

World Journal of *Obstetrics and Gynecology*

World J Obstet Gynecol 2018 July 10; 7(1): 1-16





REVIEW

- 1 Hypothyroidism during pregnancy: Controversy over screening and intervention

Mirghani Dirar A, Kalhan A

Contents

World Journal of Obstetrics and Gynecology
Volume 7 Number 1 July 10, 2018

ABOUT COVER

Editorial Board Member of *World Journal of Obstetrics and Gynecology*, Roberta Granese, MD, PhD, Professor, Department of Obstetrics and Gynaecology, University of Messina, Messina 98125, Italy

AIM AND SCOPE

World Journal of Obstetrics and Gynecology (*World J Obstet Gynecol*, *WJOG*, online ISSN 2218-6220, DOI: 10.5317) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJOG covers topics concerning pregnancy complications, obstetric surgical procedures, diagnostic imaging, endoscopy, reproductive endocrinology, tumors, pelvic diseases, evidence-based medicine, epidemiology and nursing.

We encourage authors to submit their manuscripts to *WJOG*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

INDEXING/ABSTRACTING

World Journal of Obstetrics and Gynecology is now indexed in China National Knowledge Infrastructure (CNKI).

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Yan Huang*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Li Juan Cui*
Proofing Editorial Office Director: *Ya Juan Ma*

NAME OF JOURNAL

World Journal of Obstetrics and Gynecology

ISSN

ISSN 2218-6220 (online)

LAUNCH DATE

June 10, 2012

FREQUENCY

Quarterly

EDITOR-IN-CHIEF

Zeev Blumenfeld, MD, Associate Professor, Department of Reproductive Endocrinology, Rambam Medical Center, Technion-Faculty of Medicine, Haifa 31096, Israel

EDITORIAL BOARD MEMBERS

All editorial board members resources online at <http://www.wjgnet.com/2218-6220/editorialboard.htm>

EDITORIAL OFFICE

Ya-Juan Ma, Director

World Journal of Obstetrics and Gynecology

Baishideng Publishing Group Inc
7901 Stoneridge Drive,
Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242

Fax: +1-925-2238243

E-mail: editorialoffice@wjgnet.com

Help Desk: <http://www.f6publishing.com/helpdesk>

<http://www.wjgnet.com>

PUBLISHER

Baishideng Publishing Group Inc
7901 Stoneridge Drive,
Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242

Fax: +1-925-2238243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.f6publishing.com/helpdesk>

<http://www.wjgnet.com>

PUBLICATION DATE

July 10, 2018

COPYRIGHT

© 2018 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

<http://www.wjgnet.com/bpg/gerinfo/204>

ONLINE SUBMISSION

<http://www.f6publishing.com>

Hypothyroidism during pregnancy: Controversy over screening and intervention

AbdelHameed Mirghani Dirar, Atul Kalhan

AbdelHameed Mirghani Dirar, Endocrinology and Diabetes Center, Prince Abdul Aziz Bin Mosaad Hospital, Arar 91421, Saudi Arabia

Atul Kalhan, Department of Diabetes and Endocrinology, Royal Glamorgan Hospital, Llantrisant CF72 8TA, United Kingdom

ORCID number: AbdelHameed Mirghani Dirar (0000-0002-3374-4829); Atul Kalhan (0000-0003-0542-8068).

Author contributions: Mirghani Dirar A and Kalhan A contributed equally to this work; Mirghani Dirar A and Kalhan A designed the format; Mirghani Dirar A wrote the paper; Kalhan A revised and approved the paper.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Correspondence to: Dr. AbdelHameed Mirghani Dirar, MBBS, MSc, Endocrinology and Diabetes Center, Prince Abdul Aziz Bin Mosaad Hospital, King Fahad Road, Arar 91421, Saudi Arabia. adirar@moh.gov.sa
Telephone: +966-5-08494973

Received: February 16, 2018

Peer-review started: February 16, 2018

First decision: April 3, 2018

Revised: April 13, 2018

Accepted: June 2, 2018

Article in press: June 2, 2018

Published online: July 10, 2018

Abstract

Thyroid hormones are critical for foetal neurological development and maternal health. Maternal hypothyroidism during pregnancy is associated with adverse impact on health of the mother as well as the progeny. Reduced thyroid hormone levels predispose the child to develop mental retardation and cognitive delay in early life. In the mother, hypothyroidism during pregnancy is associated with spontaneous abortion, placental abruption, preterm delivery and hypertensive disorders. Therefore, screening and therapeutic intervention is justified to prevent foetal as well as maternal co-morbidities. In view of impact of such a large-scale screening and intervention program on limited healthcare resources, it is debatable if a targeted rather than universal screening program will result in comparable outcomes. In addition, there is an ongoing debate regarding best evidence-based practice for the management of isolated hypothyroxinaemia, subclinical hypothyroidism and euthyroid women with autoimmune hypothyroidism. We have carried out a review of the literature; firstly, to determine whether universal screening for asymptomatic women in early pregnancy would be cost-effective. Secondly, we have retrospectively reviewed the literature to analyse the evidence regarding the impact of therapeutic intervention in women with subclinical hypothyroidism.

Key words: Targeted screening; Thyroid peroxidase antibodies; Isolated hypothyroxinaemia; Spontaneous abortion; Overt hypothyroidism; Placental abruption; Universal screening; Hypothyroidism during pregnancy; Subclinical hypothyroidism; Autoimmune hypothyroidism

© The Author(s) 2018. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Hypothyroidism during pregnancy poses a significant health challenge as it is associated with adverse health outcomes for mother as well as the child.

There is evidence that supports increased maternal and neonatal morbidity, even in absence of a clinically overt maternal hypothyroid state. However, in view of limited available healthcare resources, the jury is still divided regarding use of universal *vs* targeted screening programs in pregnant women. In addition, there is a lack of consensus regarding the best management approach for isolated hypothyroxinaemia and subclinical hypothyroidism. Keeping these contentious issues in mind, we have carried out a review of the literature.

Mirghani Dirar A, Kalhan A. Hypothyroidism during pregnancy: Controversy over screening and intervention. *World J Obstet Gynecol* 2018; 7(1): 1-16 Available from: URL: <http://www.wjgnet.com/2218-6220/full/v7/i1/1.htm> DOI: <http://dx.doi.org/10.5317/wjog.v7.i1.1>

INTRODUCTION

Pregnancy is a physiological state of complex metabolic stress that involves significant changes in hormonal milieu. It has a profound influence on thyroid gland structure as well as function. Hypothyroidism during pregnancy constitutes a significant health challenge, as it is associated with adverse maternal outcome along with an impact on neonatal cognitive development. The foetal thyroid gland starts to function only after 12-14 wk of gestation. As a consequence, the growing foetus remains dependent upon maternal thyroid hormones during this phase of early gestation^[1,2]. Thyroid hormones (thyroxine and triiodothyronine) are vital for normal foetal neurological development^[3,4], and decreased levels predispose the child to develop cognitive delay in early adolescence^[5]. There are studies linking untreated maternal overt hypothyroidism (OH) and subclinical hypothyroidism (SCH) with increased adverse maternal and foetal outcomes^[6-8], although, Cleary-Goldman *et al*^[9] failed to demonstrate such an association with SCH. In a study carried out by Haddow *et al*^[10], children born to pregnant women with hypothyroidism had lower intelligence quotient (IQ) scores compared with children born to pregnant women without hypothyroidism. In addition, hypothyroidism during pregnancy has also been linked with spontaneous abortion, placental abruption, preterm delivery and hypertensive disorders^[6,7,11,12]. Decreased IQ in children born to mothers with isolated hypothyroxinaemia (IH) has also been reported by Pop *et al*^[13] and Li *et al*^[14] and further supported by Henrichs *et al*^[5] in the largest prospective Generation R study. Even in euthyroid women with high titre thyroid peroxidase (TPO) antibodies, there is increased risk of adverse outcomes, such as foetal loss^[15] and pregnancy-induced hypertension^[16]. For these reasons, it is important to adopt appropriate strategies to identify women at these adverse outcomes and to implement screening tools for early detection and initiation of effective treatment.

However, there is an ongoing debate regarding cost-effectiveness of universal *vs* targeted screening in pregnant women^[17,18]. In addition, there is a lack of consensus regarding the best evidence based approach for the management of isolated hypothyroxinaemia, SCH with or without TPO antibodies and euthyroid women with high TPO antibodies^[15,19,20]. We have carried out a review of the literature; firstly, to determine whether universal screening for asymptomatic women in early pregnancy would be cost-effective. Secondly, we have retrospectively reviewed the literature to analyse the evidence regarding the impact of therapeutic intervention in women with subclinical hypothyroidism.

Physiological changes in thyroid gland during pregnancy

Pregnancy has an intense influence on the thyroid gland and provokes several changes and metabolic effects that alter thyroid function. During the first stages of gestation, there is a rise in renal blood flow and glomerular filtration rate that results in more iodide disposal and reduced iodine blood level, an effect that persists until term. Further reduction of available iodine occurs later at 12-14 wk gestation, with more transfer of iodine from the mother to the foetal circulation at the time when the foetal thyroid gland starts to function. This reduction in maternal iodine level obliges a compensatory rise in iodide entrapment into the gland and increased thyroid activity. In women with satisfactory iodine reserve, there is mild thyroid burden. However, in geographical areas where the iodine resources are poor, the iodine losses in the urine and in placental transfer could constitute a significant issue^[21].

The structural similarity between human chorionic gonadotropin (hCG) molecule and thyroid stimulating hormone (TSH) renders the hCG molecule to behave as a weak thyrotropic hormone and may even enhance growth of the thyroid gland^[22]. During the hCG peak at around the end of the first trimester, hCG stimulates thyroidal cells to secrete free thyroxine (FT₄), and a temporary mild fall in basal TSH occurs^[23].

Thyroxine-binding globulin (TBG) is a carrier protein that binds thyroid hormones in serum. It has the highest binding affinity compared to other carrier proteins despite its lowest serum level. A significant elevation of serum TBG level has been shown in women during pregnancy due in part to oestrogen stimulation and decreased clearance^[23]. Accordingly, thyroid gland production of FT₄ and FT₃ must increase to maintain adequate levels of thyroid hormone during pregnancy.

Moreover, the placenta plays a role in the metabolism of maternal thyroid hormones. Increased deiodination activity in the placenta might play a vital role in the passage of maternal thyroid hormones to the foetus^[21]. The placenta synthesizes iodothyronine deiodinases type II (DIO2), which converts T₄ to T₃ through outer ring deiodination, and type III (DIO3), which deactivates

both T₄ and T₃ via inner ring deiodination. ID3 is the major deiodinase synthesized by the placenta and has significant deiodination activity^[24]. In pregnant women treated for hypothyroidism, LT₄ should be increased to maintain euthyroidism in later stages of pregnancy^[23].

Effect of iron deficiency anaemia on thyroid status during pregnancy

Worldwide, iron deficiency is the most common cause of anaemia during pregnancy, affecting around 50% of the pregnant population^[25]. Several studies in animals and humans have suggested a link between iron deficiency anaemia and thyroid status. Thyroid peroxidase is the key enzyme in thyroid hormone synthesis. It has been shown by Hess *et al*^[26] that the activity of this enzyme is impaired and the FT₄ and FT₃ levels are significantly reduced in rats with iron deficiency anaemia. In addition, Beard *et al*^[27] showed a significant reduction in hepatic thyroxine-5'-deiodinase activity and FT₃ production in rats with iron deficiency compared with controls. In humans, previous studies showed reduced FT₄ and FT₃ levels in women with iron deficiency^[28,29]. Recently, in an observational study Li *et al*^[30] reported a significantly higher TSH and lower FT₄ during the first trimester in women with iron deficiency anaemia. They also observed a significantly higher rate of TPO antibodies in women with iron deficiency anaemia compared with control. It is worthwhile to note that the state of hypothyroidism in itself also can produce anaemia^[31]; and, therefore, future research on this topic should aim to address this point.

Mechanism of implication of hypothyroidism in maternal and foetal consequences

The risk of adverse consequences in pregnant women with hypothyroidism depends on the severity and sub-type of maternal hypothyroidism. Thyroid hormones are essential for regulation of metabolic activities in the brain, white fat, brown fat, skeletal muscle, liver and pancreas as well as regulation of growth development^[32]. The molecular means by which thyroid hormones alter foetal neurological development remains unclear. However, experimental trials in animals showed delayed maturation of major structures, such as the cerebellum, in which there is interference of Purkinje cell maturation and delayed granular cell migration^[33]. In addition, it has been reported that locally converted FT₃ in the brain from maternal FT₄ is critical for foetal brain development^[34]. However, in animal studies, replacement with FT₃ does not offer adequate brain protection, indicating that normal maternal FT₄ level during early embryonic life is essential for brain development^[35].

The pathogenesis of maternal consequences is also complex and less understood. The mechanisms for infertility and miscarriage may involve the presence of thyroid auto-antibodies. Vitamin D deficiency may also contribute to autoimmunity and was shown to be reduced in patients with autoimmune thyroiditis^[36]. In addition, a disturbance in folliculogenesis, fertilization

and embryogenesis was reported associated with the presence of TPO antibodies^[21]. Dyslipidaemia associated with hypothyroidism and pregnancy, such as hypertriglyceridaemia, could explain the occurrence of hypertensive disorders^[37].

Epidemiology and classification of hypothyroidism during pregnancy

The prevalence of hypothyroidism during pregnancy is variable, and this variability is mostly attributed to differences in geographical areas, analytical measurement and trimester-specific TSH limits used in diagnosis^[38]. In general the prevalence rates were estimated to be 0.25%-2.5% for SCH, 0.2%-0.3% for OH^[39] and 5%-15% for euthyroidism with autoimmune disease^[40].

Classification of hypothyroidism recognised during pregnancy is essential for epidemiological as well as clinical reasons. The American Thyroid Association (ATA) has defined hypothyroidism during pregnancy as the state of increased TSH level when other rare causes, such as TSH-secreting pituitary tumor and thyroid hormone resistance are excluded. Primary maternal hypothyroidism (MH) observed during pregnancy should be distinguished from preexisting hypothyroidism diagnosed prior to the pregnancy. Two main varieties of primary MH are recognised by the ATA: overt hypothyroidism (OH) and subclinical hypothyroidism (SCH) based on the presence of elevated TSH and whether FT₄ level is decreased or within normal range. However, cases of isolated hypothyroxinaemia (IH) with normal TSH have also been recognised by the ATA as a third sub-type of MH^[19]. In addition, women with increased TPO antibodies status and normal thyroid function have been observed to have an increased risk of developing SCH in early pregnancy, and this may also be recognized as a fourth sub-type of MH (Figure 1)^[15]. The ATA defines OH as a TSH > 2.5 mIU/L and a lower serum FT₄ level or a TSH ≥ 10.0 mIU/L, regardless of FT₄ level. SCH is defined as a TSH between 2.5-10 mIU/L and a normal FT₄ level, and IH is defined as a TSH within normal limits together with lower FT₄ level^[19].

