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An examination of the effect of heavy menstrual bleeding on women’s quality of life compared with women with normal menstrual loss.

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A thesis submitted in fulfilment of the requirements for the degree of Master of Philosophy in Medicine.

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Mentor: Dr Frank Manconi

Queen Elizabeth II Research Institute for Mothers and Infants, Department of Obstetrics, Gynaecology and Neonatology, Faculty of Medicine
Abstract

Aims

This study is designed to evaluate the impact of heavy menstrual bleeding on women’s quality of life and to explore their help-seeking behaviour patterns by comparing women with objectively measured heavy menstrual bleeding to women with measured normal menstrual loss, to correlate actual measured menstrual blood loss with the individual woman’s perceptions of her bleeding, and to compare women who perceive they have heavy menstrual bleeding with women who perceive their bleeding to be normal in relation to their assessment of the impact of menstrual bleeding on their quality of life.

Background & methodology

Heavy menstrual bleeding has a significant effect on women’s daily life and economic consequences for society. This thesis presents the results of a novel study of a self-selected group of women from the NSW community, who responded to an online survey by a market research company. The survey asked a range of questions around menstruation and the woman’s perception and tolerance of the menstrual cycle. Of 1,575 women who answered the original survey and 628 of these offered to participate in further research about menstruation. Most of these women were contacted later by phone and 63 agreed to take part in the present study. The sixty-three respondents had their menstrual blood loss (MBL) measured for three cycles using the alkaline haematin method. Women were categorised according to measured blood loss into normal or heavy menstrual bleeding groups. Women with more than 80 mL of blood loss for at least two cycles were included in the heavy group. Data were analysed using SPSS version 20. Alpha was set at 0.05 for all analyses.
Results

The 63 participants (10%), out of the group of 628 who were interested in further research and agreed to collect their used sanitary protection, were not significantly different from the original group. Women with measured HMB comprised 16%. Women with demonstrated HMB were more likely to be older than women with normal menstrual blood loss. There were no significant differences in quality of life parameters or seeking medical consultation between the two groups. There was no significant association between perception of women of their menstrual bleeding and estimated menstrual blood loss. However, there were significant differences between women who said that they had mild or moderate bleeding, women who said that their bleeding was heavy and women who said their bleeding was very heavy in some aspect of their quality of life assessments.

There was significant correlation between the amount of menstrual bleeding and the duration of bleeding ($r = .40$, $p < 0.001$). There was also a significant strong correlation between the amount of the menstrual blood loss (the mean of the three cycles) with serum ferritin, transferrin, TIBC, and a weak correlation with haemoglobin. There was a significant association between menstrual pain and quality of life parameters and also a strong association between the degree of menstrual pain and seeking a medical consultation. However, there is no correlation between the severity of the menstrual pain and the amount of menstrual blood loss. There was no significant difference in variability of menstrual cycles between women with measured HMB and women with measured NMB. In the sample of 25 women, low serum ferritin levels were not associated with low general health parameters.
Conclusion

In conclusion, estimated heavy menstrual bleeding was found not to have any a significant impact on women’s physical, psychological and social well-being, quality of life or their medical consultation behaviour. It could be said that women’s perceptions of their menstrual bleeding does not reflect the amount of their menstrual bleeding but can affect their quality of life assessment and thus their behaviour regarding medical consultation. There is a strong association between women’s perception of menstrual bleeding and their scores on quality of life. Women who perceive their bleeding as heavy have a low score on quality of life and these women tend to have more medical consultations than women with normal quality of life scores. Pain during the menstrual period can profoundly effect women’s quality of life. Women who have moderate or severe pain during the period were more likely to have poor quality of life and more likely to ask for medical consultation than women with mild pain. The study also indicates that menstrual blood loss is positively correlated with age, duration of menstrual bleeding and practical difficulties and is negatively correlated with serum ferritin, transferrin, total iron binding capacity and haemoglobin level.
Acknowledgements

In this section, I wish to express my gratitude to all people who assisted; guided and accompanied me throughout the period of working on the thesis. Firstly, I would like to offer my deepest appreciation to my supervisor, Dr.Edith Weisberg and my associate supervisor Prof. Ian Fraser. Dr.Edith Weisberg has guided me whole-heartedly and provided me with lots of support. She was like a mother to me and she was very patient with me in my difficult circumstances. I thank her for her advice and guidance throughout the project. Prof. Ian Fraser has shared his invaluable experience and knowledge and helped me in building up my own professionalism within the gynaecology research field. I thank him for all encouragement and support throughout the project.

I would also like to express my sincere thanks to Dr. Robert, Dr. Frank Manconi and all doctors and scientists at Queen Elizabeth II Research institute for Mothers and Infants, Department of Obstetrics & Gynaecology, University of Sydney, for their help, appreciation and organising all the activities in the department. Special thanks to my mentor Dr. Frank Manconi who help me in laboratory work. He patiently tolerated my mistakes during the laboratory work period. The process could not have been facilitated so smoothly and successfully without his assistance.

Also, I wish to give special thanks to Jane Hangan and all the staff at the Family Planning NSW Ashfield Centre. Jane was the person responsible for teaching participating women how to collect their sanitary protection. She helped me and gave me all the information about the participating women that I needed. The support she has given to me will never be forgotten. She deserves thanks for her support and tolerance.
Thanks also go to the women who have participated in this study. They have spent their time completing the questionnaires and collecting their sanitary protection, sharing their valuable experiences thus providing us with a clear picture and understanding of the needs and sufferings of women with heavy menstrual bleeding.

Lastly, I would like to present my warmest thanks to all of my family members they have provided me with unlimited support throughout my study period and taken good care of me.
Declaration

I declare that this thesis represents my own work, except where due acknowledgement is made, and that it has not been previously included in a thesis submitted to this University or to any other institution for a degree, diploma or other qualification

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<td>AUB</td>
<td>Abnormal uterine bleeding</td>
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<tr>
<td>BBT</td>
<td>Basal body temperature</td>
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<td>BMI</td>
<td>Body mass index</td>
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<td>COCs</td>
<td>Combined oral contraceptives</td>
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<td>DNA</td>
<td>Deoxyribonucleic acid</td>
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<td>DNG</td>
<td>Dienogest</td>
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<tr>
<td>E2V</td>
<td>Estradiol valerate</td>
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<tr>
<td>ECM</td>
<td>Extracellular matrix</td>
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<tr>
<td>EGF</td>
<td>Epidermal growth factor</td>
</tr>
<tr>
<td>FIGO</td>
<td>International Federation of Gynecology and Obstetrics</td>
</tr>
<tr>
<td>FPNSW</td>
<td>Family Planning New South Wales</td>
</tr>
<tr>
<td>Hb</td>
<td>Haemoglobin</td>
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<tr>
<td>HMB</td>
<td>Heavy menstrual bleeding</td>
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<tr>
<td>IMB</td>
<td>Irregular menstrual bleeding</td>
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<tr>
<td>LMP</td>
<td>Last menstrual period</td>
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<td>LNG-IUS</td>
<td>Levonorgestrel-intrauterine system</td>
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<tr>
<td>Measured NMB</td>
<td>Normal measured menstrual bleeding</td>
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<tr>
<td>MBL</td>
<td>Menstrual blood loss</td>
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<td>MEAEA</td>
<td>Microwave endometrial ablation</td>
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<tr>
<td>MMP</td>
<td>Matrix metalloproteinase</td>
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<td>NCS</td>
<td>Nucleolar channel system</td>
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<td>Non-steroidal anti-inflammatory drugs</td>
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<td>PGE2</td>
<td>Prostaglandin E2</td>
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<td>PGI2</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>PR</td>
<td>Progesterone receptor</td>
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<tr>
<td>RCOG</td>
<td>Royal College of Obstetricians and Gynaecologists</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised clinical trial</td>
</tr>
<tr>
<td>SLE</td>
<td>Systemic lupus erythematosus</td>
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<tr>
<td>TIBC</td>
<td>Total iron binding capacity</td>
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<tr>
<td>VEGF</td>
<td>Vascular endothelial growth factor</td>
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<tr>
<td>VSMC</td>
<td>Vascular smooth muscle cell</td>
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Chapter 1: Normal menstruation

This chapter provides a background to the main focus of this thesis, which is an exploration of the characteristics of women experiencing heavy menstrual bleeding, compared with those who have normal menstrual periods. This initial chapter provides a review of relevant aspects related to normal menstrual bleeding and includes: definition, history and epidemiology of normal menstrual bleeding and variability of the menstrual cycle with different clinical parameters. At the end of this section, the relevance and interactions of iron stores and metabolism on women’s wellbeing in relation to menstruation are included. This chapter will also describe endometrial changes during the menstrual cycle and evaluate the role of steroid hormones and their interaction with epithelial and stromal cells of the endometrium.

1.1. Menstruation - definition, myths and historical issues

At the end of each primate ovarian cycle, a superficial part of the endometrium undergoes necrosis with sloughing of the tissue coupled with some blood loss. At same time, the circulating gonadal steroids reach their lowest level in the cycle (Shaw et al., 2003). Withdrawal of these steroids is responsible for triggering the onset of this menstrual endometrial breakdown.

There has been confusion about an agreed definition for the process of normal menstruation but most physicians have agreed with a clinical definition that includes words such as a periodic, regular discharge of blood and tissue from the uterus and vagina of reproductively mature females, which follows a specific sequence of ovarian oestradiol and progesterone changes, and which usually lasts between 3 and 6 days per month (Woolcock et al., 2008). Patterns and perceptions of menstruation have been studied in cross-cultural studies on
women’s patterns and perceptions of menstruation. Data from a World Health Organization international study (Christian et al., 1983) suggest that family planning providers should be aware of women’s preferences about menstruation. Later, an international project (The FIGO Menstrual Disorders Working Group) was established to develop an agreement process to recommend clear, simple terminologies and definitions with wide acceptance (Fraser et al., 2006). According to the FIGO recommendations (Fraser et al., 2011), normal menstruation and the normal menstrual cycle should be defined according to the following parameters: (1) regularity of menses, (2) frequency of menses, (3) heaviness of menstrual flow, and (4) duration of menstrual flow, and these parameters should be defined on the basis of previously published population studies using medians and confidence intervals, and anything outside these limits should be regarded as abnormal uterine bleeding (AUB). The limits of these parameters will be discussed further in this chapter in relationship to data from population studies (Chistian et al., 1983, Belsey et al., 1997, Treloar et al., 1965, and Hallberg et al., 1966).

In historical times, there were conflicting views about the origins of this mysterious recurring process and many myths arose about its meaning (Fraser et al., 2011). Menstruation was initially assumed to be a periodic excretion of blood and mucus from the uterus occurring at the time of ovulation (as in the oestrous cycle of animals), and it is only in the middle of the last century that, decidualisation and then necrosis of this differentiated tissue at around 14 days post-ovulation were defined as essential features of the normal menstrual process (Fraser et al., 2011).

The unique physiological phenomenon of menstruation and the range of symptoms and consequences which have been discovered to sometimes be associated with disturbances of
this process have provided an enormous literature in both historical and modern times, ranging through definitions, descriptions, terminologies, myths, epidemiology, anatomy, mechanisms and physiology, cyclical symptoms, pathophysiology, classifications of pathologies, and a wide range of clinical issues around the diagnosis, investigation and management of abnormal uterine bleeding and related symptoms (Woolcock et al., 2003).

During the seventeenth century, a different style of language was used to refer to menstruation. The terminology ranged from words considered to be poetic, for example "the flowers", through the neutral, "the terms", "the courses" and "the months", to expressions which provide a picture of female weakness, "her sickness", "her monthly disease" and "the monthly infirmity" (Crawford et al., 1981). Numerous bizarre myths have arisen and been perpetuated over the millennia since formal literature became recorded in Greek and Roman times. The Greek philosopher Aristotle first stated that exposure to menstrual fluid could take the shine off a mirror. Some of the most disturbing myths were promoted by Pliny the Elder, the Roman philosopher and historian in the second century AD. His negative views were to have a major influence on male perspectives of menstruation well into the mediaeval era. Even as late as the 19th century, it was believed that a menstruating woman may give dog intestinal worms by patting it on its head (Burliuk et al., 1987).

Throughout history, consideration of menstruation by different societies has taken many diverse social directions (Hoskins et al., 2002). Many societies have considered normal menstruation to be a “problem” (Fraser et al., 2011). Publication of ‘blood magic’ (Buckley & Gottlieb, 1988) explains three aspects in understanding the myths of menstruation. First, it refutes the view of a universal taboo, which exists in all societies. It also suggests that menstruation is not always linked to female subordination, and that in some societies
menstrual fluids may have some empowering, rather than negative characteristics (Hoskins et al., 2002). In 1993, the biologist Margie Profet raised the controversial theory that menstruation functions as a defence against pathogens transported by sperm into the female reproductive tract (Clough et al., 2002). Lastly, it is only in the last one to two decades that the word “menstruation” has become used widely in the public arena in most societies. However, it has been used as a scientific and medical term since the 17th century (Crawford et al., 1981). Current scientific terminology also uses “monthly periods” and “menses” widely, whereas vernacular speech uses a very wide range of euphemisms, which are often appropriate to a particular community (Woolcock et al., 2008).

1.2. The variability of the menstrual cycle

The menstrual cycle is an integral part of women’s reproductive lives. There is considerable variability between women in patterns of bleeding and in the amount of blood lost during menstruation and also between cycles in individual women, especially at both ends of their reproductive life (Woolcock et al., 2008). Excessive menstrual blood loss has considerable impact on a woman’s wellbeing and health. Making an accurate clinical diagnosis of heavy menstrual bleeding is difficult, because usually it is based on the individual’s subjective experience, perception, tolerance and reporting of periods, which makes it difficult for a physician to estimate volume and pattern of blood loss. Terminologies and definitions around the parameters that describe the “normal” menstrual cycle as a whole were even more uncertain and controversial than those which describe normal menstrual bleeding (Woolcock et al., 2008). Indeed, population variations in amount and duration of menstrual flow have been explored only in limited research worldwide (Harlow et al., 2004).
1.3. Normal menstrual parameters

The variability of different menstrual characteristics from different population studies created difficulty in finding agreement about normality of the menstrual cycle. According to Fraser et al. (2007), the suggested normal limits for explaining normal menstrual parameters (such as regularity, frequency, duration, volume of menstrual blood loss) are briefly explained in the following sentences. Normal frequency of menses is considered from 24-38 days, and cycles lasting more than 38 days are considered as fairly infrequent and less than 24 days as frequent. These slightly irregular cycles (and longer or shorter cycles) are more likely in women who have polycystic ovary syndrome or are at the extremes of the reproductive life cycle. Cycle variation over 12 months is considered regular if the variation is between 2 to 20 days. A variation of more than 20 days means clinically relevant irregularity of the cycle.

Duration of flow (days) for a normal period is between 4.5 to 8 days. A prolonged period lasts more than 8 days, while short duration is less than 4.5 days. The volume of monthly blood loss is defined, for research purposes, as normal between 5 and 80 mL, > 80mL as heavy, <5 mL as light (Fraser et al., 2007). These parameters will be discussed in more detail in the epidemiology of menstruation section in relation to length, duration and amount of flow of the menstrual period, variability of menstrual phases and ovulation, relation of ovarian steroids and menstrual characteristics, and the variability of the menstrual cycle in women with variants of normal physiology and some chronic diseases.

1.4. Variation in menstrual cycle length, duration and amount of flow

1.4.1. Menstrual cycle length

Knowledge of the length and variation of the menstrual cycle is required for the assessment of menstrual irregularities and assessment of fertility, and these variables have been studied in
large prospective studies over many decades. Treloar et al. (1968) examined data from 2,700 US women aged 10-56 years extending initially over a period of 29 years. His study revealed that the normal cycle length varied, at all ages, around a median value of 28 to 29 days (Treloar et al., 1965). Other large cross-sectional studies were made by Chiazze et al. (1968) and by the WHO Task Force on Methods for the Detection of the Fertile Period (World Health Organization, 1983). In most studies, the women were often drawn from selected groups such as college women or patients in general practice. In the longitudinal studies, a significant percentage of women, for undetermined reasons, were sometimes unable to be followed up. Therefore, the degree to which these women’s menstrual patterns were representative of all women in the population is unclear. Moreover, changes in contraceptive use and decrease in the number of births in the past 35 to 40 years probably have an effect on current menstrual patterns (Munster et al., 1992).

1.4.2. The length of menstrual cycle in relation to the age

Among a review of different studies regarding menstrual cycle length, those that describe the distribution of cycle lengths by age include a series of cross-sectional analyses of population mean cycle length and population variation from menarche to menopause. They reveal that population variability in menstrual cycle length is high immediately after menarche and shortly before menopause, with transition time to or from regular cycles lasting 2-5 years (Harlow et al., 1995). A systematic review of 15 studies in developing countries has examined the age at menarche, timing of reproductive maturation and menstrual characteristics, including normative patterns of menstrual function and rate of occurrence of dysmenorrhoea (Harlow et al., 2004).
Menstrual periods after menarche and before menopause are characterized by an increased frequency of both very long and very short cycles and consequently, by an increased range of cycle lengths. In the literature, the most consistent predictor of cycle length is a woman’s age. Cycles become shorter as women get older through the early menopause transition and then become markedly more variable in the mid to late-menopause transition (Jukic et al., 2007).

Figure 1.1 shows the scope of changes in variability of intervals between onsets of menstrual cycles with age through the years of menstrual occurrence. The two decades from age of 21 to 39 are notable for comparative compactness in variation. Beyond these two decades, the dispersion increases rapidly below 20 or above 40 years (Treloar et al., 1965).
Figure 1.1: Contours for frequency distribution (medians and centiles) of all menstrual intervals changing with age of the woman (Treloar et al., 1965).
1.4.3. Duration of bleeding and amount of flow

Duration of bleeding is the duration from the onset of the 1st day of menses up to the end of the last day (Fehring et al., 2006). Duration of bleeding after an ovulatory cycle can range from 2 to 12 days and over 80% of women have bleeding lasting 3 to 6 days, with the heaviest flow usually occurring on the second day of the cycle (Harlow et al., 1995). Information on variation in amount of menstrual blood loss was provided by a Swedish population–based study (Hallberg et al., 1966). Among women who considered their blood loss as normal, the mean loss was 38.5 mL, and according to this study, based on declining haemoglobin levels, a blood loss of 80 mL is the upper limit of normal for menstrual flow. Figure 1.2 shows the distribution of menstrual blood loss in the Swedish study and it is seen that it is skewed to the right, which could be partly explained by an increased frequency of values from abnormal subjects in the right tail of the distribution curve. In a WHO (1983) five country study using the ovulation method to detect menstrual cycle phases, the mean length of bleeding was 5.0 ± 1.3 days although the mean varied from 4.3 days for women in Manila to 5.9 days for women in Dublin (Fehring et al., 2006).

A systematic review of some adolescent studies in developing countries provided data on early variations in menstrual flow. In Nigeria 1% of girls had menses that lasted more than 7 days, 4% considered they had heavy flow and 24% had cycles shorter than 21 days (Harlow et al., 2004). In another Nigerian study, 12% of teenage girls had heavy menstrual bleeding based on a blood loss of more than 80 mL measured by the alkaline haematin method (Barr et al., 1998). In Turkey, short cycles were reported in 7% of adolescent girls in a study based on questionnaire assessment of the menstrual cycle (Vicdan et al., 1996).
In the Hallberg et al. (1966) population study, self-judgment of menstrual blood loss did not provide an accurate indicator of the amount of bleeding. Among women with measured blood loss exceeding 80 mL, 37% considered their bleeding to be moderate and 4% considered it as light. However, in women with measured blood loss less than 20 mL, 14% considered their blood loss as heavy. In a study of women presenting with a convincing clinical history of heavy bleeding, only 38% had objective heavy menstrual bleeding with a measured loss greater than 80 mL (Fraser et al., 1984). Therefore, it appears that women often cannot reliably assess the normality of their own blood loss. In fact, the high possibility of misclassifying blood loss indicates that simple self-reports are not adequate for clinical research assessment of heavy menstrual bleeding (Harlow et al., 1995).

Figure 1.2: Menstrual blood loss in a population sample of women working in a single factory in Goteborg (Hallberg et al., 1965)
1.5. Variability of menstrual cycle phases and ovulation

There are different causes of menstrual cycle variability that essentially disrupt or suppress the rhythms of the hypothalamic-pituitary-ovarian axis. Most of the variability in the follicular phase is attributed to defects in the process of follicular growth (Jukic et al., 2007). Variability in the luteal phase may be due to defects in the ovulatory process, defects in development of the corpus luteum or defective corpus luteum function leading to insufficient production of oestrogen and progesterone. The variability of the luteal phase is thought to be less than that of the follicular phase. How the variability of each phase differs or relates to one another in individual women is unknown (Jukic et al., 2007).

The mean length of the follicular phase declines with age, from approximately 14 days at age 18-24 years to about 10.5 days at age of 45-55 years (Harlow et al., 1995). However, one recent publication observed an increase of follicular phase length after the age of 37 from 14.6 to 15.9 days (Fitzgerald et al., 1994).

The timing of ovulation can be very variable within and between women and the source of this difference is essentially unknown. On the other hand, the time between ovulation and the onset of the next menses is relatively stable. Thus, variability in the length of the follicular phase is a significant contributor to menstrual cycle variability (Jukic et al., 2007). One review of studies conducted in 1995, 1999 and 2000 demonstrated that the fertile phase of the menstrual cycle is about 6 days including the day of ovulation and the 5 days prior (Fehring et al., 2006). In many studies, ovulation is detected by different methods. Some have used the basal body temperature (BBT) shift as a sign of ovulation and determined that the follicular phase ranged from around 11 to 27 days and the luteal phase from 7 to 15 days (Fehring et al.,
2006). Others used the peak day of cervical mucus or daily measurements of serum oestradiol and progesterone. These differences in methods used to assess ovulatory status create disparities in detecting menstrual phase length (Harlow et al., 1995).

1.6. Variability of ovarian steroid and menstrual characteristics

Many studies have examined the hormone profile of the menstrual cycle, but the value of some studies is questionable, because some collected single or infrequent samples for hormone measurement. Those studies of daily samples through the whole cycle are able to assess the day-to-day, within-woman variation in oestrogen and progesterone production and the significant variability, although these studies are of small size. Cross-sectional studies of multiple single specimens typically collected from cycling women are a relatively weak indicator of integrated ovarian hormone production throughout the whole menstrual cycle or longer periods of time (Westhoff et al., 1996). A review of studies looking at factors affecting serum progesterone and oestradiol levels during the menstrual cycle reported conflicting results (Westhoff et al., 1996). One population study evaluating the relationship between hormone levels and cycle characteristics (Harlow et al., 1995) revealed that a high preovulatory peak oestradiol was often associated with a shorter follicular phase. Another study looking at hormone levels during the cycle in relation to menstrual and demographic characteristics documented that late age at menarche was associated with increased urinary and serum progesterone levels. Increased body weight was associated with decreased progesterone levels but no association was found between weight and age at menarche and oestrogen levels. Cigarette smoking was associated with a decline in mid-cycle and luteal-phase oestradiol levels (Westhoff et al., 1996). However, in another cohort study, there was a suggestion of no difference in maximum luteal-phase serum progesterone by age at menarche (Apter et al., 1989).
1.7. Epidemiology of dysmenorrhoea, amenorrhoea and infrequent bleeding

1.7.1. Dysmenorrhoea

Dysmenorrhoea is a symptom characterised by severe uterine pain during menstruation, which occurs as cyclical lower abdominal or pelvic pain, and may radiate to the back and thighs. Primary dysmenorrhoea is defined when there is no detected co-existent pathology, and secondary dysmenorrhoea when there is an underlying pathological condition known to contribute to painful menstruation (Deligeorglou et al., 2000). The pain associated with secondary dysmenorrhoea may be associated with other gynaecological symptoms caused by the underlying pathology, such as cycle irregularity, heavy periods, dyspareunia, vaginal discharge, inter-menstrual bleeding and post-coital bleeding (Deb et al., 2008). Endometriosis is a disease commonly associated with secondary dysmenorrhoea. One large study found that a later age of menarche is inversely associated with the subsequent development of endometriosis and early dysmenorrhoea is often an indication of endometriosis (Jungheim et al., 2010). Women who were aged 14 years or older at menarche were less likely to develop endometriosis than women with an earlier menarche.

There are some cross-sectional studies studying dysmenorrhoea in different aged women. In one cross-sectional survey 30-60% of women of reproductive age had experienced menstrual pain. However, the proportion of women with severe pain which interfered with daily activity was considerably lower, ranging from 7 to 15% (Harlow et al., 2000, Klein et al., 1981). It was noted that young women (17-24 years old) have a greater prevalence of dysmenorrhoea, (67 to 72%). In fact, with the onset of ovulatory cycles it could be expected that the prevalence of dysmenorrhoea during adolescence increases with gynaecological age (Klein et al., 1981). In a systematic review of studies from developing countries, about 25–50% of
adult women and around three-quarters of adolescents gave a history of pain with menstruation, with about 5–20% of women reporting severe pain which interfered with their usual activities. These data were comparable to those noted in studies of American, European and Australian women (Harlow et al., 2004).

1.7.2. Amenorrhoea and infrequent menstrual bleeding

Primary amenorrhoea is defined as no spontaneous occurrence of menstruation by the age of 16 years, and secondary amenorrhoea is the absence of menstruation for 6 months or longer if the patient has a previous history of regular cycles or for 12 months or more if the patient has infrequent cycles (Munster et al., 2010). Infrequent cycles are defined as a reduction in occurrence of menstruation, where menstrual intervals may vary between 6 weeks and 6 months. However, regular but long cycles of 6 weeks often cannot be distinguished physiologically from normal shorter, 28-day cycles in regard to follicular formation, ovulation and hormonal profile. On the other hand, long irregular cycles often indicate chronic anovulation, other ovulatory disturbances, absence of mid cycle gonadotrophin surges and prolonged hypo-oestrogenism. Therefore, infrequent cycles can include a range of conditions between normality and amenorrhoea (Munster et al., 2010). Concerns or worries of affected women about their menstrual variability may vary greatly, depending on their awareness of menstrual physiology, their understanding of the probable aetiology of the menstrual dysfunction, as well as their personal beliefs, acceptance, and cultural background.

