GUIDELINES FOR

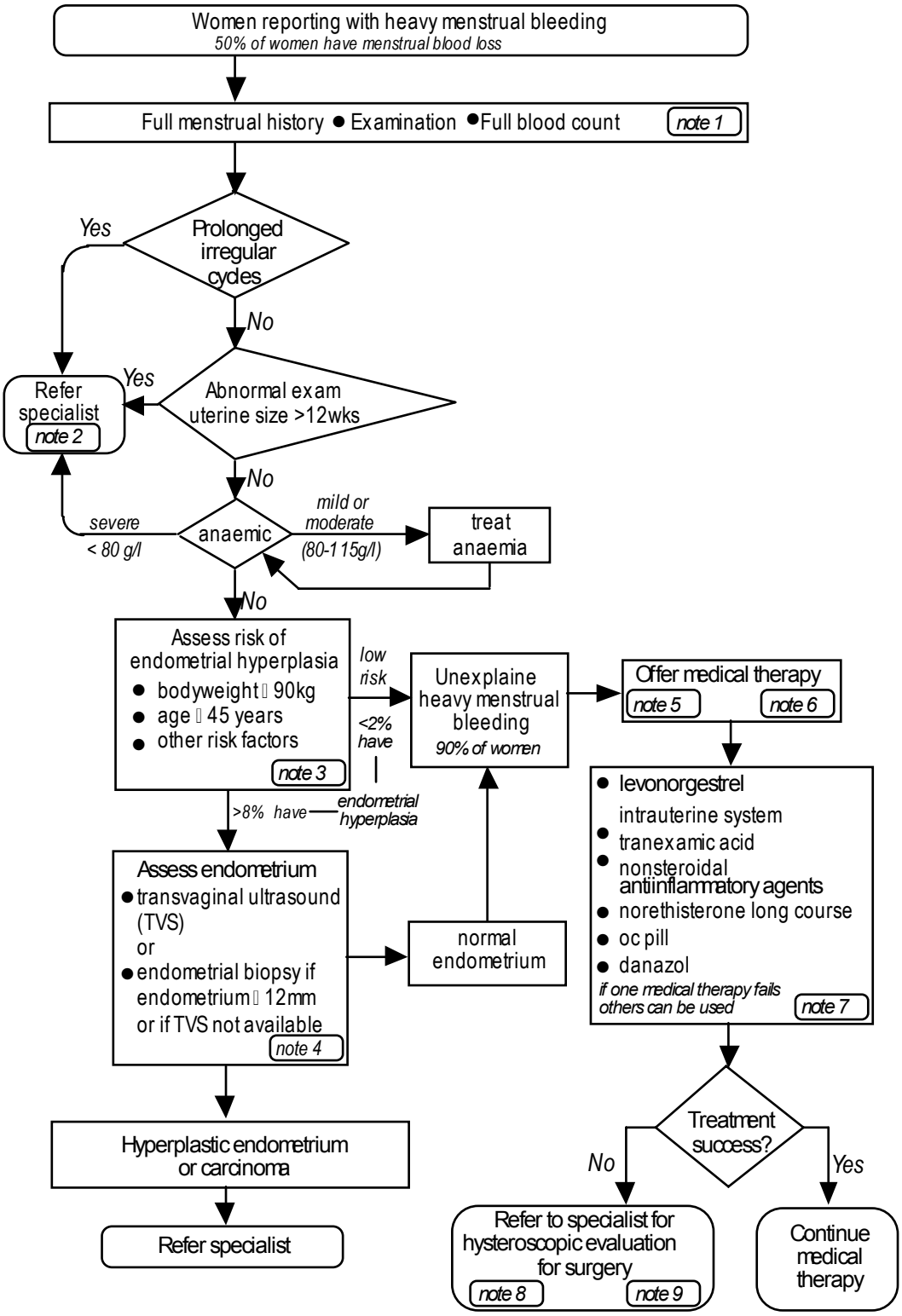
THE MANAGEMENT OF

HEAVY MENSTRUAL BLEEDING

Prepared by a Working Party on behalf of the

National Health Committee

MAY 1998


Women reporting with heavy menstrual bleeding
50% of women have menstrual blood loss
Full menstrual history ● Examination ● Full blood count
note 1
Yes
Prolonged irregular cycles
No
Refer specialist
note 2
Yes
Abnormal exam uterine size >12wks
No
severe
< 80 g/l
anaemic
mild or moderate
(80-115g/l)
treat anaemia
No
Assess risk of endometrial hyperplasia
● bodyweight 90kg
● age 45 years
● other risk factors
note 3
low risk
<2% have
Unexplaine heavy menstrual bleeding
90% of women
Offer medical therapy
note 5
note 6
>8% have
endometrial hyperplasia
Assess endometrium
● transvaginal ultrasound (TVS)
or
● endometrial biopsy if endometrium 12mm
or if TVS not available
note 4
normal endometrium
● levonorgestrel intrauterine system
● tranexamic acid
● nonsteroidal antiinflammatory agents
● norethisterone long course
● oc pill
● danazol
if one medical therapy fails others can be used
note 7
Hyperplastic endometrium or carcinoma
Refer specialist
Treatment success?
No
Yes
Refer to specialist for hysteroscopic evaluation for surgery
note 8
note 9
Continue medical therapy

note 1

- In women <20 years old pelvic examination is unlikely to contribute to management of heavy bleeding (C) and the likelihood of pathology is small (C)
- Increased likelihood (70%) of heavy menstrual blood loss >80mls/cycle if Hb <120g/l (A)
- Consider pictorial blood loss assessment charts (appendix 6.5) for women with normal Hb (A)

[Levels of Evidence *synopsis*]

note 2

- **The following women are recommended to see a specialist at the initial consultation because of increased likelihood of pathology*:**
  - **Women with erratic menstrual cycles (regardless of loss) (B)**
  - **Women with an abnormal pelvic examination (confirmed by transvaginal ultrasound if possible) (C)**
  - **Perimenopausal women with less frequent cycles but normal blood loss do not require referral (C)**
  - **Women with severe anemia (C)**

- **It is estimated that approximately 15% of all women with HMB will require specialist referral at the initial consultation**

  *** It is beyond the scope of this guidance to provide recommendations for management in these instances**

[Levels of Evidence *synopsis*]

note 3

Risk of Endometrial Hyperplasia or Carcinoma in women with heavy menstrual bleeding:

all women	4.9%
<45yo and <90kg	2.3%
≥90kg	13%
≥45 years	8%

Other risk factors for endometrial hyperplasia: **(B)**

- **Infertility + nulliparity**
- **exposure to unopposed endogenous or exogenous estrogen/tamoxifen**
- **family history of endometrial & colonic cancer**

(C)

Endometrial hyperplasia with atypia may progress (if untreated) to endometrial carcinoma in 20-75% of cases over a 13 year period **(B)**

It is estimated that 20% of women with regular HMB will require endometrial assessment because of increased risk factors

[Levels of Evidence *synopsis* **]**

note 4

Assessment of the endometrium:

- transvaginal ultrasound is recommended as first option for endometrial assessment but if not possible then an endometrial sample should be taken (A)
- if endometrial thickness on transvaginal ultrasound ≥12mm then an endometrial sample should be taken (A)
- consider specialist referral if abnormal transvaginal ultrasound suggestive of submucous fibroids (B)
- fifty percent of women ≥90kg, who have an endometrial thickness ≥12mm on TVS, have endometrial hyperplasia (A)
- less than 1% of women≥90kg, who have an endometrial thickness <12mm have endometrial hyperplasia (A)
- the number of endometrial samples needed to detect 1 case of endometrial hyperplasia overall is 23. In women [3]90kg the number needed to detect 1 case is 8 (B)

[Levels of Evidence *synopsis*]

note 5

COMPARATIVE TABLE OF MEDICAL THERAPY FOR THE TREATMENT OF HEAVY MENSTRUAL BLEEDING

Drug	Mean reduction in blood loss (%)	Women benefiting -proportion with MBL <80ml/cycle (%)
Levonorgestrel IUS	94%	100%
Oral progesterone (days 5-25)*	87%	86%
Tranexamic acid	47%	56%
NSAIDs	29%	51%
OC pill	43%	50%
Danazol	50%	76%
Oral progesterone (luteal phase)	-4%	18%

* based on only one randomised controlled trial

[Levels of Evidence *synopsis* **]**

note 5

COMPARATIVE TABLE OF MEDICAL THERAPY FOR THE TREATMENT OF HEAVY MENSTRUAL BLEEDING		
Drug	**Specific benefits**	**Adverse benefits**
Levonorgestrel IUS	contraception no requirement to take tablets	menstrual cramps expulsion of system (5%) intermenstrual bleeding (27%)
Oral progesterone (days 5-25)*	cycle regularity	bloating, mood swings, PMS nausea diarrhoea
Tranexamic acid	none	
NSAIDs	relief of dysmenorrhoea and headaches	nausea diarrhoea headache
OC pill	contraception relief of dysmenorrhoea and PMS	nausea, breast tenderness headache
Danazol	none	weight gain, acne hot flushes, bloating, mood swings, PMS
Oral progesterone (luteal phase)	cycle regularity	

[Levels of Evidence *synopsis*]

note 6

The choice of medical therapy will be dependent on individual patient requirements

For example :

Does the patient require contraception ?

Consider: LNG-IUS
OC pill

Does the patient have painful menstruation ?

Consider: LNG IUS
NSAIDs
OC pill

Is the patient unable to tolerate hormone treatments ?

Consider: NSAIDs
Tranexamic A
LNG-IUS

Is the patient trying to conceive?

Consider: NSAIDs
Tranexamic A

- **See decision analysis (Appendix 6.4)**
- **Some women who have completed their family may decline medical therapy and choose surgery as a first option**

(A)

[Levels of Evidence *synopsis*]

note 7

MEDICAL THERAPY *	Ranking according to decision analysis** (A)
Levonorgestrel intra-uterine system	1
Tranexamic acid	2
Non steroidal antiinflammatory drugs	2
Oral contraceptive pill	3
Norethisterone (D5-25 15mg daily)	3
Danazol	4

* NB: more than one therapy can be considered

** based on efficacy, side effect profile and acceptability to women over 12 months (Lethaby et al, 1998)

(see appendix 6.5 for full description)

[Levels of Evidence *synopsis*]

note 8

If Medical Therapy Fails*:

- **women who have no improvement in menstrual blood loss with medical therapy should have a TVS and be referred to a specialist for hysteroscopy as submucous fibroids may be present (B)**

Surgical options (A)

Endometrial ablation	or Hysterectomy
• shorter operating time	• greater satisfaction
• fewer complications	• improved quality of life
• faster rates of recovery	• greater improvement symptoms
• less need for analgesia	• ease in taking replacement
• decreased cost of procedure	
• requirement for repeat	

No difference in mood states, mental health or sexual interest between ablation and hysterectomy (A)

[Levels of Evidence *synopsis*]

note 9

Surgical Options

- Endometrial destruction
  - laser
  - diathermy (heat)
  - balloon (heat)
- Hysterectomy
  - vaginal
  - abdominal
  - laparoscopic

[Levels of Evidence *synopsis*]

SYNOPSIS

GUIDELINES FOR THE MANAGEMENT OF HEAVY MENSTRUAL BLEEDING

Explanation of grading of evidence
The working party accepted a grading of evidence recommended by the Department of Health, UK and endorsed by the National Health Service Executive, UK (Mann 1996).

Grade A - based on randomised controlled trials*
B - based on robust experimental or observational studies
C - based on more limited evidence but the advice relies on expert opinion and has the endorsement of respected authorities

* in diagnostic testing comparative cross sectional studies with a gold standard are Grade 'A'. A gold standard test is defined as best available test.

BACKGROUND
- In New Zealand 2-4% of consultations by premenopausal women with a general practitioner are for menstrual problems and 11% of general practice referrals to a specialist are for assessment of these menstrual problems.
- Women with heavy menstrual blood loss (>80 mls/cycle) have a greater likelihood of becoming iron deficient and anaemic.
- Seven thousand women have hysterectomies each year in New Zealand: In premenopausal women 80% of these are for heavy menstrual bleeding.

RECOMMENDATIONS
(Level of evidence given for these recommendations is given in brackets)

Assessment
- Women who have a normal haemoglobin level should be encouraged to chart their menstrual blood loss by using a pictorial blood loss assessment chart (Fig 6.1) (Grade B).
- Women with erratic menstrual bleeding should be referred to a specialist as endometrial polyps and submucous fibroids are more likely to be present (Grade B).
- Perimenopausal women with irregular cycles but normal blood loss do not require referral (Grade C).
- An abdominal and pelvic examination should be performed in women presenting with heavy menstrual bleeding with the possible exception of women under the age of 20 as the likelihood of pathology is small (Grade C).
- Women with an abnormal pelvic examination, should have an ultrasound to confirm the findings and specialist referral (Grade C).
- A full blood count should be offered to all women presenting with heavy menstrual bleeding (Grade A).
- Women with severe anaemia (<80 g/l) should be referred to a specialist because of the increased likelihood of need for surgery (Grade C).
- Thyroid function tests do not need to be routinely performed in women with heavy menstrual bleeding unless the woman has symptoms or signs of hypothyroidism (Grade C).

- The following women with heavy menstrual bleeding are recommended to have a transvaginal ultrasound of the endometrium
  - weight $\geq$ 90 kg
  - age $\geq$ 45 years old
  - other risk factors for endometrial hyperplasia or carcinoma such as infertility or nullipairty, family history of colon or endometrial cancer, exposure to unopposed oestrogens (Grade B).
- If transvaginal ultrasound is not available then an endometrial sample should be taken (Grade C).
- If the endometrial thickness on TVS is $\geq$12 mm an endometrial sample should be taken to exclude endometrial hyperplasia (Grade A).
- Failure to obtain sufficient material for histological diagnosis does not require further investigation unless the endometrial thickness is $\geq$12 mm (Grade B).
- Hysteroscopy and biopsy is indicated for women with erratic menstrual bleeding, failed medical therapy, or transvaginal ultrasound suggestive of intrauterine pathology such as polyps or submucous fibroids (Grade B).
- Tests for coagulopathy are only indicated in women who have suspicious features in the history or examination (Grade C).

Medical Management

- The following treatments are effective in reducing regular heavy menstrual bleeding:
  Levonorgestrel intrauterine system
  Tranexamic acid (menstruating days only)
  Non-steroidal anti-inflammatory agents (menstruating days only)
  Oral contraceptive pill (Day 5-25)
  Long course of high dose norethisterone (Day 5-25)
  Danazol (daily continuous) (All Grade A)
- Progestogens (norethisterone or medroxyprogesterone acetate) given in the luteal phase (Day 12-26), are not effective in reducing regular heavy menstrual bleeding (Grade A).
- Treatment with norethisterone for 21 days (Day 5-25) is effective in reducing menstrual blood loss (Grade A)
- Emergency suppression of a heavy prolonged menstrual bleed can be achieved by norethisterone 15 mg/day or medroxyprogesterone acetate 30 mgs/day for 3 weeks (Grade C).

Surgical Management

- Dilatation and curettage is not effective for therapy in women with heavy menstrual bleeding (Grade B).
- The endometrium can be destroyed with a variety of techniques but there may be a 40% reoperation rate after 5 years (Grade A).
- Women are more likely to be satisfied with endometrial ablation than oral medical therapy (Grade A).
- There is a similar satisfaction rate and efficacy with endometrial ablation and the levonorgestrel intrauterine system (Grade A).
- Vaginal hysterectomy is associated with reduced operating time, earlier hospital discharge and reduced costs when compared with laparoscopically assisted vaginal hysterectomy (Grade A).
- Endometrial destruction techniques and vaginal hysterectomy are preferable to abdominal hysterectomy (Grade B).

GUIDELINES FOR THE MANAGEMENT OF HEAVY MENSTRUAL BLEEDING

CONTENTS

1 INTRODUCTION

1.1 Introduction

Heavy menstrual bleeding (HMB) is a common and disruptive condition for many New Zealand women. Between 2 and 4% of women aged < 50 years of age will consult their general practitioner each year with menstrual problems (Waimedca, RNZCGP data). Eleven percent of all general practice referrals to a gynaecologist are for menstrual problems (Waimedca data 1991-1992) and they represent 25% of all consultations to gynaecology outpatient clinics (Middlemore Hospital data, 1997). Surgical management of this problem is common and as a result one in five New Zealand women will have had a hysterectomy by the age of 54 (Paul et al 1988).

1.2 Objectives of Guideline

The objective of this Guideline is to provide recommendations for the management of regular heavy menstrual bleeding in women where no pathology is detected that are based on the best evidence available. It is primarily aimed at general practitioners and gynaecologists, but it is hoped that a wider audience will find it helpful.

1.3 Membership of Group

The membership of the group who developed the Guideline included:

Cindy Farquhar, Associate Professor in Reproductive Medicine, Department of Obstetrics & Gynaecology, School of Medicine, University of Auckland (Convenor)
Sue Crengle, Maori Health Researcher, Dept of Maori and Pacific Island Health, School of Medicine, University of Auckland, and General Practitioner, Auckland
Moera Douthett, Pacific Island Health Consultant, Health Research Council, Auckland
Alec Ekeroma, Senior Lecturer in Obstetrics & Gynaecology, School of Medicine, University of Auckland
Gary Fentiman, Obstetrician and Gynaecologist, Private Practice, Dunedin
Wayne Gillett, Associate Professor of Obstetrics and Gynaecology, Otago School of Medicine, Dunedin
Anne Lethaby, Researcher, Cochrane Menstrual Disorders & Subfertility Group, School of Medicine, University of Auckland
Hine Martin, (Consumer representative), Maori Health Counsellor, Whangarei
Ruth Patton, Nurse Consultant, Well Women's Nursing Service, Auckland
Linda Rademaker, General Practitioner, RNZCGP, Hamilton
Ann Richardson, Epidemiologist, Department of Public Health & General Practice, School of Medicine, University of Otago, Christchurch
Dereck Souter, Consultant Obstetrician and Gynaecologist, National Women's Hospital, Auckland
Judi Strid, (Consumer representative), Women's Health Action, Auckland

1.4 Process

In preparing this Guideline a broad based multidisciplinary working party was formed to include both professional and consumer perspectives. These organisations were contacted for representation by the convenor. The group met on four occasions over 12 months and a draft report was prepared. A more detailed description of the process is provided in appendix 6.3.

1.5 Identifying and sifting the evidence

For each question and topic, evidence was sought from either the original scientific publications, systematic reviews, or meta-analyses. Randomised controlled trials (RCTs) were identified through extensive electronic searches using MEDLINE (1966-1996) and EMBASE and smaller databases such as Current Contents, Biological Abstracts, Social Sciences Index, Psych LIT and CINAHL. Attempts were also made to identify and include unpublished work and conference abstracts. The database of the Cochrane Menstrual Disorders and Sub-Fertility Group was made available to the Working Party which included the efforts of handsearching and in some trials extra data has been made available by researchers. The full text of all publications was sought.

The evidence from these publications is summarised into evidence tables (see section 3). In the therapeutics section new meta-analyses were performed where possible. Where evidence was available from RCTs or metanalysis recommendations were based on these, but where there was a lack of evidence then recommendations were based on the best available evidence or expert opinion.

The Working Party agreed to rank the evidence from Grades A - C for decision points as follows:

Grade A - based on RCTs*
B - based on robust experimental or observational studies
C - based on more limited evidence but the advice relies on expert opinion and has the endorsement of respected authorities

* For diagnostic testing comparative cross-sectional studies with a “gold standard” test are Grade A. A gold standard test is defined as the best available data.

The grading system used was adapted from a system recommended by the National Health Service, United Kingdom (Mann 1996). The grading system that our group adopted differs from that of the NHS in that we have graded comparative cross sectional studies for diagnostics as Grade A.

2 EVIDENCE SUMMARY FOR THE MANAGEMENT OF HEAVY MENSTRUAL BLEEDING (HMB)

2.1 Background

For the purpose of this Guideline heavy menstrual bleeding (HMB) is defined subjectively as excessive menstrual bleeding or objectively as menstrual blood loss of ≥80 mls for the whole of a woman's period (Hallberg 1966). In approximately 80-90% of women the menstrual pattern will be regular (cycle length between 21 and 35 days) and this Guideline has therefore been developed to consider primarily the management of regular heavy menstrual bleeding (Coulter 1991). The extent of the problem of HMB in New Zealand women is difficult to quantify. A database of 44 general practitioners from across the country (RNZCGP Research Unit, Dunedin) found that 2.3% of consultations for women < 50 years old are for heavy menstrual bleeding. Eleven percent of all specialist referrals from a group of 259 general practices were to gynaecologists for menstrual disorders (Waimedca data, 1991-1992). These figures are echoed by data from the United Kingdom where 1 in 20 women aged 30-49 consult their general practitioner each year for heavy menstrual bleeding (Vessey 1992). Menstrual problems represent 25% of all consultations to gynaecology outpatients (Westgate J. Middlemore Hospital data, 1997).

Is there a gap between current practice and effective care of women with HMB in New Zealand? The utilization of hysterectomy in New Zealand would suggest there is. Seven thousand hysterectomies are performed annually and it is estimated that the majority are in premenopausal women (Scott 1995). Eighty percent of hysterectomies in premenopausal women performed at National Women's Hospital are for women with heavy menstrual bleeding (Farquhar 1997). Throughout the last decade the figures have not changed significantly and 1 in 5 New Zealand women will have had a hysterectomy by the age of 50 (Paul 1988). Regional variations exist with up to a fourfold difference in hysterectomy rates between regions (MacIntosh 1987). International variations in hysterectomy rates further suggests uncertainty in practice. In the United Kingdom 17% of women undergo a hysterectomy by 50 years (Vessey 1992), while in Denmark and the United States the lifetime probability is 10% (Settnes & Jørgensen 1996) and 40% respectively (Pokras & Hufnagel 1988).

There are a number of uncertainties in clinical management that illustrate the need for this Guideline. For example, it is unclear which women should have endometrial sampling. Some authorities recommend sampling for all women over the age of 35 years old (Keye 1988, Bayer and DeCherney 1993) while others recommend it only for women 40 years and older (RCOG Guidelines 1994). There are a number of options for the investigation of the endometrium that have been recommended; dilatation and curettage, endometrial sampling, transvaginal ultrasound and hysteroscopy. In the area of therapeutics there is some evidence of a failure to offer effective treatments. In a survey of New Zealand gynaecologists in 1995 50% preferred to use luteal phase progestogens to treat heavy menstrual bleeding as a first line treatment (Farquhar & Kimble 1996), yet this is a treatment that has been repeatedly shown to be ineffective (Cameron 1990, Bonduele 1991, Higham & Shaw 1993, Preston 1995). One of the more effective treatments, tranexamic acid, was prescribed in less than 10% of cases.

