to our knowledge never been studied before.

The information reported in this study is valuable for parents, carers, health care professionals and educators as it highlights the trajectory through puberty and in the management of menstruation it highlights what menstrual suppressants are being used and the issues experienced. This is valuable information as many menstrual suppressants have been found to have serious health consequences such as deep vein thrombosis, osteopenia and other bone dysmorphologies (H. Leonard, et al., 1995; H. Leonard, Thomson, Glasson, Fyfe, Leonard, Bower, et al., 1999; H. Leonard, Thomson, Glasson, Fyfe, Leonard, Ellaway, et al., 1999; Watson, Lentz, & Cain, 2006) For health professionals this study highlights the need for education programmes or interventions to be run for the individuals and their parents to best prepare them for this challenging transition in life.

Occupational therapists could assist individuals with intellectual disabilities and their families through this transition, by running education groups to prepare both the individual and their families of what to expect, provide recourses relating to menstrual suppressants, contraceptives and strategies in managing menstruation. As mentioned earlier the side effects associated with many of the suppressants have serious health consequences for the individuals, as part of a multidisciplinary team Occupational therapist could assist in informing parents of the options available and their advantages and disadvantages.

To our knowledge this is the first study to explore pubertal trajectory and management of menstruation in females with Rett syndrome and Down syndrome. To further assist individuals in these populations and expand health care professionals knowledge in the area further population based longitudinal research is needed.

References

- Allison, P. D. *Survival Analysis using SAS: A practice Guide*. USA: SAS Institute Inc.
- Amir, R. E., Van Der Veyver, I. B., Wan, M., Tran, C. Q., Francke, U., & Zoghbi, H. U. (1999). Rett syndrome is caused by mutations in x-linked MECP2 encoding methyl-CpG-binding protien 2. *Nature Genetics*, 23, 185-188.
- Anderson, S., E, Dallal, G., E, & Must, A. (2003). Relative weight and race influence average age at menarche: Results from two nationally representative surveys of US girls studied 25 year appart. *Journal of the American Academy of Pediatrics* 111(4), 844-849.
- Arnell, H., Gustafasson, J., Ivarsson, S. A., & Anneren, G. (1996). Growth and pubertal development in Down Syndrome. *Acta Paediatrics*, 85, 1102-1106.
- Bebbington, A., Anderson, A., Ravine, D., Fyfe, S., Pineda, M., Klerk, N., et al. (2008). Investigating the genotype phenotype relationship in Rett syndrome using an international data set. *Neurology*, 70(868-875).
- Bourke, J., Ricciardo, B., Aiberti, K., Jacoby, P., Dyke, P., Msall, M., et al. (2008). Physical and mental health in mothers of children with Down syndrome *The Journal of Paediatrics*, 153(3), 320-326.
- Bower, C., Rudy, E., Callaghan, A., Quick, J., Cosgrove, P., & Nassar, N. (2009). *Reports of the birth defects registry of Western Australia*.
- Colvin, L., Fyfe, S., Leonard, H., Schiavello, S., Ellaway, C., Klerk, N., et al. (2003). Describing the phenotype in Rett syndrome using a population database. *Archives of Disability and Childhood*, 88, 38-43.

Colvin, L., Leonard, H., Klerk, N., Weaving, L., Davis, M., Williamson, S., et al. (2004).

Refining the phenotype of common mutations in Rett syndrome. *Journal of Medical Genetics*, 41, 25-30.

Denzer, C., Weibel, A., Muche, R., Karges, B., Sorgo, W., & Wabitsch, M. (2007). Pubertal development in obese children and adolescents. *International Journal of Obesity*, 31, 1509-1519.

Ellis, B. J. (2004). Timing of pubertal maturation in girls: An intergrated life history approach. *Psychological Bulletin*, 130(6), 920-958.

FileMaker. (2010). FileMaker Retrieved 7th October, 2010, from <http://www.filemaker.com/>

Gibson, P., Newton, R., Selby, K., Price, D., Leyland, K., & Addison, G. (2005).

Longitudinal study of thyroid function in Down syndrome in the first two decades. *Archives of Disability and Childhood*, 90, 574-578.

Hawli, Y., Nasrallah, M., & Fuleihan, G. (2009). Endocrine and musculoskeletal abnormalities in patients with Down syndrome. *Endocrinology*, 5, 327-334.

Herman-Giddens, M. (2006). Recent data on pubertal milestones in United States children: the secular trend toward earlier development. *International Journal of Andrology*, 29, 241-246.

Holm, V. A. (1986). Physical growth and development in patients with Rett syndrome. *American Journal of Medical Genetics*, 24, 119-126.

Hosmer, D., Lemeshow, S., & May, S. (2008). *Applied Survival Analysis* (2 ed.). Canada: John Wiley & Sons.

Huppke, P., Roth, C., Christen, H., Brockmann, K., & Hanefeld, F. (2001). Endocrinological study on growth retardation in Rett syndrome. *Acta Paediatrics*, 90, 1257-1261.

Kaplowitz, P., B. (2008). Link between body fat and the timing of puberty. *Pediatrics*, 121, 208-217.

- Klein, J. P., & Moeschberger, M. L. *Survival Analysis: Techniques for Censored and Truncated Data*. USA: Springer.
- Kuczmarski, R., & Flegal, K. (2000). Criteria for definition of overweight in transition: background and recommendations for the United States. *Am J Clin Nutr*, 72, 1074-1081.
- Laurvick, C., L, Klerk, N., Bower, C., Christodoulou, J., Ravine, D., Ellaway, C., et al. (2006). Rett syndrome in Australia: A review of the epidemiology. *The Journal of Pediatrics*, 148, 347-352.
- Leonard, H., Bower, C., & English, D. (1997). The prevalence and incidence of Rett syndrome in Australia. *European Child & Adolescent Psychiatry*, 6, 8-10.
- Leonard, H., Bower, C., & English, D. (1997). The prevalence and incidence of Rett syndrome in Australia. *European Child and Adolescent Psychiatry*, 6, 8-10.
- Leonard, H., Colvin, L., Christodoulou, J., Schiavello, S., Williamson, S., Davis, M., et al. (2003). Patients with the R133C mutation: is their phenotype different from patients with Rett syndrome with other mutations. *Journal of Medical Genetics*, 40, 1-7.
- Leonard, H., Thomson, M., Bower, C., Fyfe, S., & Constantinou, J. (1995). Skeletal abnormalities in Rett syndrome: Increasing evidence for dysmorphogenetic defects. *American Journal of Medical Genetics*, 58, 282-285.
- Leonard, H., Thomson, M., Glasson, E., Fyfe, S., Leonard, S., Bower, C., et al. (1999). A population based approach to the investigation of osteopenia in Rett syndrome. *Developmental Medicine & Child Neurology*, 41, 323-328.
- Leonard, H., Thomson, M., Glasson, E., Fyfe, S., Leonard, S., Ellaway, C., et al. (1999). Metacarpophalangeal pattern profile and bone age in Rett syndrome: Further radiological clues to the diagnosis. *American Journal of Medical Genetics*, 83, 88-95.

