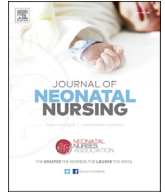




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Review

Down syndrome: An integrative review

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ABSTRACT

Down syndrome is a complex genetic disorder resulting in three copies of chromosome 21. Babies with this genetic disorder will have recognisable characteristic facial features that will differ from one baby to another. They will also have some degree of cognitive impairment and learning difficulties. There are many medical conditions associated with Down syndrome, however, due to recent medical advances there have been improvements in their health and longevity. This has led to a rise in people with Down syndrome developing Alzheimer's disease as they age.

The purpose of this review is to provide insight into the impacts that Down syndrome has on foetal development as well as ongoing health issues up to adulthood. There were many ethical issues raised surrounding the Baby Doe case and will also be explored in this review. CINAHL (EBSCO) was the primary medical database for this review retrieving 147 results in relation to Down syndrome and foetal development. An additional search was made retrieving 12 results in relation to ethical issues surrounding prenatal diagnosis of Down syndrome. Further resources such as websites and neonatal nursing textbooks were also used.

This review aims to provide a snapshot of Down syndrome with consideration given to the short and long-term outcomes for the baby, and the consequences for the growing child and his/her family. It is essential for neonatal nurses to understand the complexities of this genetic disorder, how to care for babies with Down syndrome, and how to provide support to parents and families.

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1. Introduction

Down syndrome is one of the most common genetic disorders that impacts foetal development, affecting 1 in every 1150 live births in Australia (Tracy, 2011). It is also known as Down's syndrome or trisomy 21 and was discovered by John Langdon Down in 1866. It is a chromosomal disorder where the individual has an additional copy of chromosome 21, either full or partial (Your Genome, 2015). Genetics plays a major role in foetal development and is where chromosomal abnormalities occur. Chromosomal abnormalities with Down syndrome occur during the meiotic cellular division phase (Perkins, 2017). This can happen due to increased maternal age, although there are mothers younger than 35 that have conceived a baby with Down syndrome (Perkins, 2017). It is important to have prenatal screening to monitor foetal development and to make an accurate diagnosis during this period. Differences in culture and ethnicity can impact prenatal screening discussion and decision making, raising many ethical issues.

Over recent decades, the health and life expectancy of Australians with Down syndrome has improved resulting in more people living into adulthood (Tracy, 2011). Furthermore, there are a number of medical conditions associated with Down syndrome, the most common being cardiac defects, leukaemia, gastrointestinal issues, vision and hearing issues, dental issues, thyroid disease, obstructive sleep apnoea, epilepsy, and Alzheimer disease (Perkins, 2017). Surgical interventions may be required to correct any medical issues to improve baby's outcomes. Down syndrome is also one of the leading causes of intellectual disability (Asim et al., 2015). Neonatal nurses are advocates for babies and their families and need to be able to provide the emotional support as well as educate parents and families about Down syndrome (Kenner and Lott, 2014). It is also paramount for neonatal nurses to understand how Down syndrome impacts families as well as how to care for babies with this genetic disorder.

2. Methodology

Relevant research relating to Down syndrome and foetal development was identified by searching the health databases for primary research material. A total of five research databases were searched for this review; CINAHL (EBSCO), MEDLINE (OVID), PubMed, ProQuest Health & Medicine, and SCOPUS (Elsevier), although, key articles were obtained primarily from CINAHL (EBSCO). In order to ensure that relevant studies were not missed, the search terms remained broad. The terms were 'Down syndrome', 'pregnancy', and 'fetus/foetus' using a Boolean search type approximately 447 results were retrieved. From these results the search criteria were further filtered to approximate the results from the last ten years and were selected based on their peer-reviewed status. From this, 147 results were retrieved. The articles were then selected based upon their relevance to Down syndrome and foetal development and, where possible, Australian data was a preferred resource.

A further search was undertaken to explore the ethical issues surrounding prenatal diagnosis of Down syndrome. The terms were 'Down syndrome' and 'ethics', using a Boolean search type with 12 results retrieved. All 12 articles were reviewed and related to

prenatal diagnosis. Articles selected dated back to the 1980s, although included due to their relevance to ethical issues surrounding prenatal diagnoses of Down syndrome.