The frequency of amenorrhoea according to some studies in developing countries is about 5-9%, which is comparable to the prevalence documented in population-based surveys in Europe (Pettersson et al., 1973). In one study, prevalence was 11.3% for infrequent cycles (lengths of 35-90 days) and 2.6% for amenorrhea of more than 90 days among US college
women. Although irregular cycles per se are not often associated with adverse health outcomes, irregular cycles or amenorrhea may be associated with polycystic ovary syndrome and infertility, which is most distressful for women in many developing countries (Inhorn et al., 1998). Irregular bleeding may also be a sign of cancer, particularly in postmenopausal women. In one systematic review, women with cervical cancer were almost six times more likely and women with pelvic tenderness or adhesions were about three times more likely to have spotting than other women (Harlow & Campbell, 2004). Lastly, evaluation of abnormal menstrual patterns in adolescence may assist in early recognition of potential health conditions in adulthood. Figure 1.3 demonstrates some conditions, which may result in irregularities or loss of the menstrual cycle (Popat et al., 2008).

1.8. Life style and environmental factors associated with menstrual cycle variability

There is limited information in the literature on population variation in duration and amount of menstrual bleeding in regard to socio-demographic, behavioural and reproductive characteristics. In Western populations, longer menstrual cycles were associated with higher body mass index (BMI), later age of menarche, high parity, and current use of oral contraceptives (in the last 90 days). Shorter menstrual cycles and shorter follicular phases were associated with less education, excessive caffeine intake, and more alcohol consumption (Jukic et al., 2007). In one study, recent smoking was associated with shorter cycle lengths and inter-menstrual bleeding (Kato et al., 1999) but another one found it had no effect (Hornsby et al., 1998).

Assessment of regional differences in menstrual parameters is very limited in the literature. Some data suggest that Mexican and Latin American women have shorter bleeding episodes (mean = 4 days) while European women have longer episodes (mean = 5.9 days) than women
in other regions (Belsey et al., 1988). Studies in Chinese women suggest they have both longer and heavier bleeding (Harlow et al., 1995). One study has also suggested an association between socioeconomic-status and variability in menstrual cycle functions (Jeyaseelan et al., 1993). Age of ovulation onset has been examined as an important factor in regional differences in menstrual function. In one systematic review, one epidemiological survey in Nigeria revealed that Nigerian girls have ovulatory cycles earlier compared with girls from industrialized countries (Harlow & Campbell, 2004). Timing of follicular development is also relevant to menstrual cycle length. The shorter bleeds noticed in Mexican women may be related to shorter follicular phases and longer luteal phases, compared with women from other countries (World Health Organization, 1983).

Figure 1.3: Some pathological conditions associated with amenorrhoea or irregular menstrual cycles (Popat et al., 2008).

According to many studies, life style and physical activity can affect menstrual function. Women athletes, particularly ballet dancers and runners, have a high frequency of
amenorrhoea, anovulation and luteal phase defects compared with non-athletes (Lawson et al., 2011). Several studies have evaluated the relation between shift work and menstrual cycle pattern or length, but most of them have small sample sizes or few women exposed to shiftwork (Lawson et al., 2011). One study found an increased risk of short and long menstrual cycles and cycle irregularity in nurses who worked rotating shifts (Lawson et al., 2011). Similarly, intercontinental flight attendants tend to have increased irregularity of their cycles.

1.9. Variability of menstrual cycle in relation to women with certain chronic diseases
Menstrual cycle characteristics, most particularly length of the menstrual cycle, have also been identified as risk factor for some health conditions such as coronary heart disease, and risk of bony fracture (Harlow & Ephross, 1995, Weinstein et al., 2003). Some researchers have also found a link between diabetes and cycle characteristics. However, recent work found no association between adult-onset diabetes and mean cycle length, number of long cycles, or cycle variability. In this regard, current data on menstrual cycle characteristics as a risk factor for chronic disease suggest areas of research which can be productive in explaining women’s long-term health status and identify prevention strategies for pre-menopausal women (Weinstein et al., 2003).

1.9.1. Polycystic ovary syndrome
Polycystic ovary syndrome (PCOS) is considered the most common cause of anovulatory infertility in women of reproductive age. It is typically characterised by hyper-androgenism and chronic anovulation. Hyper-androgenism may present as hirsutism, acne, or male-pattern alopecia. Anovulation is manifest as irregular, usually infrequent, menstrual cycle or even amenorrhea, and infertility (Diamanti-Kandarakis & Panidis, 2006).
1.9.2. Immune function and autoimmune disease

Sex hormones affect differentiation, and function of lymphocytes, modulate immune regulatory mechanisms, and have an influence on monocyte and macrophage activity (Ansar et al., 1985). Some reports have recognized worsening of systemic lupus erythematosus (SLE) symptoms during the luteal phase (Oertelt-Prigione, 2012). Some have found a worsening of multiple sclerosis (MS) symptoms premenstrually in several clinical cohorts (Oertelt-Prigione, 2012).

1.9.3. Asthma

Premenstrual exacerbations of asthma have been confirmed by several studies. In addition to premenstrual exacerbation of asthma, a high rate of hospitalisation rates for complications and respiratory failure occurred at the same time during the hormonal cycle (progesterone acts as a smooth muscle relaxant on bronchial muscles and increases respiratory rates (Oertelt-Prigione, 2012).

1.9.4. Diabetes

Oestrogens appear to have different effects on glucose tolerance in healthy and diabetic women (Strotmeyer et al., 2003). Some studies have identified slower gastric emptying times and lower glycaemic levels during the follicular compared to luteal phase in healthy women while there is a strong suggestion of peri-menstrual worsening of glycaemic control, this may be due to slower gastric emptying in the luteal phase due to the myo-relaxant effect of progesterone (Oertelt-Prigione, 2012).
1.10. Effect of iron stores on women’s wellbeing

Iron deficiency can affect women’s quality of life and work performance even in the absence of anaemia. A decrease in blood haemoglobin is a late event of iron deficiency anaemia. Reduced iron availability and iron store depletion occur first and are reflected in low serum ferritin and transferrin levels. Then, iron deficiency anaemia will develop by iron deficient erythropoiesis, in which the levels of transferrin saturation are decreased while haemoglobin level remains normal (Martinovic et al., 2010). In one recent longitudinal study on general women’s health, 20% of women of reproductive age had a serum ferritin concentration less than 15 µg/L (indicating severe iron deficiency) and only 4% of these women had iron deficiency anaemia. In one study, non-anaemic women with unexplained fatigue had a great benefit from iron supplementation, and this benefit was more obvious in women who had low or border line serum ferritin concentration (arguably any level below 50 µg/L) (Verdon et al., 2003).

1.10.1. Iron metabolism

Iron is distributed widely throughout the human body with about two thirds contained in circulating red cells as haemoglobin, 15-25% is stored as ferritin and haemosiderin, 8% in muscle myoglobin, cytochromes and iron containing enzymes. Iron is bound and transported in the body by transferrin and stored in ferritin molecules. Plasma transferrin contains about 3 mg iron. However, the daily exchange of iron through plasma transferrin is ten times this amount. Iron is transported by transferrin to erythroid and non-erythroid cells where it binds to the transferrin receptor and the complex enters the cell by a receptor-mediated endocytosis. Inside the target cell iron is released and the transferrin receptor is recycled to the surface (Harrison & Arosio, 1996). Once iron is absorbed, there is no physiologic process for
excretion of excess iron from the body, unless in blood loss (and small amounts in skin exfoliation). Only about 1 mg Fe/day is absorbed in the body in normally healthy adults and this amount represents 10% of food iron. The main iron storage in the body is in the liver, spleen, bone marrow and muscle. Iron metabolism is a highly conserved process, characterized by recycling. Red blood cells are destroyed, their haemoglobin catabolised and the resultant iron is used in the synthesis of haemoglobin, myoglobin and a multiplicity of other iron requiring enzymes (Conrad & Umbreit, 2000) (Figure 1.4).

Figure 1.4: Iron is bound and transported in the body via transferrin and stored in ferritin molecules [adapted from Google image (2-Oct-2012)]. Originally, from the Centres for Disease Control, USA. http://www.cdc.gov/ncbddd/hemochromatosis/training/pathophysiology/iron_cycle_popup.htm.
1.11. Normal menstrual cycle

1.11.1. Introduction

The menstrual cycle is complex and regularly recurrent sequence of events that involves the hypothalamus, anterior pituitary, ovary, endometrium and a number of other organs (Hawkins et al., 2008). During a woman’s reproductive life, she experiences menstrual cycles which last approximately 28 days. However, a variable length between 24 and 38 days is considered as the normal range for a normal menstrual cycle (Fraser et al., 2011) only 80% of adult women fall in the range 25 to 38 days (Treloar et al., 1970, Matsumoto et al., 1962, Woolcock et al., 2008). It is very important that there is systematic exclusion of cases with infertility issues and disorders such as undiagnosed polycystic syndrome as these affect normal menstrual cycle variability. Variability of the ‘normal’ cycle is greatly increased by undiagnosed PCOS patients. One study found tighter between-individual variances and within-individual variances compared with other epidemiological studies on menstrual cycle length and variability after exclusion of abnormal cycles (Cole et al., 2009).

A modern woman living in a developed country and not using hormonal contraception may menstruate up to 450 times during her reproductive life. In comparison, women in primitive human societies before they had access to reliable contraception enabling them to effectively control their fertility were amenorrhoeic for long periods of their lives. This was due to a later onset of puberty, larger numbers of pregnancies, and prolonged lactation after each pregnancy (Hillard, 2008).

The length of the menstrual cycle also varies throughout a woman’s reproductive life. Cycles are generally regular between the ages 20 to 40. Cycle lengths tend to be longer and erratic in
the period after menarche and also vary greatly from short to long in the menopause transition (Treloar et al., 1970, Vollman et al., 1977). According to Hillard (2008) menstrual cycles tend to vary greatly among adolescents, with “normal” cycle lengths of 20 to 45 days and a mean cycle length of 32.2 days in the first and second years after menarche.

Many aspects of the menstrual cycle are complex and are generally considered in three or four separate phases (the menstrual, proliferative (or follicular), ovulatory and secretory (or luteal)). This part will describe the endometrial phases of the menstrual cycle and consider the roles of steroid hormones and their interactions with epithelial, stromal and other cells of the endometrium. Delineation of endometrial physiology and the ovarian cycles is essential for the development of therapies for rational management of gynaecological disorders, and can provide explanations for many pathological conditions. Indeed, understanding endometrial repair may produce new therapeutic targets for managing heavy and prolonged menstrual bleeding (HMB).

1.11.1. The menstrual cycle at the endometrial level

The endometrium is the main and most obvious end-organ for ovarian sex hormone action. It has a complex and dynamic blood and lymphatic vasculature which goes through regular cycles of growth and breakdown. These cyclic changes are results of variations in circulating sex steroids and uterine blood flow and result in cyclic patterns in tissue oxygenation, haemostasis, nutrient supply, fluid balance and leukocyte distribution (Girling et al., 2012).
The functional layer of the endometrium is the superficial layer of the uterine lining which will thicken under the effect of ovarian hormones and then slough. The endometrial cycle is divided into four phases, (1) the menstrual phase, (2) the post menstrual phase, (3) proliferative phase, (4) the secretory phase (Somers et al., 2003). In fact, the proliferative and secretory phases of the endometrium correspond to the follicular and luteal phases of the ovary respectively. The effects of different concentrations of oestrogen and progesterone during the different phases of a normal menstrual cycle have characteristic effects on the endometrium (Figure 1.5) (Siddiqui et al., 2007).

![Figure 1.5: Key aspects of the different phases of menstrual cycles (Siddiqui, 2007).](image)

### 1.11.1. The menstrual phase (Cycle days 1 to 5)

This frequently lasts from day 1 to day 5 with most women bleeding for 3 to 5 days. During this in the absence of pregnancy, the shedding of the endometrium occurs in response to falling levels of oestradiol, inhibin A and progesterone (Chemist & Druggist, 2012). Women experience this as cyclical “blood loss” although menstrual fluid contains a high percentage of tissue fluid as well as mucus from the uterine glands, glandular tissue of the endometrium and 35 to 45% blood (Doria, 1999).

### 1.11.1.2. Uterine contractility

In a normal menstrual cycle the uterine contractility is considered to be at its greatest in the first two days of the menstrual cycle (Shaw et al., 2003). These contractions assist in expulsion of necrotic endometrial fragments from the uterus. Perception of contractility by
women is varied, although it is probably fairly constant between cycles in the same woman. In fact, there is no simple objective tool to recognize abnormal from normal contractility, but it could be considered that the degree of pain associated with markedly increased contractility which interferes with a woman’s ability to carry out her daily activities, is abnormal. The pattern of natural myometrial contraction is different in each menstrual cycle phase (Deziegler et al., 2001, Show et al., 2003). In the follicular and periovulatory phases; the contractions follow the pattern of cervico-to-fundal direction in the sub-endometrial layer. It is postulated that the preovulatory cervico-fundal contractions have a function in aiding the transport of sperm through the female genital tract (Deziegler et al., 2001, Show et al., 2003).

1.11.1.3. Factors controlling the menstrual phase

There is controversy about whether the main effects in the menstrual phase are controlled by hormonal or prostaglandin effects. The absence of oestrogen and progesterone receptors in myometrial vessels demonstrated through immunohistochemistry indicates that prostaglandins are more likely to be responsible than sex hormones for the vasoconstriction phenomena (Ferenczy, 1993). On other hand, at the level of the endometrium, oestradiol and progesterone have a major role in regulation of the cyclical transformations and prevention of cell death and, also have an effect on cyclical shedding during menstruation (Chabbert et al., 2002). Indeed, as a result of a defect in coordination of oestrogen and progesterone, inappropriate thickening or decidualization of the endometrium can cause many clinical conditions like breakthrough bleeding, irregular menses or cancer. Recently, one study has shown that the expression of many genes is different in the endometrium of normal women compared to the endometrium of a patient with severe endometriosis and the most significant dysregulation occurred in the progesterone–responsive genes (Hawkins et al., 2008).
There is a concept that menstruation occurs as a consequence of enzymatic auto-digestion with matrix-metalloproteinases (MMP) and prostaglandin-mediated ischaemic necrosis of an endometrium prepared by oestrogen and progesterone. This produces irreversible cell injury (Ferenczy, 1990). The explanation of menstruation through molecular mechanisms includes complex interactions between sex steroid, endocrine and immune systems. Foci of extracellular matrix (ECM) breakdown occur in the superficial layer of the endometrium then gradually extend throughout the whole functionalis layer. Interstitial haemorrhages will occur locally due to alteration of the vascular endothelium. Appropriate interactions between these various cell types have a crucial role during menstruation (Hernier et al., 2012). According to Jabbour et al. (2006) a decrease in progesterone will firstly affect cell expression of progesterone receptors and could be reversible (Kelly et al., 2001). After that, the progesterone withdrawal events will also include vasoconstriction, cytokine changes, and subsequent activation of lytic mechanisms which include activation of a series of pro-MMPs, which is also accentuated by the effect of hypoxia (Figure 1.6). These events probably occur in an invariable manner and are not affected by progesterone levels. Therefore, it could be considered that the latter phase of menstruation does not depend on progesterone, and the involved cells may not express PR (Jabbour et al., 2006).
Figure 1.6: Progesterone withdrawal stimulates many mechanisms; the main one is related to releasing vasoactive agents. Chemotactic agents, which cooperate with vasoactive agents, are also expressed. There is a strong suggestion that MMPs, which degrade the interstitial core of the endometrium, have their main effect in the early menstruation phase, but their origin is still controversial. They may be released from resident endometrial stromal cells and/or by invading leukocytes (Jabbour et al., 2006).

An abrupt increase of consumption of nuclear thymidine which is associated with the increase of blood oestrogen levels, concentration of oestrogen and progesterone receptors and mitosis in all regenerated endothelial cells means that a new cycle will begin (Bergeron et al., 1988). At the end of menstruation the residual endometrium is approximately 1 mm in thickness: integrity of the functionalis layer is interrupted, the mucosa contains necrotic fragments of damaged glands and vessels with aggregated stromal cells, oedematous fluid, extravasated blood cells and leukocytes (Doria, 1999). The human endometrium has an active fibrinolytic system during menstruation which plays a critical role in the prevention of scarring during endometrial repair (Maybin & Critchley, 2009).
1.11.1.4. The post menstrual phase and endometrium regeneration (Cycle days 6 to 8)

The postmenstrual phase, a period of relative mitotic silence, is regarded as rebuilding the surface epithelium, and takes about two days (Somers et al., 2003). The basalis layer of the endometrium is responsible for the rebuilding process as erosion of the basal layer will initiate surface re-epithelisation from remnant stumps of basal glands on the surface epithelium of the lower uterine segment and peritubal ostia, which do not participate in the menstrual shedding phase (Ferenczy, 1993). First, the creation of spindle shaped resurfacing epithelial cells containing a micro-filamentous tubular system will help these cells in their migration over the compact layer of stromal fibroblasts. Stromal fibroblast have a significant role in post-menstrual epithelial repair as they aggregate and form a compact layer under the resurfacing epithelium providing the surface for migration of epithelial cells. They also produce regulatory factors such as epidermal growth factor (EGF) and fibronectin inhibitor (Chiquet-Ehrismann & Pearson, 1989).

The signs of endometrial scarless repair and regeneration, including new surface epithelium climbing over and enclosing functionalis remnants, frequently happen during menstruation (Henriet et al., 2012). The significant ability of the endometrium to redevelop in each menstrual cycle suggests the presence of adult progenitor cells in the local endometrial area. Stem cells have varying differentiation potential, from the totipotent zygote to tissue progenitor cells with controlled differentiation to a particular pathway. Tissue progenitor cells are intermediate cells with properties between stem cells and end-stage differentiated cells. They divide to increase the numbers of differentiated cells when they are stimulated. Regulation of these cells is through their ‘niche’ which is a specific physiological microenvironment in which the cell resides. The main role of the niche is to initiate the need
for tissue replacement and connect with the progenitor cells to initiate proliferation (Maybin & Critchley, 2009).

1.11.1.5. The roles of angiogenesis

Concepts about the role of angiogenesis in the menstrual cycle have recently been revised as they are fundamental in endometrial regeneration and repair, and occur in three phases of the cycle (Figure 1.7). In the post-menstrual phase there is a rapid repair to damaged blood vessels as well as rapid growth in the functional layer of the endometrium. However, there is coiling of the spiral arterioles and increase in development of the sub-epithelial capillary plexus during the secretory phase (Maybin & Critchley, 2009). The importance of the dynamic endometrial blood vasculature has long been observed and it is recognized that there is restricted lymphatic distribution in functional versus basal endometrial layers, as is the lack of lymphatics in areas of decidualised endometrium. The regulatory pathways responsible for lymphatic and blood vessel growth interact and there are commonalities in signalling pathways. This suggests a role for endometrial lymphatics in normal and abnormal endometrial function (Girling et al., 2012).
Figure 1.7: Hormonal changes in menstrual cycle (A & B), endometrial changes (C) and angiogenesis at every stage of the cycle (D) (Maybin & Critchley, 2009).

1.11.1.6. The proliferative phase (Cycle days 8 to 10)

The proliferative phase, which extends from the menstrual phase to ovulation, is characterized by significant growth and mitotic activity which reaches its highest level eight to ten days later (Somers et al., 2003). The proliferative phase is mainly under the control of oestrogen as the endometrial lining becomes thicker through proliferation of the stromal cells and glands and early elongation of spiral arteries (Hawkins et al., 2008). In other words, it corresponds to the increased level of oestrogen. The synthesis of the deoxyribonucleic acid (DNA) promoter enzyme, thymidilate leads to an increase in DNA synthesis followed by an increase in the
number and size of glands, stromal cells and a vascular network (Ferenczy, 1993). Most studies reveal that there is a substantial increase in oestrogen and progesterone receptors in the nuclei of endometrial cells during the proliferative phase (Ferenczy, 1990). In fact, the expression of endometrial sex steroid receptors (PRA, PRB, ERα, ERβ and AR) take different pathways throughout the cycle. There are two oestrogen receptors, ERα and ERβ, which have been identified in the endometrium and each one is derived from a separate gene. In the proliferative phase, there is up-regulation of ERα and PRA by ovarian oestradiol. On the other hand, the ERα and PRA are down regulated by progesterone in the secretory phase. In this regard the expression of the PRA is related to activation of an ER-mediated pathway, and progesterone action on ERα is responsible for down regulation of PRs in epithelial cells. Actions of oestrogen are mediated through a second intracellular messenger or through non-genomic action (through membrane bound) (Jabbour et al., 2006).

In the endometrium, the proliferative actions are considered to be greater in the upper two thirds, the functionalis layer, than the basalis layer, which is considered to be more related to epithelium regeneration in the post menstrual phase. Another feature of this phase is an increase in cilia and surface microvilli of gland cells, which are oestrogen-dependant. These cells spread along the surface gland openings, and this will support distribution of glandular secretion in the post-ovulatory phase (Ferenczy, 1993).

1.11.1.7. Ovulation (Cycle day 11 to 15)

Ovulation in the human occurs about fourteen days before menstruation. Cytological and biochemical changes in the follicle wall lead to disintegration of the follicle apex and oocyte maturation. There is remodelling of the follicle wall, which results from plasmin and collagenase activities. The thinning of the follicular apex is the result of these enzymes,
together with hydrolases liberated by dying ovarian epithelial cells. PGF and histamine also have a role in the apical dissociation (Thibault & Levasseur, 1988).

1.11.8. The secretory phase (Cycle days 16 to 28)

The secretory phase is characterised by a biochemical alteration of the endometrial functioning for about eleven to fourteen days (Somers et al., 2003). It is divided into early-, mid- and late-secretory phases. Progesterone starts to rise around ovulation and into the early secretory phase causing secretion of mucoid proteins and glycogen in the endometrium in preparation of the environment to receive an embryo in the mid-secretory phase as the endometrium decidualises. In the late secretory phase, decreasing oestrogen and progesterone and the absence of pregnancy leads to spiral arteriole vasoconstriction and then involution of the endometrium (Hawkins et al., 2008). The changes of sex steroid receptor expression in endometrial cells during the secretory phase reveal that the early secretory phase is controlled by both oestrogen and progesterone and the mid-secretory phase is mainly controlled by progesterone because there is a down regulation of oestrogen receptors in the glands and stroma during this period. Lastly, the late secretory phase is coupled to progesterone withdrawal and subsequent menstruation.

Progesterone will act only in the differentiation of endometrial cells if PRs are present, and PR expression depends on previous exposure to oestrogen. There are two isoforms of the PR, PRA and PRB. They are derived from a single gene and act as interactive transcriptional regulators of progesterone-responsive genes (Jabbour et al., 2006). It could be considered that this half of menstruation depends on progestational secretory differentiation.
A recent review elaborated the mechanisms by which progesterone activates key kinase cascades of growth factors like epidermal growth factor, and has synergistic action in the up regulation of growth genes. This supports the growth rate of cells surrounding the spiral arterioles in the progesterone-dominated uterus (Jabbour et al., 2006). Also in this phase; there is the appearance of the nucleolar channel system (NCS) in nuclear membranes in endometrial gland cells but not stromal cells. This phenomenon occurs under the effect of progesterone and indicates the early period of the post-ovulatory phase (Ferenczy, 1993).

Another pathognomonic sign of ovulation occurs on the 17th day when gland cells appear with prominent sub-nuclear vacuoles, which, in fact are glycogen granules. This is related to the production of glycoprotein-rich endometrial secretions, which will be secreted from gland cells into glandular lumens and then into the endometrial cavity. On the 21st day, the apocrine secretion reaches its highest level, while the height level of the glandular cells will be decreased due to a decrease of nuclear DNA synthesis, as well as a decrease of mitotic activity (Ferenczy, 1993). The shape of epithelial cells will change from high columnar to low cubical shape (Somers et al., 2003). Furthermore, these cellular events correspond to an increased level of progesterone and intranuclear oestrogen receptors and progesterone receptors. On the 23rd day, the appearance of endometrial stromal fibroblasts that have receptors for oestrogen and progesterone will provide the integrity of the endometrial mucosa and secrete prolactin, immuno-suppressor substances and laminin (Kearns et al., 1983). In the late secretory phase, there are many events that correspond to progesterone withdrawal, and at the cellular level there are many enzymatic actions to prepare the endometrium for the menstrual phase. Electron microscopy and enzyme tracing studies have identified the appearance of golgi–derived acid phosphatase-containing primary lysosomes in all cells of the endometrium by the 23rd day of the cycle. Following this, as ovarian steroids decrease in the secretory phase, the integrity of the lysosomal membrane in the cytoplasm will be damaged.
Proteolytic enzymes occur in the cytoplasm and intracellular space. As a result, the lytic enzymes will digest all cellular elements, desmosomes, causing damage of the endothelial surface membrane, which leads to extravasations of polymorphonuclear leukocytes and tissue necrosis (Wynn et al., 1989). These events are associated with an increased level of prostaglandins, PGF2-α and PGE2, as result of stromal degeneration. PGF2-α may have a role in stromal dehiscence through its action in constricting basal arteries and inducing myometrial contraction. An abrupt increase of consumption of nuclear thymidine, which is associated with the increase of blood oestrogen levels, concentration of oestrogen and progesterone receptors and mitosis in all regenerated endothelial cells, means that a new cycle will begin (Bergeron & Ferenczy, 1988).

**Conclusion**

This chapter began by a description of the history and the epidemiology of menstrual bleeding and its relevance to women's physiology and physical health. Variation of normal menstrual cycle length, duration and amount of flow is an integral part of a woman's experience throughout much of her reproductive life. In addition to potential fertility problems and the concern aggravated by unexplained alterations in bleeding patterns, considerable morbidity like heavy menstrual bleeding is directly attributable to menstrual disturbances.

The second part of chapter is related to physiology of menstrual cycle. The understanding of the regulation of menstruation is of major basic and clinical interest. These mechanisms largely overlap with those controlling other histopathological occurrences of tissue remodelling, such as development and cancer, and inappropriate control of menstrual features. It is highly probable that unrestrained local inflammatory events and deficient repair processes within the endometrium have a role in women's experience of heavy menstrual
bleeding. Indeed, the management of women with HMB may need to develop therapeutic approaches that optimize endometrial repair processes.
Chapter 2: Heavy menstrual bleeding

This chapter is a review of different aspects of the symptom of heavy menstrual bleeding and includes: definition, causes, mechanisms, diagnosis and management. The impact of heavy menstrual bleeding on women’s quality of life is discussed at the end of this chapter.

