

ANTENATAL AND NEWBORN SCREENING

Overseas research suggests that up to 25% of babies with severe forms of congenital heart disease are discharged from hospital undiagnosed [1]. In New Zealand, a small number of babies each year are born with inborn errors of metabolism (e.g. galactosaemia), which, if left untreated, may lead to permanent end organ damage within a relatively short period of time [2]. Even for non-life threatening conditions, delayed diagnosis may lead to the loss of opportunities for early intervention (e.g. congenital hearing loss: identified in the first three months with universal newborn screening vs. at an average age of 35.1 months if screening is based on the presence of risk factors [3]).

The early detection of these conditions confers significant advantages, and antenatal diagnosis provides the opportunity to exclude additional congenital or chromosomal abnormalities, to discuss pregnancy options with parents, and to plan for delivery in a tertiary centre, if additional services will be required [4]. For a number of conditions, however, (e.g. congenital deafness, inborn errors of metabolism where the placenta clears metabolites in-utero) antenatal diagnosis is not possible, and in such cases early detection in the neonatal period is of critical importance.

In New Zealand, a number of screening programmes have been established to detect congenital anomalies and inborn errors of metabolism in the antenatal period, or as soon as possible after birth. The following sections briefly review each of these in turn.

Screening During the Antenatal Period

Antenatal Screening for Down Syndrome and Other Conditions

Antenatal screening for Down syndrome and other conditions has been available to pregnant women since 1968 [5]. However, concerns during the mid-2000s that the existing screening processes were ad-hoc [6], led the National Screening Unit to release a set of guidelines for maternity providers in 2009 [5]. These guidelines recommended that all pregnant women be offered antenatal screening for Down syndrome and other conditions in either the first or second trimester of pregnancy as follows:

- 1. For Women Presenting in their First Trimester:** A blood test that measures two maternal serum markers (pregnancy-associated plasma protein A (PAPP-A) and Beta-human chorionic gonadotrophin (β hCG)) should be combined with the results of an ultrasound which assesses nuchal translucency (a marker which measures the fluid filled space in the tissue at the back of a fetus' neck and is a marker for chromosomal and other anomalies) and other parameters (e.g. crown-rump length). The optimal time for screening using maternal serum markers is 10–12 weeks, while the optimal time for an ultrasound to assess nuchal translucency is 11.5–13.5 weeks [5].
- 2. For Women Presenting in their Second Trimester:** A blood test that measures four maternal serum markers (β hCG, alpha-fetoprotein, unconjugated oestriol and inhibin A), best done at 14–18 weeks [5].

In its updated 2012 Guidelines for Health Practitioners [7], the National Screening Unit outlines the expectation that health practitioners will provide accurate and non-directive information to women considering antenatal screening, including informing them of their right to decline screening or further investigations. After undergoing screening, all women who are deemed to be at a high risk of having a baby with Down syndrome or other conditions should be offered an obstetric referral to discuss diagnostic testing options including: chorionic villus sampling (usually performed at 10–13 weeks); and amniocentesis (usually performed at 15–20 weeks). Maternity providers should also advise women with an increased risk of the availability of genetic counselling services [7].

In addition, while not part of a formal screening programme, ultrasounds are often undertaken at 18–20 weeks of gestation to screen for obvious structural anomalies, although such scans are not thought to be as effective for detecting Down Syndrome as the screening modalities listed above [5].



Screening During the Neonatal Period

Newborn Examination

The Well Child/Tamariki Ora Schedule recommends that a detailed clinical examination be undertaken within 48 hours of birth (initial examination usually undertaken at birth), with a further clinical examination being undertaken within 7 days, and another at 4–6 weeks (at the time of discharge from maternity services) [8]. At the initial (newborn) examination the Schedule recommends that clinicians undertake a thorough assessment which includes: the child's overall health and wellbeing, weight, length and head circumference, and a more detailed examination of their hips, cardiovascular system (heart, umbilicus, and femoral pulses), eyes (red reflex), colour, respiration, tone, Moro reflex, grasp reflex, movements, skin, head, fontanelles, ears, mouth, lungs, abdomen, umbilicus, genitalia, anus, spine, and limbs [9].

Newborn Metabolic Screening Programme

When New Zealand commenced newborn metabolic screening in 1969, screening was only undertaken for phenylketonuria (PKU) [2]. The current Newborn Metabolic Screening Programme (NMSP), however, screens for 28 metabolic disorders [2], as outlined in **Table 1**.