Interpretation of TFT during pregnancy

Due to significant alterations in thyroid functions during pregnancy, levels of TSH and FT₄ should be interpreted using gestational age-specific reference ranges. Using these specific references, it would be possible to evaluate thyroid functions accurately and to help in defining thyroid disorders^[41]. Consequently, the ATA^[19] recommends that trimester-specific reference values of thyroid function test (TFT) should be applied during pregnancy. In view of an increased thyroxine-binding globulin (TBG) level and enhanced thyrotropic activity of hCG, women during pregnancy have decreased TSH levels (< 0.4 mIU/L) compared with preconception levels^[19]. In addition, there is a significant reduction in serum FT₄ level observed with advancing pregnancy. Following delivery, restoration of TBG to preconception

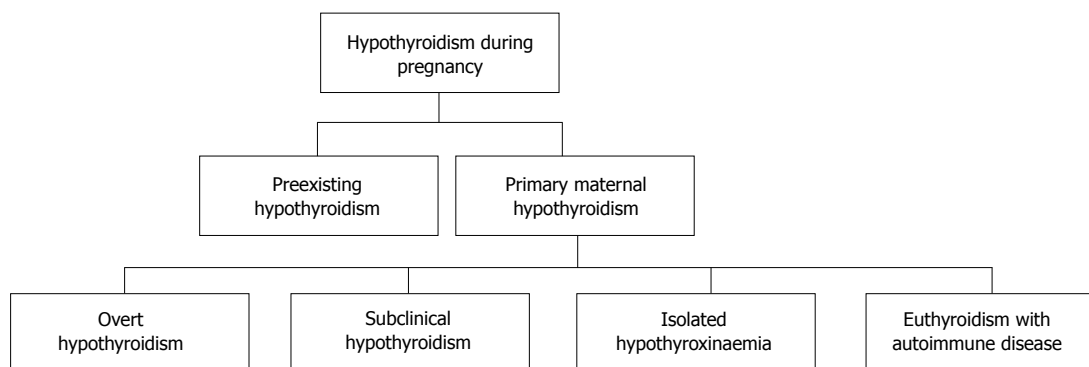


Figure 1 Classification of hypothyroidism during pregnancy^[15,19].

levels occurs within 4-6 wk together with FT₄ and FT₃ levels^[42]. Several studies demonstrated that both reference limits for TSH were reduced during pregnancy, with the greatest reduction being noted during the first trimester when the thyrotropic effect of hCG was highest^[41,43-45]. Panesar *et al*^[43] showed increasing median TSH concentration throughout pregnancy: 0.80 (0.03-2.30) in the first trimester, 1.10 (0.03-3.10) in the second trimester and 1.30 (0.13-3.50) in the third trimester. Accordingly, in 2011, the ATA recommended TSH reference limits for each gestational age provided unavailability of specific ranges in the laboratory: 0.1-2.5 mIU/L for the first trimester, 0.2-3.0 mIU/L for the second trimester and 0.3-3.0 mIU/L for the third trimester^[19]. On the other hand, accurate measurement of FT₄ concentration during pregnancy depends on the analytical technique used. Automated immunoassays (IAS) of FT₄ concentration are affected by elevated TBG, free fatty acids and reduced albumin levels, resulting in its unreliability^[46-48]. The solid phase extraction-liquid chromatography/tandem mass spectrometry (LC/MS/MS) technique to estimate the level of FT₄ in the dialysate serum was proved highly specific as compared to the IAS method^[49]. However, at present, the LC/MS/MS technique is not extensively used due to increased cost. According to Yue *et al*^[48], the reference ranges for FT₄ using the LC/MS/MS technique were found to decrease gradually with progression of pregnancy. In the 14th week gestation, the reference range was estimated between 1.08-1.82 ng/dL and decreased to 0.86-1.53 ng/dL by the end of 20th week gestation. Using the new technique, Kahric-Janicic *et al*^[49] were able to show decreasing concentrations of FT₄ levels with progress in pregnancy (Figure 2), and the same results were obtained upon using IAS method on the same samples (Figure 3). The ATA recommends the LC/MS/MS technique as the ideal method to estimate FT₄ concentration during pregnancy. However, the ATA also recommends use of IAS methods with consideration of their limitations if LC/MS/MS technique is not attainable, and obviously, TSH measurement is a better estimate of TFT during pregnancy^[19].

METHODOLOGY

Data search

An extensive literature search of multiple data sources was performed in Pubmed, Cochrane library, Google Scholar and South Wales University Library (FINDit) up to December 20, 2016 for articles published in the English language. The keywords used to search in the data sources were: "thyroid function during pregnancy"; "hypothyroidism in pregnancy"; "thyroid dysfunction in pregnancy"; "outcomes and hypothyroidism in pregnancy"; "screening for hypothyroidism in pregnancy"; "interventions for hypothyroidism in pregnancy" and "treatment of hypothyroidism in pregnancy". All study types were selected for review, including experimental and observational trials (cohort and case-control), systematic reviews, meta-analyses, review articles and clinical guidelines. In addition, some references cited in the selected publications were also reviewed to analyse additional data.

Hypotheses

After reviewing the relevant literature, two hypotheses were postulated: Hypothesis-1, universal screening for asymptomatic women in early pregnancy will be effective; Hypothesis-2, therapeutic intervention in pregnant women with SCH and IH and euthyroid women with autoimmune hypothyroidism would be associated with reduced maternal and foetal adverse outcomes.

SCREENING FOR HYPOTHYROIDISM DURING PREGNANCY

Universal vs targeted screening

The observational studies by Haddow *et al*^[10] and Pop *et al*^[50] opened up the debate regarding cost-effectiveness of targeted vs universal screening in asymptomatic pregnant women for hypothyroidism. These studies observed an increased risk of neurological and cognitive development in children born to mothers with asymptomatic hypothyroidism. Several observational studies have focused on targeted screening by identifying

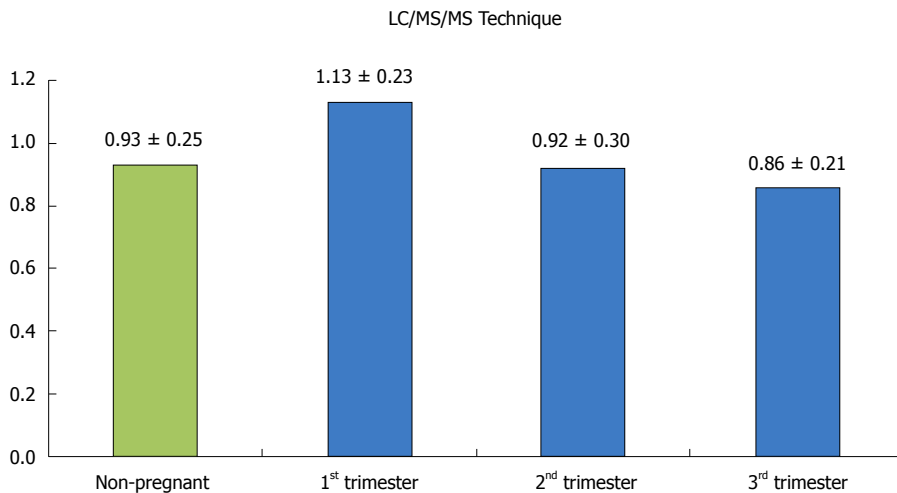


Figure 2 Concentrations of serum free thyroxine (mean ± SE) using the solid phase extraction–liquid chromatography/tandem mass spectrometry (LC/MS/MS) technique in pregnant and non-pregnant women^[49].

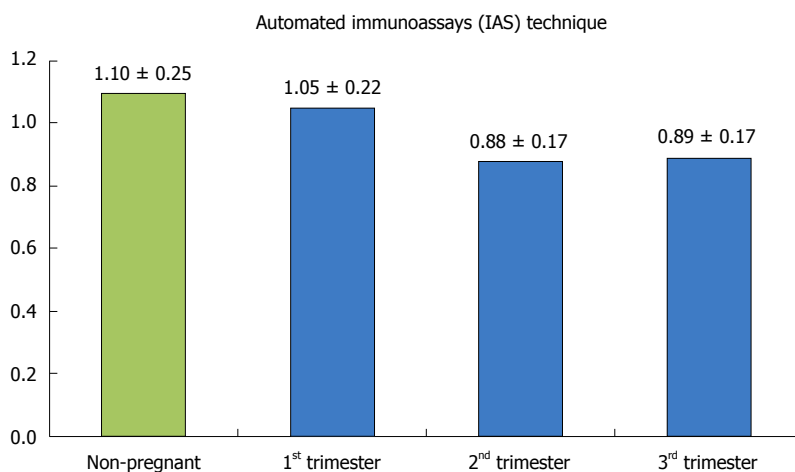


Figure 3 Concentrations of serum FT₄ (mean ± SE) using automated immunoassays technique in pregnant and non-pregnant women on the same samples^[49].

women as “high risk” to develop thyroid disease. These studies, however, have failed to spot more than 30% of pregnant women with SCH or OH^[51,52]. On the other hand, prospective studies have shown no beneficial role of universal screening over selective approach or no screening in terms of improvement of adverse outcomes. For instance, Negro *et al.*^[8] randomised 4562 Caucasian women with no prior history of thyroid dysfunction into either universal or selective screening strategies and followed them prospectively. Women in both arms were classified on the basis of risk factors to develop thyroid dysfunction as “high risk” or “low risk”. Blood samples for FT₄, TSH and TPO antibodies from all women in the universal screening strategy and “high risk” women in the selective screening arm were measured during the first trimester. In contrast, blood samples from “low risk” women in the selective screening arm were measured only during the post-partum period. Women with positive TPO antibodies and TSH more than 2.5 mIU/L received therapeutic intervention in the form of LT₄. This study

showed that 1545 women in the selective screening arm and 1559 women in the universal screening strategy developed complications. However, the difference between the two groups was not statistically significant ($P = 0.69$). Hypothyroidism developed in 1.9% of participants in the “low risk” selective arm who were only screened post-delivery, indicating that selective high-risk screening strategy missed a proportion of women with maternal hypothyroidism. Interestingly, “low risk” women in the universal screening arm who were identified to be hypothyroid and received LT₄ had fewer complications than “low risk” women in the selective screening arm. However, this difference was also statistically not significant. The strength of this study remains in its well-structured prospective design and randomization of various sub-groups, but its main drawback remains a homogeneous study population comprising of only Caucasian Italian women. As a result, the study results cannot be generalized to reflect accurately a wider heterogeneous and ethnically diverse population.

In another prospective study, Lazarus *et al.*^[53] tested 21846 pregnant women with no history of thyroid disease for TSH and FT₄ concentrations and then randomised them into either screening or control groups. In the screening, arm blood samples were analysed instantaneously at around the 13th week gestation; and in the control arm, samples were frozen and only tested post-delivery. Women with a TSH more than 97.5th percentile, FT₄ less than 2.5th percentile, or together were considered hypothyroid and were treated with 150 µg of LT₄, with doses adjusted according to TSH concentrations (target TSH range 0.1-1.0 mIU/L). The IQ of children born to women with hypothyroidism was assessed at the age of 3-years by two psychologists. This study demonstrated that 12.1% of children in the screening strategy scored an IQ < 85 compared with 14.1% in the control arm. However, the difference was not statistically significant between the two groups ($P = 0.39$), indicating that screening and treatment of hypothyroidism at around the 13th week gestation was not clinically beneficial in improving intellectual abilities in children at the age of 3-years. These results could be attributed to delayed gestational screening and a later initiation of LT₄ treatment, which might not have a significant effect on neurological development. Moreover, the IQ assessment of children at the age of 3-years could be too early to obtain an effect of LT₄ therapy, unlike in Haddow *et al.*^[53], where children were assessed at the age of 7-years. The statistically insignificant difference obtained between the two groups could also be attributed to the risk of bias, as about 25% women were lost to follow-up.

Based on history taking, clinical examination and previous laboratory findings, the Endocrine Society recommends identifying a group of women as "high risk" to develop thyroid disease that should be targeted for selective screening (Table 1)^[20]. One observational study that tested the efficacy of targeting "high risk" women in detection of thyroid abnormalities during pregnancy observed that women grouped as "high risk" have over six times increased risk to develop OH or SCH during pregnancy^[52].

General criteria for justification of disease screening

In general, screening is recommended to provide early detection of a particular condition among the apparently well asymptomatic individuals with the aim of reducing its burden in the community and consequently offering an opportunity to start specific an intervention at an earlier stage. Screening process should fulfill several criteria to be deemed appropriate as well as cost-effective. An effective screening program has significant influence on health care planning services. Historically, Wilson and Jungner, (1968) had set certain criteria that form the basis of the World Health Organization (WHO) to screen for a particular disease (Table 2)^[54]. In view of the key role of screening in health care, it is important to examine the advantages of universal screening for hypothyroidism during pregnancy using the Wilson and

Jungner criteria.

Is hypothyroidism during pregnancy an important health issue?

Hypothyroidism during pregnancy is the second most common endocrine disorder, with only gestational diabetes mellitus (GDM) being more common^[55,56]. The prevalence of hypothyroidism may even be higher if women with recently redefined trimester specific TSH values (TSH > 2.5 mIU/L) recommended by the ATA were included as a cut off for diagnosis of SCH. In addition, women with increased TPO antibodies and cases of isolated hypothyroxinaemia may be included in the spectrum of hypothyroidism^[19]. In areas of iodine sufficiency, half of women with SCH have autoimmune hypothyroidism, as evidenced by positive TPO antibodies^[57]. Recently, Blatt *et al.*^[17] extracted laboratory information for 502036 women during pregnancy from the Quest Diagnostics Informatics Data Warehouse. Of these women, 117892 underwent screening for OH and SCH by TSH measurement using trimester-specific reference limits. This study showed that 15.5% of women have OH or SCH, as evidenced by elevated TSH measurement, and the rate was 15.1% after adjustment for age. These results suggested that hypothyroidism during pregnancy could be even more widely prevalent than what is commonly accepted. Clearly, the epidemiological data supporting a relatively widespread prevalence of thyroid dysfunction in pregnant women justifies the need for universal screening.

Evidence of associated adverse outcomes

From a historical perspective, Man and Jones^[58] reported compromised cognitive capabilities in children born to mothers with hypothyroidism. They included 1394 pregnant women into the study and measured their butanol extractable iodines to identify hypothyroid women along with assessment of mental and motor development in their children using Bayley's scales. Later, Matsuura and Konishi^[3] also suggested that intellectual development is critically compromised in children born to mothers with hypothyroidism caused by Hashimoto's thyroiditis.