A comprehensive search was made of internet resources in Australia to find current diagnostic and genetic information on Down syndrome. The search terms were 'Down syndrome', 'genetics', and 'diagnosis'. A number of sites were searched, although the key sites used were Baby Center Australia, Pregnancy Birth & Baby, and Your Genome. Other resources such as nursing textbooks were also used to gather research material to ensure a comprehensive approach. The nursing textbooks used for this review were 'Maternal, fetal, & neonatal physiology 4ed.' by Blackburn (2013), and 'Merenstein & Gardener's handbook of neonatal intensive care 8ed.' by Gardner et al. (2016).

An integrative review can play an important role in evidence-based nursing by detailing specific understandings of healthcare issues and practices. This type of review is comprehensive which summarises past empirical and theoretical literature, it surveys a diverse set of data on a particular healthcare issue, in this case; Down syndrome (Whittemore and Knaf, 2005).

3. The genetics associated with Down syndrome

During the prenatal period (conception to birth), pregnant women will experience major physiologic and psychologic changes that support maternal adaptations, support foetal growth and development, and preparation for birth. Supporting this development are the placenta, foetal membranes (amnion and chorion), and amniotic fluid. These structures protect and nourish the embryo and foetus and are essential for survival, growth, and development (Blackburn, 2013). Human development begins with the fertilisation of an ovum (female gamete) by a spermatozoon (male gamete). When a spermatozoon comes into contact with the ovum, the zona pellucida and the plasma membrane fuse, preventing entry by other sperm (Kenner and Lott, 2014). During fertilisation, meiotic cell division occurs where the male and the female pronucleus fuse. This results in two haploid numbers (23) of chromosomes (22 autosomes and 1 sex chromosome) from each gamete cell. The zygote is formed and contains the diploid number (46) of chromosomes necessary to create a unique human being (Blackburn, 2013).

Genetic disorders can influence the course of the foetal development and pregnancy and have implications for both the mother and the baby (Blackburn, 2013). All human cells, except for the gamete cells (ovum and sperm), normally contain 46 chromosomes (diploid number) consisting of 1 pair of sex chromosomes and 22 pairs of autosomes (Blackburn, 2013). Chromosomes are made up of genes that determine how the foetus forms in utero and how the baby grows after birth. They also influence physical characteristics, such as eye and hair colour, and the probability of developing a disease in the future (Perkins, 2017).

The genetic basis of Down syndrome was first described by Jerome Lejeune in 1959 (Sheets et al., 2011). An individual with Down syndrome has an additional copy of chromosome 21 (HSA21), either full or partial. The almost complete sequence of the long (q) arm of HSA21 was published in 2000, however the complete sequence of the short (p) arm has not been completed

(Patterson, 2009). Currently, over 420 genes and gene models exist on HSA21q and another four have been assigned to HSA21p (Patterson, 2009). It is unknown why Down syndrome occurs or how many factors are involved. It can come from either parent regardless of whether the error occurred from the mother or father (Perkins, 2017). Chromosomal abnormalities with Down syndrome, occurs during meiosis (Perkins, 2017). In meiosis, a single cell, containing 46 chromosomes, divides twice to produce two cells of 23 chromosomes. These two cells then divide to produce four cells (called gametes) each with half a set of chromosomes. Occasionally one pair of chromosome fails to separate, in the case of Down syndrome it is chromosome 21 (Khan Academy, 2017). Due to this, in the resulting cells one will have 24 chromosomes and the other will have 22 chromosomes, in a cell division error known as nondisjunction. When the gamete cell containing 24 chromosomes is combined with a gamete cell from the other parent containing 23 chromosomes, the fertilised egg (zygote) will now have 47 chromosomes, with an extra copy (full or partial) of chromosome 21 (Khan Academy, 2017).