2.1. Definition and nomenclature

Heavy menstrual bleeding is defined as a complaint (a symptom) of excessive bleeding which occurs over minimum of 6 months (Fraser et al., 2011). According to the NICE Guidelines, heavy menstrual bleeding can be defined for clinical purposes as excessive menstrual blood loss which interferes with the woman’s physical, emotional, social and material quality of life (NICE, 2007). Any management should be organized to improve quality of life measures. This is basically a subjective definition. Objectively, for research purposes, heavy menstrual bleeding has been defined as blood loss of more than 80 mL in any menstrual period, whether regular or irregular. It is considered that approximately 30% of women will complain of heavy menstrual bleeding at some time, and around 5% will complain of this in any one year (Rees et al., 1998). Heavy menstrual bleeding is the commonest gynaecological symptom presenting to general practitioners and then being referred to gynaecologists and it represents about two third of all hysterectomies for benign disease in the United Kingdom (Warner et al., 2001). Therefore, it is considered as a very important public health problem.

Over the past decade, there has been recognition of the considerable confusion regarding terminologies, definitions and related issues about abnormal uterine bleeding (Critchley et al., 2011). Similar terms are used in different ways in different countries and some of them with Greek and Latin roots are still extensively used in the English language to illustrate different abnormalities of menstrual bleeding (Fraser and Inceboz, 2000). There was international
agreement that most of these terms are ill-defined and may be used quite differently in different parts of the world. This confusion has prohibited much collaborative research and international clinical trials (Fraser et al., 2006). The parameters of normality for the menstrual cycle and menstruation possibly will be realistically set at the 5th–95th percentiles from population studies (Fraser and Inceboz, 2000). This would let ‘heavy’ to be above the 95th percentile of the normal population and ‘light’ would be below the 5th percentile. Regarding Fraser et al. (2006), these terminologies should be probably replaced by simple descriptive terms which cover regularity of the cycle, frequency of menstruation and volume and duration of the menstrual flow. Furthermore, these terms should also be understandable to women in the community and be able of translation into other languages.

Through the 20th century, heavy menstrual bleeding has been described by many different terms, including: menorrhagia, hypermenorrhoea, dysfunctional uterine bleeding, excessively heavy menstrual loss, ovulatory menorrhagia, anovulatory menorrhagia and others (Table 2.1). These terms were used to express the doctor’s explanation of subjective complaining of heavy menstrual bleeding (Woolcock et al., 2008). However, all these terminologies were discarded according to international agreement by the FIGO Menstrual Disorders Working Group in October 2009 (Critchley et al., 2011). Heavy menstrual bleeding has been approved according to FIGO 2009 as the appropriate term to explain the complaint of excessive heaviness of menstrual flow (Critchley et al., 2011). The first reliable use of the term “heavy menstrual bleeding” was made in the New Zealand Guideline for the management of heavy menstrual bleeding (Woolcock et al., 2008). This term seems to be more logical to explain the complaint of heavy menstrual bleeding than the use of a term of direct Greek origin like “menorrhagia”, which patients cannot understand.
Table 2.1: Menstrual terminologies used over the past 100 years (Woolcock et al., 2008).

<table>
<thead>
<tr>
<th>Terms used during the past 100 years to describe increased or heavy menstrual bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menorrhagia—to “burst forth each month”—excessive uterine bleeding =</td>
</tr>
<tr>
<td>Hypermenorrhoea—synonymous with menorrhagia</td>
</tr>
<tr>
<td>Menometrorrhagia—irregular and heavy bleeding (many authors)</td>
</tr>
<tr>
<td>Dysfunctional uterine bleeding—some authors use this to describe the symptom</td>
</tr>
<tr>
<td>Functional uterine haemorrhage</td>
</tr>
<tr>
<td>Excessively heavy menstrual loss</td>
</tr>
<tr>
<td>Ovulatory menorrhagia; anovulatory menorrhagia (many authors)</td>
</tr>
<tr>
<td>Functional menorrhagia</td>
</tr>
<tr>
<td>Essential menorrhagia</td>
</tr>
<tr>
<td>Idiopathic menorrhagia</td>
</tr>
<tr>
<td>Primary menorrhagia</td>
</tr>
<tr>
<td>Uncomplicated menorrhagia</td>
</tr>
<tr>
<td>Symptomatic menorrhagia</td>
</tr>
<tr>
<td>Persistent menorrhagia</td>
</tr>
<tr>
<td>Unexplained menorrhagia</td>
</tr>
<tr>
<td>Genuine menorrhagia</td>
</tr>
<tr>
<td>Idiopathic uterine haemorrhage</td>
</tr>
<tr>
<td>Anomalous uterine haemorrhage</td>
</tr>
<tr>
<td>Epimenorrhoea—too frequent menstruation</td>
</tr>
<tr>
<td>Epimenorrhagia—too frequent menstruation with too great a loss</td>
</tr>
<tr>
<td>Polymenorrhoea—frequent menstrual bleeding</td>
</tr>
<tr>
<td>Polymenorrhagia—frequent and heavy menstrual bleeding</td>
</tr>
<tr>
<td>Metropathiahaemorrhagica—irregular and excessive bleeding associated with endometrial hyperplasia</td>
</tr>
</tbody>
</table>

2.2. Causes of heavy menstrual bleeding

The causes of heavy menstrual bleeding could be divided into two discrete groups: those due to ‘structural’ lesions of the reproductive tract; and those which are not caused by ‘structural lesions’ – ‘non structural causes’. The current classification system for explanation of causes of abnormal menstrual bleeding, which has been approved by the International Federation of Gynaecology and Obstetrics (FIGO) (Figure 2.1), can be used to explain the main causes of heavy menstrual bleeding (Munro et al., 2011).
The classification system consists of 4 categories that have structural criteria (PALM) which can be recognised by ultrasound or other imaging processes, and 4 that have no obvious structural abnormalities (COEI) and one N which is, as yet, considered as unclassified (Munro et al., 2011).

2.2.1. Polyp (AUB-P)

Endometrial polyps are common benign lesions, but their pathogenesis is not well known. They may be asymptomatic, but may also contribute in development of irregular or heavy uterine bleeding (Munro et al., 2011).

2.2.2. Leiomyoma (AUB-L)

Fibroids, especially when involving the uterine cavity (sub-mucosal), are the most common structural lesion causing heavy menstrual bleeding (Figure 2.2). They have been reported in at least 10% of women with blood loss of 80–100 mL or more per cycle (normal loss is < 80 mL/cycle), and 40% of those with severe HMB (> 200 mL/cycle) (Rybo et al., 1985).

However, it has been found that only 50% of women with fibroids have HMB.
2.2.3. Malignancy and hyperplasia (AUB-M)

Malignancy is generally an uncommon cause of abnormal uterine bleeding (Woolcock et al., 2008). Endometrial carcinoma is unusual below the age of 40 years. However, it can present as HMB but, more often, it causes irregular bleeding (Dockery et al., 1987).

2.2.4. Coagulopathy (AUB-C)

The term of ‘coagulopathy’ includes the spectrum of systemic disorders of haemostasis that may be associated with abnormal uterine bleeding (Munro et al., 2011). Bleeding disorders which can cause HMB include bleeding diatheses such as Von Willebrand disease, deficiencies of factors V, VII, X, XI and thrombocytopenic purpura (Dilley et al., 2001) Von Willebrand disease is the primary cause in a small but significant number of women with HMB (James et al., 2004). There is clear evidence that systemic disorders of haemostasis, especially Von Willebrand disease, represent about 13% of women with HMB (Munro et al., 2011). A systematic review of 11 studies of women with HMB found prevalence ranging from 5% to 24% (Shankar et al., 2004). Bleeding disorders should be considered when there is no evident pelvic structural cause, and when the woman has other bleeding symptoms; most studies reveal that it is more common in Caucasian women than in women of African descent.

2.2.5. Ovulatory dysfunction (AUB-O)

Although different structural pathologies have a role in HMB, in 50% of cases of objective HMB, no structural pathology is found in hysterectomies (Clarke et al., 1995). Dysfunctional uterine bleeding was the terminology used to describe the underlying cause of this “non-structural” abnormally heavy or prolonged menstrual bleeding. It was therefore a diagnosis of
exclusion. However, this poorly defined, imprecise and confusing term was strongly discarded by international agreement by FIGO 2007 (Fraser et al., 2011).

Ovulatory dysfunction typically occurs in adolescent women, those with polycystic ovary syndrome or in those at the perimenopause (Dockray et al., 1987). The bleeding is usually irregular, may be prolonged heavy bleeding, or short cycles with minimal blood loss. In ovulatory cycles and some anovulatory cycles, excessive menstrual loss has been related to abnormal uterine levels of prostaglandins (Hagenfeldt et al., 1987). Ovulatory cycles produce regular menstrual bleeding which is the most clinical presentation of HMB (see AUB-E).

2.2.6. Endometrial (AUB-E)

Some molecular and cellular abnormalities have been detected in the endometrium of women with regular ovulatory HMB, such as increased fibrinolytic activity (Dockray et al., 1987, Rees et al., 1984) and abnormal prostaglandin secretion (Smith et al., 1981). In addition, this includes increased local production of substances that cause vasodilatation, such as prostaglandin E2 and prostacyclin. Despite this evidence, which has been available for more than two decades, tests measuring such abnormalities are still not practical (Munro et al., 2011). During periods of menstruation, the primary bleeding source is the spiral arteries of the endometrium, and the amount of blood lost may be related to their degree of constriction and dilatation, which is partly controlled by prostaglandins (Dockray et al., 1987).

2.2.7. Iatrogenic (AUB-I)

Iatrogenic causes of HMB include intrauterine devices, systemic corticosteroids, some chemotherapy agents and anticoagulants. Anti-coagulants are usually included in the AUB-C category in the FIGO classification. Steroid hormones and chemotherapy agents interrupt the
The normal menstrual cycle, which usually returns to normal after stopping the medications (Dockray et al., 1987). Systemically-administered, single-agent or combination gonadal steroids including oestrogens, progestogens, and androgens have effects on the control of ovarian steroidogenesis through effects on the hypothalamus, pituitary, and/or the ovary, and also have direct effects on the endometrium. Therefore, these features are seen in those using hormonal contraceptive agents, such as oral, transdermal, vaginal and injectable progestogen or oestrogen–progestogen compounds. When oestrogen–progestogen agents are administered cyclically, periodic uterine bleeding generally occurs in conjunction with the periodic withdrawal of the steroidal agents. But when break-through bleeding occurs in the context of cyclic administration, the woman may be categorized as AUB-I (Munro et al., 2011).

2.2.8. Not Yet Classified (AUB-N)

Some rare diseases, such as arterio-venous malformations of the uterus, myometrial hypertrophy or diseases cannot yet be identified or defined. These are currently considered as Not Yet Classified (Munro et al., 2011). Hypothyroidism has been suggested as a cause of HMB, but the relationship between them is still a controversial issue (Weeks et al., 2000). The Royal College of Obstetricians and Gynaecologists (RCOG) recommend that thyroid function tests should not considered in the initial evaluation of HMB, unless the woman has symptoms or signs of hypothyroidism (RCOG, 1998).

2.3. Mechanism of HMB

2.3.1. Expression of vasoactive mediators and their relation to HMB

During menstruation, higher levels of prostaglandin E2 and prostaglandin F2α in menstrual fluid of women with HMB is found as compared to those with normal menstrual cycles (Rees et al., 1991). It is also found that release of prostaglandin E2, prostaglandin F2α and
prostacyclin by endometrium and myometrium in menstruation is elevated from tissues taken from women with heavy menstrual bleeding (Rees et al. 2011). In addition, a number of prostaglandin E receptors are found high in the myometrium that is collected from women with HMB (Adelantado et al., 1988). It is noted that fibrinolytic system is significantly increased in endometrium of most women with ovulatory dysfunctional uterine bleeding (Gleeson et al., 1993).

The role of the prostaglandin synthesis pathway has also been evaluated in women with objective measurement of their menstrual blood loss. Analysis of gene expression in endometrial biopsies from the secretory phase shown significant elevation of COX-2 mRNA expression in women with blood loss more than 80 mL. Increased signalling of PGE2 through its EP2 and EP4 receptors has also been suggested due to elevated production of cyclic AMP and decreasing of enzyme involved in cAMP hydrolysis, phosphodiesterase E4 were observed in women with heavy versus normal menstrual bleeding. These findings suggest excessive prostaglandin production and signalling in the endometrium of women with HMB. The resulting exaggerated inflammation may result in increasing and prolonged tissue damage at the time of menstruation (Maybin et al., 2011). It is reported that increasing of PGI2 may stimulate endometrial tissue plasminogen activator content, increased local fibrinolytic activity and excessive endometrial heparin-like activity. These cascades of increased PGI2, fibrinolysis and heparin-like activity will leads to very limited and deficient haemostatic plug formation (Livingstone & Fraser, 2002).
Figure 2.2: Uterine fibroid with large, thin-walled and fragile vessels on its surface (Bulmer, 2008).

2.3.2. Blood vessel structure changes and disturbance of angiogenesis in women with HMB

Endometrial blood vessel structure in women with HMB is disturbed, in that it has reduced vascular smooth muscle cell (VSMC) proliferation in mid–late secretory phase, decrease in myosin heavy chain contractile protein and increased endometrial endothelial cells proliferation (Critchley et al., 2011). Data from Western blot studies reveal delayed expression of endometrial repair factors, such as vascular endothelial growth factor (VEGF), in women with heavy menstrual bleeding and this can cause delay in repair of damaged vessels and increase in the amount of menstrual blood loss (Critchley et al., 2011). Women with heavy menstrual bleeding also have increased uterine blood flow, which is related to inefficient vasoconstriction. Women with menstrual blood loss in excess of 90 mL have been shown to have a considerably decreased PGF2/PGE2 ratio and. Excessive PGE2 production at
the expense of PGF2 may lead to less constriction of the spiral arterioles prior to menstruation. Decreased endometrial expression of the potent vasoconstrictor endothelin-1 in women with HMB may also lead to defective perimenstrual constriction of vessels. Furthermore, vessel wall circumference and focal discontinuities were noted to be larger in the endometrium of women with HMB than normal (Maybin et al., 2011).

2.4. Diagnostic approach to heavy menstrual bleeding
The NICE guidelines for heavy menstrual bleeding (2007) declare that if the history indicate the suspension of heavy menstrual bleeding with no structural or histological abnormality, treatment could be started and no need to a physical examination or other investigations at initial consultation in primary care (Bulmer, 2008), unless the chosen treatment is the Mirena coil. If the history suggests that there is heavy menstrual bleeding with structural or histological abnormality, symptoms such as inter-menstrual bleeding or post-coital bleeding, pelvic pain, a physical examination and/or other investigations (such as ultrasound) should be performed (Bond, 2010).

2.4.1. The history
It is important to explore specifically the menstrual history of the patient including her last menstrual period (LMP), cycle length and number of days of bleeding, use of tampons or pads, passing clots or flooding and also history of discharge, pelvic pain, dysmenorrhoea or dyspareunia (Bond, 2010). A detailed menstrual history will also focus on subjective assessment of blood flow, intermenstrual intervals, and any observation of changes from previous bleeding patterns. Women with ovulatory bleeding are probably have heavy regular menstruation along number of consecutive cycles without any intermenstrual or postcoital bleeding. They may also have dysmenorrhoea with passage of clots. Anovulatory bleeding is
often not associated with any of these symptoms and occurs in unpredictable manner (Bond, 2010). In addition, it is important to ask about details of sexual history and the contraceptive history, obstetric history including number of pregnancies, most last smear, family history of bleeding disorders and any history of bleeding gums or easy bruising. It is important to ask about the perception of patient of emotion and social quality of life in relation to her menstrual cycle (Bulmer, 2008, Bond, 2010).

A need of structured menstrual history has taken the concern in FIGO 2009. A structured menstrual history have two parts approach: a diagnostic element and symptom impact element. The first part covered the questions which in related to menstrual characteristics. Question about regularity, frequency, duration of the bleeding give clue about the possible diagnosis. For example, regulatory of the bleeding can distinguish the ovulatory dysfunction from endometrial dysfunction. Screening for disorders of coagulation in women with heavy menstrual bleeding has been developed and it is could help clinicians to identify patients who would benefit from further laboratory investigation for coagulation studies (Kouides et al., 2005). The second part of the structured menstrual history is related to the symptom impact on the patient quality of life. It is found that it is very important to develop valid questionnaire which is correlated to clinical diagnostic elements outcomes and other methods of assessment of quality of life (Matteson et al., 2011).
Table 2.2: Screening for disorders of coagulation in women with heavy menstrual bleeding (Kouides et al., 2005)

<table>
<thead>
<tr>
<th>Primary evaluation for an underlying disorder of haemostasis in females with excessive menstrual bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Structured history—positive screen if</td>
</tr>
<tr>
<td>a. Excessive menstrual bleeding since menarche,</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td>b. History of one of the following—postpartum haemorrhage, surgery-related bleeding,</td>
</tr>
<tr>
<td>or bleeding associated with dentalwork, or</td>
</tr>
<tr>
<td>c. History of two or more of the following—bruising greater than 5 cm once or twice/month,</td>
</tr>
<tr>
<td>epistaxis once or twice/month, frequent gum bleeding, family history of bleeding symptoms.</td>
</tr>
<tr>
<td>2. Initial laboratory evaluation:</td>
</tr>
<tr>
<td>Complete blood cell count</td>
</tr>
</tbody>
</table>

2.4.2. The clinical assessment

A recent international review has taken the concern about the aims of HMB investigation which including: detection of the degree of HMB and other related symptoms and signs, determination of the effect of symptoms on the patients (e.g. iron deficiency anaemia) and further investigation to find underlying causes (Munro et al., 2011).

2.4.2.1. The examination

General examination includes observing appearance, BMI, any signs of endocrine disorders or haematological signs such as anaemia or bruising (Bond, 2010). Abdomen and pelvic examination is for any pelvic masses and may need a speculum examination. For the cervix, the NICE guidelines recommend that a physical examination should be done before using the Mirena coil and before investigations for structural or histological abnormalities (NICE, 2007, Bulmer, 2008). Women with fibroids that are palpable abdominally should be offered immediate referral to a specialist (Bond, 2010). Facilities with colposcope and
histopathological assessment of tissue biopsies should be available for the diagnosis of premalignant and early malignant lesions (Munro et al., 2011).

2.4.2.2. Blood test

A full blood count test should be done for all women with HMB. Testing for coagulation disorders (e.g. Von Willebrand’s disease) should be considered in women who have heavy menstrual bleeding since menarche or have family history with suggestion of coagulation disorder (Bulmer, 2008, Bond, 2010). A administration of well-validated questionnaire such as one which developed by Kadier and colleagues for bleeding disorders is considered as highly sensitive tool to further evolution of coagulopathies (Table2) (Critchely et al., 2011, Munro et al., 2011). A full blood count is required to determine the degree of anaemia. Ferritin is not recommended as a routine test in women complaining of HMB (Bulmer, 2008). Testing for bleeding disorders should only be done if there is any clinical indication (RCOG, 1998, Hope et al., 2000). Thyroid function tests should also only be done if clinically indicated and no other endocrine investigations are necessary (RCOG, 1998, Hope et al., 2000).

2.4.2.3. Ultrasound scanning

Transvaginal ultrasound scan is a non-invasive, no painful technique and represents a suitable test for the diagnosis of endometrial abnormalities including polyps, submucous fibroids and hyperplasia. Transvaginal ultrasound could be used to assess endometrial thickness and detects polyps and fibroids with a sensitivity of 80% and specificity of 69% (Vercellini et al., 1997). Imaging should be done if the uterus is palpable abdominally, vaginal examination reveals a pelvic mass of unknown origin or if pharmacological treatment does not work (Bulmer, 2008, Bond, 2010).
Endometrial thickness at ultrasound could be used as indicative of pathology in postmenopausal women. A meta-analysis of 35 studies revealed that in menopausal women, endometrial thickness of 5 mm at ultrasound has a sensitivity of more than 92% for detecting endometrial disease such as polyp, atypical hyperplasia or cancer and 96% to identify endometrial cancer and at the same time it is not related to hormonal therapy (Smith Bindman et al., 1998).

Review of The British ‘COG Guideline Development Group’ for number of studies involving premenopausal women resulting in that 10–12 mm could be considered as a practical cut-off for using transvaginal ultrasound scanning as the method before using more invasive technique of endometrial assessment (RCOG et al., 1999). A transvaginal ultrasound could be considered as screening procedure, however, ultrasound is not worked for histological diagnosis and this needs endometrial biopsy.

2.4.2.4. Endometrial sampling and hysteroscopy

A sampling should be done to exclude endometrial cancer or atypical hyperplasia. Indications for biopsy in cases of persistent IMB in women aged 45 and over, those at risk of endometrial cancer and treatment failure or ineffective treatment (Bond, 2010). In addition, endometrial biopsy can be needed if abnormal bleeding is the main symptom or there is unusual finding in ultrasound (Balen et al., 2000, Spencer et al., 1999). Office endometrial sampling can detect 67% to 96% of endometrial carcinomas. However, insufficient tissue for diagnosis has been noted in 4% to 20% of cases (Munro et al., 2011). Hysteroscopy should be used as a diagnostic tool only when ultrasound cannot give the diagnosis or the conclusive result (Bond, 2010).
The endometrial sampling can be done through dilation and curettage (D&C), endometrial biopsy or hysteroscopy. D&C is a blind procedure and cannot sample the whole uterine cavity. It can miss uterine pathology such as polyps, fibroids, hyperplasia and carcinoma. It is found that more than 50% of cases of D&C cannot found the endometrial pathology (Bettochi et al., 2001). D&C has used to be therapeutic as well as diagnostic procedure. However, objective measurement of menstrual blood loss reveal that they are just first few periods is lighter than those before D&C but following ones are not that different (Haynes et al., 1977).

There is variety of instruments which is developed for endometrial biopsy over last decade. The two commonly used devices are Pipelle and Vabra aspiration biopsy. In one study, Vabra aspirator was not as effective as the Pipelle device in making a histopathological diagnosis. Despite of it highest cost, the Pipelle device is a more efficient tool for outpatient endometrial assessment. The study reveal that the tip of the vabra cannula has two opposing ports, which could have been targeted to aspirate more tissue, but those ports causes number of unsuccessful procedures. This is because the area between the two ports constituted a weaker insertion point for the sampler compared to the Pipelle device (Naim et al., 2007). In some studies, a vacuum pump with more suction power were used to help in the process of tissue collection, however, the steps involved in Vabra aspiration were in fact more complicated when compared to the Pipelle device (Naim et al., 2007). In addition, it is also approved that blind endometrial biopsy is insensitive in diagnosis of benign and organic causes of heavy menstrual bleeding. The two principal techniques to investigate the uterine cavity pathologies such as polyps and fibroids are transvaginal ultrasound and hysteroscopy (RCOG 1999, Pasqualotto et al., 2000).
Hysteroscopy is more sensitive to detect endometrial polyps and submucosal fibroids than endometrial biopsy procedures and blind curettage (Pasqualotto et al., 2000, Mortakis et al., 1997). However, many studies evaluate this method and how it could be more superior in sensitivity than D&C in detection of endometrial hyperplasia and carcinoma (Yehuda et al., 1998, Epstein et al., 2001). Regarding the precaution in using hysteroscopy, some reveal that hysteroscopy could cause dissemination of malignant cells into the abdominal cavity if the uterus contain endometrial cancer (Arikan et al., 2001). However, hysteroscopy cannot alone diagnose endometrial cancer and need endometrial sampling to exclude endometrial neoplasia (Vercellini et al., 1997, Nagele et al., 1996). It is considered that even if hysteroscopy is available, hysteroscopy could be used more selectively in therapeutic procedures such as targeted biopsy, polpectomy or myomectomy (Munro et al., 2011).

2.5. Assessment of menstrual blood loss

Treatment for HMB often does not depend mainly on the amount of menstrual blood loss. It has been estimated that 40% often who complain from HMB have bleeding more than 80 mL/cycle (Hallberg et al., 1966). For this reason, objective measurement of menstrual blood loss is very important issue in research field. However, it is difficult in routine clinical practice; there are different methods to assess the amount of menstrual blood loss which are continuing developed over last decade.

2.5.1. Women’s judgment of menstrual blood loss

Estimation of menstrual loss by woman’s self judgment of heavy menstrual loss is one method to detect the amount of menstrual blood loss. Many studies have suggested that women cannot provide accurate estimation of quantity of menstrual blood loss. A comparison of women’s subjective estimate with objective methods reveal that 38–76% of women
complaining of heavy menstrual bleeding truly have objective heavy menstrual bleeding (Chimbira et al., 1980, Rybo, 1966, Fraser et al., 1984). This would support the idea of that many women undergo invasive investigations and treatment for a condition that they do not have. In fact, this method seems to be not accurate in diagnosis of HMB. However, this method is appropriate regarding NICE definition of HMB, as excessive menstrual blood loss which interferes with the woman’s physical, emotional, social and material quality of life (NICE, 2007).

2.5.2. Duration of menstrual period
Duration of menstruation is one of the most stressful symptoms regarding the woman’s opinion. It also does not represent a perfect method of quantifying the menstrual blood loss. One research shows that 78% of the total menstrual loss occurred by the second day and 91% by the third day of menses (Rybo, 1966). Another study reported that women with heavy menstrual loss tended to have an increased loss in the first three days of menstrual cycle (Haynes et al., 1977). A comparison of measurement of length of menstruation with the actual amount of the menstrual blood loss reveals that only 45% of the women who bled for more than seven days had a measured menstrual loss of more than 80 mL (Rybo, 1966). Indeed, this test has a low sensitivity for the diagnosis of heavy menstrual bleeding.

2.5.3. Counting of number of used sanitary products
Counting the number of sanitary products is another non accurate method to measure menstrual loss and subsequently diagnosis of HMB. In fact, studies show that the number of sanitary products depends on the woman’s personal hygiene practices, frequency of attention to menstrual flow and level of the income (Higham et al., 1990, Grimes, 1990). One example from a study revealed that one woman used 18 sanitary pads to collect 32 mL of menstrual
blood while another woman used the same number and brand of pads to collect 399mL (Higham et al., 1990).

2.5.4. Weighing of used sanitary product

Weighing used sanitary products and subtracting the weight of the unused product is also a method of estimation of menstrual blood loss (Pendergrass et al., 1984). However, this method could be fair if all menstrual fluid constituted blood. In this regard, the proportion of blood in menstrual fluid is different among women, ranging from 1.6% to 81.0%. In fact, blood is about 36.1% of the total menstrual loss (Fraser et al., 1985). Indeed, a significant amount of menstrual fluid comes from other sources such as endometrial tissue exudates, endometrial glands, and cervical and vaginal secretions.

2.5.5. Using haemoglobin level

Regarding haemoglobin (Hb) level, RCOG guidelines suggest that it is one of the first investigations in HMB cases but it is not an accurate way to diagnosis or exclude HMB. One study which compares women’s Hb levels with their menstrual blood loss, measured by the alkaline haematin method, reported that anaemia was 74% predictive for having HMB (Janssen et al., 1995). Whereas, haematocrit, serum iron and protoporphyrin levels were inversely correlated to the amount menstrual blood loss (Barr et al., 1998, Janssen et al., 1995). However, it cannot be depended on Hb for a conclusive diagnosis of HMB.

