Congenital Disorders

Background information on Prenatal Care and Screening

This document gives a brief overview of Prenatal Care and Screening (PNS). It focuses mainly on information and activities that are relevant to reducing the burden of congenital disorders.

What is Prenatal Care and Screening?

The aim of Prenatal Care is to assist women during pregnancy to remain healthy, finding and mitigating adverse conditions when present, and thus aiding the health of the unborn. Preconception and prenatal care are part of the reproductive health care pathway and can include family planning services, regular physical examination of the pregnant woman, prenatal screening and diagnosis (including tests for detecting diseases or conditions in the fetus) and also counselling or advice given to pregnant women with the aim of reducing risks of diseases in the newborn. For routine prenatal care, the WHO recommends a standard programme of four prenatal visits with additional visits as required. According to the WHO antenatal care model[1], the first prenatal visit should be carried out at around or before 12 weeks of pregnancy, the second visit should be scheduled close to 26 weeks of pregnancy, the third visit should be around 32 weeks, and the fourth visit should be between 36 and 38 weeks. A larger number of visits are recommended in many countries.

Trimesters of pregnancy are classified in the following way:

1st trimester: 12th week of pregnancy
2nd trimester: 13-28 weeks of pregnancy
3rd trimester: 28 weeks of pregnancy till birth.

Prenatal Care and Screening in the health care pathway

Prenatal care and screening is part of an integrated care pathway that includes:

- Family planning and reproductive health care services
- Preconception care, focusing on preparation for a healthy pregnancy and incorporating preconception carrier testing where appropriate
- Prenatal care and screening services including consideration of termination of pregnancy for severe congenital disorders where this is a legal and culturally acceptable option
- Newborn screening services

- Care planning and service delivery.

What are the main risk factors for congenital disorders detected by PNS?

Prenatal care and screening may detect conditions such as haemoglobin disorders including sickle cell disease and thalassaemia, infections such as rubella and syphilis, structural anomalies such as neural tube defects, and chromosomal disorders such as Down's syndrome.

Prenatal care includes evaluation (history taking, physical examination and basic investigations), intervention (prevention/prophylaxis and treatment), and promotion (health education/counselling and health service information dissemination).

Appendix 1 lists various general characteristics of screening programmes that are relevant to a PNS service.

Components of a PNS programme

Prenatal lifestyle advice

Guidelines and advice for a healthy pregnancy and for minimising the risk of congenital disorders include the following:

Nutritional supplements

Supplementation with multivitamins containing folic acid, or at least folic acid only, before conception and throughout the first 12 weeks (usually 400 μg/day of folic acid is recommended, unless the woman is at higher risk, when larger doses are required)[2].

Avoiding infection

Women should be advised about how to reduce the risk of infections especially those which increase the risk of congenital disorders e.g. syphilis and rubella.

Management of chronic conditions

Management of conditions such as diabetes and obesity is recommended as they may increase risk of congenital disorders.

Medicines

As few medicines as possible should be prescribed and only in circumstances where the benefit outweighs the risk. Examples of drugs associated with congenital anomalies include trimethoprim-sulfonamide, sulfasalazine, carbamazapine and phenytoin. Women should be advised to avoid over-the-counter medicines and complementary therapies as much as possible, and to avoid vitamin A supplementation (above 700 μg) and liver products, due to the risk of congenital disorders[3]. Details of safety or risk of specific drugs and teratogens during pregnancy can be found in the following websites:

http://www.motherisk.org/women/drugs.jsp
http://www.otispregnancy.org/otis-fact-sheets-s13037
http://gravidez-segura.org/.

Alcohol and recreational drugs

Women should avoid alcohol, especially in the first 3 months of pregnancy. If women choose to drink alcohol, they should be advised to limit alcohol intake to no more than 1 to 2 Units once or twice a week (1 Unit equals half a pint of ordinary strength lager or beer, or one shot [25 ml] of spirits. One small [125 ml] glass of wine is equal to 1.5 Units). Women should be advised to avoid binge drinking. Recreational drugs should be avoided[2].

Smoking

Smoking status should be discussed and information about harms of smoking during pregnancy and options for stopping smoking given.