There are three different types of Down syndrome; trisomy 21 or nondisjunction, Robertsonian translocation, and mosaicism. Nondisjunction is the most common type, accounting for 95% of all cases (Perkins, 2017). This occurs during meiosis when either the sperm or ovum fails to separate which results in an additional copy of chromosome 21. As the cells divide and multiply, the extra copy of chromosome 21 is repeated in every cell. Normally, each cell will only contain two copies of this chromosome. Robertsonian translocation is rare, accounting for 4% of all cases (Perkins, 2017). This occurs when the long arm of chromosome 21 is attached to another chromosome, typically chromosome 14. The individual with Robertsonian translocation Down syndrome has 46 chromosomes but the genetic material of 47 chromosomes, caused by the adherence of a full or partial copy of chromosome 21 (Perkins, 2017). Mosaicism is the most uncommon, accounting for only 1% of all cases (Perkins, 2017). This type of Down syndrome results in multidivision after fertilisation, leading to two cell lineages. The tissues and organs of the individual with mosaicism have some cells with 46 chromosomes and some with 47 (which contains the extra chromosome 21). These individuals tend to acquire less characteristics of Down syndrome than those with nondisjunction and Robertsonian translocation. It is believed that the characteristics seen with mosaicism vary depending on how many cells are affected.

4. Risk factors for Down syndrome

Increased maternal age is the most common risk factor for Down syndrome, although 80% of babies with Down syndrome are born to women younger than 35 (Perkins, 2017). The actual number of Down syndrome conceptions is unknown, although occurrence of the disorder increases significantly with advancing maternal age, with evidence that advanced paternal age could also be implicated (Bittles and Glasson, 2004). The chance of conceiving a baby with Down syndrome ranges from 1 in 1400 for a 20-year-old woman to just 1 in 32 for a 45-year-old woman (Tracy, 2011). The only other identified risk factor is heredity, although this is extremely rare, and only affects approximately 1% of all cases of Down syndrome (Perkins, 2017).

5. Down syndrome statistics

Although mothers of all ages can deliver a baby with Down syndrome, there is a worldwide shift among developed nations, in the age distribution of women giving birth, with the proportion of women over age 35 years increasing quite markedly (Collins et al.,

2008; Loane et al., 2013). This means that there are more babies born with Down syndrome. Worldwide, there is very little known about the actual prevalence rate of Down syndrome, because currently there is no reliable estimate of the number of people living with Down syndrome (Presson et al., 2013). Individual countries may keep their own national population-based statistics at birth, however these registry systems do not necessarily provide follow-up after birth, so the deaths of individuals with Down syndrome are not kept with the original statistics (Presson et al., 2013).

Even in developed nations there is a significant difference in the prevalence of Down syndrome. Statistics from the USA, UK and Australia and the Down syndrome organisations in those countries will be used to illustrate the prevalence of the condition. Worldwide, the overall prevalence of Down syndrome is 14 per 10,000 live births and the prevalence depends on sociocultural and religious variables such as the availability of abortions (Weijerman et al., 2008; Presson et al., 2013). The population of people with Down syndrome in Australia is now over 13,000 making it 1:1100 or 10 per 10,000 live births. This is lower than the worldwide rate of around 1 in 700 because of the high termination rates in Australia (Down Syndrome Australia, 2016). In the USA about 6000 babies are born each year with Down syndrome, which is about 1 in 700 babies born, or 14 per 10,000 live births (Centres for Disease Control and Prevention, 2017; Presson et al., 2013). In the UK the prevalence rate is 0.61 per 1000 or 12.6 per 10,000 live births and approximately 750 babies with Down syndrome are born every year. There are approximately 40,000 people with Down syndrome living in the UK (Down's Syndrome Association UK, 2017).

6. Prenatal screening

Prenatal screening is routinely offered to many Australian women in the first and second trimester to look for birth defects. In the first trimester, a combined screening test is performed, which involves an ultrasound and a blood test. The blood test is usually carried out around 9–12 weeks gestation. This measures two markers passed from the foetus to the mother, which are called the human chorionic gonadotrophin (hCG) and the pregnancy associated plasma protein (PAPP-A) (Baby Center Australia, 2017). If the foetus has Down syndrome, the blood test will show abnormal levels of these markers. The ultrasound is usually performed around 12 weeks gestation which is called the nuchal translucency scan. This scan measures the width of the nuchal fold, which is the fluid build-up at the back of the baby's neck. The likelihood of having a baby with Down syndrome is determined by gathering data from the blood test in combination with maternal age and nuchal translucency measurement. The combined screening test has an 87% detection rate (Baby Center Australia, 2017). There is another screening test available privately in Australia called the non-invasive prenatal test (NIPT) which involves taking a small blood sample from the mothers arm from 9 weeks gestation. The blood sample is then analysed for fragments of DNA from the foetus. It is 99% accurate at showing whether the mother is at risk of having a baby with Down syndrome (Baby Center Australia, 2017). In the second trimester, the maternal serum screening test, also known as triple or quadruple test, is based on blood tests which are performed around 15–20 weeks gestation. These blood tests investigate abnormal levels of proteins and hormones such as the human chorionic gonadotrophin (hCG), oestriol (uE3), alpha foeto-protein (AFP), and inhibin A. The triple test measures hCG, uE3, and AFP, and the quadruple test measures hCG, uE3, AFP and inhibin A. If the baby has Down syndrome the blood test results will show elevated levels of hCG and inhibin A, and reduced levels of AFP and uE3 (Baby Center Australia, 2017; Pregnancy, Birth & Baby, 2016). Diagnostic tests such as chorionic villi sampling (CVS) or

