WORKING GROUP ON ACUTE PURCHASING

The Use of Ultrasound (Viability) Scans in Early Pregnancy Bleeding

May 1998

GUIDANCE NOTE FOR PURCHASERS 98/06

Series Editor: Nick Payne

InterDEC Report No. 17/1998

Trent Development and Evaluation Committee

The purpose of the Trent Development and Evaluation Committee is to help health authorities and other purchasers within the Trent Region by commenting on expert reports which evaluate changes in health service provision. The Committee is comprised of members appointed on the basis of their individual knowledge and expertise. It is chaired by Professor Sir David Hull.

The Committee recommends, on the basis of appropriate evidence, priorities for:

- the direct development of innovative services on a pilot basis;
- service developments to be secured by health authorities.

The statement that follows was produced by the Development and Evaluation Committee at its meeting on 20 October 1998 at which this Guidance Note for Purchasers (in a draft form) was considered.

THE USE OF ULTRASOUND (VIABILITY) SCANS IN EARLY PREGNANCY BLEEDING

AUTHORS: Calvert N W, Singleton C D, Tromans P M. Sheffield: Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield 1998. Guidance Note for Purchasers: 98/06.

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(The recommendations made by the Committee may not necessarily match the personal opinions expressed by the experts)

DECISION: The Committee recommended that scans for fetal viability are made available to patients in all health districts according to an agreed protocol. The Committee was impressed by the argument that careful clinical appraisal, counselling and support could avoid the necessity for the use of scans and further interventions, and would wish to see this approach explored.

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Conflict of Interest None of the authors of this document has any financial interests in the drug or product being evaluated here.

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ABOUT THE TRENT INSTITUTE FOR HEALTH SERVICES RESEARCH

The Trent Institute for Health Services Research is a collaborative venture between the Universities of Leicester, Nottingham and Sheffield with support from NHS Executive Trent.

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- undertakes Health Services Research (HSR), adding value to the research through the networks created by the Institute;
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- provides training in HSR for career researchers and for health service professionals;
- provides educational support to NHS staff in the application of the results of research;
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FOREWORD

The Trent Working Group on Acute Purchasing was set up to enable purchasers to share research knowledge about the effectiveness and cost-effectiveness of acute service interventions and determine collectively their purchasing policy. The Group is facilitated by The School of Health and Related Research (ScHARR), part of the Trent Institute for Health Services Research, the ScHARR Support Team being led by Professor Ron Akehurst and Dr Nick Payne, Consultant Senior Lecturer in Public Health Medicine.

The process employed operates as follows. A list of topics for consideration by the Group is recommended by the purchasing authorities in Trent and approved by the Purchasing Authorities Chief Executives (PACE) and the Trent Development and Evaluation Committee (DEC). A public health consultant from a purchasing authority leads on each topic assisted by a support team from ScHARR, which provides help including literature searching, health economics and modelling. A seminar is led by the public health consultant on the particular intervention where purchasers and provider clinicians consider research evidence and agree provisional recommendations on purchasing policy. The guidance emanating from the seminars is reflected in this series of Guidance Notes which have been reviewed by the Trent DEC, chaired by Professor Sir David Hull.

In order to share this work on reviewing the effectiveness and cost-effectiveness of clinical interventions, The Trent Institute's Working Group on Acute Purchasing has joined a wider collaboration, InterDEC, with units in other regions. These are: The Wessex Institute for Health Research and Development, The Scottish Health Purchasing Information Centre (SHPIC) and The University of Birmingham Department of Public Health and Epidemiology.

Professor R L Akehurst,
Chairman, Trent Working Group on Acute Purchasing.

LIST OF ABBREVIATIONS

CA125	Carcinoma Associated Antigen Tumour Markers
CNDRH	Chesterfield and North Derbyshire Royal Hospital
EPAUs	Early Pregnancy Assessment Units
EPF	Early Pregnancy Factor
ERPC	Evacuation of Retained Products of Conception
HCG	Human Chorionic Gonadatrophin
PAPP-A	Pregnancy Associated Plasma Protein
PID	Pelvic Inflammatory Disease
PSA	Prostate Specific Antigen
RCOG	Royal College of Obstetricians and Gynaecologists
SDs	Standard Deviations
SP1	Pregnancy Specific Beta 1-Glycoprotein

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EXECUTIVE SUMMARY

Introduction - The use of ultrasound scanning in cases of early pregnancy bleeding has increased rapidly as a routine test to assess fetal viability. A result indicating non-viability is frequently followed by in-patient intervention for evacuation of retained products of conception (ERPC), although evidence suggests that most non-viable pregnancies would resolve naturally anyway. In a 'typical' district of 500,000 people, some 1,600 women are estimated to experience early pregnancy bleeding each year. Around two thirds of these will have a viability scan, of which some one third will require rescans to obtain a clear result.

Question Considered - This guidance note explores the evidence for the effectiveness and costs of investigation of women with bleeding in early spontaneous pregnancy by ultrasound scanning to assess fetal viability. Although this guidance note accepts that ultrasound is of proven value for conditions such as ectopic pregnancy, there is concern about the value of viability scanning in routine spontaneous pregnancy where bleeding occurs at an early gestational age, (within the first nine weeks). Patients involved in assisted conception or recurrent abortion are specifically excluded from the analysis.

Evidence Base - There is little documented evidence about appropriateness, or about the safety for the fetus, of scanning at such an early stage. The potential for using biochemical markers as a substitute for scanning is reported and reference is made to Dutch clinical guidelines which emphasise the use of non-interventionist primary care and counselling.

Economic Modelling - In the absence of documented economic research evidence, a simple decision tree model for costing three alternative scanning policies is undertaken. The results indicate that the potential savings for a 'typical' district from employing a protocol-based approach to viability scanning is only about £17,000 per annum (16% of the modelled cost of the scanning for all policy). Some of these savings would inevitably have to be used to re-educate patients and staff. Extensive sensitivity analysis shows costs to be relatively insensitive to changes in the model assumptions. Possible implications for ectopic management imply relatively good cost-effectiveness ratios for a scanning for all policy, although whether a protocol-based access policy would affect the identification and management of ectopic pregnancies is largely unproven.

Conclusions and Further Research - The benefits and risks of viability scanning at such an early gestation are not reported in the literature. In the light of the costing results, there is

clearly a need to address the value of such a service and the information made available to women about the likely risks and benefits of scanning in the early gestation period.

Need for Agreed Protocol - A protocol-based access to viability scanning is likely to be an acceptable option compared to the extremes of allowing free access to scanning at any gestation or no viability scanning service. However, there is also a clear need for agreement about the specific protocols to be included in such a policy.

1. INTRODUCTION

This guidance note provides a summary of current evidence regarding the investigation of women with bleeding in early spontaneous pregnancy by ultrasound scanning to assess fetal viability. The authors consider the benefits and costs of such a service, review cost-effectiveness and offer options for future provision.

Women who become pregnant through assisted conception techniques, and those with reproductive problems such as recurrent abortion, previous termination of pregnancy, previous ectopic pregnancy, a previous episode of pelvic inflammatory disease (PID), or tubal surgery, are specifically excluded from the discussion in this guidance note.

Blood loss during the first 13 weeks (first trimester) occurs in around 20% of all known pregnancies. More than 10% of pregnancies ascertained by conventional routine pregnancy tests end in miscarriage. When tests which are able to indicate pregnancy soon after conception are used, this percentage is considerably higher. There are several causes of bleeding in early pregnancy and one of the most important differential diagnoses is that of ectopic pregnancy.

There has been increasing use of ultrasound scanning to assess fetal viability in pregnancies where early bleeding occurs since the late 1970s and early 1980s. Mainstream gynaecological services are increasingly offering ultrasound scans as a routine to women with bleeding in early pregnancy, in order to assess fetal viability and to ensure the diagnosis is not that of ectopic pregnancy. In some hospitals, early pregnancy assessment units (EPAUs) have been set up.

1.1 Epidemiology

Gynaecological complaints are amongst the most common presenting to GPs, and gynaecological disease accounts for nearly 5% of hospital activity within the NHS. Around 20% of total gynaecological workload is related to early pregnancy problems, which comprise 50% of emergency gynaecological activity.

Bleeding in early pregnancy is common, occurring in around one-fifth of pregnancies. In over half of these cases the pregnancy ends in spontaneous abortion (miscarriage), with

40% - 45% of such pregnancies continuing to term.[1] Causes of bleeding in early pregnancy include:-

- threatened miscarriage, missed abortion, blighted ovum;
- extrauterine pregnancy;
- cervical erosion;
- cervical or uterine polyp;
- hydatidiform mole.

1.1.1 Miscarriage

Miscarriage is the commonest complication of pregnancy, affecting 12-15% of all pregnant women.[2] The frequency in very early pregnancy is difficult to determine as the pregnancy may not be recognised. Whittaker et al.[3] showed that 8% of human pregnancies are lost at such an early stage of development that parents are unaware of conception. Estimates suggest that the occurrence of subclinical pregnancy loss may be as high as 40-60%.[4,5] Most (around 60%) of early fetal losses are abnormal karyotypes.

Over the years, there has been a shift towards hospital management and treatment of miscarriage by uterine curettage. Patients admitted to hospital with miscarriage generally undergo surgical evacuation of retained products of conception (ERPC), which comprises 75% of all emergency gynaecological operations. Unfortunately, no national statistics on miscarriage are published except for such hospital activity. It is important to note that miscarriage is normally a self-regulating process with at least 75% of cases resolving spontaneously and naturally within a week.

More recently, women with incomplete or missed abortions including blighted ovum are being managed medically with a combination of anti-progesterone and prostaglandins.

Spontaneous abortion occurs in around 150 per 1,000 pregnancies.

1.1.2 Ectopic Pregnancy

Ectopic pregnancy, the siting of a pregnancy outside the uterine cavity, may result in severe morbidity and accounts for some 10% of direct maternal deaths,[6] mainly from haemorrhage. It occurred in 1.15% of pregnancies in the UK in 1994-96 and the incidence appears to be rising in industrialised countries.[6,7,8] Factors associated with an increased incidence include tubal surgery, the use of the progestogen-only pill, PID, and the use of intrauterine

contraceptive devices. Around 50% of cases can be attributed to PID.[9] Ectopic pregnancies can miscarry spontaneously or resorb. They may not present at all or may present as an acute emergency with pain, bleeding and shock.

Early diagnosis affords the opportunity to use minimal access surgical techniques such as salpingostomy or medical treatment using methotrexate.[10]

1.1.3 Other Causes of Bleeding in Early Pregnancy

Cervical ectropion and cervical and uterine polyps may be the cause of bleeding in early pregnancy. Cervical lesions are usually detectable on clinical examination. The risk of hydatidiform mole increases with age and it is very rare under the age of 30; diagnosis requires ultrasound. The frequency differs between countries, but it is very low in all developed countries.

1.2 Scale of the Problem in a 'Typical' District

A district of 500,000 population can expect to have around 5,800 births annually, with around 7,000 recognised pregnancies, 64 ectopic pregnancies and 920 spontaneous abortions. Around 1,600 women will experience bleeding during their pregnancy. These figures do not include those with unrecognised or unsuspected early pregnancy loss.

Between 63% and 73% of women with bleeding in early pregnancy (around 1,000 - 1,160 women in a 'typical' district) currently have an ultrasound scan to determine fetal viability.[1] Around one third of these will require two or three scans to establish a definite diagnosis.[11]

2. THE USE OF ULTRASOUND (VIABILITY) SCANS IN EARLY PREGNANCY BLEEDING: SUMMARY OF EVIDENCE OF EFFECTIVENESS

There have been several studies which have attempted to define clinical, biological, and ultrasonic markers which can predict outcome following early pregnancy bleeding. However, there are no effective treatments which can maintain an intrauterine pregnancy when adverse factors are recognised. Any investigations or tests performed, therefore, have no therapeutic consequences in terms of maintaining pregnancy for these patients, although ERPC may be required.