Recent studies have demonstrated conflicting results regarding the association of maternal hypothyroidism with cognitive impairment in the offspring. For instance, Haddow *et al.*^[10] in a large-scale prospective study observed an adverse impact on neuropsychological status of children born to mothers with undiagnosed hypothyroidism. The neuropsychological status in children of hypothyroid women and controls was recorded using the full-scale IQ scores (15 tests). An average of 4 points lower IQ scores was observed in children born to women with hypothyroidism who were treated as compared with the controls (children born to euthyroid women), although this reduction was deemed statistically no significant ($P = 0.06$). However, a significant reduction in IQ scores, by an average of 7 points, was reported among untreated hypothyroid women compared with the controls ($P =$

Table 1 Risk factors for thyroid disease defined by the endocrine society^[20]

| |
|--|
| Women over the age of 30 |
| Family history of autoimmune thyroid illness or hypofunction |
| Women with thyroid swelling |
| Women with thyroid antibodies (mainly TPO) |
| Symptoms or signs indicative of hypothyroidism |
| Women with T1DM, or with any autoimmune diseases |
| Women with previous history of abortion and premature birth |
| Women with history of previous head or neck radiation or thyroidectomy |
| Women on thyroid hormones replacement therapy |
| Women living in a geographical area lacking iodine |

TPO: Thyroid peroxidase.

Table 2 Wilson and Jungner criteria for disease screening^[54]

| |
|--|
| The condition sought should be an important health problem |
| There should be an accepted treatment for patients with recognised disease |
| Facilities for diagnosis and treatment should be available |
| There should be a latent or early symptomatic stage |
| There should be a suitable test or examination |
| The test should be acceptable to the population |
| The natural history of the condition should be adequately understood |
| There should be an agreed policy on who to treat as patients |
| The cost of case finding should be cost-effective |
| Case finding should be a continuing process and not a "once and for all" project |

0.005). This study remained observational in design; and, therefore, it would be difficult to conclude about the efficacy of screening and treatment in neuropsychological achievement without adjustment of major confounders, such as direct measurement of parental IQ.

In contrast to observational studies, Lazarus *et al.*^[53] showed in a prospective randomised trial that screening and treatment of hypothyroidism were not significantly beneficial in improvement of cognitive abilities in children born to mothers with hypothyroidism. However, this trial was criticised due to significant loss to follow-up (25% of women) and initiation of LT₄ therapy beyond a critical time that might have a significant influence on cognitive function. In addition, women included in this trial might have had milder hypothyroidism (mean TSH level 3.8 mIU/L)^[53] than women in the Haddow trial (mean TSH level 13.2 mIU/L)^[10].

The association of maternal hypothyroidism with obstetric complications was also reported in several trials and results were also conflicting. For instance, Casey *et al.*^[7] recruited pregnant women for measurement of TSH and FT₄ during routine antenatal care at around the 20th week gestation or less and followed them prospectively to assess for obstetric outcomes associated with SCH. In this study, 404 out of 17298 pregnant women were identified to have SCH, and they were found to have three-fold increased risk to develop abruptio placentae and two-fold risk of preterm delivery. In another study,

using data from prospective prenatal population-based study, Wilson *et al.*^[59] found a significant association between SCH and risk of preeclampsia in pregnant women ($P = 0.03$). Negro *et al.*^[60] conducted a secondary analysis of the original prospective and randomised Negro *et al.*^[8] that tested the influence of LT₄ therapy on adverse outcomes. Women with negative TPO antibodies were grouped into either TSH between 2.5-5.0 mIU/L or < 2.5 mIU/L. There was a significant difference in the rate of pregnancy loss between the two groups (6.1% in the group with higher TSH level vs 3.6% in the group with lower TSH level) ($P = 0.006$).

On the contrary, Cleary-Goldman *et al.*^[9] used stored blood samples from the prospective multicenter First And Second Trimester Evaluation of Risk (FASTER) to evaluate whether maternal hypothyroidism was associated with adverse obstetric outcomes. In the secondary analysis, SCH was observed in 2.2% of women and was not associated with an increased risk of obstetric complications, such as preterm labor, hypertensive disorders, preterm delivery and miscarriage. IH was observed in 2.3% of women and was associated with fewer obstetric complications (preterm labor, macrosomia in the first trimester and GDM in the second trimester). This study also demonstrated that both thyroglobulin autoantibodies (TGAb) and thyroid peroxidase (TPO) antibodies were associated with an increased risk of premature rupture of membranes^[9].

Is universal screening cost effective?

Ideally, well-designed randomised controlled trials (RCTs) can provide evidence to ascertain benefits of universal screening over a selective "high risk" approach. However, even if such evidence was to show a clear advantage of universal screening and clinical benefits of initiating LT₄ therapy, it is not debatable if this approach would be preferable from a health-economic point of view. Danese *et al.*^[61] conducted a cost-utility analysis of screening adults above 35 years old for thyroid dysfunction utilising costs in dollars and health benefits in quality adjusted life year (QALY) gained. They demonstrated that the cost-effectiveness of screening adults above 35 years old using measurement of TSH was \$9223/QALY, \$22595/QALY for women and men respectively and that the screening was markedly cost-effective in older women. Similarly, Bona *et al.*^[62] showed that screening was cost-effective in adults above 60 years old.

Cost analyses evaluating screening for hypothyroidism in pregnant women have suggested cost-effectiveness of universal screening. Dosiou *et al.*^[63] compared costs and clinical benefits of universal screening against no screening using the Markov model. Women without history of thyroid dysfunction were included in the model and screened for autoimmune thyroid dysfunction with TSH and TPO antibodies measurement. It was observed that screening with TSH saved \$102 and raised QALY by 5.84 d compared with no screening, while testing with TPO antibodies cost \$212 and raised QALY by 5.11

d compared with TSH screening. Likewise, Thung *et al.*^[39] compared the two screening strategies in asymptomatic SCH during pregnancy; universal screening vs no screening using a decision analysis model. Women in the universal screening strategy were screened with TSH measurement and received LT₄ therapy if diagnosed with SCH. This analysis model showed that universal screening is cost-effective and that screening 100000 women during pregnancy saved \$8356383 and gained 589.3 QALYs.

The major limitation of these studies remains the fact that this analyses were based on data from observational trials, such as Haddow *et al.*^[10] and Pop *et al.*^[50], rather than from RCTs. As a consequence, a universal screening approach should not be adopted based on what can be deemed as level 2 evidence. However, Dosiou *et al.*^[64] recently conducted a cost-effectiveness study on screening asymptomatic pregnant women for autoimmune thyroid dysfunction based on data from RCTs. They used "TreeAge Pro" model to compare universal screening approach vs selective screening or no screening by measurement of TSH and TPO antibodies. This analysis demonstrated that universal and selective screenings were both cost-effective compared with no screening. The incremental cost-effectiveness ratio (ICERs) of universal screening was \$7138/QALY and that for selective screening was \$6753/QALY. In addition universal screening was found to be greatly cost-effective compared with selective screening, with an ICER of \$7258/QALY. This study is unique in that it is the only cost analysis model that used data from RCTs^[8,65] regarding rates of the effect of treatment on adverse outcomes. Therefore, it would be wise to consider this analysis in future recommendations of universal screening for hypothyroidism during pregnancy.

Is there an intervention that can lead to improvements in the outcomes?

Levothyroxine (LT₄) is currently the synthetic thyroid hormone of choice to treat hypothyroidism and is highly effective with very minimal risk for adverse complications^[66]. A few studies have demonstrated a beneficial role of LT₄ therapy in reducing obstetric complications^[6,65,67,68] and improving outcomes in women with SCH who had underwent *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI)^[69]. However, in the Negro *et al.*^[8] study, the reduced adverse outcome with therapeutic intervention was not statistically significant, and similar results regarding a lack of beneficial role of LT₄ therapy were obtained from another trial^[53]. The conflicting results obtained could be related to the design of these studies, which were mostly observational and thereby limited their ability to provide robust evidence regarding the role of LT₄ therapy in pregnant women with SCH.

Is there an appropriate test to screen for hypothyroidism during pregnancy?

The TSH measurement with trimester-specific reference

limits is a first-line simple marker of thyroid dysfunction^[19,20]. Studies have shown that the serum TSH estimation remains the most specific test to evaluate thyroid function, with greatly increased sensitivity upon using recent generation tests that utilize chemiluminescence labels rather than radio-isotopic substances^[70]. Notably, serum TSH assays may not be sensitive enough in certain clinical scenarios, such as central hypothyroidism, adrenal insufficiency, renal failure, severe non-thyroidal illnesses and ingestion of certain medications^[66]. In consideration of inaccuracy of TSH assays in these circumstances, it has been suggested to measure both TSH and FT₄ in all women for screening purposes.

FT₄ measurement distinguishes between SCH and OH and identifies cases of IH^[71]. However, the gold-standard LC/MS/MS technique is too expensive and not routinely performed in most of the health facilities^[49]. Consequently, the ATA recommends using other methods with consideration of different laboratory reference ranges^[19]. Measurement of TPO antibodies may also be considered to identify euthyroid women with autoimmune disease and to predict later development of postpartum thyroiditis^[71]. Due to significant risk of miscarriage and premature deliveries associated with positive TPO antibodies, some authors suggest to screen women for autoimmunity along with thyroid function early in pregnancy^[65,72].

Is the TSH test acceptable to the population of women?

TSH measurement in women during pregnancy is a less invasive procedure. It is accomplished by means of extracting blood sample with almost no harm to both mother and child, except for slight distress during the procedure. It is also timesaving when compared with other approved screening techniques, such as mammography and colonoscopy. There does, however, remain a possibility of inducing unfavorable effects on the mother, such as social stigma, stress and anxiety^[39].

TREATMENT OF HYPOTHYROIDISM DURING PREGNANCY

There is no doubt that all pregnant women with OH should receive intervention with LT₄^[6,19]. The evidence base for treating OH during pregnancy is derived from observational studies rather than RCTs, since allocation of some women to a non-treatment strategy would clearly be unethical^[19]. On the other hand, there is no general agreement on treating women with SCH, isolated hypothyroxinaemia and euthyroid women with autoimmune hypothyroidism^[11,19,20]. The lack of a general consensus in treating these specific conditions reflects the scarcity of interventional randomised trials that have tested the efficacy of treatment vs no treatment on adverse outcomes^[19].

Beneficial effects of interventional therapy

LT₄ therapy: The evidence for a clear benefit of LT₄

therapy in pregnant women who are identified with mild hypothyroidism is controversial. Abalovich *et al*^[6] showed that adequate LT₄ therapy aiming to maintain TSH level < 4.0 mIU/L reduced the rate of obstetric complications. In a secondary analysis of this trial, it was shown that in women who received adequate LT₄ therapy, the rate of preterm delivery was 1.6% compared with 12.5% in those inadequately treated ($P = 0.05$)^[67]. Similarly, Tan *et al*^[68] showed in a retrospective study that obstetric complications were less frequently encountered when hypothyroidism was treated compared with women who were euthyroid. However, being a retrospective study with the data derived from a single center limits the strength of evidence.

In a well-designed RCT, Negro *et al*^[65] recruited 984 pregnant women to evaluate autoimmune hypothyroidism and the effect of LT₄ therapy in improvement of obstetrical adverse outcomes. Women with positive TPO antibodies were randomised into LT₄ intervention vs non-treatment strategies, and women with undetected TPO antibodies acted as a control strategy. They showed that in women treated with LT₄ therapy, the rate of miscarriage was 3.5% compared with 13.8% in women who were not treated ($P < 0.05$). Similarly, the rate of premature deliveries was 7% compared with 22.4% in women not treated ($P < 0.05$). However, the difference was not statistically significant with regards to other adverse obstetric outcomes.

In an attempt to evaluate the effect of LT₄ doses adjustments on TSH and FT₄ levels, Rotondi *et al*^[73] enrolled 25 pre-conception women who were under treatment with LT₄ therapy and who were wishing to conceive and later confirmed pregnant. They showed that in hypothyroid women receiving modified doses of LT₄ therapy, there were significantly increased FT₄ and reduced TSH levels compared with women who remained under the same LT₄ doses before pregnancy ($P = 0.001$). Similarly, Yassa *et al*^[74] demonstrated that LT₄ therapy is effective in maintaining TSH concentration < 5.0 mIU/L during the first trimester. A significant reduction in TSH level below 0.5 mIU/L has been shown in 32% of women who received lower supplementary doses compared with 65% of women who received higher doses of LT₄ therapy ($P < 0.01$).

Recently, in a large prospective randomised trial, women who received LT₄ therapy had fewer adverse outcomes than women who were not, but the difference was not statistically significant^[8]. In another prospective randomised trial, it was demonstrated that LT₄ therapy significantly improved embryo implantation, live birth and miscarriage rates in women with SCH who underwent IVF/ICSI^[69]. In contrast to these findings, Lazarus *et al*^[53] failed to demonstrate a beneficial role of LT₄ therapy in improvement of neuropsychological abilities in 3 years old children born to mothers with high TSH or low FT₄ levels. Moreover, a recent Cochrane review of four RCTs showed that at present there is no sufficient evidence to support routine treatment with LT₄ of SCH during pregnancy^[75].

Selenium therapy: Another intervention used in recent years is the trace element selenium (also known as 21st amino acid), which has been shown to be beneficial in treating women with positive TPO antibodies to prevent thyroid inflammatory process^[76]. In the thyroid tissue, the activity of glutathione peroxidase is dependent on the availability of selenium, and its deficiency predisposes to increased formation of free radical, hydrogen peroxide and lipid and phospholipid hydro-peroxides. These metabolic intermediates have destructive effects within thyroid tissue and also affect both humoral and cell-mediated immunity, increasing the possibility of autoimmune thyroiditis. Therefore, it has been suggested that selenium supplementation might have immune modulatory effects in autoimmune thyroiditis^[77]. The number of studies testing selenium as a therapeutic intervention during pregnancy is limited. Negro *et al*^[78] identified 169 out of 2143 pregnant women who screened positive for TPO antibodies. They noted a significant risk reduction of 28.6% in postpartum thyroiditis in the group of women who received selenium compared with 48.6% in the placebo group (P value < 0.01). A statistically significant (P value < 0.01) reduction of persistent maternal hypothyroidism in patients who received selenium (11.7%) was observed as compared with women who received placebo (20.3%). Benefits of selenium intervention were also evidenced by significant reduction in the TPO antibodies and improved thyroid ultrasonography findings in women who received selenium compared with the placebo group.