Prenatal screening

Screening for haematological conditions

Haemoglobin level below the normal country range (e.g. <11g/dl) may be used to diagnose anaemia in the first instance[2]. When there is a suspicion of iron deficiency, more sensitive and specific tests may be considered, e.g. serum ferritin, which at a cut-off of 30 μg/l has a sensitivity of around 90%[3]. A cheaper alternative is measurement of serum iron and total iron binding capacity.

Screening for haemoglobin disorders

The aim of prenatal testing is to inform parents if their child has a serious haemoglobin disorder and provide them with the option of terminating the pregnancy where this is legal and acceptable, or preparing for the birth of an affected child.

The decision of whether to establish a screening programme will depend on the prevalence of these conditions and other factors such as cultural acceptability and the legality of abortion. Risk assessment for a couple may be based on each parent's family origin (done by questionnaire in the UK), followed by laboratory testing if high risk. The screening process usually involves testing the woman for carrier status and then testing her partner if she is proven to be a carrier. Laboratory screening tests may include the following: full blood count with red blood cell indices, haemoglobin, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and high-performance liquid chromatography (HPLC). If HPLC is not available or affordable then solubility tests or electrophoresis may be used to test for sickle cell trait[3].

If both parents are confirmed as carriers, prenatal diagnosis and counselling may be offered, with fetal cells sampled by chorionic villus sampling (CVS). It is recommended that where possible the whole process including the offer, uptake of and reporting of diagnostic tests and subsequent action of the screening should be complete by 12 weeks of pregnancy[3].

Identifying rhesus D status

Women are ideally tested for ABO blood group and rhesus D status as early in pregnancy as possible, usually at 8 to 12 weeks of gestation. To prevent haemolytic anaemia of the newborn, rhesus negative pregnant women need to be identified and offered appropriate prenatal and postnatal immunoprophylaxis (unless the father is also rhesus negative)[3].

Screening for rubella and syphilis

The aim of screening for rubella early in pregnancy is to identify susceptible women so that they may be advised on risk of infection if they have contact with cases, and on postpartum

vaccination to protect future pregnancies against rubella infection and its consequences. Susceptibility may be assessed by assaying IgM and IgG antibodies against the rubella virus[3].

Screening for syphilis is ideally offered to all pregnant women at an early stage in prenatal care so that affected women can be treated with penicillin[4] and transmission to the fetus can be prevented. There are two main types of serological tests for syphilis. Non-treponemal tests, which detect non-specific treponemal antibodies, are inexpensive but lower in sensitivity, specificity and positive predictive value than treponemal tests, which detect specific treponemal antibodies. Examples of treponemal tests include enzyme immunoassays, which are over 98% sensitive and over 99% specific[3]. WHO recommends confirming a positive non-treponemal test by a treponemal test. However, since the latter is expensive, in countries with few resources and high prevalence of syphilis, treatment may be offered to all pregnant women who test positive with the non treponemal test[4].

Toxoplasmosis

According to the WHO[4], pregnant women should be informed that simple and feasible primary prevention measures may effectively protect against toxoplasmosis infection. These include washing hands before handling food, avoiding undercooked, raw or cured meat, and avoiding contact with cat faeces. Some countries or regions carry out routine serological screening for toxoplasmosis antibodies (examples include Italy, Uruguay, and some regions of Germany, Switzerland and Belgium), followed by monthly or 3-monthly re-testing for seroconversion in those who test positive. However, the test has a high percentage of false positive results. Treatment of seropositive women with spiramycin may be recommended; however it is not clear whether prenatal antibiotic treatment reduces transmission to the fetus.

Screening for other infections

HIV

Pregnant women should be offered screening for HIV infection early in the first prenatal visit[5] because appropriate antenatal interventions can reduce mother-to-child transmission of HIV infection[4].

Malaria

In areas of stable P. falciparum transmission, prevention of asymptomatic malaria infection in pregnant women through a two-pronged approach of intermittent preventive treatment (IPT) and insecticide-treated nets (ITNs) will result in the greatest health benefits. In areas of unstable P. falciparum transmission, antenatal care should include use of ITNs, malaria diagnosis, and treatment with antimalarial drugs that have an adequate safety and efficacy profile for use in pregnancy[6].