2.5.6. Vaginal caps

Another method in which the cervix is covered with a silicone or latex cup or seals that retains all the menstrual blood discharge and decreases the use of sanitary wear. There are two known methods, the Gynaeseal (Gleeson et al., 1993) and the menses cup (Cheng et al.,
Now-a-days there are many different menstrual cups, Figure 2.3 shows a Mooncup which is one type of menstrual cups. The Gynaeseal consists of an inner cup that seals by gentle suction which surrounds and covers the cervix and an outer collection pouch in which the menstrual blood is collected. The menses cup is a soft silicone rubber cone which is put into the vagina with the wider opening sits under the cervix. The narrower end is plugged, allowing drainage of the collected menses at appropriate times. It is known that women use the seals easily in insertion but is trickier to remove when successfully containing the blood loss (Cheng et al., 1995). Consequently, the cup seems inappropriate for quantification of menstrual loss and are rarely used for clinical or research purposes.

Figure 2.3: The Mooncup menstrual cup (Day, 2012).

2.5.7. Alkaline haematin technique

The use of the alkaline haematin technique to measure menstrual blood loss was developed by Hallberg et al. (1964). The side effect of this method is considered as expensive, labour intensive and time consuming. It also needs the women to collect, store and submit all of their used sanitary products for analysis, which may be unacceptable for some women. Thus, this method is not common in clinical practice and its use is usually limited to research (Hallberg
et al., 1964, Newton et al., 1977). Some problems arise with this method, such as interfering of new (ultra-slim) sanitary products with the absorbance of haem, leading to underestimation of Hb concentration. Another defect of this method is that it only estimates blood loss on sanitary wear and misses the extraneous blood loss which could happen with many women. It is considered that 12% of menstrual blood loss as extraneously lost (Pendergrass et al., 1984). However; this method could be the most reliable method for measurement of blood loss.

2.5.8. Pictorial blood assessment chart

The pictorial blood loss assessment chart (PBAC) is a visual illustration of blood loss from which a numerical score is derived (Higham et al., 1990). The chart indicates not only the number but also the degree of soiled items of sanitary wear. The patient scores the number of lightly, moderately or heavily soiled tampons or sanitary towels which are used daily. Although in wide general use, results of studies correlating PBAC scores and menstrual blood loss are contradictory (Pendergrass et al., 1984). In fact, this method is not accurate in assessment of large amount of menstrual loss and extraneous blood loss. Also, it needs careful attention to scoring which preferred to done by one person to ensure reliability (Matteson et al., 2011). Moreover, using of specific sanitary products for some techniques are not now commonly available, which may make it less accurate (Reid et al., 2000).

2.5.9. The menstrual pictogram

The menstrual pictogram was developed from a modification of the previous PBAC technique (Figure 2.4). One advantage for the modified charts is that the score is calculated in millilitres and is equivalent to the actual volume of blood lost (Wyatt et al., 2001). A validation study reveal that there is a significant positive correlation between a woman’s ability to assess her blood loss on sanitary wear using the menstrual pictogram and her accurate blood loss
assessed using the alkaline haematin technique. Another advantage of the menstrual pictogram is the estimation of the extraneous blood loss. In one study, heavy menstrual bleeding was confirmed objectively in 36% of the study group presenting with heavy menstrual bleeding when only the sanitary products were assessed but when extraneous blood loss was taken into consideration the percentage increased to 74% (Wyatt et al., 2001). Therefore, extraneous blood loss is considered as important figure in menstrual blood assessment. The menstrual pictogram could be used in primary and secondary care as a simple, effective method in assessment of heavy menstrual bleeding, which will advance clinical treatment decisions and could result in improved outcomes from any management (Wyatt et al., 2001).

![Table 2.4: Assessment of menstrual blood loss by using menstrual pictogram (Wyatt et al., 2001).](image)

**Figure 2.4: Assessment of menstrual blood loss by using menstrual pictogram (Wyatt et al., 2001).**

### 2.6. Treatment options for heavy menstrual bleeding

The treatment of HMB could be medical (hormonal/non-hormonal) or surgical. Medical treatment should be considered when there is no structural or histological abnormality, or for fibroids which are less than 3 cm in diameter and are not causing any distortion to the uterine
cavity. Medical treatment is considered as first line and preferred treatment of HMB (Haththotuwa et al., 2011). The woman’s medical history and investigations may help in determining whether medical treatment is appropriate. If either hormonal or non-hormonal treatment is appropriate then NICE recommends that the first line treatment should be the levonorgestrel-releasing intrauterine system (LNG-IUS) if at least 12 months use is expected (Bulmer, 2008). Tranexamic acid, non-steroidal anti-inflammatory drugs (NSAIDs) or combined oral contraceptives (COCs) are considered for the treatment of HMB after LNG-IUS (NICE 2007). The aims of the management are to exclude any kinds of cancer, discover any underlying cause, correct and prevent HMB (Haththotuwa et al., 2011).

2.6.1. Correction of iron deficiency anaemia
Iron deficiency anaemia can affect women’s quality of life and can lead to morbid complications. Iron could be given orally as a ferrous preparation or paraenteral injection in cases of oral intolerance. The oral iron therapy should be continued for a period of 4 to 6 months after Hb is corrected to reload the iron stores (Haththotuwa et al., 2011).

2.6.2. Medical treatment
The choice of medical treatment depends on various factors such as effectiveness, acceptability and tolerability of the drug (Haththotuwa et al., 2011). However, patients should shire in choosing the kind of the drug. Women should be given all the information on potentially adverse outcomes (NICE, 2007).

2.6.2.1. Non-steroidal anti-inflammatory drugs (NSAIDs)
The relationship of endo-myometrial prostaglandins to the mechanism of heavy menstrual bleeding provided an opportunity to evaluate therapy by cyclooxygenase inhibitors which is
considered as NSAIDs. They reduce endometrial prostaglandin levels by inhibiting cyclooxygenase, the enzyme which is mainly responsible for conversion of arachidonic acid to prostaglandins (Anderson et al., 1976). NSAIDs can reduce menstrual blood loss, especially in women with mild to moderate symptoms. It can reduce the menstrual blood loss by 20% to 50% and improve dysmenorrhea in 70% of cases (Haththotuwa et al., 2011). Based on results of 17 randomised clinical trials (RCTs), any kind of NSAIDs can be more effective than placebo, but not as effective for heavy bleeding as tranexamic acid, danazol, or the LNG-IUS (Lethaby et al., 2007). According to NICE guideline, use of NSAIDs should be stopped if it does not improve symptoms within three months (NICE, 2007).

2.6.2.2. Antifibrinolytics

Plasminogen activator inhibitors (antifibrinolytic agents) have been used in the treatment of heavy menstrual bleeding. The level of plasminogen activators has been found to be higher in women with heavy menstrual bleeding compared to women with normal menstrual loss. Seven RCTs found antifibrinolytics were better than placebo and other medical treatments, such as luteal-phase progestins or NSAIDs, with comparable side effects (Lethaby et al., 2000). Tranexamic acid, a synthetic derivate of the amino acid lysine, its mechanism of action is through the reversible blockade of plasminogen (Callender et al., 1970, Gleeson et al., 1994). Tranexamic acid can reduce MBL by up to 50% (Calender et al., 1970, Edlund et al., 1995, and Lee et al., 2000). However, it has no effect on blood coagulation or dysmenorrhea (Haththotuwa et al., 2011).
2.6.2.3. Hormonal treatment of heavy menstrual bleeding

2.6.2.3.1. Combined hormonal contraceptives

One RCT and other studies reveal that there is no significant difference among COCs, mefenamic acid, danazol, or naproxen (Fraser et al., 1991). Observational studies suppose that an approximately 50% decrease in menstrual blood loss (MBL) by using COCs. Another RCT found that the bleeding pattern was affected by choice of agent. A pill containing 1000 mcg of norethindrone acetate was combined with fewer days of bleeding and spotting than when pills contained 100mcg of levonorgestrel. Because of the risk of thromboembolic events especially in the older age group (Jick et al., 1995, Spitzer et al., 1996, Lewis et al., 1999), the COCs is not the favoured treatment for heavy menstrual bleeding unless contraception is also required (Irvine et al., 1999). In a study to assess the efficacy of estradiol valerate/dienogest (E2V/DNG) through use of an oestrogen step-down and progestogen step-up approach in 28 day regimen of treatment of heavy menstrual bleeding. The authors found that E2V/DNG is highly effective in the treatment of HMB (Figure 2.5) (Fraser et al., 2012).

![Figure 2.5: The reduction in median MBL with use of E2V/DNG (Fraser et al., 2012).](image)
2.6.2.3.2. Progestogens

Progestogen-only therapy could be considered if there are any contraindications to estrogens. Among the 7 RCTs on progestogens, luteal-phase, progestogens were less effective than tranexamic acid, danazol, and the LNG-IUS (Cameron et al., 1987, Lethaby et al., 2000, Fraser et al., 1990). Progestogens on days 5 through 26 were considerably less effective and less acceptable than the LNG-IUS. Depending on response to therapy, progestogens can begin on cycle day 14 and continue for 14 days and this help in anovulatory cycle (Hathhotuwa et al., 2011), or else begin on cycle day 7 and continue for 21 days (Viols et al., 2001) which has risk of breakthrough bleeding. According to NICE guideline, northisterone is given as 15 mg daily from day 5 to day 26 of the menstrual cycle (NICE, 2007) which can reduce the menstrual blood loss by 87% (Hathathotuwa et al., 2011). Injected long-acting progestogens given once in 1 to 3 months causes atrophy of the endometrium and may lead to amenorrhea in about 80% of women (Hathathotuwa et al., 2011).

2.6.2.3.3. Intrauterine systems

A commonly medicated devices used is the LNG-IUS. The LNG-IUS secretes progestin locally in the endometrium, with advantages of avoiding systemic side effects of injectable progestogens, having the contraceptive efficacy near of that of surgical sterilization, and use for up to 5 years. The LNG-IUS may be the best option when the target is the absence of bleeding, as at least 20% of women have no bleeding by the end of 1 year after insertion (Higham et al., 1990, Pendergrass et al., 1984). The LNG-IUS also has the potential to treat a range of pre-existing gynaecological conditions such as heavy menstrual bleeding due to a
wide range of underlying causes, including endometrial hyperplasia, uterine fibroids, adenomyosis, and endometriosis (Fraser et al., 2010).

One study which recruits women with menstrual loss of more than 80 mL/cycle including women with bleeding related to fibroids and adenomyosis revealed that the LNG-IUS was associated with a progressive decrease in blood loss over time as follow: reductions of 78.7% by 6 months, 83.8% by 12 months, and 97.7% by 24 months (Figure 2.6). The reduction in blood loss was associated with considerable increases in Hb and serum ferritin levels (Xiao et al., 2003). The LNG-IUS device norethindrone was significantly superior to oral norethindrone (Lethaby et al., 2005). There are few contraindications for the use of LNG-IUS as it is restricted to women with uterine cavities from 6 to 9 cm and are not distorted by submucous fibroid (Haththotuwa et al., 2011). LNG-IUS has shown to be as effective as the thermal balloon endometrial ablation in treating HMB for 6 months, and 24 months in New Zealand (Haththotuwa et al., 2011).
Figure 2.6: Comparison between amount of menstrual blood loss before and after insertion of levonorgestrel-releasing intrauterine system (Xiao et al., 2003).

2.6.2.3.4. Danazol

Danazol acts on the hypothalamic-pituitary-ovarian axis suppressing ovulation and directly on the endometrium leading to atrophy (Barbieri et al., 1990). Nine RCTs reveal that danazol; a synthetic steroid is more effective than placebo, progestins, NSAIDs, oral contraceptives, and the LNG-IUS (Beaumont et al., 2007). Small sample sizes make results difficult to interpret, however, and despite the efficacy of danazol, the androgenic side effects have limited its use for heavy menstrual bleeding. NICE guidelines recommended that danazol should not be routinely used for management of HMB (NICE, 2007).
2.6.2.4. Surgical treatment

Surgical treatment is considered in women who do not tolerate medical treatments or their treatments have failed. Hysterectomy has traditionally been regarded as the classic surgical treatment for heavy menstruation and was the most frequently performed operation for this reason. In the early 1990s, it was estimated that at least 60% of women presenting with heavy menstrual loss had a hysterectomy for this reason (NICE, 2007). Over the last 20 years, some new less invasive operative techniques of endometrial ablation have been developed and these are now extensively used for management of heavy menstrual bleeding.

According to NICE guideline, woman with HMB and a uterus no bigger than 10 week pregnancy, endometrial ablation should be preferred than hysterectomy (NICE, 2007). These techniques together with the wide use of LNG-IUS have decreased the number of hysterectomies performed for heavy menstrual loss. A Cochrane systematic review reveal that surgery is more successful than oral medications for most women in reducing menstrual bleeding and improving quality of life (Marjoribanks et al., 2006). In one trial, 53% of women randomised to medical treatment had surgery in period of 2 years (Kuppermann et al., 2004). When LNG-IUS was compared to surgery, endometrial ablations were more effective in controlling menstrual loss with one year follow up, but there was no considerable difference in women’s satisfaction and quality of life (Hurskainen et al., 2001).

2.6.2.4.1. Hysterectomy versus endometrial ablation

From a Cochrane review of five randomized trials comparing hysterectomy with endometrial ablation (Munro et al., 2011), there were considerable advantages in direction of hysterectomy in decreasing menstrual flow and satisfaction rates (> 95% up to 3 years post
surgery) compared with endometrial destruction techniques. There was no significant
difference in quality of life assessment between the two types of surgery, however, there was
evidence that those who had a hysterectomy had some benefits in relation to their general
health at one and two years after surgery compared with those who had hysteroscopy, and
also an improvement in social function and feeling of pain at 2 years.

Regarding the kind of endometrial ablation, a current British survey carried out 10 years after
treatment with microwave endometrial ablation (MEAEA) or trans-cervical resection of the
endometrium revealed that women were equally satisfied with either treatment. Most women
stopped bleeding—83% with ablation and 88% with resection regardless the treatment they
used. However, 38 women in the resection group (28%) versus 22 in the MEAEA group
(17%) then underwent hysterectomies. The treatments were not different in relation to
menstrual symptoms, health-related quality of life, and high rates of patient satisfaction
endorsed MEAEA as the more effective and efficient choice for heavy menstrual bleeding
(Sambrook et al., 2009). In one study with at least 4 years of follow up, 38% of those who had
endometrial ablation received further surgical treatment of some kind (Bridgman et al., 2000).
The direct expenses for hysteroscopic endometrial ablation were about half those for
hysterectomy within months of the procedure. But as the frequency of visits and reoperation
increased, the costs of both became more equal over the time. After 4 years of follow up,
endometrial ablation was found to be only 5–11% less costly than the cost of hysterectomy.
This was compared with 24% and 29% less expensive at one and two years of follow up
(Lethaby et al., 2000). Because the combination of the two procedures increased around 25%
per year, endometrial ablation can either decrease the threshold for intervention or increase
greater access to the health system (Aberdeen, 1999).
2.7. The impact of heavy menstrual bleeding on women’s quality of life

HMB has a negative impact on quality of life in terms of social, physical, and emotional well-being (Jensen et al., 2011, Duckitt et al., 2006). Menstruation can have a major effect on the quality of women’s lives, practically those who have heavy menstrual cycles. The effect of menstrual bleeding may extend beyond the individual women, to society more broadly to include the workplace. In the Swedish questionnaire survey (Edlund et al., 1994) more than one in two women who perceived their menstruation as heavy felt forced to leave from social activities because of their period and 15% were absent from work in most heavy days of the period. However, only 38% of women who felt that their blood loss was excessive had consulted a doctor about it. Heavy menstruation and menstrual pain can also lead to restrictions at work and school and create problems for educational and academic success.

In an electronic survey of 767 university female students, 268 (35%) felt their menstrual loss as heavy menstruation, 60% of them felt quality of life was affected by their menstrual cycles with one quarter missing at least 1 lecture per month, about half of them had an exam affected and more than a half missing a social activity every month. Dysmenorrhoea looks to have a considerable effect on their quality of life, and 47 (18%) were housebound for at least 1 day a month due to the intensity of pain (Anastasakis et al., 2008). For younger adolescent girls, heavy menstruation also has a negative impact on school attendance and participation in school activities (Pawar et al., 2008). In a survey of 45 adolescents (age 15–27 years), 25 (56%) had measured HMB by the PBAC scores and it revealed that the high menstrual score was associated with the high possibility of adverse effect on quality of life. Those with HMB were more likely to miss school, restrict travel and sleep overs and miss social events during menstruation (Figure 2.7) (Pawar et al., 2008).
2.7.1. Quality of life measurement issues

The most suitable methodology and tool for evaluating quality of life in patients with HMB is still an issue (Shankar et al. 2004). Some questions on nonspecific quality of life instruments, such as the Short Form 36 (SF-36) have problems of reliability for patients with HMB, therefore, they could be considered as a suboptimal tool for this population (Habiba et al., 2010, Jenkinson et al., 1996). Defects in standardized quality of life tools have led to a proliferation of questionnaires, where their validity and reliability have not been fully recognized (Shankar et al., 2004, Matteson et al., 2010). Different instruments for estimation of health outcomes in heavy menstrual bleeding research have been developed (Moos, 1968, Lamping et al., 1998). A review of these HMB-specific measures showed that there is no specificity to HMB (Moos, 1968), uncertain responsiveness statistics (Moos, 1968, Lamping
et al., 1998), and insufficient validity among US patients with heavy menstrual bleeding (Moos, 1968, Lamping et al., 1998), recalls problems and unclear scoring issues (Shaw et al., 1998).

One systematic review found that there is problems of use of HR quality of life measures especially SF-36. However, there is no specific HR quality of life measure for HMB (Clark et al., 2002). Four studies have examined the use of general HR quality of life measures in HMB (Jenkins et al., 1996, Abbott et al., 2003). One study investigated the use of SF-36. Of eight scales in SF-36, two (mental health and general health perceptions) had lower internal reliability when assessed in women with HMB compared with those of the general population (0.50 versus 0.83 and 0.51 versus 0.80, respectively). The result of this study reveals that SF-36 is not specific enough to reveal the HR quality of life issues of women with HMB (Jenkinson et al., 1996). Three qualitative studies which use interviews and focus groups reported the occurrence of women with HMB. These studies found that impact involves physical, psychological and social factors, with women talking about amount of blood loss, mood changes and becoming self-conscious. These studies reveal that women need more information, with more acceptance and understanding of the problem by clinicians (Byles et al., 1997, Marshall et al., 1998). Therefore, it could be considered that quality of life assessment requires further studies. Quality of life instrument should be appropriate, reliable, valid, responsive, precise, interpretable, acceptable and feasible (Matteson et al., 2011).

**Conclusion**

The historical literature provides an interesting insight into the way in which terminologies and descriptions of a culturally sensitive symptom and diseases like heavy menstrual bleeding. An understanding of this literature also gives clues as to the way in which individual
medical writers have expressed their own terms or put their own interpretations on the definitions of existing terminologies. Heavy menstrual bleeding is a symptom indicative of underlying conditions. Even though, the range of differential diagnosis for HMB includes such disparate conditions as uterine fibroid, renal disease, bleeding disorder and menopause, approach focused on age, associated symptoms and risk factors can lead to appropriate diagnosis and treatment. There are different methods to measure the heaviness of menstrual blood objectively and alkaline haematin method is considered as the ideal one to assess the amount of the menstrual bleeding. Quality of life is increasingly popular as an outcome determining of the heavy menstrual bleeding effect on women’s physical, mental and social well-being.
Chapter 3: Hypotheses, aims and objectives

Primary hypothesis
1. Women with heavy menstrual bleeding, confirmed by objective measurement, will experience a greater impact on their quality of life than the cyclical symptoms experienced by women with normal menstrual blood loss.

Secondary hypotheses
1. Around 10% of the women volunteering for this menstruation study will have objectively confirmed heavy menstrual bleeding.

2. The effect of HMB on quality of life will be demonstrated through a greater impact on regular work attendance and effectiveness, and through effects on social and family activities, compared to women with normal bleeding.

3. Women with heavy menstrual bleeding will have lower haemoglobin, ferritin and transferrin levels and lower transferrin receptor saturation than women with menstrual bleeding within the normal range.

Aims and objectives of the study
1. This study is designed to investigate the impact of heavy menstrual bleeding on women’s quality of life and to explore their help-seeking behaviour patterns by comparing women with objectively measured heavy menstrual bleeding to women with measured normal menstrual loss. Their quality of life will be assessed by the degree to which it affects their ability to work and their social, family and sexual life. The relationship between the amount of
measured menstrual blood loss and the individual woman’s efforts to seek a consultation with a general practitioner or specialist will be reviewed.

2. To correlate actual measured menstrual blood loss with the individual woman’s perceptions of her bleeding.

3. To compare women who perceive they have heavy menstrual bleeding with women who perceive their bleeding to be normal in relation to their assessment of the impact of menstrual bleeding on their quality of life, the degree to which it affects their ability to work in or outside the home, limitation in physical activities, limitation in social and family activities and their psychological health and medical-seeking behaviours.

4. To correlate the relationship between amounts of measured menstrual blood loss with objective factors such as haemoglobin, serum ferritin, transferrin and transferrin receptor saturation levels.

5. Based on the findings of (1) (2) (3) and (4), to assess the depth of understanding of women’s perception of their menstrual bleeding, the knowledge deficit of these women about heavy menstrual bleeding and how their thinking about menstrual bleeding may be different from their actual blood loss. Furthermore, this study will explore how inaccurate knowledge can affect medical-seeking behaviour.

6. Based on previous findings, this study will explore the menstrual symptoms that most affect women’s quality of life, including women with normal measured menstrual bleeding and how this affects their medical-seeking behaviour. This study will also examine how help-
seeking behaviours among women complaining of both normal and heavy menses may be related to other factors.

7. Lastly, accurate knowledge of the degree of impact of HMB on different aspects of women’s quality of life will provide clinicians with descriptive measures to determine the magnitude of the most important changes in quality of life, and provide suggestions about appropriate management.
Chapter 4: Clinical and Laboratory Methodology

This chapter will discuss the study design, the underlying principles that support the instruments chosen for this study, challenges of the methodology, data collection procedures, recruitment procedures, and the methods of data analysis.

4.1. Overview

The first phase of the study consisted of a detailed questionnaire on experiences of menstruation completed online by 2,397 women who were members of an established market research group representative of NSW women in the reproductive years. The questionnaire was designed to assess various aspects of menstruation, including the impact on quality of life. The questionnaire (appendix I) included items on subjective assessment of blood loss, effect on social, leisure and various physical activities, as well as the ability to work. Among the respondents, 628 agreed to participate in further research into menstruation. In the second phase 63 respondents had their menstrual blood loss (MBL) measured for three cycles using the alkaline haematin method. Recruitment for this phase is still ongoing. Women were categorised according to measured blood loss into normal or heavy menstrual bleeding groups. In the final phase a comparison was made of the responses to the questionnaires between the two groups. The study was approved by the FPNSW Ethics Committee (Ethics number R 2008-08) and all women gave written informed consent to participate.

The study consisted of three stages:

1. Development of a detailed menstruation questionnaire in suitable format for ‘online’ completion, and testing in a pilot form.

2. Administration of the final questionnaire to women living in NSW, aged 18-50 years, selected from an established market research panel.
3. Objective measurement of total menstrual blood loss in consenting women for three menstrual episodes.

4. Classification of women according to MBL results into those with normal bleeding (less than 80 mL) or heavy menstrual bleeding (HMB; 80 mL or greater) and comparison with their answers to the online questionnaire.

4.2. Questionnaire development

A steering group was set up consisting of two expert gynaecologists, one of them with research experience in menstrual problems, two clinicians with expertise in sexual and reproductive health, a psychologist with experience in women’s health research and the development of decision tools, a health economist and a statistician. Initially three focus groups were conducted consisting of 3-5 women in each who identified themselves as having HMB. Thematic analysis identified the domains which needed inclusion in a questionnaire to identify women with HMB. The questions covering these domains were selected from a number of validated questionnaires in the literature. The questionnaire then was trialled with a small group of women with known HMB to examine the appropriateness of response scales and assessment of acceptability and time required for completion.

To establish test–retest reliability the questionnaire was administered to 10 women with known HMB and 10 women with normal menstrual bleeding and re-administered after a two week interval. The content validity was determined through agreement between the steering group members, following the interviews with women, and reviews of existing measures in the literature. The construct validity, which means the extent to which the instrument measures the attribute intended to be measured, was determined through analysis of the measure and other measures with the same and different attributes, examination of the
correlation between the different measures and assessment of the extent that the question was able to detect differences in women with and without HMB. Lastly, questions were assigned a score by the steering group to detect the factors which will provide an accurate indication of HMB.

4.3. Administration of the questionnaire

A commercial social research sampling organisation provided eligible respondents from their proprietary database of people willing to participate in research surveys. The database provided a representative sample of NSW women in the reproductive years. An online research marketing company (www.researchers.pureprofile.com) has a large database with an in depth profile of individual participants which is updated over time and allows for careful targeting of surveys depending on the criteria required by the research.

Eligible women were menstruating women, living in NSW aged 18-50 years. Exclusion criteria was women who had a hysterectomy or endometrial ablation, bilateral oophorectomy, using hormonal contraceptives except for management of HMB or post-menopausal.

4.4. Participants and recruitment

Women who completed the online survey and indicated that they were interested in participating in further research on menstruation were contacted by a research assistant (RA) and given information about the MBL collection phase of the study. If they indicated interest they were sent the information sheet and contacted by the RA one week later to answer any questions. Women who agreed to participate were given an appointment to attend the clinic.
At the clinic visit each woman was given an identity code consisting of the first two letters of her first name and surname with additional sequential numbers from 001 and consented to the study. The women were instructed in great detail on how to collect their menstrual blood. Venous blood was collected for haemoglobin and iron studies. Women were given an individually labelled cooler box (‘esky’), cold packs, handbag, plastic sealable bags labelled with their ID and study number, and sanitary protection sufficient for one collection cycle as well as a menstrual diary (appendix II) on which to mark bleeding and spotting days and number of pads and tampons used each day. A sheet labelled with ID, date of birth and study number for recording results of daily blood loss was included in the esky for completion by laboratory staff. Women were offered the option of taking supplies for 3 cycles or a single cycle. They were instructed to place each soiled piece of sanitary protection in an individual bag and to complete the label with day, date and time of collection. All plastic bags from a single day were placed in a larger plastic bag and the ID, day and date of collection entered on the label and placed in the esky.