Intravenous immunoglobulin therapy: Clinical evidence on the use of intravenous immunoglobulin (IVIG) therapy in treatment of thyroid autoimmunity during pregnancy is scarcely available and conflicting. Kiprof *et al*^[79] observed a reduction in circulating auto-antibodies and improvement of miscarriage rate in women with immunologic abnormalities suffering recurrent miscarriage. In a prospective non-randomized clinical trial, Stricker *et al*^[80] evaluated 47 women with recurrent miscarriage who had multiple autoimmune diseases (53% were identified with thyroid autoimmunity). They found a significant difference in miscarriage rate between women treated with IVIG and women in the untreated group. In contrast, Vaquero *et al*^[81] found a significant reduction in miscarriage rate in 11 women with thyroid auto-antibodies who received LT₄ therapy compared with 16 women treated with IVIG therapy.

Who should be treated?

In the setting of treating hypothyroidism, in accordance with ATA and Endocrine Society recommendations, all women diagnosed with OH during pregnancy should be treated with LT₄ therapy. However, treatment of pregnant women with SCH remains controversial. While the ATA guideline do not recommend LT₄ therapy in women with SCH and negative TPO antibody, the Endocrine Society recommends treating them regardless of thyroid

autoimmune status^[19,20]. In addition, due to insufficient evidence suggesting harm, the ATA guidelines does not recommend treatment of isolated hypothyroxinemia in pregnant women^[19].

Subclinical hypothyroidism: Several observational studies have demonstrated a significant association between subclinical hypothyroidism (SCH) during pregnancy and obstetrical complications^[7,12,59,60]. However, Cleary-Goldman *et al.*^[9] failed to demonstrate such association. These observational studies were mostly prospective, and the differences in results obtained could be related to using different biochemical definitions for SCH and various timing during gestation to test for TSH. One RCT by Negro *et al.*^[8] found a significant reduction in the rate of obstetrical complications in women with SCH during pregnancy when these women were treated with LT₄ therapy.

The cognitive and neurophysiologic outcomes in offspring born to mothers with SCH have also been tested in several studies, and the results were controversial. The largest observational study of Haddow *et al.*^[10] showed a significant reduction in IQ scores by 7 points among women with SCH compared with controls. Smit *et al.*^[82] in a small prospective observational study demonstrated a significant reduction in the mean mental developmental index (MDI) in children born to mothers with SCH compared with children of euthyroid mothers. Similarly, in another small prospective observational study, Li *et al.*^[14] showed a significant reduction in the Bayley's scale scores and the MDI of children born to women with SCH compared with children born to women with maternal euthyroidism. On the contrary, Lazarus *et al.*^[53] did not find a significant difference in improvement of IQ of children born to women with SCH who had received LT₄ therapy compared to children of women in the control group.

Euthyroid status with autoimmune hypothyroidism: In iodine replete regions, autoimmune thyroiditis remains the most common cause of hypothyroidism during pregnancy^[75]. Autoimmune thyroiditis is defined as the presence of increased levels of TPO and TGAb antibodies in the circulation of pregnant women^[83], but TPO antibodies are considered distinctive and the most sensitive marker^[84].

Several studies have observed the presence of thyroid auto-antibodies in euthyroid mothers associated with adverse obstetric complications; however, these results are inconsistent. In an observational case-control study, Bussen *et al.*^[85] found a significant increase in the incidence of thyroid auto-antibodies in women who presented with a history of recurrent abortions. A Finnish prospective population-based study found that women with TPO and TGAb antibodies had two to three times increased risk of perinatal mortality compared with antibody negative women, regardless of TSH and FT₄ levels^[86]. A meta-analysis of observational studies

reported an odds ratio (OR) of 2.73 for miscarriage in women with thyroid autoimmunity in eight case-control studies and OR of 2.30 in ten longitudinal studies^[76]. Similarly, a recent meta-analysis found the OR for miscarriage in case-control and prospective studies to be 2.55 and 2.31, respectively^[87]. In another recent meta-analysis, Thangaratinam *et al.*^[88] showed an OR of 3.90 and 1.80 for miscarriage in women with autoimmune thyroiditis in prospective cohort studies and in case-control studies, respectively. In a prospective randomized trial, Negro *et al.*^[89] showed a significant increased risk of miscarriage in women with positive TPO antibodies and subfertility undergoing assisted fertilization. In a meta-analysis, Toulis *et al.*^[83] demonstrated a significant two-fold higher risk for miscarriage in women with thyroid auto-antibodies compared with women in the control group ($P < 0.001$).

The cognitive and neurologic development in children born to euthyroid mothers with thyroid auto-antibodies has also been investigated. In a prospective study, Pop *et al.*^[90] reported a significant reduction on the McCarthy's scale scores in children born to euthyroid mothers with positive TPO antibodies compared with mothers who screened negative for TPO antibodies. In a recent retrospective case-control study, Li *et al.*^[14] used stored blood samples from a group of Chinese women who were screened for Down syndrome in 2004. They observed that the mean intelligence and the mean motor scores on the Bayley's scale of 34 children were 10.56 and 9.03 points lower than that of 142 children in the control arm, respectively ($P = 0.001$ in both). However, being retrospective in design, it would be difficult to avoid important confounders such as parental IQ, which might affect the intellect of children. Based on data derived from 3139 women within the Generation R Study, Ghassabian *et al.*^[84] reported an OR of 1.64 for externalizing disorders in the offspring (age 3 years) of women with increased levels of TPO antibodies compared with children born to women with negative TPO antibodies (P value = 0.004). In contrast, children born to women with positive TPO antibodies did not show significant delayed language development (including vocabulary and phrase development) and nonverbal cognitive delay at the age of 3 years.

Treatment with LT₄ therapy may improve miscarriage rates in women with thyroid autoimmunity, however, the results are inconsistent. For instance, in a well-designed RCT, Negro *et al.*^[65] demonstrated a significant reduction in the rate of miscarriage and premature deliveries upon treatment with LT₄ therapy in women with positive TPO antibodies during pregnancy. Previously, Negro *et al.*^[89] did not find that LT₄ therapy improved miscarriage rate. However, a meta-analysis of both studies revealed a significantly reduced relative risk of 52% in miscarriage rate upon treatment with LT₄ therapy^[88].

Isolated hypothyroxinemia: The association between isolated hypothyroxinemia (IH) during pregnancy and

obstetrical complications is controversial. Casey *et al*^[91] identified 233 out of 17298 pregnant women with IH and found no associated increased risk of obstetric complications. In contrast, Cleary-Goldman *et al*^[9] found in their secondary analysis a significant association of IH and increased risk of preterm labor, macrosomia and GDM.

Recent evidence suggests that IH may adversely affect offspring's cognitive and neurologic outcomes, although the results are equivocal. In a prospective observational study, Pop *et al*^[13] showed a significant reduction in the mental and motor functions of the Bayley's scale scores in the offspring of women with IH compared with those of the offspring of women in the control group. Similarly, in a small prospective observational study, Li *et al*^[14] showed a significant reduction in the intelligence and motor scores of children born to women with IH compared with children born to women with maternal euthyroidism. Recently, Henrichs *et al*^[5] showed in the largest prospective Generation R study (a population-based cohort) that there was a significant risk of impairment in expressive language and nonverbal cognition in children born to mothers with IH. However, the assessment of children's cognitive development in this study was totally dependent on mothers reporting, a fact which might increase the risk of observer bias. In contrast, Lazarus *et al*^[53] did not show a significant difference between the children's IQ of women with IH who received LT₄ therapy as compared to the control group. This randomized trial had several criticisms though, including significant loss to follow-up. Similarly, in an observational case-control study, Craig *et al*^[92] found that the Bayley's scale scores of children born to women with FT₄ level below the 3rd percentile did not differ significantly from scores of children born to women with FT₄ level between the 10th and 90th percentile.

Hypothesis-1

From the foregoing discussion it is obvious that screening pregnant women for hypothyroidism meets most of the Wilson and Jungner criteria that justify screening for disease. However, the evidence of associated adverse outcomes is not clear enough. There is also a lack of good quality evidence regarding impact of maternal subclinical hypothyroidism on neuropsychological development in children. The association of maternal hypothyroidism with obstetric complications also remains contentious. In addition, the evidence for a clear benefit of therapeutic intervention in pregnant women with mild hypothyroidism is also not convincing. Inadequacy of clear evidence for both associated adverse complications and efficacy of intervention may partially act against Hypothesis-1. Studying the impact of screening and treatment on improvement of children neurocognitive status and obstetric complications in large RCTs will be important to understand further the impact of milder thyroid under-activity upon outcomes for mother as well

as the child.

On the other hand, previous cost analyses models were based on data from observational studies, unlike recent models that used data from RCTs. The recent analysis model of Dosiou *et al*^[64] supports the cost-effectiveness of universal screening. This significant study supports Hypothesis-1 and could potentially influence feasibility to adopt universal screening for hypothyroidism during pregnancy. Moreover, hypothyroidism during pregnancy should be considered an important health issue with wide-spread prevalence as per the study of Blatt *et al*^[17]. Further inclusion of women with EAD and IH adds further weight in favour of Hypothesis-1.

The screening program will identify both overt as well as subclinical hypothyroidism and other subtypes. There is level 1 evidence that suggests adverse maternal and foetal outcomes if overt hypothyroidism remains untreated in pregnancy; on the other hand, there is lack of evidence on the beneficial impact of therapeutic intervention in subclinical hypothyroidism. Therefore, universal screening, if cost effective, will improve obstetric as well as foetal outcomes in a subset of patients (overt hypothyroidism) even though the other subgroup (subclinical hypothyroidism) may not be benefited by this approach. Although screening for hypothyroidism during pregnancy does not satisfy most of the Wilson and Jungner criteria for a standard screening test, it is difficult to rationalize only a "high risk" screening approach for this condition associated with maternal as well as neonatal morbidity. It is worthwhile to note that the patient population to screen is already well defined (cohort of pregnant women), which further enhances cost effectiveness. In addition, the easy access of the TSH test as an appropriate tool and acceptability to the population of women may further augment justification of screening and supports Hypothesis-1.

Hypothesis-2

We have reviewed the available literature to evaluate complications and efficacy of intervention in SCH, IH and euthyroid women with autoimmune hypothyroidism during pregnancy. To discuss and analyze Hypothesis-2, these three sub-groups will be discussed separately.

Firstly, observational studies in women with SCH are not homogenous with regard to using different biochemical definitions for SCH and different timing to test for TSH. Therefore, the quantity and consistency of data are suggestive, although not conclusive, in demonstration of an association with adverse obstetrical complications. These studies suggest a possible association of SCH and increased risk of hypertensive disorders, pregnancy loss, abruptio placentae and preterm delivery^[7,12,59,60], but Cleary-Goldman *et al*^[9] found no such association. It could be possible that the increased risk for adverse obstetrical outcomes in women with SCH in these studies was a consequence of an additive effect of women being at risk to develop these

complications. The women populations in Negro *et al*^[60] were Caucasian Italian and that in Casey *et al*^[7] were medically indigent from a single hospital, and as such, the generalizability of their findings remains a genuine concern. In addition, the population in Cleary-Goldman *et al*^[9] belongs to heterogeneous backgrounds.

On the other hand, evidence from one RCT convincingly demonstrated that LT₄ therapy promoted improvement of adverse obstetric complications in women with SCH (Negro *et al*^[8]). The data of this study were used in the recent cost effectiveness analysis by Dosiou *et al*^[64], which demonstrated that universal screening is clearly cost-effective based on the rates of the effect of LT₄ therapy on adverse outcomes. The evidence obtained from this RCT and the cost effectiveness analysis supports Hypothesis-2 with regard to the benefits of treating SCH in pregnant women. The evidence for impaired cognitive outcomes in offspring born to mothers with SCH was obtained mostly from observational studies^[10,14,82], but intervention with LT₄ therapy in a prospective randomised trial has not shown beneficial impact in improving cognitive outcomes^[53]. However, there are two important drawbacks of this study: the significant loss to follow-up and the late initiation of LT₄ therapy during gestation. Therefore, with regards to cognitive outcomes, it seems difficult to support Hypothesis-2 based on evidence derived mainly from observational rather than well-designed RCTs.

Secondly, observational studies showed that thyroid autoimmunity has been linked with an increased risk of habitual abortion, miscarriage, preterm delivery and increased risk of perinatal mortality^[85,86]. These observations were further supported by a prospective randomized trial (but not placebo controlled) of Negro *et al*^[89] and four recent meta-analysis of observational and cohort studies^[76,83,87,88]. This significant association does not infer a causal relationship between autoimmune thyroiditis and risk of miscarriage because other autoimmune diseases, such as antiphospholipid syndrome and systemic lupus erythematosus, could also influence pregnancy outcomes. Impaired cognitive outcomes in offspring born to mothers with thyroid autoimmunity were demonstrated in observational studies^[14,90]. However, this was not the case in the recent Generation R Study^[84]. Although large, prospective and population-based, the main drawback of this study is that, unlike previous studies, the assessment of children's cognitive development was totally dependent on parental subjective assessment, a fact that might increase the possibility of an observer bias. However, both father and mother were asked separately to report on their child's behavior, and both were blinded to the results of thyroid function. A benefit of intervention with LT₄ therapy was not clear and inconsistent^[65,88,89]. In view of the limited number of studies investigating the effect of LT₄ therapy in euthyroid women with autoimmune disease and their smaller sample size, it is difficult to make a clear conclusion of effectiveness. However, the trend for reduced miscarriage and preterm delivery in women treated with

LT₄ therapy may suggest a beneficial role. On the other hand, use of other interventions, such as selenium and IVIG therapies, to treat thyroid autoimmunity in pregnant mothers has not been extensively studied, and results are conflicting. Moreover, the beneficial results obtained need validation in a larger group of women using well-designed trials, bearing in mind the issues of safety and cost effectiveness. Therefore, in view of these findings regarding the benefits of intervention in euthyroid women with thyroid autoimmunity and lack of RCTs and cost effectiveness analyses, it seems unjustifiable to support Hypothesis-2.

Finally, the results of observational studies investigating the association of IH with adverse obstetrical outcomes^[9,91] and that with adverse cognitive and neurological outcomes^[5,13,14,53,92] have been inconsistent. In addition, there has been no improvement in cognitive and neurological outcomes in children born to mothers with isolated hypothyroxinaemia upon intervention with LT₄ therapy^[53]. Therefore, in view of these findings and a lack of clear evidence indicating poor outcome of isolated hypothyroxinaemia, it seems difficult to recommend firmly treating this condition during pregnancy. Moreover, routine FT₄ immunoassays are affected by elevated TBG and other binding proteins, whereas the gold-standard LC/MS/MS technique is not available in most of the health facilities^[48]. Consequently, choosing appropriate candidates for treatment based on accurate FT₄ measurements might not be cost effective, and it remains difficult to support Hypothesis-2.