Table 1. Conditions Included in New Zealand's Newborn Metabolic Screening Programme

Disorder	Incidence
Congenital Hypothyroidism	1 in 4,000 babies (≈15 babies a year)
Cystic Fibrosis	1 in 7,000 babies (≈ 8 babies a year)
Amino Acid Disorders (14 disorders including e.g. Phenylketonuria (PKU))	1 in 12,000 babies (≈ 5 babies a year)
Fatty Acid Oxidation Disorders (9 disorders including e.g. Medium Chain acyl-CoA Dehydrogenase Deficiency)	1 in 12,000 babies (≈ 5 babies a year)
Congenital Adrenal Hyperplasia	1 in 20,000 babies (≈ 3 babies a year)
Galactosemia	1 in 100,000 (≈ 1 baby every 2 years)
Biotinidase Deficiency	1 in 150,000 (≈ 1 baby every 3 years)

Source: National Screening Unit <http://www.nsu.govt.nz/current-nsu-programmes/2097.aspx>

Lead Maternity Carers (LMCs) are responsible for undertaking newborn metabolic screening. Their tasks include: giving information and advice, offering screening, ensuring informed consent, taking the sample and following up on the results. The National Screening Unit recommends that LMCs take samples when the baby is 48 hours old, or as soon as possible thereafter. Timing is important, as samples taken earlier (e.g. at the time of birth) may be negative due to the placenta having eliminated abnormal markers, while samples taken later may result in a lost window for early intervention, as severe forms of some metabolic disorders may be fatal within 7–10 days, and the baby may not show any signs or symptoms until irreversible damage has occurred [2]. Blood samples are usually taken by heel prick, and the blood is collected onto a blood spot card, which has two main parts: a smaller portion with specimen collection paper for the sample itself, and a larger portion for demographic and other information [2]. When the sample is taken, parents are asked whether they wish the card to be stored for possible future use, or returned to them, after analysis.

National Newborn Hearing Screening Programme

In New Zealand each year, it is estimated that 135–170 babies are born with mild to profound permanent congenital hearing loss, representing an incidence of 3 per 1,000 births [10]. In response to concerns regarding the late age of diagnosis of congenital hearing losses, which occurred at an average age 35.1 months when screening was based on the presence of risk factors [3], the Government announced, in its 2006 Budget, a funding package to establish a National Newborn Hearing Screening Programme (\$16 million over four years). The Programme was rolled out progressively across the country

during 2007–2010, and screening is now underway in all 20 DHBs [11]. For further detail see the Newborn Hearing Screening Section.

Conditions Detectable by Antenatal and Newborn Screening

This report reviews a number of conditions which are potentially detectable by antenatal or newborn screening. These include:

- Congenital Anomalies Evident at Birth
- Cardiovascular Anomalies Evident at Birth
- Down Syndrome
- Neural Tube Defects
- Newborn Hearing Screening
- Cystic Fibrosis

While local policy documents and evidence-based reviews relevant to these conditions are reviewed at the end of each chapter, **Table 2** provides an overview of publications which consider antenatal and newborn screening more generally.

Local Policy Documents and Evidence-Based Reviews Relevant to Antenatal and Newborn Screening

In New Zealand there are a number of policy documents which provide guidance on antenatal and newborn screening. These are summarised in **Table 2**, along with a range of evidence-based reviews which consider these issues in the overseas context. Note: Publications which considered antenatal screening for maternal infectious disease status were seen as being outside of the scope of this review including HIV, syphilis, Hepatitis B, and rubella.

In addition, Table 32 (Local Policy Documents and Evidence-Based Reviews Relevant to Congenital Anomalies) on Page 105 considers publications relevant to congenital anomalies collectively, while Table 38 (Policy Documents and Evidence-Based Reviews Relevant to Cardiovascular Anomalies) on Page 118 considers cardiovascular anomalies, Table 44 (Local Policy Documents and Evidence-Based Reviews Relevant to Down Syndrome and Other Chromosomal Anomalies) on Page 128 considers Down syndrome and other chromosomal anomalies, and Table 49 (Local Policy Documents and Evidence-Based Reviews Relevant to Neural Tube Defects) on Page 138 considers neural tube defects. Finally Table 56 (Local Policy Documents and Evidence-Based Reviews Relevant to the Early Detection and Management of Permanent Hearing Loss in Children) on Page 154 provides a brief overview of publications relevant to newborn screening for congenital hearing loss.