amniocentesis are offered when screening indicates the baby is at an increased risk of having Down syndrome (Tracy, 2011). CVS and amniocentesis involves obtaining a sample of the baby's genetic material for examination, however they are both invasive procedures. Amniocentesis is typically carried out in the second trimester, around 15–20 weeks gestation, and CVS is done in the first trimester, around 9–14 weeks gestation (Perkins, 2017). Although, amniocentesis and CVS are very reliable diagnostic tests, they do carry an increased risk of miscarriage. Prenatal screening and diagnostic tests don't have the ability to assess the full impacts of developmental delays or issues related to Down syndrome. Screening raises many ethical issues and can be a very difficult and emotional time for parents. If Down syndrome is recognised prenatally, the parents have a choice whether to proceed with the pregnancy (Tracy, 2011). A study by Collins et al. (2008) found that pregnancies in Victoria, from 1986 to 2004 in which there was a foetus diagnosed with Down syndrome, over 90% were terminated. However, these statistics may vary around Australia as there are different laws and legislation around abortion in each state and territory.

No screening procedure accurately detects all individuals who have the abnormality (sensitivity) and excludes all those who do not have it (specificity). This means that there will inevitably be false positive and false negative results (Georgsson Öhman et al., 2006). A false positive test screening for Down syndrome by ultrasound examination may cause strong reactions of anxiety and even rejection of the pregnancy. Foetal screening for Down syndrome raises sensitive issues, whereas unlike the outcome of other screening procedures, there is no treatment for Down syndrome other than the selective termination of the pregnancy. The women in Georgsson Öhman et al. (2006) study found the period of waiting was long, hard, and sometimes even unbearable, with the highest reactions of anxiety to be associated with the higher risk posed by their age. Women currently self-select to have invasive diagnostic testing and karyotyping based on real or perceived risks of Down syndrome (Susman et al., 2010).

Women making decisions about invasive diagnostic testing following high risk screening must weigh up the risk of the pregnancy having Down syndrome, with the risk of miscarriage from invasive testing (Jaques et al., 2010). Palomaki et al. (2011) suggest that 1 of every 16 screened positive women offered invasive diagnostic testing will have an affected pregnancy, therefore 15 will not, however 1 in 200 invasive procedures are associated with foetal loss (Palomaki et al., 2011), or 0.3–1.0% of the pregnancies investigated (De Jong et al., 2010).

7. Informed choice and decision making

Informed choice and the ability to make decisions about whether to terminate or continue a pregnancy with Down syndrome is at the heart of the principle of autonomy. Being able to exercise autonomy requires the provision of information, however, Skirton and Barr (2010) found that midwives lacked knowledge about screening, and the conditions for which screening was offered. There is a need for the provision of balanced information that gives an experiential account of the lives of people with Down syndrome, however, parents and professionals might not have had personal contact with a person with Down syndrome (Skirton and Barr, 2010). Doctors in a study by Williams et al. (2002) felt they spent more time describing and explaining the screening process for Down syndrome, rather than Down syndrome the condition. The doctors were aware that how they described Down syndrome might affect the decisions made by pregnant women. Many doctors gained their information about Down syndrome from textbooks, yet textbooks are written from a medical model approach focusing

on the potential problems (Williams et al., 2002).