2.1 Use of Ultrasound in Confirming Viability of Fetus in Early Pregnancy Bleeding

The use of ultrasound in the assessment of fetal viability in patients with early pregnancy bleeding appears to be generally accepted as good practice in the UK. There are still questions about the timing and purpose of the test and long-term safety of children who have been exposed in utero.

Gilling-Smith assessed the use of guidance on routine vaginal examination and ultrasound in patients with bleeding prior to the 20th week of pregnancy attending an accident and emergency department in London. Around 70% of patients had first trimester bleeding. A diagnosis was made on the basis of the clinical examination alone in 47% of cases and ultrasound was used in 38% of women. The introduction of this guidance on management reduced the numbers of unnecessary admissions from 28% to 12%, referrals to gynaecological colleagues from 44% to 22% and the number of re-attendances to the department from 15% to 4%.[12]

In 1987, the Dutch College of General Practitioners developed a guideline policy programme and one of the first evidence-based guidelines to be developed was the management of (threatened) miscarriage in 1989 (NHG guidelines).[13] This is under review at present, but there are not expected to be any major changes to the guidance.[14] The Dutch guidelines promote the use of expectant management for women with threatened abortion to allow events to take their natural course, and discourage the use of ultrasound as a routine investigation. However, they recognise the value of an ultrasound investigation where there is suspicion of an ectopic pregnancy, where blood loss is heavy, and where it lasts longer than a week, as these symptoms would justify intervention. Studies have shown that as many as 10% of women who experience a miscarriage may not contact health services at all, and that for most women, the GP is the main point of contact.[15] The vast majority of GPs

were happy to support patients with light spotting in the community, but referred to hospital, for viability scanning, patients with moderate or heavy bleeding.[16] Subsequent work has shown that almost all women can be managed in the primary care setting, especially if ultrasound is available.[17]

Both the above guidelines and the Gilling-Smith study[12] confirm that, where clinical examination demonstrates a dilated cervix, ultrasound is inappropriate (as miscarriage inevitably occurs). However, in the absence of clinically recognised products of conception having been passed, an ultrasound scan may exclude retained products of conception and, therefore, reduce the need to proceed to ERPC either surgically or medically.

EPAUs with direct access from primary care to diagnostic testing facilities reduce the need for out-of-hours operating, but have not been formally evaluated.[18] Of 624 women referred to an emergency assessment clinic with a provisional diagnosis of threatened miscarriage, based on a history of amenorrhoea and vaginal bleeding, with or without pain, 25% were not pregnant and 9.6% had an ectopic pregnancy.[19] Although there is some evidence that such units are efficient, there is little evidence to suggest they provide clinically effective services.[20]

Arguments for echographic examinations are usually based on needing to address the emotional impact of bleeding in early pregnancy for the patient. However, there are no studies which have explored other options for management. Experience in the Netherlands suggests that time taken by the primary care physician in counselling and explanation may be more effective in meeting these needs.[13] A recent publication reported on the adherence to national guidelines by self-selected Dutch midwives.[21] This study showed that there was 71% overall compliance with the guidance on not performing an ultrasound scan. For those cases where a scan was performed, half were related to lack of skills to interpret a physical examination and half were in response to the clients' wishes.

2.1.1 Timing of Ultrasound

The gestational sac can be visualised with transvaginal scans at around 4½ to 5 weeks, but there are no features which are 100% reliable in differentiating viable and non-viable pregnancy on a single ultrasound examination, when the gestation is less than six weeks.[22] Fetal heart activity can be detected from five weeks and six days with good resolution ultrasound equipment, when the crown rump length is only 3mm. Fetal movements can be seen on ultrasound by eight weeks of gestation and are 100% reliable from 10 weeks'

gestation.[23,24] The interpretation as to whether an ultrasound scan is correct or not depends entirely on the gestational age prediction. The fetus grows at approximately 1mm per day from six weeks gestation, and by seven weeks there should be no difficulty in identifying fetal cardiac activity, and confirming viability. At a crown rump length of 6mm or more, absent fetal heart activity definitely indicates non-viable pregnancy (missed abortion).

Following viability demonstrated by cardiac activity using ultrasound at eight weeks' gestation, between 3.2% and 5.5% of pregnancies were lost subsequently through miscarriage .[2,25]

Experience and expertise in gynaecological ultrasound is important to minimise the risk of misdiagnosis.[26] The result of an ultrasound scan depends on the skill of the staff undertaking the scan and the quality of the machine. This is particularly relevant now that all junior trainees in obstetrics and gynaecology are expected to be able to scan. Many are forced to use small machines on the ward at night and weekends, which do not have the resolution of the larger machines typically used by ultrasonographers or consultant personnel.

Vaginal ultrasound is superior to abdominal ultrasound for detection of an intrauterine embryo and its cardiac activity before eight weeks' gestation. Indeed, any service nowadays requires a transvaginal scan facility, as it is no longer considered acceptable to rely on abdominal scanning alone as the diagnostic instrument.[27]

Local audit has suggested that around 30% of women require two or three scans to establish a definite diagnosis. The interpretation of ultrasound scanning is clearly dependent on gestational age.

Other studies have suggested that ultrasound can be misleading in up to 8% of cases overall.[28]

Routine ultrasound in early pregnancy (between 10 and 18 weeks) results in earlier detection of multiple pregnancy and reduced rates of induction for post-term pregnancy, but it does not improve clinical outcomes,[29,30] although it does reduce intervention rates (e.g. forceps, Venteuse, and caesarean sections).

2.1.2 Risk Factors Identified on Ultrasound

Subchorionic bleeding has been recognised as an important prognostic factor. In pregnancies where there is subchorionic bleeding demonstrated by ultrasound at nine weeks' gestation or more, with normal fetal cardiac activity, 80% will progress to term. Where there is no subchorionic bleeding and normal cardiac activity at this gestation, one study showed 100% progressing to term.[31] The overall miscarriage rate in women with such signs in the first trimester has been shown to be 9.3%. This rate is 2-3 times higher: with a large separation compared to moderate or small haematomas, in women aged over 35; and where vaginal bleeding has occurred at eight weeks gestation or less.[32]

The use of ultrasound in very early pregnancy with bleeding can create problems. Patients are difficult to manage if there are uterine contents in the absence of a confirmed non-viable early pregnancy. Indeed, in early 1998, a woman was granted substantial damages following scan diagnosed non-viability, which was followed by continuing pregnancy. The Royal College of Obstetricians and Gynaecologists (RCOG) has produced guidelines covering ultrasound scanning in early pregnancy.[33]

The probability of miscarriage following first trimester bleeding ranges from around 6%, if no adverse factors are present on ultrasound, to 84% if all the following adverse factors are identified: fetal bradycardia less than 1.2 standard deviations (SDs) from the mean for gestational age; a discrepancy between the diameter of the gestational sac and the crown-rump length of more than 0.5SDs below the mean; and a discrepancy between menstrual and sonographic age of more than one week.[34]

2.1.3 Safety of Ultrasound

There is a recently compiled Cochrane review of routine early pregnancy ultrasound;[35] this has demonstrated that there appear to be no long-term effects on Norwegian children exposed to ultrasound early in pregnancy in terms of adverse influence on school performance or neurobehavioural function. However, fewer of the ultrasound exposed children than expected were right-handed. Ultrasound was carried out at under 16 weeks' gestation in only one of the studies reviewed and, even then, not earlier than 10-12 weeks.[36] There are no studies which examine the long-term effects of ultrasound on children exposed under 10-12 weeks' gestation.

There is a view that women are often not informed of the possible risks when offered an ultrasound scan.

2.2 Management of Women with Threatened Miscarriage

When used to assess fetal viability, ultrasound scans have no management implications for the care of the patient in that there is no evidence to support the use of curettage if fetal death is confirmed, although a viable scan can provide some reassurance and planning of future care. There is a clinical view held by many obstetricians that curettage should be carried out to evacuate the uterus if fetal death has occurred. This procedure has the potential to create morbidity by carrying out a surgical intervention in a condition which is likely to resolve spontaneously within a few days.[1] The enthusiasm to evacuate may stem from fears of hypofibrinogenaemia, which was thought to be a possible consequence of a slow reabsorbtion of a spontaneous abortion. The psychological consequences of non-viability and, indeed, of early pregnancy bleeding itself cannot be ignored, however, it must be remembered that demonstration of viability is not a guarantee of the pregnancy continuing to term.[2,25]

The Dutch guidelines promote the use of expectant management for women with threatened abortion to allow events to take their natural course, and discourage the use of ultrasound, as miscarriage is not, *a priori*, an indication for ERPC. In particular, they cite the pressure for surgical intervention, such as ERPC, if ultrasound results suggest the death of the fetus. Other studies have suggested that, because no treatment has a documented effect on maintaining pregnancy, hospitalisation cannot be recommended.[37]

Curettage has certain risks which include infection, damage to the cervix, uterine perforation, intra-uterine adhesions, Ashermann syndrome, and risks of necrosis, as well as the emotional burden for the women concerned. In addition, there is the risk of morbidity from a general anaesthetic. A recent study has reported that surgical intervention carries a doubling in the risk of infection compared to expectant management.[38] Another study has shown a 3% infection rate after spontaneous resolution; however, the complication rate for women undergoing ERPC was 11%.[35] Further studies are continuing. ERPC may be appropriate when there is heavy blood loss, prolonged blood loss (more than one week), increasing pain or when the emotional burden is such that curettage may be beneficial.[13] It is important to note that the risks associated with ERPC in relation to miscarriage are not as high as those associated with surgical termination of pregnancy, although risks associated

with the latter have been reduced with the use of routine pre-operative prostaglandins to soften the cervix. There is now increasing use of medical management of incomplete abortion, missed abortion, and blighted ovum with progesterone and prostaglandins.

In patients with threatened miscarriage, resolution will occur within four days following commencement of blood loss in over $^{2}/_{3}$ of cases, and over $^{3}/_{4}$ will resolve spontaneously within a week. A prospective randomised trial of expectant management versus ERPC in miscarriage under 13 weeks showed that both methods of management produced similar outcomes.[35] Spontaneous resolution of the miscarriage occurred in 79% of women within three days.

The importance of assessing maternal blood group and giving anti-D immunoglobulin in those who are Rhesus negative must be emphasised.

2.3 Use of Vaginal or Abdominal Ultrasound in Diagnosing Ectopic Pregnancy

Both in the UK and USA, the failure of women with an ectopic pregnancy to seek medical attention contributes to the numbers of deaths from this condition. Studies have shown that history and physical examination do not reliably diagnose or rule out ectopic pregnancy. Of patients with ectopic pregnancy, 9% reported no pain and 36% lacked adnexal tenderness.[39]

Vaginal or abdominal ultrasound can exclude the possibility of an ectopic pregnancy by confirming an intrauterine pregnancy on the grounds that a combination of both intra- and extra-uterine pregnancies is extremely rare (1 per 30,000 pregnancies).

A comparison between vaginal and abdominal ultrasound showed that visualisation of ectopic pregnancy was 25% with abdominal and 94.7% with vaginal ultrasound. 83% of women had spotting. Abdominal ultrasound was significantly inferior and vaginal ultrasound superior to clinical examination.[40] In another study, transvaginal ultrasound definitely identified 82% of ectopic pregnancies on initial examination, with the remainder identified on repeat examination and Human Chorionic Gonadotrophin (HCG) measurement.[41] However, there can be difficulty in interpreting a pseudogestational sac in 10% to 20% of ectopic pregnancies at very early gestations.[42]

Various studies have examined the sensitivity and specificity of ultrasound in the diagnosis of ectopic pregnancy (Table 1).

