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Gynaecology problems in puberty

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With the onset of puberty a range of problems may be encountered by the young girl. Some of these include a range of gynaecological issues relating to delayed onset of puberty, delayed menarche, atypical pubertal changes and the identification of anomalies of the genital tract. The distinction between physiological events and pathological problems is important to avoid unnecessary distress and anxiety. The onset of cyclic hormonal changes also provokes a number of "non-gynaecological" problems – where the link to cyclic hormonal events is often overlooked and an important opportunity to potentially intervene and assist is missed. From a global perspective there are a range of problems that are particularly encountered with the onset of puberty including the risks of sexual violence, which in the setting of having achieved the age of reproductive potential result in unplanned pregnancies, unsafe abortions and adolescent pregnancy all of which pose life threatening risks. Sex education in its broadest sense is important for all young people. Access to contraception for adolescents is vital, such that clinicians across all streams of health care who are involved in the care of young people should take the opportunity to educate and provide this care.

Global perspective

For girls, the transition from childhood through puberty into reproductive years raises serious health issues. From a world view, sexual violence, lack of education, poor or no access to contraception,

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unsafe abortions are all critical factors impacting on the health of teenage girls. WHO data from 15 sites across 10 countries identified that 10–20% of women (in the setting of anonymous reporting) had experienced sexual abuse before the age of 15. Although sexual abuse and sexual violence may occur before puberty, the development of pubertal changes and menarche, marks the beginning of significant further risks to the reproductive and sexual life for girls in many parts of the world. Every year approximately 2.5 million girls under 16 years of age give birth in developing regions [1,2]. Complications relating to pregnancy and childbirth are the leading cause of death for 15–19 year old girls globally [3]. Unsafe abortions are undertaken in about 3.9 million girls aged 15–19 years every year [4]. With the onset of puberty, this places many of girls at risk of unplanned pregnancies, teenage pregnancies and unsafe abortions. First sexual experience was forced in up to 45% of girls when this occurred less than 15 years. Lack of education, lack of access to contraception, early age of marriage, are all critical factors in contributing to maternal mortality particularly amongst teenagers.

Early puberty

Precocious puberty – defined as the onset of menarche prior to 8 years old, is discussed in a separate chapter. One aspect of early puberty and menarche that should not be overlooked is the impact of the early physical maturation on behaviour. The young adolescent with early pubertal changes, when compared to her peers, is at higher risk of sexual behaviour that places her at additional health risks [5,6]. This includes sexual intercourse, unprotected sex and pregnancy. Awareness of this increased risk needs to be part of the consultation, with specific discussion to encompass comprehensive sexual education including contraception when caring for the girl with early or precocious puberty.

Primary amenorrhoea

The first distinction that needs to be made is between the girl who has no secondary sexual development and the girl with secondary sexual characteristics but no menses.

No secondary sexual characteristics

Delayed onset of secondary sexual characteristics is generally defined as the absence of pubertal changes by the age of 13 as 95% of girl will develop secondary sexual characteristics between 8.5 and 13 years [7].

It is recognised that genetic factors have a substantial impact, but it must be noted that there has been a trend towards earlier puberty which does appear to have plateaued, with menarche now occurring at between 12 and 13 years, whereas it was well documented to occur in Scandinavia at 17.5 in 1850 [8].

The critical information required is whether gonadal function has failed (that is primary hypogonadism) demonstrated by the presence of an elevated FSH, or whether this is secondary hypogonadism. Individual factors including poor nutrition, underweight (and eating disorders), obesity, level of physical activity and altitude are all factors that have an impact on onset of puberty and secondary hypogonadism. Many of these should be apparent by acknowledging locality or become apparent on history and clinical examination. In these cases FSH is not elevated and other investigations such as prolactin, thyroid function may assist in excluding other potential factors.

In the absence of oestrogen stimulation, the uterus can be a very small structure, and care interpreting imaging reports (both ultrasound and MRI) regarding an absent or rudimentary uterus is very important.

Where primary hypogonadism is diagnosed, the negative impact of learning about infertility due to gonadal insufficiency (whether due to Turner syndrome (TS), or Premature ovarian insufficiency (POI)), can impact on self esteem. Adding to this the potential additional challenges associated with short stature (in the setting of TS or Turner mosaic) may have a negative impact on body image and thus relationships. Choice of language with regards to future capacity to carry a pregnancy is necessary, as those with gonadal failure (POI) can clearly carry a pregnancy with assisted reproductive technologies using a donor egg – presuming the culture and national policies allow this. Carrying a pregnancy in the

setting of TS does carry increased risks of pregnancy complications, although the reported increased risk of aortic dissection risks is not as high as originally reported [9–11].

Women with hypothalamic hypogonadism have a good response to stimulation. For women with delayed puberty due to Anorexia nervosa (AN), their ongoing borderline weight tends to continue to impact on their likelihood to conceive.

Support groups for young women with these conditions will often offer positive benefits.

Primary amenorrhoea in the setting of breast development occurring but no menses

This can be clinically be divided into those with typical progression of secondary sexual characteristics and those with atypical features.

