The Duration of Menstrual Blood Loss: Historical to Current Understanding

Marwan Habiba 1,* and Giuseppe Benagiano 2

1 Department of Health Sciences, University of Leicester and University Hospitals of Leicester, Leicester Royal Infirmary, Infirmary Square, Leicester LE1 5WW, UK
2 Department of Maternal & Child Health, Gynecology and Urology, ‘Sapienza’, University of Rome, Piazzale Aldo Moro 5, 00100 Rome, Italy
* Correspondence: mab6@leicester.ac.uk

Abstract: Most published research focuses on the amount of menstrual blood loss and, to a lesser extent, on cyclicity. Little attention has been paid to the duration of bleeding, the factors that enable its cessation within a ‘normal’ timeframe, or to patterns that entail interruption and resumption of blood loss. The definition of what constitutes normal remains arbitrary and there is no therapy specifically designed to shorten the duration of bleeding. Here, we critically review the literature that addresses the duration of bleeding and the factors that trigger endometrial breakdown and repair. Available reports used population averages which mask inter- and intra-individual variations. The duration of bleeding is not necessarily linked to the amount of loss but may be influenced by age, ethnicity, habitus, region and altitude of residence, dieting and stress. The onset of bleeding has been linked to declining steroid production by the corpus luteum. There remains considerable controversy around the extent of endometrial shedding at menstruation. This is likely to vary within and between women. The significance of a change from previous patterns, very short or prolonged bleeding, days of light loss or spotting before or after days of bleeding, or of bleed-free days that punctuate flow, remain poorly understood.

Keywords: menstruation; menstrual bleeding; duration of bleeding; menstrual phase; endometrium

1. Introduction

The impact of abnormal uterine bleeding and the link between menstruation and ovarian function have long been recognised. Most of clinical data and research have so far been focused on the amount of blood loss and, to a lesser extent, on cyclicity [1,2]. Although much of this is now subsumed under the broad category of abnormal uterine bleeding (AUB), early descriptions of menstrual cycles utilised specific nomenclature when referring to the quantity of loss and its regularity. By contrast, less attention has been paid to the duration of bleeding, the factors that enable its cessation within an expected ‘normal’ timeframe, or to aberrations that entail prolonged or short bleeding. Most publications refer to the duration of bleeding only in terms of average or range. Most recent studies that address changes in the menstrual cycle in relation to COVID-19 vaccination do not comment on the duration of bleeding [3–5]. The duration of bleeding is recognised as having an impact on patients and on their satisfaction with treatment of menstrual abnormalities [6]. An international initiative proposed that bleeding be classified as normal if its duration is between 4.5 and 8 days, prolonged if >8 days and shortened if <4.5 days [7]. The original FIGO classification system includes prolonged duration of bleeding under the heading Abnormal Uterine Bleeding but does not propose cut-off points [8]. The modified classification does not refer to shortened duration but uses >8 days as the upper limit for normal [9]. The derivation of these ranges remains uncertain (Table 1). Interestingly, women regarded 3 days as the optimal duration of bleeding [10]. The duration of bleeding and its amount are not always linked, and little is understood about the significance of the lighter
loss that sometimes occurs before or after the recognised menstrual flow. Nevertheless, in
one report, treatment of women with heavy menstrual bleeding (HMB) using mefenamic
acid or misoprostol resulted in reduction of both the amount of loss and its duration [11].
Factors that may contribute to prolonged uterine bleeding may reside in disturbances of the
dynamics that control the onset of bleeding or those responsible for endometrial shedding
or its restoration. The term ‘regenerative phase’ of the menstrual cycle which was used
in the past to refer to the stage when endometrial re-epithelialization takes place is rarely
used in the modern literature. Zhang et al. stated that women who reported their bleeding
to last <4 or >5 days had lower fecundity ratio compared to those who reported 4–5 days
of bleeding [12].

Table 1. The adopted cut-off points for normal duration of menstrual blood loss.

<table>
<thead>
<tr>
<th>Study</th>
<th>Suggested Cut-Off for Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meigs (1849) [13]</td>
<td>Each woman has her own cycle</td>
</tr>
<tr>
<td>Tauszky (1879) [14]</td>
<td>10 days can be considered normal</td>
</tr>
<tr>
<td>Fraser et al. (2007) [7]</td>
<td>Between 4.5–8 days</td>
</tr>
<tr>
<td>Munro et al. (2018) [9]</td>
<td>upper limit of normal &gt; 8 days as, no lower limit</td>
</tr>
<tr>
<td>Bastianelli et al. (2023) [10]</td>
<td>Women reported preference of 3 days</td>
</tr>
</tbody>
</table>

Women often raise the question with clinicians as to the reasons why they bleed
for shorter or longer days, but in contrast with the question of the amount of blood
loss, the issue seems largely set aside and rarely, if ever, considered in the literature or
clinical guidelines.

We undertook a literature review of articles relevant to understanding the clinical
features that are considered and the cut-off points that delimit normal duration of bleeding
and the factors that determine the duration of blood loss in spontaneous cycles. The review
also addresses factors that determine the onset of flow and its cessation and thus contribute
to the control of the duration of blood loss at menstualtation.

We undertook literature search using Medline (December 2022, and repeated May
2023) using the broad terms: Menstruation, or menstrual blood loss, or menstrual cycle
combined with duration or duration of bleeding. This identified 2226 references that were
reviewed manually (title and abstract) to identify all articles that either specifically focussed
on the duration of bleeding (n = 0) or that contained a reference to the duration of bleeding
in the context of the study of menstrual patterns in natural cycles (n = 51). The identified
articles were read in detail to determine those that are relevant to the review (n = 24). Other
references were identified through a search of reference lists in the identified articles.

2. Assessing the Duration of Bleeding

The variation between women in the duration of menstrual bleeding has long been
recognised. Meigs (1849) who, like many of his contemporaries, attributed the onset of
bleeding to ovulation, wrote that ‘in the duration of the flow, as well as in the number of
fluidounces discharged, each woman obeys a law of her own nature’ [13]. Meigs went on to
suggest that no action is required in relation to such variation [13]. Early writers recognised
the variation in the duration of bleeding, and the view was held that 10 days of bleeding
should be pronounced as normal menstruation if the woman was otherwise well [14].