CONCLUSION

In conclusion, screening asymptomatic women for mild thyroid dysfunction during pregnancy could offer an opportunity to initiate early intervention and to obtain further epidemiological data to evaluate natural history of SCH. It is clear that carrying out universal screening to identify the varieties of hypothyroidism during pregnancy meets most of the general criteria that justify screening for a disease. Hypothyroidism during pregnancy could be considered an important health issue when SCH, IH and euthyroid women with autoimmune hypothyroidism were included in the diagnosis, using the recent ATA definitions. Moreover, universal screening was found to be greatly cost-effective compared with selective screening in a recent cost analysis. However, an important limitation in studies involving cost utility analysis is the lack of prospective experimental trials evaluating the effects of treatment against no treatment on neuropsychological development in children born to women with hypothyroidism. In addition, the evidence of associated adverse outcomes was also not conclusive due to a lack of well-designed randomised trials testing the evidence of a clear benefit of intervention. Few RCTs demonstrate that LT₄ therapy promotes improvement of adverse obstetric complications in women with SCH, but the evidence for impaired cognitive outcomes is

inconsistent. Similarly, it is also difficult to make a clear conclusion of LT₄ therapy effectiveness in cases of thyroid autoimmunity and isolated hypothyroxinaemia based on observational studies. Nevertheless, it seems justifiable to treat all women with SCH during pregnancy with LT₄ therapy, same as women with OH. In addition, because of uncertainty of a possible beneficial role of intervention in thyroid autoimmunity and isolated hypothyroxinaemia, it seems difficult to advise for or leaving aside treating these conditions. The conclusion drawn from most of the trials conducted has been limited by lack of statistical power and the controversial results obtained. In the future, the most favorable trial would be expected to test women with SCH, IH and thyroid auto-antibodies during pregnancy. Ideally this trial should have a larger population of different ethnic backgrounds, be double-blinded and include a well matched control group. A relatively longer follow-up of children born to mothers with SCH would be crucial to evaluate cognitive and neurological outcomes.

REFERENCES

- 1 **de Escobar GM**, Obregón MJ, del Rey FE. Maternal thyroid hormones early in pregnancy and fetal brain development. *Best Pract Res Clin Endocrinol Metab* 2004; **18**: 225-248 [PMID: 15157838 DOI: 10.1016/j.beem.2004.03.012]
- 2 **de Escobar GM**, Obregón MJ, del Rey FE. Iodine deficiency and brain development in the first half of pregnancy. *Public Health Nutr* 2007; **10**: 1554-1570 [PMID: 18053280 DOI: 10.1017/S1368980007360928]
- 3 **Matsuura N**, Konishi J. Transient hypothyroidism in infants born to mothers with chronic thyroiditis--a nationwide study of twenty-three cases. The Transient Hypothyroidism Study Group. *Endocrinol Jpn* 1990; **37**: 369-379 [PMID: 2253587 DOI: 10.1507/endocrj1954.37.369]
- 4 **Williams GR**. Neurodevelopmental and neurophysiological actions of thyroid hormone. *J Neuroendocrinol* 2008; **20**: 784-794 [PMID: 18601701 DOI: 10.1111/j.1365-2826.2008.01733.x]
- 5 **Henrichs J**, Bongers-Schokking JJ, Schenk JJ, Ghassabian A, Schmidt HG, Visser TJ, Hooijkaas H, de Muinck Keizer-Schrama SM, Hofman A, Jaddoe VV, Visser W, Steegers EA, Verhulst FC, de Rijke YB, Tiemeier H. Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the generation R study. *J Clin Endocrinol Metab* 2010; **95**: 4227-4234 [PMID: 20534757 DOI: 10.1210/jc.2010-0415]
- 6 **Abalovich M**, Gutierrez S, Alcaraz G, Maccallini G, Garcia A, Levalle O. Overt and subclinical hypothyroidism complicating pregnancy. *Thyroid* 2002; **12**: 63-68 [PMID: 11838732 DOI: 10.1089/105072502753451986]
- 7 **Casey BM**, Dashe JS, Wells CE, McIntire DD, Byrd W, Leveno KJ, Cunningham FG. Subclinical hypothyroidism and pregnancy outcomes. *Obstet Gynecol* 2005; **105**: 239-245 [PMID: 15684146 DOI: 10.1097/01.AOG.0000152345.99421.22]
- 8 **Negro R**, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Universal screening versus case finding for detection and treatment of thyroid hormonal dysfunction during pregnancy. *J Clin Endocrinol Metab* 2010; **95**: 1699-1707 [PMID: 20130074 DOI: 10.1210/jc.2009-2009]
- 9 **Cleary-Goldman J**, Malone FD, Lambert-Messerlian G, Sullivan L, Canick J, Porter TF, Luthy D, Gross S, Bianchi DW, D'Alton ME. Maternal thyroid hypofunction and pregnancy outcome. *Obstet Gynecol* 2008; **112**: 85-92 [PMID: 18591312 DOI: 10.1097/AOG.0b013e3181788dd7]
- 10 **Haddow JE**, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med* 1999; **341**: 549-555 [PMID: 10451459 DOI: 10.1056/NEJM199908193410801]
- 11 **Glinoeir D**, Soto MF, Bourdoux P, Lejeune B, Delange F, Lemone M, Kinthaert J, Robijn C, Grun JP, de Nayer P. Pregnancy in patients with mild thyroid abnormalities: maternal and neonatal repercussions. *J Clin Endocrinol Metab* 1991; **73**: 421-427 [PMID: 1906897 DOI: 10.1210/jcem-73-2-421]
- 12 **Leung AS**, Millar LK, Koonings PP, Montoro M, Mestman JH. Perinatal outcome in hypothyroid pregnancies. *Obstet Gynecol* 1993; **81**: 349-353 [PMID: 8437784 DOI: 10.1016/0020-7292(93)90343-U]
- 13 **Pop VJ**, Brouwers EP, Vader HL, Vulsma T, van Baar AL, de Vijlder JJ. Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. *Clin Endocrinol (Oxf)* 2003; **59**: 282-288 [PMID: 12919150 DOI: 10.1046/j.1365-2265.2003.01822.x]
- 14 **Li Y**, Shan Z, Teng W, Yu X, Li Y, Fan C, Teng X, Guo R, Wang H, Li J, Chen Y, Wang W, Chawinga M, Zhang L, Yang L, Zhao Y, Hua T. Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25-30 months. *Clin Endocrinol (Oxf)* 2010; **72**: 825-829 [PMID: 19878506 DOI: 10.1111/j.1365-2265.2009.03743.x]
- 15 **Glinoeir D**, Riahi M, Grün JP, Kinthaert J. Risk of subclinical hypothyroidism in pregnant women with asymptomatic autoimmune thyroid disorders. *J Clin Endocrinol Metab* 1994; **79**: 197-204 [PMID: 8027226 DOI: 10.1210/jcem.79.1.8027226]
- 16 **Lejeune B**, Grun JP, de Nayer P, Servais G, Glinoeir D. Antithyroid antibodies underlying thyroid abnormalities and miscarriage or pregnancy induced hypertension. *Br J Obstet Gynaecol* 1993; **100**: 669-672 [PMID: 8369252 DOI: 10.1111/j.1471-0528.1993.tb14236.x]
- 17 **Blatt AJ**, Nakamoto JM, Kaufman HW. National status of testing for hypothyroidism during pregnancy and postpartum. *J Clin Endocrinol Metab* 2012; **97**: 777-784 [PMID: 22170721 DOI: 10.1210/jc.2011-2038]
- 18 **Vaidya B**, Hubalewska-Dydejczyk A, Laurberg P, Negro R, Vermiglio F, Poppe K. Treatment and screening of hypothyroidism in pregnancy: results of a European survey. *Eur J Endocrinol* 2012; **166**: 49-54 [PMID: 22023792 DOI: 10.1530/EJE-11-0729]
- 19 **Stagnaro-Green A**, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, Nixon A, Pearce EN, Soldin OP, Sullivan S, Wiersinga W; American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid* 2011; **21**: 1081-1125 [PMID: 21787128 DOI: 10.1089/thy.2011.0087]
- 20 **De Groot L**, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH, Eastman CJ, Lazarus JH, Lutan D, Mandel SJ, Mestman J, Rovet J, Sullivan S. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2012; **97**: 2543-2565 [PMID: 22869843 DOI: 10.1210/jc.2011-2803]
- 21 **Lazarus JH**. Thyroid Regulation and Dysfunction in the Pregnant Patient. 2018 April 10. South Dartmouth, MA, United States; 02748. Available from: URL: <http://www.thyroidmanager.org/chapter/thyroid-regulation-and-dysfunction-in-the-pregnant-patient/>
- 22 **Hershman JM**. Physiological and pathological aspects of the effect of human chorionic gonadotropin on the thyroid. *Best Pract Res Clin Endocrinol Metab* 2004; **18**: 249-265 [PMID: 15157839 DOI: 10.1016/j.beem.2004.03.010]
- 23 **Glinoeir D**. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. *Endocr Rev* 1997; **18**: 404-433 [PMID: 9183570 DOI: 10.1210/edrv.18.3.0300]
- 24 **Patel J**, Landers K, Li H, Mortimer RH, Richard K. Delivery of maternal thyroid hormones to the fetus. *Trends Endocrinol Metab* 2011; **22**: 164-170 [PMID: 21414798 DOI: 10.1016/j.tem.2011.02.002]

- 25 **Abu-Ouf NM**, Jan MM. The impact of maternal iron deficiency and iron deficiency anemia on child's health. *Saudi Med J* 2015; **36**: 146-149 [PMID: 25719576 DOI: 10.15537/smj.2015.2.10289]
- 26 **Hess SY**, Zimmermann MB, Arnold M, Langhans W, Hurrell RF. Iron deficiency anemia reduces thyroid peroxidase activity in rats. *J Nutr* 2002; **132**: 1951-1955 [PMID: 12097675 DOI: 10.1093/jn/132.7.1951]
- 27 **Beard J**, Tobin B, Green W. Evidence for thyroid hormone deficiency in iron-deficient anemic rats. *J Nutr* 1989; **119**: 772-778 [PMID: 2498473 DOI: 10.1093/jn/119.5.772]
- 28 **Beard JL**, Borel MJ, Derr J. Impaired thermoregulation and thyroid function in iron-deficiency anemia. *Am J Clin Nutr* 1990; **52**: 813-819 [PMID: 2239756 DOI: 10.1093/ajcn/52.5.813]
- 29 **Martinez-Torres C**, Cubeddu L, Dillmann E, Brengelmann GL, Leets I, Layrisse M, Johnson DG, Finch C. Effect of exposure to low temperature on normal and iron-deficient subjects. *Am J Physiol* 1984; **246**: R380-R383 [PMID: 6703092 DOI: 10.1152/ajpregu.1984.246.3.R380]
- 30 **Li S**, Gao X, Wei Y, Zhu G, Yang C. The Relationship between Iron Deficiency and Thyroid Function in Chinese Women during Early Pregnancy. *J Nutr Sci Vitaminol (Tokyo)* 2016; **62**: 397-401 [PMID: 28202844 DOI: 10.3177/jnsv.62.397]
- 31 **Erdogan M**, Kösenli A, Ganidagli S, Kulaksizoglu M. Characteristics of anemia in subclinical and overt hypothyroid patients. *Endocr J* 2012; **59**: 213-220 [PMID: 22200582 DOI: 10.1507/endocrj.EJ11-0096]
- 32 **Mullur R**, Liu YY, Brent GA. Thyroid hormone regulation of metabolism. *Physiol Rev* 2014; **94**: 355-382 [PMID: 24692351 DOI: 10.1152/physrev.00030.2013]
- 33 **Koibuchi N**, Jingu H, Iwasaki T, Chin WW. Current perspectives on the role of thyroid hormone in growth and development of cerebellum. *Cerebellum* 2003; **2**: 279-289 [PMID: 14964687 DOI: 10.1080/14734220310011920]
- 34 **Zoeller RT**. New insights into thyroid hormone action in the developing brain: the importance of T3 degradation. *Endocrinology* 2010; **151**: 5089-5091 [PMID: 20962056 DOI: 10.1210/en.2010.0926]
- 35 **Calvo R**, Obregón MJ, Ruiz de Oña C, Escobar del Rey F, Morreale de Escobar G. Congenital hypothyroidism, as studied in rats. Crucial role of maternal thyroxine but not of 3,5,3'-triiodothyronine in the protection of the fetal brain. *J Clin Invest* 1990; **86**: 889-899 [PMID: 2394838 DOI: 10.1172/JCI114790]
- 36 **Sarkar D**. Recurrent pregnancy loss in patients with thyroid dysfunction. *Indian J Endocrinol Metab* 2012; **16**: S350-S351 [PMID: 23565424 DOI: 10.4103/2230-8210.104088]
- 37 **Tirosh D**, Benshalom-Tirosh N, Novack L, Press F, Beer-Weisel R, Wiznitzer A, Mazor M, Erez O. Hypothyroidism and diabetes mellitus - a risky dual gestational endocrinopathy. *PeerJ* 2013; **1**: e52 [PMID: 23638390 DOI: 10.7717/peerj.52]
- 38 **Amouzegar A**, Mehran L, Sarvaghi F, Delshad H, Azizi F, Lazarus JH. Comparison of the American Thyroid Association with the Endocrine Society practice guidelines for the screening and treatment of hypothyroidism during pregnancy. *Hormones (Athens)* 2014; **13**: 307-313 [PMID: 25079454 DOI: 10.14310/horm.2002.1486]
- 39 **Thung SF**, Funai EF, Grobman WA. The cost-effectiveness of universal screening in pregnancy for subclinical hypothyroidism. *Am J Obstet Gynecol* 2009; **200**: 267.e1-267.e7 [PMID: 19114278 DOI: 10.1016/j.ajog.2008.10.035]
- 40 **Glinioer D**, Abalovich M. Unresolved questions in managing hypothyroidism during pregnancy. *BMJ* 2007; **335**: 300-302 [PMID: 17690371 DOI: 10.1136/bmj.39189.513935.BE]
- 41 **Stricker R**, Echenard M, Eberhart R, Chevailler MC, Perez V, Quinn FA, Stricker R. Evaluation of maternal thyroid function during pregnancy: the importance of using gestational age-specific reference intervals. *Eur J Endocrinol* 2007; **157**: 509-514 [PMID: 17893266 DOI: 10.1530/EJE-07-0249]
- 42 **Soldin OP**, Tractenberg RE, Hollowell JG, Jonklaas J, Janicic N, Soldin SJ. Trimester-specific changes in maternal thyroid hormone, thyrotropin, and thyroglobulin concentrations during gestation: trends and associations across trimesters in iodine sufficiency. *Thyroid* 2004; **14**: 1084-1090 [PMID: 15650363 DOI: 10.1089/thy.2004.14.1084]
- 43 **Panesar NS**, Li CY, Rogers MS. Reference intervals for thyroid hormones in pregnant Chinese women. *Ann Clin Biochem* 2001; **38**: 329-332 [PMID: 11471873 DOI: 10.1258/0004563011900830]
- 44 **Haddow JE**, Knight GJ, Palomaki GE, McClain MR, Pulkkinen AJ. The reference range and within-person variability of thyroid stimulating hormone during the first and second trimesters of pregnancy. *J Med Screen* 2004; **11**: 170-174 [PMID: 15563772 DOI: 10.1258/0969141042467340]
- 45 **Soldin OP**, Soldin D, Sastoque M. Gestation-specific thyroxine and thyroid stimulating hormone levels in the United States and worldwide. *Ther Drug Monit* 2007; **29**: 553-559 [PMID: 17898643 DOI: 10.1097/FTD.0b013e31815709ac]
- 46 **Roti E**, Gardini E, Minelli R, Bianconi L, Flisi M. Thyroid function evaluation by different commercially available free thyroid hormone measurement kits in term pregnant women and their newborns. *J Endocrinol Invest* 1991; **14**: 1-9 [PMID: 2045620 DOI: 10.1007/BF03350244]
- 47 **Sapin R**, D'Herbomez M, Schlienger JL. Free thyroxine measured with equilibrium dialysis and nine immunoassays decreases in late pregnancy. *Clin Lab* 2004; **50**: 581-584 [PMID: 15481634]
- 48 **Yue B**, Rockwood AL, Sandrock T, La'ulu SL, Kushnir MM, Meikle AW. Free thyroid hormones in serum by direct equilibrium dialysis and online solid-phase extraction-liquid chromatography/tandem mass spectrometry. *Clin Chem* 2008; **54**: 642-651 [PMID: 18258669 DOI: 10.1373/clinchem.2007.098293]
- 49 **Kahric-Janicic N**, Soldin SJ, Soldin OP, West T, Gu J, Jonklaas J. Tandem mass spectrometry improves the accuracy of free thyroxine measurements during pregnancy. *Thyroid* 2007; **17**: 303-311 [PMID: 17465859 DOI: 10.1089/thy.2006.0303]
- 50 **Pop VJ**, Kuijpers JL, van Baar AL, Verkerk G, van Son MM, de Vijlder JJ, Vulsma T, Wiersinga WM, Drexhage HA, Vader HL. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. *Clin Endocrinol (Oxf)* 1999; **50**: 149-155 [PMID: 10396355 DOI: 10.1046/j.1365-2265.1999.00639.x]
- 51 **Horacek J**, Spitalnikova S, Dlabalova B, Malirova E, Vizda J, Svilius I, Cepkova J, Mc Grath C, Maly J. Universal screening detects two-times more thyroid disorders in early pregnancy than targeted high-risk case finding. *Eur J Endocrinol* 2010; **163**: 645-650 [PMID: 20682632 DOI: 10.1530/EJE-10-0516]
- 52 **Vaidya B**, Anthony S, Bilous M, Shields B, Drury J, Hutchison S, Bilous R. Detection of thyroid dysfunction in early pregnancy: Universal screening or targeted high-risk case finding? *J Clin Endocrinol Metab* 2007; **92**: 203-207 [PMID: 17032713 DOI: 10.1210/jc.2006-1748]
- 53 **Lazarus JH**, Bestwick JP, Channon S, Paradise R, Maina A, Rees R, Chiusano E, John R, Guaraldo V, George LM, Perona M, Dall'Amico D, Parkes AB, Joomun M, Wald NJ. Antenatal thyroid screening and childhood cognitive function. *N Engl J Med* 2012; **366**: 493-501 [PMID: 22316443 DOI: 10.1056/NEJMoa1106104]
- 54 **Harris R**, Sawaya GF, Moyer VA, Calonge N. Reconsidering the criteria for evaluating proposed screening programs: reflections from 4 current and former members of the U.S. Preventive services task force. *Epidemiol Rev* 2011; **33**: 20-35 [PMID: 21666224 DOI: 10.1093/epirev/mxr005]
- 55 **Klein RZ**, Haddow JE, Faix JD, Brown RS, Hermos RJ, Pulkkinen A, Mitchell ML. Prevalence of thyroid deficiency in pregnant women. *Clin Endocrinol (Oxf)* 1991; **35**: 41-46 [PMID: 1889138 DOI: 10.1111/j.1365-2265.1991.tb03494.x]
- 56 **Diéguez M**, Herrero A, Avello N, Suárez P, Delgado E, Menéndez E. Prevalence of thyroid dysfunction in women in early pregnancy: does it increase with maternal age? *Clin Endocrinol (Oxf)* 2016; **84**: 121-126 [PMID: 25488673 DOI: 10.1111/cen.12693]
- 57 **Lazarus JH**. Screening for thyroid dysfunction in pregnancy: is it worthwhile? *J Thyroid Res* 2011; **2011**: 397012 [PMID: 21765989 DOI: 10.4061/2011/397012]
- 58 **Man EB**, Jones WS. Thyroid function in human pregnancy. V.