Another major area of concern is the role of new technologies in the management of HMB. Endometrial ablation by laser, diathermy or heat are all relatively new options available in New Zealand. Few gynaecologists in New Zealand are skilled in these technologies yet in the UK 56% of National Health Service gynaecological units are already using these techniques (Overton 1997). Furthermore the role of the newly introduced levonorgestrel releasing intrauterine device needs to be considered.

2.2 Assessment

There are a number of questions that need to be addressed when considering how to assess women with heavy menstrual bleeding.

- how should the extent of heavy menstrual bleeding be assessed?
- which women require an assessment of their endometrium to exclude hyperplasia (abnormal cells that have the potential to develop into uterine cancer)?
- which is the best method to assess the endometrium - transvaginal ultrasound or endometrial biopsy or hysteroscopy?
- which is the best method for biopsying the endometrium?

This section on diagnostics attempts to answer these questions using research evidence. Comparative cross-sectional studies and randomised controlled trials (RCTs) of different diagnostic methods have been identified. If the sensitivity and specificity of the diagnostic tests were not reported or if there was no "gold standard" test they were excluded (see evidence tables Section 3.1). Sixteen diagnostic studies were identified by electronic searching and by searching reference lists. Eight compared transvaginal ultrasound and biopsy, 5 compared dilatation and curettage (D & C) and biopsy, and 2 compared objective menstrual blood loss measurements with a pictorial blood assessment chart.

2.2.1 Assessment of menstrual blood loss

A woman's perception that her own menstrual blood loss is excessive is the reason for seeking medical advice and assistance. The 90th centile for menstrual blood loss from population studies is 80 mls/cycle (Hallberg 1966). There is a poor correlation between the reporting of heavy menstrual bleeding by women and menstrual blood loss (MBL) of $\geq$ 80 mls. Only 46 - 62% of women who describe heavy menstrual periods will have a blood loss greater than 80 mls (Chimbira 1980a, Rees 1982, Fraser 1984, Janssen 1995, Gannon 1996). There is also a poor correlation between the amount of sanitary protection material used and MBL (Chimbira 1980a, Fraser 1984).

The method for measuring MBL is the alkaline haematin tests (Hallberg 1996). This involves women collecting all sanitary protection material and soaking it for 48 hours in sodium hydroxide (or detergent) and the optical density of the solution is then compared against a sample of the women's venous blood. The MBL is then calculated. This is a research technique not available in New Zealand.

A simpler, less time consuming method that does not involve the collection of all sanitary materials is the pictorial blood loss assessment chart (PBAC) (see Appendix 6.4). This method has been validated against measured MBL in 2 studies and has demonstrated a better correlation than history alone (Higham 1990, Janssen 1995). The pictorial chart records the number of minimally, moderately and completely stained pads/tampons and applies a score for each.

If the prevalence of MBL ≥80 mls/cycle is 46% in the community and a woman has a PBAC score greater than ≥185, then the likelihood of an individual woman having MBL ≥80 mls/cycle is 75%, while if PBAC score < 185 then the likelihood is 8% (Janssen 1995). Unfortunately, it has not been used widely in a general practice setting, so its value in primary care is yet to be established. It may have a role, however, in reassuring women by providing low scores or in helping to assess those women with normal haemoglobin levels.

Recommendation
Women who have a normal haemoglobin level should be encouraged to chart their menstrual blood loss by using a pictorial blood loss assessment chart (Grade B)

2.2.2 Pattern of Menstrual Bleeding

Between 80-90% of women with heavy menstrual bleeding have regular cycles (between 21 to 35 day cycles) (Wood 1975, Coulter, 1991). Women with prolonged irregular bleeding or intermenstrual bleeding are reported to have submucous fibroids or endometrial polyps in 25-50% of cases from highly selected populations (Fedele 1991, Dijkhuizen 1996, Nagele 1996). However the incidence of polyps or submucous fibroids in women with regular heavy menstrual bleeding is unknown. More research is needed to investigate the role of submucous fibroids and polyps in women with intermenstrual and irregular bleeding patterns. Perimenopausal women often have delayed menstrual cycles and unless the blood loss is excessive further investigation is unnecessary.

Recommendations
Women with erratic menstrual bleeding, (regardless of loss), should be referred to a specialist as endometrial polyps and submucous fibroids are more likely to be present (Grade B). Perimenopausal women with less frequent menstrual cycles but normal blood loss do not require further investigation as they are not at increased risk of intrauterine pathology (Grade C).

2.2.3 Pelvic Examination

Women who present with HMB should have an abdominal and pelvic examination to exclude obvious pelvic pathology prior to the commencement of treatment. A possible exception to this is for those patients under the age of 20 as the findings are unlikely to contribute to management as the likelihood of pathology is small. An ultrasound examination to confirm abnormal pelvic examination findings and referral to a specialist is indicated. A cervical smear can be taken at the time of the pelvic examination if this falls within the recommendations of the National Cervical Screening Programme.

Recommendation
An abdominal and pelvic examination should be performed in women presenting with heavy menstrual bleeding with the possible exception of women under the age of 20 (Grade C). Women with an abnormal pelvic examination should have an ultrasound to confirm the findings and specialist referral (Grade C).

2.2.4 Full Blood Count

The full blood count (FBC) is often considered an essential investigation in women with heavy menstrual bleeding (Cameron 1989, van Eijkeren 1992, Fraser 1994, Wathen 1995). More than two thirds of women with menstrual blood loss greater than 80 ml/cycle have evidence of iron deficiency anaemia (Smith 1982, Janssen 1995, Hallberg 1966, Rybo 1966). Janssen (1995) found that a low haemoglobin predicted objective heavy menstrual bleeding (>80 mls/month) better than the woman's subjective assessment. If the prevalence of MBL > 80 mls/cycle is 46% and a woman has a FBC < 120g/l then the likelihood of an individual woman having MBL > 80 mls/cycle is 70%, while if the FBC >120g/l then the likelihood of a woman having MBL >80 mls/cycle is 18% (Janssen 1995). Therefore a low haemoglobin level is considered to be a good indicator of objective heavy menstrual bleeding but a normal haemoglobin does not exclude heavy menstrual bleeding.

A FBC may also detect an iron deficiency state before a woman becomes anaemic. As symptoms and signs of anaemia do not correlate well with the haemoglobin level until the patient is moderately to severely anaemic, a FBC should be performed in all women complaining of heavy menstrual bleeding to aid recognition of the severity of menstrual blood loss. It is not recommended that iron studies are performed routinely as the haematological indices usually give some indication of the iron stores. Women who are severely anaemic (<80 g/l) should be referred to a specialist immediately because of the increased likelihood of pathology (Fraser 1986).

Recommendation:
A full blood count should be offered to all women presenting with heavy menstrual bleeding (Grade A). Women with severe anaemia (<80 g/l) should be referred to a specialist because of the increased likelihood of need for surgery (Grade C).

2.2.5 Thyroid Function Tests

The proportion of heavy menstrual bleeding that is due to thyroid disorders is unknown. There is no evidence linking heavy menstrual bleeding with thyrotoxicosis (Krassas, 1994) but there have been several small series of hypothyroid patients reporting an excess of menstrual irregularities, particularly heavy menstrual bleeding (Scott & Mussey, 1964). However these involved known hypothyroid patients and only subjective heavy menstrual bleeding was reported. A case report in 1992 demonstrated how objectively measured heavy menstrual bleeding in a hypothyroid patient improved with thyroxine replacement (Higham & Shaw, 1992). There has also been a suggestion that some women with heavy menstrual bleeding have subclinical hypothyroidism

and that thyroxine replacement may decrease their menstrual blood loss (Wilansky & Greisman 1989, Blum & Blum, 1992). These studies relied on the response to a thyrotropin releasing hormone (TRH) test in women with normal free thyroxine and TSH levels. Routine screening for thyroid disease with thyroid function tests is not recommended for asymptomatic adults (US Preventive Services Task Force, 1996) and there is no evidence to suggest different recommendations in women complaining of heavy menstrual bleeding. This topic requires further study. Most authors support measurement of thyroid function only if the history reveals symptoms suggestive of thyroid dysfunction (Cameron 1989, van Eijkeren 1992, Fraser 1994).

Recommendation
Thyroid function tests do not need to be routinely performed in women with heavy menstrual bleeding unless the woman has symptoms or signs of hypothyroidism (Grade C).

2.2.6. Assessment of the Endometrium

2.2.6.1. Is it necessary to assess the endometrium?

Endometrial pathology in premenopausal women with abnormal uterine bleeding is not common. Although 20% of cases of endometrial cancer occur before the menopause, most of these women are aged between 40-50 years (McGee 1958, Peterson 1968, Crissman 1981, Gallup & Stock 1984, Jeffrey 1987). In the United Kingdom the predicted frequency in women <36 years was 1:100,000 (McKenzie & Bibby 1978) while in women <20 years it was 1:208,000 (Fraser & Baird 1972). In New Zealand in 1993, 1.4% of cases occurred in women <40 years and only 10% of cases occurred in women aged between 40 to 50 years. Overall, the average age standardised incidence of endometrial cancer for all ages (based on the years 1991-3) for non-Maori women is 8.4/100,000 per year. However, the rate for Maori women is almost double, 15.2/100,000 per year, which is one of the highest rates in the world.

Endometrial hyperplasia is a precursor for endometrial cancer and in the absence of therapy, progression to endometrial cancer may occur. Observational studies have shown a prevalence of hyperplasia of 2-7% in premenopausal women (McKenzie & Bibby 1978, Koss 1984, Ash 1996, Farquhar 1998). The likelihood of progression depends on the degree of hyperplasia. Simple hyperplasia without atypia (untreated) progresses infrequently (2-8% of cases) over a 13 year period while women with complex hyperplasia progress in 5-23% of cases. Those hyperplasias with atypia (untreated) are more likely to progress to cancer (20%-75%) (Wentz 1966, Kurman 1985, Terakawa 1997). A proportion of atypical lesions (estimated at approximately 20%) have undetected adenocarcinoma of the endometrium at the time of the initial biopsy (Wentz 1966, Kurman 1985, Hunter 1994, Terakawa 1997). Medical treatment of endometrial hyperplasia, including atypical cases, is possible using progestational agents such as medroxyprogesterone acetate or megesterol although the followup is not reported beyond 2 years (Wentz 1966, Eichner 1971, Randall 1997). The levonorgestrel intrauterine system may also reverse endometrial hyperplasia (Perino 1987, Scarselli 1988). Patients with atypia have a greater likelihood of a missed

diagnosis of more serious disease or progression to adenocarcinoma. As a result longterm surveillance is necessary and therefore hysterectomy is often preferable.

Previously, potential risk factors for endometrial hyperplasia in premenopausal women with HMB were increased body weight, unopposed oestrogen therapy (both endogenous for long periods of amenorrhoea and exogenous), diabetes, extremes of parity, irregular cycles, delayed onset of menopause, tamoxifen therapy, PCOS, anovulation, and hypertension. The Royal College of Obstetricians and Gynaecologists recommended in 1994 that women aged 40 years or less, with heavy menstrual bleeding and regular cycles, need not have endometrial samples taken (RCOG 1994). Some authors have suggested that women with irregular bleeding or other risk factors for hyperplasia should have endometrial sampling regardless of age (Gallup and Stock 1984, Ash 1996).

An audit of over 1000 endometrial samples at National Women's Hospital 1995-1997 (30 month period) has shown an incidence of hyperplasia and carcinoma of 5% in premenopausal women under 50 years of age (Farquhar 1998). Of the 51 premenopausal women with diagnoses of hyperplasia or carcinoma in the National Women's Hospital audit, 20 had simple hyperplasia, 23 had complex hyperplasia, 3 had atypical hyperplasia and 5 had carcinoma.

The most important risk factor was weight (body mass index was not able to be calculated as height was not always recorded). Twenty one percent of the sample with endometrial hyperplasia weighed 90 kg or more and 13% had hyperplasia (Table 2.1). Women who weighed ≥90 kg had five times increased risk of endometrial hyperplasia. It was not possible to calculate body mass index as height was not consistently reported. This observation is supported by other reports (Peterson 1968, Crissman 1981, Quinn 1985, McGee 1958, Ash 1996). Age > 45 years was associated with nearly triple the risk (Farquhar 1998). Infertility + nullipairty was also significantly associated with hyperplasia. A family history of colonic cancer was also a risk factor. Cycle irregularity and duration of bleeding were not risk factors.

A small proportion (14%) of the women diagnosed with endometrial hyperplasia had none of the above risk factors. If the cases of simple hyperplasia are excluded then the risk factors for complex hyperplasia, atypia and carcinoma are weight ≥90 kg, history of infertility, nullipairty and formly history of colon or endometrial cancer.

Based on this population of selected patients over a 30 month period (1995-1997), the number of premenopausal women needed to investigate in order to detect one case of endometrial hyperplasia is 23 and for endometrial cancer nearly 200. By restricting screening for endometrial hyperplasia and carcinoma to those women at increased risk (.≥90 kg and .≥45 years old, PCOS, infertility) then the number of women needed to screen to detect 1 case of hyperplasia will be between 8 and 13 (see Table 2.2).

Although tamoxifen was not shown to be a risk factor in this audit, women who have received tamoxifen do appear to be at increased risk of endometrial hyperplasia (10%) (Barakat 1997). However, it is not recommended that routine endometrial screening occur unless abnormal bleeding is present.

Table 2.1: Independent risk factors for endometrial hyperplasia and carcinoma in women with abnormal bleeding (n=1033) (results from multivariate analyses)

	All abnormal histology		**Complex, atypia & Ca only***	
Risk factor	Odds ratio (95% CI)	p	Odds ratio (95% CI)	P
Weight ≥ 90 kg	5.5 (2.9,10.6)	<0.00001	7.3 (3.2,16.8)	<0.0001
Positive family history of colon cancer	5.0 (1.3,19.1)	0.0182	9.1(2.2,37.1)	0.002
Infertility	3.6 (1.3, 9.9)	<0.0127	3.3 (0.99, 11.1)	0.051
Age ≥45 years	3.1 (1.5, 6.1)	0.0016	NS	NS
Nullipairty	2.8 (1.1, 7.2)	0.0267	3.7 (1.2, 10.9)	0.0193
Positive family history of endometrial cancer	NS	NS	5.8 (1.1, 28.6)	0.0392

*Simple hyperplasia excluded

While this audit has been able to establish which women are at increased risk of endometrial hyperplasia, it has not been able to say whether this is a clinically relevant diagnosis. The progression from simple hyperplasia to carcinoma is uncommon. It is possible that women with normal menstrual cycles may also have hyperplasia. Only large population studies could answer this question and they are unlikely to be undertaken. The search for hyperplasia in women with HMB needs to be tailored to the clinical circumstances.

2.2.6.2 Ultrasound examination of the endometrium

Transvaginal ultrasound is an accurate test for diagnosing endometrial hyperplasia when the endometrial thickness is greater than or equal to 12 mm (Smith 1991, Scarpellini 1994, Emanuel 1995, Indman 1995, Dijkhuizen 1996). Two studies of lower quality disagreed with these findings and suggested a different cut off for endometrial thickness (Towbin 1996, Bronz 1997). Another study used a cutoff of ≥14 mm but missed some cases of pathology and therefore agreed that a lower cutoff of ≥12 mm was preferable (Vercellini 1997).

On transvaginal ultrasound when the endometrial thickness is less than 12 mm then the likelihood of endometrial hyperplasia is small (Scarpellini 1994, Emanuel 1995, Vercellini 1997). If the overall prevalence of hyperplasia in women with HMB is 3% and an endometrial thickness is ≥12 mm then there the likelihood of endometrial hyperplasia is 28% (Table 2.1). If the endometrial thickness is <12 mm then the likelihood of

endometrial hyperplasia is 0.2% (see Table 2.1). In a woman weighing more than 90 kg and an endometrial thickness ≥12 mm, then the likelihood of endometrial hyperplasia is 50% (using a pretest probability of 10%). If the endometrial thickness is <12 mm then the likelihood is 0.7%. In a woman ≥45 years old and endometrial thickness ≥12 mm then the likelihood of endometrial hyperplasia is 35% (using a pretest probability 6%) while if the endometrial thickness is <12 mm then the likelihood of endometrial hyperplasia is 0.5%. If TVS was used as a first step then further invasive testing would have been avoided in 40% of premenopausal women (Dijkhuizen 1996).

Table 2.2: The likelihood of endometrial hyperplasia*

	Endometrial thickness on TVS ≥ 12 mm	Endometrial thickness ≥ 12 mm	Number needed to detect 1 case of endometrial hyperplasia
All women with heavy menstrual bleeding (gynaecology clinic) (prevalence 5%)	30%	0.3%	23
Women < 45 yo and < 90 kg (prevalence 2.2%)	17%	0.1%	44
Women with heavy menstrual bleeding and ≥90 kg (prevalence 13%)	55%	0.6%	8
Women with heavy menstrual bleeding and ≥ 45 yo (prevalence 8%)	42%	0.3%	13

* Using positive likelihood ratio of 9.09 / negative likelihood ratio of 0.04 (Emanuel 1995)

The role of TVS in diagnosing intrauterine masses such as submucous fibroids or polyps is less clear. While some reports have suggested that it was an accurate test in more than 95% of cases (Fedele 1991), in other studies the diagnostic accuracy was lower (Dijkhuizen 1996, Towbin 1996, Kavak 1996, Vercellini 1997). For example, in one report ultrasound missed pathology (other than endometrial hyperplasia) in 10% of cases (Dijkhuizen 1996). In the largest study by Vercellini of 793 premenopausal women TVS had a sensitivity of 80% and specificity of 69% for diagnosing submucous myomas. Six submucous myomas were missed and in 31 cases intramural myomas were incorrectly diagnosed as submucous myomas. The authors concluded that TVS was suboptimal for diagnosing submucous myomas (Vercellini 1997). The introduction of fluid into the uterine cavity may improve the diagnosis of intrauterine masses (Weston 1995, Widdrich 1996) but this is not yet an established procedure.

2.2.6.3 Sampling Techniques

There are several devices available in New Zealand for endometrial sampling including inpatient D & C, outpatient vabra curettage and pipelle sample. The most common outpatient procedure is taking a pipelle sample; this has been reported to be sensitive in histopathological diagnoses in 95% of samples when compared with D & C (Stovall 1991, Ben-Baruch 1994) (see evidence tables). The pipelle is a clear, flexible polypropylene sheath measuring 23.5 cm in length with a blunt rounded distal tip. It has inner and outer diameters of 2.6 and 3.1 mm respectively. By withdrawing the inner piston, a negative pressure is created within the inner lumen, drawing the endometrial contents into the pipelle (Cornier 1984). One widely reported study had lower sensitivities and 9% of known endometrial carcinomas were missed, but the pipelle samples were taken immediately before hysterectomy for endometrial carcinoma and after a diagnostic D & C had been done at an early operation thereby reducing the volume of tissue being sampled (Ferry 1993). The pipelle is safe and perforation, haemorrhage and infection are rarely associated with its use (Eddowes 1990, Stovall 1991).

2.2.6.4 Absence of endometrial tissue at sampling

Insufficient tissue for diagnostic purposes may occur at the time of a pipelle sample; in premenopausal women this has been variously reported as occurring in between 4 and 20% of cases (Koonings 1990, Stovall 1991, Rodriguez 1993, Ben-Baruch 1994, Lipscombe 1994). Premenopausal women in whom insufficient tissue for histological analysis occurred were not found to have endometrial hyperplasia or carcinoma subsequently (Stovall 1991, Ben-Baruch 1994). When failure to enter the endometrial cavity occurs because of cervical os stenosis or excessive pain, then a transvaginal ultrasound or dilatation and sample with local or general anaesthetic are indicated.

2.2.6.5 Hysteroscopy and endometrial sampling

The main purpose of hysteroscopy is to look for intrauterine pathology such as endometrial polyps and submucous fibroids. The association of such pathology with HMB is not clear as the majority of the studies are retrospective and in women with failed medical therapy or abnormal TVS. Fraser (1990) demonstrated that women a tertiary referral clinic with menorrhagia who had submucous myomas frequently had MBL >120 mls. In women with irregular bleeding, polyps are present in up to 25% of cases and submucous fibroids are present in 15-18% of cases (Fedele 1991, Dijkhuizen 1996). In women with HMB who have failed medical treatment, have an abnormal transvaginal ultrasound, or are aged 40 years or older, they are present in 50% of cases (Nagele 1996). In women undergoing hysteroscopic sterilisation submucous myomas and other intrauterine abnormalities are only present in 13% of women (Cooper 1983). Therefore it seems likely that there may be an association between HMB and the presence of submucous myomas and they should be considered in women with an abnormal TVS, erratic bleeding or failed medical therapy.

Hysteroscopy with biopsy is now considered the best diagnostic test for intrauterine pathology and has high specificities and sensitivities (Emanuel

1995, Dijkhuizen 1996). Hysteroscopy with biopsy detects more when compared directly with D & C as a diagnostic procedure (Goldrath 1985, Gimpelson 1988, Loffer 1989). If the uterine cavity appears normal at hysteroscopy an endometrial sample should still be taken as hysteroscopy alone is not very accurate at diagnosing endometrial hyperplasia and carcinoma (Widrich 1996, Vercellini 1997). Few studies have addressed the question of whether or not resection of submucous myomas in women with HMB results in a reduction in MBL. In one report of 4 women with menorrhagia only the mean MBL was reduced by 78% at 6 months (Broadbent and Magos 1995). However a report by Derman was less encouraging with 23 of 78 women having recurrent abnormal bleeding.

Recommendations
Failure to obtain sufficient material for histological diagnosis does not require further investigation unless the endometrial thickness is ≥12 mm (Grade B). The following women with heavy menstrual bleeding are recommended to have a transvaginal ultrasound of the endometrium - weight ≥90 kg - age ≥ 45 years old Oher risk factors for endometrial hyperplasia or carcinoma such as known polycystic ovarian syndrome, infertility, nulliparity or exposure to unopposed oestrogens, family history of endometrial or colon cancer (Grade B). If transvaginal ultrasound is not available then an endometrial sample should be taken (Grade C). If the endometrial thickness on TVS is ≥ 12 mm an endometrial sample should be taken to exclude endometrial hyperplasia (Grade A). Hysteroscopy and biopsy is indicated for women with erratic menstrual bleeding, failed medical therapy, or transvaginal ultrasound suggestive of intrauterine pathology such as polyps or submucous fibroids (Grade B).