Those with typical progression of pubertal changes, with pubic and axillary hair, breast development but no menses within 4 years of the onset of these changes require careful clinical consideration.

A. The explanation may be some of the causes discussed in the previous section – with increased physical activity, onset of an eating disorder or combination of these in the form of an eating disorder not otherwise specified, or the onset of gonadal failure (in someone with POI or TS).
B. The development of cyclic abdominal, pelvic or low back pain, or pelvic mass with pressure impacting on urinary or bowel function, may lead to the identification of an obstructive anomaly in the form of an imperforate hymen, a transverse vaginal septum or segmental atresia of the vagina or an obstructive cervical anomaly.
   i) Although many young women with an imperforate hymen will present with cyclic pain, a substantial number will present with a range of other symptoms including urinary frequency, acute urinary retention, or low back pain, with many having several presentations to emergency departments with pain and given a diagnosis of “constipation”, before the diagnosis is made. Although imaging is frequently done (ultrasound), clinical examination of the genital area whilst applying gentle suprapubic pressure will allow identification of a bulging hymen (and hence the diagnosis of an imperforate hymen) and no further investigation is required.
   ii) The absence of a bulging hymen makes further investigation essential. The diagnosis may be a transverse vaginal septum or segmental vaginal atresia – which may mean there is several centimetres of absent vagina; alternatively there may be an absent or dysplastic cervix with or without a vagina. Surgery to correct some of the less common anomalies can be complex and requires specialised expertise. The correction of some anomalies may require the use of post-operative dilators, which may not be appropriate for a young adolescent who is still often very inhibited and shy about her genital area.It is almost always possible to delay surgery with menstrual suppression whilst seeking further advice or waiting for maturation of the young woman, using a combination of hormonal approaches and tranexamic acid to reduce bleeding (which can be presumed to be occurring when there is increased pain and a known haematocolpos or haematometra). The use of a GnRH analogue is another option to achieve suppression of menses during this time. The major area of change in management of complex anomalies includes the approach of undertaking a utero vaginal or utero vestibular anastomosis [12–14] rather than removing an obstructed uterine horn without a cervix. Pregnancies have been reported in young women who have had this procedure, so guarded optimism and conservation of the uterus is now appropriate.
C. Young women who have progressed through typical pubertal changes and not achieved menarche within 4 years, in the **absence of pain** will typically have utero-vaginal agenesis (MRKH). This occurs in 1 in 4000–5000 women. For 30% of these women there is an associated renal tract anomaly. For 10% their vaginal agenesis is part of a syndromic problem – with limb asymmetry, spinal anomalies or cardiac problems (MURCS association, Klippel Feil syndrome, VACTERL anomaly, Holt-Oram syndrome) [15].

The majority of young women with utero-vaginal agenesis will successfully create their own vagina with the use of dilators or sexual activity. There are a range of surgical approaches, although there is a

paucity of randomised studies comparing techniques and outcomes [16–18]. Support group and counselling remains important for the long term wellbeing of these women. In countries where surrogacy is permitted, this allows these women to have their own genetic offspring. Uterine transplant has now successfully been undertaken a number of times and may be an alternative option for some women [19].

Atypical progression through puberty

Of adolescents who have begun their pubertal changes but have followed atypical progression through puberty, there is the option that they may have evidence of virilisation, in the form of excess hair growth, deepening voice or clitoromegaly. These features suggest the possibility of an androgen producing tumour, late onset adrenal hyperplasia (CAH) (also known as non-classical CAH) or another less common difference of sex development. In the setting of absent or minimal pubic and axillary hair, the diagnosis of androgen insensitivity needs consideration.

Menstrual problems

Bleeding pattern – physiological and pathological

Irregular bleeding

With the onset of menses, the menstrual cycle is usually anovulatory, although interestingly periods that begin younger often become ovulatory sooner than menses that start at 15 or 16, when they may take 3–5 years to become ovulatory [20].

The definition of normal cycle length has changed so that menstrual duration has now been changed to normal of 1–8 days, or prolonged [21]. The recent international evidence based guidelines for PCOS recommend that the definition of irregular menstrual cycles in the interval between 1 and <3 years post menarche is <21 and >45 days, and for those who are beyond 3 years post menarche the interval narrows to <21 and >35 days or 8 cycles per year [22]. There is a little discrepancy here, given the data that suggests that those starting menarche late may be allowed a little more lee-way. Cycle regularity is accepted as regular if the variation from shortest to longest is ≤9 days, and irregular if the interval shortest to longest in the 18–25 year old age group is >10 days – again – remembering that this applies to a slightly older age group is important. Heavy is a term that applies to patient perception, where the heavy menstrual loss impacts on quality of life and wellbeing [23].

Management: Intervention for irregular bleeding can be considered if the irregular bleeding pattern is a problem that is negatively impacting on health and quality of life although stressing that the intervention is for this reason, and not required per se. More often, intervention is done for prolonged bleeding, in which case the use of progestogens (either in the form of norethisterone actetate, which is also known as norethindrone 5–10 mg, or provera 10–20 mg daily) can be used to stop the bleeding. As bleeding is likely to recommence on ceasing this, it is wiser to continue its use for 2–4 weeks. There are range of patterns for progestagens use, but in someone with infrequent cycles, then using 14 days of either norethisterone acetate 5 mg or provera 10 mg every second month, may be adequate. For someone with polymenorrhoea, then using 21 days (or more) with a 7 day break may be more appropriate. Alternatively using a low dose combined oral contraceptive pill may be simpler (and cheaper).