Differences in culture and ethnicity can impact prenatal screening discussion and decision making. Women from ethnic minority groups in a study by Fransen et al. (2010) less often made an informed decision about whether to participate in prenatal screening. Language and educational level were cited as the most common reasons for non-participation, making diversity-sensitive strategies for counselling a priority (Fransen et al., 2010).

8. The baby with Down syndrome

Babies with Down syndrome are at an increased risk of developing many different health issues as well as intellectual and developmental disabilities. Powell-Hamilton and Jefferson (2016, p. 1) state that 'as with most conditions that result from chromosome imbalance, Down syndrome affects multiple systems and causes both structural and functional defects'.

At birth, a physical examination in the first 24 hours of life is an important step for diagnosing Down syndrome (Bull, 2011). Although the clinical presentation of babies with Down syndrome varies, the following physical features are quite indicative; short neck, small ears, flat nasal bridge, epicanthal folds, brushfield spots, single palmar crease, and a small mouth with a large protruding tongue (Ivan and Cromwell, 2014a). If the doctor suspects there are enough of these features present upon examination, and the diagnosis of Down syndrome was not made prior to birth, then a blood sample is sent for chromosome evaluation (Bull, 2011). Other common physical findings or symptoms in babies with Down syndrome include cardiac murmur, hypotonia, poor respiratory effort, poor suck, abdominal distension and vomiting (Ivan and Cromwell, 2014a). The presence of a cardiac murmur and cyanosis in the newborn period requires a cardiology consultation. Even babies that do not have a murmur at birth may have a significant cardiac defect. Approximately 48% of babies with Down syndrome have congenital cardiac defects, most commonly involving the atrioventricular canal, ventricular septum, and tetralogy of Fallot (Bittles and Glasson, 2004). An echocardiogram should be performed for all babies with Down syndrome prior to discharge from the hospital (Ivan and Cromwell, 2014a). Cyanosis, cardiac murmurs, and tachycardia are supportive findings in persons with complex cardiac defects (Ivan and Cromwell, 2014b). Due to cardiac defects, babies with Down syndrome may fatigue easily and lack the energy to breastfeed, they may also have difficulty feeding correctly due to the protrusion of the tongue in conjunction with hypotonia. As the tongue protrudes, it pushes against the nipple when feeding making it difficult to maintain a proper latch. Mothers who are breastfeeding babies with Down syndrome may need to be seen more frequently by a lactation consultant during the course of their hospital admission (White, 2013). Breastmilk contains antibodies that are important for babies with Down syndrome due to their increased risk of infection and gastrointestinal issues (White, 2013). The lactation consultant and the paediatric nutritionist will outline a nutritional plan with the parents so their baby with Down syndrome can achieve proper nutrition. In certain cases, hypotonia can lead to problems along the digestive tract, causing various digestive issues such as difficulty swallowing and constipation. Parents may need to consult with a gastroenterologist to overcome these problems (National Institutes of Health USA, 2017). If the baby has slow feeding, choking, respiratory symptoms with feeding, or poor weight gain, a radiographic swallowing assessment may be undertaken (Ivan and Cromwell, 2014a). Babies with Down syndrome account for 12% of congenital gastrointestinal anomalies, which includes tracheoesophageal fistula, Meckel diverticulum, oesophageal or duodenal atresia, imperforate anus, pyloric stenosis, and Hirschsprung's disease (Tracy, 2011). Other

gastrointestinal issues include gastro-oesophageal reflux disease (GORD) and coeliac disease.

Furthermore, about 20%–40% of babies with duodenal atresia, have Down syndrome (Niramis et al., 2010). Previous reports have shown that the presence of Down syndrome indicates a poor prognosis for babies with duodenal atresia due to the increased incidence of congenital cardiac defects (Niramis et al., 2010). Duodenal atresia is present at birth, although it is not until the baby starts feeding, he/she presents with abdominal distention, bilious vomiting and failure to pass meconium (Harris et al., 2012). This occurs due to the duodenum being closed which prevents fluids from passing further into the intestine (Harris et al., 2012). A radiographic evaluation and surgery consultation may be initiated to confirm duodenal atresia and/or anal atresia (Ivan and Cromwell, 2014a). Timely surgical treatment of cardiac defects and gastrointestinal issues may prevent serious complications in the future (Asim et al., 2015).