If the woman had taken supplies for only one cycle a courier picked up an esky labelled with the woman’s ID containing supplies before going to the woman’s house to collect the esky containing the used sanitary protection. The esky containing the used protection was sealed in an ID labelled plastic garbage bag prior to collection to conform to regulations for transport of human products. The esky containing used products was delivered to the Department of Obstetrics, Gynaecology and Neonatology at the University of Sydney for MBL estimations. The empty eskies were collected at regular intervals from the Department so that the same esky, once it has been thoroughly cleaned, can be used for other participants. At the end the study women were given their results. Those with established HMB were counselled about
options for management of HMB and given an information sheet (appendix III) about these options.

4.5. **Measurement of menstrual blood loss**

Total menstrual blood loss for the cycle was measured by the alkaline haematin technique. Daily blood loss was measured and recorded. The total loss over an individual menses was determined by the addition of daily loss for the total days of bleeding per cycle.

4.5.1. **Alkaline Haematin Method: Overview**

Among calorimetric procedures, the alkaline haematin method of Hallberg and Nilsson (1964) is the most popular method. Because the method depends on the measurement of extracted haem from haemoglobin it is considered as an accurate and sensitive method (Barer & Fowler, 1936, Thomas, 1970). However, the problem is that the process of chemical digestion and oxidation of sanitary materials is very time-consuming and tedious. The Hallberg and Nilsson procedure extracts the haemoglobin in menstrual blood from the sanitary materials and converts it using 5% aqueous sodium hydroxide to alkaline haematin. The resulting solution which is brown in colour is then measured photometrically. However, if significant contaminants are present in menstrual blood they may interfere with haemoglobin extraction, conversion, and measurement of the alkaline haematin (Shaw et al., 1972, Poon et al., 1973).

The extraction, conversion, and calorimetric measurement are all direct procedures which do not require any complicated techniques or expensive tools. A simple colorimeter is the only necessary piece of equipment for this process. The use of high speed centrifugation of any extracted sanitary materials in the sodium hydroxide solution decreases the problem of turbidity. However, the use of a high speed centrifuge has led to underestimations in a number
of patient samples where the alkaline haematin colour was concentrated in the centrifuged pellet. Evaluation of different filter papers has revealed that turbidity could be successfully removed from all extracted samples by using filtration with Whatman No. 4 filter paper (Shaw, 1977).

Problems arising from the alkaline haematin procedure are the unpleasant odour which results from the mixture of sodium hydroxide solution and soiled menstrual tampons or napkins, and the necessity for manually mixing the materials until the contained haemoglobin is extracted and converted by the alkaline solution to brown haematin. The procedure of menstrual haemoglobin extraction is time and labour intensive, especially if there is a considerable number of tampons and/or napkins. The change in colour intensity of haematin occurs in the first hours after its formation and becomes stable after 24 hours. Quantification of MBL to millilitres of peripheral blood requires a comparison of haematin colour intensity of menstrual blood to that of peripheral blood. Mixing of the peripheral blood sample in aqueous sodium hydroxide is converted almost directly, while the menstrual blood sample is converted gradually and considerable time is needed for haemoglobin to be extracted from the sanitary materials. According to the type of pad material, it could take about one hour or more. Thus, it may require an hour or more if considerable pad material is present. This is usually handled by dividing the sample into smaller lots.

The colour of alkaline haematin intensity of peripheral blood and menstrual samples should be given the time to stabilise before it is ready to be assessed by photometric measurement as haematin is produced at different rates. The prolonged time which is needed for this process results in the laboratory worker being exposed to the unpleasant odour of the extracting
solutions for a considerable period of time, placing a limitation on this kind of work in the laboratory. These processes are generally undertaken with an extraction hood.

Using a mechanical device (StomacherLab-Blender™), which mechanically extracts sanitary material inside sealed plastic bags was found to offer shorter time for extraction and conversion of menstrual haemoglobin, which is nearly completed within 5 minutes. In our study, the extraction was formally tested to be complete within 15 minutes. This semi-automatic process greatly decreases the burden of the major drawbacks of the alkaline haematin technique. It seems that using an automatic blender such as the Stomacher provided considerable advantages to facilitate measuring menstrual samples in the lab.

4.5.2 Procedures of alkaline haematin protocol in this study

a. The sanitary materials from a single day’s collection were placed into thick stomacher bags. Double bags were used as a precaution against bag breakage and spillage. The bags were then placed into a Stomacher (LabBlender3500) (Figure 4.1).

b. Depending on the amount of sanitary material from each day, 1,000 to 2,000 mL of 5% sodium hydroxide was added to the bag of sanitary material and mixed in the Stomacher for 10 to 15 minutes.

c. The mixture was then left to stand for at least 10 minutes after which a part of the mulched solution was poured out into a small beaker.
Figure 4.1: Cross-sectional image of Lab Blender 3500 (Newton 1977)

d. Part of the solution was filtered slowly through a single layer of 11 cm diameter filter paper in a small cuvette.

e. The resulting eluent was then placed in a colorimeter, sometimes requiring dilution to completely fill the cuvette (Figure 4.2).

f. The Hb in the menstrual eluant was compared with grams of Hb/100ml from the standard curve. Menstrual blood loss was calculated using this standard formula:

\[ \text{MBL} = \frac{\text{Gm of Hb from Graph}}{\text{Venous Hb level}} \times 1000 \]
4.5.3. Serum iron studies

The inclusion of iron studies in the protocol was instituted after the start of the study. This test was carried out for the first 44 subjects after they had completed collection of their three cycles. Emails were sent to these 44 subjects, explaining the reason for adding this test to the study and asking them if they would be willing to have this additional blood test taken. Of the 44 emails sent, 22 subjects indicated they would be happy to have this additional blood test and request forms were sent to them to facilitate this. To date, full results of iron studies are available for only 25 subjects.

4.6. Participants

Of 555 subjects contacted by email, 446 replied by return email. Of these, some declined further contact, while those others who expressed an interest were phoned by the study nurse to discuss details of the study. Those still interested were sent the participant information
sheet (PIS). To date, 63 women of the 446 contacted have been consented into the study. Appointments were booked for two new women to be consented, and 15 women are currently reviewing the PIS, with 126 subjects yet to be contacted (Figure 4.3). Of the 63 consented subjects, 54 have completed collection of 3 menstruations. Nine subjects terminated before completing the study (Table 4.1).

**Table 4.1: Reasons for termination or withdrawal from the study**

<table>
<thead>
<tr>
<th>Reason for early termination</th>
<th>Number of women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate absorption of sanitary protection</td>
<td>3</td>
</tr>
<tr>
<td>Unwilling to stop using tranexamic acid or mefenamic acid</td>
<td>1</td>
</tr>
<tr>
<td>Apparent skin reaction to sanitary protection</td>
<td>1</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>1</td>
</tr>
<tr>
<td>Relocating to another city</td>
<td>2</td>
</tr>
<tr>
<td>Family illness</td>
<td>1</td>
</tr>
</tbody>
</table>
3,397 women were selected randomly by market research company

1,630 women completed the online survey

780 women consented to have their details forwarded for further research contact

550 women were contacted via email by research nurse regarding inclusion into the study

446 replied to the email

9 subjects: Early terminations/withdraw

15 considering participation, 2 awaiting appointment, 126 not yet contacted

63 women consented to the study, 54 subjects completed 3 menstrual collections

Figure 4.3: Flow chart of women participating in different stages of the study
4.7. Data analysis

a. Menstrual blood loss measurements were divided into two groups: heavy (HMB) and normal blood loss (NBL); a comparison between the two groups was then performed looking at the amount of total loss, daily loss and duration of bleeding.

b. Women were divided into two groups based on their MBL:
   i. Group 1: women whose loss in at least two cycles was ≥80 mL
   ii. Group 2: women whose loss in at least two cycles was < 80 mL

The responses to the HMB questionnaire for the individual women who had participated in the MBL collections were merged with their MBL results and analysed as two groups, HMB and NBL. The results were compared to determine which questions best indicated normal or heavy bleeding based upon their actual MBL. The measurement of menstrual loss for every woman was blinded to their answers on the questionnaire. The individual questionnaires were only consulted after MBL measurements were complete.

4.8. Statistical analysis

For continuous data, mean, median and standard deviations were used to summarise the data, and for categorical data, frequencies and percentages. Two group comparisons between women who answered the online questionnaire and women who agreed to further research, were made. Comparisons were made between the effect of menses on the quality of life of women with measured HMB and women with normal measured menstrual loss, and also between the duration of menstrual bleeding of normal and heavy cycles. Where the groups were compared on normally distributed continuous data (e.g. age) Student’s t tests were used. Where the two groups were compared on categorical data (e.g. marital status, education level)
Pearson’s chi-square analysis was used, except when small cell sizes led to low expected frequencies. Because of small cell sizes, responses for descriptions of heaviness of menstrual bleeding were collapsed into three groups in some analyses: women who reported their menstrual bleeding was mild or moderate, women who reported their bleeding was heavy, and women who reported their bleeding as very heavy. Women’s assessment of their period pain was collapsed into two groups: women with no, mild or very mild pain and women with moderate or severe pain. Data were entered and analysed using SPSS version 20. Alpha was set at 0.05 for all analyses.
Chapter 5: Results

This chapter reports results of a range of analyses arising from different aspects of this study of normal and heavy menstruation. It provides a summary of demographic data, a descriptive analysis of individual menstrual blood loss of the participating women, the impact of heavy menstrual bleeding on the women’s quality of life and the variation in haemoglobin and iron parameters. The analysis includes a comparison between measured menstrual bleeding and women’s subjective assessment of their menstrual bleeding and their quality of life scores in relation to both the objective and subjective assessment of menstrual blood loss. This chapter will also report on the effect of menstrual pain on women’s quality of life, and examine relationships between the volume of menstrual blood loss with serum ferritin, transferrin saturation and general health parameters.

5.1. Recruitment and participation

5.1.1. Comparison of the demographics of the women who answered the online questionnaire and the sub-group of women who agreed to be approached about further research

Of 3,397 women in New South Wales who were randomly selected by the Pure Profile Company, an international market research company, to answer an online menstruation questionnaire in 2011, 2,397 women (70.6%) completed the questionnaire (767 missed). Of these women, 628 indicated an interest in participating in further research and gave their contact details (email and phone number). The women who agreed to further research were a representative sample of the entire group. Table 5.1 shows the socio-demographic and menstrual characteristics of this sample compared to all women who answered the questionnaire. It can be seen that they were comparable in almost all parameters. Forty percent of both groups were aged between 30-39 years. Approximately a third of both groups
considered their bleeding to be heavy or very heavy (n=257, 26%, n=192, 31%, respectively).

There were some minor differences in educational status between the two groups. In the original group, a higher percentage had an undergraduate qualification (38%) while in the smaller group more had a TAFE qualification (34%).

Table 5.1: Demographic and menstrual characteristics of women who only answered the online questionnaire, compared to women interested in participating in further research

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>Women who only answered the online questionnaire (n=1,002)</th>
<th>Women who agreed to participate in further research (n=628)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-19</td>
<td>28(3)</td>
<td>11(2)</td>
<td>0.23</td>
</tr>
<tr>
<td>20-29</td>
<td>319(32)</td>
<td>185(30)</td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>402(40)</td>
<td>248(40)</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>252(25)</td>
<td>184(29)</td>
<td></td>
</tr>
<tr>
<td>50+</td>
<td>1(.1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>350(35)</td>
<td>189(30)</td>
<td>0.016</td>
</tr>
<tr>
<td>Married</td>
<td>455(45)</td>
<td>27(44)</td>
<td></td>
</tr>
<tr>
<td>De facto</td>
<td>163(16)</td>
<td>122(19)</td>
<td></td>
</tr>
<tr>
<td>Divorced</td>
<td>30(3)</td>
<td>36(6)</td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>4(.4)</td>
<td>3(.5)</td>
<td></td>
</tr>
<tr>
<td>Education status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>3(.3)</td>
<td>1 (.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Year 10</td>
<td>84(8)</td>
<td>58(9)</td>
<td></td>
</tr>
<tr>
<td>HSC</td>
<td>129(13)</td>
<td>94(15)</td>
<td></td>
</tr>
<tr>
<td>TAFE</td>
<td>254(25)</td>
<td>211(34)</td>
<td></td>
</tr>
<tr>
<td>Undergraduate</td>
<td>375(38)</td>
<td>187(30)</td>
<td></td>
</tr>
<tr>
<td>Postgraduate</td>
<td>156(16)</td>
<td>77(12)</td>
<td></td>
</tr>
<tr>
<td>Work status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full-time</td>
<td>466(47)</td>
<td>273(44)</td>
<td>0.35</td>
</tr>
<tr>
<td>Part-time</td>
<td>188(19)</td>
<td>141(23)</td>
<td></td>
</tr>
<tr>
<td>Casual</td>
<td>71(7)</td>
<td>40(6)</td>
<td></td>
</tr>
<tr>
<td>Home duties</td>
<td>170(17)</td>
<td>117(19)</td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>69(7)</td>
<td>40(6)</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>37(4)</td>
<td>17(3)</td>
<td></td>
</tr>
<tr>
<td>Duration of bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3 days</td>
<td>73(7)</td>
<td>34(5)</td>
<td>0.46</td>
</tr>
<tr>
<td>3-7 days</td>
<td>836(84)</td>
<td>537(86)</td>
<td></td>
</tr>
<tr>
<td>8-10days</td>
<td>61(6)</td>
<td>43(7)</td>
<td></td>
</tr>
<tr>
<td>&gt; 10 days</td>
<td>21(2)</td>
<td>14(2)</td>
<td></td>
</tr>
<tr>
<td>Length of cycle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21-35 days</td>
<td>859(87)</td>
<td>563(90)</td>
<td>0.08</td>
</tr>
<tr>
<td>More than 35 days</td>
<td>132(13)</td>
<td>60(10)</td>
<td></td>
</tr>
<tr>
<td>Demographic characteristics</td>
<td>Women who only answered the online questionnaire (n=1,002)</td>
<td>Women who agreed to participate in further research (n=628)</td>
<td>P value</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----------------------------------------------------------</td>
<td>-----------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td><strong>Heaviness of the cycle</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light</td>
<td>117(12)</td>
<td>70(11)</td>
<td>0.02</td>
</tr>
<tr>
<td>Moderate</td>
<td>609(62)</td>
<td>366(58)</td>
<td></td>
</tr>
<tr>
<td>Heavy</td>
<td>218(22)</td>
<td>145(23)</td>
<td></td>
</tr>
<tr>
<td>Very heavy</td>
<td>39(4)</td>
<td>47(8)</td>
<td></td>
</tr>
<tr>
<td><strong>Heavy days of the period</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No heavy days</td>
<td>113(12)</td>
<td>59(9)</td>
<td>0.62</td>
</tr>
<tr>
<td>1-3 days</td>
<td>775(79)</td>
<td>512(82)</td>
<td></td>
</tr>
<tr>
<td>4-6 days</td>
<td>83(8)</td>
<td>52(8)</td>
<td></td>
</tr>
<tr>
<td>7-10 days</td>
<td>10(1)</td>
<td>4(6)</td>
<td></td>
</tr>
<tr>
<td>&gt; 10 days</td>
<td>2(.2)</td>
<td>1(.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Regularity of the cycle</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>743(75)</td>
<td>494(79)</td>
<td>0.09</td>
</tr>
<tr>
<td>Irregular</td>
<td>248(25)</td>
<td>134(21)</td>
<td></td>
</tr>
</tbody>
</table>

5.1.2. Comparison of the characteristics of women who collected their sanitary protection with women who did not collect but had indicated an interest to participate in further research

Of 560 women who so far were contacted by phone and given information about the study, only 63 agreed to collect their used sanitary protection (11%). There were no statistically significant differences in demographic characteristics between the two groups (Table 5.2).

The predominant age group in both was 30-39 years and the group agreeing to participate in the menstrual blood collection (MBL) had a higher but not significantly different percentage of university graduates. It can be seen that the two groups are not statistically different in all parameters. Twenty-three women from the MBL sample (37%) considered their bleeding was heavy or very heavy compared to 29% of the non-collectors and this was not significantly different.

Table 5.2: Demographic and menstrual characteristics of collectors and all women who were given study information
<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>MBL collectors (n=63)</th>
<th>Women who did not collect MBL (n=497)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 - 19</td>
<td>0 (0)</td>
<td>9(2)</td>
<td></td>
</tr>
<tr>
<td>20 - 29</td>
<td>13(21)</td>
<td>155(31)</td>
<td></td>
</tr>
<tr>
<td>30 - 39</td>
<td>28(44)</td>
<td>191(38)</td>
<td></td>
</tr>
<tr>
<td>40 - 49</td>
<td>22(35)</td>
<td>142(29)</td>
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<tr>
<td>50+</td>
<td>0 (0)</td>
<td>0 (0)</td>
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<tr>
<td>Marital status</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Single</td>
<td>20(32)</td>
<td>141(28)</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>29(46)</td>
<td>230(46)</td>
<td></td>
</tr>
<tr>
<td>De facto</td>
<td>11(18)</td>
<td>94(19)</td>
<td></td>
</tr>
<tr>
<td>Divorced</td>
<td>3(5)</td>
<td>29(6)</td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Education status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>0 (0)</td>
<td>0(.2)</td>
<td></td>
</tr>
<tr>
<td>Year 10</td>
<td>4(6)</td>
<td>53(10)</td>
<td></td>
</tr>
<tr>
<td>HSC</td>
<td>9(14)</td>
<td>77(16)</td>
<td></td>
</tr>
<tr>
<td>TAFE</td>
<td>16(25)</td>
<td>166(33)</td>
<td></td>
</tr>
<tr>
<td>Undergraduate</td>
<td>24(38)</td>
<td>141(28)</td>
<td></td>
</tr>
<tr>
<td>Postgraduate</td>
<td>10(16)</td>
<td>59(12)</td>
<td></td>
</tr>
<tr>
<td>Work position</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full-time</td>
<td>29(46)</td>
<td>208(42)</td>
<td></td>
</tr>
<tr>
<td>Part-time</td>
<td>16(25)</td>
<td>113(23)</td>
<td></td>
</tr>
<tr>
<td>Casual</td>
<td>4(6)</td>
<td>33(7)</td>
<td></td>
</tr>
<tr>
<td>Home duties</td>
<td>10(16)</td>
<td>97(20)</td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>4(6)</td>
<td>30(6)</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>0 (0)</td>
<td>16(3)</td>
<td></td>
</tr>
<tr>
<td>Duration of cycle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3 days</td>
<td>1 (2)</td>
<td>27(5)</td>
<td></td>
</tr>
<tr>
<td>3-7 days</td>
<td>60(95)</td>
<td>421(85)</td>
<td></td>
</tr>
<tr>
<td>8-10days</td>
<td>2(3)</td>
<td>38(8)</td>
<td></td>
</tr>
<tr>
<td>&gt; 10 days</td>
<td>0 (0)</td>
<td>11(2)</td>
<td></td>
</tr>
<tr>
<td>Heaviness of the cycle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light</td>
<td>6(10)</td>
<td>54(11)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>34(54)</td>
<td>299(60)</td>
<td></td>
</tr>
<tr>
<td>Heavy</td>
<td>18(29)</td>
<td>106(21)</td>
<td></td>
</tr>
<tr>
<td>Very heavy</td>
<td>5(8)</td>
<td>38(8)</td>
<td></td>
</tr>
<tr>
<td>Heavy days of the period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No heavy days</td>
<td>5(8)</td>
<td>50(10)</td>
<td></td>
</tr>
<tr>
<td>1-3 days</td>
<td>56(89)</td>
<td>400(81)</td>
<td></td>
</tr>
<tr>
<td>4-6 days</td>
<td>2(3)</td>
<td>43(9)</td>
<td></td>
</tr>
<tr>
<td>7-10 days</td>
<td>0(0)</td>
<td>3(.6)</td>
<td></td>
</tr>
<tr>
<td>&gt; 10 days</td>
<td>0 (0)</td>
<td>1(.2)</td>
<td></td>
</tr>
<tr>
<td>Demographic Characteristics</td>
<td>MBL collectors (n=63)</td>
<td>Women who did not collect MBL (n=497)</td>
<td>P value</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-----------------------</td>
<td>---------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td><em>Regularity of the cycle</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>53(84)</td>
<td>390(79)</td>
<td>.298</td>
</tr>
<tr>
<td>Irregular</td>
<td>10(16)</td>
<td>107(22)</td>
<td></td>
</tr>
</tbody>
</table>

5.2. Correlation between women’s perceived heaviness of their menstrual blood loss and their measured menstrual blood loss

Fifty-four (%) of the 63 women who were consented to the study collected their menstrual blood for three complete cycles, five women collected for only two cycles and four women collected for only one cycle. The women who did not complete three cycles were classified as women with normal menstrual loss as they had one or two measured menstrual periods with normal blood loss. Women with heavy menstrual bleeding (HMB) (two out of three cycles with MBL >80 mL) comprised 16% of the entire sample of 63 women. Of 53 women with measured NMB, 15 women (28%) considered their bleeding to be heavy and three women (6%) considered their bleeding to be very heavy. Half the women with measured HMB correctly judged their loss to be heavy or very heavy while five women (50%) considered their bleeding to be moderate.
Figure 5.1: Measured menstrual loss compared to the subjective judgment of women regarding the amount of their menstrual blood loss.

5.3. Effect of measured blood loss on women’s quality of life compared to women with normal measured menstrual loss

In this sample of 63 women with measured menstrual blood loss, the prevalence of women with heavy menstrual bleeding was 16% (10 women). Table 5.3 shows the distribution of women with heavy and normal menstrual bleeding according to socio-demographic characteristics. Although women with heavy menstrual bleeding were generally older than women with measured NMB, 6 women (60%) were in the 30-39 age group and more likely to be in part time work (5; 50%) and the differences were not significant. There was a significant difference in marital status between the two groups (p = 0.03). Single women accounted for 36% of normally menstruating women while they accounted for only 10% in the heavy group.
A comparison between the two groups on the effect of different aspects of menses on the women’s quality of life is shown in Table 5.4. There were no significant differences between the two groups in any quality of life parameters. The majority of women with poor quality of life due to menses had normal measured menstrual loss. One woman with measured NMB reported severe interruptions to her work during menstruation. Two women (20%) of those with measured HMB reported frequent disruption in their work and daily life. Five women (9%) from the normally menstruating group reported that their periods limited social activity, two women (4%) reported effects on their family life while one woman experienced severe disruption in her ability to carry out her family activities. Similarly in the group with measured HMB, 20% reported frequent interruption to their daily work during menses while 60% reported occasional disruption. Four women (40%) with HMB complained of tiredness during the cycle while 21 (40%) women in the normal group felt tried or very tired.

There was little difference in the effect of menstruation on social life with almost half of both groups reporting no effect while 50% of women with measured HMB and about 45% of women with normal MBL reporting that family life was unaffected. Two women (20%) with measured HMB reported feeling down and worried during menses while six women (11%) with normal MBL reported similar feelings. Forty percent of the women with measured heavy menstrual bleeding were not sexually active during menstruation.

