Singapore Journal of Obstetrics and Gynaecology
March 2002; 33(1): 1-9

REVIEW ARTICLE

The effect of medical disorders on the menstrual cycle

S. Nadarajah

ABSTRACT

While the majority of menstrual irregularities stem from a gynaecological disorder, in a small but significant number, an underlying medical disorder or its treatment is the cause. Regular menstrual cycles result from the complex interplay between various endocrine systems. Derangement of these endocrine systems is responsible for most of the non-gynaecological causes of menstrual irregularities. Hyperthyroidism, hypothyroidism, hyperprolactinemia, congenital adrenal hyperplasia and diabetes mellitus can all disrupt normal periods.

Classical coagulation disorders such as thrombocytopenia, hemophilia and von Willebrand's disease are all known to cause menorrhagia. However it is increasingly being recognised that mild forms of coagulation disorders are responsible for menorrhagia as well.

The increased life expectancy of patients with β-thalassemia and childhood cancer has resulted in more patients reaching the reproductive age. This has brought a new dimension to the treatment of these patients. Chronic illnesses, such as renal and liver failure can be responsible for various mechanisms associated with menstrual irregularity. At the same time the treatment of chronic illnesses such as shizophrenia and epilepsy can also predispose the patient to menstrual irregularity.

The various conditions and their treatment are discussed.

Key words: Medical conditions, irregular menstruation, menorrhagia, oligoamenorrhea

INTRODUCTION

The menstrual cycle is determined by complex interplay between endocrine factors, hypothalamic influence and hemostatic function. Any medical condition that affects the normal functioning of these will in turn have an effect on the menstrual cycle. Medical conditions from diverse origins have a profound effect on these systems. Therefore a wide spectrum of medical disorders can give rise to menstrual abnormality.

The vast majority of menstrual problems stem from gynaecological conditions of uterine and endometrial origin. Among the rest, a significant proportion will have an underlying endocrine disorder and the remainder, a chronic medical condition.

Correspondence:
Dr. S. Nadarajah
Associate Consultant
Reproductive Medicine Unit,
KK Women's and Children's Hospital
Singapore 229899

HYPERPROLACTINEMIA

Hyperprolactinemia can result from overproduction of prolactin from a pituitary adenoma or from reduction in the amount of dopamine reaching the pituitary gland. Dopamine from the hypothalamus has an inhibitory effect on prolactin secretion by the pituitary gland. Tumours involving the pituitary stalk or the hypothalamus can interrupt the flow of dopamine to the pituitary.

Hyperprolactinemia can also accompany several other medical problems. Primary hypothyroidism can either increase the secretion of prolactin or reduce its clearance from the system. Similarly in Cushings disease, 20 to 25% of patients have hyperprolactinemia, again due to either stalk

compression or dual production of ACTH and prolactin by the tumour.

Menstrual abnormalities due to hyperprolactinemia can be due to derangement of ovarian function or it can be due to reduced GnRH production in response to increased dopamine activity that follows hyperprolactinemia[1]. There is a spectrum of presentation with mild elevations giving rise to luteal phase defects[2] and the more severe cases having anovulation, amenorrhea and hypoestrogenism[1,3]. Therefore patients may present with subfertility, oligoamenorrhea, secondary amenorrhea and occasionally primary amenorrhea.

The diagnosis can be made when elevation in levels of prolactin is detected. Breast and pelvic examinations as well as stress are known to elevate prolactin levels. Therefore these must be excluded before a blood sample is taken. An increased level should be confirmed with a second sample. If the levels are persistently raised a MRI scan is essential to rule out pituitary or hypothalamic lesions.

The mainstay of treatment for hyperprolactinemia is the use of ergot derivatives. If fertility is desired it may have to be used in combination with ovulation induction agents.

ACROMEGALY/GIGANTISM

Hypersecretion of growth hormone before the end of puberty produces gigantism and after puberty gives rise to acromegaly. Gigantism is an extremely rare condition with only about a hundred cases reported in the literature. Acromegaly however has an estimated prevelance of 30–40 cases/million[4,5]. The mean age at presentation in women is 44 years[4,5,6]. The most common cause of acromegaly is a growth hormone secreting adenoma of the anterior pituitary[7].

The classical features of acromegaly are protruding chin, coarse facial features, deep nasolabial furrows, big hands and feet. Excessive growth hormone also causes hyperstimulation of cutaneous appendages which can result in hirsutism and oily, seborrheic skin. Menstrual irregularity is common in women with acromegaly with an estimated prevalence of 50–75%[4–6]. Occasionally it is the presenting symptom.

Gonadotrophin deficiency resulting from tumour mass effect accounts for the majority of cases[8]. Patients with large tumours develop hypoestrogenism, amenorhea or oligomenorrhea. This can be compounded by hyperprolactinemia that is evident in up to 40% of acromegalics[9]. Hyperprolactinemia can be a result of pituitary stalk compression or co-production of prolactin by the tumour.

Patients with smaller tumours with sufficient estrogen, have been found to have PCO like clinical and biochemical features[6] such as oligomenorrhea, increased free androgens and exaggerated response to GnRH stimulation[8]. This is thought to be through a growth hormone mediated or insulin-like growth growth factor effect on ovaries, or directly through associated insulin resistance that accompanies acromegaly[10].