Hepatitis B

Pregnant women with unknown serological status for hepatitis B virus (HBsAg) or with new or continuing risk factors for hepatitis B virus infection (such as injection drug use or evaluation or treatment for a sexually transmitted disease) should receive screening in the first trimester[7]. Effective postnatal intervention can be offered to infected women to decrease the risk of mother-to-child transmission[4].

Screening for gestational diabetes

Risk factors for gestational diabetes include a body mass index above 30 kg/m^2, previous baby weighing 4.5 kg or above, previous gestational diabetes, first-degree relative with diabetes, or family origin with a high prevalence of diabetes, such as South Asian, black Caribbean or Middle Eastern[3].

Screening tests for gestational diabetes include measurement of random blood glucose (as recommended by the International Association of Diabetes and Pregnancy Study Groups Consensus Panel) or the 2-hour 75 g oral glucose tolerance test (OGTT), which is recommended by the UK's National Institute for Health and Clinical Excellence. Diagnosis may be made using the criteria defined by the WHO (fasting plasma venous glucose concentration greater than or equal to 7.0 mmol/l or 2-hour plasma venous glucose concentration greater than or equal to 7.8 mmol/l). Women who have had gestational diabetes in a previous pregnancy may be offered early self-monitoring of blood glucose or an OGTT at 16 -18 weeks, and a further OGTT at 28 weeks if the results are normal. Women with any of the other risk factors for gestational diabetes may be offered an OGTT at 24 - 28 weeks. Targets for blood glucose control are similar to those for women with pre-existing diabetes[8].

Control of gestational diabetes may be achieved with diet and exercise alone, but insulin or oral hypoglycaemic agents may also be needed.

Screening for Down's syndrome

Screening for Down's syndrome should ideally start with the provision of unbiased, evidence-based information about the condition, preferably early in the pregnancy. Advanced maternal age alone is not effective as a screening tool. In most developed countries screening is offered to all women regardless of age and it is recommend that ideally, screening for Down's syndrome should be performed in the first trimester, but provision should be made to allow later screening (from 20 weeks 0 days).

Screening tests may include the following:

- Between 10 weeks + 0 days and 14 weeks + 1 day:
  combined test (NT + hCGa + PAPP-Ab)
- Between 14 weeks + 2 days and 20 weeks + 0 days:
  quadruple test (hCG, uE3, AFP, inhibin A).

AFP: Alphafetoprotein
hCG: Human chorionic gonadotrophin
PAPP: Pregnancy associated plasma protein A
uE: Unconjugated oestriol

Once a screening test has been performed, the chance of the fetus having Down's syndrome is calculated taking into account maternal age and gestation. Results are classified as 'screen positive' if the chance is equal to or greater than an agreed cut-off level. When a screen-positive result is returned, the woman will usually be offered amniocentesis or CVS to obtain fetal cells for diagnostic chromosomal analysis by karyotyping or a molecular/cytogenetic method such as FISH or QF-PCR. Comparison between amniocentesis and CVS is shown in Appendix 2. The invasive procedure is associated with

an excess risk of fetal loss of approximately 1% compared with women with no invasive testing.

According to the WHO[4], the best set of tests to offer is an integrated test, which includes nuchal translucency (assessed through ultrasonography at 10 - 14 weeks gestation) plus serological tests conducted at 11 - 14 weeks and at 14 - 20 weeks. The sensitivity of the integrated test is around 90% and the false positive rate is around 2.8%. However, there are concerns about the practicality and acceptability of screening by this method, particularly with regard to the issue of non-disclosure of results after the first phase of screening. For this reason, women may prefer a one-stage test. The combined test in the first trimester has good diagnostic value for detection of Down's syndrome and other chromosomal anomalies. The quadruple test seems to have the best screening performance but the measurement of inhibin A (the fourth analyte) is not generally available in many countries.

Screening for structural anomalies

The tests used commonly for screening of structural anomalies are:

- Ultrasound scan undertaken in first and second trimesters including nuchal translucency measurement
- Serum screening – maternal serum AFP.