Table 1 Sensitivity and Specificity of Transvaginal Ultrasound in the Diagnosis of Ectopic Pregnancy

	Sensitivity	Specificity	Likelihood ratio[#]	Positive Predictive Value	False Positive Rate	Study
Diagnosis	69% 90%	99% 88%	69 7.5		 16.6%	Kaplan[39] Durham[43] Bonilla[44]
Transvaginal B mode	98%			86%		Chew[45]
Free pelvic fluid	96.2%	99.4%	160			Sadek[46]
Tubal mass	81.6%	99.6%	204			Sadek[46]
Solid adnexal mass	Low	High				

The combined application of ultrasound and plasma HCG levels seems to be useful in the diagnosis of ectopic pregnancy when the gestational age is known.[47,48] Several studies have suggested that the risk of ectopic pregnancy is raised by up to four fold with HCG levels of less than 1,000 iu/l.[39,40,49] An intrauterine sac should be visualised with HCG levels of greater than 1,000iu/l and its absence should raise the suspicion of ectopic pregnancy.[50]

The diagnostic use of laparoscopy provides a positive diagnosis in more than 90% of cases and a falsely negative diagnosis in 3-4% of cases, which tend to be early in pregnancy.[51] The longer the diagnosis of ectopic gestation is delayed, the more likely it is that rupture will take place, requiring emergency laparotomy and tubal loss by salpingectomy and increased risk of maternal death. Furthermore, a ruptured ectopic and collapse is a particularly traumatic experience for a patient and those with previous ectopics are often anxious about the management of their early pregnancy.

There is increasing use of laparoscopy in the treatment of ectopic pregnancy. Its use would be greater if more junior doctors were trained in the use of minimal access surgical techniques, and out-of-hours theatre staff were familiar with the use of such equipment. Apart from the obvious advantage to the patient of avoiding large scars, there is less discomfort, reduced morbidity, a shorter hospital stay and an earlier return to normal

[#] A likelihood ratio for a given diagnostic test result gives the odds that the test result comes from a person who has the disease for which the test was ordered. When this likelihood ratio is multiplied by the pre-test odds that the patient has the disease, the product is the post-test odds that the person has the disease. In this context, the likelihood ratio = sensitivity / (1- specificity) ref page 119 - in Sackett DL, Haynes RB, Gutatt GH, Tugwell P. Clinical Epidemiology: A basic science for Clinical Medicine. 2nd ed Little, Brown and Co. London)

activities.[52,53] A summary shows that there is fair evidence of benefit, although most studies are poorly controlled or uncontrolled.[54]

There is some interest in conservative treatment, including salpingostomy and medical treatments such as methotrexate, in appropriate patients. The latter has been shown to have a success rate of 71%-100% with tubal patency rates of 72%-93%.[55,56] Spontaneous resolution of ectopic pregnancy has been observed in at least 15% of patients. Earlier diagnosis has shown that spontaneous regression of tubal pregnancies is more common than previously thought.[42]

The treatment of ectopic pregnancy is the subject of a current Cochrane protocol for a future review and is not considered further here.[10]

2.4 Other Diagnostic Tests for Bleeding in Early Pregnancy

A useful summary of the current state of biochemical tests can be found in chapter 10 of 'Problems in Early Pregnancy: Advances in Diagnosis and Management'.[33]

i) **Human Chorionic Gonadotrophin**

HCG estimation should be the primary biochemical diagnostic test used in the differential diagnosis of abdominal pain in women of reproductive age. Recent recommendations to establish protocols and algorithms for the management of patients with early pregnancy bleeding using HCG measurement have been made.[33] Free beta-HCG concentrations have been found to be significantly lower in non-continuing, threatened miscarriage and tubal pregnancy patients. A cut-off value of 20ng/ml differentiates between viable and abnormal/non-viable pregnancies with 88.3% sensitivity and 82.6% positive predictive value.[57] In another study the predictive value of HCG in patients with threatened abortion was 93%, the sensitivity 84%, and the prediction of viability at the given gestations was 81%.[58] However, free beta-HCG testing is currently a research procedure only and is not available in routine practice.

Generally, the prediction of abortion is more accurate than that of successful outcome. However, a single normal value of HCG in women with threatened abortion between six and nine weeks' gestation, where gestation is accurately known, has been shown in one study to be associated with a successful outcome in every case.[59] HCGs are frequently undertaken serially, and it is the adequate rise with time that determines the prognosis

for viability. In a viable pregnancy the HCG levels double every 48 hours. A sub-optimal rise suggests a non-viable intra-uterine pregnancy or ectopic pregnancy.

For HCG measurement, it is important to acknowledge that interpretation is dependent on gestational age. There is disagreement between professionals about how good women are at knowing their dates and, thus, how important the need is for ultrasound scanning to ascertain gestational age.

In one study of women where gestational age was known, a single transvaginal scan and plasma HCG were used. Using figures for the natural logarithm of HCG value, Ln(HCG), a result below a pre-defined limit on the distribution of values had a poor predictive capacity with a sensitivity of 31% and a specificity of 97% for distinguishing viable from non-viable pregnancy.[60]

ii) **Progesterone**

Serum progesterone levels are lower in non-viable pregnancies. Values less than 14.2 ng/ml in asymptomatic pregnancy and 10.5 ng/ml in women with threatened miscarriage are 100% sensitive in the detection of non-viability.[61] A cut-off value of 45 nmol/l as a single measurement has been found to differentiate between viable and non-viable pregnancy with a 87.6% sensitivity and 87.5% specificity.[62] The addition of serum progesterone estimations to HCG measurement may increase sensitivity and specificity in the identification of ectopic pregnancy or failed intrauterine pregnancy, but there is insufficient evidence at present to recommend routine use.[33]

Progesterone measurement does not appear to be dependent on gestational age in early pregnancy.

iii) **Other Biochemical Markers**

There are several other biochemical markers whose use has been studied in the management of early pregnancy bleeding, however, none is in current routine clinical use. These are included for completeness below.

- Oestradiol: Levels of oestradiol higher than 30 pg/ml have been shown to correlate in 100% of cases with favourable outcome following bleeding in early pregnancy.[22] Oestradiol assays are not used in the UK.

- Carcinoma Associated Antigen Tumour Markers (CA125): Mean serial serum CA125 levels have been found to be higher in women with an unfavourable pregnancy outcome, as it may help to determine the extent of decidual destruction in threatened abortion. Levels above 65 U/ml on the first test and 60 U/ml on the second gave a risk of termination of the pregnancy of 83%; when associated with vaginal bleeding for three days or more, the risk was 100%.[63]

- Pregnancy Specific Beta 1-Glycoprotein (SP1): Maternal concentrations of pregnancy-specific beta 1-glycoprotein (SP1) have been shown to be reduced in cases with an unfavourable outcome. The test has been shown to have a sensitivity of 65%, specificity of 98% and predictive value of 96%.[47]

- Early pregnancy factor (EPF): This has been studied as a potential marker for assessing fetal viability in women with bleeding in early pregnancy. Sensitivity of the test was 78.9% and specificity 95.6%. The positive predictive value was 93.8% and the negative predictive value 84.6% and, thus, it could well be a useful prognostic marker in threatened abortion.[64]

- Pregnancy Associated Plasma Protein A (PAPP-A): This test has been shown to be significantly lower in women with bleeding, but has a positive predictive value of only 18.7% for actual miscarriage and is, therefore, of no clinical value in the assessment of patients with bleeding in early pregnancy.[65,58]

- Folate: Although folate levels have been shown to be low in a substantial proportion of pregnant women, low folate levels do not appear to be associated with an increased risk of pregnancy loss or adverse outcome.[66]

2.5 Summary of Evidence

Bleeding in early pregnancy is a common problem. In over half of these cases the pregnancy will end in miscarriage. Miscarriage is a natural process and ¾ of cases do not require medical intervention.

There is a substantial emotional impact on women which should be addressed. However, there are no studies which have examined the most appropriate and effective way(s) to provide support. Experience in the Netherlands suggests that support, advice and

counselling from primary care team members is important. There is some disagreement in the profession about which of the primary and secondary sectors is better placed to provide such support.

The use of ultrasound to detect fetal viability has gained acceptance as part of routine medical practice despite a lack of directly applicable studies of good quality. It is important that the patient and physician understand that there is very little prognostic value in the test. Although results can allow a care plan to be arranged if fetal viability is shown, there may be pressure to perform ERPC in non-viability, which will be unnecessary in a high proportion of women and increases morbidity significantly above that experienced by women undergoing spontaneous resolution. Medical management of retained products of conception is safer and uses fewer health service resources than surgical intervention.

There are no studies which have examined women's views on viability scanning, although uptake of local services suggests women may find it acceptable and reassuring. There is a view that women with previous experience of early pregnancy loss and particularly ectopics are very keen to have early scans.

Ultrasound examinations in early pregnancy should be performed transvaginally.

Evidence suggests that there should be a lower limit on gestation for the use of ultrasound in threatened miscarriage. Using the test before the eighth or ninth week of pregnancy requires a high proportion to be repeated in order to determine the diagnosis (although this proportion is lower with the use of transvaginal compared with abdominal ultrasound). The few studies which have looked at EPAUs have found a high proportion of women not to be pregnant. There is, however, some evidence that the use of ultrasound in women who present to hospital as an emergency can reduce gynaecological referrals and out-of-hours operations. Misdiagnosis from ultrasound examination is reduced by restricting the use of the test to those with appropriate experience and expertise, but there will always be a significant proportion of women who will require a repeat test to establish a diagnosis.

Transvaginal ultrasound scanning has a good sensitivity and specificity for ectopic pregnancy, although studies reporting high false positive rates are of concern. There is no published evidence that the use of ultrasound in all women presenting with early pregnancy bleeding is an effective screening test for ectopic pregnancy.

There is no published evidence that outcomes for women with ectopic pregnancy are improved by the use of ultrasound in women presenting with early pregnancy bleeding. However, there is a clinical view that current best practice should include ultrasound. More ectopic pregnancies are diagnosed before tubal rupture where there is an EPAU.[67]

Other diagnostic tests have been studied. Use of HCG measurement has been demonstrated to be helpful in investigation and management of early pregnancy bleeding. Progesterone assays may also be of use.

The safety, longer-term effects and outcomes of the use of ultrasound in pregnancies under 10 weeks' gestation have never been studied. It is important also to offer women balanced and full information on such matters. Also, the introduction of a Dutch style healthcare programme of managing early spontaneous abortion, up to nine weeks, in the home for the majority of women, would require re-education of general practitioners, healthcare workers, and the general public.

Expectant and medical management of miscarriage, and of ectopic pregnancy, have potential benefits and should be considered for all suitable patients.

3. COST AND BENEFIT IMPLICATIONS

3.1 Introduction

There are no known published papers looking at the cost-effectiveness of viability scanning using ultrasound in early pregnancy. Consequently, this section of the report describes a modelling approach to costing. Three theoretical policy models are presented. In brief, Option 1 suggests sonography for all women presenting with bleeding in the early stages of pregnancy irrespective of gestational age. Option 2 is an example of a simplified protocol-based access policy, which excludes sonography for women presenting with bleeding before nine weeks' gestation. Option 3 is a policy of no ultrasound viability scanning for the group of patients under consideration.

It is worth reiterating here that this guidance note, and hence the costing model discussed below, is concerned only with women who experience bleeding in early spontaneous pregnancy. They exclude women who become pregnant through assisted conception techniques, and those with reproductive problems as listed in the introduction to this guidance note. They also explicitly exclude ectopic pregnancies in the initial analysis, although ectopics will be discussed under the sensitivity analysis sub-section of this chapter. It is important to stress that the following models are not offered as clinical models of care, but simply as tools with which to estimate likely cost differences between the various policy options.

A decision tree modelling approach is adopted. This approach makes the assumptions used in the modelling process transparent. By definition, models are simplifications of reality and in no way is the model designed to capture all the details of the 'real world'. In brief, decision trees describe decision-making processes using activity branches, and decision and chance nodes. Decision trees can be used to represent decision-making processes for individuals or cohorts of individuals in a population. Time is represented on the horizontal axis running from left to right, so that the far right of the tree represents the end-points or outcomes of the decision making process. The square nodes represent points in time when a decision or choice is made by decision makers. Round nodes are chance nodes from which branches emanate representing subsequent events which occur with a given probability. The model described in this guidance note is a population-based model and, hence, the chance points usually describe points in time when different sub-groups of the population take different routes in varying proportions.