9. Ongoing health issues

Children with Down syndrome are predisposed to an array of medical comorbidities that may present as ongoing health issues that increase their risk of recurrent episodic illness and infections (Sheets et al., 2011). The most common medical conditions associated with Down syndrome are cardiac defects, leukaemia, gastrointestinal issues, vision and hearing issues, dental issues, thyroid disease, obstructive sleep apnoea, epilepsy, and Alzheimer disease (Perkins, 2017). Children with Down syndrome are unique and not every child will have all these medical conditions. The various types of medical conditions associated with Down syndrome can be treated with medication, surgery, or other interventions (National Institutes of Health USA, 2017). The infant mortality rate is considered to be 24.3 times greater in children with Down syndrome than in the general population, however, mortality for infants with Down syndrome has fallen from 14.2% to 2.3% (Weijerman et al., 2008).

Although almost 50% of babies with Down syndrome have a congenital cardiac defect (Tracy, 2011), Down syndrome has not been shown to confer a greater mortality risk for the cardiac operations in this population. However, patients with Down syndrome who underwent atrial septal defect, ventricular septal defect, and tetralogy of Fallot repair were shown to have prolonged lengths of stay and higher rates of postoperative complications. A larger proportion of patients with Down syndrome undergoing ventricular septal defect repair were found to experience post-operative complete heart block requiring permanent pacemaker placement (Fudge et al., 2010). These babies will require cardiac monitoring throughout their lives. Children with Down syndrome are also at a high risk of becoming obese due to hypothyroidism and hypotonia. This can then lead to cardiovascular disease, stroke, hypertension and diabetes (Wong et al., 2014). A balanced diet and regular exercise during childhood and beyond are required to maintain an appropriate weight and to prevent obesity. Obstructive sleep apnoea can be caused by obesity and if left untreated can lead to hypertension and cardiac failure (Wong et al., 2014).

As Down syndrome is one of the leading causes of intellectual disability, it is important to understand that the severity of impairment will vary (Asim et al., 2015). Disabilities may include learning, speech and language delays. Delayed development and behavioural issues are also common in individuals with Down syndrome, although most will attend mainstream schools to help promote social and language skills (Perkins, 2017; Tracy, 2011). Sign language is a method that helps children with Down syndrome bridge communication until the development of speech and language is achieved (Toth, 2009). Speech can also be affected by

hearing and/or visual impairments as well as anatomical differences in the oropharynx (Tracy, 2011). Sensory losses are detected in 40–80% of individuals with Down syndrome, usually related to hearing loss and cataracts (Bittles and Glasson, 2004).

With medical advances over the years, the average lifespan of an individual with Down syndrome has increased. In 1910, a baby born with Down syndrome often didn't live past ten years old. Today, a baby with Down syndrome can expect to live to 60 and above, depending on the severity of his/her condition (Perkins, 2017). Life expectancy in people with Down syndrome is influenced by gender, with males outliving females by more than three years (Bittles and Glasson, 2004). Down syndrome is associated with premature ageing, which can become apparent around 40 years of age. Such aging is approximately 20 years earlier than the rest of the population (Glasson et al., 2014). Due to this increased life expectancy there has been evidence that shows that Alzheimer's is linked with Down syndrome. Adults with Down syndrome are at an increased risk for developing Alzheimer's disease after the age of 40 (Powell et al., 2014). Alzheimer's disease (AD) may affect at least 90% of individuals with Down syndrome, and dementia is now a common cause of death of older individuals with Down syndrome (Zis and Strydom, 2018). Amyloid precursor protein (APP) is an important membrane protein concentrated in the synapses of neurons. The gene for APP is located on chromosome 21. The neuropathological features of Alzheimer disease are believed to develop in most people with Down syndrome, due to an extra copy of the amyloid- β precursor protein (APP) gene on chromosome 21 (Bittles and Glasson, 2004). The dementia associated with Down syndrome consists of a progressive build-up of extracellular amyloid beta ($A\beta$) plaques and intraneuronal hyperphosphorylated tau (proteins that stabilise neurons of the central nervous system). Amyloid-beta has been postulated as a potential biomarker for AD in the general population, as individuals with Down syndrome show higher plasma amyloid beta levels than those individuals without Down syndrome (Zis and Strydom, 2018).