- Incidence of maternal serum low butanol-extractable iodines and of normal gestational TBG and TBPA capacities; retardation of 8-month-old infants. *Am J Obstet Gynecol* 1969; **104**: 898-908 [PMID: 4183108 DOI: 10.1016/0002-9378(69)90644-9]
- 59 **Wilson KL**, Casey BM, McIntire DD, Halvorson LM, Cunningham FG. Subclinical thyroid disease and the incidence of hypertension in pregnancy. *Obstet Gynecol* 2012; **119**: 315-320 [PMID: 22270283 DOI: 10.1097/AOG.0b013e318240de6a]
 - 60 **Negro R**, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Increased pregnancy loss rate in thyroid antibody negative women with TSH levels between 2.5 and 5.0 in the first trimester of pregnancy. *J Clin Endocrinol Metab* 2010; **95**: E44-E48 [PMID: 20534758 DOI: 10.1210/jc.2010-0340]
 - 61 **Danese MD**, Powe NR, Sawin CT, Ladenson PW. Screening for mild thyroid failure at the periodic health examination: a decision and cost-effectiveness analysis. *JAMA* 1996; **276**: 285-292 [PMID: 8656540 DOI: 10.1001/jama.1996.03540040029029]
 - 62 **Bona M**, Santini F, Rivolta G, Grossi E, Grilli R. Cost effectiveness of screening for subclinical hypothyroidism in the elderly. A decision-analytical model. *Pharmacoeconomics* 1998; **14**: 209-216 [PMID: 10186461 DOI: 10.2165/00019053-199814020-00009]
 - 63 **Dosiou C**, Sanders GD, Araki SS, Crapo LM. Screening pregnant women for autoimmune thyroid disease: a cost-effectiveness analysis. *Eur J Endocrinol* 2008; **158**: 841-851 [PMID: 18505905 DOI: 10.1530/EJE-07-0882]
 - 64 **Dosiou C**, Barnes J, Schwartz A, Negro R, Crapo L, Stagnaro-Green A. Cost-effectiveness of universal and risk-based screening for autoimmune thyroid disease in pregnant women. *J Clin Endocrinol Metab* 2012; **97**: 1536-1546 [PMID: 22399510 DOI: 10.1210/jc.2011-2884]
 - 65 **Negro R**, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. *J Clin Endocrinol Metab* 2006; **91**: 2587-2591 [PMID: 16621910 DOI: 10.1210/jc.2005-1603]
 - 66 **Roberts CG**, Ladenson PW. Hypothyroidism. *Lancet* 2004; **363**: 793-803 [PMID: 15016491 DOI: 10.1016/S0140-6736(04)15696-1]
 - 67 **Stagnaro-Green A**. Maternal thyroid disease and preterm delivery. *J Clin Endocrinol Metab* 2009; **94**: 21-25 [PMID: 18984665 DOI: 10.1210/jc.2008-1288]
 - 68 **Tan TO**, Cheng YW, Caughey AB. Are women who are treated for hypothyroidism at risk for pregnancy complications? *Am J Obstet Gynecol* 2006; **194**: e1-e3 [PMID: 16647887 DOI: 10.1016/j.ajog.2005.11.028]
 - 69 **Kim CH**, Ahn JW, Kang SP, Kim SH, Chae HD, Kang BM. Effect of levothyroxine treatment on in vitro fertilization and pregnancy outcome in infertile women with subclinical hypothyroidism undergoing in vitro fertilization/intracytoplasmic sperm injection. *Fertil Steril* 2011; **95**: 1650-1654 [PMID: 21193190 DOI: 10.1016/j.fertnstert.2010.12.004]
 - 70 **Vanderpump MP**, Neary RH, Manning K, Clayton RN. Does an increase in the sensitivity of serum thyrotropin assays reduce diagnostic costs for thyroid disease in the community? *J R Soc Med* 1997; **90**: 547-550 [PMID: 9488012 DOI: 10.1177/01410768970901006]
 - 71 **Brent GA**. Diagnosing thyroid dysfunction in pregnant women: Is case finding enough? *J Clin Endocrinol Metab* 2007; **92**: 39-41 [PMID: 17209222 DOI: 10.1210/jc.2006-2461]
 - 72 **Poppe K**, Glinier D. Thyroid autoimmunity and hypothyroidism before and during pregnancy. *Hum Reprod Update* 2003; **9**: 149-161 [PMID: 12751777 DOI: 10.1093/humupd/dmg012]
 - 73 **Rotondi M**, Mazzziotti G, Sorvillo F, Piscopo M, Cioffi M, Amato G, Carella C. Effects of increased thyroxine dosage pre-conception on thyroid function during early pregnancy. *Eur J Endocrinol* 2004; **151**: 695-700 [PMID: 15588235 DOI: 10.1530/eje.0.1510695]
 - 74 **Yassa L**, Marqusee E, Fawcett R, Alexander EK. Thyroid hormone early adjustment in pregnancy (the THERAPY) trial. *J Clin Endocrinol Metab* 2010; **95**: 3234-3241 [PMID: 20463094 DOI: 10.1210/jc.2010-0013]
 - 75 **Reid SM**, Middleton P, Cossich MC, Crowther CA, Bain E. Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy. *Cochrane Database Syst Rev* 2013; CD007752 [PMID: 23728666 DOI: 10.1002/14651858.CD007752.pub3]
 - 76 **Prummel MF**, Wiersinga WM. Thyroid autoimmunity and miscarriage. *Eur J Endocrinol* 2004; **150**: 751-755 [PMID: 15191343 DOI: 10.1530/eje.0.1500751]
 - 77 **Gärtner R**, Gasnier BC, Dietrich JW, Krebs B, Angstwurm MW. Selenium supplementation in patients with autoimmune thyroiditis decreases thyroid peroxidase antibodies concentrations. *J Clin Endocrinol Metab* 2002; **87**: 1687-1691 [PMID: 11932302 DOI: 10.1210/jcem.87.4.8421]
 - 78 **Negro R**, Greco G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H. The influence of selenium supplementation on postpartum thyroid status in pregnant women with thyroid peroxidase autoantibodies. *J Clin Endocrinol Metab* 2007; **92**: 1263-1268 [PMID: 17284630 DOI: 10.1210/jc.2006-1821]
 - 79 **Kiproov DD**, Nachtigall RD, Weaver RC, Jacobson A, Main EK, Garovoy MR. The use of intravenous immunoglobulin in recurrent pregnancy loss associated with combined alloimmune and autoimmune abnormalities. *Am J Reprod Immunol* 1996; **36**: 228-234 [PMID: 8911631 DOI: 10.1111/j.1600-0897.1996.tb00168.x]
 - 80 **Stricker RB**, Steinleitner A, Bookoff CN, Weckstein LN, Winger EE. Successful treatment of immunologic abortion with low-dose intravenous immunoglobulin. *Fertil Steril* 2000; **73**: 536-540 [PMID: 10689009 DOI: 10.1016/S0015-0282(99)00572-5]
 - 81 **Vaquero E**, Lazzarin N, De Carolis C, Valensise H, Moretti C, Ramanini C. Mild thyroid abnormalities and recurrent spontaneous abortion: diagnostic and therapeutic approach. *Am J Reprod Immunol* 2000; **43**: 204-208 [PMID: 10836249 DOI: 10.1111/j.8755-8920.2000.430404.x]
 - 82 **Smit BJ**, Kok JH, Vulsma T, Briët JM, Boer K, Wiersinga WM. Neurologic development of the newborn and young child in relation to maternal thyroid function. *Acta Paediatr* 2000; **89**: 291-295 [PMID: 10772276 DOI: 10.1111/j.1651-2227.2000.tb18424.x]
 - 83 **Toulis KA**, Goulis DG, Venetis CA, Kolibianakis EM, Negro R, Tarlatzis BC, Papadimas I. Risk of spontaneous miscarriage in euthyroid women with thyroid autoimmunity undergoing IVF: a meta-analysis. *Eur J Endocrinol* 2010; **162**: 643-652 [PMID: 19955261 DOI: 10.1530/EJE-09-0850]
 - 84 **Ghassabian A**, Bongers-Schokking JJ, de Rijke YB, van Mil N, Jaddoe VW, de Munck Keizer-Schrama SM, Hooijkaas H, Hofman A, Visser W, Roman GC, Visser TJ, Verhulst FC, Tiemeier H. Maternal thyroid autoimmunity during pregnancy and the risk of attention deficit/hyperactivity problems in children: the Generation R Study. *Thyroid* 2012; **22**: 178-186 [PMID: 22175242 DOI: 10.1089/thy.2011.0318]
 - 85 **Bussen S**, Steck T. Thyroid autoantibodies in euthyroid non-pregnant women with recurrent spontaneous abortions. *Hum Reprod* 1995; **10**: 2938-2940 [PMID: 8747048 DOI: 10.1093/oxfordjournals.humrep.a135823]
 - 86 **Männistö T**, Vääräsmäki M, Pouta A, Hartikainen AL, Ruokonen A, Surcel HM, Bloigu A, Järvelin MR, Suvanto-Luukkonen E. Perinatal outcome of children born to mothers with thyroid dysfunction or antibodies: a prospective population-based cohort study. *J Clin Endocrinol Metab* 2009; **94**: 772-779 [PMID: 19106271 DOI: 10.1210/jc.2008-1520]
 - 87 **Chen L**, Hu R. Thyroid autoimmunity and miscarriage: a meta-analysis. *Clin Endocrinol (Oxf)* 2011; **74**: 513-519 [PMID: 21198746 DOI: 10.1111/j.1365-2265.2010.03974.x]
 - 88 **Thangaratnam S**, Tan A, Knox E, Kilby MD, Franklyn J, Coomarasamy A. Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence. *BMJ* 2011; **342**: d2616 [PMID: 21558126 DOI: 10.1136/bmj.d2616]
 - 89 **Vilain R**. [Treatment of keloids and hypertrophic cicatrices]. *Sem Ther* 1964; **40**: 122-124 [PMID: 5878930 DOI: 10.1093/humrep/deh843]
 - 90 **Pop VJ**, de Vries E, van Baar AL, Waelkens JJ, de Rooy HA, Horsten M, Donkers MM, Komprou IH, van Son MM, Vader