- Leonard, S., Bower, C., Petterson, B., & Leonard, H. (2000). Survival of infants born with Down syndrome. *Paediatric and Perinatal Epidemiology*, 14, 163-171.
- Lin-Su, K., Vogiatzi, M., & New, M. (2002). Body mass index and age at menarche in an adolescent clinic population. *Clinical Pediatrics*, 41(7), 501-506.
- Lin, K., & Barnhart, K. (2007). The clinical rational for menses free contracteption. *Journal of Women's Health*, 16(8), 1171-1180.
- Marshall, W., A, & Tanner, J., M. (1969). Variations in pattern of pubertal changes in girls. *Archives of Disease in Childhood*, 44, 291-303.
- Marti-Henneberg, C., & vizmanos, B. (1997). The duration of puberty in girls is related to the timing of its onset. *The Journal of Pediatrics*, 131(4), 618-621.
- McEvoy, M., Chang, J., & Coupey, S. (2004). Common menstrual disorders in adolescence. *Nursing Interventions*, 29(1), 41-49.
- Mount, R. H., Hastings, R. P., Reily, S., Cass, S., & Charman, T. (2001). Behavioural and emotional features in Rett syndrome. *Disability and Rehabilitation*, 23(3/4), 129-138.
- Msall, M., E, DiGaudio, K., Rodgers, B., T, LaForest, S., Catanzaro, N., L, Campbell, J., et al. (1994). The functional independance measure for children (WeeFIM). *Clinical Pediatrics*, 33, 421-430.
- Msall, M., E, Ottenbacher, K., Duffy, L., Lyon, N., Heya, N., Phillips, L., et al. (1996). Reliability and validity of the WeeFim in children with neurodevelopmental disabilities. *Pediatric Research*, 39, 2251.
- Neul, J., L. (2008). Specific mutations in Methyl-CpG-Binding Protien 2 confer different severity in Rett syndrome. *Neurology*, 70(16), 1313.
- Nosek, M., A, Foley, C., C, Hughes, R., B, & Howland, C., A. (2001). Vulnerabilities for abuse among women with disabilities. *Sexuality and Disability*, 19(3), 177-189.

- Ogden, C., Kuczmarski, R., Flegal, K., Mei, Z., Guo, S., Wei, R., et al. (2002). Centres for Disease Control and Prevention 2000 growth charts for the United States : Improvements to the 1977 National Centre for Health Statistics version. *Official Journal of the American Academy of Pediatrics*, 109(1), 45-60.
- Onland-Moret, N., Peeters, P., Van Gills, C., Clavel-Chapelon, F., Key, T., Tjonneland, A., et al. (2005). Age at menarche in relation to adult height. *American Journal of Epidemiology*, 162(7), 624-632.
- Petterson, B., Leonard, H., Bourke, J., Sanders, R., Chalmers, R., Jacoby, P., et al. (2005). Idea intellectual disability exploring answers: A population-based database for intellectual disability in Australia. *Annals of Human Biology*, 32(2), 237-243.
- Plant, T., & Barker-Gibb, M. (2004). Neurobiological mechanisms of puberty in higher primates. *Human Reproduction Update*, 10(1), 67-77.
- Prasher, V., & Gomez, G. (2007). Natural history of thyroid dysfunction in adults with Down syndrome - 10 year follow up study.
- Scola, P. S., Siegfried, M., & Pueschel, M. D. (1992). Menstrual cycles and basal body temperature curves in woman with Down syndrome. *Obstetrics & Gynecology*, 79(1), 91-93.
- Servais, L., Jaques, D., Leach, R., Conod, L., Hoyois, P., Dan, B., et al. (2002). Contraception for women with intellectual disability: prevalence and determinants. *Journal of Intellectual Disability Research*, 46(2), 108-119.
- Shah, N. (1997). Delayed puberty. *Indian Journal of Pediatrics*, 64, 159-164.
- STATA. (2010). Data Analysis and Statistical Software Retrieved 7th October, 2010, from <http://www.stata.com/>
- Terasawa, E., & Fernandez, D. (2001). Neurobiological mechanisms of the onset of puberty in primates. *Endocrine Reviews*, 22, 111-151.

Watson, K., Lentz, M., & Cain, K. (2006). Associations between fracture incidence and use of depot medroxyprogesterone acetate and antiepileptic drugs in women with developmental disabilities. *Women's Health Issue, 16*, 346-352.

Figures

Figure 4

Kaplan Meier Graph, the trajectory to Tanner stage two in Rett syndrome

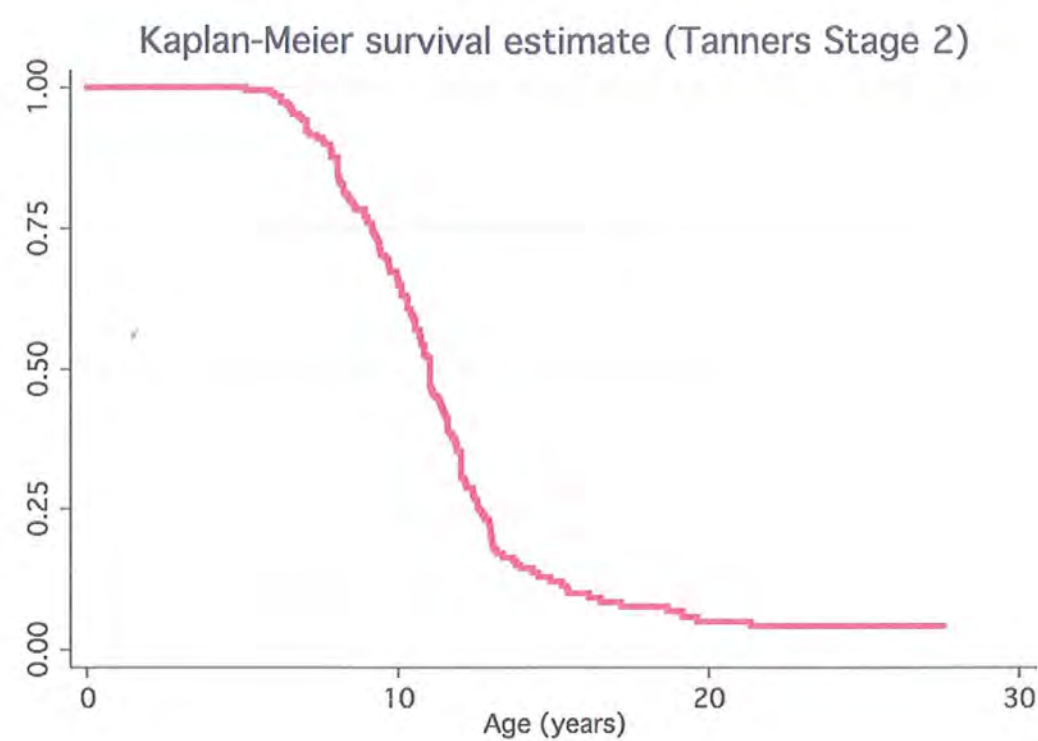


Figure 5

Kaplan Meier Graph, Effect of BMI on the trajectory to Tanner stage two in Rett syndrome