There is evidence that, for detecting major fetal malformations, a routine second trimester ultrasound scan is sufficient. Routine ultrasound screening for fetal anomalies is offered between 18 and 20 weeks according to the UK guideline[3]; WHO recommends it before 24 weeks. It may be conducted earlier, particularly if timing for legal termination of pregnancy is more restricted, but sensitivity will be lower. The purpose of the scan is to identify fetal anomalies and allow reproductive choice (termination of pregnancy) or, if parents decide to continue with an affected pregnancy, an opportunity to prepare for any treatment, disability etc., for managed birth in a specialist centre or, in a few cases, for intrauterine therapy.

The woman should be given information about the purpose, limitations and implications of the anomaly scan to enable her to make an informed choice. Standardised procedures with appropriate ultrasound equipment, experienced ultrasonographers and monitoring of screening performance are important for ensuring quality.

Maternal serum AFP level may have a role as a screening test for some structural anomalies such as neural tube defects. However, it is generally recommended that when routine ultrasound screening is performed to detect neural tube defects, AFP testing is not required.

Screening for hypothyroidism

Those likely to be at risk of thyroid disease should have their thyroid function tested early in pregnancy. Women with overt hypothyroidism or with subclinical hypothyroidism who are thyroid peroxidase (TPO) antibody test positive should be treated with oral levothyroxine[9].

Some major prenatal screening tests are compared in Appendix 2.

Cost-effectiveness of screening (main reference: WHO 2005[4])

In the absence of adequate evidence to determine whether selective (i.e. screening of high risk groups only) or universal screening is effective in improving health outcomes for pregnant women and babies, making reliable estimates of the cost-effectiveness of screening is difficult. WHO advises countries to undertake their own analysis of cost-effectiveness of interventions, bearing in mind that many measures of cost-effectiveness do not take into account the burdens imposed on carers or families.

Screening for haemoglobin disorders

Evidence reviewed by UK National Institute for Health and Clinical Excellence (NICE) suggests that screening and prevention of births with haemoglobin disorders is likely to produce cost savings in the healthcare system and would therefore be cost-effective. This result would be more pronounced in areas with a large population that has high disease prevalence. In low resource countries where the economic burden of treatment often falls directly on the family and unless covered by medical insurance, both health services and the families themselves are unable to afford the costs of long-term treatment. This cost is largely driven by the cost of the iron chelation therapy itself. This harsh reality increases the importance of prevention, which are relatively inexpensive due to low labour costs in these low resource countries, and can be significantly more 'cost-effective' than care. For example, in Hong Kong a universal prenatal screening programme for thalassaemia where both α and β thalassaemia were prevalent was found to be cost-effective with savings estimated at HK$40.4 million in 2002. This point is further highlighted in Iran where the cost of treating 15,000 patients for thalassaemia in the year 2000 was estimated by WHO as costing US$200 million.

Anti-D administration to Rh-negative women

Economic evaluations (performed mainly in UK) show that routine anti-D prophylaxis, together with postpartum prophylaxis for Rh-negative pregnant women, is cost-effective when there is a moderate or high probability of subsequent pregnancies.

Syphilis

A cost-effectiveness analysis conducted by the UK National Collaborating Centre for Women's and Children's Health concludes that universal screening of the whole population of pregnant women (as currently performed in UK) is more cost effective than either screening high-risk groups or no screening at all. Screening for syphilis was also considered cost-effective both in developed and developing countries in a recent WHO review.

Gestational diabetes mellitus (GDM) screening

Evidence is insufficient to draw a conclusion about the cost-effectiveness of GDM screening.

Down's syndrome screening

In the UK context the integrated test seems to be more cost-effective than other screening strategies. This is because additional costs due to the screening tend to be offset by savings in the cost of diagnosis arising from the low false-positive rate with the integrated approach. However, further analyses are recommended to confirm this finding and local studies may be essential to establish cost-effectiveness in particular settings.

What are the main ethical legal and social issues (ELSI) to consider?

Equity of access to prenatal care

Around 98% of women utilise prenatal care services in industrialised countries, compared with only 68% women in lower income countries. In many low and middle income countries (LMIC), knowledge and education about safe motherhood is lacking, and there is uneven access to healthcare facilities. For young mothers, especially those in early teen years, unequal access issues may be further exacerbated.