2.2.7 Other investigations

Systemic disorders such as coagulopathy are rare causes of heavy menstrual bleeding and most authors recommend specific investigation only if there are suspicious features in the history or examination, or failure of treatment to control symptoms (Cameron 1989, van Eijkeren 1992, Fraser 1986, Fraser 1994, Wathen 1995). Two recent studies, however, indicated a significant increase in Von Willebrands Disease in women with heavy menstrual bleeding compared to the normal population and recommended that screening be considered (Edlund 1996, Kadir 1998). The significance of these findings depends upon the availability of a safe effective therapy to correct the underlying coagulopathy. One such trial is underway.

Recommendation

Tests for coagulopathy are only indicated in women who have additional suspicious features in the history or examination (Grade B & C).

2.3 Medical Management

A wide variety of drugs have been used for the treatment of heavy menstrual bleeding, including nonsteroidal anti-inflammatory drugs (eg. mefenamic acid, naproxen), anti-fibrinolytics (eg. tranexamic acid), hormones (eg. norethisterone, danazol, oral contraceptive pills) and intrauterine devices (eg. progestogen-releasing intrauterine systems).

There are many options for medical management that are effective but the symptoms usually return once therapy is stopped. Since long term therapy may be necessary, the severity and frequency of side effects should be taken into account.

Table 2.3: Randomised controlled trials of medical and surgical therapy for heavy menstrual bleeding

MEDICAL THERAPY	
Nonsteroidal anti-inflammatory drugs (NSAIDs) vs placebo	**No. of patients**
Mefenamic acid vs placebo	
van Eijkeren et al 1992	11
Fraser et al 1981	69
Muggeridge & Elder 1983	15
Guillebaud et al, 1978	25
Tsang et al 1987	10
Grover et al, 1990	80
Naproxen vs placebo	
Davies et al 1981	34
Rybo et al 1981	4
Ylikorkala & Pekonen 1986	14
Ibuprofen vs placebo	
Makarainen & Ylikorkala 1986	13
Meclofenamic acid vs placebo	
Varygas et al 1987	29
Diclofenac vs placebo	
Ingemanson et al 1991	9
Anti-fibrinolytic drugs vs placebo	
Tranexamic acid vs placebo	
Nilsson & Rybo 1967	36
Callender et al 1970	16
Edlund et al 1995	68
Vermylen et al 1968	16
Petersen et al 1983	17
Ethamsylate vs placebo	
Harrison & Campbell 1976	22
Aminocaproic acid vs placebo	
Nilsson & Rybo 1965	37
Danazol vs placebo	
Chimbira et al 1980b	40
Lamb 1987	76
Need et al 1992	11

OTHER COMPARISONS (non placebo controlled trials)

Trial	**No. of patients**
Mefenamic acid vs danazol	
Dockeray et al 1989	39
Mefenamic acid vs norethisterone	
Cameron et al 1990	32
Mefenamic acid vs ethamsylate vs tranexamic acid	
Bonnar et al 1996	76
Mefenamic acid vs danazol vs norethisterone vs prog coil	
Cameron et al 1987	30
Mefenamic acid vs naproxen vs danazol vs combined oral contraceptive	
Fraser & McCarron 1991	38
Mefenamic acid vs ethamsylate	
Chamberlain et al 1991	34
Mefenamic acid vs naproxen	
Hall et al 1987	35
Flurbiprofen vs tranexamic acid	
Milsom et al 1991	15
Diclofenac vs tranexamic acid	
Ylikorkala & Viinikka 1983	19
Ethamsylate vs aminocaproic acid	
Kasonde & Bonnar 1975	22
Tranexamic acid vs norethisterone	
Preston et al 1995	42
Danazol vs norethisterone	
Higham & Shaw 1993	54
Bonduelle et al 1991	24
Norethisterone vs Levonorgestrel Intrauterine System	
Irvine 1997	44
SURGICAL THERAPY	
Endometrial resection/ablation vs hysterectomy	
Gannon et al 1991	51
Dwyer et al 1993	196
Pinion et al 1994	204
Crosignani et al 1997	85
O'Connor et al 1997	172
Transcervical resection vs laser ablation	
Bhattacharya et al 1997	372
SURGICAL VS MEDICAL THERAPY	
Endometrial ablation vs Levonorgestrel IUS	
Crosignani et al 1996	60
Endometrial ablation vs Medical Therapy	
Cooper et al 1997	187

Assessment of the efficacy of drug therapy in the treatment of heavy menstrual bleeding is ideally based on placebo comparisons with active treatment but only a small subset of the trials included placebo comparison groups. Therefore, the decision analysis was also performed to assess the relative 'value' of different medical

treatments in terms of their efficacy but also the trade off patients are prepared to make to tolerate side effects and the inconvenience of taking pills.

There are 33 RCTs of medical therapy and 6 RCTs of surgical treatment for heavy menstrual bleeding (Table 3.2 and 3.3). A further two RCTs have compared medical with surgical treatments of heavy menstrual bleeding (Table 3.4). No trials specifically addressed irregular menstrual bleeding.

It has been argued that a course of medical therapy should be the first-line treatment before recourse to surgery (Macdonald 1990) although a significant proportion of women with completed families may prefer surgery (Cooper 1997b).

2.3.1 Non steroidal anti-inflammatory drugs (NSAIDs)

Endometrial prostaglandins are elevated when menstruation is excessive (Willman 1976, Smith 1981, Cameron 1987a, Elder 1993). NSAIDs reduce prostaglandin levels by inhibiting the enzyme cyclo-oxygenase. Twenty one randomised controlled trials have shown that NSAIDs decrease menstrual blood loss by between 20-50% when taken during menstruation (see evidence tables). Mefenamic acid, flurbiprofen, meclofenamic acid, ibuprofen, naproxen and diclofenac given during menstruation have all been shown to be effective. In two studies comparing mefenamic acid and naproxen there is no evidence of a difference in effectiveness (Hall 1987, Fraser 1991). NSAIDs are also helpful for women who have dysmenorrhoea (menstrual cramps) and up to 70% of women experience significant relief of pain. The common side effects reported are headaches and gastrointestinal disturbances, including dyspepsia, nausea, vomiting and diarrhoea. These disturbances can be avoided by taking the medication with a meal and are unlikely to occur if taken for a short time or intermittently. Women with active gastrointestinal ulceration or a history of intolerance to NSAIDs should not be given NSAIDs. Women with asthma should be informed of the possibility of exacerbation of asthma. Compared to other treatments mefenamic acid was more effective than luteal phase progestogens (Cameron 1987b) but less effective than tranexamic acid (Bonnar 1996), and danazol (Dockeray 1989, Fraser 1991).

Recommendation:
Non steroidal anti-inflammatory drugs are effective for reducing heavy menstrual bleeding (Grade A).

2.3.2 Antifibrinolytic agents:

Antifibrinolytic agents such as tranexamic acid have been shown in 10 randomised placebo controlled trials to decrease menstrual blood loss by about 40% (range of reduction 33-55%) (see evidence tables). Their mode of action is to depress the fibrinolytic activity of peripheral blood through the inhibition of plasminogen activation (Hoylaerts 1981, Astedt 1987). Specific side effects reported in approximately one third of women include nausea and leg cramps. There is no impact on dysmenorrhoea. There have been two cases of intracranial thrombosis reported in Finland but in a large epidemiological population based study over 19 years this was shown to be no higher than would be expected in the normal population (Rybo 1991). Although it is currently restricted in New Zealand to specialist prescribing it is hoped that this will be changed so that general practitioners can prescribe it.

Recommendation
Tranexamic acid is effective for reducing heavy menstrual bleeding (Grade A).

2.3.3 Ethamsylate

Ethamsylate is a non-hormonal agent that is thought to act by increasing capillary vascular wall resistance and platelet adhesiveness in the presence of trauma to the blood vessel lining (as occurs in the arterioles of the endometrium). The efficacy of ethamsylate has been assessed but only 1 placebo controlled RCT has been undertaken (Kasonde 1975, Harrison 1976, Chamberlain 1991, Bonnar 1996). The results have been conflicting ranging from no effect to a reduction of MBL of 46% from baseline. It is not commonly used in New Zealand.

Recommendation
There is no conclusive evidence of the effectiveness of ethamsylate for reducing heavy menstrual bleeding (Grade A)

2.3.4 Danazol:

Danazol is a synthetic steroid with mild androgenic properties. It causes atrophy (shrinkage) of the endometrium and is therefore potentially useful in the treatment of dysfunctional uterine bleeding. Danazol produces a highly significant reduction in blood loss, often reduced to 20% or less of pretreatment levels (Chimbira 1980, Lamb 1987, Need 1992). Unfortunately adverse side effects, such as weight gain, depression, acne, and headaches limit its usefulness. Furthermore, it is necessary to take it daily for up to 12 weeks. Nevertheless, it may be a valuable therapy for women with severe heavy menstrual bleeding who need time to make decisions about surgery or other therapy.

Recommendation
Danazol is effective for reducing heavy menstrual bleeding but side effects limit it to a second choice therapy or short term use only (Grade A).

2.3.5 Progestogens:

Progestogen therapy given in the luteal phase of the menstrual cycle has been widely used in the treatment of dysfunctional uterine bleeding (Fraser 1990). However, there have been no placebo controlled trials and randomised controlled trials have shown it to be ineffective in regular heavy menstrual bleeding compared to NSAIDs and tranexamic acid (Cameron 1987b & 1990, Higham & Shaw 1993, Preston 1995). One study has demonstrated a 20% increase from patients own baseline in menstrual blood loss with luteal phase progestogens compared with tranexamic acid (Preston 1995).

It may be useful for those women with irregular cycles (<21 or >35 days) as it can induce a regular withdrawal bleed when given for seven to ten days of each month. Once menstruation commences other therapies may be given such as NSAIDs or tranexamic acid.

A longer treatment time with norethisterone (15 mg from day 5-25) has been shown to be effective in one trial (Irvine 1997). In this RCT it was shown to reduce menstrual blood loss by 87% from baseline in women with ovulatory heavy menstrual bleeding. However, only 44% of women said that they liked

the treatment 'well' or 'very well' and only 22% elected to continue with the treatment. In an earlier small non-randomised study (Fraser 1991) a lesser reduction of menstrual blood loss (33% in ovulatory women and 51% in anovulatory women) was recorded using either norethisterone (NET) or medroxyprogesterone acetate (MPA) for 21 days (days 5-25) in ovulatory women and 14 days (days 12-25) in anovulatory women.

Although the role of luteal phase progestogen therapy is unhelpful in women with regular HMB it has been used for the emergency suppression of a heavy and prolonged menstrual bleeding episode. This can be achieved by giving norethisterone (15 mg/day) or medroxyprogesterone acetate (30 mgs/day) for up to 3 weeks. The dosage is reduced once bleeding has ceased. Bleeding should stop in the first week but if it does not the dosage can be increased. Once the patient has been free of bleeding for 3-4 weeks progestogen can be stopped and a withdrawal bleed should occur. Maintenance therapy with other agents can then be instituted. Another regimen is to give medroxyprogesterone acetate 10 mg/day initially and increase the dosage each day until the bleeding has stopped (up to 100 mg/day). This emergency regimen is not supported by evidence from RCTs.

Recommendations
Progestogens (norethisterone or medroxyprogesterone acetate) given in the luteal phase of the menstrual cycle, are not effective in reducing regular heavy menstrual bleeding (Grade A).
Treatment with norethisterone for 21 days (day 5-25) is effective in reducing menstrual blood loss (Grade A). Emergency suppression of a heavy prolonged menstrual bleed can be achieved by norethisterone 15 mg/day or medroxyprogesterone acetate 30 mgs/day for 3 weeks (Grade C).

2.3.6 Combined oral contraceptive pill:

Reduction of menstrual blood loss with the combined oral contraceptive (COC) pill is most probably the result of inducing endometrial atrophy. In the only randomised controlled trial of the COC pill (30 microgram), a significant reduction in menstrual blood loss of 43% from baseline was reported, although the study numbers were very small (6 women in each group) (Fraser 1991). In a series of 164 women given a 50 microgram pill in the 1960s, a 53% reduction in menstrual blood loss was reported (Nilsson & Rybo 1971). There is some support for the use of the COC from cohort studies. Two longitudinal case control studies have found that users were less likely to experience heavy menstrual bleeding or anaemia (RCGP, Ramcharan 1980). Use of the COC pill has the additional advantage of reducing the symptoms of dysmenorrhoea and providing contraception, and providing contraception and hormone replacement in the perimenopausal phase.

Recommendation
Combined oral contraceptive pill can be used to reduce heavy menstrual bleeding (Grade A).

2.3.7 Levonorgestrel Intrauterine System

The levonorgestrel intrauterine system (LNG-IUS) is a T shaped intrauterine device which releases a steady amount of levonorgestrel (20 µg/24 hrs) from a steroid reservoir around the vertical stem of the device. The local effects of the released levonorgestrel result in endometrial atrophy and thickened cervical mucus. In a non-randomised study of women with HMB the LNG-IUS reduced menstrual blood loss by 82% after three months of use, and by 97% after 12 months of use. However there was an 11% dropout rate due to bleeding problems initially (Milsom 1991). A randomised controlled trial of the LNG IUS and 21 days of norethisterone reported a 94% reduction in MBL from baseline at three months of use compared with 87% of patients taking a long (21 day) course of norethisterone (Irvine 1997). It also provides contraceptive protection, has a low infection rate and can be used as a long term solution to heavy bleeding since the duration of action is five years. Although initially there can be prolonged bleeding (although not usually heavy) the number of days of bleeding gradually decreases until 12 months when it is just one day each month (mean). Some women become anovulatory and 15% are amenorrhoeic at 12 months. After removal of the LNG-IUS menstruation returns within 30 days. The LNG IUS duration of action is 5 years.

Satisfaction with the LNG-IUS is high (93%) (Crosignani 1996). In a group of women on a waiting list for hysterectomy who were randomised to LNG-IUS or a control group which continued with existing treatment, 67% of women with LNG IUS cancelled their hysterectomy compared to only 15% of controls (Puolakka 1996).

The LNG-IUS device has only recently become available in New Zealand.

Recommendation
The levonorgestrel releasing intrauterine system is effective in reducing heavy menstrual bleeding (Grade A).

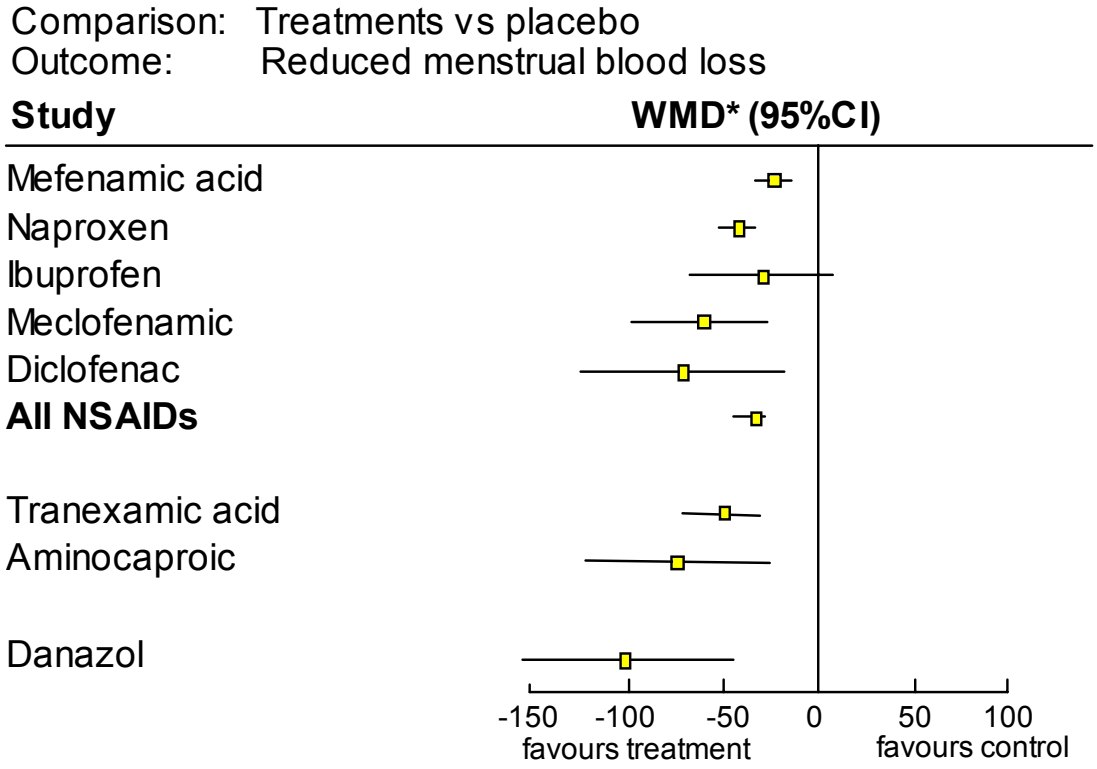
2.3.8 Meta-analysis of RCTs (placebo comparisons only)

It is clear that there are a number of different medical therapies which are effective in reducing menstrual blood loss from the patients own baseline menstrual blood loss (Coulter 1995). These assessments, however, may be influenced by time dependent confounding factors, (such as a spontaneous improvement in heavy menstrual bleeding). A proportion of the identified RCTs compared individual treatments with placebo and the remainder directly compared the efficacy of two or more treatments. A metanalysis was carried out of the trials comparing medical treatments (NSAIDs, antifibrinolytic agents and danazol) with placebo. These indicated:

1 The mean difference of menstrual blood loss for each NSAID tested (mefenamic acid, naproxen, meclofenamic acid, ibuprofen and diclofenac) was significantly different from placebo, except for ibuprofen. The mean difference ranged from -23 ml (mefenamic acid) to -74 ml (diclofenac). When all the NSAIDs were combined into one category, the weighted mean difference from placebo was 35 ml (27-43) reduced blood loss.
2 The mean difference of menstrual blood loss for the two anti-fibrinolytic agents (tranexamic acid and aminocaproic acid) was significantly different from placebo and ranged from -52 (tranexamic acid) to -75 ml (aminocaproic acid).
3 The weighted mean difference for danazol was significantly different from placebo (-108 ml) (Fig 2.I).

To conclude, the metanalysis of the proportion of RCTs which compare medical treatments with placebo indicated that, if ranked by efficacy, danazol was the most effective followed by anti-fibrinolytic agents and NSAIDs.

Figure 2.I: Meta-analysis of medical treatments for heavy menstrual bleeding (treatment vs placebo comparisons)



* Weighted mean difference

2.3.9 Side effects

Evaluation of efficacy must also take into account the incidence of side effects and acceptability of treatment. There is no evidence of an increase in incidence or severity of side effects between either the individual NSAIDs, hormone therapy or the antifibrinolytics compared to placebo. Side effects, when reported, were minimal and some studies reported an improvement in

symptoms of dysmenorrhoea for women taking NSAIDs (Vargyas 1987, Muggeridge 1983). There is, however, evidence of a greater incidence and severity of side effects in patients taking danazol (Dockeray 1989). Forty percent of the danazol patients experienced unacceptable side effects which resolved after treatment was discontinued. Side effects from danazol treatment include: weight gain, musculoskeletal pain, hot flushes, dizziness, behavioural changes, acne, tiredness, breast atrophy, hirsutism and hoarseness. Although overall patient acceptance of treatment (50% of both the danazol and mefenamic acid groups) was similar, the majority of danazol patients who refused to continue treatment did so due to adverse effects compared to the lack of efficacy in the mefenamic acid group.

Recommendation
Although danazol is highly effective in reducing menstrual blood loss, the severity of side effects and need for continuous therapy limit its usefulness. All other medical therapies have limited and well tolerated side effects (Grade A).

2.3.10 When medical therapy fails

There is some evidence that when medical therapy fails to adequately reduce MBL to acceptable levels, undetected intrauterine pathology such as submucous myomas may be present.

A retrospective study of 78 women with HMB who underwent hysteroscopic resection of submucous myomas has shown that up to 30% of women continue to have abnormal bleeding (Derman 1995). Other studies report subjectively improved periods following resection of submucous myomas in 80% of women (Brooks 1989, Cravello 1996).

2.4 Decision analysis

Decision analysis was performed to assess the relative 'value' of different medical treatments for heavy menstrual bleeding (Lethaby 1998) (Appendix 6.4). Probabilities were derived for response to treatment (reduction of MBL to <80 ml/cycle) and probability of side effects. Patient acceptability was measured by the mean values of 'utility scores' assigned by a group of 20 women with a complaint of HMB.

The LNG-IUS had the highest expected value compared to other medical therapies and was thus considered the preferred first line treatment when efficacy, side effects and patient acceptability were taken into account. The ranking of medical therapies from highest to lowest value were:

LNG-IUS
tranexamic acid
NSAIDs
progestogen therapy (21 day course)
oral contraceptive pill
danazol
progestogen therapy (luteal phase)

2.5 Surgical Management

Surgical techniques for the control of heavy menstrual bleeding include D&C, endometrial destruction (ablation and resection) and hysterectomy. When deciding about surgical options for HMB more than one outcome needs to be taken into

account. Patient satisfaction, time lost from work, relief of other symptoms (notably pain), total cost and the side effects of surgery are all important factors.