Table 2. Local Policy Documents and Evidence-Based Reviews Relevant to Antenatal and Newborn Screening

New Zealand Policy Documents and Publications
<p>National Screening Unit. 2012. Antenatal Screening for Down Syndrome and Other Conditions: Guidelines for health practitioners. Wellington: Ministry of Health. http://www.nsu.govt.nz/files/ANNB/antenatal_screening_for_down_syndrome_and_other_conditions_guidelines_for_health_practitioners.pdf</p> <p>These guidelines are intended for all practitioners who have involvement in any part of the antenatal screening process for Down syndrome and other conditions. Further detail on this publication is provided in the Down syndrome section.</p>
<p>Ministry of Health. 2011. Newborn Metabolic Screening: Policy Framework. Wellington: Ministry of Health. http://www.nsu.govt.nz/files/ANNB/Newborn_Metabolic_Screening_Programme_Policy_Framework_June_2011.pdf</p> <p>The policy framework for the Newborn Metabolic Screening programme is set out in this document for the guidance for all programme providers. The nine sections in the framework cover background information, programme policy, the responsibilities of programme providers, lead maternity carers and laboratories, the return, storage and uses of residual blood spot samples, new technologies and changes to the disorder panel.</p>



National Screening Unit. 2011. **Newborn Metabolic Screening Programme Monitoring Framework**. Wellington: National Screening Unit. http://www.nsu.govt.nz/files/NSU_Screening_Programme_2_0.pdf

There are nine national indicators used to monitor the Newborn Metabolic Screening Programme. The Monitoring Framework sets out how these are used to assess the performance of the programme. There are tables for each indicator which include a description of the indicator, the rationale for the indicator, the relevant outcome, the standard against which the indicator is to be compared, and the methodology for calculating the indicator. There is also a summary table giving the reporting frequency and details for each of the indicators

National Screening Unit. 2010. **Guidelines for Practitioners Providing Services Within the Newborn Metabolic Screening Programme in New Zealand**. Wellington: National Screening Unit
http://www.nsu.govt.nz/files/ANNB/Metabolic_Screening_Guidelines_final_February_2010.pdf

Lead Maternity Carers are contractually obliged to provide services within screening programmes endorsed by the Ministry of Health, including the Newborn Metabolic Screening Programme, under the Primary Maternity Services Notice 2007. These best practice guidelines are for all practitioners involved in the Newborn Metabolic Screening Programme including Lead Maternity Carers, hospital midwives, nurses and phlebotomists.

International Guidelines and Systematic and Other Reviews

Edwards Adrian GK, Naik G, Ahmed H, et al. 2013. **Personalised risk communication for informed decision making about taking screening tests**. Cochrane Database of Systematic Reviews doi:10.1002/14651858.CD001865.pub3
<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001865.pub3/abstract>

In order to make an informed choice about whether to undergo screening, patients need information about the risk of having the condition being screened for, the nature of the condition, the advantages and disadvantages of screening and the accuracy of the screening tests. Personalised risk communication is the provision of risk information that is tailored for a specific person, based on characteristics such as age, family history, and cultural and/or educational background. This review compared personalised vs. general risk communications for promoting informed decision making about screening participation. The review included 41 RCTs, only one of which related to antenatal screening (most related to breast or colorectal cancer). The authors concluded that there was strong evidence, from three trials, that inclusion of personalised risk estimates in screening programme information enhanced informed choice. They stated that the evidence that personalised information increased uptake of screening was weak and that it was unclear if increased uptake was associated with informed choice. Because of the diversity of the screening programmes, the authors were unable to draw any conclusions about the best ways to provide personalised risk communications.

Walter John H, Jahnke N, Remington T. 2011. **Newborn screening for homocystinuria**. Cochrane Database of Systematic Reviews: Reviews, DOI: 10.1002/14651858.CD008840.pub2.
<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008840.pub2/abstract>

Homocystinuria is a rare genetic disorder in which a deficiency of the enzyme cystathione beta synthetase causes raised levels of the amino acids homocystine and methionine in the blood and tissues. Children with this disorder appear normal initially but later develop a number of severe health problems including learning difficulties, bone and eye problems and a high risk of blood clots. If started very early in life, dietary intervention can prevent the development of these complications. This review considered whether newborn screening for homocystinuria leads to clinical benefits compared to later diagnosis based on symptoms. The authors found no RCTs addressing this issue and therefore stated that they could not draw any conclusions based on controlled studies, but they stated that they did know of uncontrolled case series which supported the efficacy of newborn screening and early treatment for homocystinuria.