Heavy menstrual bleeding

Of adolescents with **heavy menstrual bleeding**, the reported rate of mild bleeding disorders, most frequently von Willebrand's disease or platelet dysfunction, is 10+% [24], although of girls admitted with heavy menstrual bleeding only half will have a bleeding disorder and the remainder will have excessive, anovulatory bleeding.

Abnormal uterine bleeding

The terminology around abnormal uterine bleeding (AUB) has also been updated, away from the all encompassing but unhelpful expression of dysfunctional uterine bleeding (DUB). The new

classification of **PALM COEIN** [25] – includes a number of condition not relevant in adolescents, but nevertheless this new structure offers advantages in terms of classification.

The first cluster – PALM – refers to structural abnormalities. (Polyps, adenomyosis, leiomyomas and malignancy/hyperplasia). **Polyps** and **leiomyoma**s are both very uncommon in adolescents, although malignancies such as rhabdomyosarcomas, which are even rarer, do need to be considered if lesions are identified and are increasing in size then biopsy and appropriate management is necessary. **Adenomyosis** has now being described in adolescents [26,27], usually in the setting of significant dysmenorrhoea rather than abnormal bleeding, with the use of imaging identifying the asymmetrical thickening of uterine walls and venetian blind appearance [28]. With the advances in imaging – both ultrasound or MRI and its application in new settings, it is likely that adenomyosis will be identified more often.

Management of adenomyosis. In adolescents, reports have also described resolution of the dysmenorrhoea as well as the findings with suppression using either the oral contraceptive pill (OCP), Progestogen bearing intra-uterine system (Mirena IUS) or gonadotropic releasing hormone agonist (GnRHa) [29,30].

Thickened endometrium, which in older women would be associated with concerns of endometrial **hyperplasia** and potentially a pre-malignant change, do not warrant the same response in perimenarchal girls. The thickened endometrium is usually identified in the context of early gynaecological age (ie within the first years post menarche) with anovulatory cycles, and a presentation of prolonged irregular bleeding. Resolution is usually spontaneous with onset of ovulatory cycles, but management of adolescents with symptoms and an ultrasound finding of thickened endometrium can be achieved over several months of progestogens or progestogens and oestrogens in the form of the OCP – which are used to manage the heavy irregular bleeding rather than specifically targeted to altering the endometrial thickening as identified by imaging. Endometrial sampling or curettage is not required if detected in the first few years post menarche.

COEIN refers to non-structural causes for abnormal uterine bleeding (AUB), and encompasses coagulation problems, ovulation, endometrial, iatrogenic and Not otherwise classified [21], some of which have already been mentioned.

With regards to **coagulopathies, AUB-C,** low rates of recognition of bleeding disorders amongst adolescents with heavy menses remains a problem, with many young women never having their bleeding disorder identified [31]. This is apparent when it is recognised that many women do not have their problem identified until adulthood, with already a lengthy history and reduced quality of life [32]. This is not an issue if their menstrual problems – of heavy loss and often ovulation related pain, premenstrual spotting, post coital bleeding are managed, but for many the symptoms are ignored or inadequately managed, having a significant impact on their quality of life, causing iron deficiency anaemia and increasing their risk for endometriosis [33]. Although taking a menstrual history and assessing blood loss in a young teenager can be challenging [34], identification of the young women who require pad or tampon changes more often than 2 hourly, or require pad changes over night are features that should provoke further screening questions, in an attempt to identify a bleeding diathesis. A readily available online, standardised validated questionnaire to screen for a bleeding disorder exists [35].

Management: Heavy menstrual bleeding can be managed with measures such as the use of tranexamic acid (where there is no thrombosis actually present), even in those on anticoagulants. The use of combined oral contraceptive pills (COCP) (continuously, skipping all periods as there is no evidence that withdrawal bleeds are required), continuous progestogens (norethisterone acetate, medroxy progesterone acetate (Provera), or the levonorgestrel (LNG) IUS are all options. It needs to be remembered that the LNG IUS does not impact on ovarian function, hence those with bleeding diathesis may require ovarian suppression with COCP, or continuous progestogens (oral or implantable), potentially combined with LNG IUS.

For **young women with special needs**, the occurrence of bleeding may have a negative impact on quality of life even when the bleeding is not particularly heavy [36]. As the definitions and managements are directed to the impact on the individual, the same approaches to minimise the negative impact of menses apply, such that the use of continuous OCP, or continuous progestogens may be appropriate [37], although noting the concerns that long term DMPA may have on bone health,

particularly in the setting of an adolescent who may have reduced mobility or be wheelchair dependent or have additional risk factors for osteoporosis due to anticonvulsant use or limited sunlight exposure and Vitamin D deficiency. Thus, monitoring of bone density and potentially using add back oestrogen may be required. The LNG IUS is often a good option, as the scant brown spotting often experienced may not be of any concern for someone with a disability who is otherwise in nappies (diapers) due to failure to achieve bladder or bowel training [38].

