Sub-Clinical Thyroid Disorders in Women Having Dysfunctional Uterine Bleeding

Thesis

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Summary

It is estimated that about one third of all gynecological consultation are carried out for abnormal uterine bleeding, 80% of them are due to hormonal disorders, called dysfunctional uterine bleeding, the other 20% is due to organic causes.

Thyroid hormones directly influence the menstrual pattern through impact on the ovaries and indirectly through impact on SHBG, PRL and GnRH secretion and coagulation factors. Treating thyroid dysfunction can reverse menstrual abnormalities.

The aim of the current study (a cross sectional case-control study) is to evaluate the functional status of the thyroid gland in apparently euthyroid women with dysfunctional uterine bleeding. 80 female patients were recruited from out patient clinic of gynecology in Ain Shams University Maternity Hospital; they were divided into two groups according to the pattern of their menstrual cycle (study group and control group). All of the patients were subjected to written informed consent, clinical history and examination, pelvic U/S and measurement of thyroid hormones (Free T3, Free T4, and TSH). Finally, all data was statistically analyzed.

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List of Abbreviations

AITD : Auto-immune thyroid disease
AUB : Abnormal uterine bleeding
AVF : Anteverted uterus
DUB : Dysfunctional uterine bleeding
EBAF : Endometrial bleeding associated factor
FSH : Follicular stimulating hormone
GnRH : Gonadotropin releasing hormone
HCG : Human choriogonadotropin
HPO : Hypothalamic pituitary ovarian axis
HPT : Hypothalamic pituitary thyroid axis
HTN : Hypertension
IUD : Intrauterine contraceptive device
LBW : Low birth weight
LH : Luteinizing hormone
PCOs : Polycystic ovarian syndrome
PGs : Prostaglandins
PRL : Prolactin
RVF : Retroverted uterus
SCTD : Subclinical thyroid disease
SD : Standard deviation
SHBG : Sex hormone binding globulin
SPCC : Statistical package for social science
T3 : Triiodothyronine
T4 : Thyroxin
TBG : Thyroid binding globulin
TG : Thyroglobulin
TGFβ : Transforming growth factor β
TPO : Thyroperoxidase
TRH : Thyroid releasing hormone
TSH : Thyroid stimulating hormone
TV /US : Transvaginal ultrasound
VEGF : Vascular endothelial growth factor

Introduction

Abnormal uterine bleeding (AUB) is a very common gynecological problem that affect one third of women at child bearing period **(Morano et al., 2003).** 80% of AUB cases during reproductive years occur due to hormonal disorders, and the other 20% are due to organic causes **(Steiner and Fink, 2002)**. During these reproductive years AUB may occur secondary to pregnancy, to systemic defects in hemostasis, to structural pathology of the genital tract or to dysfunctional uterine bleeding (DUB) **(Munro, 2001).**

DUB is a problem commonly occurring at extreme of reproductive years (just after puberty and before menopause) **(Bongers et al., 2004).** It is considered a common cause of the symptom menorrhagia **(Fraser and Sungurtekin**, **2000).** DUB can be defined as uterine bleeding with no demonstrable organic cause either genital or extra-genital **(Saha, 2003).** It is a diagnosis of exclusion after pregnancy, iatrogenic causes, obvious genital tract pathology and systemic conditions have been ruled out **(Goodman, 2000).**

DUB may be either ovulatory or an-ovulatory but each of which is unrelated to structural abnormalities of the genital tract **(Abel and Baird, 1980)**. Ovulatory dysfunctional uterine

bleeding appears to occur secondary to defects in local endometrial hemostasis, while an-ovulatory dysfunctional uterine bleeding is a systemic disorder occurring secondary to endocrinal, neurochemical or pharmacological mechanisms **(Munro, 2001).**

On the other hand, thyroid gland interferes with the physiology of reproduction. Any disorder in thyroid functions has significant effects on estrogen and androgen metabolism, menstrual functions, and fertility **(Burrow, 1986).** The menstrual pattern is influenced by thyroid hormones directly through impact on the ovaries and indirectly through impact on sex hormone binding globulins (SHBG), prolactin (PRL) and gonadotropin releasing hormones (GnRH) secretion and coagulation factors. Treating thyroid dysfunction can reverse menstrual abnormalities and thus improve fertility **(Poppe et al., 2007).**

It has been reported in many studies that both hypo-and hyper-thyroidism are associated with failure of ovulation, heavy menstruation and/or oligomenorrhea **(Krassas, 2000).**

The concept that there are specific thyroid hormone receptors at the ovaries suggests that thyroid gland may play a regulatory role in the reproductive functions. Furthermore, there

is an increasing evidence suggest that the Hypothalamic-Pituitary-Thyroid axis (HPT) and Hypothalamic- Pituitary-Ovarian axis (HPO) act together as a unified system in a number of pathological conditions **(Doufas and Mastorakos, 2000).**

There is an evidence that in sub-clinical thyroid disorders, the thyrotrophs respond to minor changes in thyroid hormone level before clinical symptomatology becomes apparent **(Trbojevic, 2003)** and those patients show normal free thyroid hormone level, and respectively undetectable elevated TSH level **(Helfand and Redfern, 1998).**