Considerable effort was spent during the 1960–1970s on agreeing on methods to assess
menstrual blood loss. The impetus for this stemmed from the need to develop and compare
the then emerging methods of contraception. One such effort was the workshop held at
the University of Exeter, UK, in March 1976. This workshop had as an aim the reaching
of agreement on a prospective method for data collection that relied on easily obtained
information. The emphasis was placed on simplicity of both the definitions and analytical
methods [15,16]. The 90-day reference period method was adopted by the workshop to
avoid the difficulty entailed in accounting for episodes of intermenstrual bleeding that
can occur during the menstrual cycle. The proposal drawn at the workshop also included
drawing a distinction between ‘bleeding’ and ‘spotting.’ Statistical comparisons were made based on features such as the average number or average duration of episodes of bleeding and the difference between study groups, rather than on cyclicity or reproducibility of cycles for the individual. No particular emphasis was placed on the duration of what might constitute ‘menstrual loss’ [15]. Spotting was defined in terms of light bleeding where sanitary protection is not used. It is interesting to note that workshop participants debated the inclusion of spotting not from a pathophysiological standpoint, but because of the likely impact this may have on the analysis and based on their appreciation of women’s behaviour or attitude. Rodriguez et al. pointed out that the appropriateness and reliability of the distinction between bleeding and spotting can vary and, as such, should be judged by each individual investigator [17]. Despite it being still widely used, the term ‘spotting’ that is used in relation to menstrual loss is curious because this is not the manner in which light bleeding manifests clinically.

The 90-day reference period [17] considers the duration of bleeding in terms of bleeding episodes or as an aggregated mean duration rather than in terms of its tendency to recur in subsequent cycles. Thus, while analysis based on reference period avoids the difficulties entailed in defining the menstrual cycle, it obscures cyclicity, cycle predictability and the relation between bleeding that may precede or follow menstruation or hormone withdrawal, and other bleeding episodes.

### 3. Identifying the Onset of Bleeding and Its Cessation

The onset and end of menstrual bleeding continues to be determined through the recognition by the woman herself. Vollman (1977) observed that this carries a methodological error of one day when it comes to determining the onset of bleeding because little is known about the interval between the appearance of blood at the external cervical os and subjective perception of onset of menstruation [18]. The same can be said about the end of bleeding. Furthermore, as recognised in relation to neonatal uterine bleeding, a distinction could be made based on whether bleeding is observed macroscopically or biochemically. Defining the exact onset point of endometrial breakdown rather than the point of manifest blood loss has relevance to research. Early investigators pointed out that the difficulty in defining the onset of menstruation impacts on the interpretation of histological features [19].

As referred to above, defining the onset of bleeding remains problematic. Li et al. (2020) defined a period as ‘the sequential days of bleeding (greater than spotting and within 10 days after the first greater-than-spotting bleeding event) unbroken by >1 day on which only spotting, or no bleeding occurred’ [20]. In the study by Bull et al., participants were instructed not to log very light bleeding that may occur just before the period, but to wait until the flow increases. In this study, bleed length was defined as the number of consecutive days of bleeding excluding spotting, and spotting was defined as very light bleeding (a few drops of blood) or the appearance of brown/pink fluids [21]. There does not appear to be any scientific rationale for excluding days of spotting that may precede or follow heavier loss.

Another feature identified in early studies of uterine bleeding is that the shed material remains in the uterine cavity for some time. This view, however, was based on a limited number of observations from normal uteri. Dallenbach-Hellweg pointed out that there are great variations in the length and the extent of shedding and of shrinkage without shedding [22]. Thus, some women shed only the upper functionalis layer, others the lower functionalis and others yet do not shed the endometrium at all. This is perhaps linked to the phenomenon defined as ‘silent menstruation’ [23,24].

### 4. Assessing Variability

When it comes to comparing contraceptives, the assumption has been made that minor variations in the length of the 24 h period (indicating that duration can be considered based on the day not the hour of onset) and in the exact start and end of bleeding are not important,
provided there is consistency in applying an agreed rule [25]. However, such variations can affect studies concerned with the mechanisms that control blood loss. There is lack of clarity on how an isolated day of manifest bleeding or ‘spotting’ followed or preceded by a bleed free day or days should be included in the analysis of menstrual cycles [25]. Such distinctions are particularly important when examining variations in the duration of bleeding because of the narrow range of variability. Interestingly, bleeding commenced during the night or in the first 4 h after rising in 70.4% of cycles, and premenstrual spotting for more than 3 h was reported in 67% of women [26].

There are limited reports that address the duration of bleeding. Goldzieher et al. reported on 524 cycles (500 of which were ovulatory) that were recorded by 109 healthy women. Ovulation was detected by assessing the basal body temperature. The authors reported that the duration of the progestogenic phase was fairly consistent (69.5% falling between 11 and 14 days), and none were shorter than 8 days or longer than 19 days. The duration of bleeding was available in 481 cycles. In 68.4% of cases, bleeding lasted for 3–5 days, and in 95.4% of cases, bleeding lasted for 3–7 days [27]. The study did not report on cycle-to-cycle variability for individuals. In the study by Najmabadi et al. (2020) that reported on the duration of bleeding in women with no known subfertility (n = 537) who were followed up for one year (n = 2645 cycles), the mean duration of bleeding was 6.2 (±1.5) days, but bleeding duration ranged from 3 to 15 days. The within-woman difference in the duration of bleeding was >3 days in 11.6% of women. The study found no difference between women based on their age (<30 years vs. ≥30 years) or parity (nulliparous vs. parous) [28].

Belsey et al. analysed the menstrual diary data that were originally collected by Dr Alan Treloar from untreated women as a baseline for comparison with users of contraception [29]. This study did not distinguish ‘menstrual losses’ from other episodes lasting one or more days whether consecutive or separated by only one bleeding-free days. Using this definition, the mean duration of bleeding reduced from 6.6 days at the age of 15 years to 6.0 days by the age of 20 years and remained largely unchanged until the age of 49 years [29]. Fewer than 5% of women had a <4-day average duration of bleeding and only 5% had bleeding averaging 8 days. The duration of bleeding varied little for individual women. At least 25% of women and >50% in some single-year age groups had bleeding episodes that varied by only 1 day over a year. At ages of 15–43 years, 75% of women had bleeding that varied by ≤3 days. Variability increased after the age of 44 as 75% of women had a 4–5-day difference between their shortest and longest bleeding episodes [29].

Large-scale prospective studies [18,29–32] also used summary data on menstrual cycle length across the calculated measures of central tendency stratified by age. They measured population mean and range, but not cycle-to-cycle variability for individual women. A different approach was taken by Harlow and Zeger (1991) in their analysis of menstrual diaries from university students experiencing spontaneous cycles [33]. The authors calculated the transition probabilities of any given cycle length to a different cycle length. The most probable transition for a segment of any length (except for segments <17 days) was to a segment of 26–34 days. Here, the term ‘menstrual segment’ was used in reference to menstrual cycle to acknowledge that diary data cannot distinguish between menstrual and non-menstrual bleeding episodes. The longest and shortest segments had greater probabilities than segments closer to the mean of being followed by either a short or a long segment. Harlow and Zeger (1991) reported that within-women variability in cycle length is approximately twice as large as variability between women [33]. Habiba et al. (1996) used this approach when assessing the transition probability and the likelihood that a particular cycle in women on cyclical hormone replacement therapy (HRT) is followed by a cycle of similar or of different length [34]. There are no comparable analyses of the cycle-to-cycle changes in the duration of bleeding. Treloar et al. reported on a major study of menstrual bleeding patterns in women who recorded their bleeding for up to 30 years [30]. The authors pointed out that the occurrence of spotting just prior to the first day of flow, which was more common in the premenopausal years, presented a problem...
for determining the onset of menstruation [30]. But neither this study nor the other major study by Vollman provided an analysis of the duration of bleeding [18].