Ovulatory disorders (AUB-O). Ovulatory disorders (AUB-O) are a frequent cause for 'abnormal menstrual bleeding' in adolescents-to the extent that they should be considered as normal events in this age group. The onset of ovulatory bleeds can be 1–4 years post menarche, with early onset of menses associated with earlier onset of ovulatory cycles [20]. Nevertheless, other contributors such as thyroid disease, obesity, anorexia, weight loss, mental stress, and extreme exercise need to be considered – but often detectable on history and clinical examination (see above in irregular menses, for management).

Endometrial factors (AUB-E). When ovulatory and coagulation factors have been considered and excluded, then abnormal uterine bleeding may relate to endometrial factors [39]. Although these have been characterised, with a range of quality studies demonstrating deficiencies in the local production of vasoconstrictors such as endothelin-1 [40] and prostaglandin $F_{2\alpha}$ [41,42], or increased clot breakdown secondary to increased production of plasminogen activator [43] or local substances that produce vasodilatation such as prostaglandin E_2 and prostacyclin [41,44].

Iatrogenic (AUB-I). Medications may also contribute to anovulation via interference with prolactin, or contribute to weight gain and hence anovulation. Medications influencing the coagulation pathways to prevent or treat venous thrombotic events can provoke heavy menstrual bleeding but also increased intermenstrual bleeding. Medications that alter circulating hormone levels by altering absorption (antibiotics such as rifampicin and griseofulvin [45]) or re-absorption, or metabolism (by altering liver metabolism, such as valproate). Likewise, medications specifically designed to interfere with ovulation such as contraceptives including progestogen only, either orally, implant or injectable, or combined oestrogen–progestogens pills or patches may in themselves cause irregular bleeding. Unscheduled bleeding on the OCP is termed "breakthrough bleeding". Intrauterine devices, both hormonal and non hormonal, are also associated with altered bleeding patterns and hence are "iatrogenic" causes for AUB [46].

Not otherwise classified (AUB-N) includes some rare conditions including vascular malformation, but also includes potential new unclassified or unidentified causes.

Dysmenorrhoea and associated symptoms

Physiology of menstruation

To understand the problems associated with menstruation, it is first important to understand the physiology of menstruation. Menstruation is largely an inflammatory process involving 2 basic functions of tissue destruction and vasoactivity. Tissue destruction includes the action of matrix metalloproteinases (MMPs) as enzymes to degrade the extracellular matrix between the endometrium, basal laminar and blood vessels and is released from endometrial cells and activated leukocytes. Tissue destruction is aided by migration of lympho-myeloid cells into the endometrium and activation of the mast cells. Vasoactivity is achieved through endothelin and nitrous oxide, prostaglandins, inflammatory cytokines such as TNF-α, chemokines including IL-1β, CXCL8 and endothelin as well as bradykinin [47]. The process of menstruation involves the destruction of 4–6 mm of endometrium with associated bleeding. Many of the symptoms documented to be associated with menstruation, including nausea, vomiting, diarrhoea, headaches, generalised aches and fatigue [48] can be readily explained by prostaglandins and these inflammatory substances.

Prevalence, risk factors for and impact of dysmenorrhoea

The rate of reported period pain varies around the world but has been reported as high as affecting 94% of teenagers [49], although most studies give figures between 30 and 80% [50–55]with higher

rates generally reported in girls and young women. The rate of severe dysmenorrhoea also varies between 0.9% in Korea [49] to 30% [56]. There is evidence that suggests that family history of period pain is a risk factor, as is distress and post traumatic stress disorder, as demonstrated in a post tsunami study in Japan [57]. Whilst many girls experience dysmenorrhoea, only a limited number seek assistance and often those that do have had their symptoms normalised, resulting in girls reporting school absenteeism and an inability to participate in social and physical activities [56].

In some parts of the world there is considerable emphasis placed on the possibility that period pain may reflect endometriosis. The studies regarding the laparoscopic finding of endometriosis in adolescents with pain despite the use of non-steroidal anti-inflammatory agents and the oral contraceptive pill, report rates of 38–100% [58–60] with most studies report only mild-minimal disease. Symptoms alone have been shown to be poor predictors of finding endometriosis [61,62]. Furthermore there is only a limited correlation between pain severity and location with severity and pain location and the extent and site of endometriosis thus failing to fulfil the Bradford–Hill criteria of causality of pain [63].

A further challenge in interpreting the reported rate of endometriosis at laparoscopy relates to those studies which have been undertaken in the setting of cyclic use of the OCP, which means that ongoing retrograde menstruation is occurring as well as the cyclic inflammatory process provoking menstruation and the menstrually related symptoms. There is ample evidence that almost all women experience retrograde menstruate, that endometriosis is more prevalent in women with heavy menses [64,65], that there is resolution of moderate to severe endometriosis in adolescents with obstructed Müllerian anomalies following correction of the outlet obstruction [66,67], that endometriosis is not reported in women with uterine agenesis and that there is resolution of recurrent symptoms with the use of continuous OCP [68]. This all supports the concept that in the setting of reduced menses and reduced retrograde loss, endometriosis is less likely. Further to this, the best predictors of further laparoscopy for pelvic and period pain is age at first surgery [69] and severity of pain at first laparoscopy (not the presence of endometriosis) [70].