2.5.1 Dilatation & Curettage

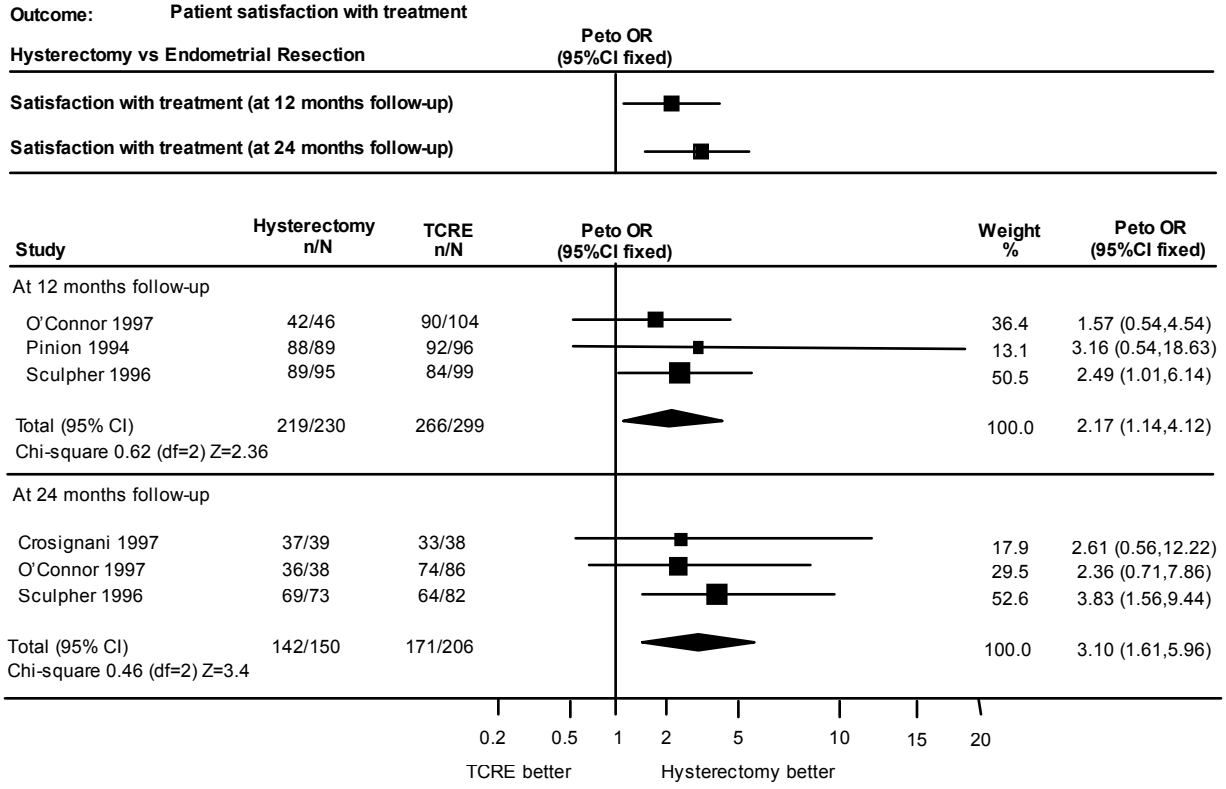
There are no published reports of RCTs of D & C against no treatment (Grimes 1982, Lewis 1993). It may have a role as a diagnostic procedure if the pipelle is unsuccessful and the TVS suggests pathology but a hysteroscopy is a better procedure. The only study to measure blood loss before and after D & C found a reduction in menstrual blood loss immediately after the procedure, but losses returned to previous levels or higher by the second menstrual period (Haynes 1977).

Recommendation
Dilatation and curettage is not effective for therapy in women with heavy menstrual bleeding (Grade B).

2.5.2 Endometrial destruction

Endometrial destruction can be performed by several different surgical techniques: cryosurgery, laser ablation, resection, roller ball and heat destruction by balloon. Five randomised controlled trials have compared hysterectomy with endometrial ablation or resection (Gannon 1991, Dwyer 1993, Sculpher 1993, Pinion 1994, Sculpher 1996, Alexander 1996, O'Connor 1997, Crosignani 1997). These trials showed that the advantages of the less invasive endometrial destruction compared with hysterectomy, especially in the short term, were: shorter operating time, fewer complications, faster rates of recovery, less need for analgesia and reduced cost (although one trial reported that at 4 years after the operation the difference in cost had narrowed to 7%) (Mollison 1997). High levels of patient satisfaction were reported for both procedures, but significantly higher for hysterectomy than resection or ablation (see Fig 2.2). Quality of life scores and improvement in menstrual symptoms were also both higher for hysterectomy patients. The disadvantage of endometrial destruction was the high rate of re-operation (either repeat resection or ablation and/or hysterectomy) ranging from 11 to 40% with the higher rates found in studies with longer follow-up.

Fig 2.2: Meta-analysis of Hysterectomy vs Transcervical resection of the endometrial (TCRE)



One RCT has compared endometrial laser ablation (ELA) with transcervical resection of the endometrium (TCRE) and found no differences in operative complications, recovery, satisfaction rates, relief of symptoms and need for further treatment (Bhattacharya 1997). Laser ablation was more costly and resection was a significantly faster procedure (additional cost of ELA $145 per procedure). At one year, there was no clear difference in clinical outcome between ELA and TCRE. Both had low morbidity and high satisfaction rates.

A newer technique involving a balloon which is inflated within the uterus and fluid heated (uterine balloon therapy) has been compared to rollerball therapy (endometrial ablation) (Loffer 1997). The rate of amenorrhoea at 6 months followup between the two treatments was similar. The uterine balloon therapy takes 15 minutes but is not suitable if submucous fibroids exist.

Recommendation
The endometrium can be destroyed with a variety of techniques but reoperation rate at 5 years may be up to 40% (with rollerball ablation) (Grade A).

Table 2.4: Summary of results in surgical trials

(RCTs comparing hysterectomy vs endometrial resection or laser ablation, n=5)

ENDOMETRIAL RESECTION OR LASER ABLATION	vs	HYSTERECTOMY
For		

- Shorter operating time (30-45 vs 45-67 mins)
- Fewer complications (0-15% vs 15-47%)
- Faster rates of recovery (2-3 weeks vs 8-11 weeks)
- Less need for analgesia (16-39% vs 99%)
- Less costly (7-70% less) depending on length of follow up
- Greater satisfaction with treatment (89-96% vs 78-85%)
- Improved quality of life (73% vs 48%)
- Greater improvement in menstrual symptoms (95-96% vs 79-90%)

Against:

- Greater probability of having repeat surgery at 2 yrs (23%) and at 4 years (40%)
- Higher complication rate
- Greater need for analgesia

No difference between the two procedures in:

- anxiety and depression present before the operation
- mental health @ 12 months after the operation
- sexual interest after the operation

2.5.3 Hysterectomy

The satisfaction rates with hysterectomy are 95% compared to a rate of 87% for endometrial destruction (see previous section). Time lost from work varies according to advice given but is reported to be at least 2 weeks longer than for endometrial destruction.

Side effects from hysterectomy are common (Table 2.5). Wound and urinary tract infections are frequent and recent reports of total post-operative complication rates range from 7 to 35% (Nathorst-Boos 1992, Raju 1994, Clarke 1995, Langebrekke 1996, Persson 1996). There is no evidence of a difference in complication rates between the 3 techniques, total abdominal hysterectomy, vaginal hysterectomy and laparoscopic assisted vaginal hysterectomy. However, for all but a small percentage of women, the symptoms of pain and bleeding and transient complications have resolved by six weeks after surgery (Clarke 1995). Some new symptoms may appear following hysterectomy, notably depression and lack of interest in sex (Carlson 1994).

Five randomized controlled trials have been identified (see Evidence Tables 3.4). Three trials compared laparoscopically assisted vaginal hysterectomy (LAVH) with total abdominal hysterectomy (TAH) and two trials compared LAVH with vaginal hysterectomy (VH). LAVH is associated with longer operating times, earlier discharge from hospital and earlier return to work. The operating costs are higher but total costs are lower when compared with TAH. LAVH also has longer operating times, similar recovery time and costs are likely to be doubled when compared with VH.

Some authors have contended that most hysterectomies could be performed vaginally; laparoscopic surgery has the disadvantages of longer operative times and increased costs (Kovac 1990, Richardson 1995).

The long term impact of hysterectomy on cardiovascular and ovarian function is often the subject of speculation but as yet is unknown.

Discussion regarding the conservation of the ovaries or cervix is beyond the scope of this Guideline.

Recommendation
Endometrial destruction techniques and vaginal hysterectomy are preferable to abdominal hysterectomy (Grade B).

Table 2.5: Early complications following abdominal or vaginal hysterectomy+*

	ABDOMINAL HYSTERECTOMY All rates (%)	**VAGINAL HYSTERECTOMY** All rates (%)
Haemorrhage		
intra op**	0.2-3.7	0.5-3.5
post op***	0.24-2.3	0.4-5.7
Infection		
unexplained fever	1.9-38	1.8-10
operative site	6.6-24.7	3.9-21
wound	16-11	N/A
pelvic	3.2-21	3.9-21
urinary tract	1.1-11	1.7-45
pneumonia	0.12-2.6	0.29-2.0
Injury		
bladder	0.2-2.3	0.3-1.5
bowel	0.1-1	0.1-0.8
ureter	0.1-1.7	0-0.1
vesicovaginal fistula	0-0.25	0.05-0.6
Thromboembolic disease	0.4-2.6	0.2-1.7

\+ Case series only, over 60 publications
* Adapted from Harris 1995, excluded studies of laparoscopic and radical and caesarean hysterectomies
** >1,000 mls
*** required further surgical intervention

2.6 Medical vs surgical therapies

Two recent RCTs have compared medical therapy with TCRE (Crosignani 1996, Cooper 1997a&b). Results from the Cooper trial have not yet been fully reported. Crosignani found that treatment of women with HMB with LNG-IUS and TCRE were equally effective and satisfaction rates similar. However, the former procedure requires less training and is less invasive and thus underscores the value of this option.

By contrast, Cooper compared the effect of medical treatment versus TCRE on treatment satisfaction and acceptability, relief of symptoms, change in haemoglobin, and an improvement in quality of life at 4 months follow up. Effect on objective blood loss was not evaluated.

TCRE had a significantly greater effect on all outcomes when compared to medical treatment, irrespective of type of medical management. A number of different drug treatments were given to those women allocated to medical therapy, but the choice of treatment was selected by experienced clinicians and not randomly allocated. Satisfaction with treatment was remarkably consistent in this group irrespective of type of drug used but the proportion satisfied was significantly lower than the proportion in the TCRE group (27% vs 76%, $p<0.001$).

3 EVIDENCE TABLES

3.1 Explanation of Evidence Tables for Investigations

Where data was available the sensitivity, specificity, pre test probability, post test probability, positive and negative likelihood ratios were included in the evidence tables. The likelihood ratios enable comparison of diagnostic values of tests in a prevalence independent way of differing populations. The likelihood ratios of a positive test result was calculated as sensitivity divided by 100 minus specificity (100-specificity). The negative likelihood ratio is calculated as 100 minus sensitivity (divided by specificity). Likelihood ratios represent a score that allows categorisation of test results. A positive likelihood ratio of 2-5 indicates a fair clinical test, 5-10 is good and above 10 is excellent. A negative likelihood ratio of .5-.2 indicates a fair clinical test, 0.2-0.1 is good, and less than 0.1 is excellent (Jaeschke 1994). Because likelihood ratios refer to an actual test result before the disease status is known they are considered to be more useful to clinicians than sensitivity and specificity. After LR ratios were calculated, if the prevalence (pretest probability) was known then post test probability was estimated using Fagan's nomogram (Fagan 1975). Positive and negative predictive values were not included because they are dependent on the disease prevalence.

		Gold Standard		
		Patient *has* the disease	Patient does *not* have the disease	
Test result (conclusion drawn from the results of the test)	**Positive**: Patient appears to *have* the disease	True positive a	False positive b	a+b
	Negative: Patient appears *not* to have the disease	False negative c	True negative d	c+d
		a+c	b+d	a+b+c+d

Stable properties (independent of the prevalence of disease)

- a/(a+c) = sensitivity = the ability of the test to detect disease
- d/(b+d) = specificity = the ability of the test to detect the disease free state
- Likelihood ratio + = sens / 100-spec
- Likelihood ratio - = 100-sens / spec

Frequency dependent properties (dependent on the disease prevalence):

- Positive predictive value (PPV) = a/(a+b) = Probability of the patient with a positive test having or developing the disease

  = post test probability (has disease)
- Negative predictive value (NPV) = d/(c+d) = Probability of the patient with a negative test not actually having or developing the disease

  = post test probability (no disease)

Prevalence = a+c/a+b+c+d

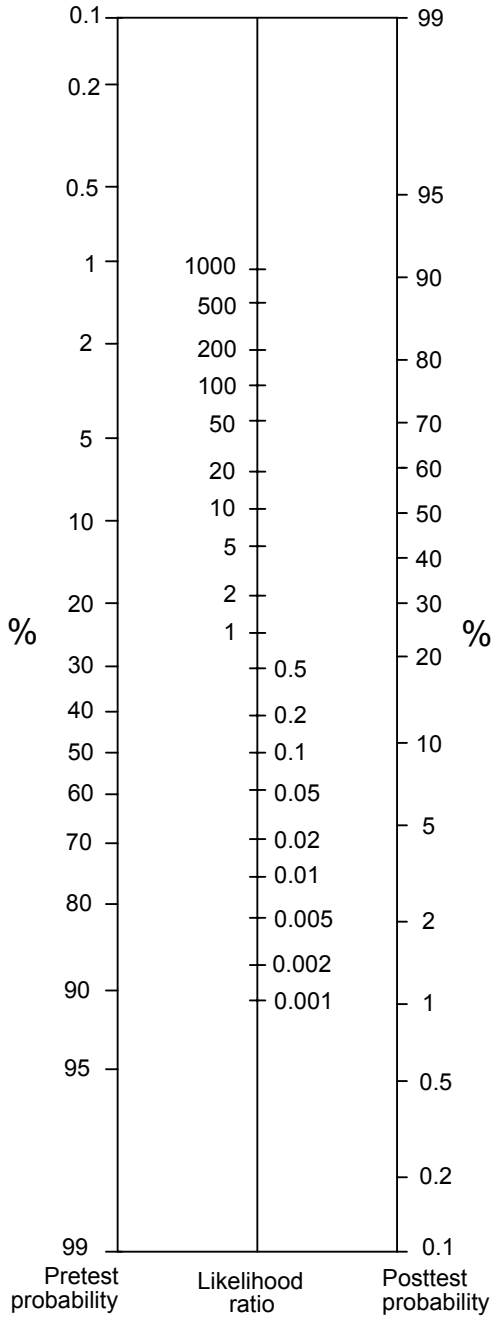
Scoring system of quality for diagnostic testing

Different blind assessors? Yes/No/DK
Prospective study? Yes/No/DK
Consecutive recruitment? Yes/No/DK

A = All 3
B = 2 of the above
C = 1 of the above
D = none

Comparative studies were excluded if the sensitivity and specificity were not reported or if there was no gold standard test.

Figure 3.1: Likelihood ratio



Reproduced from Sackett et al 1997, p 127

Table 3.1: Diagnostics

Comparative: Transvaginal ultrasound exam (TVS) and endometrial sampling (± hysteroscopy) of endometrium in premenopausal women

Author Study	Study design	Study participants	New test	Reference Test	Outcomes	Sensitivity	Spec-ificity	LR +ve	LR -ve	Pretest probab-ility	Notes
Smith 1991	Prospective Comparative Different assessors ("blind")	Premeno-pausal women n=51 mean age 44.5 yrs SD 4.5 Only 6% had abn histo-pathology	TVS	Histo-pathology from D & C Hyster-oscopy	Abnormal histology Cutoff ≥ 8 mm used	.67	.75	2.7	0.44	6%	Quality A
Fedele 1991	Prospective Comparative Assessors not 'blind'	Women 37-54 yrs n=71	TVS	Histopath ology	Submucous myomas Polyps	1.00 1.00	.94 .96	16.5 25.0	0 0	18% 8%	Quality A TVS unable to distinguish between a polyp or myoma
Dijkhuizen 1996	Prospective Comparative study "blind" assessors	Premeno-pausal women n=67	TVS	Hyster-oscopy & biopsy	5mm single hyperplastic endo layer cut off (= 10 mm double layer) All hyper-plastic endo ≥10 mm (20-24 mm) Polyps & myomas All	.100 .85 .88	.100 .62 .68	 2.8 (CI 1.66-4.55)	 0.18 (CI 0.07 - 0.46)	9% 40%	Quality A Concluded that in premeno-pausal women with irregular bleeding TVS was of limited use
Emanuel 1995	Prospective Comparative study No "blind"	Premeno-pausal women n=227	TVS	Hyster-oscopy & biopsy	Normal endo-endo thickness ≤12 mm	0.96 (0.91-0.99)	0.89 (0.83-0.94)	9.09 (5.22-15.97)	0.04 (0.01-0.10)	0.42 (0.36-0.48) (95% CI)	Quality A

Author Study	Study design	Study participants	New Test	Reference Test	Outcomes	Sensitivity	Spec-ificity	LR +ve	LR -ve	Pretest probab-ility	Notes
Scarpellini 1994	Prospective Comparative Assessors not "blind"	Premeno-pausal women n=69	TVS	Histo-pathology	Normal endo - 5-11mm prolif phase - 7-13 mm secretory phase Hyperplastic endo - 12-25 mm	.67	.79	3.1	0.29	40.5	Quality B numbers don't add up
Indman 1995	Comparative study (not prospective). Single assessor	Post & pre-menopausal women n=105 <50 yrs old	TVS	Hyster-oscopy & biopsy	Abnormal histology No cutoff for endometrial thickness stated	.94	. 89	8.5	0.06		Quality C Unable to completely separate out postmenopaus al women
Towbin et al 1996	Prospective comparative study Not "blind"	Pre menopausal women n=133 n= 65 who had either hyster-ectomy or hyster--oscopy	TVS and hyster-oscopy	Histo-pathology	Myomas were present in 34% of hyst Cutoff ≥15 mm	TVS vs biopsy .54 Hyst vs biopsy .79	.90 .93	5.4 11.2	0.51 0.22	Myomas 34%	Quality B
Bronz 1997	Prospective comparative study Assessors not "blind"	Premeno-pausal women with menor-rhagia/DUB N=83	TVS	Histo-pathology	TVS all pathol hyperplastic endo ≥8 mm benign polyps 40% submucous fibroids 26% hyperplasia 6%	.97	.22	1.24	0.13	Myomas 26% Hyperplas ia 6% Ployps 40%	Quality C
Vercellini 1997	Prospective comparitive study	Premenopaus al women with menorrhagia diagnosed by PBAC n=793	TVS Endo-metrial thickness ≥14 mm cutoff	Hyster-oscopy Histo-pathology	All intrauterine abnormalities Submucous myomas Hyperplasia	.96 .80 .98	.86 .69 .99	6.8 2.5 98	0.04 0.64 0.02	57% 30% 8.3%	Quality A

Author Study	Study design	Study participants	New Test	Reference Test	Outcomes	Sensitivity	Spec-ificity	LR +ve	LR -ve	Pretest probab-ility	Notes
Comparative: D & C vs various endometrial sampling techniques or hysteroscopy											
Ben-Baruch 1994	Comparative study	Pre and post-menopausal women n=45	Pipelle	Histo-pathology at D & C	95% agreement between pipelle & D & C	Data not suitable					Quality B
Stovall 1991	RCT	Pre and post-menopausal women n=275	Pipelle	Histo-pathology at hyster-ectomy	96% agreement	Data not suitable					Quality A
Kaunitz 1988	Comparative study	Pre and post-menopausal women n=56	Pipelle vs vabra	Histo-pathology	Endo hyper	.8	.100	80	0.2	8.9	Quality A Pipelle less painful than vabra
Rodriguez 1993	RCT	Pre and post menopausal women n=25	Pipelle vs vabra	Histo-pathology (hyster-ectomy)	Pipelle sampled 4% (0-12.3%) Vabra sampled 42% (1-79%)	.83	-	28.3	0.15	12%	Quality A
Eddowes 1990	Comparative study	Pre and post-menopausal women n=55	Pipelle	Histo-pathology at D & C	Abnormal endometrium	.85	.97	12%	28.3	.15	Quality B
Comparative: Menstrual blood loss and pictorial bleeding assessment chart (PBAC)											
Higham & Shaw 1990	Comparative study Independent assessors	Women with heavy menstrual bleeding	Pictorial bleeding assess-ment charts	Menstrual blood loss (mls)	P1	.87	.89	4	0.25		Quality A/B
FBC and MBL											
Janssen 1995	Comparative study Independent assessors	Women with heavy menstrual bleeding	FBC + PBAC	Menstrual blood loss(mls)	FBC PBAC	.74 .91	.80 .82	3.7 5.0	0.3 0.1	46%	Quality A

Table 3.2: Excluded diagnostic studies

Ultrasound vs histopathology ± hysteroscopy

Author	**Reason**
Malpani 1990	Transabdominal ultrasound only
Goldchmit 1993	Did not separate postmenopausal women from premenopausal women
Kavak 1996	Transvaginal ultrasound - 5 mm cut off

Endometrial sampling techniques

Author	**Reason**
Gimpelson 1988	Unable to calculate sensitivity and specificity
Frishman 1990	Tis-u-trap not used in New Zealand
Koonings 1990	Tis-u-Trap not used in New Zealand
Silver 1991	Novak not used in New Zealand
Fothergill 1992	No data suitable for calculating sensitivity and specificity calculations
Ferry 1993	Women all had endometrial carcinoma and had already had D & C thereby reducing tissue available to sample
Batool 1994	Postmenopausal women only
Lipscomb 1994	Accurette & Explora not used in New Zealand
Loverro 1994	Comparison of hysteroscopy vs biopsy
Litta 1996	Comparison of hysteroscopy (without biopsy) vs biopsy
Teale 1998	Did not separate pre and postmenopausal women

Table 3.3: Medical Therapy

Trial	Selection Criteria	Intervention	Outcome Measures	Duration	Results
Nilsson & Rybo (1965)	Women aged 17-50 with suspected menorrhagia. Subjective. Trial: double-blind, cross-over. Size: N=37	EACA (18g 1st 3 days, 12g day 4, 9g day 5, 6g day 6, 3g day 7) Placebo	mbl, side-effects.	2 months 0% dropout	EACA reduced mbl by 59.1% in the whole group. In a subset (N=26) of women with mbl >60ml, EACA reduced mbl by 62.9%. Side-effects: 13 when receiving EACA only, 4 when receiving placebo only and 7 with both placebo and EACA.
Nilsson & Rybo (1967)	Women aged 15-19 with suspected menorrhagia. Subjective. Trial: cross-over, double-blind. Size: N=36	Low dose tranexamic acid (250mg 4 hourly) High dose tranexamic acid (500mg 4 hourly) Placebo	mbl, side-effects.	3 months 0% dropout	Low dose of tranexamic acid reduced mbl by 38%, high dose by 51% and the placebo by 8%. Side effects: 7 in low dose group. 13 in high dose group and 8 in placebo group (mainly diarrhoea and abdominal pain).
Vermylen, Verhaegen, Declercq, Verstraete et al. (1968)	Women with a history of menorrhagia. Subjective. Trial: cross-over, double-blind. Size: N=16.	Tranexamic acid (500mg 4 hourly from day 1 till bleeding stops) Placebo	mean haemoglobin loss, pads used, side-effects.	6 months 36% dropout.	Tranexamic acid reduced mbl by 35%. No blood loss reported, just percentage. Side-effects: no difference between active and placebo groups.
Callender, Warner and Cope (1970)	Women with anaemia, complaining of menorrhagia with no abnormality. Trial: cross-over, double-blind. Size: N=16.	Tranexamic acid (500mg qds for first 4 days of period) Placebo	mbl (Oxford total body counter), duration, number of pads, side-effects.	6 months 20% dropout	Tranexamic acid reduced mbl by 36%, reduction of 6% in placebo group. Side-effects: 2 in tranexamic acid group and 2 in placebo group.
Kasonde and Bonnar (1975)	Women complaining of excessive menstrual bleeding while using IUDs. Trial: parallel group. Size: A=11, B=12.	Group A: ethamsylate (500mg qds during period). Group B: EACA (3g qds during period).	mbl.	4 months 8% dropout.	Ethamsylate reduced mbl by 7%, EACA by 50%. Side-effects: not reported.