Activity branches emanating from decision nodes usually imply a financial cost. In our model, the cost of sonography or the cost of medical or surgical management of miscarriage are examples of such activity costs. By multiplying the probability of chance events by the costs of subsequent decision events, the expected cost of each branch of the decision tree can be calculated and compared.

Decision tree models can be used to model costs alone, outcomes alone, or combinations of the two, such as cost-effectiveness or cost-benefit analyses. The topic under discussion makes it difficult to define a specific outcome of interest (see discussion below) and, as such, the economic analysis in this guidance note is confined to costs only.

The first two of the three policy options under discussion are represented in Figures 1a and 1b in the form of a decision tree. The third policy option is effectively a sensitivity on the second and is not, therefore, presented as a separate tree diagram.

3.2 Model Description

The tree models two possible options, the first is where all women presenting between six and nine weeks' gestation are given a viability scan using ultrasound. In the second option, a protocol-based policy is assumed in which ultrasound is not given before nine weeks' gestation. By the very nature of the modelling process, it is necessary to make a number of simplifying assumptions.

It is assumed that interest is confined to modelling the costs of managing those women who present with bleeding between six and nine weeks' gestation. This time period has been chosen because it is this gestational age for which the value of ultrasound is most in question. Both ectopic pregnancies and pregnancies with no bleeding between six and nine weeks are represented in the tree, but assigned a probability of zero occurrence to indicate that they are explicitly excluded from the initial analysis.

Figure 1a The Scanning For All Policy Decision Tree Model

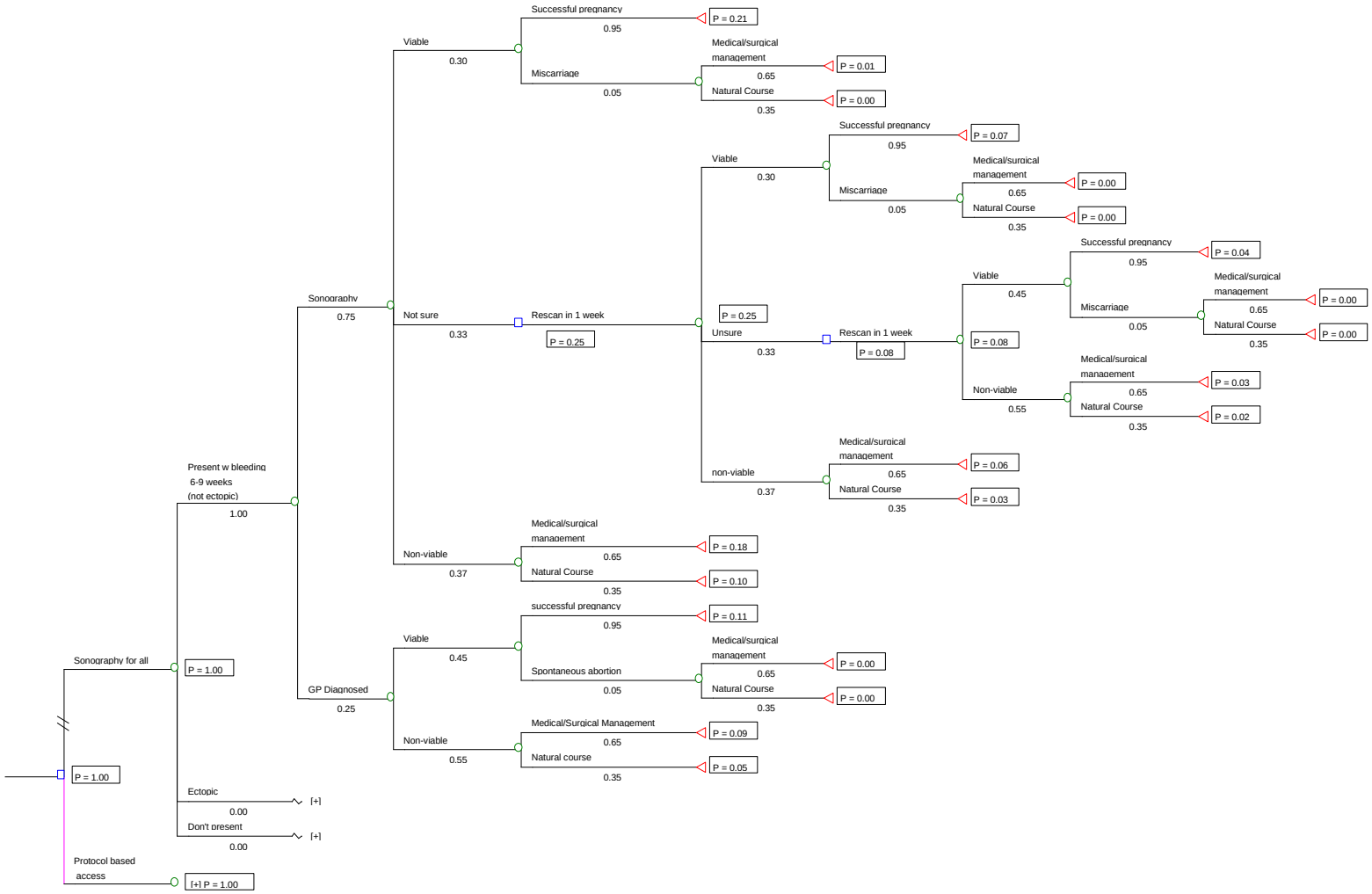
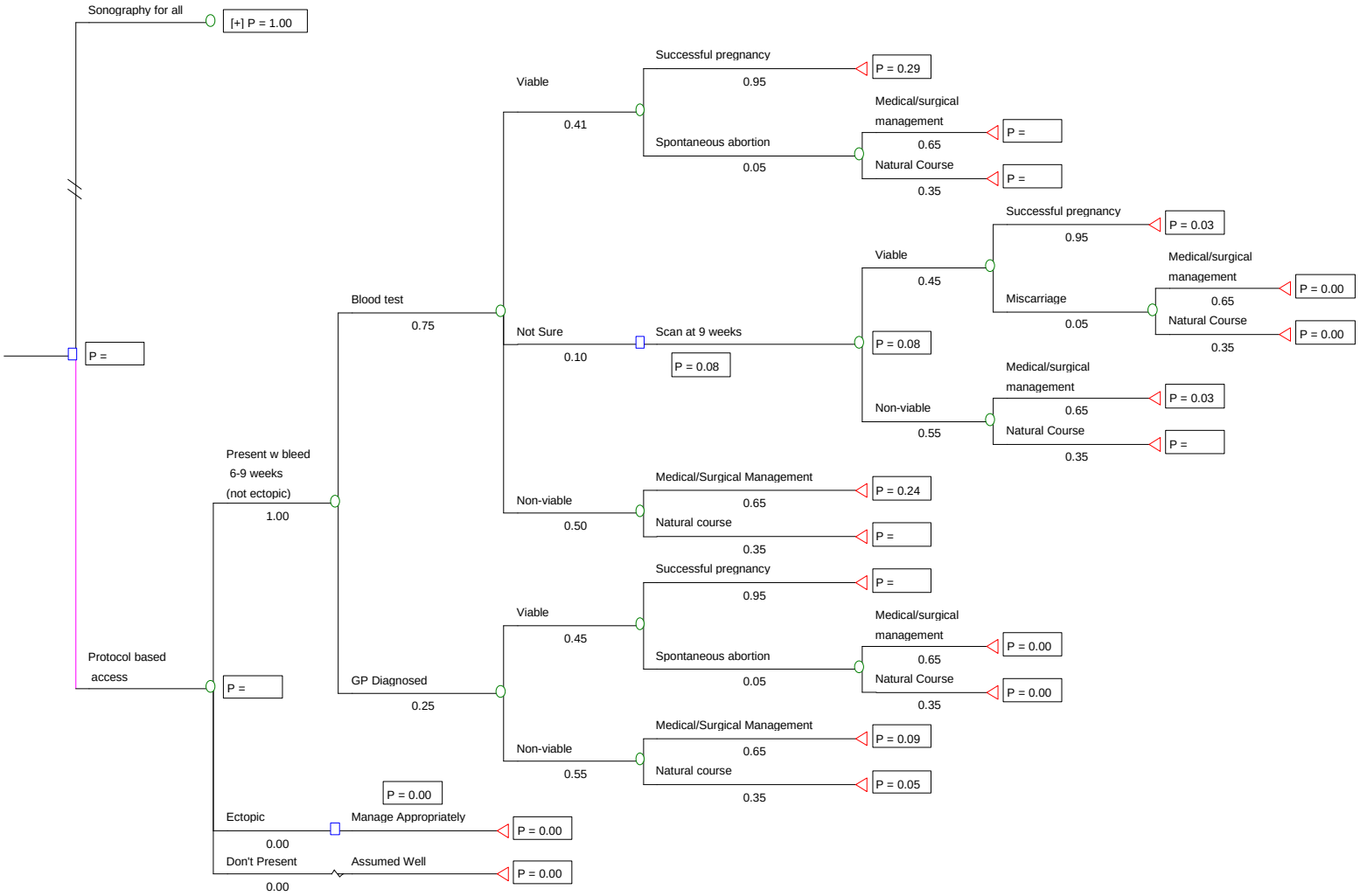


Figure 1b A Protocol-based Access Policy Decision Tree Model



Model 1:- Sonography For All

The top sub-branch of the tree (figure 1a) represents the 'sonography for all' policy. Even with a policy of guaranteed access to ultrasound, Everett and Gilling-Smith indicate that 27% and 17% of referrals with bleeding in the first 20 weeks of pregnancy can be diagnosed clinically without the need for ultrasound.[1,12] On the basis of these results, and given that an audit at Chesterfield and North Derbyshire Royal Hospital (CNDRH) has indicated that between 63% and 73% of women presenting with early bleeding are given ultrasound, it has been assumed that 75% of all women presenting with bleeding between six and nine weeks are given an ultrasound scan. As such, the model assumes that 25% of presentations can be managed by GPs, without recourse to scanning.

The model then assumes that the first ultrasound scan indicates either viable pregnancies, non-viable pregnancy, or gives an unclear result in given proportions. Results from an audit carried out in Chesterfield,[11] indicate that an estimated $^1/_3$ of all ultrasound scans under nine weeks' gestation give an unclear result and, therefore, require re-scanning. Another paper[17] described a re-scan figure of only 3%, although this was for gestation of up to 20 weeks and all the re-scans were for pregnancies of less than eight weeks. The model assumes that $^1/_3$ of scans between six and nine weeks' gestation do not give a clear positive or negative result.

Everett's work[17] indicates that the ratio of positive to negative scans is more or less 50:50. To reconcile these results to producing a result of 40-45% of early bleeds leading to a successful pregnancy,[1] our model assumes that 45% of all clear scans give a positive result (indication of a viable pregnancy) and 55% are negative (indication of a non-viable pregnancy).

For scans indicating a viable pregnancy, there is then assumed to be a chance event that the pregnancy goes on to full term or ends in spontaneous abortion. Everett[17] has shown that 95% of positive scans go on to full term. This assumption is used throughout the model.

Using evidence from Everett,[1] 43% of all women presenting with early bleeding were admitted to hospital. 86% of these admissions miscarried and required evacuation. That is, 37% of early bleeds required an evacuation in hospital. 42 of the 66 (64%) miscarriages for which hospitalisation information is known from Everett's study required ERPC. The model assumes, therefore, that 65% of all non-viable pregnancies require a hospital intervention

for evacuation. The other 35% are assumed to resolve naturally. These two assumptions are used throughout the model.

For the 33% of initial scans assumed to give an indeterminate result, the model allows for a maximum of two re-scans, so that the second re-scan is forced to indicate a viable or non-viable result. The sub-tree representing the first re-scan is a clone of the sub-tree representing the initial scan. The second re-scan sub-tree is similar to those of the first two scans, but without the branch representing the option of an unclear scan result.

In the sonography for all option, it is assumed that 25% of presenters can be diagnosed by GPs without recourse to any tests. In line with the assumptions described above, 45% of these 25% are assumed to be sent home with a viable pregnancy. The other 55% are assumed to be non-viable. Of the latter, 65% are assumed to require hospital intervention and 35% to resolve naturally. Of the 45% assumed viable, 95% are assumed to go to full term, and 5% to abort spontaneously. The latter group is then again subject to the 65:35, hospital to natural resolution probability assumptions.