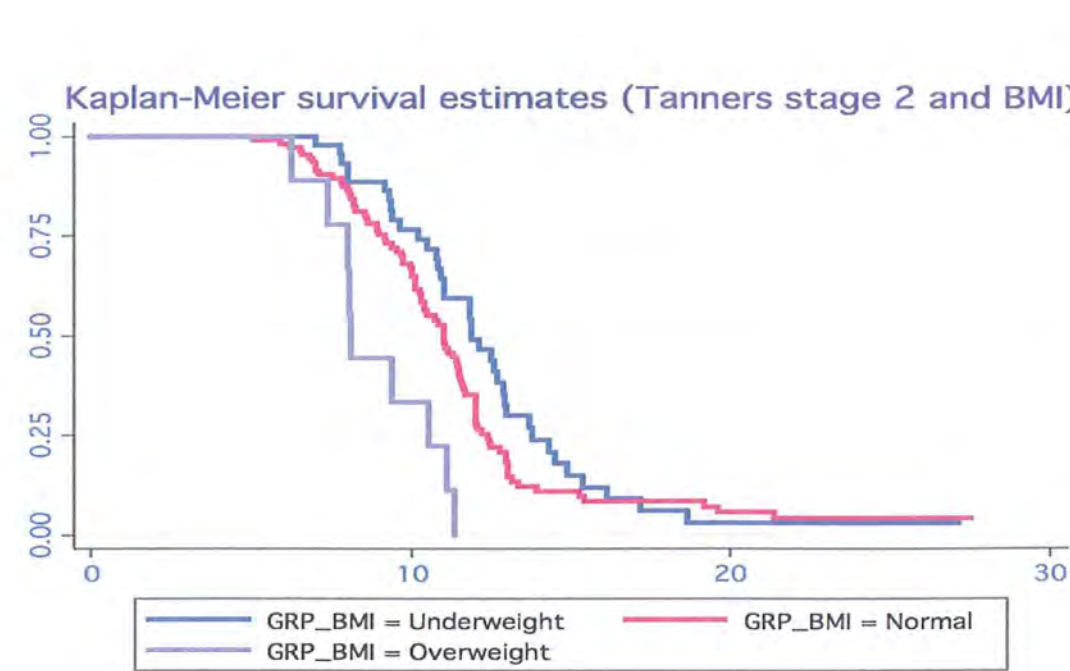


Figure 6

The relationship between Tanner stage two and mutation

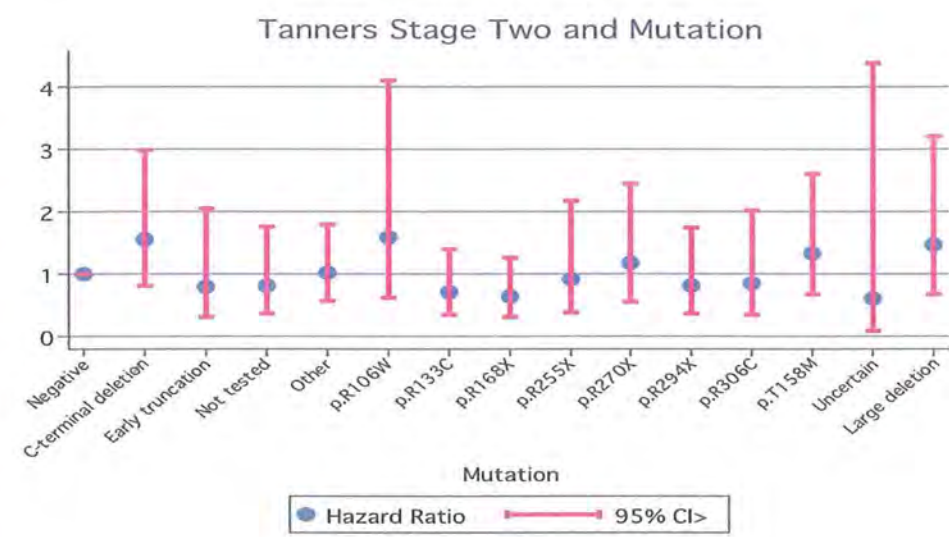


Figure 7

Kaplan Meier Graph, the trajectory to Tanner stage two in Rett syndrome

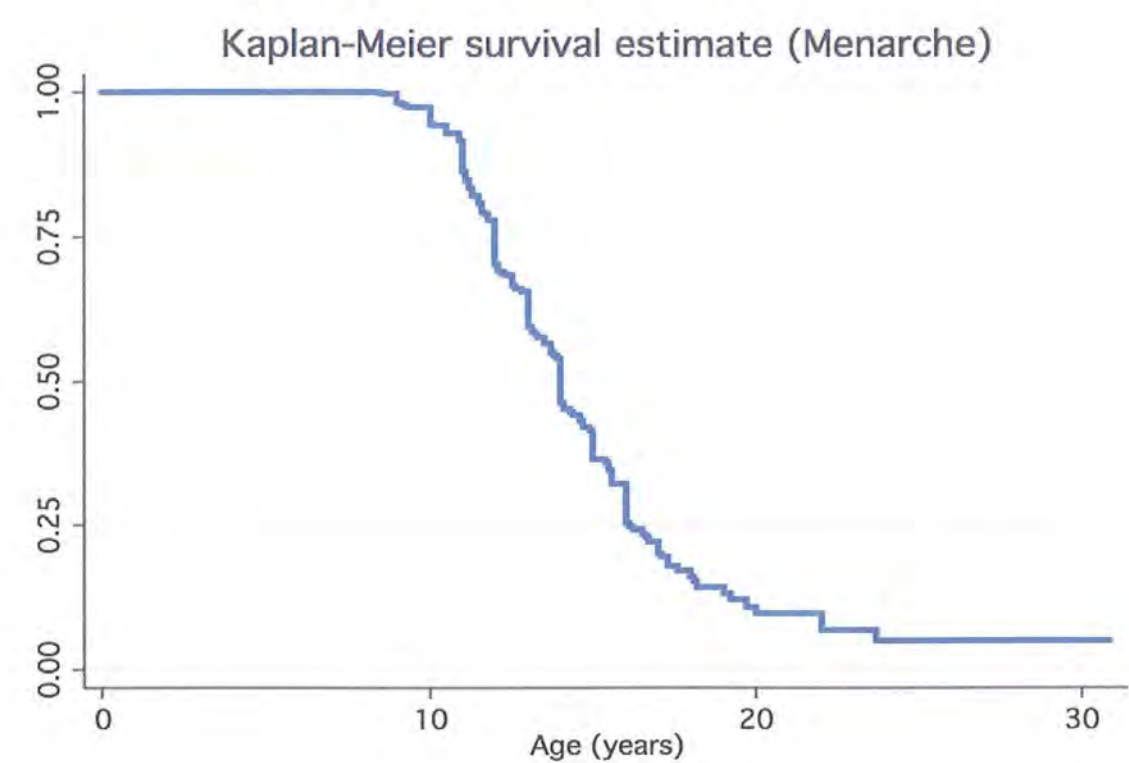


Figure 8
Kaplan Meier Graph, Effect of BMI on the trajectory to Menarche in Rett syndrome