5. The Relation between the Amount of Loss and Its Duration

The relation between the duration and the amount of blood loss has been subject to debate. In a population study involving 362 women aged between 15 and 50 years whose blood loss was measured daily, Rybo reported that bleeding for more than a week was linked to heavy menstrual loss. Women with menorrhagia experienced 69% of the total loss during the first 2 days and 86% in the first 3 days of the period. Women who bled <80 mL per cycle lost 79% during the first 2 days and 92% during the first 3 days of the period [35]. Another study in a healthy population found limited correlation between the amount of loss and its duration [36]. Other studies found no relation between the duration of menstruation and the total amount of blood loss in women with menorrhagia [37,38]. Another study that included women with normal menstruation and women with menorrhagia found little relation between the amount of loss and its duration [39]. Women with inherited bleeding disorders were reported to experience longer duration of bleeding and shorter cycles [40]. However, the authors pointed out that the difference may be related to different response rates amongst participants [40]. Most blood loss occurs within the first 48–72 h of the onset of bleeding, which may explain the lack of correlation between the amount and duration of loss.

6. Factors That Affect the Duration of Bleeding

Bull et al. described the characteristics of 612,613 ovulatory menstrual cycles from real-world users of an electronic menstrual record. The mean duration of bleeding was 4.0 ± 1.5 days. The duration of bleeding was shorter by 0.5 days for cycles < 21 days long and longer by 0.2 days for cycles > 35 days long [21]. The bleeding duration was 4.2 ± 1.4, 4.0 ± 1.4, 3.9 ± 1.5, 3.8 ± 1.5 and 3.7 ± 1.5 days for the age groups of 18–24, 25–29, 30–34, 35–39 and 40–45 years, respectively. The duration of bleeding varied in relation to body mass index (BMI) and was statistically significantly longer by 0.2 days (95% CI: 0.18–0.22 days) in the 15–18.5 BMI group and shorter by 1 day in the 35–50 BMI group (Table 2).

Table 2. The relation between the duration of menstrual blood loss and body mass index [21].

<table>
<thead>
<tr>
<th>BMI Range</th>
<th>Number of Cycles</th>
<th>Duration of Bleeding (Mean ± Std)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15–18.5</td>
<td>25,735</td>
<td>4.2 ± 1.5 *</td>
</tr>
<tr>
<td>18.5–25</td>
<td>431,667</td>
<td>4.0 ± 1.5</td>
</tr>
<tr>
<td>25–30</td>
<td>100,228</td>
<td>3.9 ± 1.4 *</td>
</tr>
<tr>
<td>30–35</td>
<td>26,483</td>
<td>3.9 ± 1.4 *</td>
</tr>
<tr>
<td>35–50</td>
<td>12,011</td>
<td>3.0 ± 1.5 *</td>
</tr>
<tr>
<td>All cycles</td>
<td>621,613</td>
<td>4.0 ± 1.5</td>
</tr>
</tbody>
</table>

*p = < 0.0001 compared to all reported cycles.

Another large-scale study that relied on menstrual cycle information provided electronically reported on the duration of bleeding [20]. Participants (n = 378,694) were 21–33 years old. The average cycle length was 29.7 days, and the mean duration of bleeding was 4.08 ± 1.76 days. The study compared participants whose cycles varied by ≤9 or >9 days. This threshold divided participants into two groups: the ‘consistently not highly variable’ group (CNHV) = 92.3% who provided 96.31% of the cycles and the ‘consistently highly variable’ group (CHV) = 7.68% who provided 3.69% of the cycles. The duration of bleeding for the CNHV group was statistically significantly lower compared to the CHV group (4.07 ± 1.72 vs. 4.28 ± 2.54 days, p < 0.0001) [20]. The authors pointed out an overlap in the duration of bleeding probability distribution amongst the two groups and a higher peak in periods lasting for only one day. They also noted that this may be due to incomplete recording of the duration by participants who only tracked the day of onset of bleeding [20].
Thus, whilst electronic recording provides a large volume of data, it may be less reliable for studies of the duration of bleeding. In addition, the degree by which participants reflect the general population is difficult to determine. The concept of cycle length difference as an index of cycle regularity is interesting, but there remains a need to provide a scientific rationale of any chosen cut-off point, and cycle to cycle variability in cycle length and in the duration of bleeding are not necessarily linked.

Research that reports duration of bleeding in terms of mean and range obscures variations between participants and from one cycle to subsequent cycles. In one study that reported a median duration of bleeding of 5 days amongst participants, the range varied from 1 to 16 days. The amount of blood loss also varied, and the days of bleeding were equally divided between light, medium and heavy days [41]. It should be reiterated that the amount of bleeding can vary from day to day during menstruation.

In a study that included 581 women who contributed 3324 cycles, the majority were <30 years of age (74.5%), non-Hispanic white (88.6%), and nulliparous (70.4%). The mean menses length was 6.2 days (SD = 1.5, range 3–15), and 11.6% of all participants experienced a >3-day difference between the longest and shortest menses length [42]. The study by Park et al. reported an average duration of bleeding of 5.6 days; 95.2% reported bleeding between 2 and 7 days and 4.8% reported more than 8 days of bleeding [43]. But this study relied on retrospective recollecting of data. In another study that relied on retrospective data collection, there was no difference in the duration of bleeding between women with early, average, or late menarche [44].

A recent study that reported on the duration of bleeding in a large cohort from China found that average duration of bleeding was 5.01 ±1.13 days and that >80% of women had an average duration of 4–8 days. There was a wide variation in the duration of bleeding in the youngest age group (<18 years). The highest proportion of those bleeding for 1 day was amongst the young cohort and the duration of bleeding also gradually decreased with age. The mean (SD) duration of bleeding for those aged <18, 18–25, 25–30 and >30 years was 5.13 ± 1.12, 5.03 ± 1.08, 5.0 ± 1.14, 4.93 ± 1.27 days, respectively. Women who were underweight tended to experience a more prolonged duration of bleeding, and obese women had short duration of bleeding [45]. Cycle-to-cycle variability was not assessed, but out of the n = 24,670 cycles reported, the duration of bleeding was ≤1, 2–3, 4–8 or ≥9 days in 3.95%, 12.97%, 81.96% and 1.09% of cases, respectively [45].