In summary, the assumptions used in the modelling of the sonography for all policy imply that 57% of all women presenting with bleeding between six and nine weeks' gestation will have a spontaneous abortion. The other 43% continue to full term. Of the 57% who miscarry, 65% require a hospital intervention to complete the abortion. The latter implies that 37% of all women presenting with bleeding between six and nine weeks' gestation will require a hospital admission for an evacuation or medical intervention. 75% of women presenting are assumed to require sonography. One third of this 75% are assumed to need at least 1 re-scan and one ninth of the 75% are assumed to need two re-scans.

Model 2:- Protocol-based Access

The bottom half of the decision tree (figure 1b) represents a protocol-based policy model for access to sonography for women between six and nine weeks' gestation. The model assumes that all women presenting with bleeding between six and nine weeks' gestation (not suspected ectopics) are given a blood test (e.g. progesterone or serial HCG) to assess viability. Based upon the indicated sensitivity and specificity of HCG tests, it is assumed that 90% of women presenting can be given a clear positive or negative indication of viability from the blood test. The assumed ratio of viable to non-viable indications is 45:55 as explained above. These respective sub-trees then branch out as described under model 1 with the following exceptions. The 10% of cases which cannot be diagnosed from the blood

test are assumed to be asked to 'watch and wait' until week nine, at which point they are given an ultrasound scan. Because the scan is taking place beyond the nine weeks' gestation period, it is assumed that the scan gives a definite positive or negative result. As such, this scanning sub-tree then takes on the same shape and properties as the second re-scan sub-tree from the sonography for all policy branch of the decision tree. The proportions of the population who go to full term, miscarry, and require hospital interventions are the same as assumed in the sonography for all policy arm of the decision tree.

Model 3:- No Ultrasound

The 'no ultrasound' model can be represented in the protocol-based tree by assuming that the probability of an unclear blood test result is zero. That is, any woman with an unclear blood test result is asked to watch and wait indefinitely until the GP is able to give a diagnosis of viable or non-viable pregnancy. Therefore, all women follow the viable and non-viable branches in the given ratios.

Input Cost Assumptions

Central case estimates for costing have been made. The costs for an ultrasound scan using prices quoted by local Trusts range from around £20 to £36. The model uses a central case estimate of £30 per scan. A paper comparing the costs of treating miscarriage using surgical and medical management[68] implies that the costs of medical management of patients is about £50 less expensive than surgical management (£347 and £397 respectively). A central assumption estimate of £375 is used in the model. An assumed cost estimate of £10 is made for the cost of a GP consultation.[69] The cost of a blood test (e.g. progesterone or HCG) is quoted as £5.25 by a local Trust and, as such, the cost of a blood test has been assumed to be £5.

3.3 Results

Using these cost assumptions, the greatest cost under the sonography for all policy is estimated at £465 for a woman requiring three scans and who eventually miscarries and requires a hospital intervention to complete the abortion. The greatest cost under the protocol-based access is £420 for women who have an unclear blood test and, therefore, are given a scan at nine week's gestation, and who then go on to miscarry and require hospital treatment.

The lowest cost paths under both policies are for those women whose pregnancies are diagnosed as viable by their GPs and go on to full term, or those diagnosed as non-viable by their GP and who abort naturally. The cost assigned to such patients is £10 for the GP consultation.

The central scenario assumptions described above produce an expected (average) cost per woman presenting with early pregnancy bleeds of £182 for the sonography for all policy and £156 for the protocol-based access policy. The expected cost per early bleed for the no sonography policy is estimated at £153 per patient.

This guidance note has indicated that the number of early bleeds for a district of 500,000 population is 1,600 per annum. Based on miscarriage data presented by Everett,[1] it is assumed that 40% of all bleeds occur in weeks six, seven and eight. Therefore, the estimated number of women presenting with bleeding between six and nine weeks is 640 per annum. The total costs as modelled for a district are, therefore, £116,512 for the sonography for all policy, £99,552 for the protocol-based access policy, and £98,112 for the no sonography policy. The estimated marginal savings of the protocol-based access model compared with the sonography for all model is, therefore, estimated at £16,960. Having no sonography at all saves only an estimated additional £1,440 per annum.

3.4 Sensitivity Analysis

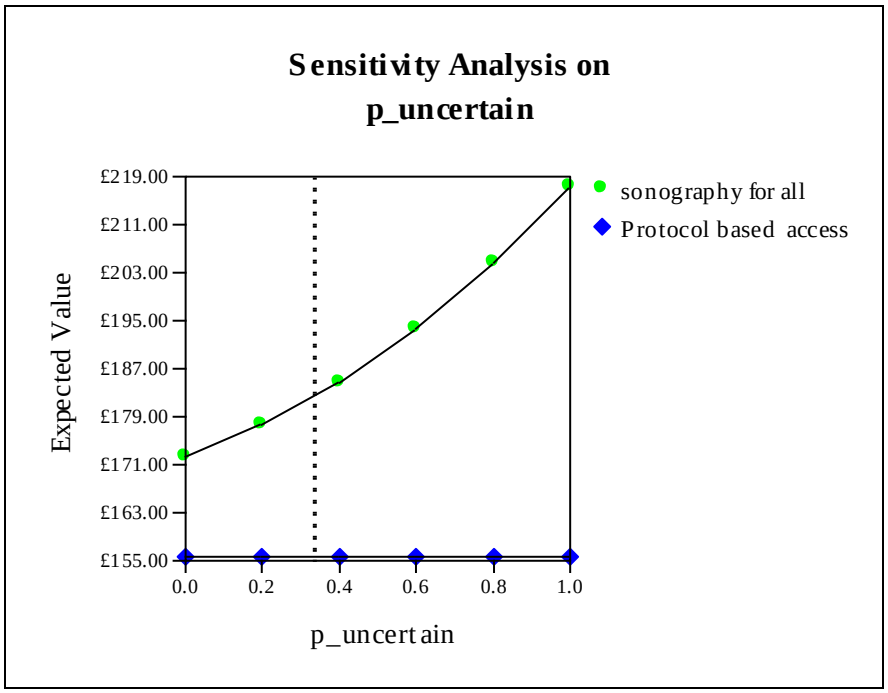
i) Proportions and probabilities

The above model contains many assumptions, some of which are based on the results of research which was not designed to provide the information required for this guidance note. None of the papers quoted analysed specifically the six to nine weeks' gestation period. As such, it is important to assess the sensitivity of the relative costs of each policy model to changes in input assumptions.

Many of the assumptions are common to the sub-trees representing the two main policies of interest (sonography for all and a protocol-based access). Changes in these assumptions will not affect the £26 per patient difference shown in the central case assumptions for the two policies. Only the magnitude of the relative costs per patient will change. The latter is true for the probability of hospitalisation, and the probability of a test or scan proving to be positive or negative. It is also true for the assumed costs of hospitalisation and GP consultations.

The probability of a scan providing an unclear result is assumed to be 0.33. Figure 2 below illustrates how the expected costs of the sonography for all policy change as the probability of an unclear result is changed.

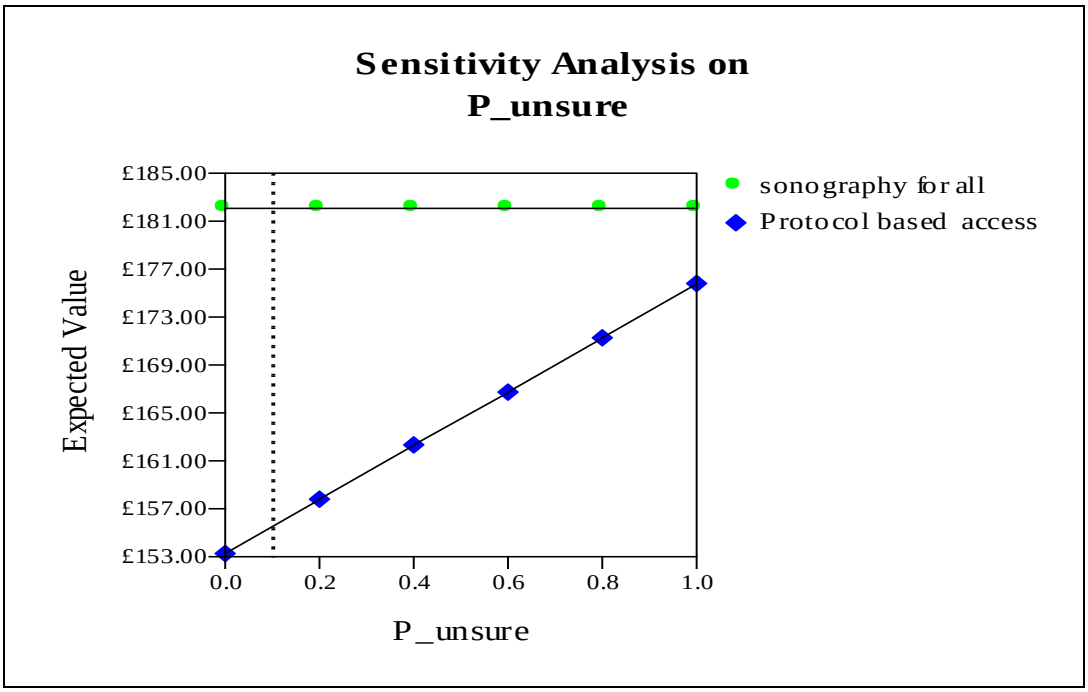
Figure 2 Sensitivity Analysis of a Scan Providing an Unclear Result (p_uncertain)



Technically, expected cost is relatively insensitive to a change in the probability of an uncertain scan in that a change of y per cent in the probability of an uncertain scan result leads to a less than y per cent change in expected cost. Raising the probability to an extreme value of 1 increases the expected cost of a sonography for all policy to £217 per patient. Reducing the probability of an uncertain outcome to zero only reduces the expected cost to £172 per patient, £16 per patient more than the protocol-based access policy.

Figure 3 illustrates the results of changing the assumed probability of an unclear blood test result.

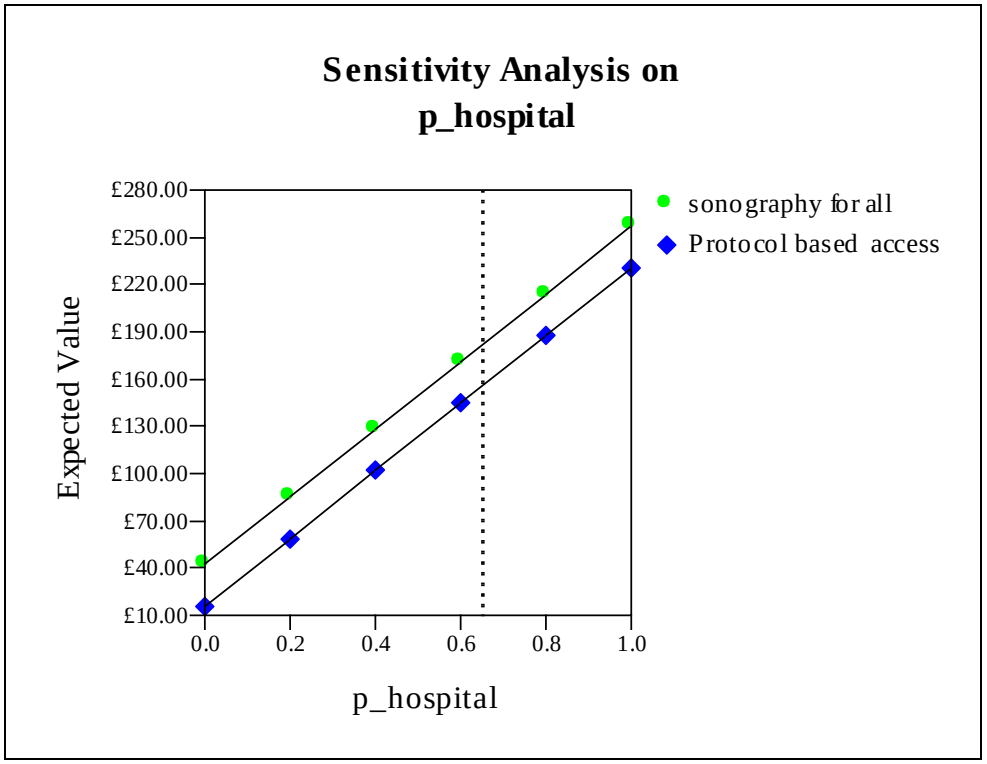
Figure 3 Sensitivity Analysis of an Unclear Blood Test (p_unsure)



Again, the changes in the expected cost of the protocol-based access policy are relatively insensitive to changes in the probability of an unclear blood test result. Even assuming all blood tests are unclear only increases the cost per patient to £176.