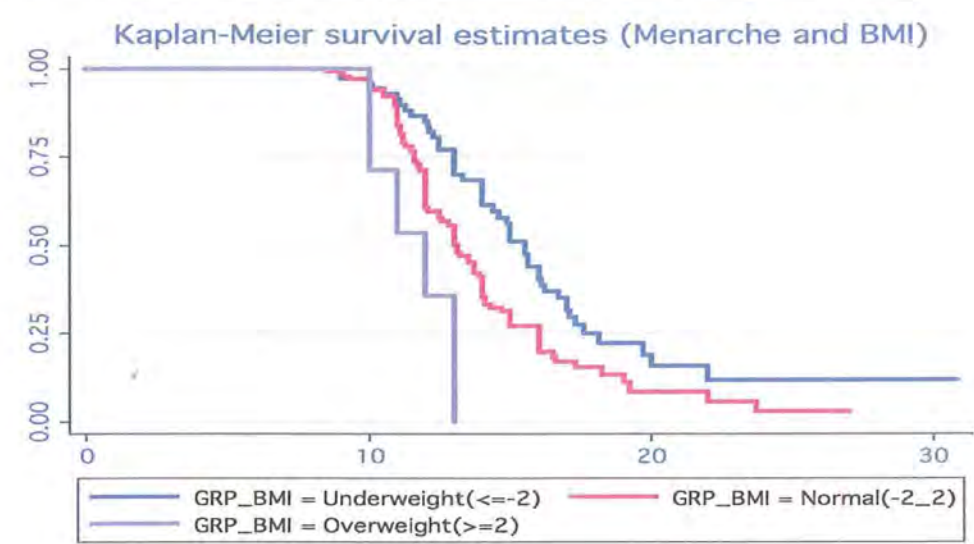


Figure 9
The relationship between the Trajectory to Menarche and mutation

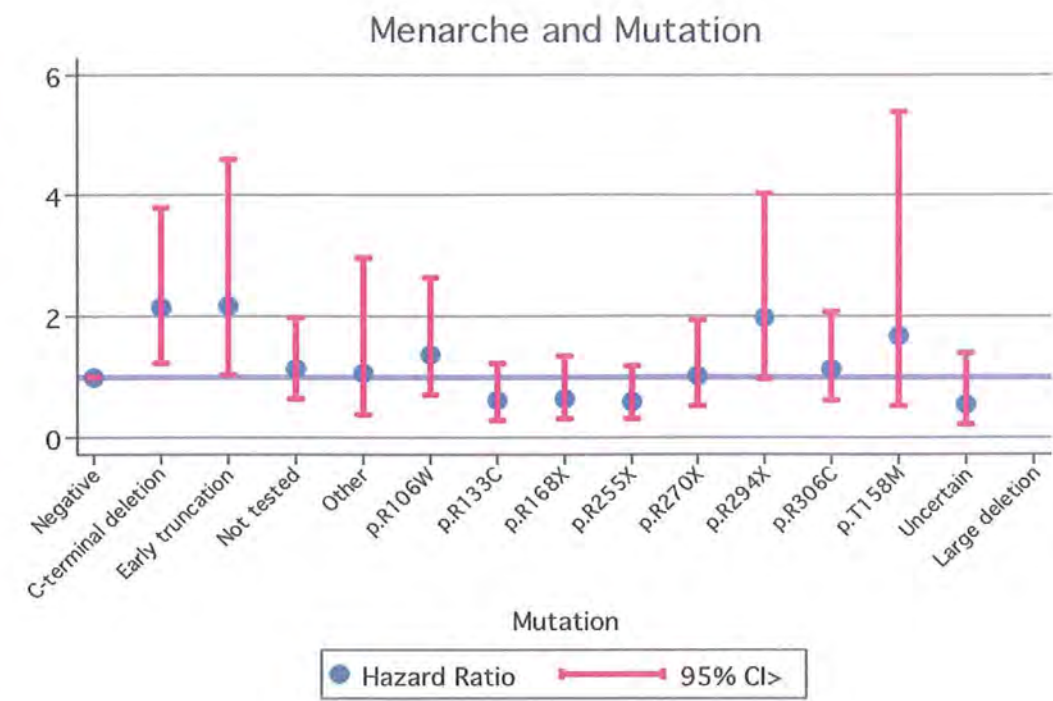


Figure 10

Kaplan Meier Graph, the trajectory between Tanner stage two and menarche in Rett syndrome

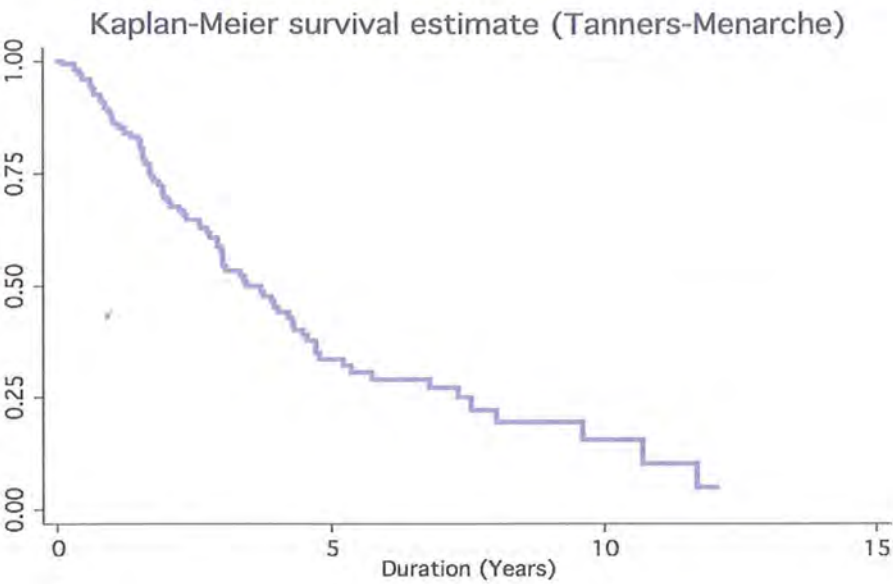


Figure 11

Kaplan Meier Graph, Effect of BMI on the trajectory between Tanner stage two and menarche in Rett syndrome

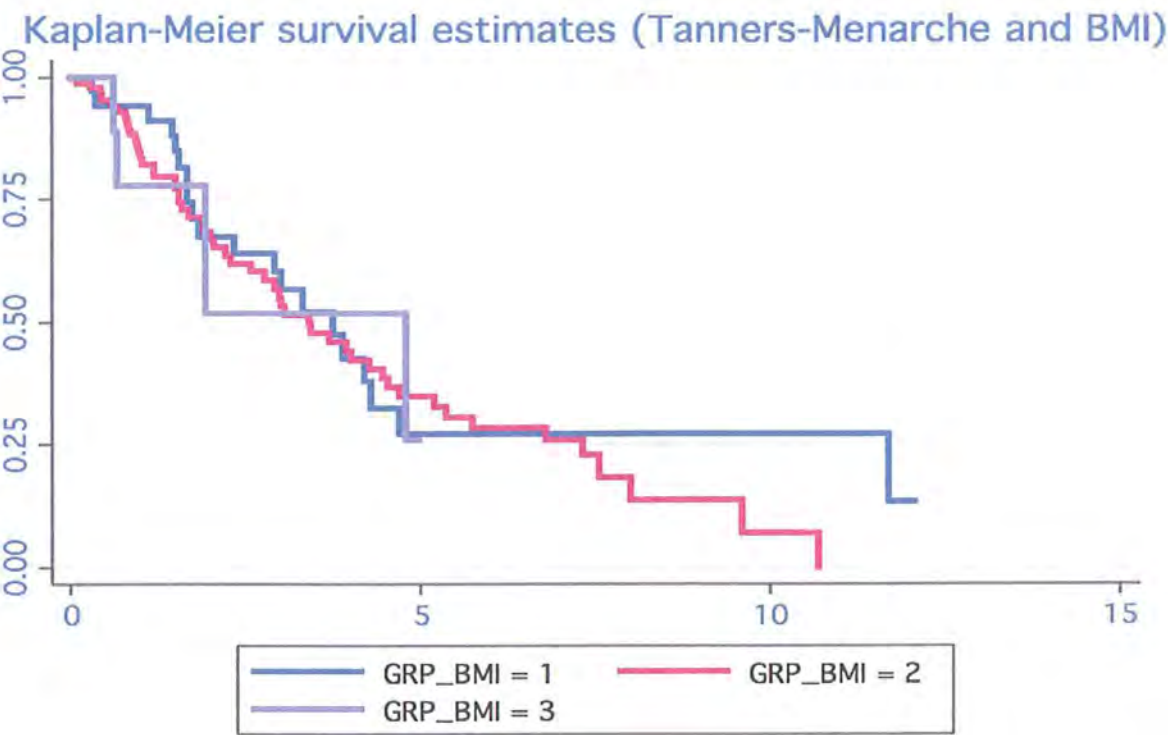


Figure 12

The relationship between the Trajectory from Tanner stage two to Menarche and mutation