The most precise screening test for growth hormone excess is the measurement of serum IGF-1 concentration. Unlike growth hormone, serum IGF-1 concentrations do not fluctuate hourly according to food intake, exercise, or sleep, but instead reflect integrated growth hormone secretion during the preceding day or longer. The diagnosis is confirmed by demonstrating a failure to suppress growth hormone secretion after a glucose load.

Treatment has to be directed at excising or controlling the pituitary tumour with surgery, pharmacotherapy and radiotherapy either alone or in combination.

CUSHING'S SYNDROME

Cushing's Syndrome is 4 times more common in women than men. Menstrual irregularity is quoted to be present in 69–84%[11–13] of the patients. The majority of women present with amenorrhea or oligomenorrhea. The presenting signs and symptoms of Cushings syndrome can closely resemble Polycystic Ovarian Syndrome. Obesity, oligoamenorrhea, hirsutism raised free androgens, exaggerated gonadotrophin response to GnRH stimulation are features common to both conditions. Therefore a high index of suspicion is needed so as not to miss the diagnosis[14]. The presence of pink/purple striae and proximal weakness warrants further investigation.

The mechanism responsible for menstrual disturbance is not known for certain. However it is widely believed that adrenal androgen excess, which is a feature of Cushings syndrome, is one possible reason[15]. The other is thought to be the inhibition of GnRH by hypercortisolemia[11], leading to hypogonadotrophic hypogonadism. A negative correlation between estradiol and cortisol levels has been demonstrated[11]. With moderately elevated cortisol levels, gonadotrophin stimulation of the ovaries was found to be maintained but higher levels of cortisol resulted in suppression of GnRH secretion, with resulting hypogonadotrophic hypogonadism[14]. Therefore the higher the cortisol level, the more profound the hypoestrogenic state.

Hyperprolactinemia is evident in about 20% of patients with Cushings syndrome[11,16]. However, the marginally raised prolactin levels, are not thought to be responsible for the menstrual disturbances[11].

If Cushings syndrome is suspected, a 24 hour urine cortisol level should be measured. If this is raised,the diagnosis can be confirmed with low and high dose dexamethasone suppression tests. Treatment of course should be directed at treating the underlying cause, and normalisation of the cortisol levels will restore regular periods.

THYROID DISORDERS

Disorders of thyroid function are one of the most common endocrine causes of menstrual disturbance. The incidence of menstrual abnormality was quoted to be between 56–68%[17,18] in the older series. The more recent studies have found it to be only about 21–23%[19,20]. The discrepancy has been attributed to earlier diagnosis of the condition now as compared to before when the patients probably presented with a more severe picture.

Patients with hyperthyroidism have classically been reported to have oligoamenorrhea and those with hypothyroidism, menorrhagia. However this is not absolute and the pattern of bleeding is variable. The menstrual irregularity evident in hypothyroidism is due to estrogen breakthrough bleeding from anovulation[19]. The underlying pathophysiology in hyperthyroidism however remains more obscure. It is probably due to the effect of excess thyroid hormones on the hypothalamo-pituitary axis resulting in alterations in gonadotrophin secretion and to increased sex hormone binding globulin, which is evident in hyperthyroidism. The increased SHBG levels lead to low free estradiol and estrone levels.

Treatment with anti-thyroid medication or thyroxine replacement, where appropriate, will restore normal periods.

Interestingly, the onset of hyperthyroidism before puberty has been reported to delay menarche[21], and untreated hypothyroidism from infancy leads to sexual immaturity[22], while that occurring before puberty may result in precocious puberty[23].

CONGENITAL ADRENAL HYPERPLASIA

Congenital adrenal hyperplasia (CAH) can be simply divided into classical and non-classical forms. Classical, refers to the traditionally severe forms of CAH seen in the neonate and young infant. With early detection and intervention many of these patients have now survived into adulthood. However a significant proportion continue to have irregular periods and problems with fertility[24]. Menstrual irregularity and amenorrhea have been reported in up to 30% of patients. Excess production of adrenal androgen and progesterone[25] are thought to be responsible for this. Treatment is aimed at achieving adequate adrenal suppression.

The non-classical variants tend to manifest symptoms of the disease in late childhood and beyond. The most common of these is non-classical 21 – hydroxylase deficiency. The patients may have a history of premature pubarche (early onset of pubic and axillary hair growth) without concomitant thelarche. Features of androgen excess such as hirsutism and acne may ensue. Frank virilisation is an uncommon problem. Oligo-amennorrhea and infertility are associated features.

Non-classical CAH and polycystic ovarian syndrome are very similar in the way they present. ACTH stimulation test will help differentiate the two, however the treatment for both conditions is virtually the same i.e. anti-androgens. The use of steroids with its attendant risks is not justified in the treatment of non-classical CAH, which has essentially a benign course.

DIABETES MELLITUS

Girls with insulin dependant diabetes mellitus (IDDM) have been found to have a later onset of puberty and menarche when the onset of IDDM is before menarche and the age of 10[26,27]. Among women whose onset of IDDM was after the onset of menarche, there was no such delay[26].