The duration of bleeding can vary from cycle to cycle between individuals as well as between women. In relation to the latter, the mean duration of bleeding episodes was reported to be lower in women with higher ponderal index [21,46]. However, two reports that relied on retrospective recollection linked indices of obesity to prolonged bleeding [47,48]. The study by Parker et al. asked teenage girls about their ‘usual’ menstrual cycle and reported the average duration of bleeding as 5.93 days [49]. Region- [50–53], age-, [54,55] and altitude-related [56] variability in duration of flow have also been reported.

There is no agreement on the relation between bleeding duration and the occurrence of ovulation. This may be related to difficulties in detecting ovulation because distinguishing anovulation based on clinical features is unreliable. Anovulation has been linked to short or long cycles. Anovulation is believed to be more common at the beginning and the end of reproductive years. Bleeding linked to anovulation is related to exposure to unopposed oestrogen [57]. In a study of the menstrual bleeding patterns of regularly menstruating women, Dasharathy et al. reported longer duration of bleeding in ovulatory compared to anovulatory cycles (5.4 days vs. 4.5 days; p = 0.025) [41]. However, this estimate was derived from a subset of their study participants. In another study involving women approaching the menopause, both short (1–3 days) and prolonged (>8 days) bleeding were associated with anovulation in 18% and 23% of cases, respectively. A lower incidence of anovulation (9.8%) was reported in cycles where the bleeding lasted 4–7 days [58]. Both studies were based on one menstrual cycle and reported a lower incidence of heavy menstrual loss in women with anovulatory cycles [41,58]. The study design does not enable commenting on cycle-to-cycle variability.
Examining the impact of hormonal status on bleeding is necessarily linked to the changes in hormone levels during the cycle and to the timing of ovulation and regression of the corpus luteum. The variability in menstrual cycle and in the timing of the LH peak are well recognised [59–62]. In another study of healthy women, the length of the luteal phase ranged from 9 to 20 days [61]. Cole et al. calculated the mean luteal phase to be 13.2 ± 2.0 days (95% CI 9–17 days). The individual variance in the luteal phase was 2.6 ± 3.1 days [63]. The authors attributed the tighter range in their study to the exclusion of atypical cases, such as those with no clear LH peak (attributed to anovulation), cases with exceptionally elevated LH and women with >40-day cycles [63].

Higher FSH was linked to heavier and more prolonged bleeding and higher progesterone levels to heavier loss [41]. For every log unit increase in FSH, menses length increased by 3% (survival time ratio 1.03, 95% CI: 1.01–1.05). There was no association between LH, progesterone or oestrogen and the duration of bleeding when adjusted for confounders [41]. On the other hand, Van Voorhis et al. (2008) found that after correction for anovulation, daily and integrated hormone production had no independent effect on the duration of bleeding in the subsequent cycle [58].

Harlow and Campbell studied menstrual diaries collected over one year from healthy women aged 17–19 years. The median duration of bleeding was 5 days, but cycles varied widely (range 1–19 days, 97% between 3–8 days). The duration of bleeding was not associated with the length of the preceding cycles, history of long cycles, change in body weight, college entry, or being away from home [64]. Late menarche was linked to a slight increase in the duration of bleeding. Women with low weight-for-height (using Benn’s index [65]) [64] bled for about 0.4 days longer. Bleeding was 0.15 days longer in women at the 90th centile of perceived stress. Dieting reduced bleeding by about 0.5 days and moderate-to-hard exercise reduced bleeding by 0.23 days. Harlow and Campbell (1994) speculated that dieting prolonged bleeding through increasing anovulatory cycles [66].

The duration of bleeding was considered in the WHO prospective study of bleeding patterns at the onset of puberty in girls from different ethnic background. Participants who were 11–15 years old at recruitment were followed up for 2 years [67]. Days of spotting that were not separated by more than one day were counted as days of bleeding. The mean duration of bleeding of all participants was 4.7 days (SD = 1.8) and for those who reached menarche before recruitment it was 4.9 days (SD = 1.4). There was a wider variation in the duration of bleeding immediately following menarche. The duration of bleeding varied between girls from different countries: participants in Hong Kong bled for 6 days (85.8% of cycles were between 3 and 7 days) compared to 4.3 days (90.7% between 3 and 7 days) for participants in Colombo, Sri Lanka [67].

Harlow and Campbell compared menstrual bleeding patterns of American women of African (AfA) and European (EuA) descent. Most (85%) participants who were between 12 and 14 years reported 12 cycles. The median duration of bleeding was 5 days (range 1–34 days), 96.5% of bleeding episodes lasted 3–8 days; 15 (6.5%) participants reported having at least one episode of bleeding of >10 days. Ethnicity was the strongest determinant of bleeding duration which was longer in EuA (5.6 days) compared to AfA (5.1 days). For AfA, low and high body mass were linked to shorter bleeding (0.3 and 0.2 days, respectively). For EuA, low body mass increased the duration of bleeding by 0.25 days, but high body mass had no impact. Stress affected the two groups differently. Being at the 90th centile of perceived stress reduced bleed duration by 0.1 days in EuA but had no impact on AfA. Dieting decreased bleed duration by about 0.1 days. The duration of bleeding was slightly longer in those who had late menarche, but was unaffected by exercise, previous cycle length or gynaecologic age [67].

Studies that compared bleeding patterns among contracepting and non-contracepting women used the 90-day bleeding interval. Belsey and Farley (1988) reported a world-wide study and found that bleeding patterns were more closely related to women’s region of residence than to any other factor [26]. For instance, European women using the ovulation detection method of contraception tended to have more bleeding/spotting days than
women in other regions. The reason for this is unclear, but it was proposed that it may be related to the way women completed their diaries. It is also possible that the duration of bleeding is influenced by age, altitude, and weight [25,66,68].

The duration of bleeding may be subject to hypothalamic-pituitary control. In a group of healthy nulliparous women aged 18–23 years, Nikolova et al. reported that menstrual cycle length ranged between 23 and 31 days in left-handed women and between 24 and 35 days in right-handed women ($p < 0.001$) [69]. The duration of bleeding (4.69 ± 0.05) days was significantly shorter in left-handed than right-handed women (5.75 ± 0.004, $p < 0.001$). This observation may be explained by an association between left-handedness and higher testosterone and oestradiol levels [70]. Uterine factors may also affect the duration of bleeding. In one study, women with self-reported past diagnosis of fibroids had longer duration of bleeding [58]. The duration and quality of sleep and fatigue have been linked to menstrual cycle irregularity and to the quantity of blood loss, but whether these factors affect the duration of bleeding has not been reported [71]. The duration of bleeding was not affected by the administration of chamomile (traditionally believed to affect menstruation) capsules to a group of university students [72]. The duration of bleeding is linked to obesity in some studies [47,48,73], but not in others [74]. Exposure to high concentration of organophosphate pesticides has been linked to shorter duration of bleeding [75]. Summary of factors that may be linked to the duration of bleeding is provided in Table 3.

