The principles of screening tests as applied to obstetrics and gynaecology

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Abstract

Screening in reproductive healthcare in the UK has expanded rapidly since the introduction of cervical screening by the NHS in 1981. Women are offered comprehensive antenatal care screening for a range of pregnancy complications, now including pre-eclampsia and gestational diabetes, with the aim of early disease detection and management. With the advances in molecular medicine in recent years, novel biomarkers are being developed that have the potential to accurately predict these diseases long before their clinical onset. Likewise, non-invasive testing in fetal medicine for a variety of genetic conditions may supersede traditional first trimester screening. In oncology, new tools for population screening for ovarian cancer are being sought via prospective samples stored in biobanks. Tracking serial measurements from each patient may optimize the current use of CA125 rather than using predetermined thresholds. These developments highlight the move towards more personalized medicine. However challenges in implementing new screening will include cost efficacy and ethical considerations such as informed consent.

Keywords non-invasive fetal testing; ovarian cancer; pre-eclampsia; screening

Introduction

The use of cervical cytology for the early detection of cervical cancer is one of the most widely cited, and successful, examples of a medical screening programme. Most other screening strategies within gynaecology are related to early detection of gynaecological cancers. Within obstetrics, the aim of screening is to detect women at risk of adverse pregnancy outcomes. This involves screening the expectant mother for pre-existing conditions which may worsen during pregnancy, the development of pregnancy-specific conditions, and disorders with postnatal and even long-term health consequences (Table 1). Screening with a combination of serum markers and ultrasound scanning aims to detect those pregnancies at high risk of intrauterine growth restriction and certain genetic as well as structural anomalies in the fetus. In this review, we will discuss the principles of screening in obstetrics and gynaecology in light of new advances in the field. We have selected three key areas for review: screening for pre-eclampsia (PE), Down's syndrome, and ovarian cancer.

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The concept of screening

Historical

The concept of screening in medicine tool accelerated in the late 1800s with the development of health checks on well people with the aim of identifying early disease. The periodic examination was introduced in the USA from 1900, with the intention of improving the health and thereby productivity of the workforce. This was performed by physicians but driven by employers, insurance companies and the desire for healthy armed forces personnel. By the 1950s in the USA, blood tests and questionnaires became incorporated into this idea of annual screening. The 1951 Commission on Chronic Illness Conference defined screening as "the presumptive identification of unrecognised disease or defect by application of tests, examination, or other procedures which can be applied rapidly".

In 1968, Wilson and Jungner were commissioned to report on screening for the World Health Organisation (WHO). In their landmark paper, Wilson and Jungner classified screening into mass population screening, selective screening of high-risk groups, and multiphasic screening (ie including radiology, blood tests etc). They laid out the key principles that ensure the validity of screening tests, namely efficiency, reliability, good disease yield and economic viability (Box 1). Their report highlighted the importance of having an acceptable treatment for the disease of interest, to avoid doing harm to the patient. Screening for cancer of the cervix, anaemia, venereal disease, urinary tract infections and streptococcus are all mentioned in their recommendations.

Modern screening programmes

In the UK, screening programmes such as cervical cytology were adopted within the NHS, but their oversight and implementation within a national framework were formalized by the introduction of the National Screening Committee (NSC) in 1996. For example, the NSC has regulated cervical cancer detection by introducing Quality Assessment and Reporting Guidelines, Liquid Based Cytology, Human Papilloma Virus triage and standards for the reporting of results.

A central tenet of the NSC is to look at new screening technologies carefully prior to their introduction. This role of the NSC, and other bodies with an interest in screening, is likely to be of particular importance in the coming years, with scientific advances broadening the capabilities of screening programmes.