21% to 54% of women with IDDM have been found to have irregular periods[26–28]. Irregular periods are positively correlated with a high HbA1c level and low body mass index[26,28]. Therefore the patient who has poor metabolic control and who is underweight, probably as a result, is predisposed to irregular periods. A more recent study has shown that patients with IDDM menopaused on the average at 41.6 years of age, 8 years earlier than their non-diabetic sisters[29].

Patients with IDDM should be monitored for menstrual irregularity and possibly early menopause. They should be advised about the long-term effects of poor metabolic control on menstruation and fertilty.

Relatively little is known about menstrual cycle patterns and non-insulin dependant diabetes (NIDDM). However, disturbances in insulin secretion and action have been documented in women with PCOS[30]. And there is evidence suggesting that women with PCOS are at increased risk of developing NIDDM[31].

Therefore it can be assumed that patients with NIDDM are more likely to have PCOS. They should be screened for menstrual abnormalities. If a history of oligo-amenorrhea is evident, cyclical progesterone should

be commenced to reduce the risk of endometrial hyperplasia and endometrial carcinoma.

COAGULATION DISORDERS

Menorrhagia is a common problem in women with coagulation disorders. The prevelance of menorrhagia was objectively assessed (using a pictorial blood assessment chart) in women with von Willebrand's Disease, carriers of haemophilia and factor XI deficiency. It was found to be 73%, 57% and 59% respectively[32]. In comparison, it is 9–11% in the general population[33].

It is widely being recognised that undiagnosed bleeding disorders, especially in their mild forms, can be a significant underlying factor in patients presenting with menorrhagia. In a study of 150 women with menorrhagia with a normal pelvic examination and sonography, 17% were shown to have an inherited bleeding disorder (13% vWD, 4% factor XI deficiency)[34]. Therefore when managing a woman with menorrhagia in the absence of a pelvic pathology, screening for mild forms of vWD is recommended[32].

The bleeding time and APTT, usually prolonged in patients with von Willebrand's disease, may be normal in most patients with mild disease and therefore not sensitive enough for screening and diagnosis. The APTT reflects deficiencies of factors VIII, IX, XI and XII, but when the concentration of these factors is more than 30% of the normal the APTT will not be prolonged[35].

Mild von Willebrand's disease is best screened for by measuring, factor VII:C, vWF:Ag, vWF:Ac levels. The levels are variable at different times of the menstrual cycle and it is best measured in the early follicular phase when they are at their lowest[36–38].

The treatment options for menorrhagia resulting from an inherited bleeding disorder are tranexamic acid, the combined oral contraceptive pill and more recently intranasal DDAVP spray. Tranexamic acid reduces plasminogen activator as well as plasmin activity in the menstrual fluid[39]. The combined oral contraceptives are known to increase factor VIII:Ac and vWF:Ac[40–42]. Intranasal DDAVP has been shown to increase factor VIII and vWF in patients with mild hemophilia A or vWD Type I[43,44]. Non-steroidal anti-inflammatory agents are not effective and may even exacerbate the bleeding in patients with menorrhagia[45].

If a patient presents with acute bleeding, the underlying coagulopathy should be corrected with appropriate blood products and the endometrium stabilised with the combined oral contraceptive pill. This should be given continuously even after the bleeding has ceased and withdrawn at a later date when the patient is stable and a menstrual bleed is not contraindicated. For patients with recurrent heavy bleeds of a life threatening nature there is a place for long-term GnRH agonist therapy with estrogen add-back treatment[46].

β-THALASSEMIA MAJOR

With improvements in the treatment of homozygous β-thalassemia, more patients are reaching the reproductive age and beyond. Delayed puberty, primary or secondary amenorrhea is a common feature. This is due to hypogonadotrophic hypogonadism resulting from hemosiderosis of the hypothalamus and pituitary[47]. Investigations will reveal the FSH and LH and estrogen levels to be below normal. Patients should be followed up for onset of puberty. Hormone replacement therapy should be started when indicated.

Anovulation though common is not universal. There are several reports of spontaneous conception. Successful pregnancies have also been reported with ovulation induction[48].

CANCER

Increased survival rates in childhood malignancies has resulted in a significant number reaching puberty and reproductive age. This has resulted in the recognition of the long-term effects of radiotherapy and chemotherapy on ovarian function. Of the 312 females studied at the Long-Term Follow-Up Clinic at the Memorial Sloan-Kettering Cancer Center, 106 had primary ovarian failure and 25 patients had premature puberty[49].

Damage to the ovaries from radiotherapy is dependent on the dose of radiation as well as the position of the ovaries with respect to the field of radiation. In addition the older the woman the lower the ovarian reserves and therefore increased susceptibility to ovarian failure after radiotherapy. In a study of ovarian failure in long-term survivors of childhood malignancy, it was reported that ovarian failure occurred in 68% of patients when both ovaries were within the radiation field, 14% when the ovaries were at the edge of the treatment beam, and none when one or both the ovaries were outside it[50].

Cranial radiation affects the hypothalamo-pituitary axis resulting in hypogonadotrophic hypogonadism. Interestingly, early and precocious puberty can develop in girls treated with cranial irradiation for acute lymphoblastic leukemia[51].

Chemotherapy can cause perifollicular agenesis in the ovary that can progress to premature ovarian failure. The severity of damage is dependent on the

chemotherapeutic regime, the total dose as well as the age of the patient at the time of therapy[52–54].