Hence, management of period pain requires active intervention and not trivialisation of the symptoms. First line management should be nonsteroidal medications preferably commenced prior to the onset of symptoms. It may require efforts to reduce menstrual loss (with the use of tranexamic acid, 1 g QID on days of heavy menses), particularly in those with heavy menses, and in those who experience their worst pain on days of heavy bleeding. Second line management is with cyclic or continuous progestogens or OCP, and then consideration of other methods such as the levonorgestrel intrauterine system which in young adolescents may require a general anaesthetic.

Cyclic "non-gynaecological"events and premenstrual symptoms (PMS)

With the onset of puberty there are a range of problems that exacerbate specifically with the reproductive hormones including symptoms relating to fluid retention causing bloating and headaches. It is likely that it is not only the changing oestrogen and progesterone levels themselves in many cases, but the inflammatory cytokines and prostaglandins released from within the uterus as part of the process of triggering endometrial shedding that drive these effects and symptoms. Once it is acknowledged that the process of menstruation is an inflammatory process that occurs in the setting of falling hormones, then it is easier to understand the range of non-gynaecological problems that can also be present [71].

Gastrointestinal: The prevalence of nausea, vomiting and altered bowel habits both constipation and diarrhoea, with menses is well documented [48]. In the setting of other gastrointestinal problems such as inflammatory bowel disease and irritable bowel symptoms [72], identification of the menstrual influences can be helpful and provide another avenue of intervention.

Management: Early, prophylactic use of non steroidals (prior to the onset of nausea) can prevent these symptoms. The use of the OCP is another option although in the young woman with nausea, which is exacerbated at the time of menses, this can be more challenging, as intolerance to oestrogens of the OCP may preclude their use in an effort to suppress the menstrual cycle. In these cases, progestogens alone may be helpful, although newer natural oestrogen containing oestrogen–progestogens may also be tolerated.

Cardiovascular symptoms: Dizziness and feeling faint is also reported in a significant number of adolescents in association with their menses [48,73]. Exacerbation of postural orthostatic hypotension also occurs at this time. Both are likely to be related to inflammatory mediators.

Management: Although non steroidals are likely to help, it is often simpler to suppress the cycle, skipping periods and hence avoiding the cyclic release of the inflammatory mediators.

Respiratory symptoms exacerbating either with ovulation or prior to menses are reported in up to 40% of women, particularly in the perimenstrual time [74]. This phase has also been associated with the more severe episodes, including intensive care admissions. Although sex hormones are known to have an effect influencing and modulating the course and incidence of several autoimmune diseases, they also exert their actions directly on immune cells [75]. Nevertheless, it would appear that the role of the inflammatory processes of menstruation and mast cell degranulation at the basal layer of the endometrium, combined with systemic inflammation, in the young woman who already has hyperactive mast cells present in her lung/bronchial tissues is likely to be critical [76].

Sinusitis and epistaxis are also symptoms reported to exacerbate cyclically.

Management: Understanding and recognising the cyclic nature of these symptoms can lead to appropriate adjustment of usual asthma medications, although the option of cycle suppression is also useful particularly in those with severe exacerbations.

Dermatological changes occurring with the menstrual cycle include exacerbations of atopic eczema, irritant dermatitis, psoriasis and acne. Increased responsiveness of the skin to skin-prick test reactions has been demonstrated in both atopic and non-atopic women – with increased responsiveness demonstrated midcycle with peak oestrogens [77]. Oestrogens in general increase skin thickness due to increased water content, thus improving barrier function. In general skin conditions tend to be exacerbated at peak progesterone, when it is postulated that there may be reduced immunity and reduced barrier function [78].

Urinary symptoms, in particular bladder pain syndrome/interstitial cystitis, characterised by urinary frequency, urgency and pelvic or bladder pain have been reported to exacerbate with menses [79]. It is unclear whether this is due to retrograde menstruation irritating the bladder peritoneum or the release of inflammatory cytokines activating already hypersensitive pain nerve fibres or a combination of these factors.

Management: The approach to urinary symptoms may include one of several different options or a combination depending on the severity and pattern of symptoms. Hence reducing menstrual loss with the use of tranexamic acid may be helpful, suppressing the menstrual cycle and avoiding menses may be required in others, and the use of pain modulators in the form of low dose amitriptyline 10–20 mg at night can assist in others, particularly if nocturia is a prominent feature.

The effects of menses and mental health: The onset of depression and anxiety has been clearly documented to correlate with the onset of menarche in a large population based study [80], which is apparent even after exclusion of measures of perceived social stress are taken into account. Self-harm has also been demonstrated to be linked to the menstrual cycle [81]. Psychosis occurring cyclically either prior to menarche or shortly after menarche has been reported, as well as occurring at other phases of the reproductive life in women [82,83].