The (HPT) axis in patients with sub-clinical thyroid dysfunction is significantly modified with respect to normal subjects **(Falaschi et al., 2004).**

Some studies conclude that thyroid gland dysfunction is increased among patients with menorrhagia even the sub-clinical cases and that sub-clinical thyroid disorder especially sub-clinical hyper-thyroidism can be a potential risk factor for DUB. Therefore, there is an increasing need to investigate thyroid function in cases of DUB even in the absence of clinical symptoms and signs of thyroid disorder **(Attia et al., 2007).**

Aim of the work

The present work aims to evaluate the functional status of the thyroid gland in apparently euthyroid women with dysfunctional uterine bleeding.

Dysfunctional Uterine Bleeding

Mechanism of normal menstruation

Menstruation occurs as a universal endometrial event following the withdrawal of estrogen and progesterone subsequent to a normal ovulatory cycle. Disruption of a regulated sequence of molecular, cellular, and vascular events can lead to a range of menstrual disturbances **(Mote et al., 1999).**

The first morphological effect of hormone withdrawal is shrinkage of the tissue due to fluid absorption and spiral arteriole vasoconstriction, probably predominantly under the influence of prostaglandin and endothelin-1 leading to reduced blood flow **(Marsh et al., 1995).** The arterioles undergo episodic vasoconstriction and relaxation leading to endometrial ischemia and reperfusion damage, contributing to local release of a range of substances including cytokines, such as tumor necrosis factor alpha, and other signaling molecules. The vasoconstriction process is limited to the first 24h **(Tabibzadeh, 1996).**

Complex changes occur in the cellular and extracellular compartments of the endometrium under the influence of estradiol and progesterone during the menstrual cycle. The

endometrial regression preceding menstruation coincides with the loss of hyaluronic acid and water from the tissue, and extensive destruction of the extracellular matrix can be observed immediately prior to and during menstruation **(Salamonsen et al., 1999).** It is not yet clear whether the activation of pro inflammatory cytokines and release of certain endometrial matrix metalloproteinases (MMPs) in response to the falling level of progesterone precedes, accompanies or follows vasoconstriction but it is clear that several MMPs are upregulated by falling progesterone levels **(Nayak et al., 2000).** these molecules are active indegrading the extracellular matrix leading to the breakdown of endometrial architecture and basement membrane independently from the vasoconstrictive mechanism. Prominent expression of MMPs occurs in areas of endometrium undergoing menstrual breakdown **(Marbaix et al., 1996).**

Endometrial lysosomes can be particularly sensitive to the falling progesterone levels and probably release of hydrolytic enzyme prior to the onset of menstruation which contribute to tissue breakdown, the further release of PGs and subsequent remodeling of the tissue **(Wang et al., 2000).**

Endometrial macrophages, polymorphs and granulated lymphocytes increase greatly around the time of menstruation

and probably influence vascular permeability and tissue breakdown through the release of a series of regulatory molecules **(Salamonsen and Wooley, 1999).**

Cytokines, such as interleukin 8 which is released adjacent to the blood vessels in the endometrium,are chemotactic for the leucocytes are essential in leucocytes migration to facilitate tissue breakdown **(Arici et al.,1998).**

Thrombin –induced fibrin generation is an essential part of normal blood clotting and is stimulated by endometrium by tissue factor through extrinsic pathway. Tissue factor increasers in decidualized endometrial cells under the effect of progesterone and decreased by progesterone withdrawal **(Lockwood et al., 1993).**

Fibrin –platelet plugs appear within the superficial vessels but not in the surrounding tissue because of the highly active fibrinolytic mechanisms in endometrium. The balance between generation of coagulation factors to control bleeding and fibrinolysis to prevent clot organization and intrauterine adhesions, shifts from being hemostatic dominant in the secretory phase and becomes heavily biased towards fibrinolysis during menstruation **(Livingstone and Fraser, 2002).**

With further shrinkage and a combination of apoptosis and necrosis, a variable quantity of the functional layer breaks down into fragments which are shed into the cavity and expelled. A variable quantity of blood and tissue fluid is also lost during this process. Prolonged vasoconstriction, release of local growth factors and effect of increasing oestradiol terminate the blood loss and lead to epithelial repair. Angiogenic factors such as vascular endothelial growth factors (VEGF) are very important in the repair process. Hypoxia which presumed to occur in the endometrium at perimenstrual time is considered one of the most potent stimuli for VEGF release that lead to epithelial repair processes **(Sharkey et al., 2000).**

Abnormal uterine bleeding

Abnormal uterine bleeding (AUB) is a very common gynecological problem that affect one third of women at child bearing period **(Morano et al., 2003).** Abnormal uterine bleeding includes any change in menstrual –period frequency or duration or amount of flow, as well as bleeding between cycles **(Livingstone and Fraser, 2002).** 80% of AUB cases during reproductive years occur due to hormonal disorders, and the other 20% are due to organic causes **(Steiner and Fink, 2002)**. During these reproductive years AUB may occur secondary to