Although there are many health implications associated with Down syndrome, with medical advances many are able to lead a normal life. Asim et al. (2015) states that regular check-ups will be required to maintain health, from consultants such as a paediatrician, cardiologist, ophthalmologist, speech pathologist, occupational therapist, oncologist, and audiologist just to name a few. Studies that address the direct costs attributable to children and young adults with Down syndrome found that the costs were highest in the first years of life, and were higher when there was a diagnosis of congenital cardiac defects (Geelhoed et al., 2011). The costs were also dependent on the level of functioning and the employment opportunities for the young adult. It is noteworthy that in Geelhoed et al. (2011) research, the costs did not address the overall costs to families affected by Down syndrome, such as special education, individual transport needs, housing modifications, and related costs to family. The demands on health services were found to decline significantly towards adolescence, but increased during times of respite care (Geelhoed et al., 2011).

10. Ethical issues – Baby Doe

The ethics literature from the mid 80s onwards discusses the case of Baby Doe a baby born with Down syndrome. Baby Doe was born in Bloomington, Indiana, USA with Down syndrome and a trachea-oesophageal fistula (TOF) with an oesophageal atresia (OA) (where the stomach is not connected to the intestines, with a fistula into the lungs) (Lund, 1985; Newman, 1989). Surgery for TOF and OA was fairly standard for newborns, however the parents of Baby Doe (both teachers of intellectually disabled children) withheld medical treatment following advice from a paediatric surgeon. At

the time, C. Everett Koop, was the Surgeon General of the USA. He argued that Baby Doe should have surgery for the TOF and OA, however he stated Baby Doe was denied treatment based on his disability. In 1984, the Reagan administration, led by C. Everett Koop, passed an amendment to the Child Abuse Law (called the Baby Doe Law). It mandated that states receiving federal money for child abuse programs, develop procedures to report medical neglect (defined as withholding of treatment unless a baby is irreversibly comatose or the treatment for the newborn's survival is virtually futile) in cases involving the withholding of treatment to disabled newborns. As part of the Baby Doe law, the assessment of quality of life was not a valid reason for withholding medical care (Lund, 1985; Newman, 1989).

The obstetrician who delivered Baby Doe told the parents that their baby would have only a 50 percent chance to survive surgery TOF/OA, and that even with successful surgery he would remain severely retarded [sic]. Consequently he advised the withholding of treatment and to let their baby die. The case was taken to court, however the Indiana courts ruled that there was no violation of the 'Child in Need of Services' statute, and that the parents had the right to decide the fate of their child, soon named Baby Doe by the press. Baby Doe died of dehydration and pneumonia on April 15, 1982 (Pence, 2004). The legal reach of the Baby Doe Law might not be fully known, however it awakened physicians and hospitals to discrimination against disabled newborns. An excellent account of the Baby Doe case can be seen in the book "Playing God in the nursery" by Lyon (1983).

11. The future

Perhaps the biggest question in relation to Down syndrome is whether the increased availability of prenatal diagnosis will result in a decrease in the incidence of Down syndrome. The research suggests that it will. Firstly, the availability of new and modified genetic testing will be offered very early in the first trimester, meaning that women and their partners will be able to make a decision about the pregnancy, before they show any physical signs of the pregnancies. Secondly, it is anticipated that the new tests will be non-invasive, carrying no risk to the foetus, unlike CVS and amniocentesis, therefore this increases the likelihood that women will request these tests, and in countries where it is acceptable, there will be an increase in rate of terminations of the pregnancy (Skotko, 2009).

The key to improving the lives of individuals with Down syndrome is genetics research. Park et al. (2008) describe the generation of stem-cells in-vitro to enable disease investigation and drug development. Currently, research is being carried out on adult mice (Down syndrome mouse models Ts65Dn) to determine the possibility of gene therapy prenatally and postnatally. Early results have shown an improvement in learning and memory and brain structure in the mice (Patterson, 2009). It has been hypothesised that with further sequencing of the genes related to Down syndrome (HSA21), that treatments, such as medications, will be able to be devised to ameliorate the negative life-long effects of Down syndrome (Patterson, 2009), and improve the quality of life of individuals with Down syndrome and their families.