Management: Recognition of these events as menstrually related has led to the successful use of continuous OCP rather than antipsychotic medications [84].

Neurological symptoms: There is good evidence regarding the existence of catamenal seizures (seizures occurring at time of menstruation) and an understanding of the mechanisms, particularly in reference to those seizures occurring at the time of progesterone withdrawal [85]. The fall in progesterone correlates with a fall in allopregnanolone, a potent modulator of the gamma amino-butyric acid receptor [85]. Progesterone has been shown to be effective in women whose seizures are perimenstrual [86,87].

The peak first episode of migraines is between 15 and 19 years in adolescent girls. This combined with the three fold higher rates of migraines in women then men make migraines a significant problem for young women and one that is clearly related to hormones, puberty and menarche [88]. Furthermore, not only do they seem to be related to oestrogens, but menstrual migraines are generally more resistant to therapy, last longer and are associated with more functional disability. Evidence suggests that there may be potential interaction with excitatory circuits including serotonergic components.

Management: The use of oestrogen (either in the form of low dose patches of oestradiol valerate) commencing a day or 2 prior to the menses for 5–7 days can be helpful and can also be used in those using the OCP cyclically and experiencing headaches or migraines at this time, that is coinciding with the oestrogen and progestogen fall.

Sleep disturbance and altered sleep patterns arises in the setting of menstrual pain, irregular menses and heavy menses. This has been particularly documented in a large study on sleep quality in young adolescents where insomnia occurred particularly in those with early menarche [89]. Sleep disturbance in the form of recurrent menstrually related hypersomnia has also been reported [90,91].

Immune function is known to be altered by sex with higher rates of autoimmune conditions in women [92] as well as sex differential immune responses to vaccinations [93].

Anaphylaxis occurring with menses has been reported on a number of occasions [94–96], although interestingly many cases do not begin at menarche. Although systemic mastocytosis needs consideration, there appears to be some evidence to suggest that these cases may reflect a less well defined mast cell disorder some of which may respond to inhaled sodium cromoglycate [97]. Altered immune function undoubtedly explains the occurrence of monthly exacerbations of genital or oral herpes although the mechanism is not clear.

Management: Although intermittent use of antivirals may suffice for those with recurrent herpes, suppression of the cycle is clearly an option with those with serious systemic problems,; and use of antihistamines and other specific mediators may be continue to have a place as complete suppression may be challenging or not well tolerated in some.

Diabetes control and diabetic ketoacidosis (DKA) are associated with menstruation more often than expected than by chance alone [98]. DKA has been also been reported to occur cyclically, that is every 3–5 weeks, premenarchal [99] with the pattern not necessarily being recognised until menarche occurs. The fluctuations in glucose control have been documented through the menstrual cycle [100,101], although the mechanism to explain them has not yet been adequately explored. In particular, an explanation needs to look beyond a correlation between cycle phases and take into account potential factors such as pain and altered food intake, albeit driven through hormonal changes and the inflammatory mediators of menstruation.

Management: Recognition and identification of the problem can lead to appropriate adjustments in dosing in a preventative, prophylactic manner. Additionally the use of non steroidals may be helpful.

Ovarian physiology and pathology

Normal physiology

Normal physiology of the ovary dictates that there are many follicles visible on imaging in each ovary in adolescents. Although the criteria of 12–15 follicles/cysts was a longstanding upper limit of follicle ('cyst') count, this failed to acknowledge or adjust to the substantial changes that occurred in imaging technology over the 30 years from the original study. More recent studies have challenged both the significance of the finding [102], and have also shifted the normal values for follicle counts in young women in their twenties, to 25 follicles [103]. There is still no standardised data on the number in adolescents.

Recognition that ovulation normally requires the maturation of a follicle that will achieve a diameter of at least 3 cm is important, as many adolescents (and their mothers) become distressed regarding the presence of this cyst, with inadequate reassurance from primary care clinicians that this is normal, healthy and physiological. With ovulation and release of the egg, haemorrhage from the highly vascular ovulation cyst surface is not infrequent, with the formation of a haemorrhagic corpus luteum. Expert imaging will assist in the identification of these, and a repeat scan in 3 months to ensure expected resolution of the cyst has occurred.

Added to the information regarding the "normal" number of follicles seen on ultrasound imaging of young women [102,103], is the recommendation in the most recent guidelines regarding PCOS [22] that ultrasound imaging of ovaries should not be used for diagnosing PCOS in girls who are <8 years from time of menarche, due to the high incidence of multi-follicular ovaries in these young women.

Pathological cysts

These are defined by their size (>6 cm), persistence or complexity. The majority of neoplasms seen in childhood and adolescence are benign and consist of ovarian teratomas or dermoid cysts which may have a complex appearance, although usually with recognisable features. The factors associated with an increased risk for malignancy include younger age of 0–8 years (Odds ratio 3.02), imaging information regarding size >8–10 cm, solid; elevated tumour markers βHCG, αfeto-protein (reflecting their germ cell origin), LDH and CA125; symptoms of mass (OR 4.48) and precocious puberty (OR 5.67) [104–106]. In the setting of a adolescent girl with a complex mass, it is worth clarifying if menses have begun, as the adolescent who is prepubertal and with a complex mass, then a FSH is worth adding – as an elevated level would raise concerns of a dysgerminoma in the setting of a 46,XY gonadal dysgenesis.