Figure 4 shows the sensitivity of costs to changes in the proportion of non-viable pregnancy patients who are given a hospital intervention. Because the model assumes that the same proportion of patients are hospitalised, the lines representing the two policies are parallel. As such, the difference in expected costs between the two policies would remain as in the central case. The range of costs per patient are greater than those seen in figures 2 and 3 indicating the greater sensitivity of costs to the hospitalisation assumption.

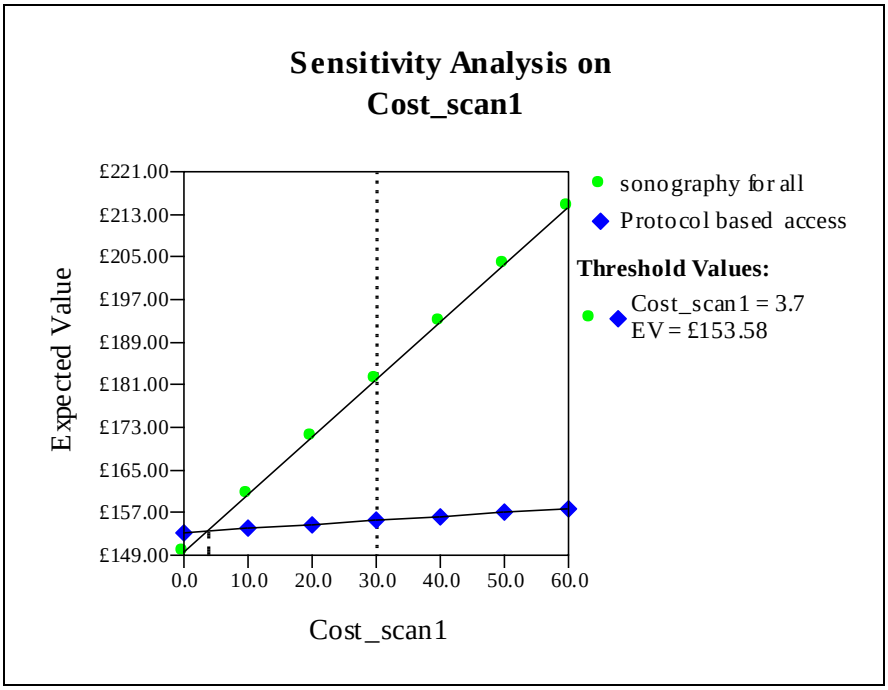
Figure 4 **Sensitivity Analysis of Changes in the Proportion of Non-Viable Pregnancy Patients who are Given a Hospital Intervention (p_hospital)**



ii) **Costs**

Figure 5 illustrates the cost of changing the assumed cost of a scan around the central case of £30.

Figure 5 **Sensitivity Analysis of the Costs of a Scan (cost_scan1)**

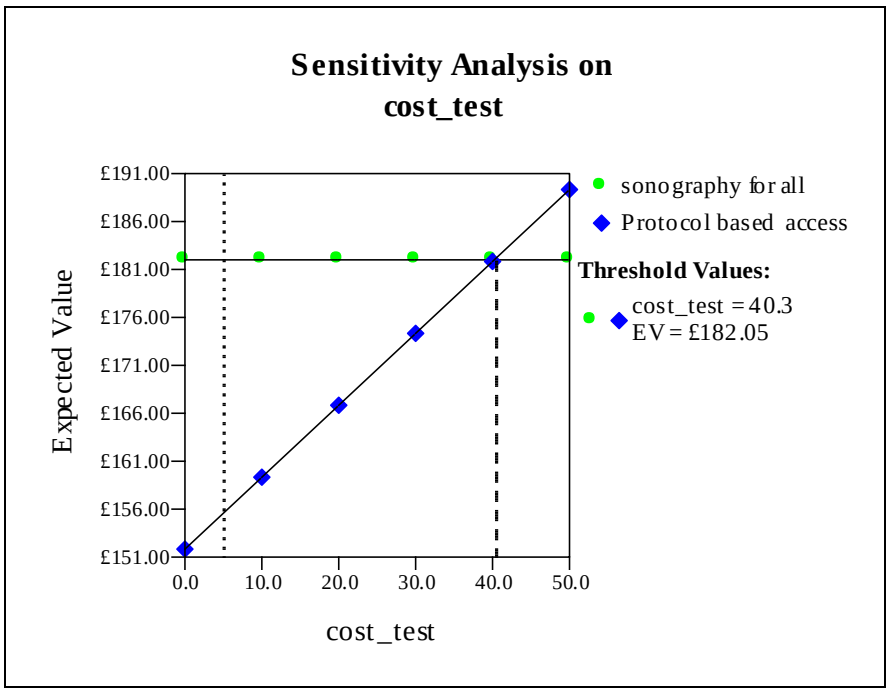


Clearly, the cost of the sonography for all policy is more sensitive to changes in the cost of scanning than is the protocol-based access policy. The difference in the expected costs increases with the costs of the scan. The threshold value of the scanning cost (the cost at which both policies produce the same expected costs) is £3.70.

Figure 6 illustrates the effects on the expected costs per patient of changing the assumed cost of a blood test around the central case of £5. Obviously, the costs of the sonography for all policy are totally insensitive to the blood test cost. The expected costs of the protocol-based policy are relatively insensitive, so that the threshold value of the blood test cost is as high as £40, the equivalent of eight serial blood tests per patient.

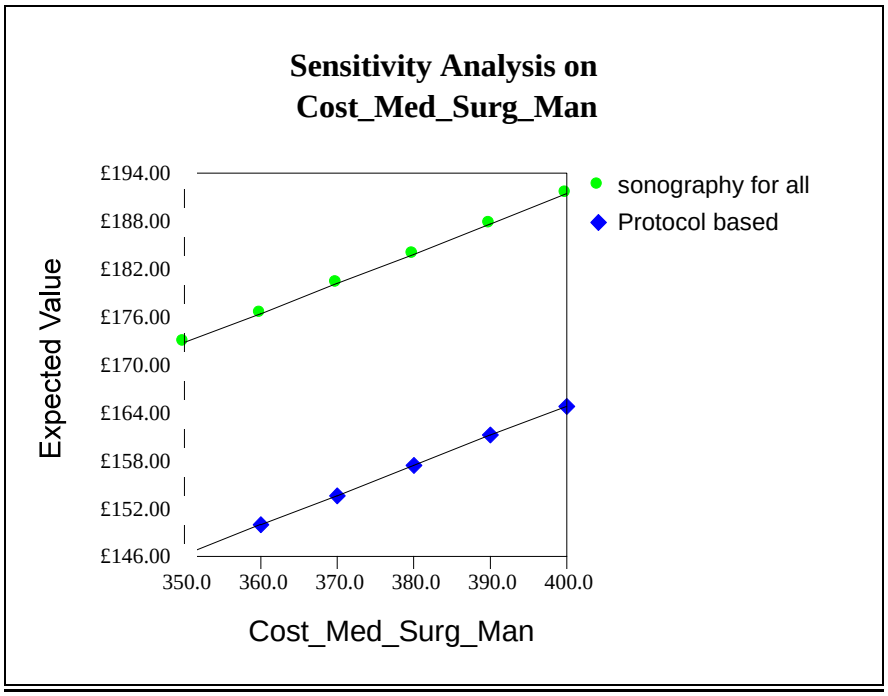
To allow for the possible need for serial testing, the cost of the blood tests can be doubled to allow for two tests. Doing so, only increases the expected costs of options 2 and 3 to £159 and £157 from £156 and £153 respectively.

Figure 6 Sensitivity Analysis of the Cost of a Blood Test (cost_test)



The sensitivity of the modelled policy costs to changes in the hospitalisation costs are shown in Figure 7.

Figure 7 Sensitivity Analysis of Costs of Hospitalisation (cost_med_surg_man)



Compared to the analyses of the cost variables presented above, the expected costs of both policies are relatively sensitive to changes in the cost of the in-patient interventions.

iii) **Ectopic Pregnancies**

There is a concern amongst many clinicians that any policy which reduces the use of scanning could have implications for the detection and management of ectopic pregnancies. There is also a concern that a change in policy might lead to an increase in undetected ectopics and, thus, an increased risk of rupture and haemorrhage together with an increase in the associated mortality risk. The following table presents some estimates of the potential costs per life year gained of having an ultrasound for all policy based on the results of the cost modelling presented in this guidance note. The marginal cost of the ultrasound for all policy compared to the protocol-based access policy is £17,000 per annum. The costs per life year saved have been calculated assuming the scanning for all policy would be associated with an improved early detection of ectopics and, thus, could prevent one maternal death in every 1, 10, or 50 years. The life years saved have been calculated with and without discounting a rate of 6%.

Table 2 Maternal Deaths from Ruptured Ectopic Pregnancies: A 'What If' Analysis of Estimated Cost per Life Year Gained.

Incremental Maternal Deaths	Discount Rate For Life Years	
	0%	6%
1 every year	£340	£1,018
1 every 10 years	£2,653	£7,938
1 every 50 years	£5,681	£17,000

Even under the most conservative scenario, the implied cost per life year saved is only £17,000, which is well within the range of acceptability compared with other commissioned treatments. On the other hand, there is no firm evidence to suggest that the protocol-based access policy for the six to nine weeks' gestation group would create any ectopic maternal deaths.

3.5 Discussion

No published economic assessment of ultrasound viability scanning has been found in the literature. Bigrigg has demonstrated potential resource savings amounting to between £95,000 and £120,000 from the introduction of an EPAU including ultrasound for a population of 310,000.[20] These potential savings were due to reduced hospital admission rates which accompanied the setting up of the EPAU. Pro rata, these potential savings amount to £150,000 - £190,000 for a population of 500,000. 'The Cost-Effectiveness of Routine Ultrasound Scanning in the First Trimester of Pregnancy' is the title of a paper by Temmerman and Buekens[70] although, again, there is no obvious measure of effectiveness. Estimated marginal cost savings of US$22,000 per annum for 1,000 patients are indicated for routine first trimester ultrasound compared with a more selective based policy.

Modelling in this guidance note has been concerned primarily with estimating costs for three possible policy options for managing women presenting with bleeding in weeks six to nine of pregnancy. The models developed have been kept deliberately simple in order not to over-work the limited information available. Even so, the model contains 79 decision or chance nodes. Analysis of central scenarios has indicated that the cost savings from changing from a sonography for all to a protocol-based, or a no sonography policy are relatively small (£17,000 out of £116,500) for a population of 500,000.

Good modelling is dependent upon reliable data inputs. Because of the lack of papers dealing specifically with the gestation period in which we are interested in this guidance note, most of the information used to estimate probabilities and proportions in the models should be treated with some caution. Most of the costs used are crude average costs obtained from local NHS Trusts. Ideally, the costs used should be marginal opportunity costs, which will vary by location depending on factors such as the current level of investment in ultrasound equipment, and the changes in demand for ultrasound which different policies will generate.