Alkylating agents are toxic to the ovaries, Cyclophosphamide, chlorambucil, busulfan melphalan, and the combination regimes MOPP (mechlorethamine, vincristine, procarbazine, and prednisolone), MVPP (nitrogen mustard, vinblastine, procarbazine and prednisolone) and ChlVPP/EVA (chlorambucil, vinblastine, prednisolone, procarbazine, doxorubicin and etoposide) have all been associated with premature ovarian failure[50,54–58].

Children and adolescents seem more resistant to the deleterious effects of these drugs than adults. This is probably explained by the fact that they have larger ovarian reserves. In addition alkylating agents are particularly toxic to rapidly dividing cells. The ovaries in a prepubescent girl are quiescent and therefore protected from the cytotoxic effects of the drug. However even in girls who go through normal puberty after chemotherapy for leukemia, the FSH levels were elevated[59,60] and even if ovarian failure does not occur immediately after treament, there is a substantial risk of premature menopause[53]. This suggests that there is some amount of ovarian damage in all patients.

Patients who have previously undergone chemotherapy or radiotherapy should be followed up for the onset of puberty. In the event of ovarian insufficiency hormone replacement therapy should be commenced. Patients with spontaneous menarche and regular periods should be advised not to delay childbearing in view of premature menopause.

RENAL DISEASE

Chronic renal failure is often accompanied by endocrine disorders, which lead to menstrual irregularity. In a study of 100 females with renal failure 85% were found to have a menstrual disorder[61]. The majority had menorrhagia while the rest amennorrhea. Whatever the menstrual pattern, anovulation appears to be the underlying pathology[62,63].

Prolactin levels are often elevated in uremic patients on haemodialysis[64]. It may contribute to the menstrual disturbance but is not thought to be causative. FSH levels are comparable to normal patients and LH levels are normal or elevated and show an absence of cyclicity[62,63,64].

Menorrhagia may exacerbate underlying anaemia in a patient with chronic renal disease. More importantly, if severe, may necessitate blood transfusions, which may lead to the formation of atypical antibodies, which reduce the chances of successful organ matching for patients awaiting a renal transplant. Menorrhagia may be treated with cyclical progesterone, failing which high doses of progesterone such as medroxyprogesterone acetate may be given with the aim of achieving amenorrhea secondary to endometrial atrophy. Prostaglandin synthetase inhibitors are contraindicated in view of the risk of renal artery constriction and impairment of glomerular function.

Premature ovarian failure affected 14% of patients in the Cochrane study[61]. It can be attributed to the fact that Lupus and other autoimmune conditions that result in renal impairment, can also cause ovarian failure. In addition pulsed cyclophosphamide that is used in the treatment of Lupus nephritis can impair ovarian function. Premature ovarian failure together with long term steroid usage and chronic renal disease predispose these patients to osteoporosis. Such patients should be counseled with regards to the benefits of hormone replacement therapy.

LIVER DISEASE

Patients with liver disease may develop menstrual irregularity, menorrhagia or amenorrhea. In patients with liver disease secondary to alcoholism, there is evidence showing alcohol to be directly toxic to the ovaries. Estrogen and progesterone production was reduced and the patients entered menopause earlier than their normal counterparts[65–67]. In addition, the gonadotrophin release in response to GnRH analogues and clomiphene citrate, as well as to decreased sex steroids is blunted. Therefore there appears to be a dual defect in alcoholism induced liver disease.

The pathogenesis of menstrual dysfunction in women with chronic liver disease, unrelated to alcohol however, is not as clear. These patients may present with amenorrhea secondary to hypogonadotropic hypogonadism as is apparent in many a chronic debilitating illness. Alternatively, they may have normal gonadotrophins and increased levels of estradiol secondary to reduced metabolism of sex steroids[68]. This may alter the factors controlling the hypothalamo-pituitary axis leading to menstrual irregularity and possibly amenorrhea.

Menstrual dysfunction has also been noted with primary biliary cirrhosis. When compared with control subjects and patients with chronic active or alcoholic liver disease, patients with primary biliary cirrhosis were more likely to have undergone dilatation and curettage or hysterectomy for menorrhagia. These procedures were done 10 to 13 years prior to diagnosis of liver cirrhosis. Pathologic evaluation revealed endometrial hyperplasia in 24% of these patients[69].

Menorrhagia in liver disease results from a combination of anovulation, increased estrogen action on the

endometrium, thrombocytopenia and decreased production of clotting factors by diseased liver. The use of oral estrogens in the treatment of menorrhagia is contraindicated in view of the impaired metabolism of sex steroids by the liver and risk of hepatic cholestasis. Medroxyprogesterone acetate (Provera), GnRH analogues and estrogen patch with oral progesterones have all been used successfully in controlling menorrhagia in patients with liver dysfunction[70,71]. Occasionally medical treatment fails and in such instances, dilatation and curettage is indicated.

Normal menstrual function and fertility are often restored in women after liver transplantation. Resumption of normal periods have been noted to occur in 60 to 82% of the patients after liver transplantation.