Shah Vibhuti S, Ohlsson A. 2011. **Venepuncture versus heel lance for blood sampling in term neonates**. Cochrane Database of Systematic Reviews doi:10.1002/14651858.CD001452.pub4
<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001452.pub4/abstract>

The use of a heel lance is the usual way blood samples are collected from neonates for screening purposes. There are easy to use automated heel piercing devices. Venepuncture is a procedure that requires some training and skill. This review considered whether venepuncture is a more effective and less painful method than heel lancing for obtaining blood samples from neonates. It included 6 studies, of variable quality, which were either RCTs or quasi-RCTs (478 babies in total) comparing pain responses (assessed by validated behavioural pain measures) in infants who had blood samples collected by venepuncture, with those in infants who had heel lancing. In some studies both groups of infants received a sweet tasting solution before the procedure. Meta-analysis of the data for 288 infants who did not receive a sweet tasting solution indicated a significant pain reduction in the venepuncture group vs. the heel lance group (Standard mean difference -0.76, 95% CI -1.00 to -0.54, $I^2 = 0\%$). For the infants who did receive a sweet tasting solution, the difference was less but still significant: SMD -0.38, 95% CI -0.69 to -0.07. Data from four studies ($n = 254$) yielded the risk difference for requiring more than one skin puncture for venepuncture vs. heel lance: (RD = -0.34 95% CI -0.43 to -0.25; $I^2 = 97\%$) and gave a number needed to treat with venepuncture to avoid one repeat skin puncture of 3 (95% CI 2 to 4). The authors concluded that venepuncture performed by a skilled phlebotomist was the method of choice for collecting blood samples from term neonates and that sweet tasting solutions should be provided to reduce pain before both venepuncture and heel lancing.

Desilets V, Oligny LL. 2011. **Fetal and perinatal autopsy in prenatally diagnosed fetal abnormalities with normal karyotype.** J Obstet Gynaecol Can, 33(10), 1047-57. <http://sogc.org/wp-content/uploads/2013/01/gui267TU1110E.pdf>

This technical update from the Society of Obstetricians and Gynaecology Canada provides concise information on the benefits of fetal or perinatal autopsy, the consent process and the alternatives when the family decline a full autopsy in situations where there has been a prenatal diagnosis of non-chromosomal malformations followed by fetal loss, stillbirth or neonatal death. Autopsy is important for obtaining an accurate diagnosis of the cause of death, which is necessary for genetic counselling and may permit prenatal diagnosis for future pregnancies. The guidelines are based on a review of the published literature (restricted to systematic reviews, RCTs/controlled clinical trials and observational studies) and grey (unpublished) literature sourced from clinical practice guideline collections, national and international medical specialty societies, clinical trial registries and websites of health technology assessment and health technology assessment-related agencies. The quality of the evidence is graded and the strength of the recommendations are classified according to criteria adapted from the Canadian Taskforce on Preventive Healthcare.

Whitworth M, Bricker L, Neilson James P, et al. 2010. **Ultrasound for fetal assessment in early pregnancy.** Cochrane Database of Systematic Reviews doi:10.1002/14651858.CD007058.pub2
<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007058.pub2/abstract>

This review considered whether routine ultrasound in early pregnancy has an effect on diagnosis of multiple pregnancies, fetal malformations, intervention rates, or the incidence of adverse fetal outcomes, compared to selective use of early pregnancy ultrasound (for particular indications). It found that there was good evidence that routine ultrasound improved the detection of multiple pregnancies before 24 weeks' gestation and was associated with a reduction in inductions for "post term" pregnancy. Only two of the 11 RCTs addressed the diagnosis of fetal malformations (the RADIUS study from the U.S. and the Helsinki ultrasound trial). In the 17,158 pregnancies in these two studies, there were 387 congenital abnormalities reported, with most of these (346, 89%) not detected at 24 weeks. Those who received ultrasound screening were more likely than control groups to have fetal abnormalities detected by 24 weeks (unweighted percentages 16% vs. 4%, risk ratio 3.46, 94% CI 1.67 to 7.14). The Helsinki trial showed better fetal abnormality detection rates than RADIUS, leading to increased terminations and reductions in perinatal mortality. The authors noted that considerable expertise is needed to detect fetal malformations using ultrasound and that since these two studies were done (in the 1990s) there have been advances in equipment and expertise which mean that the results of these trials are probably not relevant to the current situation.