Further developments are expected as the result of breakthroughs in other areas. In 2001, Nature published the initial sequencing and analysis of the human genome. This has enabled the rapid identification of candidate disease genes. At the time of that publication, at least 30 disease genes had been cloned secondary to the availability of the genome. Sequencing also revealed mechanisms leading to chromosomal deletion disorders, such as Di George syndrome on chromosome 22. Although

Current standard NHS antenatal care package

Area	Screening
Down's syndrome	Dating USS, nuchal translucency, triple or quadruple test (depending on gestation)
Haematology	Anaemia, blood group and red-cell alloantibodies, haemoglobinopathies
Pre-eclampsia	Hypertension, proteinuria
Infectious diseases	Asymptomatic bacteriuria, HIV, syphilis, hepatitis B, rubella
Social circumstances	Drug use, domestic violence, housing and working conditions
Others	BMI, extremes of maternal age, mental health conditions, pre-existing medical conditions
Selective screening for at-risk women	Gestational diabetes, thrombophilia, Group B streptococcus carriage

Table 1

the rapid advances in genomics may lead to large public health gains through genetic screening, the ability of doctors and policymakers to review the benefits versus disadvantages of introducing new tests into clinical practice may be lagging behind. This moves Wilson & Jungner's concept of early disease detection towards pre-clinical disease detection, using a combination of molecular and non-molecular diagnostics. The validity of their 'gold standard' principles of screening has therefore been called into question. There have been multiple attempts to re-invent their criteria, such as the 2009 ACCE evaluation tool for the newborn screening programmes; an acronym for analytical validity, clinical validity, and clinical utility, ethical, legal and social implications. As genetic screening tests become more widely available and economical, adequate resources will be required to ensure appropriate regulation, education, counselling and follow-up services are provided.

The principle of screening in resource-poor settings also needs consideration. Wilson & Jungner recognized the difficulties with screening in the developing world, referring to "the admirable method of combating disease" but "snags" in practice. Cervical cancer remains the leading cause of cancer-associated death in women in most resource-poor countries. Hindrances to effective screening include the technical expenses and follow-up of patients. Alternative approaches to cervical screening have been trialled, such as direct visualization of the cervix, followed by HPV detection or smear test only if the first inspection appeared abnormal.

The 10 Wilson-Jungner principles of early disease detection

1. The condition should be an important health problem
2. There should be an accepted treatment for patients with recognised disease
3. Facilities for diagnosis and treatment should be available
4. There should be a recognisable latent or early symptomatic stage
5. There should be a suitable test or examination
6. The test should be acceptable to the population
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood
8. There should be an agreed policy on whom to treat as patients
9. The cost of case-finding should be economically balanced in relation to possible expenditure on medical care as a whole
10. Case-finding should be a continuing process and not a 'once and for all' project

Box 1

Screening for adverse pregnancy outcomes

Pre-eclampsia (PE)

Although PE is not part of the current NHS screening programme, the justification for its prediction is based on the premise that detection in the early clinical stages of the disease will reduce the risk of pregnancy complications for both mother and baby. Pre-eclampsia is certainly an important health problem, being one of the commonest causes of premature delivery. Severe PE can also lead to life-threatening complications for the mother, such as eclampsia, intracerebral haemorrhage and pulmonary oedema. Current screening is based upon mass screening to identify maternal risk factors (Box 2), and checking blood pressure and urine at appointments. These tests fulfil the screening criteria of being cost-effective and acceptable to the public and may be successful at detecting the disease in its early stages. However, the prospect of developing tools to accurately predict PE before its onset, enabling patient-specific care, is an exciting one.

Potential screening tests have now been targeted through improved understanding of the various aetiologies of PE. The disease has long been regarded as having familial inheritance; twin studies suggest that the heritable component of PE is greater than 50%. A 10-year analysis of the Swedish national birth registry estimated the contribution of maternal genetics to the development of PE to be 35%, the fetal genome in 20%, couple effects in 13%, shared sibling environment in 1%, and 30% due to the environment. A Norwegian study of 400,000 women looking at the paternal contribution found that patients whose male partners were the offspring of a PE pregnancy were more likely to develop PE themselves.

Attempts to unravel the genetic aspects of PE have included genome-wide association studies (GWAS), microarray studies of