EPILEPSY

Reproductive endocrine disorders (hyperandrogenism and polycystic ovaries) are unusually common in women with epilepsy. Whether this is due to the disease itself or its treatment is the subject of much controversy. There is data showing that epilepsy per se is associated with reproductive endocrine disorders[72,73]. At the same time, a number of studies have shown that anti-epileptic drugs, namely Valproic acid, play a bigger role in the development of these disorders than the epilepsy itself[74–83].

Valproic acid is particularly useful in the treatment of juvenile-onset idiopathic generalised epilepsies and has been used for more than 30 years in the treatment of epilepsy. Unlike other anti-epileptic drugs, it does not have enzyme-inducing properties which can reduce the effectiveness of oral contraceptives. It therefore represents a major treatment option in young women.

The prevalence of polycystic ovaries in the general population is about 22–23%[84]. Polycystic ovarian syndrome, (PCOS) consisting of PCO together with hyperandrogenism and menstrual irregularity, has been found to be present in 3–4% of the general population[85]. Isojarvi et al found PCO and or hyperandrogenism in 70% of women treated with Valproic acid for epilepsy[81]. In an earlier study, PCOS was found in 13% of women taking Valproic acid[74]. These figures suggest that there is a significant risk of PCO and PCOS with the use of Valproic acid. With this in mind, the clinician should monitor these patients for PCOS and consider alternative treatment should they develop it.

MENTAL HEALTH DISORDERS

The use of psychotrophic drugs such as phenothiazines and tricyclic anti-depressants can give rise to hyperprolactinemia. These patients in turn present with anovulation and amenorrhea. The estrogen status in these patients must be assessed because of the risk of osteoporosis from hypoestrogenism. This can be simply done by giving a progesterone challenge. An absence of a withdrawal bleed signifies a hypoestrogenic state. Estrogen can be replaced either in the form of oral contraceptives or hormone replacement therapy.

CONCLUSION

Menstrual disorders are a common problem among women. In the majority of women the underlying pathology is gynaecological in origin. Among the rest, many will have an underlying endocrine problem such as PCOS, hyperprolactinemia or thyroid dysfunction. When all the common conditions have been excluded, a high index of suspicion must be entertained for the other rare endocrine disorders such as Cushing's syndrome and growth hormone excess. The ultrasound and endocrine features of these disorders may mimic PCOS, therefore one has to be cautious when a diagnosis of PCOS is made.

NIDDM is the most common endocrine disorder among the adult population. Its association with PCOS has become increasingly clear over the last few years. The increased risk of endometrial hyperplasia and endometrial carcinoma must be borne in mind when treating these women.

Among patients with menorrhagia in the absence of an obvious pelvic pathology, a coagulation disorder has to be excluded. This includes screening for mild forms of von Willebrand's disease. Patients with chronic illnesses such as renal and liver failure, tend to be stoic in their attitude towards menstrual irregularities. Therefore the clinician has to elucidate the information and treat them accordingly.

Advances in the treatment have improved life expectancies of children with malignancies and blood dyscrasias such as β-thalassemia. The clinician has to be aware of the long-term effects of treatment on the reproductive function of these patients and manage them accordingly.

Finally, drugs used frequently in the treatment of epilepsy and shizophrenia can result in menstrual disorders. The menstrual disorder, when it occurs, signifies drug induced endocrine disturbances leading to subfertility in these women. Knowledge of these complications will help allay the patient's anxiety and allow appropriate steps to be taken.