Trial	Selection Criteria	Intervention	Outcome Measures	Duration	Results
Harrison and Campbell (1976)	Women with primary menorrhagia. IUD users also recruited. One pre-treatment control cycle. Trial: double-blind, cross-over. Size: A=9, B=13.	Ethamsylate (500mg qds five days before onset and for 10 days). Placebo Group A: primary menorrhagia Group B: IUD users.	mbl, side-effects.	4 months 29% dropout.	Ethamsylate reduced mbl by 50% in the primary menorrhagia group, 19% in the IUD group and no change for the placebo group. Side-effects: reported in 18 out of 53 ethamsylate cycles and 17 out of 50 placebo cycles - but reportedly not serious.
Irvine, Campbell-Brown, Lumsden (1997)	Women aged 30-45 with mbl >80ml. Trial: parallel group. Size: A=22, B=22	Group A: levonorgestrel (LNG) IUCD within 1st 7 days of menses Group B: norethisterone (NET) 5mg tds from day 5 to 26 of cycle.	mbl, haematologic parameters, side-effects, patient satisfaction.	3 months 18% dropout	LNG reduced mbl by 94% and norethisterone reduced mbl by 87% from baseline after 3 cycles of treatment. Side-effects: intermenstrual bleeding - LNG (53%), NET (17%) p = 0.005. All other effects, no differences between groups. 77% of LNG group and 22% of NET group wished to continue with treatment. Patient satisfaction: LNG (64%), NET (44%).
Guillebaud, Anderson & Turnbull (1978)	Healthy, parous women using IUDs. MBL measured before entry. Trial: cross-over, single blind. Size: A=15, B=10.	Mefenamic acid (500g bd from onset till bleeding ceased) and placebo Group A: mbl >80ml Group B: mbl <80ml	mbl, duration of menses, side-effects.	4 months	Group A: mefenamic acid 34% reduction; Group B: mefenamic acid 23% reduction. Side-effects: 1 indigestion, 1 headaches and dizziness (both withdrew).
Chimbira, Anderson, Naish et al (1980b)	Women referred to gynaecology outpatient clinics with mbl >60ml. Trial: single-blind. Size: A=8, B=16, C=16.	Group A: placebo Group B: danazol (200mg od for 12 weeks) Group C: danazol (100mg od for 12 weeks).	mbl, duration, side-effects.	5 months 0% dropout	200mg of danazol reduced mbl by 86%, 100mg of danazol reduced mbl by 75% and no change for the placebo group. Side-effects: tiredness 5, musculoskeletal pain 4, skin rashes 3, headaches 6, irritability 3, vaginitis 3, average weight gain 2.3kg.

Trial	Selection Criteria	Intervention	Outcome Measures	Duration	Results
Davies, Anderson and Turnbull (1981)	Women using IUDs and mbl >80ml Trial: double-blind, cross-over. Size: N=34	High dose: naproxen (500mg bd, plus 250mg od for 5 days) Low dose: naproxen (500mg loading dose then 250mg tds for 5 days).	mbl, pads & tampons used, intensity of bleeding, assessment of drug effect, side-effects	4 months 29% dropout	High dose reduced mbl by 32%, low dose reduced mbl by 22%. Side-effects: no adverse reactions to naproxen, 1 patient with nausea/vomiting.
Fraser, Pearse, Shearman (1981)	Women with convincing history of menorrhagia, enrolled through radio/tv discussion. Subjective. No pre-treatment control cycles. Trial: cross-over, double-blind. Size: A=30, B=39, C=14	Mefenamic acid (500mg tds) during period and placebo. Group A: >80ml Group B: <80ml Group C: <35ml	mbl, menstrual symptoms, pain, pad and tampon usage, side-effects.	4 months (2 months each) 19% dropout	Mefenamic acid gave 28% reduction in mbl for all women, 30% for >80ml, 19% for <80ml. Side-effects: no significant differences between mefenamic acid and placebo.
Roy and Shaw (1981)	Healthy volunteers who had used IUD for at least 5 months with no side-effects. Subjective. One pre-treatment control cycle. Trial: double-blind, cross-over. Size: N=20	Ibuprofen (400mg qds) Placebo	mbl.	2 months 0% dropout.	Overall percentage reduction in mbl 32% for ibuprofen and 6% increase for the placebo group. Mean values not given. Side-effects: 2 on ibuprofen (swelling around eyes and mouth & mild stomach cramps), 2 on placebo (mild stomach cramps & nausea headaches and dizziness).
Rybo, Nilsson, Sikstrom and Nygren (1981)	Women with primary menorrhagia. Women without primary menorrhagia were fitted with IUD. Trial: double-blind, cross-over. Size: A=4, B=5, C=5	Naproxen (500mg in morning, then 250mg in afternoon for 2 days, then 250mg bd for up to 7 days). Placebo Group A: primary menorrhagia Group B: IUD & mbl >80ml Group C: IUD & mbl <80ml.	mbl.	4 months 0% dropout	In primary menorrhagia group naproxen reduced mbl by 24%. Group with IUD & >80ml mbl reduced by 38% and IUD group with mbl <80ml reduced by 9%, reduction in placebo of 2-4%. Side-effects: not reported.
Muggeridge & Elder (1983)	Women with mbl >75ml. Trial: cross-over, double-blind. Size: N=15.	Mefenamic acid (500g tds started at onset of period) and placebo	mbl, dysmenorrhoea	4 months (2 months each) 25% dropout	Mefenamic acid 30% reduction, placebo 12% reduction. Side-effects: incidence low, no difference between groups.

Trial	Selection Criteria	Intervention	Outcome Measures	Duration	Results
Ylikorkala & Viinikka (1983)	Women with IUDs and mbl >70ml. Trial: cross-over, double blind. Size: N=19	Tranexamic acid (1.5g tds for 5 days) Diclofenac sodium (50mg tds day 1 and 25mg tds for 4 days).	mbl, duration, intermenstrual bleeding, side-effects, restricted activity, pelvic pain, subjective assessment.	5 months 10% dropout	Tranexamic acid reduced mbl by 56%, diclofenac sodium by 24%. Side-effects: 12 women in tranexamic acid group, 5 in diclofenac sodium group.
Makarainen and Ylikorkala (1986)	Women complaining of excessive menstrual bleeding and primary menorrhagia over 70ml mbl. No pre-treatment control cycle. Trial: double-blind, cross-over. Size: N=13	High dose: Ibuprofen (400mg tds) Low dose: Ibuprofen (200mg tds) Placebo	mbl, duration, pain, side-effects.	3 and 6 months 23% dropout	High dose ibuprofen reduced by 25% and low dose by 16%. Side-effects: 5 on high dose, 6 on low dose, included headache, dizziness, nausea, diarrhoea and dyspepsia on high dose.
Ylikorkala and Pekonen (1986)	Women with mean mbl >80ml. Trial: double-blind, cross-over. Size: N=14	Naproxen (250mg qds for days 1 - 5 of cycle). Placebo	mbl, duration, side-effects.	4 months 0% dropout	Naproxen reduced mbl by 36% and 11% increase in mbl for the placebo group. Side-effects: 1 patient on placebo showed mild side-effects, but none on naproxen.
Cameron, Leask, Kelly and Baird (1987b) and Cameron (1989)	Women with mbl >50ml. Trial: random allocation Size: A=6, B=8, C=8, D=8	Group A: danazol (200mg od) Group B: mefenamic acid (500mg tds for days 1-5 of period) Group C: norethisterone (5mg bd from day 15-25 of cycle) Group D: progestasert coil (releasing 65ug progesterone daily).	mbl prostaglandin measurement.	2 months 0% dropout	Danazol reduced mbl by 71%, mefenamic acid by 25%, norethisterone increased mbl by 12% and progestasert coil reduced mbl by 23%. Side-effects: not reported.

Trial	Selection Criteria	Intervention	Outcome Measures	Duration	Results
Hall, MacLachlan, Thorn (1987)	Women with dysfunctional uterine bleeding. MBL measured before entry. Trial: cross-over, double-dummy. Size: A=18, B=18.	Group A: naproxen sodium (550mg initially then 275mg qds for 5 days) then mefenamic acid (500mg tds) Group B: mefenamic acid then naproxen sodium.	mbl, patient and doctor preferences, side-effects.	4 months 15% dropout	Mefenamic acid gave 46% reduction and naproxen sodium gave 47% reduction in mbl. Side-effects: Gastrointestinal (nausea, diarrhoea, abdominal discomfort and anorexia) - 13 naproxen sodium, 6 mefenamic acid. Central nervous system (light-headedness, dizziness, tiredness and headache) - 6 mefenamic, 5 naproxen sodium.
Tsang, Domingo and Spence (1987)	Women with symptomatic menorrhagia Trial: double-blind crossover Size: N=14	Mefenamic acid (500mg initially then 250mg qds for 3-5 days), Placebo	mbl	29% dropout	Reduction in mbl (plo.05) in 80% of patients during mefenamic acid treated cycles compared to combined nontreatment and placebo cycles
Vargyas, Campeau and Mishell (1987)	Women aged 16-42 with mbl >60ml. Trial: double-blind, cross-over. Size: N=29	Meclofenamate sodium (100mg tds for 6 days or until bleeding ceased) Placebo	mbl, duration, dysmenorrhoea, side-effects, pads & tampons used.	4 months 9% dropout	Meclofenamate sodium reduced mbl by 49%: a 4% reduction for the placebo group. Side-effects: dysmenorrhoea, backache, headache less severe on active drug. Nausea and vomiting no difference between groups.
Dockeray, Shephard, Bonnar (1989)	Women with mbl >80ml. Trial: not clear if blinded Size: A=19, B=20.	Group A: mefenamic acid (500mg tds for 3-5 days beginning at period) Group B: danazol (100mg bd for 60 days beginning last day of period).	mbl, dysmenorrhoea side-effects, patient acceptability.	2 months 3% dropout	Mefenamic acid reduced mbl by 22% and danazol reduced mbl by 56%. Side-effects: mefenamic acid had 11 events; danazol had 51 events.
Cameron, Haining, Lumsden (1990)	Women with mbl >80ml. Trial: parallel group. Size: A=17, B=15.	Group A: mefenamic acid (500mg tds on days 1-5 of period) Group B: norethisterone (5mg bd on days 19-26 of cycle)	mbl, duration, side-effects.	2 months 0% dropout	Mefenamic acid gave 24% reduction, norethisterone gave 20% reduction. Side-effects: 10 in mefenamic acid group, 11 in norethisterone group including headache, abdominal pain and nausea.

Trial	Selection Criteria	Intervention	Outcome Measures	Duration	Results
Chamberlain, Freeman, Price (1991)	Women aged 18-55, with regular cycles and mbl >80ml. Trial: double-dummy, double-blind, allocation by minimization. Size: A=16, B=18.	Group A: ethamsylate (500mg 4 qds during period) Group B: mefenamic acid (500mg tds during period).	mbl, side-effects.	4 months 23% dropout	Ethamsylate reduced mbl by 20%, mefenamic acid by 24%. Side-effects: 5 in ethamsylate group, 10 in mefenamic acid group (abdominal discomfort, headache being the most frequently observed).
Fraser & McCarron (1991)	Women with convincing clinical history of menorrhagia. Trial: cross-over (2 drugs each), not blinded Size: A=15, B=15, C=15.	Group A: mefenamic acid and naproxen (500mg, 250mg for 5 days) Group B: mefenamic acid and oral contraception (low dose od 21 days) Group C: mefenamic acid and danazol (200mg od from day 5 of cycle) All groups: mefenamic acid 500mg tds or qds on days 1 to maximum of 5.	mbl	6 months 16% dropout	Overall mbl reduced by 31% on mefenamic acid, 12% on naproxen, 43% on oral contraceptives and 50% on danazol. Side-effects: not reported.
Ingemanson Sikstrom, Rybo and Bjorkman (1991)	Women using IUDs and mbl >80ml. Trial: double-blind, cross-over. Size: N=9	Diclofenac (50mg tds for 5 days of period) Placebo	mbl, duration, subjective assessment, side effects.	4 months 0% dropout	Diclofenac reduced mbl by 29% and a 4% reduction for the placebo group. Side-effects: None attributed to diclofenac.
Milsom, Andersson, Andersch and Rybo (1991)	Women aged 34-49 with mbl >80ml and no pelvic pathology. Trial: First 20 women given IUD, next 15 randomised to cross-over design. Size: IUD=16, drugs=15.	IUD Group: Levonorgestrel IUD (release rate of 20ug per day) Drugs Group: Flubriprofen (100mg bd for 5 days) cross-over with : Tranexamic acid (1.5g tds for days 1-3, then 1g bd for days 4 and 5).	mbl, side-effects.	4 months 11% dropout (from IUD group)	IUD group: at 3 months 82% reduction, at 6 months 88% reduction and at 12 months 96% reduction in mbl. Drugs: Flurbiprofen reduced mbl by 21% and tranexamic acid by 44%. Side-effects: 7 tranexamic acid, 4 flurbiprofen.

Trial	Selection Criteria	Intervention	Outcome Measures	Duration	Results
Van Eijkeren, Christiaens Geuze (1992)	Women under 45 years, scheduled for hysterectomy, mbl >80ml. One pre-treatment control cycle. Trial: double-blind Size: A=6, B=5	Group A: mefenamic acid (500mg tds taken from 5 days before the period until bleeding ceases) Group B: placebo. Hysterectomy during second menstruation.	mbl	2 months 42% dropout	Mefenamic acid 40% reduction vs. 25% increase in mbl for placebo group. Side-effects: mefenamic acid - 1 stomach pains, 2 itching. placebo - 1 headache, 1 itching.
Higham and Shaw (1993)	Women aged 20-50 with proven menorrhagia. Trial: single-blind. Size: A=17, B=19, C=18.	Group A: danazol (dose reduced each cycle - 200mg, 100mg, 50mg od) Group B: danazol (200mg od) Group C: Norethindrone (5mg tds days 19-26).	mbl, duration, interval between cycles, dysmenorrhoea subjective assessment, side-effects.	3 months (4 months after treatment) 24% dropout	Danazol reduced mbl by 28% on the reducing dose and by 40% on the 200mg dose. Side-effects: 15 women on reducing dose, 17 on 200mg dose, 11 on norethindrone
Edlund, Andersson Rybo (1995)	Women > 18 years with mbl >80ml and regular menstrual cycles. Trial: double-blind, parallel group. Size: A=26, B=27, C=14	Group A: KABI (1200mg bd days 1-5) Group B: KABI (600mg qds days 1-5) Group C: Placebo	mbl, duration, patient estimation of mbl, number of sanitary pads, side effects.	5 months 25% dropout	KABI (1200mg dose) reduced mbl by 41%, KABI (600mg dose) reduced mbl by 33% and there was no reduction with placebo. In groups A and B there was a significant reduction in estimated blood loss and number of pads used compared to placebo. Side-effects: no differences found between run in period and treatment periods
Preston, Cameron, Adams and Smith (1995)	Patients complaining of menorrhagia with actual mbl >80ml. Trial: double-blind. Size: A=25, B=21	Group A: tranexamic acid (1g qds days 1-4). Group B: norethisterone (5mg bd on days 19-26).	mbl, subjective assessment, side-effects	2 months 9% dropout.	Tranexamic acid reduced mbl by 45%, norethisterone increased mbl by 20%. Side-effects: 8 headaches & 3 GI on tranexamic acid, 10 headache & 7 GI on norethisterone.
Bonnar & Sheppard (1996)	Women with mbl >80ml. Trial: double-blind. Size: A=27, B=25, C=29.	Treatment for 5 days during cycle Group A: tranexamic acid (1g qds) Group B: mefenamic acid (500mg tds) Group C: ethamsylate (500mg qds)	mbl, side-effects.	3 months 27% dropout	Group A: 54% reduction in mbl; Group B: 20% reduction in mbl; Group C: 0% reduction in mbl. Side-effects: A=4, B=5, C=13.

Trial	Selection Criteria	Intervention	Outcome Measures	Duration	Results
Puolakka, Nilsson, Haukkamoa (1996)	Women aged less than 50 years and awaiting hysterectomy for menorrhagia. Trial: randomised parallel group. Size: A=27, B-27	Group A: levonorgestrel (LNG) intrauterine system (IUS) (20 pg/24h) Group B: unspecified medical treatment (control)	acceptability, tolerability, patient wellbeing (visual analogue scales), side effects	6 months 0% dropout	Two thirds (67%) of patients with LNG IUS cancelled their planned hysterectomy because of satisfaction with treatment compared to 15% of controls. In the LNG IUS group 70% found the treatment 'tolerable' compared to 19% in controls. The LNG IUS group had significantly more beneficial effects on patients wellbeing, work performance, physical activity, other leisure time activities and sexual activity than the other treatments (visual analogue scales). There were no differences in side effects between the two groups.

Key:
mbl = menstrual blood loss
od = once a day
bd = twice a day
tds = three times daily
qds = for times daily
ug = micrograms
GI = Gastro-intestinal
Note: All trials included at least 2 pre-treatment control cycles except if otherwise indicated.

Table 3.4: Surgical Therapy

Study	Selection Criteria	Outcome Measures	Follow-up	Results
Gannon, Holt and Fairbank (1991)	Women aged 29-51 (median of 40) awaiting abdominal hysterectomy for menorrhagia at the Royal Berkshire Hospital Reading. Found suitable after history, physical examination and pelvic ultra-sonography with a vaginal probe. Exclusions: women known to have leiomyomata, endometrial or cervical neoplasia, concomitant ovarian pathology, pelvic inflammatory disease or endometriosis. 51 of 78 women without pelvic pathology on the waiting list and consenting to participate, allocated at random to 2 groups: A: abdominal hysterectomy = 26 B: endometrial resection = 25	Requirement for analgesia; complications; post-operative recovery time; menstrual status. Diary record of symptoms after discharge from hospital, noting first day without analgesic drugs, date felt fit to return to work. Women requiring hysterectomy or a repeat hysteroscopic procedure.	9-16 months with a mean of 12 months. Loss to follow-up: not reported.	Recovery after endometrial resection was substantially shorter (median 16 days) than for hysterectomy (median 58 days). 12 women (46%) in the hysterectomy group had complications and none of the women who had endometrial resection. 4 (16%) of the women who had endometrial resection required any post-operative analgesia. 4 women (16%) had repeat resections; no woman required a hysterectomy within the mean follow-up of one year. The mean theatre and ward cost for endometrial resection was 407 and 1270 for hysterectomy. Authors point to the need for larger numbers and longer follow-up to estimate complications and long term efficacy of endometrial resection.
Dwyer Hutton and Stirratt (1993) Sculpher (1993) Sculpher (1996)	Women aged under 52 (mean of 40) complaining of menorrhagia which could not be controlled by conservative means and who were candidates for hysterectomy, attending the gynaecological department of Bristol's teaching hospital. Exclusions: women with uterine size >12 weeks, additional symptoms or other pathology made hysterectomy the preferred treatment. A histological assessment of the endometrium was undertaken if hyperplasia due to anovulatory menstruation was suspected. 196 of 216 women found suitable and agreeing to participate,	Requirement for analgesia; complications; post-operative recovery time; menstrual status; sexual activity; psychiatric morbidity using the 60 item General Health Questionnaire (GHQ). Self-recording of degree of pain each day for a week; booklet recording post-operative problems, amount and duration of vaginal bleeding, date of return to work and normal daily activities. Failure rate of endometrial resection as assessed by the number of women not satisfied or who had severe synechiae. Degree of satisfaction with their	4 months, with a 2% drop-out rate. 69% completed the EuroQol health questionnaire sent at 4 months after the operation. At an average of 2.2 years, lost to follow-up: Group A: 25% Group B: 17%	Post-operative morbidity, length of stay and time taken to return to work, normal daily activities and sexual intercourse were significantly lower in the endometrial group. Premenstrual symptoms, symptoms of dysmenorrhoea, bloating and breast tenderness were less frequent after hysterectomy. After endometrial resection, 13 women were amenorrhoeic while 76 had hypo-menorrhoea. 46 (47%) of the women having a hysterectomy had complications compared to 4 (4%) of those having an endometrial resection. Only 1 woman having a hysterectomy did not require analgesia for post-operative pain compared to 39 of

Study	Selection Criteria	Outcome Measures	Follow-up	Results
	allocated at random to 2 groups: A: abdominal hysterectomy = 97 B: endometrial resection = 99 Note: 43 (44%) in group A vs 34 (34%) in group B had pre-intervention GHQ scores of 12 or more.	operation 4 months and 2.8yrs after operation. Restricted version of the EuroQol health questionnaire, completed a minimum of 4 months after the operation; asking the women to value their health on average one month prior to and 2 weeks after the operation and at the time of completing the questionnaire. Short Form-36 as part of longer term follow-up together with the EuroQol and assessment of menstrual symptoms. Total health care cost of managing the women until 4 months after their operation and longer term at a mean of 2.8 yrs after their operation.		the endometrial resection group. After 4 months, there was a statistically significant difference in satisfaction in favour of hysterectomy with 94% (vs 85%) being very satisfied or satisfied with the results of their treatment and no statistical difference in EuroQol scores. At 2.8 yrs, satisfaction in favour of hysterectomy was 96% vs 79% (p=0.002) Hysterectomy patients: 23% no improvement in menstrual symptoms and 4% time off work due to menstrual symptoms, Endometrial resection patients: 57% and 23% respectively. Hysterectomy patients had better mean scores on quality of lie (p=0.001) but there was no statistical difference in EroQol scores. The mean total cost of resection was 53% of the cost of hysterectomy at 4 months. This increased to 71% at a mean overall follow up of 2.2 yrs but this difference was still statistically significant (p = 0.0001).
Pinion, Parkin and Abramovich (1994) Alexander, Naji, Pinion et al (1996)	Women attending general gynaecological clinics at Aberdeen's teaching hospital, aged under 50, weighing under 100kg, with a clinical diagnosis of dysfunctional uterine bleeding (uterus less than size of a pregnancy of 10 weeks, and normal endometrial history) and who would otherwise have undergone a hysterectomy. 204 women allocated at random to 3 groups: A: hysterectomy = 99 B: endometrial laser ablation = 53 C: transcervical resection of endometrium = 52	Requirement of analgesia; complications; post-operative recovery time; menstrual status; urinary, incontinence, premenstrual and menopausal symptoms and dyspareunia. Woman's grading of heaviness and pain for each day of the period. Patient satisfaction - how does your health compare with that a year ago? what effect has the operation had on symptoms? how satisfied are you with the effect of treatment. Women requiring hysterectomy or a repeat hysteroscopic procedure.	12 months Non-attenders for follow-up: At 1 month: 5% At 6 months: 12% At 12 months: 9%	Women treated by hysteroscopic surgery had less morbidity and a significantly shorter recovery period than those treated by hysterectomy. Five women in the hysterectomy group had major complications, 2 from the anaesthesia, 1 from intra-abdominal bleeding and 2 pelvic abscesses. One woman given laser ablation had a small bowel obstruction. 16% of the women in the hysteroscopic group had had a hysterectomy 12 months later; 10% a repeat hysteroscopic procedure; 43% were amenorrhoeic or had only a brown discharge and 33% light periods.