- HL. Maternal thyroid peroxidase antibodies during pregnancy: a marker of impaired child development? *J Clin Endocrinol Metab* 1995; **80**: 3561-3566 [PMID: 8530599 DOI: 10.1210/jcem.80.12.8530599]
- 91 **Casey BM**, Dashe JS, Spong CY, McIntire DD, Leveno KJ, Cunningham GF. Perinatal significance of isolated maternal hypothyroxinemia identified in the first half of pregnancy. *Obstet Gynecol* 2007; **109**: 1129-1135 [PMID: 17470594 DOI: 10.1097/01.AOG.0000262054.03531.24]
- 92 **Craig WY**, Allan WC, Kloza EM, Pulkkinen AJ, Waisbren S, Spratt DI, Palomaki GE, Neveux LM, Haddow JE. Mid-gestational maternal free thyroxine concentration and offspring neurocognitive development at age two years. *J Clin Endocrinol Metab* 2012; **97**: E22-E28 [PMID: 22031521 DOI: 10.1210/jc.2011-1772]

P- Reviewer: Dahiya K **S- Editor:** Cui LJ **L- Editor:** Filipodia
E- Editor: Huang Y





Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>



World Journal of *Obstetrics and Gynecology*

World J Obstet Gynecol 2018 October 22; 7(2): 17-23





EDITORIAL

- 17 Endorphins, oxytocin, sexuality and romantic relationships: An understudied area

Khajehei M, Behroozpour E

Contents

World Journal of Obstetrics and Gynecology
Volume 7 Number 2 October 22, 2018

ABOUT COVER

Editorial Board Member of *World Journal of Obstetrics and Gynecology*, Xiu-Quan Zhang, MD, PhD, University of Utah School of Medicine, Cardiothoracic Surgery, Reproductive Genetics, Salt Lake City, UT 84132, United States

AIM AND SCOPE

World Journal of Obstetrics and Gynecology (*World J Obstet Gynecol*, *WJOG*, online ISSN 2218-6220, DOI: 10.5317) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJOG covers topics concerning pregnancy complications, obstetric surgical procedures, diagnostic imaging, endoscopy, reproductive endocrinology, tumors, pelvic diseases, evidence-based medicine, epidemiology and nursing.

We encourage authors to submit their manuscripts to *WJOG*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

INDEXING/ABSTRACTING

World Journal of Obstetrics and Gynecology (*WJOG*) is now indexed in China National Knowledge Infrastructure (CNKI), and Superstar Journals Database.

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Yun-Xiao Jian Wu*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Li-Jun Cui*
Proofing Editorial Office Director: *Jin-Lei Wang*

NAME OF JOURNAL

World Journal of Obstetrics and Gynecology

ISSN

ISSN 2218-6220 (online)

LAUNCH DATE

June 10, 2012

EDITOR-IN-CHIEF

Zeev Blumenfeld, MD, Associate Professor, Department of Reproductive Endocrinology, Rambam Medical Center, Technion-Faculty of Medicine, Haifa 31096, Israel

EDITORIAL BOARD MEMBERS

All editorial board members resources online at <http://www.wjgnet.com/2218-6220/editorialboard.htm>

EDITORIAL OFFICE

Fang-Fang Ji, Director
World Journal of Obstetrics and Gynecology
Baishideng Publishing Group Inc

7901 Stoneridge Drive,
Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242

Fax: +1-925-2238243

E-mail: editorialoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/helpdesk>

<http://www.wjgnet.com>

PUBLISHER

Baishideng Publishing Group Inc
7901 Stoneridge Drive,
Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242

Fax: +1-925-2238243

E-mail: bpgoffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/helpdesk>

<http://www.wjgnet.com>

PUBLICATION DATE

October 22, 2018

COPYRIGHT

© 2018 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

<http://www.wjgnet.com/bpg/gerinfo/204>

ONLINE SUBMISSION

<http://www.wjgnet.com>

Endorphins, oxytocin, sexuality and romantic relationships: An understudied area

Marjan Khajehei, Elmira Behroozpour

Marjan Khajehei, Department of Women's and Newborn Health,
Westmead Hospital, Westmead 2145, Australia

Marjan Khajehei, School of Women's and Children's Health,
University of New South Wales, Sydney 2000, Australia

Marjan Khajehei, Westmead Medical School, University of
Sydney, Sydney, Australia 2000

Elmira Behroozpour, Department of Microbiology, Azad
University of Saveh, Saveh 367546, Iran

ORCID number: Marjan Khajehei (0000-0002-0648-7871);
Elmira Behroozpor (0000-0002-8336-3186).

Author contributions: Khajehei M and Behroozpor E
contributed to literature search, summarising the findings,
preparing the manuscript draft and approving the final draft.

Conflict-of-interest statement: The authors declare no conflict
of interest.

Open-Access: This article is an open-access article which was
selected by an in-house editor and fully peer-reviewed by external
reviewers. It is distributed in accordance with the Creative
Commons Attribution Non Commercial (CC BY-NC 4.0) license,
which permits others to distribute, remix, adapt, build upon this
work non-commercially, and license their derivative works on
different terms, provided the original work is properly cited and
the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited Manuscript

Correspondence to: Marjan Khajehei, BSc, MSc, PhD,
Department of Women's and Newborn Health, Westmead
Hospital, Westmead, Room 3046, Westmead 2145,
Australia. marjan.khajehei@health.nsw.gov.au
Telephone: +61-2-88903706
Fax: +61-2-98458664

Received: June 22, 2018

Peer-review started: June 22, 2018

First decision: September 3, 2018

Revised: September 10, 2018

Accepted: October 12, 2018

Article in press: October 12, 2018

Published online: October 22, 2018

Abstract

Endorphins are the body's natural opioids that are created and released by the central nervous system, hypothalamus and pituitary gland. Endorphins have a reputation for pain reduction, enhancing excitement or satisfaction, boosting confidence, enabling control of emotions and generating feelings of euphoria, and are involved in the natural reward cycle. There is also evidence in the literature suggesting the role of endorphins in sexuality (including sexual function and sexual behaviours), as they may regulate the release of sex hormones, prolactin and growth hormone, which are involved in sexual function and love. Endogenous oxytocin is another intrinsic hormone whose role in inducing labour contractions, the delivery of the baby and stimulating lactation has been well studied. However, the potential impact of endorphins and oxytocin on sexuality and romantic relationships is not well understood. This article reviews the research on endorphins and endogenous oxytocin and how they relate to human sexuality and romantic relationships. Some animal studies report the effect of endorphin and oxytocin on sex hormones and mating behaviours, but these findings have not been supported by research into human behaviour, indicating many gaps in knowledge relating to the association between these hormones and human sexuality.

Key words: Romantic relationship; Sexual behaviour;
Sexual function; Endorphins; Oxytocin; Sexuality

© **The Author(s) 2018.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Less is known about the association between endogenous opioids and sexual function and behaviors in

humans. There are mixed reports regarding the impact of oxytocin on sexuality and romantic relationships. The importance of physiological changes during sexual activity and how they can affect human relationships and the gaps in the literature highlight the need for high-quality research to extend our understanding of the hormonal physiology of sexual function and the role of endorphins and oxytocin in human sexuality.

Khajehei M, Behroozpour E. Endorphins, oxytocin, sexuality and romantic relationships: An understudied area. *World J Obstet Gynecol* 2018; 7(2): 17-23 Available from: URL: <http://www.wjgnet.com/2218-6220/full/v7/i2/17.htm> DOI: <http://dx.doi.org/10.5317/wjog.v7.i2.17>

INTRODUCTION

Endorphins are the body's natural opioids, or endogenous opioids, that are created and released by the central nervous system (CNS), hypothalamus and pituitary gland. Endorphins have a reputation for pain reduction, enhancing excitement or satisfaction, boosting confidence, enabling control of emotions and generating feelings of euphoria, and are involved in the natural reward cycle. The release of endorphins in the human body is triggered by a variety of factors, including massage and bodywork^[1], exercise^[2], active performance of music^[3], consumption of certain foods such as dark chocolate^[4], environmental factors such as ultraviolet light^[5], and childbirth^[6]. There is also evidence in the literature suggesting the role of endorphins in sexuality. It is suggested that endorphins regulate the release of other hormones, such as sex hormones, prolactin and growth hormone, which are involved in sexual function and love^[7,8].

Endogenous oxytocin is another intrinsic hormone whose receptors were first discovered in 1984 because of their role in inducing labor contractions, the delivery of the baby and stimulating lactation. Endogenous oxytocin is primarily synthesised in the hypothalamus and is then stored in the posterior pituitary gland, from where it is released into the bloodstream^[9]. The release of endogenous oxytocin can be provoked by a variety of stimuli including sexual and reproductive stimuli (copulation, genital and breast stimulation, birth, olfactory stimuli, and sucking)^[10] and non-sexual stimuli (*i.e.*, grooming, massage and contact with offspring)^[11].

The roles of endorphins and oxytocin are well researched and understood in some areas of health, but their potential impacts on sexuality and romantic relationships are only beginning to be understood. The purpose of this editorial is to review current understanding of endorphins and endogenous oxytocin and how they relate to human sexuality (including sexual function and sexual behaviours, for the purpose of this review).

EFFECT OF BETA-ENDORPHIN ON SEXUALITY AND ROMANTIC RELATIONSHIPS

Human studies

The association between beta-endorphin and sexuality and romantic relationships is mutual, with endogenous sex steroids affecting the neurobiology of sexual function by directly influencing receptors at the nuclear and membrane level or by indirectly affecting the neurotransmitters of neuropeptides (endogenous oxytocin and endorphins)^[12]. For this reason, it has been suggested that endorphins may be involved in the regulation of sexual function in humans.

It has been suggested that a mild increase in the beta-endorphin level creates a sense of wellbeing, and that a greater increase may lead to analgesia and euphoria. A variety of behavioral experiences can activate the release of beta-endorphin. For example, exercise stimulates secretion of corticotropin-releasing hormone, resulting in an increase in ACTH and endorphins that may enhance an individual's sexuality^[13]. In addition to aerobic exercise, discontinuation of tobacco use and illicit drug use and reduced alcohol consumption improve tissue oxygenation, promote metabolism, reduce body mass index and stimulate endorphin release that may, in turn, boost sexual response^[14].

An increase of endorphin levels during sexual activity in humans is presumed to contribute to attachment and bonding between partners, similar to that of a mother and her newborn^[8]. However, contradictory reports in the literature question the association between sexuality and endorphin levels. For example, in a small study on 10 healthy women, sexual arousal and orgasm resulted in a sharp increase in cardiovascular parameters and plasma catecholamine concentrations along with an increase in the concentration of plasma prolactin, but no changes were seen in the plasma concentrations of beta-endorphin^[15]. A similar neuroendocrine response pattern to sexual arousal and orgasm in men was reported in an earlier study by Krüger *et al.*^[16]. Although they showed a transient increase in heart rate and blood pressure as well as noradrenaline and prolactin plasma levels, no changes were seen in the plasma beta-endorphin and other endocrine variables.

Less is known about the association between endogenous opioids and sexual function and behaviors in humans, but it is known that exogenous opiates negatively affect the sexuality of male and female who misuse opiate drugs and contribute to their reduced sexual desire, impaired sexual arousal, decreased genital response, delayed or blocked ejaculation, orgasm dysfunction and infertility^[17]. Opiate drugs negatively affect sexual function through reducing the levels of sex hormones, and their effect on the endocrine system begins immediately after they are taken^[18]. Although little is known about the exact mechanism of sexual

dysfunction in people who are opioid-addicted, and studies in this area are small, the available evidence shows a high prevalence of opioid-induced hypogonadism (up to 90%) in patients who take opiate drugs such as heroin^[19], methadone^[20], intrathecal opioids^[21] and systemic (oral or transdermal) opioids^[22,23]. According to a systematic review and meta-analysis^[24] of the testosterone levels in men and women while using opiate drugs, regular use suppresses the testosterone level in men regardless of the type of opioid being ingested. Testosterone levels in women are not affected by opiate drugs. This sex difference suggests that opiate drugs may have differential mechanisms for endocrine disruption in men and women, and this should be taken into consideration when treating sexual problems in people who are opiate-dependent^[24]. Since there may be different endocrine targets to aim for even in non-opioid-dependent men and women while trying to treat their sexual dysfunction using pharmaceutical drugs, any future drug development for sexual dysfunction needs to consider these differences.

The negative effects of opiate drugs on male sexual function are reversible after opiate withdrawal^[25] or administration of opiate antagonists^[26]. The positive effects of opiate antagonists are increased luteinizing hormone (LH) pulsatility, raised serum testosterone levels^[27], increased *in vitro* sperm motility after administration of naloxone^[28], recurrent spontaneous penile erections, frequent orgasms and more intense sexual arousal and orgasm in healthy adult men who were not addicted to opiates, after administration of naltrexone^[29]. However, these findings are not supported by animal research, indicating a lack of substantial influence of acute or chronic naloxone administration on different sexual activities of isolated and group-housed male rats^[30]. Details of other animal research are discussed in the next section.

The limited research in humans, especially in women, has created inconsistent but, in some cases, interesting results. For example, in the study by Goldstein and Hansteen^[31], a single male subject was recruited and the researchers prematurely concluded that there is no evidence of the involvement of endorphins in male sexual arousal. Other research by Gillman and Lichtigfeld^[32] found that administration of a 2 mg dose of naloxone on two separate occasions enhanced orgasm and pleasure in women, while a single 2 mg dose of naloxone inhibited arousal and orgasm for up to 10 min, suggesting that the relationship of naloxone to orgasm is dose-dependent and potentially parabolic. This is consistent with the notion that endogenous opiates, such as beta-endorphin, have both inhibitory and excitatory effects, but the explanation for the dose-response effect remains obscure^[7].

Animal studies

Findings of animal studies suggest that opioid peptides may have both excitatory and inhibitory effects on sexual

performance and behaviours^[7,33]. When opioid peptides are released in response to stress, they impose their inhibitory effects by acting in the medial preoptic area and the paraventricular nucleus that, in turn, impairs sexual performance^[34]. According to animal studies, it is suggested that endorphins regulate the release of other hormones, such as sex hormones, prolactin and growth hormone, that are involved in sexual function and attachment^[7,8]. It has also been suggested that this may be relevant to the low level of sexual desire in people with symptoms of depression^[35].