REFERENCES

1. Katz E, Adashi EY. Hyperprolactinemic disorders. Clin Obstet Gynecol 1990; 33(3): 622–39.
2. del Pozo E, Wyss H, Tollis G, Alcaniz J, Campana A, Naftolin F. Prolactin and deficient luteal function. Obstet Gynecol 1979; 53(3): 282–6.
3. Yen S. Prolactin in human reproduction. In: SSC Yen RJ, editor. Reproductive endocrinology. 3rd edition ed. Philadelphia: W.B. Saunders; 1991. P. 357–88.
4. Jadresic A, Banks LM, Child DF, Diamant L, Doyle FH, Fraser TR, et al. The acromegaly syndrome. Relation between clinical features, growth hormone values and radiological characteristics of the pituitary tumours. Q J Med 1982; 51(202): 189–204.
5. Nabarro J. Acromegaly. In: Clinical Endocrinology: Oxford; 1987. P. 481–512.
6. Barbieri RL, Ryan KJ. Hyperandrogenism, insulin resistance, and acanthosis nigricans syndrome: a common endocrinopathy with distinct pathophysiologic features. Am J Obstet Gynecol 1983; 147(1): 90–101.
7. Melmed S. Acromegaly. N Engl J Med 1990; 322(14): 966–77.
8. Kaltsas GA, Mukherjee JJ, Jenkins PJ, Satta MA, Islam N, Monson JP, et al. Menstrual irregularity in women with acromegaly. J Clin Endocrinol Metab 1999; 84(8): 2731–5.
9. Luboshitzky R, Dickstein G, Barzilai D. Bromocriptine-induced pregnancy in an acromegalic patient. JAMA 1980; 244(6): 584–6.
10. Moller N, Schmitz O, Joorgensen JO, Astrup J, Bak JF, Christensen SE, et al. Basal- and insulin- stimulated substrate metabolism in patients with active acromegaly before and after adenomectomy. J Clin Endocrinol Metab 1992; 74(5): 1012–9.
11. Lado-Abeal J, Rodriguez-Amao J, Newell-Price JD, Perry LA, Grossman AB, Besser GM, et al. Menstrual abnormalities in women with Cushing's disease are correlated with hypercortisolemia rather than raised circulating androgen levels. J Clin Endocrinol Metab 1998; 83(9): 3083–8.
12. Urbanic RC, George JM. Cushing's disease – 18 years' experience. Medicine (Baltimore) 1981; 60(1): 14–24.
13. Ross EJ, Linch DC. Cushing's syndrome – killing disease: discriminatory value of signs and symptoms aiding early diagnosis. Lancet 1982; 2(8299): 646–9.
14. Kaltsas GA, Korbonits M, Isidori AM, Webb JA, Trainer PJ, Monson JP, et al. How common are polycystic ovaries and the polycystic ovarian syndrome in women with Cushing's syndrome? Clin Endocrinol (Oxf) 2000; 53(4): 493–500.
15. Nelson D. Cushing's Syndrome. In: LJ Degroot GM, JF Cahill Jr et al, editor. Endocrinology. Philadelphia: Saunders; 1989. P. 1660–1675.
16. Caufriez A, Desir D, Szyper M, Robyn C, Copinschi G. Prolactin secretion in Cushing's disease. J Clin Endocrinol Metab 1981; 53(4): 843–6.
17. Benson R. Menstrual pattern in hyperthyroidism and subsequent post-therapy hypothyroidism. Surgical Gynaecology Oncology 1955; 100: 19–26.
18. Joshi JV, Bhandarkar SD, Chadha M, Balaiah D, Shah R. Menstrual irregularities and lactation failure may precede thyroid dysfunction or goitre. J Postgrad Med 1993; 39(3): 137–41.
19. Krassas GE, Pontikides N, Kaltsas T. Papadopoulou P, Batrinos M. Menstrual disturbances in thyrotoxicosis. Clin Endocrinol (Oxf) 1994; 49(5): 641–4.
20. Krassas GE, Pontikides N, Kaltsas T, Papadopoulou P, Paunkovic J, Paunkovic N, et al. Disturbances of menstruation in hypothyroidism. Clin Endocrinol (Oxf) 1999; 50(5): 655–9.
21. Reilly. Thyrotoxicosis. American Journal of disease in children 1940; 60: 79–87.
22. PR Larson TD, ID Hay. The thyroid gland. In: JD Wilson DF, HM Krokenberg, PR Larson, editor. Williams textbook of endocrinology. 9 th ed. Philadelphia: Saunders WB; 1998. P. 389–515.
23. Wyek V. Syndrome of precocious menstruation and galactorrhea in juvenile hypothyroidism. An example of hormonal overlap pituitary feedback. Journal of Paediatrics 1960; 57: 416–35.
24. Mulaikal RM, Migeon CJ, Rock JA. Fertility rates in female patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. N Engl J Med 1987; 316(4): 178–82.
25. Holmes-Walker DJ, Conway GS, Honour JW, Rumsby G, Jacobs HS. Menstrual disturbance and hypersecretion of progesterone in women with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Clin Endocrinol (Oxf) 1995; 43(3): 291–6.
26. Kjaer K, Hagen C, Sando SH, Eshoj O. Epidemiology of menarche and menstrual disturbances in an unselected group of women with insulin-dependent diabetes mellitus compared to controls. J Clin Endocrinol Metab 1992; 75(2): 524–9.
27. Yeshaya A, Orvieto R, Dicker D, Karp M, Ben-Rafael Z. Menstrual characteristics of women suffering from insulin-dependent diabetes mellitus. Int J Fertil Menopausal Stud 1995; 40(5): 269–73.
28. Adcock CJ, Perry LA, Lindsell DR, Taylor AM, Holly JM, Jones J, et al. Menstrual irregularities are more common in adolescents with type 1 diabetes: association with poor glycaemic control and weight gain. Diabet Med 1994; 11(5): 465–70.
29. Dorman JS, Steenkiste AR, Foley TP, Strotmeyer ES, Burke JP, Kuller LH, et al. Menopause in type 1 diabetic women: is it premature? Diabetes 2001; 50(8): 1857–62.
30. Holte J. Disturbances in insulin secretion and sensitivity in women with the polycystic ovary syndrome. Baillieres Clin Endocrinol Metab 1996; 10(2): 221–47.
31. Dunaif A. Hyperandrogenic anovulation (PCOS): a unique disorder of insulin action associated with an increased risk of

non-insulin-dependent diabetes mellitus. Am J Med 1995; 98(1A): 33S–39S.

32. Economides DL, Kadir R.A., Lee C.A. Inherited bleeding disorders in obstetrics and gynaecology. British Journal of Obstetrics and Gynaecology 1999; 106(1): 5–13.

33. Hallberg L NL. Determination of menstrual blood loss. Scand J Clin Lab Invest 1964; 16: 244–248.

34. Kadir RA, Economides DL, Sabin CA, Owens D, Lee CA. Frequency of inherited bleeding disorders in women with menorrhagia. Lancet 1998; 351(9101): 485–9.

35. Lusher JM. Screening and diagnosis of coagulation disorders. Am J Obstet Gynecol 1996; 175(3 Pt 2): 778–83.

36. Edlund M, Blomback M, von Schoultz B, Andersson O. On the value of menorrhagia as a predictor for coagulation disorders. Am J Hematol 1996; 53(4): 234–8.