Ovarian torsion

Admissions for ovarian torsion have been reported to occur at a reasonably stable rate of 4.9 per 100,000 admissions [107]. Despite the rate appearing to be stable over a decade, there has been a substantial change in practice over the same time period, with a marked reduction in oophorectomy rate [107,108]. The symptoms of pain with associated nausea, vomiting and dizziness, and the presence of ovarian asymmetry on ultrasound remain the critical diagnostic clues. The presence of blood flow to an ovary on ultrasound does not preclude the possibility of ovarian torsion.

Repeated studies have demonstrated that the detorted ovary, irrespective of colour, duration of symptoms, size and appearance has a >90% chance of having follicular activity on follow up [109].

Contraception

Access to contraception is highly variable, due to regional cultural views which influence not only availability but also impact on education provided to young people regarding human relationships, sex, pregnancy and contraception. There is ample evidence that countries where no sex education or no sex before marriage approach is taken have higher rates of poor contraception and hence far higher rates of unplanned teenage pregnancies. Education has repeatedly been shown to be critical for delaying age of first sexual contact.

Contraceptive options are often limited by cost and availability.

Increasing evidence supports the use of long acting reversible contraceptives (LARCs) in adolescents, due to their reliability on the one hand and the features of adolescents that makes the use of other forms of contraception unreliable. Expecting a young teenager to be able to negotiate with a partner regarding the use of a condom is not likely to be successful. Adolescents often have unplanned sexual encounters. Likewise the expectation that a teenager will remember to use a progestogen only pill at exactly the same time everyday or take the COCP at much the same time every day is not always realistic. The use of implantable contraceptives such as etonorgestrel (Implanon) which last 3 years, or the use of an intrauterine device which lasts 5 years both offer excellent contraception which is completely safe even in this younger age group.

Two online resources are readily available to guide contraception decisions. The ***WHO Medical Eligibility Criteria for Contraceptive use*** [110] is primarily intended for use in developing countries where pregnancy risks are very high and thus the balance of risks is not the same for all countries and has been adapted for other settings. ***The UK Medical Eligibility Criteria for Contraceptive use (UKMEC)*** [46] is such a set of guidelines adapted by the Faculty of Sexual and Reproductive health for the UK Royal College of Obstetricians and Gynaecologists. Detailed information regarding contraception options is available from these online resources.

Oral contraceptive pills

These require daily usage, which may pose challenges for adolescents. Although there remains significant debate regarding the relative risk of thrombo-embolic events, there is some evidence that suggests that the second generation oral contraceptive pills are probably safer than the newer ones, and in many parts of the world, these may also be cheaper (These are mainly the OCP containing ethinyl oestradiol as oestrogen and either levonorgestrel or norethisterone as their progestogen).

The oestrogens of the OCP can be a source of problems in addition to being responsible for the VTE risk. There is little evidence to distinguish 20 mcg versus 30 or 35 mcg ethinyl oestradiol doses in terms of VTE risk. If one is aiming to correct a menstrual symptom or problem (rather than using the OCP for its contraceptive purposes) then a 30 mcg ethinyl oestradiol pill is preferable to the 20 mcg forms. Migraines can be an additional problem for some, although it must be remembered that some young women experience migraines and headaches with withdrawal of oestrogen, or as part of the inflammatory mediated process that triggers menstruation. The data on migraines with or without aura and stroke risk arises from one poorly designed study. Higher doses of oestrogen (that is, a pill containing 50 mcg of ethinyl oestradiol) are required in those on anticonvulsant medications.

It should be remembered that there are many non-contraceptive benefits of the OCP including an 80% reduction in ovarian cancer, 50% reduction in endometrial cancer, a reduction in bowel cancer [111], as well as reduced risk of fibroids, reduced dysmenorrhoea and endometriosis [68] and hence less school absenteeism, ovarian cysts, reduced blood loss and hence less iron deficiency anaemia. Long term follow up of users of the OCP when it first came on the market in the 1960s have revealed that OCP users have no increased mortality and less malignancies [111–113].

Furthermore, there has been a shift towards the use of the OCP continuously, omitting withdrawal bleeds, as there is no evidence that withdrawal bleeds are required. The beneficial effects of the OCP are achieved by the progestogen causing differentiation of the endometrium, not by the endometrial shedding. Many young women are now "skipping periods" for months and years, obtaining many non-contraceptive benefits.

Progesterone only

Progesterone only pills require reliable timed dosing daily – making them unsuitable for the lifestyle of many adolescents.

Depo medroxy progesterone acetate (DMPA) given 3 monthly does achieve amenorrhoea in many young women after 6–9 months use, but waiting this duration is not always acceptable. Side effects of weight gain are an additional problem, often occurring through increased appetite or decreased mood can be assessed with a 2–4 week trial of oral medroxy progesterone acetate (MPA) 20 mg daily, if immediate contraception is not required or where DMPA is being used for non-contraceptive reasons. Although there is a risk of loss of bone density with prolonged usage, this is not consistent, hence monitoring bone density with the option of adding back oestrogen may have some value but not explored to date in any trial. In those with increased risk factors for bone fragility such as adolescents with severe disability associated with immobility, add back oestrogen is advised.