The results of the sensitivity analyses indicate that the hospitalisation variables are relatively influential. The model has assumed that the probability of hospitalisation is the same under all policies. Consequently, the differential costs between the policies do not change by changing the hospitalisation probabilities or the costing assumptions. Given that there is evidence that the use of ultrasound increases the likelihood of a hospital intervention to complete an abortion, then our assumption of equivalent hospitalisation across policies is invalid and there are implications, therefore, for the size of the relative costs. The model has not included the effects of hospitalisation for bed rest.

This guidance note has not attempted to model the potential benefits of the alternative policies on offer. There is no obvious measure of benefit in this context except for the value of information. Again, we have found no published papers attempting to value ultrasound viability scanning. Research by Berwick[71] in 1985 implied that women were willing to pay an average of US$709 for the information they obtained from ultrasound in a normal pregnancy. Most of this information had no clinical or decision-making consequences and highlights the non-medical value of scanning for these women. Potential disbenefits of scanning include reduced safety for the fetus. There is no research evidence looking at the long-term safety aspect of ultrasound for fetuses during the first nine weeks of pregnancy and, because of the length of follow-up required, there is unlikely to be any in the near future, if at all.

The model assumed initially that the management of ectopic pregnancies would not be influenced by the choice of policies presented in this guidance note. A ‘what if’ sensitivity analysis has indicated that the additional cost of the scanning for all policy was likely to produce acceptable cost per life year saved figures. Because this guidance note is not primarily concerned with the cost-effectiveness of scanning in the management of ectopic pregnancies, it has not included an analysis of any potential savings resulting from early

detection of ectopics using ultrasound. The latter is clearly beneficial if early detection leads to medical management at home rather than a surgical procedure and an in-patient stay, (which could cost in the region of £1,000 per patient). Also, early detection of ectopics using ultrasound may mean salpingostomy rather than salpingectomy and all its implications for saving tubes and, thereby, increasing the possibilities for natural rather than assisted conception.

Given the relatively small differences in the modelled costs between the scanning policies examined, the choice between them almost certainly revolves around differences in their potential benefits. Such an assessment should include any implications for the management of ectopics, about which there is little evidence and some disagreement in the consensus view.

4. OPTIONS FOR PURCHASERS AND PROVIDERS

There is clearly a place for the discretionary use of ultrasound in secondary care practice for specific groups of patients such as women using assisted conception treatments, those with recurrent miscarriage, or those with a history of ectopic pregnancy.

However, this guidance note has demonstrated the lack of published evidence to support the routine use of ultrasound in assessing fetal viability, despite which the service is becoming widespread and is accepted as good practice.

We have identified three possible options for future provision of such a service:-

Option 1 To provide access to ultrasound viability scanning for all patients who experience bleeding in early pregnancy (at any gestation).

Option 2 To provide limited access for patients where management and outcomes would be influenced by the result of the test.

Option 3 To disinvest from such services.

These are considered in more detail below.

Option 1 *To provide access to ultrasound viability scanning for all women who experience bleeding in early pregnancy at any gestation.*

Advantages:

- This option would ensure that a majority of women with ectopic pregnancy are identified.

- Possibly, the emotional impact of bleeding in early pregnancy may be reduced by early confirmation of viability or non-viability, although there is no firm evidence to support this. Local experience in North Derbyshire suggests that such support could be provided by trained EPAU nursing staff, whereas the Dutch evidence suggests that this can be provided in the primary care setting.

Disadvantages:

- There is no evidence that the use of ultrasound in all women presenting with early pregnancy bleeding assists the management of patients with miscarriage, although it may be of use in women with ectopic pregnancy.

- A significant proportion of women will require repeat tests which could increase the emotional impact on them.

- A significant, albeit small, proportion of such women will be falsely reassured of the viability of their pregnancy.

- The finding of non-viability is likely to increase the numbers of women undergoing potentially unnecessary interventions such as ERPC, which will increase the levels of morbidity, such as, infection and which may have longer-term sequelae such as infertility. (It is possible that infection could be addressed by providing antibiotic cover and by chlamydia screening).

- There may be a risk that referral for such testing may discourage appropriate counselling and support for women and unnecessarily 'medicalise' what is a natural process.

- The safety of using the test at gestations under 10 weeks, if the pregnancy continues, has not been confirmed.

- Cost-effectiveness is not known with certainty.

Option 2 *To provide limited access to ultrasound scanning for patients where management and outcome could be influenced by the result of the test.*

Advantages:

- This approach should encourage the most (cost)-effective and efficient use of this resource by using the evidence base available.

- Limited access could be achieved by the application of the following criteria:
  - ◊ There should be appropriate prior and follow-up counselling.
  - ◊ Gestation should ideally be *at least* 7 weeks.

- ◊ Prior use of urinary beta HCG can confirm pregnancy and, thus, avoid the costs of scanning women who are not pregnant.
- ◊ Scanning is not appropriate where the only sign is minor painless bleeding.
- ◊ If intrauterine pregnancy is confirmed, even if viability is still questioned, there is no reason to repeat the test as results will not change the management of the patient, unless further fresh bleeding and pain occurs.
- ◊ Referral for specialist assessment when ectopic pregnancy is a strong possibility.

Disadvantages:

- There is no evidence that this test assists the management of patients with early pregnancy bleeding, although it may be a useful test for patients with ectopic pregnancy.

- Although this may not be the best use of the resource, pragmatically, a total disinvestment from the service may be impossible.

Option 3 *Disinvest from viability scanning services*

Advantages:

- There is an opportunity cost of such services and the money could be better spent in other areas.

- The emotional impact of false reassurance about pregnancy viability would be avoided.

- Ultrasound could still be available to specialists within hospitals, if there is suspicion of ectopic pregnancy.

- Safety concerns would be avoided.

Disadvantages:

- With public awareness of the availability of this service, there may be strong public pressure to maintain it.

- There would need to be sensitive and appropriate information available - a possible model is the Prostate Specific Antigen (PSA) leaflet produced by the National Centre for Reviews and Dissemination at York University.

- Although there may be major concerns about missing a diagnosis of ectopic pregnancy, there is no published evidence which suggests this would be a serious problem.

- Women may self refer to A&E with a consequent increase in emergency gynaecological admissions.

- GPs may be more likely to admit women as emergencies.

Note:- Re-education of primary care staff and the general public will be required regarding the management of early pregnancy bleeding at home. This must address the need for assessing maternal blood group and administering anti-D where appropriate.

5. DISCUSSION AND CONCLUSIONS

This paper has explored the evidence for the effectiveness and cost-effectiveness of ultrasound for the investigation of women with bleeding in early spontaneous pregnancy. It is not concerned with certain groups which include anyone using assisted conception techniques or those with recurrent abortion problems, previous terminations or ectopic pregnancy and those with PID. The paper accepts, a priori, the value of transvaginal ultrasound for the detection and management of ectopic pregnancies. There is, however, some concern that there may be over-use of scanning in early pregnancy which has no implications for the management of the patient in terms of maintaining the pregnancy, and may mean the exposure of the fetus to unnecessary risks from radiation. Clinical practice guidelines for Alberta, Canada, published after the drafting of this guidance note concluded that

> '..... *at this time no recommendation can be made to support or refute the use of serial ultrasound in the management of threatened spontaneous abortion.'* [72]

Bleeding in early pregnancy is a common problem. It is estimated that in a 'typical' district of 500,000 population, some 1,600 women will experience bleeding in early pregnancy. Between 63% and 73% of these will have ultrasound to determine fetal viability and around a third of these will require rescans for a definite diagnosis. It has been argued that miscarriage is a natural process and that three quarters of cases resolve naturally. The Dutch have developed guidelines which clearly favour the use of a primary care led service, which discourages the use of medical and surgical interventions where these are thought not to be necessary. The introduction of such a system in the UK would mean a re-education of patients and primary and secondary care staff.

Evidence suggests that there should be a lower limit on gestational age for the use of ultrasound because of the high proportion of unclear results necessitating rescanning at a later date. This is a waste of resources. On the other hand, early detection of ectopics may allow an increased use of medical (e.g. Methotrexate) rather than surgical in-patient management and, thus, may lead to savings from reduced in-patient admissions. However, there is no good evidence that the use of ultrasound for all women presenting with bleeding is an effective screening test for ectopic pregnancy.

It has been argued that there may be more scope for the use of biochemical markers such as progesterone and HCG.

There are no studies which have examined the views of women on viability scanning although the demand for the service suggests that it is acceptable.

No published papers looking at the economics of ultrasound for viability scanning have been found. As a result, this paper presented a simple cost modelling approach for three theoretical policy options. A decision tree approach was taken which made explicit the assumptions used in the modelling process. The results implied only a £17,000 per annum difference for a 'typical' district between a 'scanning for all' policy costing £116,500 and a 'protocol-based access' policy. A 'no scanning' policy was estimated to save only a further £1,000.

The quantity and quality of the evidence used to populate the model was not good. Consequently, it has been made clear that in no way are the models presented meant to represent suggested clinical models of care, and the assumptions used should be treated with some caution. A fairly rigorous sensitivity analysis indicated that the policy costs as modelled were technically insensitive to changes in the values of key input assumptions. The cost associated with, and the propensity to, hospitalise patients for in-patient interventions, were the most sensitive variables.

Although the cost modelling was not explicitly concerned with ectopic pregnancies, a 'what if' sensitivity analysis was presented which produced cost per life year gained estimates. Having said this, there is no evidence that such a policy would reduce maternal deaths.

The economic analysis has not considered any other potential benefits of screening and no published evidence about the benefits of ultrasound in viability scanning was found. Results of research were presented which indicated that women were willing to pay amounts well above the costs of routine ultrasound scanning for the perceived benefits of the information offered, even though such information has no clinical consequences.

Uncertainty about the value of the benefits of scanning for the modelled group is unfortunate given that the cost differences have been demonstrated to be relatively small. Given the small cost differences, the relative benefits will be particularly important to the assessment of the cost-effectiveness of the various viability scanning policy options.

Section 4 offers three broad policy options for purchasers ranging from a policy of ultrasound for all, at any gestation, to disinvesting in viability scanning. The latter is almost certainly unworkable and there is a lack of evidence to support the former. Almost certainly the favoured option is the second policy which is a protocol-based access policy designed to provide ultrasound for those women where the results of the tests are most likely to influence management and outcome. The policy suggests an absolute minimum gestational age of seven weeks and outlines situations where ultrasound would be deemed not appropriate. It has been suggested that, as most ectopic pregnancies rupture at about 8 to 10 weeks, a viability scanning policy from 7 weeks would identify most of these ectopic pregnancies but, again, there is no published evidence to support the view that using routine ultrasound as a screening policy for ectopics is clinically effective or a cost-effective option.

The consequences for the detection and management of ectopic pregnancy is a key issue within the profession. Also, the information made available to women and the choices offered to them would appear to be an issue which needs addressing, whichever policy option is adopted. The details of any protocol-based policy need to be agreed locally.

REFERENCES

1. Everett C. Incidence and outcome of bleeding before the 20th week of pregnancy: prospective study from general practice. *BMJ* 1997; 315: 32-4.

2. Simpson JL, Mills JL, Holmes LB, et al. Low fetal loss rates after ultrasound proved viability in early pregnancy. *JAMA* 1987; 258: 2555-7.

3. Whittaker PG, Taylor A, Lind T. Unsuspected pregnancy loss in healthy women. *Lancet* 1983; i: 1126-7.

4. Chard T. Frequency of implantation and early pregnancy loss in natural cycles. *Balliere's Clin Obstet Gynecol* 1991; 5: 179-89.

5. Miller JF, Williamson E, Glue J, et al. Fetal loss after implantation. *Lancet* 1980; ii: 554-6.

6. Dept of Health. Why mothers die: report on confidential enquiries into maternal deaths in the United Kingdom 1994-1996. London: Stationary Office, 1998.

7. Norman SG. An audit of the management of ectopic pregnancy. *Br J Obstet Gynaecol* 1991; 98: 1267-72.

8. Chow WH, Daling JR, Cates W et al. Epidemiology of ectopic pregnancy. *Epidemiol Rev* 1987; 9: 70-94.

9. Stabile I, Grudzinskas JG. Ectopic pregnancy: a review of incidence, etiology and diagnostic aspects. *Obstet Gynecol* Survey 1990; 45: 335-47.