Study	Selection Criteria	Outcome Measures	Follow-up	Results
	Note: study focuses on a comparison between hysterectomy and hysteroscopic surgery as insufficient power to explore for differences between laser ablation and endometrial resection.	Date collected before randomisation and at 1.6 and 12 months after treatment. Mental state, marital relationship, psychosocial and sexual adjustment in assessments conducted before the operation and one month, 6 months and 12 months later.		After 12 months, 89% of the hysterectomy group (and 78% of the hysteroscopic group) were very satisfied with the effect of surgery; 95% (90%) thought there had been an acceptable improvement in symptoms; 73% (48%) indicated that their health was much better than a year before. Both hysterectomy and hysteroscopic surgery significantly reduced the anxiety and depression present before the operation, and there were no differences in mental health between the groups at 12 months. Sexual interest after the operation did not vary with treatment. Overall, 46 out of 185 (25%) women reported a loss of sexual interest and 50 out of 185 (27%) reported increased sexual interest. Marital relationships were unaffected.
O'Connor, Broadbent, Magos et al (1997)	Women with symptomatic menorrhagia in several centres in the UK, age 30-50 with regular cycles and normal endometrial histology and cervical smear. Trial: parallel group Size: N=202 Randomised in a ration of 2: 1 Group A: transcervical resection of the endometrium or laser endometrial ablation = 116 Group B: abdominal hysterectomy = 56	Patient satisfaction with the results of RX; avoidance of further gynaecological surgery. Also, operative and post-operative complications, duration of hospital stay, time taken to return to normal activities/work, other symptoms, use of primary-health-care services, psychiatric and social states.	3 yrs Initial dropout: Grp A: 11% Grp B: 16% At 3 mths: Grp A: 2% Grp B: 2% At 1 yr: Grp A: 10% Grp B: 18% At 2 yrs: Grp A: 17% Grp B: 17% At 3 yrs: Grp A: 37% Grp B: 26%	Satisfaction scores were higher for hysterectomy than for TCRE throughout follow-up (median 2yrs) but the differences were not significant (at 3 yrs, 27 of 28 (96%) in hysterectomy group vs 46 of 54 (85%) in TCRE group were satisfied (p = 0.16%)). 25 (22%) women in the TCRE group and 5 (9%) in the hysterectomy group required further surgery (relative risk 0.46 [95% CI 0.2 - 1.1], p = 0.053). TRCE had shorter operating time, fewer complications and faster rates of recovery.
Bhattacharya, Cameron, Parkin et al (1997) extension of previous 1994 Pinion study	See selection criteria for Pinion (1994) study. An additional 267 women were recruited, so a total of 372 eligible women were randomly allocated to 2 groups. A: endometrial laser ablation (ELA) = 188	Operative complications, post-operative recovery, relief of menstrual and other symptoms, need for further surgical treatment, satisfaction with treatment after 6 to 12 months, and differential resource use.	12 months Loss to follow-up: At 6 months: 11% At 12 months: 14%	TCRE was significantly quicker with lower rates of fluid overload. Perioperative morbidity was low and similar in both groups and outcome at 12 months was similar : 45% in the ELA group and 49% in the TCRE group had amenorrhoea. 16% vs 20% had received further

Study	Selection Criteria	Outcome Measures	Follow-up	Results
	B: transcervical resection of the endometrium (TCRE) = 184			surgical treatment. Anxiety and depression, dysmenorrhoea and pre-menstrual symptoms were improved by both procedures and bladder symptoms were affected by neither. At 12 months, 90% in the ELA group and 91% in the TCRE group were satisfied with their treatment. The estimated additional cost of ELA was □145 per procedure
Crosignani, Vercellini, Apoloni et al (1997)	Women with menorrhagia not responding to medical treatment and requiring hysterectomy from a third-level outpatient clinic Exclusions: evidence of atypical hyperplasia, adnexal tumours, positive cervical smear, uterus with volume >12 wk pregnancy, PID or endometriosis, urinary stress incontinence, genital prolapse, clotting disorders, IUD, unstable general conditions, sub-mucous myomas >3cm in diameter or >50% intramural extension. 92 of 118 eligible women were allocated at random to 2 groups: A: vaginal hysterectomy = 44 B: endometrial resection = 41	Patient satisfaction with treatment, health-related quality of life, psychological status, sexual functioning	2 years	87% of patients undergoing TCRE were satisfied with their treatment compared to 95% of hysterectomy patients. Social functioning and vitality scores (within SF-36 scale) were significantly better in the hysterectomy group than in the resection group. Significantly lower hospital anxiety and depression scale anxiety scores were observed in TCRE than in hysterectomy patients. The Sabbatsberg Sexual Rating Scale scores were similar in the 2 groups.

Table 3.5: Medical vs Surgical Therapy

Study	Selection Criteria	Outcome Measures	Follow-up	Results
Crosignani, Vercellini, Oldani et al (1996)	Premenopausal women with menorrhagia, not wanting children, with normal findings at hysteroscopy and endometrial biopsy at Obstetrics & Gynecology Clinic at University of Milan. Exclusions: women with intramural or subserous uterine leiomyomas of > 3cm in diameter or adnexal abnormalities at ultrasonography 60 of 70 eligible women were allocated at random to 2 groups: A: Lng-IUD = 30 B: Endometrial resection = 30	mbl (measured by PBAC pictorial chart), patient satisfaction.	12 months Loss to follow-up: not reported.	In the LNG-IUD group, the baseline and 12 month follow-up mean ISD PBAC scores were 181 $\pm$ 59 and 39 $\pm$ 37. In the endometrial resection group, these scores were 204 $\pm$ 83 and 23 $\pm$ 33 respectively. The menstrual pattern at 12 months in women with a LNG-IUD was amenorrhoea in 4 (13%) cases, hypomenorrhoea or spotting in 16 (53%) cases, eumenorrhoea in 8 (27%) cases versus, respectively, 6 (20%), 16 (63%), 7 (23%) and 1 (3%) for those who underwent endometrial resection. In all, 11 (37%) subjects from the former group and 12 (40%) from the latter were very satisfied with their treatment, 17 (56%) and 18 (60%) were satisfied and 2 (7%) were uncertain in the IUD group.
Cooper, Parkin, Garratt et al (1997)	Premenopausal women with menorrhagia attending general gynaecology clinics. 187 eligible women allocated at random to 2 groups: A: Medical therapy = 94 B: TCRE = 93	SF-36 scores, treatment satisfaction, treatment acceptability, relief of symptoms, change in haemoglobin	4 months Loss to follow-up: 0.5%	The TCRE group was more likely to be satisfied ($p < 0.001$), find the treatment acceptable ($p < 0.001$). Relief of symptoms was also greater in this group ($p < 0.001$) and haemoglobin levels significantly increased. SF - 36 scores improved in both groups but only TCRE returned them to normal values.

Table 3.6: Method of Hysterectomy

Study	Selection Criteria	Outcome Measures	Follow-up	Results
Summitt & Stovall et al 1992	Women aged 18 - 65 years selected as suitable for VH then randomised to VH (n=24) LAVH (n=29). Uterine size <16/40 (32/56 had fibroids and contraindications). Trial: parallel group. Preop antibiotics given.	Complication rate Operating time Hospital stay Analgesia Cost	Day 2	Mean operating time for LAVH 122 mins and for VH 65 mins. Mean blood loss for LAVH was 2093 mls and for VH 376 mls. No difference in uterine weight No significant intraoperative complications occurred in either group. Post op complications: 2 in LAVH group (laceration of inferior epigastric artery, bladder injury) VH - nil Cost: LAVH - US$7905 VH - US$4891
Phipps, John and Nayak 1993	LAVH + BSO vs TAH + BSO Trail: parallel group Women allocated at random to 2 groups Women age 30 - 50 Uterine size <8/40 LAVH n=24 TAH n=29 17 in LAVH group had HMB or fibroids 20 in TAH group had HMB or fibroids	Operating times Complication rates Narcotic analgesia Inpatient stay	6 weeks	LAVH had longer operating time than TAH (65 vs 30 mins) Length of stay was reduced in LAVH (2 days) than in TAH (6 days). Reduced requirement for narcotics in LAVH group compared to TAH. Earlier return to work with LAVH (2 - 4 weeks) and TAH (5 - 7 weeks)
Raju & Auld, 1994	LAVH & BSO and TAH & BSO Uterine size <14/40 Trial: parallel group 80 women randomised to 2 groups Aged: 30 - 55 LAVH & BSO n=40 TAH & BSO n=40 28 in each group for HMB	Operating time Hospital stay Analgesia Complication rate	6 weeks	Mean operative time for LAVH 100 mins compared to TAH 57. Post op stay for LAVH 3 - 5 days and TAH 6 days. Recovery for LAVH 13 and TAH 26 days. Return to work for LAVH 21 days and for TAH 42 days.

Study	Selection Criteria	Outcome Measures	Follow-up	Results
Richardson, Bounas & Magos, 1995	LAVH and VH Uterine size <16 weeks Trial: parallel group Women randomised to 2 groups Women aged 27 - 68 years old LAVH n=22 VH n=23 16 in each group had HMB or fibroids	Operating times Complication rates Narcotic analgesia Inpatient stay Discomfort Return to normal activities 1 week	6 - 8 weeks	LAVH had longer operating time than VH (131 min vs 77 min). Complication rates (36% LAVH and 30% VH) Blood loss, analgesia requirements and recovery was similar for both procedures.
Langebrekke, Eraker, Nesheim et al 1996	LAVH vs TAH Trial: parallel group 100 women randomised to 2 groups Age : not stated LAVH n=46 TAH n=54	Operating time Complication rate Analgesia In patient stay Return to work		LAVH had a longer operating time of 100 mins vs TAH of 60 mins. Length of stay was reduced in LAVH (2 days) compared to TAH (5 days) Return to work for LAVH was shorter (19.5 days) than TAH (36.5 days). No difference in complication rate.

LAVH = Laparoscopically assisted vaginal hysterectomy
VH = Vaginal hysterectomy
TAH = Total abdominal hysterectomy
BSO = Bilateral salpingoopherectomy

Table 3.7: Comparative results of the five surgical randomised controlled trials: Hysterectomy vs Endometrial Resection

STUDY	Reading study (Gannon 1991)		Bristol study (Dwyer 1993)		Aberdeen study (Pinion 1994)		London study (O'Connor 1997)		Italian study (Crosignani 19??)*	
TREATMENT	Abdominal hysterectomy	Endometrial resection	Abdominal hysterectomy	Endometrial resection	Abdominal hysterectomy	Endometrial ablation or resection	Abdominal or vaginal hysterectomy	Endometrial resection	Vaginal hysterectomy	Endometrial resection
Study size	26	25	97	99	99	105	56	116	44	41
Followup time	av 12 mth	av 12 mth	av 2.8 yrs	av 2.8 yrs	12 mth	12 mth	av 2 yrs	av 2 yrs	2 yrs	2 yrs
Process of care:										
operating time (median	50	30	45	35	61	45 (mean)	67 (mean)	32 (mean)	71	13
mins)	7	1	6	2	7	3 (mean)	6 (mean	1 (mean)	5	1
length of stay (median days)	46%	0%	47%	4%	47%	15%	32%	13%	2%	0%
Post-op complications	1	0	-	-	1-2	<1	-	-	-	-
Duration of analgesia (median										
weeks)	-	-	14%	82%	-	-	-	-	-	-
No pain at 7 days	8	2-3	4	1	8-12	2-4	4-8	2-3	4	2
Time to resume activities										
(median wks)										
Menstrual outcomes:	100%	64%	100%	13%	100%	22%	100%	21%	100%	23%
no bleeding	-	-	-	70%	-	62%	-	-	-	40%
light bleeding	-	-	19%	64%	-	-	-	-	-	-
menstrual pain	-	-	6%	-	13%	-	-	-	-	-
Pelvic pain										
Emotional outcomes:	-	-	25%	8%	26%	29%	-	-	-	-
GHQ score <25%										
Satisfaction:	-		96%	79%	99	96%	96%	85%	95%	87%
satisfied with improvement	-	16% (12mth)	4%	21%	5%	6%	-	-	-	-
insufficient improvement	-	16% (12mth)	-	11% (4 mth)	-	27% (12 mth)	9% (2 yrs)	22% (2 yrs)	-	10%
Re-operation rate				23% (2 yrs)						

* The only comparison of vaginal hysterectomy vs TCRE

Table 3.8: Comparative results of the five surgical randomised controlled trials on total abdominal hysterectomy (TAH) vs laparoscopically assisted vaginal hysterectomy (LAVH) and vaginal hysterectomy vs TAH

STUDY	**Summit et al 1992**		**Raja et al 1994**		**Richardson et al 1995**		**Langebrekke et al 1996**		**Phipps et al 1993**	
TREATMENT	LAVH	VH	LAVH + BSO	TAH + BSO	LAVH	VH	LAVH	TAH	LAVH + BSO	TAH + BSO
Study size	29	27	40	40	22	23	46	54	24	29
Uterine size (wks gestation)	<16	< 16	<14	< 14	<16	<16	< 12	<12	<8	< 8
Followup time (weeks)	6	6	6	6	6	6			6	6
Mean operating time (mins)	120	65	100 (median)	57	131	77	100	61	65	30
Mean blood loss (mls)	204	376	260	220	272	181				
Mean length of hospital stay (days)	-	-	3.5	6	3.2	3.3	2	5	2	6
Mean time to return to work (weeks)	-	-	3	6	6.4	5.7	2.5	5.2	2	6
Postoperative complications	3%	7%	-	-	36%	30%	25%	35%	0%	0%
Mean hospital cost	$7,905	$4,891	£1,260	£1,750						

4 IMPLEMENTATION

4.1 Driving forces. There are a number of driving forces that will assist the implementation of this Guideline. These will include the following; patient and practitioner demand for effective treatments, avoidance of ineffective treatments, accreditation requirements, requirements for cost effective and inexpensive treatments and assessment of quality of service audits.

4.2 Restraining forces that will hinder the implementation of this Guideline. These include the following; reduced access of patients to diagnostic tests and specialist services, perception by patients that medical treatments are ineffective, reluctance of practitioners to change current practice, cost of retraining of GPs in diagnostic tests and specialists in newer surgical techniques (endometrial ablation), fee for service structure for primary care, and private specialist services, decreased access to certain treatments including tranexamic acid, levonorgestrel intrauterine system, transvaginal ultrasound and endometrial ablation techniques.

4.3 Suggested implementation strategies

4.3.1 Provide increased government funding for the following

4.3.1.1 Tranexamic acid is currently only available under specialist only prescribing provisions of Pharmac. Although this was reviewed in 1997 it was declined by Pharmac. The cost of the medication has come down in recent years and as it is more effective than other preparations such as low dose norethisterone, it would seem mandatory for this to be released from specialist only prescribing restrictions. It is also only available from hospital pharmacies and this also means that the patient is inconvenienced.

4.3.1.2 Levonorgestrel intrauterine system. This system has recently been licensed in New Zealand but is not currently publicly funded for patients. The cost of $285 includes GST but as it lasts for 5 years it is equivalent to $5 per month.

4.3.1.3 Increased provision of ultrasound services to GPs and increased provision of training in transvaginal ultrasound will be necessary in order to have wider access to publicly funded ultrasound services for primary healthcare provided. This will involve the establishment of more ultrasound units with transvaginal facilities in rural districts.

4.3.2 Ensure funding for training

4.3.2.1 Very few GPs currently do endometrial sampling in New Zealand. If GPs are able to do endometrial sampling it will reduce the need for specialist referral. It is possible to train GPs in this during their Diploma in O & G training as it is very similar to inserting an intrauterine device.

4.3.2.2 Increased training of specialists in hysteroscopic surgery. Currently very few specialists across the country are doing hysteroscopic surgery. Of 140 specialists it is

estimated that only 15 are doing hysteroscopic surgery. In the United Kingdom over 60% of units are providing a service for hysteroscopic surgery which includes endometrial ablation and resection of submucous fibroids. In New Zealand increased training needs to be provided for specialists to upskill in this area as well as greater access to other hysteroscopic techniques such as balloon ablation.

4.3.3 Provision of streamlined specialist services.

There is great potential for the provision of a streamlined service for women with heavy menstrual bleeding. In a single outpatient visit a patient could be reviewed by a gynaecologist, have either a transvaginal ultrasound and endometrial sample taken, and then once treatment options are discussed, have either medical treatment instituted including the siting of the levonorgestrel intrauterine system, or undergo outpatient hysteroscopy and endometrial ablation by balloon therapy all in the one visit. One example of a clinic with a similar service already exists in Wellington (Dr A Ansari, personal communication) and a one clinic has reported similar service in the United Kingdom (Baskett, 1996).

4.3.4 Dissemination of Guideline by members of the working party and the Ministry of Health

The following suggestions have been made. All the members of the working party were supportive of promoting this Guideline in their own fields. However the following were also suggested;

- New Zealand Guideline Group web page
- Articles in NZ Medical Journal, GP, NZ Doctor, Kaitiaki
- pullout laminated for easy access
- National Health Committee mailout to all doctors
- Pamphlets for consumers
- NZ Women's Weekly
- Press release

The Guideline has been endorsed by both the Royal New Zealand College of Obstetricians and Gynaecologists, and the Royal New Zealand College of General Practitioners and it is hoped that it will be utilised widely. Provision of a laminated section that could be left in a doctor's surgery may improve utilisation. A pamphlet for consumers has been prepared and it is hoped that these will be available in all general practices and gynaecology clinics throughout the country.

4.3.5 Provide specific targeted information and strategies to Maori and Pacific Island women.

A survey of 70 premenopausal women from Maori (19%), Pacific Island (22%), European (33%) and other (26%) background was undertaken. Attitudes to diagnostic testing and treatments were recorded. Women's preferences, regardless of age or race, were for less invasive tests such as transabdominal ultrsound but when it was explained the benefits of TVS or pipelle sampling, most stated that they would agree to these tests if it was medically indicated. With

regard to interventions, there was a preference for surgical therapy over medical therapy with the exception of Maori and Pacific Island women. Side effects, including the LNG IUS, was the stated reason for declining medical therapy in most instances (C Farquhar, personal communication 1998).

This survey suggests that for this Guideline to be implemented, careful explanation of diagnostic testing and medical therapy will be necessary.

5 REFERENCES

Alexander DA, Naji AA, Pinion SB, Mollison J, Kitchener HC, Parkin DE, Abramovich DR, Russell IT. Randomised trial comparing hysterectomy with endometrial ablation for dysfunctional uterine bleeding: psychiatric and psychosocial aspects. BMJ 1996;312:280-

Ash SJ, Farrell SA, Flowerden G. Endometrial Biopsy in DUB. J Reprod Med 1996;41:892-896.

Astedt B. Clinical pharmacology of tranexamic acid. Scand J Gastroenterol 1987;22:22-25.

Barakat RR. Benign and hyperplastic endometrial changes asscoiated with tamoxifen use. Oncology 1997;1:35-37.

Baskett TF, O'Connor H, Magos AL. A comprehensive one stop menstrual problem clinic for the diagnosis and management of abnormal uterine bleeding. Br J Obstet Gynaecol 1996;103:76-7.

Batool T, Reginald PW, Hughes JH. Outpatient pipelle endometrial biopsy in the investigation of postmenopausal bleeding. Br J Obstet Gynaecol 1994;101:545-546.

Bayer SR, DeCherney AH. Clinical manifestations and treatment of dysfunctional uterine bleeding. JAMA 1993;269:1823-1828.

Ben-Baruch G, Seidman ES, Shiff E, Moran O, Menczer J. Outpatient endometrial sampling with the pipelle curette. Gynecol Obstet Invest 1994;37:260-262.

Bhattacharya S, Cameron IM, Parkin DE et al. A pragmatic randomised comparison of transcervical resection of the endometrium with endometrial laser ablation for the treatment of menorrhagia. Br J Obstet Gynaecol 1997; 104: 601-607.

Blum M and Blum G. The possible relationship between menorrhagia and occult hypothyroidism in IUD wearing women. Advances in Contraception 1992;8: 313-317.

Bonduelle M, Walker JJ, Calder AA. A comparative study of danazol and norethisterone in dysfunctional uterine bleeding presenting as menorrhagia. Postgrad Med J 1991;67:833-836.

Bonnar J, Sheppard BL. Treatment of menorrhagia during menstruation: randomised controlled trial of ethamsylate, mefenamic acid, and tranexamic acid. BMJ 1996;313:579-582.

Broadbent JAM, Magos AL. Menstrual blood loss after hysteroscopic myomectomy. Gynaecol Endoscopy 1995;4:41-44.

Bronz L, Suter T, Rusca T. The value of transvaginal sonography with and without saline instillation in the diagnosis of uterine pathology in pre and post menopausal women with abnormal bleeding or suspect sonographic findings. Ultrasound Obstet Gynecol 1997:53-58.

Brooks PG, Loffer FD, Serden S. Resectoscopic removal of symptomatic intrauterine lesions. J Reprod Med 1989;34:435-437.