Nabhan Ashraf F, Faris Mohammed A. 2010. **High feedback versus low feedback of prenatal ultrasound for reducing maternal anxiety and improving maternal health behaviour in pregnancy.** Cochrane Database of Systematic Reviews doi:10.1002/14651858.CD007208.pub2
<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007208.pub2/abstract>

This review compared high and low feedback provided to women receiving prenatal ultrasound scans. During high feedback scans, women can see images of their fetus on a screen and they receive detailed explanations of the images, while during low feedback scans women do not view the screen and are told the results of the scan at the end of the procedure. The review included four RCTs (365 women). The authors concluded that there was insufficient evidence to determine whether high or low feedback during scans is better for reducing maternal anxiety and promoting maternal health behaviour such as stopping smoking or drinking.

Mujezinovic F, Prosnik A, Alfirevic Z. 2010. **Different communication strategies for disclosing results of diagnostic prenatal testing.** Cochrane Database of Systematic Reviews doi:10.1002/14651858.CD007750.pub2
<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007750.pub2/abstract>

Women tend to experience anxiety while waiting for prenatal test results. This review considered whether providing amniocentesis or chorionic villus sampling (CVS) results on a fixed date as opposed to "when available" altered maternal anxiety. It also considered whether providing early results from a rapid molecular test altered maternal anxiety and whether the method of communication (e.g. phone, fax, email, in person) made a difference to parents' satisfaction and anxiety levels. The authors identified two randomised trials (286 women in total) which compared the impact of receiving early results from rapid testing with waiting, on average for 18 days, for definitive karyotype results. One study reported a significant difference and the other did not. The authors concluded that there was no conclusive evidence that issuing early results from rapid testing while awaiting karyotype results reduced maternal anxiety nor was there any evidence to support the view that it is better to issue amniocentesis results as soon as they are available rather than on a pre-specified date. They stated that studies on the different methods of communicating test results are needed.

Kai J, Ulph F, Cullinan T, et al. 2009. **Communication of carrier status information following universal newborn screening for sickle cell disorders and cystic fibrosis: qualitative study of experience and practice.** Health Technol Assess, 13(57). <http://www.hta.ac.uk/fullmono/mon1357.pdf>

In the U.K. there is newborn screening for both cystic fibrosis (CF) and sickle cell anaemia. New Zealand does not screen for sickle cell anaemia as relatively few people belong to ethnic groups with high rates of the condition (mostly those of African descent). Screening for CF is a 2-stage process. All blood spot samples are tested for levels of immunoreactive trypsin and then those with levels above the 99th percentile undergo DNA testing for the most common CF mutations. A child with two CF mutations is likely to have CF, while a child with one is probably a carrier. Although the testing process is not designed to test for carrier status and aims to identify a minimum number of carriers, nevertheless the end result of the testing process is that some babies are identified as carriers of CF (indicating that at least one parent is almost certainly a carrier). This information has implications for the child (in adulthood) and the parents regarding their risk of having a child with CF. This study explored the practice, methods and experiences related to communicating carrier status following newborn screening in the U.K. It found that there was considerable variation from place to place and that parents' needs for timely and appropriate information were not always met. It recommended that professionals involved in testing receive guidance in communication and that notification of carrier status should be done in person by a well-trained professional.

Bennet M J, editor. 2009. **Follow-up testing for metabolic diseases identified by expanded newborn screenings using tandem mass spectrometry.** Washington, DC: National Academy of Clinical Biochemistry. http://www.aacc.org/members/nacb/LMPG/OnlineGuide/PublishedGuidelines/newborn/Documents/Expanded_NewbornScreening09.pdf

The use of tandem mass spectrometry (TMS) has made it possible to test for multiple conditions using the same blood spot and so the number of diseases that are potentially detectable by newborn screening has increased considerably. These guidelines from the National Academy of Clinical Biochemistry (NACB) in the U.S. cover the evidence-based rationale for expanded newborn screening (a summary table gives details on 47 inborn errors of amino acid, fatty acid, or organic acid metabolism; testing for most of these is recommended by the NACB), technical and analytical issues relating to follow-up testing of newborns with positive screens, disease-specific follow-up testing recommendations, patient outcomes from early diagnosis by expanded newborn screening, and future directions in the field. It is acknowledged that in some conditions, such as maple syrup urine disease, infants may become severely ill before screening results are available and in others there may be no clinical evidence of disease despite the identified metabolic abnormality. The NACB has ranked diseases that can be detected by TMS according to the strength of evidence for improved patient outcomes in neonatally-detected patients (in descending order): medium chain acyl-CoA dehydrogenase deficiency (MCAD: A-I; 16–18), maple syrup urine disease (MSUD:A-I; 19), glutaric acidemia type 1 (GA-1: A-I; 20–23), and the so-called "classical" organic acidemias, propionic acidemia, methylmalonic acidemia, and isovaleric acidemia (A- II; 11). Within the guidelines the NACB has graded the quality of the overall evidence on a three point scale and determined the strength of the recommendations using criteria modified from those in the US Preventive Services Task Force Recommendations for Preventive Services.