Etonorgestrel implant

It is an implant placed under the skin, usually on the medial aspect of the upper arm which lasts for 3 years. This provides highly reliable contraception, although reliability may be reduced with anticonvulsants. Only approximately 10% of users are amenorrhoeic and 30% have irregular bleeding with the implant, and hence this is not a particularly good option for those trying to improve menstrual symptoms.

Intrauterine devices

Copper IUDs – often cause heavier and more painful periods, although both of these side effects respond well to nonsteroidal agents. Their duration of action is usually 5 + years. They can be used in nulliparous women.

The uptake of the levonorgestrel intrauterine system (LNG IUS) for use in adolescents has been progressively increasing. The benefits consist of markedly reduced menstrual loss, reduced dysmenorrhoea as well as very reliable contraception lasting 5–6 years, but access partly due to cost, remains an issue in many parts of the world.

Abortion

Unplanned pregnancies and unsafe abortions amongst teenagers remain a major global problem and a major cause for mortality [4]. In many parts of the world safe abortions are not available for any

reason, in some parts restricted for special circumstances and in others more readily available. Medical termination of pregnancy is now an option available in many parts of the world for use in unplanned pregnancies which are intrauterine and of less than 9 weeks gestation, utilising a combination of ulipristal and misoprostil. Surgical termination of pregnancy can be carried out as an outpatient procedure under minimal analgesia and sedation or under general anaesthetic.

Female genital mutilation/cutting (FGM/C)

Female genital mutilation (FGM) is defined and classified by severity by the World Health Organization (2008) as all procedures involving partial or total removal of the external female genitalia or other injury to the female genital organs for non-medical reasons [114]. Around the world there are 130–140 million women and girls who have undergone the procedure [115]. There is some debate and concern regarding the language, with the term female genital cutting (FGC) now being advocated as more respectful to the women who have undergone the procedure [116]. Alternative expressions considered more respectful to families and their communities include traditional female cutting or female circumcision, with the result that the expression FGM/C is now often used.

FGM/C covers a spectrum of procedures, from minor cutting to the clitoral hood (where women may be unaware this had occurred to them in infancy), to more significant procedures where the labia minor and/or majora may be excised and/or sutured together. These procedures are mostly performed without analgesia and in circumstances which may places the girl with significant immediate as well as long-term health risks.

The appearance of the genitals post FGM/C may cause some confusion and clinical concerns to a clinician who is unfamiliar with the appearance. Clarifying if a cutting or circumcision has been performed, or if these procedures were done in the girl/young woman's country of origin, may at least partly resolve concerns regarding the “labial fusion” and hence concerns regarding a possible DSD.

There is considerable debate as to whether the cosmetic procedures to the labia and the genitals undertaken in developed countries (known as labioplasty or female genital cosmetic surgery (FGCS) to encompass all the forms) should also be considered FGM/C as this too is largely culturally driven. Care needs to be taken when commenting on genital appearance, as the failure of clinicians to adequately recognise the diversity of genital appearance contributes to concern and requests for surgery.

Practice points

- The onset of puberty marks a range of physiological changes but for many young women this marks a time of increased risk of sexual violence and unwanted or unplanned sexual activity: education is of importance to prevent the former and contraception is of utmost importance to prevent unplanned pregnancies and the potential consequences.
- Care must be taken to recognise the negative impact on self esteem of having a condition that will make pregnancy or fertility challenging or difficult (eg TS, POI, MRKH).
- Structural abnormalities as a cause for abnormal uterine bleeding are uncommon in adolescents.
- Mild bleeding disorders are present in >10% of adolescent girls with heavy menses.
- Structural anomalies need to be considered in the setting of significant dysmenorrhoea – a careful ultrasound will usually suffice and is usually better than a laparoscopy at identifying these.
- Psychosocial factors need to be considered in dysmenorrhoea, as do structural anomalies. There is little evidence for an early laparoscopy.
- Many symptoms (including symptoms that are considered non-gynaecological) can occur in a cyclic menstrual pattern due to the release of inflammatory mediators that provoke endometrial shedding that provoke these symptoms.
- Suppressing menses is an effective management for heavy and painful periods as well as a means of suppressing any other cyclic symptoms. This includes any symptoms that are impacting on the quality of life in the adolescent (thus applies to menses having a negative impact on a young woman with an intellectual disability).

Research agenda

- The best ways of achieving social change to i) provide increased education to girls in developing and other countries where sex education is restricted, thus reducing teenage pregnancy, and unplanned pregnancies ii) increase access to contraception in those parts of the world where this is limited.
- Clarification of the role of menstrual factors in provoking pain and associated symptoms, including their role in triggering persistent pelvic pain problems, would be valuable. Likewise improving the identification of young women at risk for significant endometriosis that will affect their future fertility would also be beneficial.

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