37. Mandalaki T, Louizou C, Dimitriadou C, Symeonidis P. Variations in factor VIII during the menstrual cycle in normal women. N Engl J Med 1980; 302(19): 1093–4.

38. Blomback M, Eneroth P, Landgren BM, Lagerstrom M, Anderson O. On the intraindividual and gender variability of haemostatic components. Thromb Haemost 1992; 67(1): 70–5.

39. Dockeray CJ, Sheppard BL, Daly L, Bonnar J. The fibrinolytic enzyme system in normal menstruation and excessive uterine bleeding and the effect of tranexamic acid. Eur J Obstet Gynecol Reprod Biol 1987; 24(4): 309–18.

40. Alperin JB. Estrogens and surgery in women with von Willebrand's disease. Am J Med 1982; 73(3): 367–71.

41. Schiffman S, Rapaport SI. Increased factor 8 levels in suspected carriers of hemophilia A taking contraceptives by mouth. N Engl J Med 1966; 275(11): 599.

42. Gluek HI FH. Control of hemorrhage in von Willebrand's disease and a haemophilliac carrier with norethenodrelmestranol. Thromb Res 1972; 1: 253–266.

43. Lethagen S, Harris AS, Nilsson IM. Intranasal desmopressin (DDAVP) by spray in mild hemophilia A and von Willebrand's disease type I. Blut 1990; 69(3): 187–91.

44. Rose EH, Aledort LM. Nasal spray desmopressin (DDAVP) for mild hemophilia A and von Willebrand disease. Ann Intern Med 1991; 114(7): 563–8.

45. Makarainen L, Ylikorkala O. Primary and myoma-associated menorrhagia: role of prostaglandins and effects of ibuprofen. Br J Obstet Gynaecol 1986; 93(9): 974–8.

46. Laufer MR RM. Treatment of abnormal uterine bleeding with gonadotrophin releasing hormone analogues. Clinical obstetrics and gynaecology 1993; 36: 678.

47. Canale VC, Steinherz P, New M, Erlandson M. Endocrine function in thalassemia major. Ann N Y Acad Sci 1974; 232(0): 333–45.

48. Jensen CE, Tuck SM, Wonke B. Fertility in beta thalassaemia major: a report of 16 pregnancies, preconceptual evaluation and a review of the literature. Br J Obstet Gynaecol 1995; 102(8): 625–9.

49. Sklar CA. Overview of the effects of cancer therapies: the nature, scale and breadth of the problem. Acta Paediatr Suppl 1999; 88(433): 1–4.

50. Stillman RJ, Schinfeld JS, Schiff I, Gelber RD, Greenberger J, Larson M, et al. Ovarian failure in long-term survivors of childhood malignancy. Am J Obstet Gynecol 1981; 139(1): 62–6.

51. Oberfield SE, Soranno D, Nirenberg A, Heller G, Allen JC, David R, et al. Age at onset of puberty following high-dose central nervous system radiation therapy. Arch Pediatr Adolesc Med 1996; 150(6): 589–92.

52. Schilsky RL, Sherins RJ, Hubbard SM, Wesley MN, Young RC, DeVita VT. Long-term follow up of ovarian function in women treated with MOPP chemotherapy for Hodgkin's disease. Am J Med 1981; 71(4): 552–6.

53. Whitehead E, Shalet SM, Blackledge G, Todd I, Crowther D, Beardwell CG. The effect of combination chemotherapy on ovarian function in women treated for Hodgkin's disease. Cancer 1983; 52(6): 988–93.

54. Rivkees SA, Crawford JD. The relationship of gonadal activity and chemotherapy-induced gonadal damage. JAMA 1988; 259(14): 2123–5.

55. Damewood MD, Grochow LB. Prospects for fertility after chemotherapy or radiation for neoplastic disease. Fertil Steril 1986; 45(4): 443–59.

56. Bookman MA, Longo DL, Young RC. Late complications of curative treatment in Hodgkin's disease. Jama 1988; 260((5): 680–3.

57. Watson AR, Taylor J, Rance CP, Bain J. Gonadal function in women treated with cyclophosphamide for childhood nephrotic syndrome: a long-term follow-up study. Fertil Steril 1986; 46(2): 331–3.

58. Clark ST, Radford JA, Crowther D, Swindell R, Shalet SM. Gonadal function following chemotherapy for Hodgkin's disease: a comparative study of MVPP and a seven-drug hybrid regimen. J Clin Oncol 1995; 13(1): 134–9.

59. Quigley C, Cowell C, Jimenez M, Burger H, Kirk J, Bergin M, et al. Normal or early development of puberty despite gonadal damage in children treated for acute lymphoblastic leukemia. N Engl J Med 1989; 321(3): 143–51.

60. Dacou-Voutetakis C, Kitra V, Grafakos S, Polychronopoulou S, Drakopoulou M, Haidas S. Auxologic data and hormonal profile in long-term survivors of childhood acute lymphoid leukemia. Am J Pediatr Hematol Oncol 1993; 15(3): 277–83.

61. Cochrane R, Regan L. Undetected gynaecological disorders in women with renal disease. Hum Reprod 1997; 12(4): 667–70.