10. Hajenius PJ, Mol BWJ, Van der Veen F, et al. Treatment of ectopic pregnancy (protocol). *Cochrane library.*

11. Tromans P. Management of bleeding in early pregnancy - audit report 1995. Chesterfield and North Derbyshire Royal Hospital Audit Report 1995-6.

12. Gilling-Smith C, Zelin J, Touquet R, et al. Management of early pregnancy bleeding in the accident and emergency department. *Arch Emerg Med* 1988; 5: 133-8.

13. Dutch College of General Practitioners. Nederlands Huisartsen Genootschap (NHG). Standard (threatened) miscarriage. English version June 1993.

14. Flikweert S. Dutch College of General Practitioners. Personal communication, August 1997.

15. Oakley A, McPherson A, Roberts H. *Miscarriage*, London: Fontana 1984.

16. Everett C, Ashurst H, Chalmers I. Reported Management of Threatened Miscarriage by General Practicioners in Wessex. *BMJ* 1987; 295: 583-586.

17. Everett CB, Preece E. Women with bleeding in the first 20 weeks of pregnancy: Value of general practice ultrasound detecting fetal heart movement. *Br J Gen Prac* 1996; 46: 7-9.

18. Ed. Stevens A and Rafferty J. Health Care Needs Assessment - second series. Ch 8, Gynaecology p500. Radcliffe Medical Press, 1997.

19. Stabile I, Campbell S, Grudzinskas JG. Ultrasonic assessment of complications during first trimester of pregnancy. *Lancet* 1987; ii: 1237-40.

20. Bigrigg MA and Read MD. Management of women referred to early pregnancy assessment unit: care and cost-effectiveness. *BMJ* 1991; 302: 577-9.

21. Fleuren M, Grol R, de Haan M, et al. Adherence by midwives to the Dutch national guidelines on threatened miscarriage in general practice: a prospective study. *Quality in Health Care* 1997; 6: 69-74.

22. Bernard KG, Cooperberg PL. Sonographic differentiation between blighted ovum and early viable pregnancy. *Am J Roentgenol* 1985; 144: 597-602.

23. Jouppila P. Fetal movements diagnosed by ultrasound in early pregnancy. *Acta Obstet Gynaecol Scand* 1976; 55: 131-5.

24. Melis GB, Strigini F, Fruzzetti F, et al. Ultrasound and estradiol plasma levels in threatened abortion. *Acta Eur Fertil* 1984; 15: 287-94.

25. Tongsong T, Srisomboon J, Wanapirak C, et al. Pregnancy outcome of threatened abortion with demonstrable fetal cardiac activity: a cohort study. *J Obstet Gynecol* 1995; 21: 331-5.

26. O'Brien MC, Rutherford T. Misdiagnosis of bilateral ectopic pregnancies: a caveat about operator expertise in the use of transvaginal ultrasound. *J Emerg Med* 1993; 11: 275-8.

27. Pennell RG, Needleman L, Pajak T, et al. Prospective comparison of vaginal and abdominal sonography in normal early pregnancy. *J Ultrasound Med* 1991; 10: 63-7.

28. Iyer LJ, Bhattacharya M. Role of ultrasound in early pregnancy complications. *J Postgrad Med* 1992; 38: 115-6.

29. Neilson JP. Routine ultrasound in early pregnancy. In: Neilson JP, Crowther CA, Hodnett ED, Hofmeyr GJ, Keirse MJNC (eds). Pregnancy and childbirth module of the Cochrane database of systematic reviews. Available in The Cochrane Library (database on disk and CDROM). The Cochrane Collaboration: Issue 3, Oxford. Update Software 1997 updated quarterly.

30. Crowley P. Interventions to prevent, or improve outcome from, delivery at or beyond term. *Cochrane library.*

31. Goldstein SR, Subramanyam BR, Raghavendra BN, et al. Subchorionic bleeding in threatened abortion: sonographic findings and significance. *Am J Roentgenol* 1983; 141: 975-8.

32. Bennett GL, Bromley B, Lieberman E, et al. Subchorionic haemorrhage in first trimester pregnancies: prediciton of pregnancy outcome with sonography. *Radiology* 1996; 200: 803-6.

33. Recommendations from the 33rd RCOG Study Group: Problems in early pregnancy: Advances in diagnosis and management. Ed. Grudzinskas JG and O'Brien PMS. *RCOG* Press, 1997.

34. Falco P, Milano V, Pilu G, et al. Sonography of pregnancies with first trimester bleeding and a viable embryo: a study of prognostic indicators by logistic regression analysis. *Ultrasound Obstet Gynecol* 1996; 7: 165-9.

35. Nielson S, Hahlin M. Expectant management of first trimester spontaneous abortion. *Lancet* 1995; 345: 84-6.

36. Ewigman B, LeFevre M, Hessar J. A randomized trial of routine prenatal ultrasound. *Obstet Gynecol* 1990; 76: 189-194.

37. Rasmussen KL, Freund C. Vaginal blodning i forste trimester [Vaginal bleeding in the first trimester]. *Ugeskr-Laeger* 1993; 155: 2448-50.

38. Hamilton-Fairley D and Donaghy J. Surgical versus expectant management of first trimester miscarriage: a prospective observational study. In: Grudzinskas JG and O'Brien PMS, editors. Problems in Early Pregnancy: Advances in Diagnosis and Management. *RCOG* Press; 1997. Chapter 24.

39. Kaplan BC, Dart RG, Moskos M, et al. Ectopic pregnancy: prospective study with improved diagnostic accuracy. *Ann Emerg Med* 1996; 28: 10-7.

40. Schurz B, Wenzl R, Eppel W, et al. Early detection of ectopic pregnancy by transvaginal ultrasound. *Arch Gynecol Obstet* 1990; 248: 25-9.

41. Stiller RJ, Haynes de Regt R and Blair E. Transvaginal ultrasonography in patients at risk for ectopic pregnancy. *Am J Obstet Gynecol* 1989; 161: 930-3.

42. Jauniaux ERM & Jurkovic D. The role of ultrasound in abnormal early pregnancy. In: Grudzinskas JG and O'Brien PMS, editors. Problems in early pregnancy: Advances in diagnosis and management. *RCOG* Press, Chapter 11; 1997.

43. Durham B, Lane B, Burbridge L, et al. Pelvic ultrasound performed by emergency physicians for the detection of ectopic pregnancy in complicated first trimester pregnancies. *Ann Emerg Med* 1997; 29: 338-47.

44. Bonilla-Musoles F, Pardo G, Sampaio M, et al. Vaginal endosonography in extrauterine pregnancy. Ultraschall Med 1989; 10: 215-21.

45. Chew S, Anandakmar C, Vanaja K, et al. The role of transvaginal ultrasonography and colour Doppler imaging in the detection of ectopic pregnancy. J Obstet Gynecol Res 1996; 22: 455-60.

46. Sadek AL, Schiotz HA. Transvaginal sonography in the management of ectopic pregnancy. *Acta Obstet Gynaecol Scand* 1995; 74: 293-6.

47. Jouppila P, Seppala M and Chard T. Pregnancy specific beta-glycoprotein in complications of early pregnancy. *Lancet* 1980; 1: 667-8.

48. Robinson HP, de Crespigny LJ, Harvey J, et al. Ectopic pregnancy - potentials for

diagnosis using ultrasound and urine and serum pregnancy tests. *Aust N Z J Obstet Gynecol* 1985; 25: 49-53.

49. Bateman BG, Nunley WC, Kolp LA, et al. Vaginal sonography findings and hCG dynamics of early intrauterine and tubal pregnancies. *Obstet Gynecol* 1990; 75: 421-7.

50. Nyberg DA, Mack LA, Laing FC et al. Early pregnancy complications: endovaginal sonographic findings correlated with human chorionic gonadotrophin levels. *Radiology* 1988; 167: 619-22.

51. Kim DS, Chung SR, Park MI et al. Comparative review of diagnostic accuracy in tubal pregnancy: a 14-year survey of 1040 cases. *Obstet Gynecol* 1987; 70: 547-54.

52. Magos AL, Baumann R, Turnbull AC. Managing gynaecological emergencies with laparoscopy. *BMJ* 1989; 299: 371-4.

53. De Cherney AH, Diamond MP. Laparoscopic salpingostomy for ectopic pregnancy. *Obstet Gynaecol* 1987; 70: 948-50.

54. Grimes DA. Frontiers of operative laparoscopy: a review and critique of the evidence. *Am J Obstet Gynaecol* 1992; 166: 1062-71.

55. Ylostalo P, Cacciatore B, Koskimies A, et al. Conservative treatment of ectopic pregnancy. *Ann N Y Acad Sci* 1991; 626: 516-23.

56. Tzafettas J, Anapliotis S, Zournatzi V, et al. Transvaginal intra-amniotic injection of methotrexate in early ectopic pregnancy. Advantages over the laparoscopic approach. *Early Hum Dev* 1994; 39: 101-7.

57. al Sebai MA, Diver M and Hipkin LJ. The role of a single free beta-human chorionic gonadotrophin measurement in the diagnosis of early pregnancy failure and the prognosis of fetal viability. *Hum Reprod* 1996; 11: 881-8.

58. Masson GM, Anthony F, Wilson MS, et al. Comparison of serum and urine HCG levels with SP1 and PAPP-A levels in patients with first trimester vaginal bleeding. *Obstet Gynaecol* 1983; 61: 223-6.

59. Hertz JB. Diagnostic procedures in threatened abortion. *Obstet Gynaecol* 1984; 64: 223-9.

60. Guerriero S, Mais V, Ajossa S, et al. The screening of embryonic viability in early asymptomatic pregnancy by a single endosonographic scan associated with plasma HCG determination. *J Assis Repro and Genetics* 1994;11: 346-52.

61. Cunningham DS, Brodnik RM, Rayl DL, et al. Suboptimal progesterone production in pathologic pregnancies. J Reprod Med 1993; 38: 301-5.

62. al Sebai MA, Kingsland CR, Diver M, et al. The role of a single progesterone measurement in the diagnosis of early pregnancy failure and the prognosis of fetal viability. *Br J Obstet Gynecol* 1995; 102: 364-9.

63. Ocer F, Bese T, Saridogan E, et al. The prognostic significance of maternal serum

CA125 measurement in threatened abortion. *Eur J Obstet Gynecol Reprod Biol* 1992; 46: 137-42.

64. Shahani SK, Moniz CL, Bordekar AD, et al. Early pregnancy factor as a marker for assessing embryonic viability in threatened and missed abortions. *Gynecol Obstet Invest* 1994; 37: 73-6.

65. Ruge S, Pedersen JF, Sorensen S, et al. Can pregnancy-associated plasma protein A (PAPP-A) predict the outcome of pregnancy in women with threatened abortion and confirmed fetal viability? *Acta Obstet Gynecol Scand* 1990; 67: 589-95.

66. Neiger R, Wise C, Contag SA, et al. First trimester bleeding and pregnancy outcome in gravidas with normal and low folate levels. *Am J Perinatol* 1993; 10: 460-2.

67. Tromans P. Personal Communication.

68. Hughes J, Ryan M, Hinshaw K, et al. The Costs of Treating Miscarriage: A Comparison of Medical and Surgical Management. *Br J Obstet Gynecol* 1996; 103: 1217-1221.

69. Netten A, Dennett J. *Unit costs of health and social care.* 1997. PSSRU University of Kent.

70. Temmerman M, Buekens P. Cost-Effectiveness of routine ultrasound examination in first trimester of pregnancy. *Eur J Obstet Gynecol Reprod Biol* 1991; 39: 3-6.

71. Berwick DM, Weinstein MC. What do patients value? Willingness to pay for Ultrasound in normal pregnancy. *Med Care.* 1985; 23: 881-893.

72. Alberta Clinical Practice Guideline Working Group. *Guideline for the use of prenatal ultrasound first trimester*. URL:http://www.amda.ab.ca/general/cpg/catalogue/documents/first-trimester/first-trimester.html [25 January 1999]

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