Table 3. The main findings in studies that commented on factors linked to the duration of bleeding.

<table>
<thead>
<tr>
<th>Study</th>
<th>Observation Related to Duration of Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bastianelli et al. (2023) [10]</td>
<td>Women regard 3 days as the optimal duration of bleeding</td>
</tr>
<tr>
<td>Zhang et al. (2017) [12]</td>
<td>Women who reported their bleeding to last &lt;4 or &gt;5 days had lower fecundity ratio compared to those who reported 4–5 days of bleeding</td>
</tr>
<tr>
<td>Najmabadi et al. (2020) [28]</td>
<td>No difference in duration of bleeding based on age ($&lt;30$ years vs $\geq 30$ years) or parity (nulliparous vs parous)</td>
</tr>
<tr>
<td>Belsey and Pinol (1997) [29]</td>
<td>Mean duration reduced from 6.6 days at 15 y, to 6.0 days by 20 y and remained largely unchanged until age 49 y</td>
</tr>
<tr>
<td>Dasharathy et al. (2012) [41]</td>
<td>Longer duration of bleeding in ovulatory compared to anovulatory cycles</td>
</tr>
<tr>
<td>Zurawiecka et al. (2021) [44]</td>
<td>No difference in the duration of bleeding between women with early, average, or late menarche</td>
</tr>
<tr>
<td>Mao et al. (2021) [45]</td>
<td>Prolonged bleeding in underweight and shorter bleeding in obese women</td>
</tr>
<tr>
<td>Kafaei-Atrian et al. (2019) [48]</td>
<td>Duration of bleeding had a significant relationship with weight, and the circumference of waist, hip and arm.</td>
</tr>
<tr>
<td>Van Voorhis et al. (2008) [58]</td>
<td>Self-reported past diagnosis of fibroids linked to longer duration of bleeding</td>
</tr>
<tr>
<td>Harlow and Campbell (1994) [64]</td>
<td>The duration of bleeding not associated with the length of the preceding cycles, history of long cycles, change in body weight, college entry, or being away from home. Slight increase if late menarche. Longer bleeding if low weight-for-height.</td>
</tr>
<tr>
<td>WHO Task Force (1986) [67]</td>
<td>The duration of bleeding varied between countries and is slightly longer if late menarche. Unaffected by exercise, previous cycle length or gynecologic age.</td>
</tr>
</tbody>
</table>
Table 3. Cont.

<table>
<thead>
<tr>
<th>Study</th>
<th>Observation Related to Duration of Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nikolova et al. (2003) [69]</td>
<td>The duration of bleeding (4.69 ± 0.05 days) was significantly shorter in left-handed compared to right-handed</td>
</tr>
<tr>
<td>Mollabashi et al. (2020) [72]</td>
<td>Duration of bleeding not affected by Chamomile</td>
</tr>
<tr>
<td>Chang et al. (2009) [73]</td>
<td>Duration of bleeding linked to obesity</td>
</tr>
<tr>
<td>Tayebi et al. (2018) [74]</td>
<td>Link between duration of bleeding and obesity not confirmed</td>
</tr>
<tr>
<td>Zhang et al. (2020) [75]</td>
<td>Exposure to high concentration of organophosphate pesticides linked to shorter duration of bleeding</td>
</tr>
<tr>
<td>Wood et al. (1979) [76]</td>
<td>Based on patient recollection, the duration of bleeding was 1–7 days and 3% of women bled for &gt;7 days</td>
</tr>
<tr>
<td>Kirchengast (1994) [77]</td>
<td>The post-cephalic height and length dimensions were positively correlated with the duration of bleeding</td>
</tr>
<tr>
<td>Fakeye and Adegoke (1994) [78]</td>
<td>Prolonged bleeding (≥8 days) occurred in less than 5% of postmenarcheal schoolgirls</td>
</tr>
<tr>
<td>Vercellini et al. (1997) [79]</td>
<td>The duration of bleeding was longer (mean difference 0.33 days) in women with endometriosis</td>
</tr>
<tr>
<td>Bata (2012) [80]</td>
<td>The duration of bleeding in 73.6% of secondary school students was between 4–7 days.</td>
</tr>
<tr>
<td>Rigon et al. (2012) [81]</td>
<td>In women and girls aged (13–21 years), the average duration of bleeding was &lt;4 days in 3.2% of participants</td>
</tr>
<tr>
<td>Farahmand et al. (2020) [82]</td>
<td>and &gt;6 days in 19% of participants</td>
</tr>
<tr>
<td>Ansong et al. (2020) [83]</td>
<td>International students in China who had high levels of stress reported abnormal duration of bleeding</td>
</tr>
<tr>
<td>Charis et al. (2022) [84]</td>
<td>In women recovering from spinal cord injury, the mean duration of bleeding was lower (4.28 ± 0.96 days)</td>
</tr>
<tr>
<td></td>
<td>compared to the duration of bleeding before the injury (4.88 ± 0.96 days)</td>
</tr>
</tbody>
</table>

6.1. Mechanisms Involved in Menstruation

Comprehensive reviews of the molecular mechanisms linked to menstruation are available [85,86], but a detailed account is outside the scope of this article. Critchley et al. emphasised the role of the fall of progesterone levels following the demise of the corpus luteum in triggering menstruation [86]. Bleeding can also be triggered by the administration of the selective progesterone receptor modulator (SPRM), mifepristone, during the secretory phase of the cycle. Re-administration of ‘rescue’ progesterone within 24 h of withdrawal can prevent endometrial breakdown in the macaque model [87].

Progesterone withdrawal triggers increased endometrial cytokine and prostaglandin (PGs) release from decidualised perivascular stromal cells [88,89]. These factors may have a role in in tissue breakdown and/or early repair. Progesterone withdrawal, hypoxia and PGE₂ regulate IL-8 and CYR61 (cysteine-rich angiogenic inducer 61) through their effect on NFkB and HIF-1 (hypoxia-inducible factor-1). Menstruation is associated with increased VEGF (vascular endothelial growth factor) which stimulates neovascularization in the regenerating endometrium [90].