The number of women seeking a medical consultation for HMB was not significantly different between the two groups. Nine women with measured NMB (17%) gave a history of having a medical consultation about HMB while only four women (40%) with measured HMB asked for medical advice about HMB (Table 5.5).
Table 5.3: Comparison of the demographic characteristics of women with measured HMB and women with normal MBL

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>Women with measured NMBL (n=53)</th>
<th>Women with measured HMB (n=10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age in years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20_29</td>
<td>14(26)</td>
<td>4(40)</td>
<td>.07</td>
</tr>
<tr>
<td>30_39</td>
<td>24(45)</td>
<td>6(60)</td>
<td></td>
</tr>
<tr>
<td>40_49</td>
<td>15(28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50+</td>
<td>49</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td><strong>Marital state</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>19(36)</td>
<td>1(10)</td>
<td>.03</td>
</tr>
<tr>
<td>Married</td>
<td>25(47)</td>
<td>5(50)</td>
<td></td>
</tr>
<tr>
<td>De facto relationship</td>
<td>6(11)</td>
<td>4(40)</td>
<td></td>
</tr>
<tr>
<td>Divorced</td>
<td>3(6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td><strong>Educational status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
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<td>0</td>
<td>.896</td>
</tr>
<tr>
<td>Year 10</td>
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<td>0</td>
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</tr>
<tr>
<td>HSC</td>
<td>8(15)</td>
<td>1(10)</td>
<td></td>
</tr>
<tr>
<td>TAFE</td>
<td>13(25)</td>
<td>3(30)</td>
<td></td>
</tr>
<tr>
<td>Undergraduate</td>
<td>19(36)</td>
<td>4(40)</td>
<td></td>
</tr>
<tr>
<td>Postgraduate</td>
<td>9(17)</td>
<td>2(20)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td><strong>Work status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full time</td>
<td>28(53)</td>
<td>2(20)</td>
<td>.09</td>
</tr>
<tr>
<td>Part-time</td>
<td>10(19)</td>
<td>5(50)</td>
<td></td>
</tr>
<tr>
<td>Casual</td>
<td>4(8)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Home duties</td>
<td>7(13)</td>
<td>3(30)</td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>4(8)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>
Table 5.4: Comparison of quality of life parameters of women with measured HMB and women with measured normal blood loss

<table>
<thead>
<tr>
<th>Quality of life parameters</th>
<th>Women with measured NMB (n=53) N (%)</th>
<th>Women with measured HMB (n=10) N (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Work and daily activity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occasional</td>
<td>28(53)</td>
<td>6(60)</td>
<td></td>
</tr>
<tr>
<td>Frequent</td>
<td>1(2)</td>
<td>2(20)</td>
<td></td>
</tr>
<tr>
<td>severe</td>
<td>1(2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td><strong>Social life</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>unaffected</td>
<td>25(47)</td>
<td>5(50)</td>
<td>.594</td>
</tr>
<tr>
<td>Slightly affected</td>
<td>23(43)</td>
<td>5(50)</td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>5(9)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td><strong>Family life/Relationship</strong></td>
<td></td>
<td></td>
<td>.895</td>
</tr>
<tr>
<td>unaffected</td>
<td>24(45)</td>
<td>5(50)</td>
<td></td>
</tr>
<tr>
<td>Suffer some strain</td>
<td>26(49)</td>
<td>5(50)</td>
<td></td>
</tr>
<tr>
<td>Suffer quite a lot</td>
<td>2(4)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Sever disrupted</td>
<td>1(2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td><strong>Physical health and wellbeing</strong></td>
<td></td>
<td></td>
<td>.909</td>
</tr>
<tr>
<td>Feeling well</td>
<td>5(9)</td>
<td>1(10)</td>
<td></td>
</tr>
<tr>
<td>Feeling well most of the time</td>
<td>27(51)</td>
<td>4(40)</td>
<td></td>
</tr>
<tr>
<td>Often feel tried</td>
<td>18(34)</td>
<td>4(40)</td>
<td></td>
</tr>
<tr>
<td>Very tried</td>
<td>3(6)</td>
<td>1(10)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td><strong>Pain interfere with normal</strong></td>
<td></td>
<td></td>
<td>.816</td>
</tr>
<tr>
<td>Not at all</td>
<td>16(30)</td>
<td>5(50)</td>
<td></td>
</tr>
<tr>
<td>Slightly</td>
<td>23(43)</td>
<td>3(30)</td>
<td></td>
</tr>
<tr>
<td>Moderately</td>
<td>11(21)</td>
<td>1(10)</td>
<td></td>
</tr>
<tr>
<td>Quite a bit</td>
<td>3(6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Extremely</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td><strong>Time of work due to menses</strong></td>
<td></td>
<td></td>
<td>.09</td>
</tr>
<tr>
<td>0</td>
<td>42(88)</td>
<td>6(67)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4(8)</td>
<td>1(11)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2(2)</td>
<td>2(22)</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
<td>-------</td>
<td>--------</td>
</tr>
<tr>
<td>3</td>
<td>1(2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

**Leisure activity**

<table>
<thead>
<tr>
<th>Category</th>
<th>18(34)</th>
<th>4(40)</th>
<th>.51</th>
</tr>
</thead>
<tbody>
<tr>
<td>No affected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mildly affected</td>
<td>28(53)</td>
<td>4(40)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>3(6)</td>
<td>2(20)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>3(6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Prevent social activities</td>
<td>1(2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

**General health**

<table>
<thead>
<tr>
<th>Category</th>
<th>7(13)</th>
<th>0</th>
<th>.145</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very good</td>
<td>28(53)</td>
<td>5(50)</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>12(23)</td>
<td>3(30)</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>6(11)</td>
<td>1(10)</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>0</td>
<td>1(10)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

**Limitation of activity**

<table>
<thead>
<tr>
<th>Category</th>
<th>3(6)</th>
<th>0</th>
<th>.734</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited a lot</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited a little</td>
<td>9(17)</td>
<td>2(20)</td>
<td></td>
</tr>
<tr>
<td>None of time</td>
<td>41(77)</td>
<td>8(80)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

**Psychological health**

<table>
<thead>
<tr>
<th>Category</th>
<th>19(36)</th>
<th>4(40)</th>
<th>.818</th>
</tr>
</thead>
<tbody>
<tr>
<td>No worries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some anxiety</td>
<td>27(51)</td>
<td>4(40)</td>
<td></td>
</tr>
<tr>
<td>Feel down and worried</td>
<td>6(11)</td>
<td>2(20)</td>
<td></td>
</tr>
<tr>
<td>Feeling depressed and cannot cope</td>
<td>1(2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>49</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

**Sex life**

<table>
<thead>
<tr>
<th>Category</th>
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<th>.257</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not affected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mildly affected</td>
<td>9(17)</td>
<td>4(40)</td>
<td></td>
</tr>
<tr>
<td>Moderately affected</td>
<td>8(15)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Severely affected</td>
<td>1(2)</td>
<td>1(10)</td>
<td></td>
</tr>
<tr>
<td>Prevent sex life</td>
<td>1(2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>No sexually active between period</td>
<td>16(30)</td>
<td>4(40)</td>
<td></td>
</tr>
<tr>
<td>Not sexually active</td>
<td>10(19)</td>
<td>1(10)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>
Table 5.5: Comparison of women with measured HMB and women with measured normal menstrual blood loss who sought a medical consultation for management of HMB

<table>
<thead>
<tr>
<th>Medical consultation about HMB</th>
<th>Women with measured NMB (n=53)</th>
<th>Women with measured HMB (n=10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>N(%) 9(17)</td>
<td>N(%) 4(40)</td>
<td>0.099</td>
</tr>
<tr>
<td>No</td>
<td>44(83)</td>
<td>6(60)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

5.4. Effect of women’s subjective judgment of heavy menstrual bleeding on their quality of life and their medical seeking behaviour

There were significant differences in some facets of their quality of life between women who self reported mild or moderate bleeding, heavy bleeding or very heavy bleeding. Twenty percent of women who reported very heavy bleeding had frequent disruption to their work life and in forty percent it also limited their social life. Table 5.6 compares women’s self-assessment of their menstrual blood loss with their quality of life parameters. Women who felt that they had heavy or very heavy bleeding often had poor quality of life parameters.
Table 5.6: comparison of women who said that their bleeding was mild or moderate with women who said their bleeding was heavy and very heavy in their quality of life parameters

<table>
<thead>
<tr>
<th>Quality of life parameters</th>
<th>Women self-reporting menstrual bleeding as mild or moderate (n=40)</th>
<th>Women self-reporting menstrual bleeding as heavy (n=18)</th>
<th>Women who self-reporting menstrual bleeding as very heavy (n=5)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Work Life</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No disruption</td>
<td>20(50)</td>
<td>4(22)</td>
<td>1(20)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Occasional disruption</td>
<td>19(48)</td>
<td>13(72)</td>
<td>2(40)</td>
<td></td>
</tr>
<tr>
<td>Frequent disruption</td>
<td>1(3)</td>
<td>1(6)</td>
<td>1(20)</td>
<td></td>
</tr>
<tr>
<td>Severe disruption</td>
<td>0</td>
<td>0</td>
<td>1(20)</td>
<td></td>
</tr>
<tr>
<td><strong>Social life</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unaffected</td>
<td>25(63)</td>
<td>3(17)</td>
<td>2(40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Slightly affected</td>
<td>15(38)</td>
<td>12(67)</td>
<td>1(20)</td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>0</td>
<td>3(17)</td>
<td>2(40)</td>
<td></td>
</tr>
<tr>
<td><strong>Family life</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unaffected</td>
<td>23(58)</td>
<td>4(22)</td>
<td>2(40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Some disruption</td>
<td>17(43)</td>
<td>12(67)</td>
<td>2(40)</td>
<td></td>
</tr>
<tr>
<td>Quite a lot of disruption</td>
<td>0</td>
<td>2(11)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Severely disrupted</td>
<td>0</td>
<td>0</td>
<td>1(20)</td>
<td></td>
</tr>
<tr>
<td><strong>Psychological Health</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.231</td>
</tr>
<tr>
<td>No worries</td>
<td>16(40)</td>
<td>5(28)</td>
<td>2(20)</td>
<td></td>
</tr>
<tr>
<td>Some anxiety</td>
<td>19(48)</td>
<td>11(61)</td>
<td>1(20)</td>
<td></td>
</tr>
<tr>
<td>Feeling down and worrying</td>
<td>5(13)</td>
<td>1(6)</td>
<td>2(40)</td>
<td></td>
</tr>
<tr>
<td>Feeling depressed and unable to cope</td>
<td>0</td>
<td>1(6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Physical health and wellbeing</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.142</td>
</tr>
<tr>
<td>Well and relaxed</td>
<td>5(13)</td>
<td>1(6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Well most of the time</td>
<td>23(58)</td>
<td>5(28)</td>
<td>3(60)</td>
<td></td>
</tr>
<tr>
<td>Feels tired</td>
<td>11(28)</td>
<td>9(50)</td>
<td>2(40)</td>
<td></td>
</tr>
<tr>
<td>Feels very tired</td>
<td>1(3)</td>
<td>3(17)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
5.5. Correlation of women’s quality of life and medical consultation

There was a significant difference between women who asked for a medical consultation and women who didn’t in some aspects of their quality of life (Table 5.7). Women reporting more disturbances to their life during menstruation were more likely to have sought medical advice. Of women asking for a medical consultation one (8%) suffered severe disruption to her work and daily life, and two women (15%) reported frequent disruption. Eight women (62%) reported only a slight effect on their social life and four women (31%) reported that social life was limited during their menses. On the other hand, of women who didn’t seek a medical consultation, 20 (40%) reported a slight effect on their social life and for one woman menstruation limited her social life (2%) (p=0.001).
Table 5.7: Quality of life parameters in women seeking a medical consultation for HMB compared to women not requesting a medical consultation

<table>
<thead>
<tr>
<th>Quality of life parameters</th>
<th>Medical consultation (Yes) (n=13) N(%)</th>
<th>Medical consultation (No) (n=50) N(%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Work Life</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No disruption</td>
<td>1(8)</td>
<td>24(48)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Occasional disruption</td>
<td>9(69)</td>
<td>25(50)</td>
<td></td>
</tr>
<tr>
<td>Frequent disruption</td>
<td>2(15)</td>
<td>1(2)</td>
<td></td>
</tr>
<tr>
<td>Severe disruption</td>
<td>1(8)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td><strong>Social life</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unaffected</td>
<td>1(8)</td>
<td>29(58)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Slightly affected</td>
<td>8(62)</td>
<td>20(40)</td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>4(31)</td>
<td>1(2)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td><strong>Family life</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unaffected</td>
<td>3(23)</td>
<td>26(52)</td>
<td>0.06</td>
</tr>
<tr>
<td>some disruption</td>
<td>8(62)</td>
<td>23(46)</td>
<td></td>
</tr>
<tr>
<td>quite a lot of disruption</td>
<td>1(8)</td>
<td>1(2)</td>
<td></td>
</tr>
<tr>
<td>Severely disrupted</td>
<td>1(8)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Psychological Health</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No worries</td>
<td>3(23)</td>
<td>20(40)</td>
<td>0.185</td>
</tr>
<tr>
<td>Some anxiety</td>
<td>7(54)</td>
<td>22(48)</td>
<td></td>
</tr>
<tr>
<td>Feeling down and worried</td>
<td>2(15)</td>
<td>6(12)</td>
<td></td>
</tr>
<tr>
<td>Feeling depressed and unable to cope</td>
<td>1(8)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Physical health and wellbeing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well and relaxed</td>
<td>0</td>
<td>6(12)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Well most of the time</td>
<td>4(31)</td>
<td>27(54)</td>
<td></td>
</tr>
<tr>
<td>Feels tired</td>
<td>6(46)</td>
<td>16(32)</td>
<td></td>
</tr>
<tr>
<td>Feels very tired</td>
<td>3(23)</td>
<td>1(2)</td>
<td></td>
</tr>
</tbody>
</table>

5.6. Correlation between pain during the period and quality of life parameters

There was a significant association between women’s menstrual pain score and some quality of life parameters. Woman with moderate or severe pain experienced more severe disturbance to their life than women with no or mild pain. Table 5.8 shows the comparison between women with no or mild pain to women with moderate or severe pain in their quality of life.
assessment. Of women with moderate or severe pain, three women (1%) had frequent disruptions in their work life and one woman (3%) had severe disruption to both her work and daily life. Of this group, five women (17%) had a limited social life and for 16 women (53%) moderate or severe pain had a slight effect on their social life while 12 women (36%) with no or mild period pain also reported a slight effect on their social life (p<0.001).

Table 5.8: A comparison of quality of life parameters in women with no or mild dysmenorrhoea and women with moderate or severe pain

<table>
<thead>
<tr>
<th>Quality of life parameters</th>
<th>Degree of dysmenorrhoea (None, very mild, mild) N (%)</th>
<th>Moderate or severe dysmenorrhoea N (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work life</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No disruption</td>
<td>17(52)</td>
<td>8(27)</td>
<td>0.065</td>
</tr>
<tr>
<td>Occasional disruption</td>
<td>16(49)</td>
<td>18(60)</td>
<td></td>
</tr>
<tr>
<td>Frequent disruption</td>
<td>0</td>
<td>3(10)</td>
<td></td>
</tr>
<tr>
<td>Severe disruption</td>
<td>0</td>
<td>1(3)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Social life</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Unaffected</td>
<td>17(62)</td>
<td>9(30)</td>
<td></td>
</tr>
<tr>
<td>Slightly affected</td>
<td>16(49)</td>
<td>16(53)</td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>0</td>
<td>5(17)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Family life</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unaffected</td>
<td>24(73)</td>
<td>5(17)</td>
<td></td>
</tr>
<tr>
<td>some disruption</td>
<td>9(27)</td>
<td>22(73)</td>
<td></td>
</tr>
<tr>
<td>disrupted quite a lot</td>
<td>0</td>
<td>2(7)</td>
<td></td>
</tr>
<tr>
<td>Severely disrupted</td>
<td>0</td>
<td>1(3)</td>
<td></td>
</tr>
<tr>
<td>Psychological Health</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>No worries</td>
<td>18(55)</td>
<td>5(17)</td>
<td></td>
</tr>
<tr>
<td>Some anxiety</td>
<td>14(42)</td>
<td>17(57)</td>
<td></td>
</tr>
<tr>
<td>Feeling down and worried</td>
<td>1(3)</td>
<td>7(23)</td>
<td></td>
</tr>
<tr>
<td>Feeling depressed and unable to cope</td>
<td>0</td>
<td>1(3)</td>
<td></td>
</tr>
<tr>
<td>Physical health and wellbeing</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Well and relaxed</td>
<td>5(17)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Well most of the time</td>
<td>20(69)</td>
<td>10(36)</td>
<td></td>
</tr>
<tr>
<td>Feels tired</td>
<td>4(14)</td>
<td>14(50)</td>
<td></td>
</tr>
<tr>
<td>Feels very tired</td>
<td>0</td>
<td>4(14)</td>
<td></td>
</tr>
</tbody>
</table>

5.7. Relationship between pain during the menstrual period and having a medical consultation
Women with a history of medical consultation for heavy menstrual bleeding were significantly different in their pain perception to women who had not had a medical consultation (Table 5.9). The majority of women (5; 39%) with severe menstrual pain sought a medical consultation while only two women (4%) who also had severe menstrual pain and had not sought a medical consultation. However, 15 women (30%) with very mild menstrual pain also sought a medical consultation (p = 0.01).

<table>
<thead>
<tr>
<th>Intensity of dysmenorrhea</th>
<th>Medical consultation</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>YES N (%)</td>
<td>NO N (%)</td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td>5(10)</td>
</tr>
<tr>
<td>Very mild</td>
<td>3(23)</td>
<td>15(30)</td>
</tr>
<tr>
<td>Mild</td>
<td>1(8)</td>
<td>9(18)</td>
</tr>
<tr>
<td>Moderate</td>
<td>4(31)</td>
<td>19(38)</td>
</tr>
<tr>
<td>Severe</td>
<td>5(39)</td>
<td>2(4)</td>
</tr>
</tbody>
</table>

Table 5.9: A comparison of the intensity of dysmenorrhea in women seeking a medical consultation for HMB compared to women who did not have a medical consultation

5.8. Correlation between severity of menstrual pain and the amount of menstrual blood loss

The severity of menstrual pain and the amount of menstrual blood loss were not correlated. Among the women with heavy menstrual bleeding only two had severe throbbing pain, two had no pain and 4 had very mild pain. There was a marked difference among the women with normal bleeding: only three women had no menstrual pain, 22 had moderate pain and five women had severe pain (Table 5.10). Figure 5.2 shows a comparison of women’s assessment of their menstrual pain according to their measured MBL (NMB and HMB).

Table 5.10: Comparison of women with measured NMB and women with measured HMB in relation to the intensity of their menstrual pain
<table>
<thead>
<tr>
<th>Classification of women according to volume menstrual blood loss</th>
<th>Intensity of dysmenorrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None N (%)</td>
</tr>
<tr>
<td>Normal</td>
<td>3(60)</td>
</tr>
<tr>
<td>Heavy</td>
<td>2(40)</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
</tr>
</tbody>
</table>
Figure 5.2: A comparison of the intensity of menstrual pain in women with measured HMB (dotted line) and women with normal menstrual blood loss (continuous line).
5.9. Variability of menstrual blood losses over three consecutive cycles for each woman

There was no significant difference between the median correlation of variation of menstrual cycles for women with normal measured blood loss (38%) and women with measured HMB (46%; p = 0.681). However, the variation in the amount of blood loss between the three collected cycles was greater in women with HMB than those with normal loss. The median of the three cycles of women with normal menstrual loss varied from 19 mL (IQR 26), 22 mL (IQR 19) and 25 mL (IQR 27) while the median of the three cycles of women with HMB varied from 86 mL (IQR 76), 124 mL (IQR 138) and 139 mL (IQR 112), respectively (Figure 5.3).

Figure 5.3: Estimated median of MBL plus 25th and 75th percentiles for three cycles in women with normal and heavy menstrual bleeding
5.10. Distribution, of normal and heavy menstrual cycles

The distribution of measured menstrual blood loss per cycle for the 63 women who collected their sanitary protection is shown in Figure 5.4. The median blood loss for the 176 measured menstrual cycles was 28 mL (IQR 37mL), mean 44 mL (95% CI 36 – 52). There was a wide variation in menstrual blood loss (range 0.49 to 322 mL) with 12% of cycles having a measured menstrual loss of greater than 80 mL.

![Figure 5.4: The distribution of measured menstrual blood loss for 176 menstrual cycles](image)

There was a significant difference in mean MBL between normal and heavy menstrual cycles ($z=-7.57$, $p<0.001$). Of the 176 measured cycles, heavy cycles (loss>80 mL) accounted for 22
cycles (12%), with a mean blood loss of 161 mL (95% CI 133-189), median 143 mL (IQR 94.8), and range 90 to 322 mL. In 154 cycles (88%) MBL was within the normal range: mean 28 mL (95% CI 25-30), median 25 mL (IQR 27 mL) and range 0 to 79.7 mL. The median, 25th and 75th percentiles of normal and heavy MBL are shown in Figure 5.5.

![Figure 5.5: A comparison of measured MBL (median plus 25th and 75th percentiles) for cycles with normal and heavy bleeding](image)

5. 11. The duration and amount of menstrual bleeding in normal and heavy menstrual cycles

There was a significant positive correlation between the amount of menstrual loss per cycle and the duration of menses ($r = 0.40$, $p<0.001$) (Figure 5.6).
The duration of menstrual bleeding ranged from 2 to 11 days, with 78% of bleeding lasting 3 to 6 days. The mean duration for normal cycles was 5 ± 1.5 days; range 2 to 9 days. The mean duration of heavy cycles was 6 ± 2.0 days, range 4 to 11 days. Figure 5.7 shows the distribution of the cycles according to the number of bleeding days. In 34% of normal cycles duration of bleeding was 5 days, 4 days in 19% and 3 days in 11%. Heavy cycles had a similar percentage (33%) lasting 5 days, 17% lasting 7 days in and 8% lasting 11 days.
Figure 5.7: A comparison of duration of bleeding between normal and heavy menstrual cycles

There was a greater variability in the amount of blood loss on different days of menstruation in heavy cycles compared to normal cycles. Day 3 was the heaviest day in cycles with normal blood loss, mean 8 ± 7.6 mL, while the heaviest day in the HMB group was day 4 with a mean loss of 50 ± 32.0 mL. The difference in the median menstrual blood loss in normal and heavy cycles, highlighting the greater variation in heavy cycles, is shown in Table 5.11 and Figure 5.8.
Table 5.11: Comparison of median MBL (mL) and interquartile range between cycles with normal MBL and heavy MBL on different days of menstruation

<table>
<thead>
<tr>
<th>Day of the cycle</th>
<th>Normal menstrual cycles Median (IQR)</th>
<th>Heavy menstrual cycles Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day1</td>
<td>4(8)</td>
<td>2(8)</td>
</tr>
<tr>
<td>Day2</td>
<td>5(9)</td>
<td>10(67)</td>
</tr>
<tr>
<td>Day3</td>
<td>7(10)</td>
<td>15(50)</td>
</tr>
<tr>
<td>Day4</td>
<td>4(7)</td>
<td>36(28)</td>
</tr>
<tr>
<td>Day5</td>
<td>3(7)</td>
<td>12(18)</td>
</tr>
<tr>
<td>Day6</td>
<td>1(3)</td>
<td>6(10)</td>
</tr>
</tbody>
</table>

Figure 5.8: Variation in the median amount of blood loss on different days of menstruation in normal and heavy menstrual cycles

5.12. Determining objective or subjective factors in relation to mean of amount of menstrual blood for each single woman

Due to the variability of MBL between cycles in individual women, the total menstrual blood loss for each woman was determined by calculating the mean of her three measured cycles.
Table 5.12 shows the association of blood loss volume (mean of three cycles) with some objective and subjective variables. The correlation of objective variables (e.g. haemoglobin, serum ferritin) with menstrual blood loss volume was obvious. There was significant negative correlation between mean MBL and serum ferritin level (r=0.43, p = 0.01) (Figure 5.9) and a strongly significant negative correlation between MBL and serum transferrin (r=-0.53, p < 0.01) as well as TIBC (r=-.6, p < 0.0001). Haemoglobin was a weak predictor of MBL with a weak negative correlation (r=-0.23, p = 0.193) (Figure 5.10). Practical difficulties in managing menses were also significantly correlated with mean MBL(r=0.26, p = 0.04). There was also a significant positive correlation between the amount of menstrual blood loss and age (r=0.23, p = 0.01). Subjective variables (e.g. disturbance in work or social life) were weakly correlated with MBL. The relationship between work performance and menstrual blood volume (r=0.14, p = 0.31) was stronger than for other factors, such as effects on social (r=-0.01, p = 0.93) or family life (r=-0.026, p = 0.84).
Table 5.12: The relationship between menstrual blood volume and objective measurements and subjective quality of life variables

<table>
<thead>
<tr>
<th>Factor</th>
<th>N</th>
<th>Spearman rank order correlation</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb level</td>
<td>63</td>
<td>-0.25</td>
<td>0.04</td>
</tr>
<tr>
<td>Transferrin receptor</td>
<td>37</td>
<td>-0.53</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>37</td>
<td>-0.24</td>
<td>0.144</td>
</tr>
<tr>
<td>TIBC</td>
<td>37</td>
<td>-0.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Iron</td>
<td>37</td>
<td>-0.12</td>
<td>0.64</td>
</tr>
<tr>
<td>Subjective heaviness of menses (light to heavy)</td>
<td>63</td>
<td>-0.24</td>
<td>0.06</td>
</tr>
<tr>
<td>Work/daily routine*</td>
<td>63</td>
<td>0.16</td>
<td>0.21</td>
</tr>
<tr>
<td>Days taken off work (0 to 5)</td>
<td>63</td>
<td>0.14</td>
<td>0.31</td>
</tr>
<tr>
<td>Social life*</td>
<td>63</td>
<td>-0.01</td>
<td>0.94</td>
</tr>
<tr>
<td>Family life/relationship*</td>
<td>63</td>
<td>-0.03</td>
<td>0.84</td>
</tr>
</tbody>
</table>

* Least effect to most effect
Figure 5.9: Correlation of mean menstrual blood loss (mL) for each woman (mean of three cycles) with serum haemoglobin (mg/dL)

Figure 5.10: Correlation between individual mean menstrual blood loss (mean of the three cycles) with serum ferritin level (ug/L)

5.13. The relationship between ferritin level and different aspects of quality of life

Twenty-five women in whom blood samples for iron studies were taken some time after completion of their blood loss collections completed a second quality of life questionnaire. For analysis the women were divided into two groups, those with low ferritin (<50 ug/L) and those with a normal ferritin (>50 ug/L) (Table 5.13). Their quality of life responses were matched to their ferritin levels. There was little difference between the two groups in their assessment of their quality of life. There was no difference between the two groups in regard to general health, with the majority stating that it was good to very good. Although there was a trend which suggested that low ferritin levels appeared to have a greater effect on women’s ability to carry out moderate activities due to their physical health (3; 30%) and women with
normal ferritin levels accomplished less at work due to emotional problems (5; 33%) the numbers were too small to determine whether these were real differences.

Table 5.13: Comparison of women with low and normal ferritin levels in relation to different aspects of their quality of life (there were no significant differences between the two groups)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group with ferritin &lt;50 ug/L (n=15)</th>
<th>Group with ferritin &gt;50 ug/L (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Health</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>3(20)</td>
<td>2(20)</td>
</tr>
<tr>
<td>Very good</td>
<td>7(47)</td>
<td>4(40)</td>
</tr>
<tr>
<td>Good</td>
<td>4(27)</td>
<td>2(20)</td>
</tr>
<tr>
<td>Fair</td>
<td>1(7)</td>
<td>2(20)</td>
</tr>
<tr>
<td>Moderate activities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td>1(10)</td>
</tr>
<tr>
<td>Yes, little</td>
<td>1(7)</td>
<td>2(20)</td>
</tr>
<tr>
<td>No, at all</td>
<td>4(93)</td>
<td>7(70)</td>
</tr>
<tr>
<td>Climbing stair</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td>1(10)</td>
</tr>
<tr>
<td>Yes, little</td>
<td>6(43)</td>
<td>3(30)</td>
</tr>
<tr>
<td>No, at all</td>
<td>8(57)</td>
<td>6(60)</td>
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<tr>
<td>Accomplishment less due to physical health</td>
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<tr>
<td>Most of the time</td>
<td>0</td>
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<tr>
<td>Some of the time</td>
<td>6(40)</td>
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<tr>
<td>Little of the time</td>
<td>2(13)</td>
<td>4(40)</td>
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<tr>
<td>None of the time</td>
<td>7(47)</td>
<td>3(30)</td>
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<tr>
<td>Work or activities less due to pelvic pain</td>
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<tr>
<td>Most of the time</td>
<td>0</td>
<td>1(10)</td>
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<tr>
<td>Some of the time</td>
<td>5(33)</td>
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<td>A little of the time</td>
<td>2(13)</td>
<td>3(30)</td>
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<tr>
<td>None of the time</td>
<td>8(53)</td>
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Conclusions

1. Among 3,397 women who were randomly selected through a market research company, women (628) who expressed an interest in being involved in further research were not significantly different in demographic and menstrual characteristics.
2. The demographic characteristics of the 63 (10%) participants from the group who expressed an interest in further research, who agreed to collect their used sanitary protection, were also representative of the original group.

3. Women with measured HMB (two of 3 cycles with MBL >80 mL) comprised 16% of the sample of 63 women who participated in the blood collection phase of the study.

4. Women’s perception of the heaviness of their menstrual bleeding was often at variance with their measured blood loss.

5. Women with objectively confirmed HMB were more likely to be older than women with normal menstrual blood loss. There were no significant differences in quality of life parameters or seeking medical consultation behaviour between the two groups.

6. There was a significant association between a woman’s perception that she had HMB and both her quality of life and her likelihood of seeking a medical consultation.