The legal status and rights of the unborn child

The rights of the pregnant woman and those of her unborn child may conflict during pregnancy. This may be relevant if a pregnant woman knowingly exposes her baby to toxins such as drugs or alcohol during pregnancy, or refuses treatment that could save the life of herself or her baby.

Protecting the health of the pregnant women and unborn child

Employment and environmental legislation may be needed to protect the life and health of pregnant women, for example by providing a legal right to paid leave to access prenatal care, or to minimise exposure to industrial or agricultural teratogens. Without these protections, for socioeconomically deprived women the benefits of employment may overwhelm potential health risks during pregnancy, particularly where well developed systems of health care and social support are lacking.

Informed choice

Pregnant women should be enabled to make an informed choice about whether or not to have prenatal tests and, as importantly, how to proceed when the results of the tests are known. It is important that information about testing is provided, before the test, in a non-directive, accessible, and culturally supportive and appropriate manner.

Prenatal population screening

Prenatal screening programmes which identify babies that have severe structural anomalies or are affected by genetic conditions such as sickle cell disease or Down's syndrome should be carried out to high ethical standards. These include ensuring equity of access, clearly documented care pathways, provision of counselling support, informed consent, and maintaining confidentiality of test results. In the case of screening for recessive genetic conditions, participants and their families may also need support to understand the significance of a carrier result. Sometimes test results might reveal unanticipated findings (such as misattributed paternity) and there need to be processes in place to decide when and how to feedback these results to screening participants.

Termination of pregnancy

Where prenatal screening indicates that a fetus is at high risk of a debilitating congenital disorder, the option of termination of pregnancy may be considered. In many LMIC, legal termination of pregnancy is unavailable for religious reasons, or is legally restricted to cases where termination is necessary to protect the woman's life. The consent of a woman's parents or spouse may be required. Where abortion is not permitted, parents may resort to illegal procedures, which are likely to carry both medical and emotional risks.

The discovery that their unborn baby is affected by a congenital disorder is likely to cause prospective parents considerable distress, regardless of their attitude to termination of pregnancy. However, the psychological consequences of an adverse prenatal diagnosis may still be less severe than the shock and distress caused by the birth of an affected child.

In some high income countries there is sometimes concern that it may be difficult for mothers to make a free choice about whether to take up an offer of prenatal screening or, once having undergone screening, whether to proceed with the pregnancy. The issue of lack of free choice may not be faced by parents in LMIC who are confronted instead with fewer options and where poverty and lack of access to health care and social support may be overwhelmingly important in influencing women's decisions.

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RELATED TOPICS

Preconception care and screening
Newborn screening
Teratogens
Down's syndrome
Neural tube defects
Orofacial clefts
Congenital heart disease
Sickle cell disease
Thalassaemia
Congenital rubella
Congenital syphillis

APPENDIX 1 General characteristic of a prenatal care and screening programme

Component heading	Comments
Protocols/policy statement	Ideally evidence based. Policies/protocols/guidelines required for all components of the programme including follow up, treatment and monitoring.
Education	Includes parents and staff. There should be processes in place for review and update. Education should be language- and culturally appropriate.
Data collection/ evaluation	Clarity on what is to be collected, by whom and when. Consideration of/decisions on whether there will be local/regional/ centralised data systems and if these will be computer/hand held/paper/mix. Clarity on who will check and analyse information and how it will be done. Consideration of confidentially issues, back-up and storage.
Equipment/technology	Consideration of requirements, availability, training for use, maintenance, quality measures, validation of results and back up.
Coverage	A predetermined target is needed; this may be mandated. Consideration of health inequalities if screening is not or is not intended to be universal. Coverage should be monitored and include details on refusals.
Resources	The programme needs to be adequately financed. There should be integration into business plans to ensure stability of the programme over the medium/long term. Resources include equipment, staff (including training), buildings, maintenance, transport and administrative support. Decisions are needed on how the programme is to be financed, e.g. family, insurance, public or outside agencies.
Responsibility	Clarity on how service is run and by whom. Clarity on how the programme is coordinated and what the structure looks like, e.g. local regional, central.