National Collaborating Centre for Women's and Children's Health. **Antenatal care: Routine care for the healthy pregnant woman.** London: RCOG Press, 2008. URL: <http://www.nice.org.uk/nicemedia/live/11947/40145/40145.pdf>

Section 9.1 of this publication covers screening for structural anomalies and reviews studies relating to the use of ultrasound and serum screening (alpha-fetoprotein, AFP) for this purpose. Second trimester ultrasound seemed in general to show high specificity but poor sensitivity for identifying fetal structural anomalies but the actual values varied considerably depending on the centre and the particular anomaly. There were only a few high quality studies looking at first trimester ultrasound. It was reported to have high specificity and positive likelihood ratio but (as reported by a single centre in the U.K.) moderate sensitivity and negative likelihood ratio. There was good evidence that routine, rather than selective, ultrasound before 24 weeks resulted in better assessment of gestational age, earlier detection of multiple pregnancies and improved detection of fetal anomalies which led to higher termination rates of affected pregnancies.

A short version of this guideline can be found at: <http://www.nice.org.uk/nicemedia/live/11947/40115/40115.pdf>

US Preventive Services Task Force. 2008. **Screening for Congenital Hypothyroidism: US Preventive Services Task Force Reaffirmation Recommendation: US Preventive Services Task Force.** The Annals of Family Medicine, 6(2), 166. http://www.annfammed.org/content/suppl/2008/03/14/6.2.166-a.DC1/TorchiaHypothy Online_RecStat-rev.pdf

Congenital hypothyroidism affects one in every 3000–4000 newborns. Without treatment, it can result in mental retardation, growth failure and neuropsychological complications including motor abnormalities, learning disabilities and speech disorders. The US Preventive Services Task Force (USPSTF) has previously published (in 1996) recommendations for screening for congenital hypothyroidism which had a strong evidence base. This reaffirmation recommendation statement from the USPSTF is the result of a targeted review of the medical literature from January 1, 1995, to September 14, 2006, which aimed to find new, high-quality evidence about the benefits and potential harms of screening for congenital hypothyroidism. The USPSTF gives newborn screening for congenital hypothyroidism as an “A” grade recommendation. A clinical summary of the USPSTF recommendations, intended for primary care clinicians, can be found here: <http://www.uspreventiveservicestaskforce.org/uspstf08/conhyppo/conhyppsum.htm>

The literature review which forms the basis for the latest USPSTF recommendations is: Meyers D, Haering S. March 2008. **Screening for Congenital Hypothyroidism: A Literature Update for the US Preventive Services Task Force.** AHRQ Publication 08-05109-EF-1. Rockville, MD: Agency for Healthcare Research and Quality. <http://www.uspreventiveservicestaskforce.org/uspstf08/conhyppo/conhyppart.htm>

This review notes that since the benefits of early treatment of congenital hypothyroidism are well-established, there have been no new RCTs on screening for this disorder. Recent studies have focused on identifying the optimal timing and dosage of thyroid replacement therapy. The authors identified three studies reporting on harms associated with screening for hypothyroidism: two on false positive rates and one on the effects of a false positive test result on family dynamics. There are wide variations in estimates of false positive rates and different programmes use different cut-off points for defining a positive test. Receiving a false positive test result may be stressful for parents. Parental anxiety may be reduced with education and good communication from health professionals.

Demott K, Bick D, Norman R, et al. 2006. **Clinical Guidelines and Evidence Review for Post Natal Care: Routine Post Natal Care of Recently Delivered Women and Their Babies.** London: National Collaborating Centre for Primary Care And Royal College of General Practitioners. <http://www.nice.org.uk/nicemedia/live/10988/30146/30146.pdf>

These British guidelines state that a basic physical examination of the newborn should be done routinely immediately after birth and that it is accepted as good practice (and recommended by the National Screening Committee) that a more thorough physical examination is performed within 72 hours after delivery in order to either reassure parents that their baby is normal if no abnormality is detected, or to act promptly if any abnormalities are detected. The guidelines include a concise outline of what should be included in the newborn physical examination and the specific recommendations of the National Screening Committee. It is stated that the examination at 6 to 8 weeks (the time of the first immunisations) should repeat the assessments made at the postnatal examination and also include an assessment of the baby’s social smile and visual fixation and following. The guidelines state that “there is no high level evidence base for the conduct and content of the physical examination of the newborn” and that therefore the guideline’s examination recommendations are based on expert opinion and good practice.