7. There was a significant association between menstrual pain and quality of life parameters and also a strong association between the degree of menstrual pain and seeking a medical consultation. However, there was no correlation between the severity of the menstrual pain and the amount of menstrual blood loss.
8. There were no significant differences in variability of the menstrual cycles between women with confirmed HMB and women with measured NMB.

9. There was significant correlation between the amount of menstrual bleeding and the duration of bleeding. There was also a significantly strong correlation between the amount of the menstrual blood loss (the mean of the three cycles) with serum ferritin, transferrin, TIBC, and a weak correlation with haemoglobin.

10. In the sample of 25 women with low serum ferritin levels there was no association with general health parameters.

11. Lastly, women with normal MBL who reported a significant effect of their menses on all or many parameters of their lives were likely to suffer from at least moderate dysmenorrhoea which disrupted their lives and made them seek medical advice, i.e. pain rather than volume of MBL was the important factor.
Chapter 6: Discussion

This thesis presents the results of a novel study of a self-selected group of women from the Sydney community, who responded to an on-line survey on the website of Family Planning New South Wales (FPNSW). The survey asked a range of questions around menstruation and the woman’s perception and tolerance of this phenomenon. The survey ended by asking whether the woman would be prepared to participate in further research about menstruation. Of 1,575 women who answered the original survey, 628 offered to participate in further research about menstruation. Most of these women were contacted later by phone and an initial 63 agreed to take part in the present study. Hence, these women were a self-selected group from the community, and, as a group, may not necessarily accurately represent the Sydney community. This issue is further addressed below.

This study is continuing, and it is anticipated that around 100 women will finally be recruited to the study. However, within the time restrictions of the Master of Philosophy degree, this thesis reports the results of the initial 63 women who completed the collection of sanitary protection for three cycles to measure menstrual blood loss.

The main finding was the discordance between women complaining of HMB and their estimated MBL and also the discordance between poor quality of life and estimated MBL. Over one third of women with measured NMB considered their bleeding to be heavy or very heavy. In these women with measured normal MBL many aspects of their quality of life were detrimentally affected: one woman reported a disrupted family life, one woman suffered severe disruption to work and daily activity, three women were very tired during their menstrual period and five women had limited social activities. In many of the study women who perceived they had HMB which affected their quality of life (but did not have objective
HMB) it appeared that significant dysmenorrhoea was probably the reason for the reduction in quality of life. The severity of their menstrual pain also strongly influenced their seeking a medical consultation. The relationship between menstrual pain and quality of life was confirmed in the 25 women who answered the second questionnaire prior to participating in the iron study. In these women, while there is no relationship between ferritin levels and quality of life there is a significant correlation between menstrual pain score and the quality of life effects.

This chapter will discuss study findings and their interpretation in relationship to the research objectives. The prevalence of heavy menstrual bleeding, variations of individual menstrual blood loss and the differences between normal and heavy menstrual cycles are discussed in relation to different menstrual characteristics. The measured menstrual blood loss compared to women’s perception of their menstrual bleeding, the effect on quality of life and seeking a medical consultation will be discussed. I will also discuss the strengths and weaknesses of the study. The findings will be compared with those of previous studies. Lastly, the implications of the results for clinicians, counsellors and policy makers, unanswered questions and directions for further research will be provided.

6.1. Heavy menstrual bleeding (HMB) and alkaline haematin method

Heavy menstrual bleeding (HMB) is defined clinically as excessive menstrual blood loss, which interferes with a woman’s physical, social, emotional and/or material quality of life (NICE 2007). HMB is defined objectively from a research perspective as excessive menstrual blood loss at a rate of more than 80mL per cycle or menstruation lasting for longer than seven days (Engstrom 1999, Rees 2001, Youngkin & Davis 2004, NHSCR 1995, Long 1990, and Prentice 1999). The issue is whether complaint of heavy menstrual bleeding reflects the
volume of blood loss or is precipitated by a broader adverse impact of menstruation and related symptoms. The statistical definition was formulated according to data taken from limited population studies. These indicate that the mean menstrual blood loss for women with HMB exceeds 80mL per cycle, and that frequent losses of such quantity are associated with an increased incidence of iron deficiency anaemia (Halberg et al 1966, Cole et al 1971). This large scale study of Swedish women (1966) excluded women with abnormal iron status or who were considered to be unhealthy or have abnormal menstruation who were more likely to have HMB. As the 95\textsuperscript{th} percentile of blood loss for the 183 normally menstruating women was 76 mL the endpoint of the normal range (80mL) was recognized as the clinical threshold for HMB (Warner 2003).

The alkaline haematin method is still considered as the gold standard for the assessment of menstrual blood loss. It was developed in the 1960s but is still used in the research setting to measure total menstrual blood loss (Hallberg et al 1964). According to Ray (2011), this technique has met or exceeded FDA guidance requirements and has been used for the measurement of menstrual blood loss on over 85,000 feminine hygiene products from different clinical protocols. However, the alkaline haematin method is not used in the clinical setting due to several limitations. It is a cumbersome, labour-intensive, and time-consuming method. In addition, there are health and safety limitations due to the large volumes of sodium hydroxide required and the risk for blood-borne viral infections. Furthermore, an alkaline haematin method measures menstrual blood loss only, not total menstrual fluid loss. Menstrual fluid is a combination of whole blood (30–50\%) and endometrial transudate. However, some data suggest that when bleeding is heavy the ratio of blood to menstrual fluid increases in comparison to normal (Fraser et al 2001, Reid, 2006). Therefore, for total menstrual blood fluid and for clinical and research purposes, there is a need for a robust,
simple protocol for the collection of soiled sanitary towels/tampons and technical expertise or equipment.

6.2. Study population and selection method

The study population was menstruating women representative of a population from an online research marketing company (www.researchers.pureprofile.com) who volunteered to take part in research about menstruation after completing an online survey and agreed to collect their sanitary protection for three cycles. Pureprofile has a large database with an in-depth profile of individual participants, which is updated over time and allows for careful targeting of surveys depending on the criteria required by the research. The database obviously does not include women without access to the internet but given the size of the database and the increasing internet access in this country the sample is a more heterogeneous group and more likely to be representative of the population of menstruating women in NSW than a sample of women who are referred to primary or secondary care for menstrual disorders.

Most published studies on heavy menstrual bleeding have been carried out amongst women who had consulted or had been referred to secondary care. This community sample enabled us to explore concerns about the effect of menstruation on the quality of life amongst a population of women whose concerns were previously under-explored, as the majority had not previously sought medical assistance for menstrual problems (Santer et al 2007, Warner et al 2004).

Missing cases at every stage of study selection could be source of selection bias. In this study, complete questionnaires were not returned by 34% of those recruited, which raises concerns. Although questionnaire surveys can exclude those with poor literacy skills this online
questionnaire was not complicated and should be understandable by such an audience with broad participation. Recruitment is the most challenging part of a clinical research study. It is frequently left for inexperienced researchers to undertake and it is not often reported adequately in the literature (Dowling & Wiener, 1997). During recruitment, non-response can affect the sampling process and results in selection bias. The proportion of eligible participants who agree to answer the questionnaire (the response rate) influences the validity of the suggestion that the sample represents the population of interest (Woods et al. 2000, Hulley et al. 2001). Women who are difficult to reach and those who refuse to participate once they have been contacted tend to be quite different from people who do not enrol. Greater age, low educational status, unemployed or low occupational status are some characteristics often associated with poor response (Armstrong et al. 1992). However, in our study education level was evenly distributed in the original sample and in the group of women who participated in our study. Very experienced research assistants were involved in the recruitment.

6.3. Results and interpretations

The important finding of this study is the apparent clinical irrelevance of the established threshold for normal menstrual blood loss and its effect on quality of life. There were no significant differences in all the quality of life domains in medical consultation behaviour between the two groups of women with normal and heavy menstrual bleeding.

In this study, the measured menstrual blood loss of participants did not correlate with the subjective assessment of their blood loss. Among the participants, just over one third of women with measured NMB considered their bleeding to be heavy or very heavy and about half of them perceived their bleeding as moderate. Since the alkaline haematin test only measures the amount of blood in menstrual fluid it is possible that women who perceive their
bleeding as heavy may have a disproportionally larger amount of other fluids and endometrial tissue in their menstrual loss, which they then interpret as heavy bleeding.

The finding suggests a significant correlation between a “subjective” assessment of HMB and quality of life. The majority of participants who reported they were suffering from stress, physical symptoms and various inconveniences stated that they suffered from HMB, while a minority (around 47%) felt tired and lethargic due to “experiencing heavy menses”. Poor quality of life was significantly associated with asking for a medical consultation about heavy menstrual bleeding. This strongly argues that a subjective assessment of HMB, although it may often not reflect the true menstrual blood volume, can still affect the physical, social and psychological well-being of women.

There was strong correlation between a low score on the quality of life questions and asking for medical help, with medical help seekers having a lower quality of life than the corresponding non-help seekers. Women, who sought a medical consultation had a significantly lower score in the social, physical functioning of the questionnaire than the non-help seekers. A possible explanation for the effect on physical and emotional well-being among the help seekers is that these women are more focussed on difficulties of their menstrual problem and thus seek help from appropriate resources. As their emotional and daily activities are affected, they tend to seek medical advice from their primary carer, who is seen as an appropriate resource for this. With appropriate advice and treatment their health problem may be solved, allowing them to return to their normal activities.

Reporting painful periods was significantly associated with a decrease in some aspects of quality of life. The majority of participants who reported they were suffering from stress,
physical symptoms and diminution in quality of life also reported moderate to severe menstrual pain. Menstrual pain unrelated to the amount of menstrual blood loss was a significant factor in affecting women’s quality of life.

This study found considerable variability in menstrual pattern on different days during menses between participants in the study. There was no significant difference between the median coefficient of variation of the menstrual cycles for women with normal measured menstrual loss or in women with measured HMB (p=0.681). There was more variability in the amount of blood loss on different days of bleeding in heavy cycles than in normal cycles. The heaviest day in normal menstrual cycles was day 3 with a mean of 8 ± 7.6mL, while in the HMB group the heaviest day was day 4 with a mean of 50 ± 32.0ml. Although the results of this study found no significant variation between cycles in normal and heavily menstruating women, another aspect which could affect the daily life of women was differences in daily blood loss. The problem for women complaining of HMB could be acute unmanageable blood loss (including “gushes”) in the first few days, rather than total volume, or it could be that a change in periods has been noted, leading to concern that something may be wrong.

The amount of menstrual blood lost in the 176 cycles measured during this study showed a wide variation with a range from 0.49 to 322mL per menstrual period. Of the total measured cycles, heavy periods (loss>80mL) accounted for 22 cycles (12%), with a mean blood loss of 161mL (95% CI 133-189mL), and a range of 90 to 322mL. In 154 cycles (88%) MBL was within the normal limits, ranging from 0 to 79.7mL and a mean of 28mL (95% CI 25-30mL). The extent to which these results can apply to any given population of women is uncertain. Other studies based upon recorded observations do present a consistent picture of variability,
and different estimates of this variability may be due to differences in study design, analytic procedures, and age composition of the study populations.

There was a positive relationship between amount of menstrual loss per cycle and the duration of menses, and also with the age of the participant \( r=0.40, p=0.0001 \). Although the duration of menstrual bleeding in 78% of women lasted 3 to 6 days the mean duration for normal cycles was 5 days \( (SD=1.5) \) with a range of 2 to 9 days, the mean duration of heavy cycles was 6 days \( (SD=2.0) \) with a range from 4 to 11 days.

From the results of the 25 women recruited to the iron study it is apparent that haemoglobin is a weak predictor of MBL, although many clinicians rely on this as an indication for treatment in women complaining of HMB. There was a significant negative correlation between mean MBL and serum ferritin level \( r=-0.43, p=0.01 \) and a very strongly significant negative correlation between it and serum transferrin \( r=0.53, p<0.01 \) as well as TIBC \( r=0.6, p<0.0001 \). Practical difficulties with managing menstruation appear to be more reliable indicators of MBL than subjective variables (e.g. disturbance of work or social life).

There were no differences between the groups of women with serum ferritin less than and more than 50mg/L in description of their general health parameters. The sample in this study was small and therefore unlikely to provide any meaningful differences between the women with normal and heavy bleeding. The women who entered this additional iron study phase were answering the menstrual questionnaire a second time and already knew their menstrual loss measurement details. Many of them had started iron supplementation which may have improved their quality of life so that serum ferritin was not a reliable indicator.
6.4. Comparison to other studies: Similarities and differences

There are difficulties in comparing studies on menstrual blood loss for several reasons. Reported differences in prevalence may be due to the way in which the blood loss was assessed, such as face to face interviews, self administered questionnaire, pictorial blood assessment chart or through objective measurement of menstrual blood loss by the alkaline haematin method. Although alkaline haematin is the only clear objective measurement, and therefore the most accurate, its use is limited in population studies. Furthermore, the variation that occurs in definition of the symptom of heavy menstrual bleeding produces inconsistency in the numerator for the calculation of rates. Another difficulty is that there is no consensus on the denominator, using menstruating women (i.e. women of reproductive age), all women or total populations (Shapley et al 2004).

6.4.1. The prevalence of HMB

The prevalence rate of objectively measured HMB in this study was 16%. This is higher than prevalence rates seen in other measurement studies in women aged 17-50 years in Western populations, which indicate prevalence rates of 9 to 14% (Barr et al 1998, Hallberg et al 1966). However, this sample was small. In China, the prevalence rates of heavy menstrual bleeding have been reported to be as high as 20% (Barr et al 1998). However, this is considerably lower than other measurement studies which have included women who presented to secondary specialist care with a complaint of HMB (Higham et al 1999, Fraser et al 1984, Hurskainen et al 2001, Higham & Shaw 1993).

The subjective prevalence of heavy menstrual bleeding in this study was 37%, which was not dissimilar to many other epidemiological studies which depended on variable subjective assessment of menstrual blood loss. A worldwide epidemiological review in 2009 revealed a
wide range of reported prevalence rates of heavy menstrual bleeding between 4% and 52%, and those studies with high prevalence rates based the diagnosis mainly on subjective assessment of HMB (Fraser et al 2009).

6.4.2. Distribution and range of menstrual blood loss

The range of menstrual blood loss in this study (0.49-322mL) was very similar to one UK study in which menstrual blood losses ranged from 2 to 366ml (Higham et al 1990). However, in another study, menstrual blood loss reached a very high value of 497mL, which was achieved by one woman with a large submusous myoma, who proceeded immediately with a planned hysterectomy (Fraser et al 1984). The range of menstrual blood loss also varies in studies from different parts of the world. In Sweden, menstrual blood loss varied from 1.6 to 199mL (Hallberg et al 1966) and in Mexico from 1.3 to 143.5mL (Hiazze et al 1968, Andrade et al 1991). In China, menstrual blood loss ranged from 4.1 to 273.6mL (Cole et al 1971, Andrade et al 1991). The reason for such discrepancies may be related to genetic, nutritional and racial differences (Andrade et al 1991). In addition, modification or variation in the alkaline haematin technique over the past 50 years may have played a role in these differences as well as how adequately women were counselled on details of collecting menstrual blood.

The distribution of the measured menstrual losses of 176 menstrual cycles from 63 women was skewed to the right, with a ‘tail’ of 12% of cycles having menstrual losses of more than 80 mL. The skewness of the distribution in this study was similar to the results of other studies (Hallberg 1966, Warner 2004). The percentage of women with MBL >80mL for at least two cycles in our study (16%) was not dissimilar to the Swedish study in 1966 of 10% (Hallberg 1966). In comparison to our study, the Swedish study sampled many times more women. In the Swedish study, 476 women selected at random by stratified sampling from the
population of Goteborg were divided into six age groups with up to 125 subjects in each group. In our study the age distribution was unequal with 13 women in the age group 20-29, 28 women aged 30-39 and 22 women aged 40-49. Our study population was derived from women with internet access who had voluntarily joined a market research database, and although they were fairly representative of the population of, we could not discount some selection bias.

The mean measured MBL of 161mL in ‘heavy’ cycles in our study was considerably higher than a 1984 Sydney study in which the mean of measured menstrual loss in heavy periods was 69.6ml and the mean of normal cycles was 42.7 mL compared to 28mL in our current study (Fraser et al 1984). Our mean value for normal menstrual periods was also lower than reported in other studies from different countries. Studies from USA, Sweden, Mexico and UK revealed means of menstrual blood losses in community studies of volunteers reporting “normal” menstrual periods of 30mL, 38.5 mL, 35.1mL, and 37.5 mL, respectively (Cole et al 1972, Andrade et al 1991).

6.4.3. Relation between menstrual blood losses and duration of bleeding

The finding in this study that increased menstrual blood loss was related to increasing duration of bleeding has been reported before (Barrer et al 1935, Rybo et al 1966) but not all studies have shown this correlation (Haynes et al 1977). The number of bleeding days in women with regular cyclical bleeding varied from 2 to 11 days, with a median of 5 days, and 79% of bleeds lasted 3-6 days, which is similar to that of previous studies. In one review, the duration of bleeding ranged from 2 to 12 days, with 80% of bleeds lasting 3-6 days (Harlow & Ephross 1995). These variations suggest that there may have been true variations in some parameters of these different populations.
6.4.4. Variation of daily menstrual losses in normal and heavy cycles

Our findings suggest that there is a difference between the distributions of total menstrual loss on a day to day basis in heavy cycles compared to normal ones. The mean of menstrual blood loss was higher in the first four days of the cycle. The heaviest day in normal menstrual cycles was day 3 with a mean blood loss of 8 ± 7.6ml, while in the HMB group the heaviest day was day 4, with a mean loss of 50 ± 32.0ml. Previous studies reported a considerable increase in menstrual blood loss for two to three days of menstruation, and on average 92% of the total blood loss occurred in the first three days in women with heavy menstrual bleeding (Haynes et al 1977). However, in a study of menstrual loss of Swedish women, there were no differences found in the amount of menstrual loss on the first three different days of the period, irrespective of whether the loss was above or below 80 ml (Rybo, 1966). This difference may be due to the wide range of total daily blood loss in our study, so that the mean does not reflect an accurate estimation. In addition, the time of day that bleeding started varied from woman to woman. Therefore, women bled for a varying number of hours on the first day, related to time of starting.

6.4.5. Variation of menstrual losses among consecutive cycles in women with normal and heavy menstruated bleeding

We found that the variation in the amount of menstrual loss from one period to the next over three cycles was not significantly different in women with normal and heavy menstruation. The median coefficient of variation was 46% in women with heavy cycles, which was not significantly different from the median coefficient of variation in women with normal loss (43%). This is supported by a study that reported a median coefficient of variation of 30-40% in women with heavy menstrual bleeding (Haynes et al 1977). However, some studies
revealed that menstrual blood loss seemed to be fairly constant in women with normal menstruation and others suggested that variations seemed more likely to occur in women with heavy menstrual bleeding (Fraser et al 2001). Measurement of menstrual blood loss in a Swedish population study over a year revealed no significant difference between periods during this time (Hallberg et al 1966). Another study in US found little difference between successive periods in women with normal menstruation (Jacobs et al 1965). However, this differed in other studies. Arens (1945) found substantial variability in menstrual blood loss from one period to another in 5 out of 7 women whose menstrual blood loss was measured more than once. Schlapphoff and Johnston (1949) also reported great variation between different menstrual periods in 6 girls aged 13 to 14 years. Baldwin, Whalley and Pritchard (1961) found a disparity in blood loss variability between cycles with some women showing a big variation, but also some women with only a small variation between periods. Hallberg and Nilsson (1964) examined 12 student nurses and made consecutive measurements over 12 periods. They concluded that a few determinations or even a single determination of menstrual blood loss is fairly well characteristic of the average individual blood loss in normal periods.

6.4.6. Relation between age and amount of menstrual blood loss

Our findings indicated a significant correlation between the amount of menstrual blood loss and age (r=.23, p=.0001). The literature supports these findings, with girls aged 15 years bleeding on average 1-2mL less and 50 year-old women bleeding about 6 mL more than women aged 20-45 years (Harlow et al 1995). It is generally accepted that women approaching the menopause are more likely to have heavy cycles, which may be related to “increased thickness of the endometrium”.(Fitzgerald et al 1994). Furthermore, population-based cross-sectional studies which were conducted in England and in the Netherlands
observed an increase in the prevalence of heavy menstrual bleeding with increasing age (Santos et al 2011). This was apparently related to the major characteristic of the perimenopausal period of intermittent disturbed ovulation or chronic anovulation. Since there is no corpus luteum, progesterone levels are low, but the follicular development still occurs resulting in high production of oestrogen. This allows continued unopposed proliferation of the endometrium so that the thickened endometrium outgrows its blood supply, undergoes focal necrosis and shedding begins. As the shedding is not uniform and the usual progesterone and prostaglandin related changes are not occurring in a coordinated fashion with oestrogen production, bleeding is more likely to be irregular, prolonged and heavy. During the perimenopausal period some women will continue to ovulate. Heavy menstrual bleeding is thought to be due to a distortion of the endometrial architecture, not so much as a structural defect but rather as an hormonal and pathway disruption of the usual molecular events of the menstrual cycle or abnormalities at a sub-cellular level in the endometrium (Duckitt 2010).

6.4.7. Comparison of women with measured normal and heavy menstrual bleeding by their quality of life parameters

Our findings that the amount of MBL does not affect quality of life is supported by a study by Warner (2003) which revealed that the objective definition of heavy menstrual bleeding is of limited clinical usefulness to distinguish interruptions to daily life. Another study which used the alkaline haematin method and included a sample of women who were referred for management of HMB also revealed that there was no difference between women with HMB and those with normal menstrual blood loss in the incidence of depression or producing a negative effect on social or sexual life (Hurskainen et al 2001). However, contrary findings were reported in other studies. Kadir et al (1998) using pictorial chart as a tool for measurement of menstrual blood losses found that HMB had a negative influence on
women’s quality of life. Since this study used pictorial charts, a less accurate measurement of menstrual blood loss than the alkaline haematin method, the results are less reliable.

The benchmark Swedish study found that when objective measures were used to determine those women with blood loss of more than 80 mls they constituted the upper 3% to 4% of the healthy Swedish population in 1966. The problem with using this objective measurement to define women with HMB does not necessarily reflect the clinical situation and the impact their bleeding has (Geoffrey & Barker 1978). Some women with heavy menstrual bleeding can manage their daily life well without much disruption to normal activities but other women with lighter bleeding and possibly associated symptoms such as pain may be less tolerant of this so that their menses impact to a greater extent on their quality of life (Warner et al 2004).

6.4.8. Medical seeking behaviour among women with measured heavy menstrual bleeding and women with normal measured menstrual bleeding

There were no significant differences in medical seeking behaviour between normal and heavily menstruating women in this study. Of women with normal measured menstrual bleeding 17% sought a medical consultation believing that they experienced HMB and more than half the women with heavy measured menstrual bleeding did not seek medical consultation. The literature suggests that many women with bothersome menstrual symptoms did not consult their doctors resulting in unnecessary suffering due to lack of treatment (Santer et al 2007). Women generally do not discuss their personal experiences with menstruation amongst themselves and often are unaware that their level of bleeding may be excessive and amenable to treatment. A UK qualitative study suggested that women of all social classes follow the rule that menstruation needs to be concealed and not usually discussed (Seear, 2009).
The degree to which women experience the effect of menstruation on normal activities depends to some extent on the social, cultural and economic background of the woman and can affect the woman’s need to seek medical help. Many women do not seek treatment because they prefer self-treatment or waiting for the problem to resolve itself (Fraser et al 2009). There is another theory relating to the conflict between menstruation as a necessity and the consideration of menstrual blood as different and unconnected to other circulating blood. Until menstrual symptoms cause a profound effect on women’s lives these beliefs may prevent them from seeking treatment. In addition, the respondent’s belief that women’s suffering is normal even for those with severe symptoms recognizes that it is “part of being a woman”. The theory that women’s models of HMB do not fit with the disease model accommodates these elements (Garside et al 2008). Women who did not seek a medical consultation although they had HMB defined themselves as unaffected women who neither experienced symptom distress nor saw menstruation as a health problem. None of them felt periods had any effect on the quality of their lives and most displayed attitudes of acceptance, although a few were fatalists. These women would need to re-define their menstruation as ‘problematic’ before seeking medical advice for any future distress (Scambler et al 1985).

6.4.9. Differences between subjective and objective assessment of menstrual blood losses

Perception of periods as a problem was related to the effect of a range of symptoms on women’s daily life which, in turn was linked to the individuals' social circumstances such as type of employment or degree of flexibility of women around their responsibilities (Santer et al 2007). Studies on measured menstrual blood loss for women who were referred with heavy menstrual bleeding found that fewer than half the women had a loss of 80 mL or more (Bonnar et al 1996) which was higher than the findings of this study in which 22% (5/23) of women
who said that they had heavy or very heavy menstrual bleeding actually had measured heavy menstrual bleeding. Furthermore, in our study sample of women complaining of heavy or very heavy menstrual bleeding, 78% of them had normal measured menstrual blood loss. It is generally accepted that menstrual blood loss of more than 80 mL for two of three consecutive cycles is regarded as heavy menstrual bleeding requiring treatment (RCOG 1998). However, this definition is problematic. Chimbria et al. (1980) found no correlation between women's subjective assessment and measured blood loss (Chimbira et al 1980) and Fraser et al (1984) have shown that women cannot assess changes in loss from day to day and from cycle to cycle. In one study, 47% of cycles which were described as heavy had a loss of less than 80 mL, Fraser et al (1984) found that 62% of women who give a convincing clinical history of heavy menstrual bleeding had real losses of less than 80 mL (Fraser et al 1984). The literature indicates that although 35% of women reported heavy periods, only 22% reported their periods presented a marked or severe problem (Santer et al 2007) showing that some women’s perception of heavy menstrual bleeding varies with some regarding it as a problem while others accept the situation as normal. Warner et al (2004) found only 34% of women complaining of heavy periods had a menstrual blood loss of more than 80 mL. However, this may be the result of variability from one cycle to another with some heavy and some normal which affects women’s judgment of their menstrual blood loss or recollection of past cycles.

Published studies differ in their findings on the correlation between women’s perception of the volume of menstrual blood loss and actual measured blood loss. Our study found no significant relationship between perceptions of menstrual blood loss and actual measured menstrual blood loss. On the other hand, one study revealed a strong correlation between the measured volume of loss with women’s subjective judgment with women who rated their period as very heavy having a mean blood loss higher than other women (Warner et al 2004).
However, Hallberg et al. (1966) and other studies have indicated that women are poor judges of their volume of menstrual loss. This discordance between the perception of HMB and measured HMB between studies is not an unexpected finding as few women think of their periods in volumetric terms and as was confirmed in many aspects of this study.