Appendix 2 Comparison of different prenatal tests (From Anderson 2009 unless otherwise noted)

	Chorionic Villus Sampling	Amniocentesis	Ultrasonography	Serum screening
Use	Genetic diagnosis; allows sampling of the placental tissue	Genetic diagnosis	Screening for fetal anomalies. Various markers of chromosomal abnormalities may be detected, eg, facial cleft, micrognathia, atrioventricular septal defects, echogenic bowel	Includes the triple test (AFP, hCG and uE3) and quadruple test (above three tests plus inhibin A) for DS and neural tube
Timing	10 - 13 wks gestation	16 - 18 wks gestation (safest); but can be done from 14 - 20 weeks	1st and/or 2nd trimester	1st and/or 2nd trimester
Procedure	Two approaches: transabdominal and transcervical	Needle inserted into the amniotic sac using ultrasound guidance, and amniotic fluid aspirated		Markers measured in maternal serum: Risk calculated using an algorithm based on the age, race, weight, and diabetic status of a patient
Advantage	Early and definitive chromosomal analysis	Complications uncommon	Can help determine whether invasive testing should be pursued	
Disadvantage	Invasive test. Has an operator dependent learning curve and may not be available in every community. CVS performed before 10 weeks increases risk of limb reduction defects to 1 - 2%	Invasive test		
Complications	Fetal loss rate may be higher than amniocentesis	Vaginal spotting. Amniotic fluid leakage. Chorioamnionitis. Failure of fetal cells to grow in culture. Fetal needle injury. Fetal loss.		

Fetal loss rate	0.6 - 4.6%	1% and as low as 1 in 370		
Cytogenetic diagnosis rate	97.8%	99.4%		
Sensitivity (Detection rate or DR)	97.8% for DS in first trimester (10 – 13 wks)	99.4% for DS in 2nd trimester (16 – 18 wks)	1st Trimester: 59.0% (95% CI 46.5% - 72.4%) (NICE 2008)[∞] 2nd Trimester (before 24 wks): 24.1% (range 13.5% - 85.7%) (NICE 2008)[∞] 2nd trimester (18 – 22 wks): 35 - 79% for DS When 1st and 2nd trimester scans combined, DR 81.0% (95% CI 67.7% - 89.2%) (NICE 2008)[∞]	With a fixed screen-positive rate* of 5%, DR is 69% for DS for triple screen and 81% for quadruple screen Maternal serum AFP to detect structural anomalies: 85.7% (NICE 2008) Serum combined test for DS and other chromosomal abnormalities: 92.6% (NICE 2008) Serum combined test for DS only: 79.6% at a FPR of 2.9%, and 82-90.3% at a fixed FPR of 5% (NICE 2008)
Specificity			1st trimester (11 - 14 wks) 99.9% (NICE 2008)[∞] 2nd Trimester (before 24 wks): 99.92% (range 99.40% - 100.00%) (NICE 2008)[∞]	Maternal serum AFP to detect structural anomalies: 97.6% (NICE 2008)
False positive rate	1 - 2% (10 – 13 wks)	0.1 - 0.6% (16 – 18 wks)	6.7% (18 - 22 wks)	Serum combined test for DS and other chromosomal abnormalities: 5.2% for detection of DS and slightly lower for trisomy 18 or 13 and other chromosomal anomalies (NICE 2008)
Comment/Note			75% of fetuses with DS can be detected using ultrasonography	Serum tests may also be done for anaemia, rhesus D status, haemoglobin disorders, syphilis, toxoplasmosis

AFP: Alphafetoprotein

CI: Confidence interval

CVS: Chorionic Villus Sampling

DR: Detection rate

DS: Down syndrome

FPR: False positive rate

hCG: Human chorionic gonadotro

uE: Unconjugated oestri

*The 'screen positive' number is chosen by the lab after looking at the statistical performance of the test. What one tries to do is pick an inflection point along the curve which maximises the detection rate while minimising the false positive rate. This number is about 5% in many triple marker studies but it could have been chosen to be 10% (which would have picked up some more anomalies, at the cost of a much higher false positive rate) or 2% (which would have decreased the detection rate for anomalies but there would have been a much smaller false positive rate.)

°Routine ultrasound scan