Callender ST, Warner GT, Cope E. Treatment of menorrhagia with tranexamic acid. A double-blind trial. Br Med J 1970; 4: 214-16.

Cameron IS. Menorrhagia - a pragmatic approach tothe understanding of causes and the need for investigations. Br J Obstet Gynaecol 1994;101:3-7.

Cameron IT, Haining R, Lumsden MA, Thomas VR, Smith SK. The effects of mefenamic acid and norethisterone on measured menstrual blood loss. Obstet Gynecol 1990;76:85-88.

Cameron IT, Leask R, Kelly RW, Baird DT. Endometrial prostaglandins in women with abnormal menstrual bleeding. Prost Leuko Med 1987a;29:249-258.

Cameron IT, Leask R, Kelly RW, Baird DT. The effects of danazol, mefenamic acid, norethisterone and a progesterone-impregnated coil on endometrial prostaglandin concentrations in women with menorrhagia. Prostaglandins 1987b;34:99-110.

Carlson KJ, Miller BA, Fowler FJ Jr. The Maine Women's Health Study: 1 Outcomes of hysterectomy. Obstet Gynecol 1994;83:556-65.

Chamberlain G, Freeman R, Price F, Kennedy A, Green D, Eve L. A comparative study of ethamsylate and mefenamic acid in dysfunctional uterine bleeding. Br J Obstet Gynaecol 1991; 98 (7): 707-711.

Chimbira TH, Anderson AB, Turnbull AC. Relation between measured menstrual blood loss and patient's subjective assessment of loss, duration of bleeding, number of sanitary towels used, uterine weight and endometrial surface area. Br J Obstet Gynaecol 1980a;87:603-609.

Chimbira TH, Anderson ABM, Naish C, Cope E, Turnbull AC. Reduction of menstrual blood loss by danazol in unexplained menorrhagia: lack of effect of placebo. Br J Obstet Gynaecol 1980b;87:152-58.

Clarke A, Black N, Rowe P, Mott S, Howle K. Indications for and outcome of total abdominal hysterectomy for benign disease: a prospective cohort study. Br J Obstet Gynaecol 1995;102:611-620.

Cooper JM, Houck RM, Rigberg HJ. The incidence of intrauterine abnormalities found at hysteroscopy in patients undergoing elective hysteroscopic sterilization. J Reprod Med 1983;28:659-661.

Cooper KG, Grant AM, Garratt AM. The impact of using a partially randomised patient preference design when evaluating alternative managements for heavy menstrual bleeding. Br J Obstet Gynaecol 1997b; 104:1367-1373.

Cooper KG, Parkin DE, Garratt AM, Grant AM. A randomised comparison of medical and hysteroscopic management in women consulting a gynaecologist for treatment of heavy menstrual loss. Br J Obstet Gynaecol 1997a; 104:1360-1366.

Cornier E. The pipelle: a disposable device for endometrial biopsy. Am J Obstet Gynecol 1984;148:109-10.

Coulter A, Bradlow J, Agass M, Martin-Bates C, Tulloch A. Outcomes of referrals to gynaecology outpatient clinics for menstrual problems: an audit of general practice records. Br J Obstet Gynaecol 1991;98:789-796.

Coulter A, Kelland J, Peto V, Rees MCP. Treating menorrhagia in primary care. Int J Tech Assess Health Care,1995; 11: 454-71.

Cravello L, D'Ercole C, Roge P, Boubli L, Blanc B. Hysteroscopic management of menstrual disorders: a review of 395 patients. Europ J Obstet Gynecol & Reprod Biol 1996;67:163-167.

Crissman JD, Azoury RS, Barnes AE, Schellhas HF. Endometrial carcinoma in women 40 years of age or younger. Obstet Gynecol 1981;57:699-704.

Crosignani PG, Vercellini P, Apolone G, De Giorgi O, Cortesi I, Meschia M. Endometrial resection versus vaginal hysterectomy for menorrhagia: long-term clinical and quality-of-life outcomes. Am J Obstet Gynecol 1997; 177: 95-101.

Crosignani PG, Vercellini P, Oldani S, De Giorgi O, Aimi G, Cortesi I. A levonorgestrel releasing intrauterine device versus hysteroscopic endometrial resection in the treatment of dysfunctional uterine bleeding. Abstract, 12th annual meeting of EHSRE, 1996;9.

Davies AJ, Anderson AB, Turnbull AC. Reduction by naproxen of excessive menstrual bleeding in women using intrauterine devices. Obstet Gynecol 1981; 57: 74-78.

Derman SG, Rehnstrom J, Neuwirth RS. The longterm effectiveness of hysteroscopic treatment of menorrhagia and leiomyomas. Obstet Gynecol 1991;77:591-594.

Dijkhuizen FP, Brolmann HA, Potters AE, Bongers MY, Heinz AP. The accuracy of transvaginal ultrasonography in the diagnosis of endometrial abnormalities. Obstet Gynecol 1996;87:345-9.

Dockeray CJ, Sheppard BL, Bonnar J. Comparison between mefenamic acid and danazol in the treatment of established menorrhagia. Br J Obstet Gynaecol 1989; 96: 840-44.

Dwyer N, Hutton J, Stirrat G. Randomised controlled trial comparing endometrial resection with abdominal hysterectomy for the surgical treatment of menorrhagia. Br J Obstet Gynaecol 1993; 100: 237-243.

Eddowes H. Pipelle: a more acceptable technique for outpatient endometrial biopsy. Br J Obstet Gynaecol 1990;97:961-962.

Edlund M, Andersson K, Rybo G, et al. Reduction of menstrual blood loss in women suffering from idiopathic menorrhagia with a novel antifibrinolytic drug (Kabi 2161). Br J Obstet Gynaecol 1995; 102: 401-6.

Edlund M, Blomback M, von Schoultz B, Andersson O. On the value of menorrhagia as a predictor for coagulation disorders. Am J Hemat 1996;53(4):234-38.

Eichner E, Abellera M. Endometrial hyperplasia treated by progesting. Obstet Gynecol 1971;38:739-742.

Elder MG. Prostaglandins and menstrual disorders. BMJ 1993;287:703-4.

Emanuel MH, Verdel MJ, Wamsteker K, Lannes FB. A prospective comparison of transvaginal ultrasonography and diagnostic hysteroscopy in the evaluation of patients with abnormal uterine bleeding. Am J Obstet Gynecol 1995;172:547-52.

Fagan TJ. Nomogram for Bayes' theorem (C). NEJM 1975;293:257.

Farquhar CM. Personal communication from ongoing study National Women's Hospital hysterectomies, 1997.

Farquhar CM, Kimble R. How do NZ gynaecologists treat menorrhagia? Aust NZ J Obstet Gynaecol 1996;36:4:1-4.

Farquhar CM, Lethaby A, Sowter M, Verry J, Baranyai J. An evaluation of risk factors for endometrial hyperplasia in premenopausal women with abnormal menstrual bleeding (In preparation) 1998.

Farquar C. Personal communication 1998.

Fedele L, Bianchi S, Dorta M, Brioschi D, Zanotti F, Vercellini P. Transvaginal ultrasonography versus hysteroscopy in the diagnosis of uterine submucous myomas. Obstet Gynecol 1991;77:745-748.

Ferry J, Farnsworth A, Webster M, Wren B. The efficacy of the pipelle endometrial bipsy in detecting endometrial carcinoma. Aust NZ J Obstet Gynaecol 1993;33:76-78

Fothergill DJ, Brown VA, Hill AS. Histological sampling of the endometrium - a comparison between formal curettage and the Pipelle sampler. Br J Obstet Gynaecol 1992;99:779-780.

Fraser IS, Baird DT. Endometrial cystic glandular hyperplasia in adolescent girls. J Obstet Gynaecol Br Commonw 1972;79:1009-1015.

Fraser IS, McCarron G, Markham R. A preliminary study of factors influencing perception of menstrual blood loss volume. Am J Obstet Gynecol 1984;149:788-793.

Fraser IS, McCarron G, Markham R, Resta T, Watts A. Measured menstrual blood loss in women with menorrhagia associated with pelvic disease or coagulation disorder. Obstet Gynecol 1986;68:630-3.

Fraser IS, McCarron G. Randomised trial of 2 hormonal and 2 prostaglandin-inhibiting agents in women with a complaint of menorrhagia. Aust NZ J Obstet Gynaecol 1991; 31: 66-70.

Fraser IS, Pearse C, Shearman RP, Elliott PM et al. Efficacy of mefenamic acid in patients with a complaint of menorrhagia. Obstet Gynecol 1981; 58: 543-551.

Fraser IS. Menorrhagia - a pragmatic approach to the understanding of causes and the need for investigations. Br J Obstet Gynaecol 1994;101:3-7.

Fraser IS. Treatment of ovulatory and anovulatory dysfunctional uterine bleeding with oral progestogens. Aust NZ J Obstet Gynaecol 1990;30:353-56.

Fraser IS. Hysteroscopy and laparoscopy in women with menorrhagia. Am J Obstet Gynecol 1990;162:1264-1269.

Frishman GJS. A randomised clinical trial comparing pipelle and Tis-U-Trap for endometrial biopsy. Obstet Gynecol 1990;76(2);315-316.

Gallup DG, Stock RJ. Adenocarcinoma of the endometrium in women 40 years of age or younger. Obstet Gynecol 1984;64:417-420.

Gannon M, Holt E, Fairbank J et al. A randomised trial comparing endometrial resection and abdominal hysterectomy for the treatment of menorrhagia. BMJ 1991; 303: 1362-1364.

Gannon MJ, Day P, Hammadien N, Johnson N. A new method for measuring menstrual blood loss and its use in screening women before endometrial ablation. Br J Obstet Gynaecol 1996;103:1029-1033.

Gimpelson RJ, Rappold HO. A comparative study between panoramic hysteroscopy with directed biopsies and dilatation and curettage. A review of 276 cases. Am J Obstet Gynecol 1988;158:489-492.

Goldchmit R, Katz Z, Blickstein I, Caspi B, Dgani R. The accuracy of endometrial pipelle sampling with and without sonographic measurement of endometrial thickness. Obstet Gynaecol 1993;82:727-30.

Goldrath MH, Sherman AI. Office hysteroscopy and suction curettage: can we eliminate the hospital diagnostic dilatation and curettage. Am J Obstet Gynecol 1985;152:220.

Grimes D. Diagnostic dilation and curettage: a reappraisal. Am J Obstet Gynaecol 1982; 142: 1-6.

Grover V, Usha R, Gupta U, Kalra S. Management of cyclical menorrhagia with prostaglandin synthetase inhibitor. Asia-Oceania J Obstet Gynaecol 1990; 16: 255-59.

Guillebaud J, Anderson AB, Turnbull AC. Reduction by mefenamic acid of increased menstrual blood loss associated with intrauterine contraception. Br J Obstet Gynaecol 1978; 85: 53-62.

Hall P, Maclachlan N, Thorn N, Nudd MW, Taylor CG, Garrioch DB. Control of menorrhagia by the cyclo-oxygenase inhibitors naproxen sodium and mefenamic acid. Br J Obstet Gynaecol 1987; 94: 554-558.

Hallberg L, Hogdahl A, Nilsson L and Rybo G. Menstrual blood loss - a population study: variation at different ages and attempts to define normality. Acta Obstetricia et Gynecologica Scandinavica 1966; 45:320-351.

Harris WJ. Early complications of abdominal and vaginal hysterectomy. Obstet Gynecol Surv 1995;11:795-805.

Harrison RF, Campbell S. A double-blind trial of ethamsylate in the treatment of primary and intrauterine-device menorrhagia. Lancet 1976; 283-4.

Haynes PJ, Hodgson H, Anderson AB, Turnbull AC. Measurement of menstrual blood loss in patients complaining of menorrhagia. Br J Obstet Gynaecol 1977;84:763-768.

Higham JM and Shaw RW. The effect of thyroxine replacement on menstrual blood loss in a hypothyroid patient. Br J Obstet Gynaecol 1992;99, 695-696.

Higham JM, O'Brien PMS, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. Br J Obstet Gynaecol 1990;97:734-9.

Higham JM, Shaw RW. A comparative study of danazol, a regimen of decreasing doses of danazol and norethisterone in the treatment of objectively proven unexplained menorrhagia. Am J Obstet Gynecol 1993;169:1134-9.

Hoylaerts M, Lijnen HR, Collen D. Studies on the mechanism of the antifibrinolytic action of tranexamic acid. Biochim Biophys Acta 1981;673:75-85.

Hunter JE, Tritz DE, Howell MG, DePriest PD, Gallion HH, Andrews SJ et al. The prognostic and therapeutic implications of cytologic atypia in patients with endometrial hyperplasia. Gynaecol Oncol 1994;55:66-71.

Indman P. Abnormal uterine bleeding. J Reprod Med 1995;40:545-548

Ingemanson C, Sikstrom B, Rybo G, Bjorkman R. Double-blind, placebo-controlled evaluation of dicofenac in the management of patients with IUD-related menorrhagia. Adv Therap 1991; 8: 287-92.

Irvine GA, Campbell-Brown MB, Lumsden MA, Heikkila A, Walker JJ, Cameron IT. Randomised comparative study of the levonorgestrel intrauterine device and norethisterone for the treatment of idiopathic menorrhagia. Abstract, Acta Obstet Gynecol Scand Suppl 1997;76:55.

Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients. JAMA 1994;271:703-707.

Janssen CA, Scholten PC and Heintz AP. A simple visual assessment technique to discriminate between menorrhagia and normal menstrual blood loss. Obstetrics & Gynecology 1995;85:977-982.

Jeffrey JD, Taylor R, Robertson DI, Stuart GC. Endometrial carcinoma occurring in patients under the age of 45 years. Am J Obstet Gynecol 1987;1256:366-370.

Kadir RA, Economides DL, Sabin CA, Owens D, Lee CA. Frequency of inherited bleeding disorders in women with menorrhagia. Lancet 1998;261:485-489.

Kasonde JM, Bonnar J. Effect of ethamsylate and aminocaproic acid on menstrual blood loss in women using intrauterine devices. Br Med J 1975; 4 (5987): 21-22.

Kaunitz AM, Masciello A, Ostiowski M, Roviva EZ. Comparison of endometrial biopsy with the endometrial pipelle and vabra aspirator. J Reprod Med 1988;33:427-43.

Kavak Z, Leyhaw N, Perkin S. Combination of vaginal ultrasonography and pipelle sampling in the diagnosis of endometrial disease. Aust NZ J Obstet Gynaecol 1996;1:63.

Keye WR. Dysfunctional uterine bleeding. In Glass RH (ed): Office Gynaecology, ed 3. Baltimore, Williams and Wilkins 1988, pp199-207.

Koonings PP, Moyer DL, Grimes DA. A randomized clinical trial comparing pipelle and Tis-U-Trap for endometrial biopsy. Obstet Gynecol 1990;75(2):293-295.

Koss LG, Schreiber K, Oberlander SG, Moussouris HF, Lesser TY. Detection of endometrial cancer and hyperplasia is asymptomatic women. Obstet Gynaecol 1984;64 (1):1-11.

Kovac SR, Cruikshank SH, Retto HF. Laparascopy-assisted vaginal hysterectomy. J Gynecol Surg 1990; 6: 185-93.

Krassas GE, Pontikides N, Kaltsas T, Papdopoulou P and Batrinos M. Menstrual disturbances in thyrotoxicosis. (1994).

Kurman RJ, Kaminski PF, Norm HJ. The behaviour of endometrial hyperplasia. A long term study of 'untreated' hyperplasia in 170 patients. Cancer 1985;56:403-12.

Lamb MP. Danazol in menorrhagia: a double blind placebo controlled trial. J Obstet Gynecol 1987;7:212-16.

Langebrekke A, Eraker R, Nesheim B-I et al. Abdominal hysterectomy should not be considered as a primary method for uterine removal. Acta Obstet Gynecol Scand 1996; 75: 404-407.

Lethaby A, Farquhar CM, Furness S, Gillett W, Milne R. A decision analysis for the medical management of heavy menstrual bleeding (In preparation) 1998.

Lewis BV. Diagnostic Dilatation and curettage in young women. BMJ 1993; 306: 225-226.

Lipscomb GH. Randomized comparison of the pipelle, Accurette, and Explora endometrial sampling devices. Am J Obstet Gynecol 1994;170:591-594.

Loffer FD. Hysteroscopy with selective endometrial sampling compared with D&C for abnormal uterine bleeding: the value of a negative hysteroscopic view. Obstet Gynecol 1989;73:16-20.

Loffer FD, Grainger D, Kung RC et al. Endometrial ablation for the treatment of menorrhagia: a randomised trial comparing uterine balloon therapy with rollerball. Acta Obs Gyn Scand 1997;76;23:C705.1.

Loverro G, Bettocchi S, Vicino M, Selvaggi L. Diagnosis of endometrial hyperplasia in women with abnormal uterine bleeding. Acta Eur Fertil 1994;25:23-25.

Macdonald R. Modern treatment of menorrhagia. Br J Obstet Gynaecol 1990; 97: 3-7.

MacIntosh M. Incidence of hysterectomy in New Zealand. NZ Med J 1987;100:345-547..

McKenzie I and Bibby J. Critical assessment of dilatation and curettage in 1029 women. Lancet 1978;2:566.

Makarainen L, Ylikorkala O. Primary and myoma-associated menorrhagia: role of prostaglandins and effects of ibuprofen. Br J Obstet Gynaecol 1986; 93: 974-978.

Mann T, Clinical Guidelines: Using clinical Guideline to improve patient care within the NSH, 1996. NHS Executive.

Mapani A, Singer J et al. Endometrial hyperplasia. J Clin Ultrasound 1990;18:173-177.

McGee WB. Carcinoma of the endometrium in women under forty years of age. Obstet Gynaecol 1958;11:388-390.

Milsom I, Andersson K, Andersch B, Rybo G. A comparison of flurbiprofen, tranexamic acid, and a levonorgestrel-releasing intrauterine contraceptive device in the treatment of idiopathic menorrhagia. Am J Obstet Gynecol 1991; 164: 879-883.

Mollison J, Bhatacharya S, McIntosh E, Pinion SD, et al. The value of long term followup in health technology assessment: the example of endometrial ablation (Poster). Cochrane Colloquia, Amsterdam, 1997.

Muggeridge J, Elder M. Mefenamic acid in the treatment of menorrhagia. Res Clin Forums 1983; 5: 83-88.

Nagele F, O'Connor H, Davies A, Badaery A, Mohamed H, Magos A. 2500 outpatient diagnostic hysteroscopies. Obstet Gynecol 1996;88:87-92.

Nathorst-Boos J, Fuchs T, von Schoultz B. Consumers attitudes to hysterecomy: the experience of 678 women. Acta Obstet Gynecol Scand 1992;71:230-234.

Need JA, Forbes KL, Milazzo L, McKenzie E. Danazol in the treatment of menorrhagia: the effect of a 1 month induction dose (200 mg) and 2 month's maintenance therapy (200 mg, 100 mg, 50 mg or placebo). Aust NZ J Obstet Gynaecol 1992;32:346-352.

Nilsson L, Rybo G. Treatment of menorrhagia with an antifibrinolytic agent, tranexamic acid (AMCA). Acta Obstet Gynecol Scand 1967; 46: 572-80.

Nilsson L, Rybo G. Treatment of menorrhagia with epsilon aminocaproic acid. Acta Obstet Gynecol Scand 1965; 44: 467-473.

Nilsson L, Rybo G. Treatment of menorrhagia. Am J Obstet Gynecol 1971;1109:713-20.

O'Connor H, Broadbent JAM, Magos AL, McPherson K. Medical Research Council randomised trial of endometrial resection versus hysterectomy in management of menorrhagia. Lancet 1997; 349: 897-901.

Overton C, Hargreaves J, Maresh M. A national survey of the complications of endometrial destruction for menstrual disorders: the MISTLETOE study. Br J Obstet Gynaecol 1997; 104: 1351-1359.

Paul C, Skegg D, Smeijers J, Spear G. Contraceptive practice in New Zealand. NZMJ 1988; 101:809-13.

Perino A, Quartararo P, Catinella E et al. Treatment of endometrial hyperplasia with levonorgestrel releasing intrauterine devices. Acta Europaea Fertilitatis 1987;18:137-140.

Persson E, Bergstrom M, Larsson P-G et al. Infections after hysterectomy. Acta Obstet Gynecol Scand 1996;75:757-61.

Petersen K, Jelert H, Diernaes E, Detlefsen GU. [Treatment of hypermenorrhoea with tranexamic acid] [Danish]. Ugeskrift for Laeger 1983.

Peterson EP. Endometrial carcinoma in young women. A clinical profile. Obstet Gynecol 1968;31:702-707.

Phipps JH, John M, Nayak S. Comparison of laparoscopically assisted vaginal hysterectomy and bilateral salpingo-ophorectomy with conventional abdominal hysterectomy and bilateral salpingo-ophorectomy. Br J Obstet Gynaecol 1993; 100: 698-700.

Pinion S, Parkin D, Abramovich D et al. Randomised trial of hysterectomy, endometrial laser ablation and transcervical endometrial resection for dysfunctional uterine bleeding. BMJ 1994; 309: 979-983.

Pokras R, Hufnagel V. Hysterectomy in the United States 1965-1984. Am J Public Health 1988;78:852-853.

Preston JT, Cameron IT, Adams EJ, Smith SK. Comparative study of tranexamic acid and norethisterone in the treatment of ovulatory menorrhagia. Br J Obstet Gynaecol 1995;102:401-406.

Puolakka J, Nilsson CG, Haukkamaa M, Riikonen U, et al. Conservative treatment of excessive uterine bleeding and dysmenorrhoea with levonorgestrel intrauterine system as an alternative to hysterectomy. Acta Obstet Gynecol Scand 1996; 75: 82.

Quinn MA, Kneale BJ, Fortune DW. Endometrial carcinoma in premenopausal women: a clinicopathological study. Gynecol Oncology 1985;20:298-306.

Raju KS, Auld BJ. A randomised prospective study of laparoscopic vaginal hysterectomy versus abdominal hysterectomy each with bilateral salpingo-oophorectomy. Br J Obstet Gynaecol 1994; 101: 1068-1071.

Ramcharan S, Fellegrin FA, Ray MR, Hsu J. The Walnut Creek Contraceptive Drug Study - a prospective study of the side effects of oral contraceptives. Vol III, A Interim Report: a comparison of disease occurrence leading to hospitalization or death in users and nonusers of oral contraceptives. J Reprod Med 1980;25:345-372.