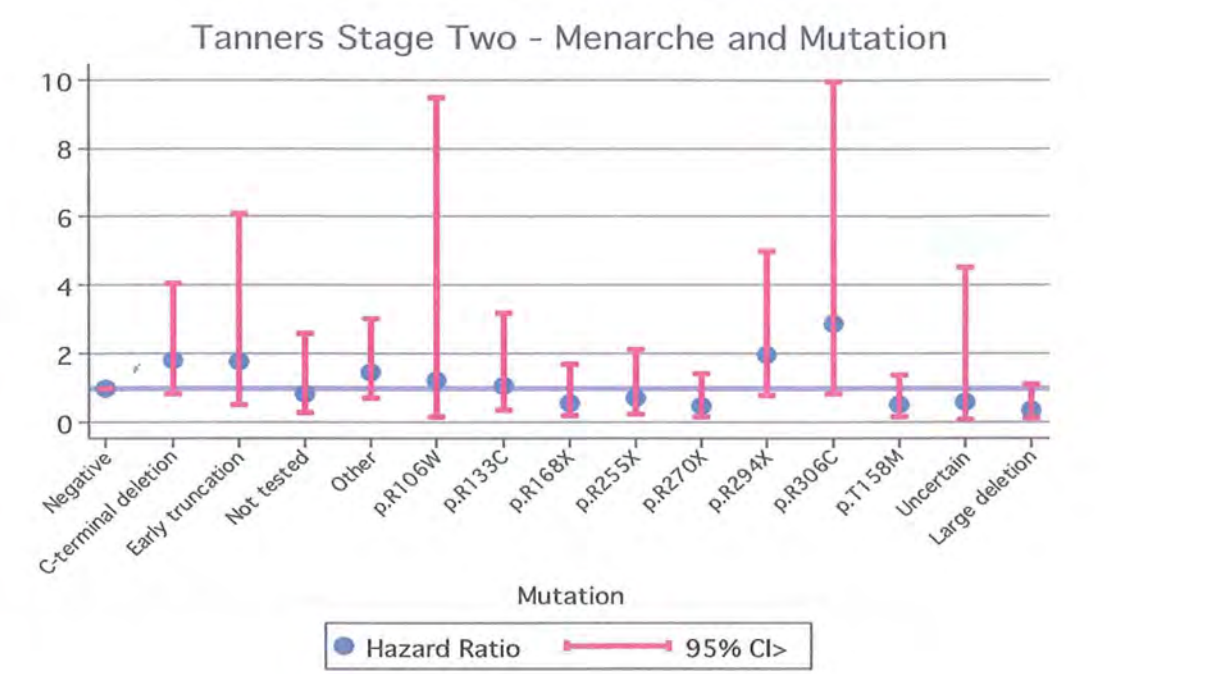


Figure 13

The relationship between Tanner stage two and Menarche

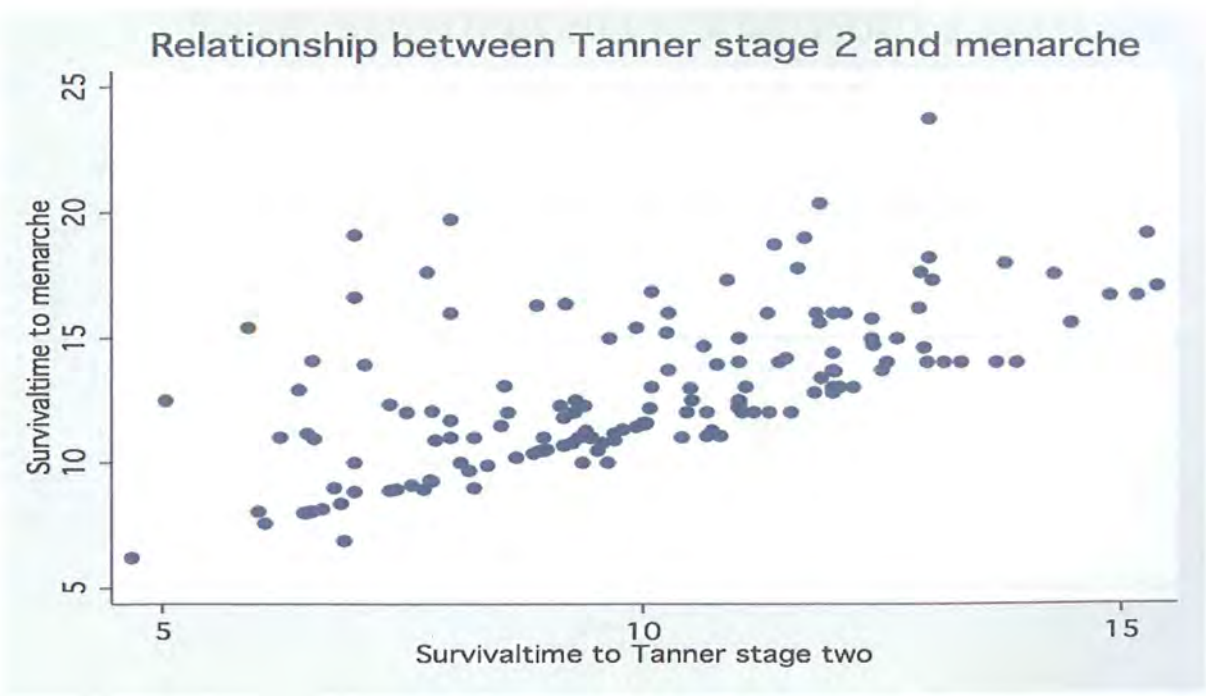


Figure 14

The use of menstrual suppressants in females with Rett syndrome

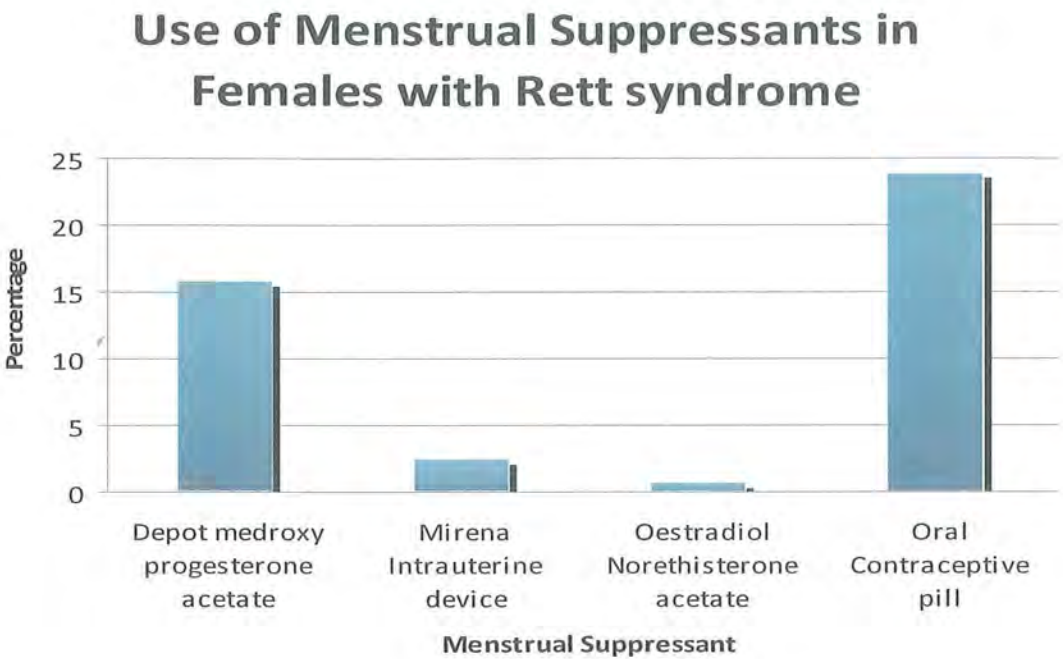


Figure 15

The issues experienced in puberty in females with Rett syndrome

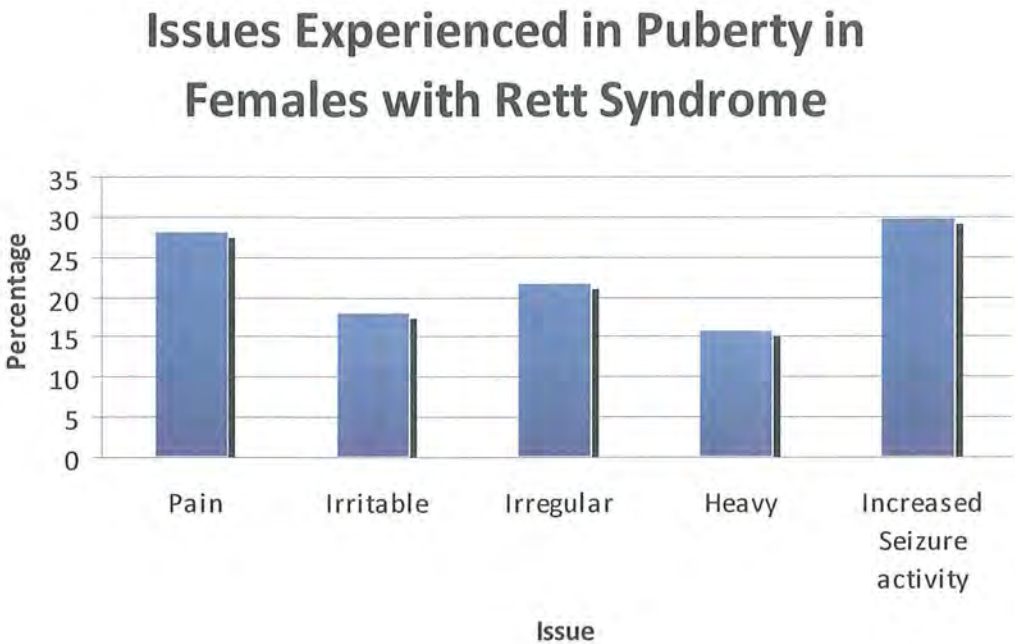


Figure 16

Kaplan Meier Graph, the trajectory to the first sign of puberty in Down syndrome

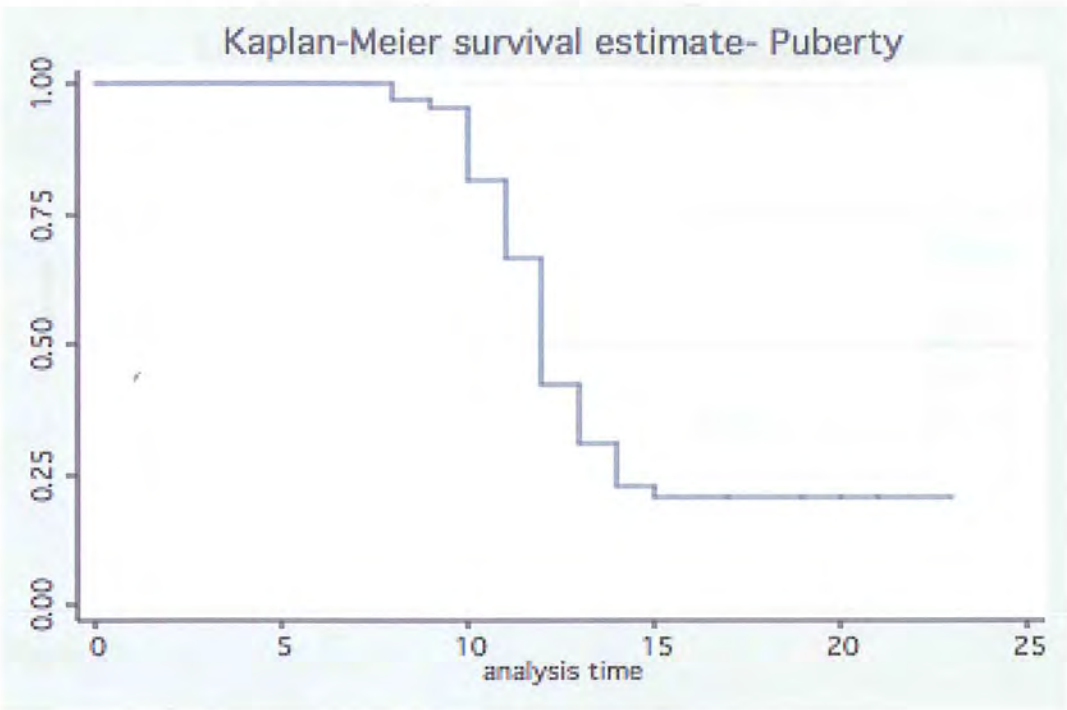


Figure 17

Kaplan Meier Graph, the trajectory to menarche in Down syndrome

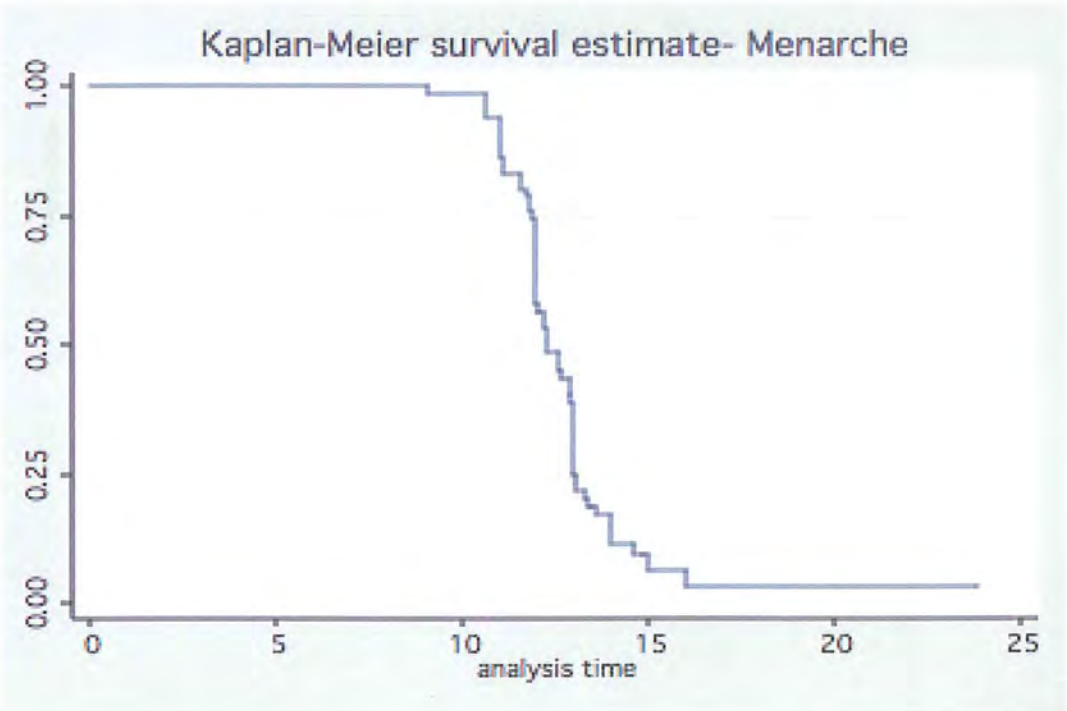


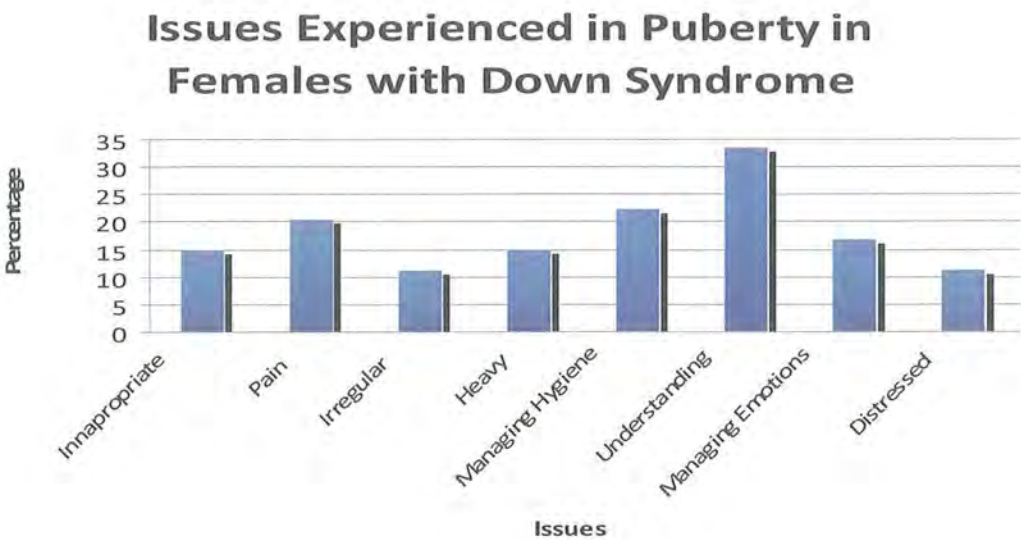
Figure 18

The use of menstrual suppressants in females with Down syndrome



Figure 19

The issues experienced in puberty in females with Down syndrome



Tables

Table 2
Life Table to Tanners Stage Two

Interval 1		Beg Total	Failure ^a	Censored ^b	Survival	SE	95% conf. Int	
2	3	221	0	2	1	1	--	--
3	4	219	0	6	1	1	--	--
4	5	213	0	14	1	--	--	--
5	6	199	2	9	0.99	0.01	0.96	1.00
6	7	188	9	5	0.94	0.02	0.90	0.97
7	8	174	12	3	0.88	0.02	0.82	0.92
8	9	159	21	6	0.76	0.03	0.69	0.81
9	10	132	17	5	0.66	0.04	0.58	0.72
10	11	110	23	5	0.52	0.04	0.44	0.59
11	12	82	26	2	0.35	0.04	0.28	0.42
12	13	54	23	2	0.20	0.03	0.14	0.26
13	14	29	8	1	0.14	0.03	0.09	0.20
14	15	20	3	1	0.12	0.03	0.07	0.18
15	16	16	3	0	0.10	0.02	0.06	0.15
16	17	13	2	0	0.08	0.02	0.05	0.13
17	18	11	1	0	0.08	0.02	0.04	0.13