Chemokines, specific chemoattractant cytokines, affect leukocyte migration principally neutrophils, uNK cells and macrophages [91]. Activated leukocytes produce inflammatory mediators such as IL-6 and contribute to degradation of the extracellular matrix (ECM). Plasminogen/plasmin, lysosomal enzymes and caspases have a role in the cascades leading to menstruation, but the most important agents responsible for ECM degradation are matrix metalloproteinases (MMP). MMPs and tissue inhibitors of metalloproteinases (TIMPs) have been identified in the human endometrium, and their expression is modulated by steroids [92]. Other factors that play a role in menstruation include IL-1α (interleukin-1α), TGFβ, LEFTY2/EBAF (left–right determination factor 2/endometrial bleeding associated
factor), Endothelin, and TNFα (tumour necrosis factor α) and factors linked to tissue hypoxia [93].

6.2. Endometrial Shedding and Its Anomalies

The endometrium is recognised as being formed of a superficial functionalis and basalis layers [94]. But these can be further subdivided into four zones: the most superficial comprises the luminal epithelium and the subjacent stroma which form the compact layer; the deeper layer of the functionalis (the spongiosa) contains the straight portion of the glands and the surrounding loose stroma. The basalis can be divided into an upper zone that contains the gland mid-region and the basal region that contains the base of the glands and a fibrous stroma [95].

During the 19th century, many influential authorities held the view that menstruation is analogous to oestrus and that it is linked to ovulation [96]. This is now understood not to be the case and menstruation is linked to progesterone withdrawal which induces features of inflammation with influx of innate immune cells and release of proteolytic MMPs leading to shedding of the functionalis. Hitschmann and Adler recorded changes in the endometrium leading to endometrial shedding during menstruation [97]. The classic studies by Markee [98,99] described bleeding from arterioles, capillaries and veins leading to subepithelial hematoma formation. Bleeding breaks through into the lumen and manifests as menstrual blood loss. According to Bartelmez, the early studies by Markee showed that there can be much variability in a given endometrium even in successive ovulatory cycles [100]. In Markee’s experiments involving endometrial implants in macaque, bleeding was shown to be a progressive phenomenon that was observed to start from individual arterioles and the process repeats from other arterioles and other regions within the endometrial implant till the endometrium is denuded over 3 to 4 days [100].

Microscopically, the human menstrual endometrium, features stromal disintegration with localised areas of blood extravasation prior to epithelial breakdown and the onset of bleeding [101]. Lesions in blood vessels were noted up to 5 days prior to menstruation [102]. There is controversy about the amount of tissue loss at menstruation, and this may vary from one uterus to another. One study reported incomplete dissolution of the spongiosa layer on day 3 [19]. Uteri obtained 3.5, 4, 5.5, 7 and 13 h after the start of menstruation exhibited diffuse or localised haemorrhages and a reduction in endometrial height from 4 mm at 3.5 h to 1.25 mm at 13 h. One uterus which featured accelerated reduction in endometrial height to 1.25 mm by 5.5 h was from a woman who reported heavy blood loss occurring in the first hours of menstruation [101]. Blood extravasation and leucocyte infiltration were absent in uteri obtained 20, 24 and 72 h after the onset of bleeding. The endometrial surface at the time of menstruation appeared pale and rough, with shedding of the functionalis. Most vessels were constricted. Platelet and fibrin were observed in the functionalis layer, and these developed and shed in the early phase of bleeding. The haemostatic plug was scanty at 5.5 and 13 h and was absent beyond that time [101]. Christiaens et al. believed that vasoconstriction rather than thrombosis played a role in the control of bleeding [102].

It is notable that earlier research has established that a sizable proportion of ‘menstrual’ cycles is anovulatory. The recognition that menstrual bleeding can occur in the absence of endometrial features of ovulation dates to the early work by Rock and Bartlett [103]. Our understanding of the impact of this on the mechanism of menstruation remains limited.

The widely held view is that the whole functional layer is shed at menstruation and that regeneration occurs from the basalis. However, the amount of endometrial shedding varies and is usually confined to the more superficial compacta and part of the spongiosa. In a small number of cases, this can extend almost to the muscularis [104]. McLennan and Rydell reported that an appreciable fraction of the spongiosa is retained, and that regeneration observed in day 4 occurs from the basalis and from secretory glands [19]. The new surface seen on day 5 is quite irregular as mounds of unshed spongiosa become covered by epithelium [19]. Flowers and Wilborn observed that most glandular areas
appear relatively unaffected by the events of menstruation and remain sufficiently viable to participate in regeneration and reorganisation of the endometrium. This suggested that regression rather than cell death is the chief event of menstruation [105]. Electron microscopy studies concluded that the only cells that die or become detached from the endometrium originate from the compact and upper spongy layers [105]. Also, secretory changes were observed in the base of endometrial glands, which challenges the classic notion of a basalis layer devoid of function [104]. Differences observed histologically in secretory features may be related to different vascular supply, or to differences in stromal collagen content [104].

Desquamation, which is almost complete by 60 h after the onset of bleeding, coexists with re-epithelialisation which appears after 36 h [104]. Dallenbach-Hellweg pointed out that the sequence of changes responsible for endometrial shedding and regeneration occasionally fails to develop uniformly and suggested that disturbance in the fall of oestrogen and progesterone can result in endometrial shedding being incomplete or prolonged and that re-epithelialisation is accelerated in situations of increased early oestrogen production [22]. Thus, irregular shedding can be brought about by a failure of regression of the corpus luteum, resulting in untimely or delayed onset of bleeding and in bleeding that may be prolonged or excessive. Weber suggested that irregular shedding may be prevented by administering oestrogen 2 days before the onset of menstruation [106]. Irregular shedding may be an isolated or a recurrent feature. In case of irregular shedding, the endometrium features various stages of regression and dissociation starting several days after the onset of bleeding. The most characteristic sign is the narrow star-shaped appearance of the glandular lumina. There is dissociation between the glandular epithelium and stromal compartments, and the cytoplasm of many glandular cells is clear and contains abundant glycogen. This contrasts with the surrounding small stromal cells that have scanty dark cytoplasm and suggests that the sequence in the protracted involution starts with stromal cells, then proceeds with glandular epithelial cells, and finally with blood vessels [22].

In most women taking cyclical combined HRT that comprised 10 or 12 days of progestogen, bleeding occurred on day 13 of commencing progestogen therapy [107]. However, only 59% had cycles that varied by ≤3 days, which suggests that in many participants, bleeding commenced during the days of progestogen administration. Habiba et al. reported that in women on cyclical combined HRT containing 12 days of progestogen bleeding commenced before day 29 in 36% of recorded cycles. The mean cycle length for women who bled before day 29 was 27 ± 2.3 days (early bleeders), and for those who bled on or after day 29 it was 30.4 ± 1.3 days (late bleeders). Early onset of bleeding occurred in women prior to progestogen withdrawal and may be related to inadequate estrogenic priming [34].