Bricker L, Neilson James P, Dowswell T. 2008. **Routine ultrasound in late pregnancy (after 24 weeks’ gestation).** Cochrane Database of Systematic Reviews doi:10.1002/14651858.CD001451.pub3 <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001451.pub3/abstract>

Diagnostic ultrasound is used in late pregnancy where there are specific clinical indications such as poor fetal growth or antepartum haemorrhage. There is debate about whether ultrasound screening for all women in late pregnancy is of value. For such screening to be useful it needs to be able to detect conditions that place the mother or the fetus at high risk of an adverse outcome and that could not be detected by other means and for which there are effective treatments or management strategies that improve perinatal outcomes. This review includes eight trials (RCTs and quasi-RCTs, involving a total of 27,024 women and of satisfactory quality overall) of routine ultrasound in late pregnancy to assess some or all of the following: fetal size, presentation or anatomy, placental site or grading and amniotic fluid volume. No differences were found between the intervention and control groups in antenatal, obstetric or neonatal interventions or in morbidity. Caesarean section rates were a little higher in the screened group but the difference was not statistically significant. Overall perinatal mortality was no better in the screened group. One trial assessed placental grading as an adjunct to third trimester ultrasound examination and found that it was associated with a significant reduction in the stillbirth rate. The authors found that there was limited information on long term outcomes such as neurodevelopment and no data on maternal psychological effects. They concluded that, based on existing evidence, routine ultrasound in late pregnancy for unselected or low-risk populations does not have benefits for mother or baby.

Bryant L, Fisher A, et al. 2007. **Fetal anomaly ultrasound screening programme study: Literature survey.** Plymouth: Social Research and Regeneration Unit, University of Plymouth. <http://fetalanomaly.screening.nhs.uk/getdata.php?id=11291>

This literature survey was commissioned by the Fetal Anomalies steering group on behalf of the UK National Screening Committee. It relates to routine mid-trimester ultrasound screening and its main purpose was to populate tables relating to the detection rates, false positives and frequencies of a specified list of anomalies, organised under the following headings: Central Nervous System (CNS), Cardio Vascular System (CVS), Chest, Abdomen, Renal, Limbs and Face. A list of more recent papers from a November 2010 literature search requested by the NHS fetal anomaly screening programme can be found here: <http://fetalanomaly.screening.nhs.uk/getdata.php?id=11283> .

Twisk M, Mastenbroek S, van Wely M, et al. 2006. **Preimplantation genetic screening for abnormal number of chromosomes (aneuploidies) in in vitro fertilisation or intracytoplasmic sperm injection.** Cochrane Database of Systematic Reviews doi:10.1002/14651858.CD005291.pub2. assessed as up to date 14 July 2010.

<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005291.pub2/abstract>

This review assessed the effectiveness of preimplantation genetic screening (PGS) in women undergoing in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) because of infertility. Such screening ensures that only embryos with a normal number of chromosomes (for the chromosomes tested) are implanted, in the hope that this will improve pregnancy rates. Nine RCTs were included in the review. IVF/ICSI with PGS was associated with significantly lower live birth rates than IVF/ICSI without PGS in women of advanced maternal age (5 studies, OR 0.59; 95% CI 0.44 to 0.81) and in women with repeated IVF failure (1 study, OR 0.41, 95% CI 0.20 to 0.88). In good prognosis patients (3 studies) the same trend was apparent but it was not significant (OR 0.50, 95% CI 0.20 to 1.26, random effects model). The authors noted that new techniques for PGS are being developed but they state that until these new developments have been properly evaluated PGS should not be offered in any form as part of routine patient care.

Green JM, Hewison J, Bekker HL, et al. 2004. **Psychosocial aspects of genetic screening of pregnant women and newborns: a systematic review.** Health Technology Assessment (Winchester, England), 8(33), iii, ix-x, 1-109.

<http://www.hta.ac.uk/fullmono/mon833.pdf>

This review considered 106 publications relating to psychosocial aspects of screening in pregnancy for genetic disorders (plus a few non-genetic disorders particularly neural tube defects and congenital hypothyroidism). It aimed to address questions in the following areas: knowledge, anxiety, factors associated with participation (or not) in screening programmes, and the long term sequelae of false positive, true positive (in newborns only) and true negative results. The authors considered that the most important issues which antenatal and neonatal screening programmes needed to address were (in order of priority): the inadequacy of current ways of achieving informed consent, the cost of providing a satisfactory service, the unmet needs of patients who receive false positive screening results and the unmet needs of women's partners particularly in carrier screening.