Life Tables to Tanner stage two continued

Interval 1		Beg Total	Failure ^a	Censored ^b	survival	std error	95% conf. Int	
18	19	10	1	1	0.07	0.02	0.03	0.12
19	20	8	2	0	0.05	0.02	0.02	0.10
21	22	6	1	0	0.04	0.02	0.02	0.09
22	23	5	0	1	0.04	0.02	0.02	0.09
24	25	4	0	1	0.04	0.02	0.02	0.09
25	26	3	0	1	0.04	0.02	0.02	0.09

^a Refers to the onset of Tanner stage two

^b Refers to the individuals who died or withdrew from the study

Table 3

Cox Proportional Hazards Ratio; Genotype and Trajectory to Tanner stage two

-t	HR ^a	SE ^b	z	p>[z]	[95% conf. Interval	
C-terminal	1.56	0.52	1.34	0.180	0.81	2.99
Early truncation	0.80	0.39	-0.46	0.646	0.31	2.06
Not tested	0.81	0.32	-0.53	0.595	0.37	1.76
Other	1.02	0.29	0.05	0.957	0.58	1.79
p.R106W	1.60	0.77	0.97	0.334	0.62	4.11
p.R133c	0.70	0.25	-1.01	0.313	0.35	1.40
p.R168X	0.64	0.22	-1.29	0.197	0.32	1.26
p.R255X	0.91	0.41	-0.21	0.831	0.38	2.18
p.R270X	1.17	0.44	0.41	0.684	0.55	2.46
p.R294X	0.81	0.32	-0.54	0.586	0.37	1.75
p.R306C	0.84	0.38	-0.39	0.700	0.35	2.02
p.T158M	1.33	0.45	0.84	0.402	0.68	2.60
Uncertain	0.60	0.61	-0.51	0.613	0.08	4.39
Larger deletion	1.47	0.59	0.97	0.332	0.67	3.21

^a Refers to Hazards Ratio

^b Refers to Standard Error

Table 4
Life table and Menarche

Interval		Beg Total	Failure ^a	Censored ^b	Survival	SE	95% conf. Int	
2	3	320	0	2	1	0	--	--
3	4	318	0	7	1	0	--	--
4	5	311	0	16	1	0	--	--
5	6	295	0	10	1	0	--	--
6	7	285	0	7	1	0	--	--
7	8	278	0	5	1	0	--	--
8	9	273	1	17	1.00	0.00	0.97	1.00
9	10	255	6	9	0.97	0.01	0.94	0.99
10	11	240	14	15	0.91	0.02	0.87	0.94
11	12	211	31	9	0.78	0.03	0.72	0.82
12	13	171	27	12	0.65	0.03	0.58	0.71
13	14	132	23	4	0.53	0.03	0.47	0.60
14	15	105	24	6	0.41	0.03	0.34	0.48
15	16	75	16	7	0.32	0.03	0.25	0.38
16	17	52	16	4	0.22	0.03	0.16	0.28
17	18	32	7	6	0.16	0.03	0.11	0.22
18	19	19	3	2	0.14	0.03	0.09	0.20

Life Tables to Menarche stage two continued

Interval		Beg Total	Failure ^a	Censored ^b	Survival	SE	95% conf. Int	
19	20	14	3	2	0.10	0.03	0.06	0.16
20	21	9	1	1	0.09	0.03	0.05	0.15
22	23	7	2	1	0.06	0.02	0.03	0.12
23	24	4	1	0	0.05	0.02	0.02	0.11
25	26	3	0	1	0.05	0.02	0.02	0.11
26	27	2	0	1	0.05	0.02	0.02	0.11

^a Refers to the onset of Menarche

^b Refers to the individuals who died or withdrew from the study

Table 5
Cox Proportional Hazards Ratio; Genotype and Trajectory to menarche

-t	HR ^a	SE ^b	z	p>[z]	[95% conf. Interval	
C-terminal	2.16	0.62	2.65	0.008	1.22	3.80
Early truncation	2.18	0.83	2.03	0.042	1.03	4.61
Other	1.13	0.33	0.43	0.666	0.64	1.99
p.R106W	1.06	0.56	0.11	0.913	0.38	2.96
p.R133c	1.37	0.46	0.95	0.343	0.71	2.64
p.R168X	0.60	0.22	-1.39	0.166	0.30	1.23
p.R255X	0.64	0.24	-1.18	0.238	0.30	1.35
p.R270X	0.60	0.21	-1.48	0.138	0.30	1.18
p.R294X	1.01	0.34	0.03	0.979	0.52	1.94
p.R306C	1.98	0.72	1.87	0.061	0.97	4.04
p.T158M	1.13	0.35	0.38	0.704	0.61	2.07
Uncertain	1.67	1.00	0.86	0.389	0.52	5.37
Larger deletion	0.56	0.26	-125	0.212	0.22	1.40

^aRefers to Hazards Ration

^bRefers to Standard Error

Table 6
Life table and Tanners stage two-Menarche

Interval ^a		Beg Total	Failure ^b	Censored ^c	Survival	SE	95% conf. Int	
0	1	150	19	1	0.87	0.03	0.81	0.92
1	2	130	22	35	0.70	0.04	0.62	0.77
2	3	73	12	6	0.58	0.05	0.49	0.66
3	4	55	11	6	0.46	0.05	0.36	0.55
4	5	38	9	6	0.34	0.05	0.25	0.44
5	6	23	3	1	0.30	0.05	0.20	0.39
6	7	19	1	4	0.28	0.05	0.19	0.38
7	8	14	2	4	0.23	0.05	0.14	0.34
8	9	8	1	1	0.20	0.06	0.11	0.31
9	10	6	1	2	0.16	0.06	0.07	0.28
10	11	3	1	0	0.11	0.06	0.03	0.25
11	12	2	1	0	0.05	0.05	0.01	0.20
12	13	1	0	1	0.05	0.05	0.01	0.20

^a Interval refers to the period of time in years

^b Refers to the onset of Menarche

^c Refers to the individuals who died or withdrew from the study

Table 7

Cox Proportional Hazards Ratio; Genotype and Trajectory between Tanner stage Two and menarche

-t	HR ^a	SE ^b	z	p>[z]	[95% conf. Interval	
C-terminal	1.82	0.74	1.46	0.144	0.82	4.06
Early truncation	1.78	1.12	0.92	0.358	0.52	6.08
Not tested	0.85	0.48	-0.29	0.769	0.28	2.58
Other	1.45	0.54	1.01	0.313	0.70	3.01
p.R106W	1.24	1.29	0.21	0.834	0.16	9.47
p.R133c	1.07	0.59	0.13	0.900	0.36	3.17
p.R168X	0.57	0.31	-1.02	0.307	0.19	1.68
p.R255X	0.71	0.39	-0.62	0.535	0.24	2.11
p.R270X	0.48	0.26	-1.33	0.182	0.16	1.41
p.R294X	1.97	0.93	1.43	0.154	0.78	4.98
p.R306C	2.86	1.82	1.65	0.098	0.82	9.93
p.T158M	0.50	0.26	-1.32	0.187	0.19	1.40
Uncertain	0.60	0.62	-0.49	0.622	0.62	4.52
Larger deletion	0.37	0.21	-1.78	0.076	0.08	1.11