The link between the APP gene and Down syndrome is substantial, especially as it is located on Chromosome 21. Research is being conducted to see if an increase in APP gene dosage can induce neurodegenerative phenotypes typical of Alzheimer's disease in mice, and whether mouse studies are predictive of events in humans with Down syndrome (Mégarbané et al., 2009). If so, there is a possibility of deciphering the molecular and genetic basis of the disabilities associated with Down syndrome and uncovering effective treatments.

12. Recommendations for neonatal nursing practice

One of the most overwhelming and life-changing events for parents is hearing that their baby has a genetic disorder. The most difficult factor for most parents to deal with is the unknown. The need for an accurate diagnosis becomes paramount. As discussed by Gardner et al. (2016) even when the diagnosis carries a very poor prognosis, parents would prefer having the information so they can realistically anticipate and prepare for what is to come.

- The neonatal staff should use the genetics team as a resource for consultation and assistance in providing babies with the most appropriate and complete health care available, and their families with support and relevant information.
- Neonatal nurses must keep up-to-date with new genomic knowledge and the prenatal/neonatal testing that can be done to impact long term health. The holistic nature of nursing extends beyond counselling and includes a broader perspective of care.
- The neonatal nurse also acts as an advocate for the family and refers them to community resources such as genetic clinics, family support groups, or specialised home health care (Kenner and Lott, 2014).
- Due to the fact that Down syndrome is a leading cause of intellectual disability, it is essential that neonatal nurses understand the disorder and how to care for patients with Down syndrome. Emotional support will be required for families as they may experience shock and grief upon learning of the diagnosis.
- It is important for neonatal nurses to maintain an unbiased attitude and provide emotional support. Parents may also go through the grieving process of denial, anger, bargaining, depression, and acceptance. They may need to grieve the loss of the baby they planned to have and to learn to accept living with a child with Down syndrome. Parents may also be concerned about the increased risk of associated health complications, therefore education and support is essential (Perkins, 2017).
- Bonding and attachment is essential for neurological development, and neonatal nurses require education to understand that the baby with Down syndrome needs to bond with his/her caregiver. Jiménez et al. (2012) have outlined the phases of grief that parents can experience as they come to terms with the birth of a baby with Down syndrome. These stages are; impact, denial, sadness and pain, adaptation and reorganisation. It is important, however, to recognise the individual nature of grief and other emotional responses, and that families will not necessarily enter and leave every phase sequentially.

13. Strengths and limitations of an integrative review

This systematic and rigorous review has presented a comprehensive and holistic understanding of Down syndrome with consideration given to statistics, risk factors, genetics, ethical issues, specific issues related to caring for the baby and family, ongoing health issues and what the future holds. The results of this evidence-based review will be useful for neonatal nurses when they are caring for the baby with Down syndrome and his/her parents. This review has included multiple data sources and is therefore able to inform nursing practice, and outline the direction for future research. Whittemore and Knaf (2005), suggest that using multiple data sources is challenging, and integrative reviews have been criticised for their potential for bias and lack of rigor, however incorporating mixed method and qualitative research to this process has the potential to decrease bias and error (Whittemore and Knaf, 2005). Integrative reviews are an excellent

way to research complex health issues, such as Down syndrome, that are important for neonatal nurses.

14. Conclusion

Down syndrome is one of the most common genetic disorders that impact foetal development and a leading cause of intellectual disability in Australia. Neonatal nurses need to understand how to care for babies with Down syndrome, and be able to provide the appropriate support to their families. Since various medical conditions are associated with Down syndrome, the management of these patients requires an organised multidisciplinary approach and continuous monitoring throughout their lives. Many of these medical conditions associated with Down syndrome can be treated with medication, surgery, or other interventions. Due to medical advances over recent decades, the health and life expectancy of individuals with Down syndrome has improved resulting in more people living into adulthood. Although, with the increase in life expectancy more adults with Down syndrome are likely to develop Alzheimer's disease. This occurs due to the triplication of chromosome 21, which results in a phenotype that is accompanied by altered brain development and other neurologic features. The research into gene therapy and the use of stem cell therapy hopefully will be the key to ameliorating the negative effects of Down syndrome, and offer a better quality of life for babies born in the future.

Conflicts of interest

There was no conflict of interest associated with this manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jnn.2018.01.001>.

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