6.3. Triggering the Onset of Bleeding

Factors that affect the events responsible for timely endometrial breakdown and its consistency remain poorly understood. The corpus luteum is a temporary endocrine organ critical to secretory transformation and to the onset of bleeding. Premature regression of the glands can result in infertility and early onset of bleeding. Similar to the ovarian follicle from which it originates, the human corpus luteum retains the capacity of producing oestrogens, while at the same time acquiring the ability to produce progesterone. Oestrogens (mostly oestradiol) are synthesised in the large luteal cells. Interestingly, it seems that FSH stimulates oestradiol synthesis in ovarian granulosa cells, but not in luteal cells [108]. The action of FSH is subserved by LH and IGF-1 [97,109,110].

The onset of bleeding in natural cycles has traditionally been linked to the drop in circulating steroid levels following the demise of the corpus luteum. Thus, the endocrine function and the timeline of the demise of the corpus luteum are critical to the breakdown of the endometrium. The traditional view based on histological studies is that 3 to 11 antral follicles are recruited in the late luteal phase and that a dominant follicle emerges from this cohort in the follicular phase. The dominant follicle is destined to ovulate leading to the formation of the corpus luteum which was believed to have a uniform lifespan [111].
However, the wide variability in the duration of the postovulatory phase of the cycle casts doubt on the traditionally held view that luteolysis and the demise of the corpus luteum occurs fairly constantly, beginning at about day 10 post ovulation.

More recent studies demonstrated that antral follicle development during the menstrual cycle occurs in multiple waves [112,113]. Around two thirds of women have two follicle waves during the inter-ovulatory interval and the remainder have three waves. Major waves feature a dominant follicle, and this may regress or ovulate [111,113]. Changes in antral follicle dynamics are associated with changes in hormone production [114]. The development of luteal phase dominant follicle (LPDF) in women of mid-reproductive age is associated with an increase in luteal phase inhibin B and oestradiol, but no change in LH, FSH, inhibin A, or progesterone. There is greater variability in LPDF dynamics in older women who have more atypical LPDFs linked to higher luteal-phase oestradiol and lower progesterone [114]. Persistent LPDFs can produce atypically high levels of oestrogen and suppress progesterone. The development of atypical LPDFs may be responsible for out-of-phase luteal cycles (LOOP), which are more common in older women. Follicular-phase oestradiol seems to increase during the transition to menopause [115]. LOOP events occur in approximately 40% of late reproductive-age women. These feature a rise in midluteal-phase oestradiol, which continues into the early follicular phase of subsequent cycle. This rise may be due to a major wave of antral follicle development [116]. A LPDF may undergo spontaneous ovulation with the associated rise in LH and progesterone [117,118]. Antral waves may be preceded by a rise in FSH [111]. Serum oestradiol concentrations during the luteal phase may derive, in part, from luteal-phase follicle waves rather than exclusively from luteal tissue [119].

The rate of luteolysis may affect endometrial breakdown and the hormone levels linked to the complex follicular, and luteal development necessarily impacts the endometrium, but the full effect of this on endometrial maturation and breakdown and on the duration of bleeding remains to be elucidated. A recent study suggested the possibility that urinary steroid metabolites can substitute for serum test [120]. This opens a new prospect for future research.

6.4. The Lifespan of the Corpus Luteum

There is considerable controversy about the diagnostic features and the significance of a short luteal phase and of luteal phase defect (LPD). Shortened luteal phase leads to early onset of bleeding. Lenton et al. reported that the luteal phase was ≤11 days in 8.2% of cycles (luteal phase length 7–18 days). They regarded all cycles with a luteal phase of <9 days and 74%, 22% and 2%, respectively, of cycles with luteal phases of 10, 11 and 12 days as abnormal [61]. In another study, luteal length ranged from 5 to 20 days, and this was divided into short, 5–11; normal, 12–15; and long, 16–20 luteal phases [121].

Little information is available on the impact of short luteal phase on the duration of blood loss. Schliep et al. reported that the duration of bleeding for cycles (n = 41) that were preceded by a short luteal phase (<10 days) was 7.0 ± 2.0 days and for cycles (n = 422) that were preceded by a normal luteal phase (≥10 days) it was 7.0 ± 2.3 days [111], although the amount of blood loss was reduced in short luteal phase cycles. Only 20 of the 41 cycles that featured a short luteal phase (clinical LPD) also had low peak progesterone (biochemical LPD). These differences indicated that clinical and biochemical LPD may reflect different underlying mechanisms [122].

It is possible that an inadequate corpus luteum function or its premature demise result in early or disorganised endometrial shedding. Luteolysis in a non-fertile cycle entails decrease in progesterone production. Determinants of luteal regression are incompletely understood but may reside in factors downstream of the LH receptor [123]. Primate studies have shown that luteal regression is caused by a large reduction in the responsiveness of the ageing corpus luteum to LH. Prolonging the lifespan of the corpus luteum requires an exponentially increasing level of LH [124]. Corpus luteum regression involves reduction in expression of the StAR (steroidogenic acute regulatory protein) gene; the protein
encoded by this gene enhances the conversion of cholesterol into pregnenolone. It also requires the action of prostaglandin PGF2α, TNF-α, interleukin-1β, endothelin, monocyte chemoattractant-1, oestrogens, and reactive oxygen species [125]. Regression of the corpus luteum involves apoptosis and possibly autophagy and necrosis [126]. Unscheduled activation of these mechanisms may contribute to alterations of the life span of the corpus luteum.

Oestradiol is produced in high levels by the corpus luteum which also expresses cytochrome P450 and catechol-O-methyl-transferase that can catabolise oestradiol. Proangiogenic oestrogen metabolites 4-hydroxyestrone and 2-hydroxyestradiol and the antiangiogenic metabolites 2-methoxyestradiol and 2-methoxyestrone have been shown to have a role in the corpus luteum regression [127]. Progesterone synthesis in the corpus luteum requires the establishment of an adequate vascular supply that enables the delivery of cholesterol from low-density lipoprotein and the passage of cholesterol from the outer to the inner mitochondrial membrane. The latter process is StAR-dependent. The action of progesterone on the endometrium may also be dependent on adequate, in-phase oestrogen stimulation [128].

In non-pharmacologically induced cycles, Jones hypothesised that delayed endometrial maturation secondary to an inadequate corpus luteum might result in infertility [129]. Estimates of the incidence of LPD vary from 5 to 10% in infertile women [130]. Whether it is possible to discriminate fertile from infertile women based on endometrial histology is debatable [131,132]. LH-dated biopsies from normal fertile women exhibited considerable inter-subject variability in histological features during the mid- and late-luteal phases of the menstrual cycle. Repeat biopsies from the same women also showed intra-individual variability that may be as wide as 2 days in up to a third of cases [132].