^a Refers to Hazards Ration

^b Refers to Standard Error

Table 8

Rett syndrome and menstrual suppressants

Suppressant	Number of people	Percentage
Depot Medroxy Progesterone Acetate	27	15.7
Mirena Intrauterine Device	4	2.33
Kliovance	1	0.58
Oral Contraceptive Pill	41	23.84

Table 9

Rett syndrome and issues experienced in puberty

Issue	Number of people	Percentage
Painful	48	27.9
Irritable	31	18.02
Irregular	37	21.51
Heavy	27	15.7
Seizure	51	29.7

Table 10
Life table and Down syndrome Puberty

Interval		Beg Total	Failure ^a	Censored ^b	Survival	SE	95% conf. Int	
8	9	66	2	0	0.9697	0.0211	0.8842	0.9923
9	10	64	1	0	0.9545	0.0256	0.8657	0.9851
10	11	63	9	0	0.8182	0.0475	0.7021	0.8924
11	12	54	10	0	0.6667	0.058	0.5393	0.7663
12	13	44	16	2	0.4186	0.0612	0.2982	0.5343
13	14	26	7	0	0.3059	0.0577	0.1983	0.4202
14	15	19	5	3	0.2185	0.0528	0.1254	0.3282
15	16	11	1	2	0.1967	0.0518	0.107	0.3062
17	18	8	0	1	0.1967	0.0518	0.107	0.3062
19	20	7	0	1	0.1967	0.0518	0.107	0.3062

^a Refers to the onset of puberty

^b Refers to the individuals who died or withdrew from the study

Table 11
Life table and Down syndrome Menarche

Interval		Beg Total	Failure ^a	Censored ^b	Survival	SE	95% conf. Int	
9	10	66	1	0	0.9848	0.0150	0.8973	0.9979
10	11	65	3	0	0.9394	0.0294	0.8465	0.9768
11	12	62	13	0	0.7424	0.0538	0.6188	0.8312
12	13	49	23	1	0.3903	0.0603	0.2731	0.5057
13	14	25	14	2	0.1626	0.0466	0.0842	0.2637
14	15	9	4	2	0.0813	0.0370	0.0279	0.1723
15	16	3	1	0	0.0542	0.0331	0.0123	0.1448
16	17	2	1	0	0.0271	0.0253	0.0025	0.1140
23	24	1	0	1	0.0271	0.0253	0.0025	0.1140

^a Refers to the onset of Menarche
^b Refers to the individuals who died or withdrew from the study

Table 12

Down syndrome and Menstrual suppressants

Suppressant	Number of people	Percentage
Depot Medroxy Progesterone Acetate	2	8.7
Mirena Intrauterine Device	1	4.3
Mini IUD	2	8.7
Oral Contraceptive Pill	9	39.1

Table 13

Down syndrome and the issues experienced in puberty

Issue	Number of people	Percentage
Inappropriate	8	14.8
Painful	11	20.4
Irregular	6	11.1
Heavy	8	14.8
Understanding	18	33.3
Managing hygiene	12	22.2
Managing emotions	9	16.6
Distressed	6	11.1

Appendix 2



AussieRett

THE AUSTRALIAN RETT SYNDROME STUDY

A questionnaire for parents

Follow-up Study 2004



Thank you very much for taking part in this study.

If you have **any** queries about the study in general or any aspect of this questionnaire,
please do not hesitate to contact:

Dr Helen Leonard (Medical Director) or

Crystal Laurvick (Clinical Coordinator)

Phone: 08 9489 7790

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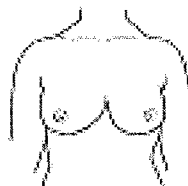
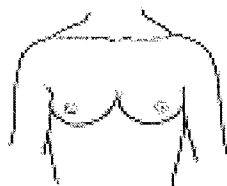
FIRST TIME FAMILIES

ID: _____

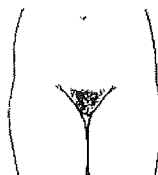
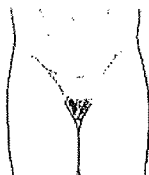
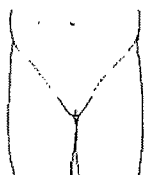
Section 11: Puberty

We are interested in the physical changes that occur with age in girls and young women with Rett syndrome. These sketches are widely used by clinicians to describe physical development.

Please circle the picture below which best describes your daughter's breast development.



Please circle the picture below which best describes your daughter's hip & pubic hair development.



Is there anything about your daughter's sexual development that you would consider to be unusual or different than what you would expect for her age?

☐

No

☐

Yes, please describe in the following space

4. **Has your daughter started having menstrual periods?**

- ☐ No, **please go to Question 7.**
- ☐ Yes--> How old was your daughter when she started her periods?

Date / / or aged ____ years & ____ months

5. **Do you have or have you ever had any problems with your daughter's menstrual periods?**

- ☐ No
- ☐ Yes, please feel free to make any comments about variations in functioning, symptoms, any aspect of your daughter relating to her menstrual cycle (eg. seizure activity) and about how you manage her periods.

6. **Is your daughter on any medication to manage her menstrual periods?**

- ☐ No
- ☐ Yes, please provide details below:

7. **Has she had any surgical procedures in relation to her periods or to any other gynaecological problem?**

- ☐ No
- ☐ Yes, please complete the following table to the best of your ability.

Type of surgery	Hospital where surgery was done	Date of procedure or age of the child at the time of surgery



DOWN SYNDROME NOW NEEDS OPINIONS WISHES STUDY

A questionnaire for parents



Thank you for taking part in this study.

If you have **any** queries about this questionnaire or the study in general,
please do not hesitate to contact:

Dr Helen Leonard (Medical Director) or

Phone: [REDACTED]

Fax: [REDACTED]

Mobile: [REDACTED]

Email: hleonard@ichr.uwa.edu.au

Crystal Laurvick (Project Coordinator)

Phone: 08 9489 7789

Email: crystall@ichr.uwa.edu.au

Section 9: Puberty

We are interested in your child's physical and emotional development during adolescence, and whether there is/was anything particularly unusual or difficult about this period.

**This section only needs to be filled out if your child is 12 YEARS OR OLDER.
If your child is younger than 12 years, please go to Section 10.**

1. **Has your child begun to display signs of puberty (eg., growth of pubic hair, breast budding, enlargement of testes)?**

☐ No

☐ Yes - Please write the age of your child when you began to notice these changes: _____

2. **Is there anything about your child's sexual development that you would consider to be unusual or different from what you would expect for his/her age?**

☐ No

☐ Yes - please describe in the following space:

3. **Is there anything about your child's social and emotional development or behaviour during puberty that you would consider to be unusual or different from what you would expect for his/her age, or that you need/needed to handle in a different way because your child has Down syndrome?**

☐ No

☐ Yes - please describe in the following space:

4. **Does your child use any methods of contraception?**

☐ No

☐ Yes - please describe which method(s) and feel free to make any further comments:

5. **Please comment on any other issues arising during puberty.**

Questions 6-10 only need to be filled out if your child is FEMALE.
If your child is male, please go to Section 10.

Has your daughter started having menstrual periods?

- ☐ No - please go to Section 10
- ☐ Yes

How old was your daughter when she started her periods?

Date / / or aged ____ years & ____ months

Do you have or have you ever had any problems with your daughter's menstrual periods?

- ☐ No
- ☐ Yes, please feel free to make any comments about variations in functioning, symptoms, any aspect of your daughter relating to her menstrual cycle (eg. seizure activity) and about how you manage her periods.

Is your daughter on any medication to manage her menstrual periods?

- ☐ No
- ☐ Yes, please provide details below:

Has she had any surgical procedures in relation to her periods or to any other gynaecological problem?

- ☐ No
- ☐ Yes, please describe the procedures in the following table:

Type of surgery	Date of OR age at surgery

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Form

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