This discrepancy between measured and perceived blood loss may be due to the findings from studies which have confirmed that menstrual blood is very dilute containing a high proportion of fluid other than blood so that menstrual loss cannot be estimated by measuring only the blood content (Levin et al 1986). Fraser et al (2001) found that women in who have HMB the proportion of blood makes up about 60% of the total menstrual loss. This could affect a woman’s assessment of her blood flow.

6.4.10. Association of subjective judgment of heavy menstrual bleeding and women’s quality of life

This study has demonstrated significant differences in quality of life parameters between women who considered their bleeding was normal and women who thought that their bleeding was heavy or very heavy. This relationship between subjective heaviness of bleeding and quality of life has been studied previously. One study of a US population revealed that women with irregular or subjective heavy menstrual bleeding had a significantly lower score on role limitations due to physical problems and social functioning when compared with women with normal menstrual bleeding. This study used the SF-36 questionnaire which is a multi-purpose, short-form health survey with only 36 questions to measure quality of life aspects and was not specifically tailored to measure the effect of menstruation on quality of life (Barnard et al 2003). Two UK studies which examined AUB impacts on all quality of life domains included in the SF-36 found limitations in usual role activities resulting in both
physical and emotional health problems as well as body pain, reduction in vitality and impairment in social function (Cooper et al 1997, 1999).

Other studies that used questionnaire assessment of quality of life based on subjective judgment of HMB showed that health related quality of life for women with abnormal uterine bleeding compared to population norms was significantly lower than normative scores for women of the same age (Fraser et al 2001, Bongers et al 2005).

In our study there was a correlation between women with objective HMB based not on subjective assessment but, based on objective results such as ferritin or practical difficulties with managing HMB and therefore less likely to have a measurement error. This was also observed in other studies (Warner et al 2004, Hallberg et al 1966).

6.4.11. Menstrual pain effect on women quality of life

In this study, women with normal measured menstrual blood who reported negative effects on their quality of life often also reported considerable period pain. This suggests that not only the volume of menstrual loss but also the existence of other menstrually related symptoms may result in women complaining of HMB and should be investigated as the volume alone may not adequately reflect the essential nature of an existing complaint of heavy periods (Warner et al 2004, O’flynn et al 2000). The adverse impact on daily life may not necessary reflect the amount of the menstrual loss but could be related to associated symptoms like period pain. It is reported that pain, mood changes, and an increase in the amount of bleeding were reported more commonly as severe problems than absolute volume and that pain around periods was more often a problem in cases in which measured blood loss was low or normal (Warner et al 2004).
Menstrual pain is a very common and important problem. One study found that at least one in four women experienced distressing menstrual pain characterised by a need for medication and absence from study or social activities (Giovanni 2012). A range of menstrual symptoms have an impact on women’s daily life, such that, in one study, pain had the greatest negative impact on women’s lives (Santer et al 2007). In one Scottish survey, severe pain was as strongly associated with problem periods as very heavy periods, and affected many more women than very heavy periods (Santer et al 2005). A cross-sectional postal survey in Lothian, Scotland of women with heavy menstrual bleeding found that pain was the symptom which caused the most distress most followed by heaviness of loss, mood changes or tiredness, and irregularity or other issues of timing. Qualitative interviews confirmed that a range of menstrual symptoms were problematic and some women were unable to distinguish which was the worst aspect (Santer et al 2007). According to the definition of Ware et al (2003), the lower the score in social performance, the more extreme and frequent the interference with normal social activities due to physical or emotional problem will be. Furthermore, the lower the score in physical and emotional aspects, the greater the related problem with work or other daily activities caused by the physical and emotional problems (Ware et al 2003).

In this study, seeking a medical consultation was significantly related to pain during the period suggesting that menstrual symptoms like pain have a greater influence on women seeking medical advice than menstrual blood volume. This is confirmed in the literature. Many studies suggest that the reason behind women finally seeking help relates to the extent of the impact of menstruation on mood, daily lives, and their ability to manage and conceal
the symptoms. One prospective cohort study found that psychological distress appears to influence the self-reporting of heavy menstrual bleeding (Shapley et al 2003).

6.4.12. Iron stores and menstrual blood losses

There is significant negative correlation between amounts of the menstrual loss (mean of the three menstrual losses) and serum ferritin, and serum transferrin. This finding is supported by the literature. The characterisation of normal menstrual blood loss is more contingent on a correlation between measured blood volume and ferritin than haemoglobin (Warner et al 2004).

In the 25 women who participated in the iron study there were no differences in general health quality of life in relation to their serum ferritin level. This finding is in agreement with study of Fordy et al (1994) who found no association between serum ferritin levels and scores in the general health questionnaire and mental health assessment in 297 male and female students. Rangan et al (1998) also found no association between serum ferritin and GHQ scores for female university students, but women with established anaemia reported more psychological distress. However, the Australian Longitudinal Study of Women’s Health (ALSWH) examined the relationship between self-reported iron deficiency (based on information from their physicians) and general health and well-being in a large sample of women. Between baseline in 1996 and follow-up in 1998, 795 women out of 8,869 women, 45-50 years of age in 1996 reported having had a diagnosis of iron deficiency. Decreases in physical health, mental health and vitality scores, as measured by the SF-36 general health and well-being questionnaire, were more obvious in this group of women than among those who were not diagnosed with iron deficiency during this period (Patterson et al 2001).
Previous studies have indicated that iron supplementation may have an effect on general health in the absence of anaemia. The effect was noted to be restricted to women with low or borderline serum ferritin concentration (Verdon et al 2003). In an Australian study, iron supplementation or a high iron diet improved the quality of life and decreased fatigue among women of child bearing age (Patterson et al 2001). The lower limit for normal serum ferritin levels is controversial. It has been suggested that iron stores in bone marrow may serve as better indicator of iron deficiency. One study found that a serum ferritin concentration of 50mg/L was associated with 50% iron deficiency in bone marrow (Guyatt et al 1992). Furthermore, there was a significant improvement in quality of life in women with baseline of serum ferritin less than 10mg/L when given iron supplementation or increased their dietary intake of iron (Patterson et al 2001) as in this study ferritin less than 15mg/L was considered as iron deficient and more than 20mg/L as normal.

6.5. Strengths of the study

The main difference between this study and many other studies examining the effect of HMB on different aspects of life was that most relied on women’s subjective judgment of menstrual blood loss whilst this study was based on an objective measurement of blood loss, the alkaline haematin method which is considered to be the most accurate method of measurement. Controversy exists about whether menstrual loss should be studied or managed using objective methods such as menstrual diaries and charts or subjective assessment based on a woman’s description of her symptoms (Shapley et al 2004). Objective methods are likely to result in lower prevalence rates than subjective assessment. Objective methods are more accurate if diaries and charts are completed daily as this makes them less liable to observer and recall bias. Recall bias increases as the interval between the event and report increases, and occurs even with daily records and charts, as some women complete them retrospectively.
A very important and novel stage in the recruitment process in our study was a detailed interview of participants by the research nurse. She gave women very detailed instructions on how to collect their menstrual blood and ensured that all steps in the collection of sanitary protection were fully understood by the participants using language that could be understood by all potential participants. To avoid any suggestion of coercion, which can easily occur in clinical situations, adequate time was provided for the participants to comprehend and give feedback. Participants who take part in research voluntarily are usually hoping that it will bring them direct diagnostic or therapeutic benefits or will eventually improve treatment for future patients. Respect for participants (and their relatives and carers) can help to establish trust and connection (Miller et al., 1998). In this study that the detailed information and instructions that all women received and the time taken to ensure they fully understood the minutia of menstrual blood collection ensured that the collections were as complete as possible.

The strength of the questionnaire used in this study was that the questions were easy to understand and the fixed choices covered written options which were equivalent to a different points in a visual analog scale. The fixed choice questions are more precise than free text questions for many reasons. Free text questions could be subject to interpretation by researchers and are also more subject to response bias due to larger amounts of missing data than fixed choice questions. With free text questions women who responded may differ from non-responders in motivation to complete the questionnaire or in literacy.


6.6. Limitations of the study

The market research company selection of women to answer this questionnaire relied on women having access to a computer which excluded women without computer skills or access. A further challenge to the generalisability of the results is the length of the initial online questionnaire which took an average hour to complete and may have been a difficult for those with poor reading skills. These factors can affect the selection and response rate of women answering the questionnaire, there is evidence to indicate that response rates are lowest for mailed, self-administered questionnaires, intermediate for telephone interviews and highest for face-to-face interviews (Bailey et al., 2010). However, use of face-to-face interviews was not an option for such a large scale survey in a state with such a widely scattered population as NSW.

Although Pureprofile is a leading provider of online research services in 45 countries and fields in excess of 3,000 research projects annually for major international research and media and communications organisations participants in its online surveys are self-selected and paid for responses. The company keeps very detailed demographic data on its participants and selects individuals who fit the criteria required by the project. However, there is obviously some selection bias as the response rate for the menstruation questionnaire was 68% and excludes computer illiterate women. Selection bias which is related to socioeconomic status has been observed in many studies even those that used random dialling digit (Bailey et al., 2010). In addition, exclusion due to lower socioeconomic status has also been reported in studies that used methods other than random dialling digit such as provincial health insurance rolls, files of residents, or primary care registers. The respondents in our study were paid to
complete the questionnaire and their education level was comparable to the general community so that it is unlikely that there was selection bias based on socioeconomic factors.

A high degree of partial or non-participation in data collection after women consented to the study was perhaps due to the use of email as the first steps in contact for the menstrual blood collection arm of the study. Women who agreed to participate and collect sanitary protection were more highly educated compared to the original sample who completed the questionnaire. Thus in the collection phase there may be some selection bias related to socio economic status and possible selection bias with respect to other factors that might be important in an HMB study.

Another limitation of this sampling strategy is that it may have led to a greater focus on women with chronic rather than acute symptoms. In reflecting on the clinical suggestion of the findings, it is important to consider the distinction between symptoms reported on questionnaire and symptoms which are reported in a consultation. The concerns of women in this study group may not reflect those of women with symptoms of more recent onset.

The advantages and disadvantages of online surveys compared to other data collection methods have often been studied. In comparison to face-to-face, telephone, and mail surveys, online surveys have the advantage of being cheaper, faster and not related to time and place. Face-to-face interviews are more costly and time-consuming and responses can be influenced by the relationship between the interviewer and the respondent (Polgar & Thomas, 2000, Hulley et al., 2001). Another weakness of face-to-face interviews is that interviewers can increase the magnitude of the error if, by their appearance, behaviour, method of
administration of the interview or method of recording responses, they may have a qualitative impact on participants’ responses (Armstrong et al., 1992).

The disadvantage of online surveys is that they completely depend on the availability of internet access (Blasius et al., 2010). Despite the increasing number of internet users, the problem of how representative of the entire population such a survey is remains problematical. One method for obtaining representative results using online surveys is to weight variables to make them representative with respect to socio-demographic characteristics such as age, sex and education (Blasius et al., 2010).

As we were unable to obtain comparative demographic data about the population of, menstruating women in NSW, we suspect that well-educated young women may be over-represented and that elderly women with low educational attainment may be under-represented. This over-representation of certain groups can also result from surveys that acquire respondents via conventional data collection methods such as doorstep surveys or telephone surveys. However, in our study the age group of 40 to 49 represents 35% of the entire group which is probably a representative sample for this age group.

Another problem of online questionnaire is related to mode effects that is how the questions are presented. Studies which depend on face-to-face or telephone interviews compared to mail surveys also may be subject to a survey mode problem (Blasius et al., 2010). Therefore, responses by individuals answering single questions and in terms of different population groups being ready to respond at all may differ depending on how the questions are presented. In addition, mode effects have an impact on a survey’s contents. Comparing a face-to-face and an online sample (Blasius et al., 2010) revealed that online survey respondents produce
higher “don’t know’’ response rates, more item non-response, and differentiate less on rating scales than face-to-face survey respondents.

The accuracy of the results of this study as far as menstrual blood loss measurement is concerned was maximised by the detailed instructions given to women for collection of their menstrual blood. However, inaccuracy in menstrual blood loss can occur as a laboratory error which may lead to an underestimation of the amount of blood lost and therefore the prevalence of HMB. The alkaline haematin method is a very expensive and labour intensive technique which limited the number of women in the study.

Courier costs also limited participation as women were required to live within a radius of 50 miles from Sydney to minimise this expense.

**Conclusion**

In conclusion, proven heavy menstrual bleeding did not have a clear and significant impact on women’s physical, psychological and social well-being, quality of life or cause great inconvenience in their daily life. Nor did it influence women to seek a medical consultation. This confirmed the clinical irrelevance of the established ‘objective’ thresholds for normal menstrual blood loss.

Women’s perceptions of their menstrual bleeding do not reflect the amount of their blood loss. However, women’s perception of their blood loss does affect their quality of life and their likelihood of seeking a medical consultation. There are strong associations between women’s perception of menstrual bleeding and their scores on the quality of life questions. Women who perceive their bleeding as heavy have low scores on quality of life questions and
tend to have had a medical consultation more frequently than women whose quality of life is unaffected.

Women are bothered by a range of menstrual symptoms which may impact on their quality of life much more than the volume of their menstrual loss. Pain during the menstrual period can profoundly affect a woman’s quality of life. Women who have moderate or severe pain during their period were more likely to have poor quality of life and more likely to ask for a medical consultation than women with mild pain.

The findings also confirmed that menstrual blood loss is positively correlated with age, duration of menstrual bleeding and practical difficulties, and negatively correlated with serum ferritin and haemoglobin level. Haemoglobin is a weak predictor of HMB because even in women with very heavy menstrual loss it was within the normal range. Lastly, women’s general health parameters did not appear to be affected by low serum ferritin.

**Implication for future research and clinical practice and recommendation on future research**

As mentioned above, this study investigated the impact of heavy menstrual bleeding on women’s quality of life. The population for our study was women living in NSW with access to answer an online questionnaire. Therefore, it is difficult to generalise the study findings to women other than those in NSW. Further studies should be conducted in different populations to investigate and compare the impact of heavy menstrual bleeding on women’s quality of life.
As with many menstrual disorders, heavy menstrual bleeding is common as a presenting symptom in the general population. This study confirmed the high prevalence of women who perceive their bleeding to be heavy and suggests a change in assessment of heavy menstrual bleeding is required. This is necessary to assist GP’s decision-making about the need to investigate or refer. It raises concern about the usefulness of current guidelines based on symptoms, advising women when to consult, and for the early detection of heavy menstrual bleeding in the community and primary care. Women would be best served if their primary care clinician carried out a detailed clinical assessment, including listening to accounts of their menstrual problems, clarifying their symptoms and how it affects their daily quality of life.

Following the findings of this study, further studies can be performed using a phenomenological approach in order to explore the in-depth feeling and perception of women having heavy menstrual bleeding. The grounded theory approach can also be used to study the phenomenon and could generate theories explaining the most important characteristics of the menstrual cycle among women with heavy menstrual bleeding. A well designed research plan such as a randomised controlled trial could be used to test the effectiveness of treatment such as stress-relieving programs or other pain treatments both chemical and behavioural among women complaining of heavy menstrual bleeding. This could strengthen the study’s findings and could provide more insight into women’s perception of their menstrual loss and finding which menstrual symptoms most affect their lives.

The study was conducted as a quantitative approach in investigating the effect of heavy menstrual bleeding on women’s quality of life. This study approach is appropriate for describing the current phenomenon. However, the causal relationship between factors could
not be identified by this study approach due to the small size of the sample. Further studies need to be conducted to isolate the causal relationship between the outcome factor of quality of life assessment and heavy menstrual bleeding. Longitudinal studies with good size sample can be used to further prove or reject the causal relationship between heavy menstrual bleeding, the quality of life of women and their seeking of medical treatment.

This study found that the perception by women of their menstrual loss was impacted by a range of menstrual symptoms, important to understanding whether the amount of menstrual loss or other symptoms such as pain was the main cause of their distress. Finding from studies of patient-centred consulting in other conditions shows that a successful understanding of a patient’s complaint contributes to improved patient satisfaction and outcome. Therefore, a simple approach to improve quality of life by careful assessment of what impacts their well-being may be more useful than more complex interventions.

Improvement of women’s knowledge about heavy menstrual bleeding should be one of the important aspects for research in the future. Therefore, it is necessary to identify their knowledge deficit and common misunderstanding of heavy menstrual bleeding, and then assess the effectiveness of the different educational tools that may help in solving their problem. Future research would help to explore different ways of delivering information to women to help in their self care and support them in their management of menstrual problems.

Lastly, the overall aim of the management of heavy menstrual bleeding should be to improve the quality of life of these women. To encourage women to seek medical help effort is needed to arouse the public awareness of heavy menstrual bleeding and advocate early detection for
their menstrual problems. Through early accurate diagnosis real problems with menstruation, complications associated with possibly unnecessary treatment interventions can be reduced.


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Appendix I

HEAVY MENSTRUAL BLEEDING Survey Draft 12 with health economic questions

Are you interested in contributing to a study about how women assess the amount of bleeding they experience with periods and how periods affect their everyday life?

This study is designed to look at the suitability of the questions included in this survey for finding out how women who are not using hormonal contraceptives assess the amount of bleeding they experience with periods and how periods affect their everyday life.

We plan to use this questionnaire for as a basis for further studies of menstruation in Australian women. The questionnaire is completely anonymous. There is no way you can be identified nor can any answer be connected to you as an individual. The information will not be used for any other purposes and will not be available to anyone other than the research team at the Sydney Centre for Reproductive Health Research at FPNSW. We do, however, need to capture some anonymous general information about age, education level and work involvement to enable us to effectively analyse the data.

If you are interested in participating please complete the attached questionnaire. If you decide to stop answering questions or do not want to answer a particular question that is your right.

Thank you for taking the time to complete the questionnaire.

1. Are you female, aged 18-50 years?
   Yes ☐ No ☐

2. Are you pregnant?
   Yes ☐ No ☐

3. Have you had a hysterectomy?
   Yes ☐ No ☐

4. Have you had both ovaries removed or endometrial ablation (the destruction of the endometrium for the control of heavy menstrual bleeding)?
   Yes ☐ No ☐

5. Have you reached menopause?
   Yes ☐ No ☐

6. Is your menstrual cycle generally between 20-40 days (i.e. from the first day of one period to the first day of the next)?
   Yes ☐ No ☐

7. Are you using hormonal contraceptives i.e. the pill, Implanon, Mirena, NuvaRing or DepoProvera Injection?
   Yes ☐ No ☐

8. If yes ...is this for the management or control of heavy menstrual bleeding?
☐ Yes, it is for both the management of heavy menstrual bleeding and contraception
☐ Yes, it is only for the management of heavy menstrual bleeding
☐ No
☐ Not sure

If you answered Yes to any of the questions 1 to 5 or yes to question 7 but no to question 8 you are not eligible as this is a study about menstrual bleeding.

Thank you for your patience and time with the eligibility questions. If you answered yes to question 8 and no to questions 1-5s you are eligible Now you can get started on the survey!

This survey is about how you have experienced your periods over the last few months and how you have been feeling generally.

1. Which age group do you fit?
   a. 15-19
   b. 20-29
   c. 30-39
   d. 40-49
   e. 50+

2. What is your postcode? ☐ ☐

3. Are you:
   a. Single ☐
   b. Married ☐
   c. Defacto relationship ☐
   d. Divorced ☐
   e. Widowed ☐

4. What is the highest education level you have attained?
   a. Primary school
   b. Year 10
   c. HSC
   d. TAFE
e. Undergraduate university
f. Postgraduate

5. What is your work position?
   a. Full time work □
   b. Part time work □
   c. Casual work □
   d. Home duties □
   e. Student □
   f. Unemployed □

6. On average during the last three months, for how many days did your period last?
   - Less than 3 days □
   - 3 to 7 days □
   - 8 to 10 days □
   - More than 10 days □

7. On average, during the last three months, were your periods regular or irregular?
   - Regular □
   - Irregular □

8. On average, during the last three months, how many days were there from the first day of a period to the first day of the next period?
   - 21 to 35 days □
   - More than 35 days □

4. On average, during the last three months, would you describe your periods as?
   - Light □
   - Moderate □
   - Heavy □
   - Very heavy □

5. On average, during the last three months, for how many days of each period was the bleeding heavy?
   - Not heavy on any day □
   - 1 to 3 days □
   - 4 to 6 days □
   - 7 to 10 days □
   - More than 10 days □

6. On average, during the last three months, how many tampons might you use on the heaviest day of your period?
   - I don’t use tampons □
   - 1 to 5 tampons □
   - 6 to 10 tampons □
   - 11 to 15 tampons □
More than 15 tampons

7. Do you use super tampons?

Never
Rarely
Occasionally
Usually
Always

8. On average, how many pads might you use on the heaviest day of your period?

I don’t use pads
1 to 5 pads
6 to 10 pads
11 to 15 pads
More than 15 pads

9. Do you use super pads?

Never
Rarely
Occasionally
Usually
Always

10. Do you use maternity pads or incontinence pads during your period?

Never
Rarely
Occasionally
Usually
Always
Only at night

11. At any time during the last three months, did you require more than one form of protection at the same time (not including mini pads or mini pant-liners)?

No
Tampon and pad together
Two pads together
Tampon and two pads together
More protection than this (i.e. disposable nappies, towels etc)

12. How often do you usually need to change a tampon or a pad on the heaviest day of your bleeding?

More frequently than every half an hour
Every half hour to one hour;
Every 1 to 2 hours;
Every 3 to 6 hours;
Every 6 to 12 hours;

13. How often do you usually need to change a tampon or a pad on the heaviest night of your bleeding?

Every 6 to 12 hours;
Every 3 to 6 hours;
Every 1 to 2 hours;
Every half hour to one hour;
More frequently than every half an hour

14. During the last three months, have you passed any clots of blood?
19. How much pain did you have during your last period?

None  
Very mild  
Mild  
Moderate pain  
Severe pain  
Very severe pain
In the next section we ask about how your period affects aspects of your everyday life. Please indicate which of the following statement describes you best.

20. PRACTICAL DIFFICULTIES:
   - I have no practical difficulties, bleed no more than I expect and take no extra precautions.
   - I have to carry extra sanitary protection with me but take no other precautions.
   - I have severe problems with flooding and need to be close to a toilet.
   - I have to carry extra sanitary protection and clothes because of the risk of flooding.

21. WORK/DAILY ROUTINE:
   - There are no interruptions to my work/daily routine during my period.
   - There are occasional disruptions to my work/daily routine during my period.
   - There are frequent disruptions to my work/daily routine during my period.
   - There are severe disruptions to my work/daily routine during my period.

22. SOCIAL LIFE:
   - My social life is.....
     - Unaffected during my period. I can enjoy life as much as usual.
     - Slightly affected during my period. I may have to cancel or modify my plans.
     - Limited during my period. I rarely make any plans.
     - Devastated during my period. I am unable to make any plans.

23. FAMILY LIFE/RELATIONSHIPS:
   - My family life and relationships are.....
     - Unaffected during my period.
     - Suffer some strain during my period.
     - Suffer quite a lot during my period.
     - Severely disrupted as a result of my period.

24. PSYCHOLOGICAL HEALTH:
   - During my period......
     - I have no worries and I can cope normally.
     - I experience some anxiety and worry.
     - I often feel down and worry about how I'll cope.
     - I feel depressed and cannot cope.

25. PHYSICAL HEALTH AND WELLBEING:
   - During my period
     - I feel well and relaxed.
     - I feel well most of the time.
     - I often feel tired and do not feel especially well.
     - I feel very tired and do not feel well at all.

26. During your last period how much did pain interfere with your normal work (including both work outside the home and housework)?
   - Not at all
   - Slightly
   - Moderately
   - Quite a bit
27. On average, during the last three months, have you been confined to bed with each period?

No, not at all ☐
Yes, usually for part of one day ☐
Yes, usually for the whole of one day ☐
Yes, usually for more than one day ☐

28. For women working outside the home (in paid or unpaid work), on average, during the last three months, how many days have you taken off work as a result of your periods ☐

29. On average, during the last three months, have your leisure activities been affected by your heavy periods?

(including sport, hobbies, social life)

Not affected by periods ☐
Mildly affected by periods ☐
Moderately affected by periods ☐
Severely affected by periods ☐
My periods have prevented any social life at all ☐

30. On, average, during the last three months, has your sex life been affected by your periods?

Not affected by periods ☐
Mildly affected by periods ☐
Moderately affected by periods ☐
Severely affected by periods ☐
Periods prevented any sex life at all ☐
Not sexually active during periods ☐
Not sexually active ☐

31. The last questions ask you for your views on your HEALTH IN GENERAL. How well you feel and how well you are able to do your usual activities. For each of the questions please tell us which of the following best describes you….

Is your general health

Excellent ☐
Very good ☐
Good ☐
Fair ☐
Poor ☐

32. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

a) Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf

Yes limited a lot ☐
Yes limited a little ☐
No not limited at all ☐

b) Climbing several flights of stairs

Yes limited a lot ☐

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The last questions ask you for your views on your HEALTH IN GENERAL

33 During the past 4 weeks have you had any of the following problems with your work or other regular daily activities as a result of your physical health
   a) Accomplished less than you would like
      
      | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
      |                |                 |                 |                    |                 |

   b) Were limited in the kind of work or other activities
      
      | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
      |                |                 |                 |                    |                 |

33. During the past 4 weeks have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?
   a) Accomplished less than you would like
      
      | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
      |                |                 |                 |                    |                 |

   b) Did work or other activities less carefully than usual
      
      | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
      |                |                 |                 |                    |                 |

34. During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?

      | Not at all | A little bit | Moderately | Quite a bit | Extremely |
      |           |             |            |            |           |
35. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week.....

a) Have you felt calm and peaceful

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

b) Did you have a lot of energy

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

c) Have you feel downhearted and depressed

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

The last questions ask you for your views on your HEALTH IN GENERAL

36. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives etc)?

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time
# HMB Study

## Monthly Menstrual Diary

**ID:** DESM  
**Study #:** 048  
**DOB:** 08/11/1968

**Cycle No 1**

<table>
<thead>
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<td>Bleeding/spotting</td>
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<tr>
<td>Number of tampons used</td>
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<tr>
<td>Number of pads used</td>
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<tr>
<td>Number of panty liners used</td>
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HMBStudy  
Protocol R2008-08  
Patient Concomitant Medication Worksheet

**ID:** EMRO  
**Study No:** #055  
**DOB:** 17/10/1973

**Cycle # 1**

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<th>Name of Medication</th>
<th>Indication</th>
<th>Route</th>
<th>Dose</th>
<th>Frequency</th>
<th>Start Date</th>
<th>Stop Date</th>
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