Histologically, out-of-phase endometrium has been documented in many studies of fertile and infertile women [131–135]. Endometrial receptivity arrays aimed at better detecting the implantation window in the developing endometrium have not improved implantation rates [136–138]. This suggests heterogeneity of endometrial development or response. The addition of immunohistological parameters of cell proliferation and of oestrogen and progesterone receptors to histological dating improved assessment of endometrial maturation but did not eliminate variability [139]. In a model designed to mimic LPD, endometrial maturation, as assessed by histology and immunohistochemical markers of receptivity, did not reflect circulating progesterone levels [140]. However, the study also suggested that the lack of detectable differences may be related to the insensitivity of these techniques and that differences might be detectable using more sensitive methods [140]. This raises important questions about the optimal method for assessing endometrial maturation in the late secretory phase and of the factors affecting endometrial maturation and subsequent breakdown.

Circulating oestradiol and its metabolites seem to vary during the cycle and between individuals. This may be related to genetic polymorphism in the metabolic enzymes involved and in polymorphisms related to encoding oestrogen receptors [141]. Endometrial gene expression during the implantation window is different in obese compared to non-obese infertile women receiving standardised oestrogen and progesterone replacement cycles [142]. This may reflect the impact of metabolic dysfunction on the endometrium. How this might affect endometrial bleeding remains speculative, but evidence from the use of HRT demonstrates that bleeding can commence prior to discontinuation of steroids and suggests a possible link between increased oestrogen catabolism and early onset of bleeding [34].

Noyes’ criteria continue to be used as the gold standard for histological dating despite the recognised range of variability and desynchrony [143]. It is noteworthy that Noyes’ criteria were derived from a study of infertile women with reference to the expected onset of the subsequent cycle and before tests for ovulation became available. There remains a need to better characterise endometrial features that are relevant to latter-stage development
leading to the onset of bleeding and to further our understanding of the factors responsible for the recognised variations in histological features.

6.5. Factors That Affect Cessation of Bleeding

As mentioned above, endometrial repair commences 36 h after the onset of bleeding, but the completion of this process may be affected by the amount and duration of desquamation. The repair process features re-epithelialization of the luminal epithelium followed by stromal expansion [85,144,145]. Studies in Rhesus monkey demonstrated that the postovulatory inhibition of epithelial and stromal mitosis is zonal as it affects the functionalis and the upper basalis. In contrast, epithelial proliferation increases steadily in deep basalis epithelium and remains steady in the stroma [146].

There is some controversy over the extent of desquamation at menstruation. The classic view that all the functionalis is shed [94,147] was disputed in several studies which suggested that the loss of mucosa is less extensive, with regeneration occurring from the spongiosa [19]. However, Ferenczy suggested that incomplete separation of the spongiosa is linked to prolonged bleeding as may be the case in anovulatory bleeding [148]. It has also been proposed that endometrial stroma has a role in endometrial epithelialisation after desquamation through a process of metaplasia [149].

Nogales-Ortiz and Nogales demonstrated glandular secretory changes that extend to the base of the glands during the late secretory phase of the cycle [150]. Thus, the functional distinction between these segments is not clearly delineated. As such, the basalis may only be the un-desquamated mucosa. It was demonstrated that ‘necrosis’ predominantly affects the compact portion of the functionalis and the subjacent spongiosa [104]. But the quantity of desquamation varied between uteri and between regions in the same uterus. Evidence of regeneration was observed as early as 28 h after the onset of menstruation in samples obtained through curettage and at 36 h in hysterectomy specimens. Regeneration starts from the edge of gland stumps and initially cells contain vacuoles filled with glycogen. Nogales et al. reported that maximum regeneration activity takes place 50–60 h after the onset of bleeding [150]. Epithelialisation is complete by 140 h [104]. Ferenczy concluded that endometrial repair lasts about 48 h from about day 2–3 to about day 4–5 and demonstrated the formation of superficial epithelium either from the exposed ends of basal glands or, less significantly, from persistent epithelium in the lower uterine segment or the cornual regions. Regeneration is accompanied by nuclear DNA synthesis [151]. The newly formed epithelial cells are flat or spindle-shaped and resemble fibroblasts, but are in direct contact with preserved epithelium. Luminal cells have a basement membrane and intercellular desmosomes suggestive of epithelial nature [152]. Post-menstrual regeneration is closely related to the underlying stromal fibroblasts that form a compact scaffold for the growing epithelium. Stromal cells may also have a role in regulating the growth through factors, such as the epithelial growth factor (EGF), or contribute to tenascin production. Re-epithelialisation occurs in the relatively oestrogen-deficient early proliferative phase and may be a response to injury rather than to hormonal stimulation. Epithelial proliferation occurs from cycle day 5, when there is a sudden increase in nuclear DNA synthesis and cell division that accompanies rising plasma oestrogen and endometrial oestrogen receptor concentration.

Views also differ on the extent of vascular contraction as a mechanism of bleeding control. Endometrial proliferation may have a role in occluding vascular lumina. This has been linked to the action of relaxin [153]. A lack of relaxin may result in prolonged shedding. A relevant observation is the lack of mitosis and ciliogenesis in the process of healing, which Ferenczy interpreted as an indication that the process is independent of oestrogenic simulation [151]. Garry et al. studied the endometrial shedding on hysteroscopy and using electron microscopy in a group of women scheduled for hysterectomy or for curettage [154]. The authors described piecemeal shedding and observed that the exposed basalis becomes rapidly covered with a fibrinous mesh that forms the base for surface epithelial growth. In their study, the new epithelial cells appeared to arise from the underlying stromal
cells rather than from residual gland stumps. This, however, raises questions about how stromal cells migrate across the fibrinoid layer, the possibility of experimental artifacts and whether differences exist that relate to the underlying disease conditions. It remains possible that stromal cells [155,156] and/or circulating progenitor cells [157] are involved in the mechanism of endometrial repair. On the other hand, others have argued against stromal fibroblasts as a source of surface epithelium [152]. Interestingly, a higher dose of the oestrogen and progesterone combination does not result in more rapid cessation of bleeding following acute onset of HMB in adolescents [158].

7. Conclusions

Women often raise questions about the duration of menstrual blood flow. However, the significance of a change from previous patterns, very short or prolonged bleeding, days of light loss or spotting before or after days of bleeding, or of bleed-free days that punctuates flow are poorly understood. Little research has been directed to understanding the duration of bleeding, and what is available reported on population averages which mask inter- and intra-individual variations. The duration of bleeding is not necessarily linked to the amount of blood loss. A number of features such as age, ethnicity, habitus, region, and altitude of residence, dieting and stress may influence the duration of bleeding. The trigger of the onset of bleeding has been linked to declining corpus luteal steroid production. There is controversy around the amount of endometrial shedding at menstruation and on the mechanisms involved in repair. This is likely to vary within and between women, but the factors that control the process of shedding and subsequent repair require further investigation.

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