Other Relevant Publications and Websites

NHS non-invasive prenatal testing and diagnostic services for pregnancy. 2013. **How does NIPT work?**

<http://www.rapid.nhs.uk/> accessed April 2013.

In the U.K. the National Institute for Health Research has funded a 5-year national research programme, the RAPID programme (Reliable Accurate Prenatal non-Invasive Diagnosis). This research programme aims to improve the quality of NHS prenatal diagnostic services by evaluating early non-invasive prenatal diagnosis (NIPD) based on cell free fetal (cff) DNA and RNA in maternal plasma. Currently in the U.K. NIPD testing is available for sex determination where there are clinical indications and for some skeletal dysplasias e.g. achondroplasia and thanatophoric dysplasia. The RAPID website has a range of resources and publications relating to non-invasive prenatal diagnosis.

UK National Screening Committee. 2013. **UK NSC Policy Database.** <http://www.screening.nhs.uk/policydb.php> accessed April 2013.

This website provides links to all the policies of the UK National Screening Committee (UK NSC). The policies are reviewed regularly on a three year cycle. The policy pages for each condition include expert reviews, the evidence base for the current policy and links to relevant publications. The UK NSC currently recommends screening in the antenatal period for the following conditions affecting babies: Down syndrome, fetal anomalies, maternal hepatitis B, syphilis, HIV, sickle cell and thalassaemia, neural tube defect and maternal rubella susceptibility. Screening is not recommended in the antenatal period for cystic fibrosis, cytomegalovirus, familial dysautonomia, fragile X, maternal HTLV, maternal hepatitis C, Tay Sachs disease, thrombophilia, toxoplasmosis and maternal varicella (chickenpox) susceptibility. For newborns, screening is recommended for congenital cataracts, heart disease and hypothyroidism, cryptorchidism (undescended testes), cystic fibrosis, developmental dislocation of the hip, hearing loss, Medium Chain Acyl CoA Dehydrogenase Deficiency, PKU and sickle cell disease. It is not recommended for amino acid metabolism disorders, biliary atresia, biotinidase deficiency, Canavan's disease, congenital adrenal hyperplasia, Duchenne muscular dystrophy, fatty acid oxidation disorders, galactosaemia, Gauchers disease, kernicterus, neuroblastoma, organic acid metabolism disorders and thrombophilia.

Wilson C, Kerruish NJ, Wilcken B, et al. 2012. **Diagnosis of disorders of intermediary metabolism in New Zealand before and after expanded newborn screening: 2004-2009.** New Zealand Medical Journal, 125(1348), 42-50.

This paper reports on a study comparing diagnosis rates for inborn errors of intermediary metabolism (IEMS) for two three year periods, before and after commencement of expanded newborn screening (ENBS) using tandem mass spectrometry in December 2006. In the three years prior to December 2006 there were 15 patients diagnosed. In the three years from December 2006 42 cases were diagnosed, 30 of these by EBNS.

Kerruish NJ, Webster D, Dickson N. 2008. **Information and consent for newborn screening: practices and attitudes of service providers.** *Journal of Medical Ethics*, 34(9), 648-52

This New Zealand study, undertaken in 2002 involved sending a questionnaire concerning provision of information and parental consent for newborn screening (NBS) to all lead maternity carers (LMCs). 93% of LMCs reported giving mothers information about NBS, mostly after delivery (73%) and in the third trimester (60%). Most (85%) LMCs get either verbal or written consent from parents for NBS and 94% consider this to be the ideal approach although 23% of LMCs thought NBS should be mandatory. Of those LMCs who believed NBS should be mandatory, most still believed parental consent should be obtained (89%) and of those who believed NBS should not be mandatory only 10% would accept parental refusal without question. The study authors stated that the survey results indicated a consensus that parents should be provided with good quality information about NBS but that there was less agreement on how much parents should be involved in the decision to allow babies to undergo NBS. They stated that a policy that strongly recommends NBS but also permits parental choice seems to be most consistent with the views of the surveyed LMCs.

Note: The publications listed were identified using the search methodology outlined in Appendix 1 (Search Methods for Policy Documents and Evidence-Based Reviews)

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11. National Screening Unit. 2012. Universal Newborn Hearing Screening and Early Intervention Programme (UNHSEIP): Monitoring Report on Newborn Hearing Screening Service Provision October 2011-March 2012. Auckland: Ministry of Health <http://www.nsu.govt.nz/health-professionals/4627.aspx>