Randall TC, Kurman RJ. Progestin treatment of atypical hyperplasia and well-differentiated carcinoma of the endometrium in women under age 40. Obstet Gynecol 1997;90:434-40.

Rees MCP, Chimbira TH, Anderson ABNM, Turnbull AC. Menstrual blood loss: Measurement and clinical correlates. Research and Clinical Forums 1982;4:69-80

Richardson RE, Bournas N, Magos AL. Is laparascopic hysterectomy a waste of time? Lancet 1995; 345: 36-41.

Rodriguez GC, Yaqub N, King ME. A comparison of the pipelle device and the Vabra aspirator as measured by endometrial denudation in hysterectomy specimens: the pipelle device samples significantly less of the endometrial surface than the Vabra aspirator. Am J Obstet Gynecol 1993;168(1):55-59.

Roy S, Shaw ST Jr. Role of prostaglandins in IUD-associated uterine bleeding - effect of a prostaglandin synthetase inhibitor (ibuprofen). Obstet Gynecol 1981; 58: 101-6.

Royal College of General Practitioners. Oral Contraceptives and Health. London: Pitman Medical, 1974.

Royal College of Obstetricians and Gynaecologists/ Guidelines Use of D & C 1994.

Royal New Zealand College of General Practitioners Research Unit (1995-1996), University of Otago. Jason Hall, personal communication.

Rybo G. Clinical and experimental studies on menstrual blood loss. Acta Obstet Gynecol Scand 1966;45:1-23.

Rybo G, Nilsson S, Sikstrom B, Nygren K. Naproxen in menorrhagia (letter). Lancet 1981; I: 608-609.

Rybo G. Tranexamic acid therapy effective treatment in heavy menstrual bleeding: Clinical update on safety. Therapeutic Advances 1991; 4: 1-8.

Sackett DL, Richardson WS, Rosenberg W, Haynes RB. Evidence Based Medicine. How to practice and teach evidence based medicine. Churchill Livingstone 1997.

Scarpellini F, Curto C, Caracussi U, Letta C, Scarpellini L. Transvaginal ultrasound versus histology in endometrial hyperplasia. Clin Exp Obstet Gynecol 1994;21:266-269.

Scott HM and Scott.WG. Hysterectomy for non malignant conditions: cost to New Zealand Society. NZ Med J 1995;108:423-6.

Scott JC and Mussey E. Menstrual patterns of myxedema. Am J Obstet Gynecol 1964; 90: 161-165.

Sculpher MJ, Bryan S, Dwyer N, Hutton J, Stirrat GM. An economic evaluation of transcervical endometrial resection versus abdominal hysterectomy for the treatment of menorrhagia. Br J Obstet Gynaecol 1993; 100: 244-252.

Sculpher MJ, Dwyer N, Byford S, Stirrat GM. Randomised trial comparing abdominal hysterectomy and transcervical endometrial resection: long-term effect on health-related quality of life and costs two years after surgery. Br J Obstet Gynaecol 1996; 103:

Settnes A, Jørgensen T. Hysterectomy in a Danish cohort. Acta Obstet Gynecol Scand 1996;75:274-280.

Silver MM, Miles P, Rosa C. Comparison of Novak and Pipelle endometrial biopsy instruments. Obstet Gynaecol 1994;78:828-830

Smith P, Bakos O, Heimer G, Ulmster U. Transvaginal ultrasound for identifying endometrial abnormalities. Acta Obstet Gynecol Scand 1991;70:591-4.

Smith SK, Abel MH, Kelly RW, Baird DT. Prostaglandin synthesis in the endometrium of women with ovular dysfunctional uterine bleeding. Br J Obstet Gynaecol 1981; 88: 434-42.

Smith SK, Abel MH, Kelly RW, Baird DT. The synthesis of prostaglandins from persistent proliferative endometrium. J Clin Endocrinol Metab 1982;55:284-289.

Stovall TG, Ling FW, Morgan PL. A prospective, randomized comparison of the pipelle endometrial sampling device with the Novak Curette. Am J Obstet Gynecol 1991;165(5);1287-1290.

Summitt RL, Stovall TG, Lipscomb GH, Ling FW. Randomised comparison of laparoscopy-assisted vaginal hysterectomy with standard vaginal hysterectomy in an outpatient setting. Obs Gynecol 1992; 80: 895-901.

Teale GR, Dunster GD. The pipelle endometrial suction curette: how useful is it in clinical practice? J Obstet Gynecol 1998;18:53-55.

Terakawa N, Kigawa J, Taketani Y, Yoshikawa H, Yajima A, Noda K. The behavior of endometrial hyperplasia: A prospective study. J Obstet Gynaecol Res 1997;28:223-230.

Towbin N, Gviazda I, March C. Office hysteroscopy versus transvaginal ultrasonography in the evaluation of patients with excessive uterine bleeding. Am J Obstet Gynecol 1996;174:1678-82.

Tsang BK, Domingo MT, Spence JEH, et al. Endometrial prostaglandins and menorrhagia: influence of a prostaglandin synthetase inhibitor in vivo. Can J Physiol Pharmacol 1987; 65: 2081-84.

U.S Preventive Services Task Force (1996). Report of the US Preventive Service Task Force: Guide to clinical preventive services. 2Nd Edition. Pp 209-218. Baltimore: Williams & Wilkins.

van Eijkeren MA, Christiaens GC, Geuze HJ, et al. Effects of mefenamic acid on menstrual hemostasis in essential menorrhagia. Am J Obstet Gynecol 1992; 166: 1419-1428.

Vargyas JM, Campeau JD, Mishell DR Jnr. Treatment of menorrhagia with meclofenamate sodium. Am J Obstet Gynecol 1987; 157: 944-950.

Vercellini P, Cortesi I, Oldani S, Moschetta M, De Giorgi O, Crosignani PG. The role of transvaginal ultrasonogrpahy and outpatient diagnostic hysteroscopy in the evaluation of patients with menorrhagia. Hum Reprod 1997;12:1768-1771.

Vermylen J, Verhaegen-Declercq ML, Fierens F, Verstraete MA. A double blind study of the effect of tranexamic acid in essential menorrhagia. Bull Soc Roy Belge Gynecol Obstet 1968; 38 (5): 385-390.

Vessey MP, Villard-Mackintosh L, McPherson K, Coulter A, Yeates D. The epidemiology of hysterectomy: findings in a large cohort study. Br J Obstet Gynaecol 1992;99:402-407.

Waimedca Data 1991-1992. B Gribben, Personal communication.

Wathen PI, Henderson MC, Witz CA. Abnormal uterine bleeding. Med Cllinics of North America 1995;79:329-44.

Weinstein MC, Fineberg HC et al. Clinical decision analysis. Philadelphia: WB Saudners Co, 1980.

Wentz WB. Treatment of persistent endometrial hyperplasia. Am J Obstet Gynecol 1966;994-1004.

Westgate J. Middlemore Hospital Data 1997. Personal communication.

Weston P, Saidi M, Sadler R, Akright B. Comparison between office sonohysterography, vaginal sonography and hysteroscopy for evaluation of abnormal vaginal bleeding. 27Th British Congress of Obstetrics and Gynaecology 1995; p no. 538.

Widrich T, Bradley LD, Mitchinson AR, Collins RL. Comparison of saline infusion sonography with office hysteroscopy for the evaluation of the endometrium. Am J Obstet Gynecol 1996;174:1327-1334.

Wilansky DL and Greisman B. Early hypothyroidism in patients with menorrhagia (see comments). Am J Obstet Gynecol 1989;160: 673-677.

Willman EA, Collins WD, Clayton SC. Studies on the involvement of prostaglandins in uterine symptomatology and pathology. Br J Obstet Gynaecol 1976;90:78-83.

Ylikorkala O, Pekonen F. Naproxen reduced idiopathic but not fibroma-induced menorrhagia. Obstet Gynecol 1986; 68: 10-1 2.

Ylikorkala O, Viinikka L. Comparison between antifibrinolytic and antiprostaglandin treatment in the reduction of increased menstrual blood loss in women with intrauterine contraceptive devices. Br J Obstet Gynaecol 1983; 90 (1): 78-83.

6 APPENDIX

6.1 Suitability screen for guidelines in heavy menstrual bleeding

A suitability screen was performed at the beginning of the Guideline process to ensure that the topic was worthwhile for investing time in producing a guideline. The screening process followed these steps and involved the convenor of the project - Dr Cindy Farquhar with assistance from other group members.

1 Can the proposed change be measured? The answer to this question is Yes. There are outcomes that can be measured which are as follows;
- hysterectomy rate in women under the age of 50 years
- prescribing rates of Tranexamic acid
- GP databases for number of consultations and referrals

2 A brief literature search was carried out. There are approximately 50 RCTs of medical and surgical therapy of heavy menstrual bleeding and at least 20 studies of diagnostic tests.

3 Is the best treatment supported by the evidence? The prescribing rate of Tranexamic acid amongst gynaecologists in this country is low with only 10% using it as a third line measure while the prescribing rate for luteal phase progestogen is 50%.

There is no use of the levonorgestrel IUCD currently.

4 Would the proposed change result in sufficient change in outcomes and justify the effort? How big is the gap between current practice and optimum care? New Zealand has the fifth highest hysterectomy rate in OECD countries. Currently 21% of New Zealand women have a hysterectomy before menopause. In a population of premenopausal women in the United Kingdom this is 17%, whereas in Denmark the lifetime prevalence is 10%.

5 How much effort will it take to close the gap? There will have to be an educational programme for primary and secondary care doctors as well as changes in access to certain diagnostics and medications.

6 Is there a reasonable likelihood that changes could be implemented? Yes, with appropriate funding.

6.2 Description of the Guideline process

All members of the Guideline Development Working Party agreed to declare any interests or connections with relevant pharmaceutical companies or other organisations, at the first meeting. No member had any paid consultancy or any other conflict of interest with any pharmaceutical company currently involved with therapeutic products for heavy menstrual bleeding. Not all members were able to attend all meetings but were circulated with drafts and minutes of the meetings.

Four meetings were held, all in Auckland. The first meeting was in February 1997 and the Group met with Dr Diana North who was one of the Guidelines Fellows from the first training workshop in 1996. The concept of guideline development was presented to the group. The next meeting was held in May 1997 and this was very much a working meeting discussing some of the more difficult issues. The next meeting was September 1997 where a preliminary draft Guideline was presented. The last meeting was held in February 1998 and a critical appraisal of the penultimate draft was undertaken.

Various members undertook to write sections of the Guideline and Dr C Farquhar collated and produced a draft in October 1997. Interested groups and individuals were circulated with the draft Guideline, in November 1997. Comments were invited and four weeks were given for the response. A final draft was circulated to the working party members in March 1998.

The development of this Guideline was funded in part by a grant from the Ministry of Health. This covered the cost of the meetings, the identification of the evidence and the costs of preparing the manuscript.

6.3: Balance sheet for implementing Guideline

	Current no	Unit Cost ($)	% of patients[1][2]	Current cost (x $1000)	Subtotal (x $1000)	% of total costs	Projected Numbers	% of patients[12]	Projected cost (x $1000)	Sub total (x $1000)	% of total costs	Differences*
Prevalence of HMB (per annum)	111,000[1]	-	-				110,000					
Prevalence of women who consult with HMB	66,000[2]	-	-				66,000					
GP visit - initial	66,000	32.00	100	2112			66,000	100	2112			
GP visit - repeat	10,560	32.00	16	347		11%	10,560	16	347			240,000
Specialist consult	9,240	107.00	14	980	3,440		6,640	10	735	3,190	10%	
Full blood count	660,000	10	100	692				100	692			
Transvaginal ultrasound		120	20	1584				25	1980			
Endometrial sampling												
pipelle		120	9.0	713				4.5	356			
hysteroscopy(GA)		800	2.5	1320				0.5	264			
hysteroscopy (outpatient)		300	0.5	99				2.5	495			
lab costs		67		533	4,940	16%[9]			333	4,120	13%	-820,000
			12					7.5				
Oral contraceptive pill	-	6.46[3]	10	626				10	568			
Progestogens												
long course	-	21.20[3]		-				4	378			
short course	-	3.37[3]	26	900				8	300			
NSAIDs	-	3.13[34]	15	160				15	160			
Danazol	-	39.81[3]		-				-	-			
Tranexamic Acid	-	17.49[3]	5	786				15				
LNG IUS	-	49.00[5]	-	-				15	5			
			54[6]		2,690	9%[10]		66[6]		4,520	15%	1,840
Endometrial ablation (public)[7]	-	1242	0.3	217				0.5	435			
Endometrial ablation (private)[8]	-	2222	0.3	389				0.5	733			

	Hysterectomy (public)[7]	-	2600	3.7	63%				2.0	3432			
	Hysterectomy (pvte)[8]	-	4000	4.8	12560				2.5	6720			
				9.0	5950	19,562	64%[11]		6		$11,320	41%[11]	-6,980
					Total cost (current)	**$30,630**				**Total projected cost**	**$24,420**	**Total Savings (projected)**	**-6,210**

Footnotes - figures are per annum unless otherwise stated and GST exclusive

1 10% of women in the reproductive age group (based on UK figures) (Coulter 1991).

2 Estimated that 60% of women with HMB consult GP, and 16% have repeat consultation and 14% specialist referral rate (RNZCGP data).

3 Mean cost per cycle, includes dispensing fee and mark up.

4 Mean cost per cycle for mefenamic acid, naprosyn, diclofenac.

5 Cost does not include repeat consultations.

6 Percentage of patients who consult and are prescribed medical therapy.

7 Public hospital costs are estimated from annual diagnostic related groups provided by North Health 1997 for uncomplicated surgery and likely to be an underestimate.

8 Costs are based on an estimate of the Southern Cross schedule.

9 The numbers having diagnostic tests are estimates only as no data available solely for premenopausal women. There may also be some overlap between transvaginal ultrasound and pipelle sampling.

10 All percentages for medical therapy are estimates only. Assumes costs for 12 months and does not include the costs of repeat prescriptions.

11 Public / private split is an estimate only.

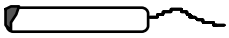
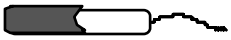
12 Percentages are rounded and current cost worked out on actual percentages

6.4 Pictorial Bleeding Assessment Chart

Fig 6.1: An example of a pictorial bleeding assessment chart

NAME .....

	DATE								
	TOWEL	1	2	3	4	5	6	7	8
1		II	I	I	I	II	I		
5			~~IIII~~	III	II				
20			II	II					

	TAMPON	1	2	3	4	5	6	7	8
1			I			I			
5			II	III	II				
10			~~IIII~~I	III					
	DAILY SCORE	2	137	101	21	3	1		

TOTAL SCORE = *265* (Jansen 1995)

If score of >185 then likelihood of menstrual blood loss ≥80 mls/cycle is increased.

6.5 Decision analysis for ranking medical therapies

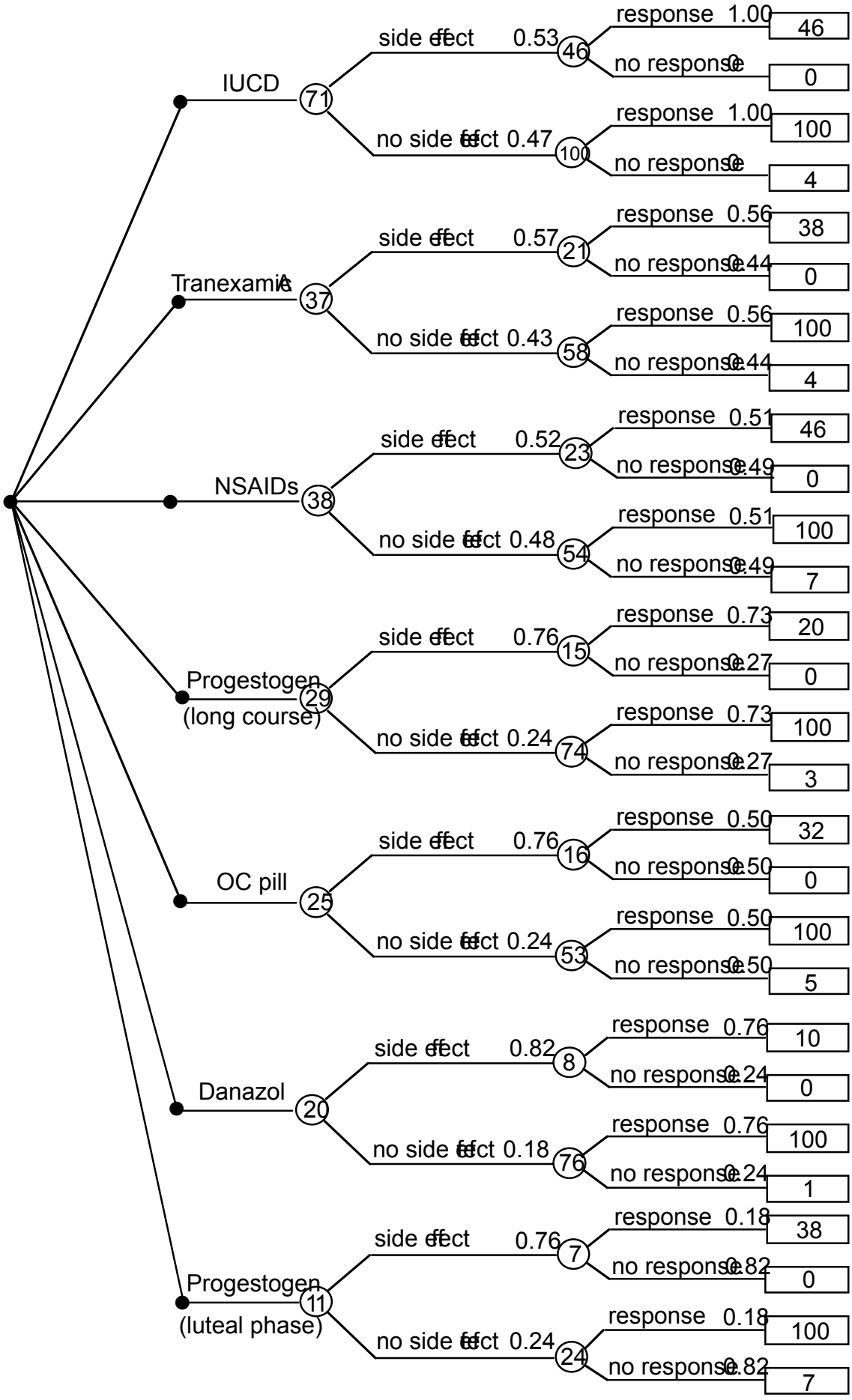
Decision analysis is a quantitative approach that assesses the relative value of different decision options (Weinstein & Fineberg 1980). It is increasingly used to help develop policies about the management of groups of patients by providing information on which of two or more strategies for approaching a medical problem has the 'best' outcome or the most value.

When assessing treatment for heavy menstrual bleeding, efficacy and side effects should be taken into account but it is also important to consider the patient's own value judgments about the outcomes. For example, danazol is highly effective in reducing menstrual blood loss but also produces side effects which many women will not tolerate. A value judgment, or utility value, reflects the trade off an individual patient is prepared to make.

Decision analysis to assess the value of medical treatments for heavy menstrual bleeding required values to be assigned to the probabilities associated with 'response' to treatment, the side effects, profile, and general acceptability of treatment. The widely accepted definition of heavy menstrual bleeding is menstrual blood loss of greater than 80 ml per cycle. We defined "response" as reduction of MBL to the 'normal' range, ie <80 ml per cycle during the treatment cycle. We defined the probability associated with side effects as the proportion of patients who reported side effects. A comprehensive search for all relevant randomised controlled trials assessing the efficacy of medical treatments for heavy menstrual bleeding was performed and the probability values assigned for response and side effects were derived from the mean values from these trials. The utility value, or patient value judgment for each outcome was derived from the mean value assigned by 15 women with a complaint of heavy menstrual bleeding using the direct rating scale. The response and side effects probability values and the utility scores were recorded on the decision tree and a pilot analysis was performed. The full analysis will be published at a later date (Lethaby 1998).

The decision tree was analysed by a process of averaging out and folding back, working backwards from the tips of the branches to the root of the decision tree. When this process was completed, the drug with the highest expected value at the root of the decision tree represented the 'best' treatment option. In this way, 'ranking' of all medical treatments was possible, while still taking into account the acceptability of the intervention and the probability of side effects.

Fig 6.2: Decision tree of medical treatments for heavy menstrual bleeding



6.6 Prescribing information for medical treatments of heavy menstrual bleeding

Generic Name	Trade Name	Recommended Dosage	Contraindications	Side Effects
Mefenamic acid	Ponstan	500 mg tds during menses	• current GI bleeding or ulceration • inflammatory bowel disease • history of hypersensitivity (asthma, angioedema) precipitated by aspirin or NSAID • renal or hepatic impairment	nausea, diarrhoea, headache, dizziness, rashes
Diclofenac	Voltaren	50 mg tds during menses	• current GI bleeding or ulceration • inflammatory bowel disease • history of hypersensitivity (asthma, angioedema) precipitated by aspirin or NSAID • renal or hepatic impairment	nausea, diarrhoea, headache, dizziness, rashes
Naproxen	Naprosyn	250-500 mg tds during menses	• current GI bleeding or ulceration • inflammatory bowel disease • history of hypersensitivity (asthma, angioedema) precipitated by aspirin or NSAID • renal or hepatic impairment	nausea, diarrhoea, headache, dizziness, rashes
Combined oral contraceptive pills	Mercilon Marvelon Microgynon 30 Brevinor Triphasie Femodene Minulet Diane 35	One pill daily for 21 days, repeated after 7 day interval	• severe or multiple risk factors for heart disease • valvular heart disease • hypertension • thromboembolic disease • focal or crescendo migraine • liver disease • hormone dependent disease	nausea, vomiting, headache, breast tenderness

Tranexamic acid	Cyklokapron	1gm tds or qvd during days of heavy menstrual bleeding	• thromboembolic disease	nausea, vomiting, diarrhoea [rarely - transient colour vision disturbance (withdraw if occurs)]
Primolut N	Norethisterone	5 mg tds daily for 21 days repeated after 7 day interval	• severe liver dysfunction • pruritis of pregnancy • active thromboembolic disease	• nausea • bloating
Levonorgestrel Intrauterine system	Mirena	20 µg/24 hours for 5 years	• acute pelvic inflammatory disease • abnormal uterine cavity • caution with rheumatic or congenital heart disease • active thromboembolic disease • severe liver dysfunction	• irregular menses • perforation • expulsion

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