62. Ginsburg ES OW. Reproductive endocrinology and pregnancy in women on hemodialysis. Semin Dial 1993; 6:105.

63. Lim VS, Henriquez C, Sievertsen G, Frohman LA. Ovarian function in chronic renal failure: evidence suggesting hypothalamic anovulation. Ann Intern Med 1980; 93(1): 21–7.

64. Perez RJ, Lipner H, Abdulla N, Cicotto S, Abrams M. Menstrual dysfunction of patients undergoing chronic hemodialysis. Obstet Gynecol 1978; 51(5): 552–5.

65. Van Thiel DH, Lester R. The effect of chronic alcohol abuse on sexual function. Clin Endocrinol Metab 1979; 8(3): 499–510.

66. Hugues JN, Perret G, Adessi G, Coste T, Modigliani E. Effects of chronic alcoholism on the pituitary-gonadal function of women during menopausal transition and in the post menopausal period. Biomedicine 1978; 29(8): 279–83.

67. Jones-Saumty DJ, Fabian MS, Parsons OA. Medical status and cognitive functioning in alcoholic women. Alcohol Clin Exp Res 1981; 5(3): 372–7.

68. Cundy TF, Butler J, Pope RM, Saggar-Malik AK, Wheeler MJ, Williams R. Amenorrhoea in women with non-alcoholic chronic liver disease. Gut 1991; 32(2): 202–6.

69. Stellon AJ, Williams R. Increased incidence of menstrual abnormalities and hysterectomy preceding primary biliary cirrhosis. Br Med J (Clin Res Ed) 1986; 293(654): 297–8.

70. Nicholas SL, Rulin MC. Acute vaginal bleeding in women undergoing liver transplantation. Am J Obstet Gynecol 1994; 170(3): 733–6.

71. Blumenfeld Z, Enat R, Brandes JM, Baruch Y. Gonadotropin-releasing hormone analogues for dysfunctional bleeding in women after liver transplantation: a new application. Fertil Steril 1992; 57(5): 1121–3.

72. Herzog AG, Seibel MM, Schomer DL, Vaitukaitis JL, Geschwind N. Reproductive endocrine disorders in women with partial seizures of temporal lobe origin. Arch Neurol 1986; 43(4): 341–6.

73. Bilo L, Meo R, Nappi C, Annunziato L, Striano S, Colao AM, et al. Reproductive endocrine disorders in women with primary generalized epilepsy. Epilepsia 1988; 29(5): 612–9.

74. Isojarvi JI, Laatikainen TJ, Pakarinen AJ, Juntunen KT, Myllyla V V. Polycystic ovaries and hyperandrogenism in women taking valproate for epilepsy. N Engl J Med 1993; 329(19): 1383–8.

75. Isojarvi JI, Laatikainen TJ, Pakarinen AJ, Juntunen KT, Myllyla V V. Menstrual disorders in women with epilepsy receiving carbamazepine. Epilepsia 1995; 36(7): 676–81.

76. Isojarvi JI, Laatikainen TJ, Knip M, Pakarinen AJ, Juntunen KT, Myullyla V V. Obesity and endocrine disorders in women taking valproate for epilepsy. Ann Neurol 1996; 39(5): 579–84.

77. Vainionpaa LK, Rattya J, Knip M, Tapanainen JS, Pakarinen AJ, Lanning P, et al. Valproate-induced hyperandrogenism during pubertal maturation in girls with epilepsy. Ann Neurol 1999; 45(4): 444–50.

78. Murialdo G, Galimberti CA, Magri F, Sampaolo P, Copello F, Gianelli MV, et al. Menstrual cycle and ovary alterations in women with epilepsy on antiepileptic therapy. J Endocrinol Invest 1997; 20(9): 519–26.

79. Murialdo G, Galimberti CA, Gianelli MV, Rollero A, Polleri A, Copello F, et al.Effects of valproate, phenobarbital, and carbamazepine on sex steroid setup in women with epilepsy. Clin Neuropharmacol 1998; 21(1): 52–8.

80. Roste LS, Tauboll E, Berner A, Isojarvi JI, Gjerstad L. Valproate, but not lamotrigine, induces ovarian morphological changes in Wistar rats. Exp Toxicol Pathol 2001; 52(6): 545–52.

81. Isojarvi JI, Tolonen U, Ansakopi H, et al. Effects of epilepsy type and anti-seizure medication on the occurrence of polycystic ovaries and hyperandrogenism in women with epilepsy (Abstract). Epilepsia 1999; 40(suppl 7): 237.

82. Isojarvi JI, Tauboll E, Pakarinen AJ, et al. Valproate related endocrine risks in women with epilepsy: a multicenter study (Abstract). Epilepsia 1998; 39(suppl 6): 220–1.

83. Tauboll E IJ, Flinstad Harbo H, et al. Effects of long-term valproate treatment on sex steroid hormone levels and ovarian morphology in female Wister rats. Seizure 1999; 8: 490–3.

84. Polson DW, Adams J, Wadsworth J, Franks S. Polycystic ovaries – a common finding in normal women. Lancet 1988; 1(8590): 870–2.

85. Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. J Clin Endocrinol Metab 1998; 83(9): 3078–82.