Preliminary studies have investigated the mechanisms of inhibition of sexual behavior by opioids. Myers and Baum^[36] showed that naloxone, the opiate receptor antagonist, has a facilitatory effect on masculine sexual performance in rats, resulting in the release of gonadotropin releasing hormone (GnRH). A later study^[37] indicated that infusion of opioid antagonists into the mesencephalic central gray matter increases neuronal GnRH output that in turn enhances the likelihood of lordosis behavior in estrogen-primed female rats. Other studies have shown that acute treatment with opioid antagonists augmented GnRH secretion followed by raised levels of serum LH and testosterone^[38,39].

In a study by Csaba *et al.*^[40], administration of a single dose of endorphin to neonatal rats showed that sexual activity permanently decreased in females after five months and their tendency to refuse the male increased, in addition to male aggression increasing. Female rats showed a permanent increase in the density of uterine estrogen receptors, and male rats showed a decline in the serotonin level in the brain. Although little is known about the interaction of endorphin and other hormones or neurotransmitters in relation to human sexuality, results of the study by Csaba *et al.*^[40] suggest that there is a role for hormone imprinting at birth and that endorphin treatment influences sexual hormone production, which can affect sexual behaviors in later life.

During labor, the level of endorphin in the mother's blood increases and is dependent on the intensity of pain and the duration of labor^[41]. Therefore, it is presumed that neonatal endorphin imprinting affects later-life events such as sexual activity and aggression, because of the association between brain serotonin levels and aggressive behaviours^[42]. However, this hypothesis is based solely on data from rodent models, and its generalizability to other species, including primates (*e.g.*, humans) is currently unclear.

The opioid peptides impose their excitatory effects by acting in the ventral tegmental area, increasing the activity of the mesolimbic dopaminergic system and promoting sexual arousal and motivation. There appears to be no research investigating the role of beta-endorphin in human sexuality, making it impossible to determine whether this is a general effect of all opioid peptides or if it is specific for other peptides such as enkephalin, as reported in the literature^[33].

Research in animal models has found that beta-

endorphin affects brain activity and maintains a sense of balance and wellbeing by allowing the animals to perform feeding and drinking activities as well as social grooming^[43]. A systematic review of animal studies^[44] has also suggested that beta-endorphin plays its main role in the appetitive and precopulatory phase of sexual behavior, in preparation for copulatory activities. Further, there is a relationship between beta-endorphin and sex hormones.

EFFECT OF OXYTOCIN ON SEXUALITY AND ROMANTIC RELATIONSHIPS

Human studies

Oxytocin is known as the "hormone of love". Endogenous oxytocin arouses feelings of pleasure, peace and security when in the company of a partner^[45]. The release of endogenous oxytocin from the pituitary gland into the bloodstream is triggered by sexual stimuli such as hugging, touching, and genital and nipple stimulation in both genders, and its plasma level is correlated with the levels of arousal and lubrication, reaching a peak during orgasm^[46]. The release of endogenous oxytocin decreases fearfulness and works as an anxiolytic agent, diminishing the level of anxiety through inhibiting fear responses in the amygdala, which contains substantial numbers of oxytocin receptors^[47]. The release of endogenous oxytocin from the brain during intimate touching or sexual activity with a partner has been suggested to have a vital role in sexual monogamy in men and women^[48].

Ecstasy [(3,4-methylenedioxymethamphetamine (MDMA))] is a recreational psychoactive drug and is often called the "love pill". Research has shown that ecstasy stimulates endogenous oxytocin activity *via* activation of serotonin 5-HT1A receptors resulting in an increase in feelings of love, empathy and connection to others^[49].

A rise in endogenous oxytocin results in an increase of plasma endorphins, natural pain-killers that can diminish pain in women who suffer dyspareunia, due to anxiety or a lack of trust in their partner during the first stages of their relationship^[50]. Despite these, research has suggested that endogenous oxytocin may not be high before the commencement of sexual activity and it may not be the main trigger of sexual drive and desire preceding the initiation of sexual activity. According to this, the level of endogenous oxytocin increases after the woman receives appropriate stimulation and starts enjoying the sexual activity^[51]. This claim is supported by data from self-report studies indicating that some women may enjoy sexual activity and reach orgasm when sexual stimulation and intercourse occur^[52], although they may not be the initiator of the sexual activity^[53,54].

Higher plasma concentrations of oxytocin have been shown in people who have fallen in love as well as during the transition to parenthood. A magnetic resonance imaging study of 10 women and 7 men (mean age

21.4 years) has shown that brain areas involved in the formation of romantic attachment are rich in oxytocin receptors^[55]. The same brain regions are activated in new parents with great parental-infant attachment and new lovers in prolonged romantic relationships^[56]. These reports suggest that parent-child attachments and romantic bonds may share some fundamental mechanisms mediated by the oxytocinergic system, though it is not evident in the literature.

Postpartum loss of sexual desire, arousal and orgasm have been reported across many studies and have been shown to remain as long as one year^[53] to many years after childbirth^[57]. Research suggests that changes in sexual function in postpartum women may not be only because of physical changes during the transition to motherhood, but may also be due to psychological and neuroendocrine alterations during and after childbirth. Neuroimaging assessments of seven mothers have shown changes in the prefrontal-limbic system during the transition to motherhood, including the amygdala, which is responsible for the expression of oxytocin receptors, suggesting that the amygdala may be less responsive to sexual images and stimuli in postpartum women^[58]. Another suggested alteration is that the brain may not release the expected amounts of endogenous oxytocin during sexual activity in postpartum women, and this may result in decreased self-reported feelings of sexual desire in these women^[59].

A modest body of evidence suggests that any factor that can interfere with the release of endogenous oxytocin can cause sexual dysfunction in postpartum women. Among the various factors contributing to sexual problems in postpartum women^[60-62] is the use of intravenous synthetic oxytocin during labour and birth. This factor is not subject to the standard mechanisms regulating endogenous oxytocin and affects the normal behaviors of the amygdala^[63,64].

Considering the low levels of endogenous oxytocin in women experiencing sexual problems, and the different mechanisms of action of intranasal and intravenous synthetic oxytocin, researchers have attempted to address the sexual problems of women by using an intranasal spray of synthetic oxytocin which was supposed to deliver lower doses of synthetic oxytocin to the body compared with intravenous synthetic oxytocin administered during labour. A case report by Anderson-Hunt and Dennerstein^[65] showed copious vaginal transudate and a subsequent intense sexual desire two hours after the use of intranasal spray of synthetic oxytocin to facilitate breastfeeding. However, findings of their report may not be generalised to the entire population as they studied only one woman for a short period of time. Another study showed that intranasal administration of synthetic oxytocin improved attachment-related behaviors, such as eye gazing^[66], interpersonal trust, compassion and positive communication^[67].

The use of intranasal synthetic oxytocin in men has been shown to result in a remarkable increase in their

endogenous oxytocin levels together with increased secretion of catecholamines when they were engaged in sexual activity in a laboratory setting^[68]. Nevertheless, no further evidence in the literature supports the use of synthetic oxytocin for female sexual dysfunction.

As mentioned earlier, there are mixed reports regarding the impact of oxytocin on romantic relationships. Some studies have indicated links between plasma oxytocin and positive communication, affiliation, emotional support and love^[69,70], but others have shown associations between elevated peripheral oxytocin and post-conflict anxiety and decreased levels of forgiveness in romantic couples^[45,71]. These results, however, should be interpreted with caution due to controversy about the reliability of plasma oxytocin levels as a peripheral proxy for central concentrations.

Animal studies

A comprehensive review of animal studies on the effect of neuropeptides on the regulation of the brain, social cognitive processing and associated social behaviors has suggested a link between the oxytocinergic system and dopamine which promotes sexual behaviors such as pair bonding and sexual arousal^[72]. This association may also contribute to an expectancy of future reward and the sexual arousal reward that are naturally expected later, as shown in rodents^[73].

When synthetic oxytocin is administered intranasally, it proceeds through the fluid-filled perineural channels created by the cells ensheathing the olfactory receptor neurons. It then travels through the cribriform plate in the skull and reaches the CNS^[74]. In their study on primates, Chang *et al.*^[75] showed increased levels of endogenous oxytocin in cerebrospinal fluid (CSF) after synthetic oxytocin spray inhalation, supporting the likelihood of central effects of synthetic oxytocin.

Unlike intranasal oxytocin, when intravenous synthetic oxytocin is administered, the blood-brain barrier inhibits it from reaching the brain and it therefore does not function as the "hormone of love"^[74]. Other animal studies have reported that synthetic oxytocin may reach the brain, but it may act differently from the endogenous oxytocin and have different effects on the body^[76,77]. They have shown that there is not always a correlation between peripheral and cerebral levels of oxytocin, suggesting that the two systems may be controlled independently and that intravenous synthetic oxytocin does not essentially raise oxytocin levels within the brain. Research on male prairie voles has shown inhibitory effects of synthetic oxytocin on pulsatile secretion of endogenous oxytocin that may last year^[78].

CONCLUSION

There is a lack of up-to-date data on the mechanism of action of endorphins and their role in regulating human sexuality. Some animal studies report the effect of beta-endorphin on GnRH, LH and testosterone, but these findings have not been supported by human research.

A thorough review of the literature has identified inconclusive reports and many gaps in knowledge of the association between endogenous oxytocin and sexuality. Further to this, there is no strong evidence supporting the positive effects of synthetic oxytocin on human sexual function and relationships. Although research in humans suggests a central role of these hormones in sexuality, the most reliable findings to date involve peripheral activation, mainly based on animal research.

The importance of physiological changes during sexual activity and how they can affect human relationships, and the gaps in the literature on the topic, highlight the need for high-quality research to extend our understanding of the hormonal physiology of sexual function and the role of endorphins and oxytocin in human sexuality. To fill the gap, further future studies are required to investigate the role of these hormones in human sexuality and their mechanism of action in men and women.

The inter-relationship between these two endogenous hormones and human sexuality is still unclear and no previous research has explored this association. Further future research is required to apply a methodological triangulation of qualitative and quantitative methods for analysing determinants of various aspects of human sexuality considering the role of endorphins and endogenous oxytocin. While the qualitative analysis may focus on behavioural sex differences, the quantitative analysis concentrates on how the two endogenous hormones influence human sexuality and sexual behaviours.

REFERENCES

- 1 **Bolbol-Haghighi N**, Masoumi SZ, Kazemi F. Effect of Massage Therapy on Duration of Labour: A Randomized Controlled Trial. *J Clin Diagn Res* 2016; **10**: QC12-QC15 [PMID: 27190898 DOI: 10.7860/JCDR/2016/17447.7688]
- 2 **Hiramoto K**, Kobayashi H, Sekiyama A, F Sato E, Tsuruta D, Ishii M. Mild exercise suppresses exacerbation of dermatitis by increasing cleavage of the β -endorphin from proopiomelanocortin in NC/Nga mice. *J Clin Biochem Nutr* 2013; **52**: 58-63 [PMID: 23341699 DOI: 10.3164/jcbs.12-51]
- 3 **Dunbar RI**, Kaskatis K, MacDonald I, Barra V. Performance of music elevates pain threshold and positive affect: implications for the evolutionary function of music. *Evol Psychol* 2012; **10**: 688-702 [PMID: 23089077 DOI: 10.1177/147470491201000403]
- 4 **Parker G**, Parker I, Brotchie H. Mood state effects of chocolate. *J Affect Disord* 2006; **92**: 149-159 [PMID: 16546266 DOI: 10.1016/j.jad.2006.02.007]
- 5 **Robinson KC**, Fisher DE. Tanning as a substance abuse. *Commun Integr Biol* 2014; **7**: [PMID: 26842945 DOI: 10.4161/cib.29890]
- 6 **Qu F**, Zhou J. Electro-acupuncture in relieving labor pain. *Evid Based Complement Alternat Med* 2007; **4**: 125-130 [PMID: 17342250 DOI: 10.1093/ecam/nel053]
- 7 **Bancroft J**. The endocrinology of sexual arousal. *J Endocrinol* 2005; **186**: 411-427 [PMID: 16135662 DOI: 10.1677/joe.1.06233]
- 8 **Esch T**, Stefano GB. The Neurobiology of Love. *Neuro Endocrinol Lett* 2005; **26**: 175-192 [PMID: 15990719]
- 9 **Leng G**, Meddle SL, Douglas AJ. Oxytocin and the maternal brain. *Curr Opin Pharmacol* 2008; **8**: 731-734 [PMID: 18656552 DOI: 10.1016/j.coph.2008.07.001]
- 10 **Baskerville TA**, Douglas AJ. Interactions between dopamine and oxytocin in the control of sexual behaviour. *Prog Brain Res* 2008; **170**: 277-290 [PMID: 18655889 DOI: 10.1016/

- S0079-6123(08)00423-8]
- 11 **Gimpl G**, Fahrenholz F. The oxytocin receptor system: structure, function, and regulation. *Physiol Rev* 2001; **81**: 629-683 [PMID: 11274341 DOI: 10.1152/physrev.2001.81.2.629]
- 12 **Frye CA**. Neurosteroids' effects and mechanisms for social, cognitive, emotional, and physical functions. *Psychoneuroendocrinology* 2009; **34** Suppl 1: S143-S161 [PMID: 19656632 DOI: 10.1016/j.psyneuen.2009.07.005]
- 13 **Mastorakos G**, Pavlatou M, Diamanti-Kandarakis E, Chrousos GP. Exercise and the stress system. *Hormones (Athens)* 2005; **4**: 73-89 [PMID: 16613809]
- 14 **Basson R**, Brotto LA, Laan E, Redmond G, Utian WH. Assessment and management of women's sexual dysfunctions: problematic desire and arousal. *J Sex Med* 2005; **2**: 291-300 [PMID: 16422860 DOI: 10.1111/j.1743-6109.2005.20346.x]
- 15 **Exton MS**, Bindert A, Krüger T, Scheller F, Hartmann U, Schedlowski M. Cardiovascular and endocrine alterations after masturbation-induced orgasm in women. *Psychosom Med* 1999; **61**: 280-289 [PMID: 10367606 DOI: 10.1097/00006842-199905000-00005]
- 16 **Krüger T**, Exton MS, Pawlak C, von zur Mühlen A, Hartmann U, Schedlowski M. Neuroendocrine and cardiovascular response to sexual arousal and orgasm in men. *Psychoneuroendocrinology* 1998; **23**: 401-411 [PMID: 9695139 DOI: 10.1016/S0306-4530(98)00007-9]
- 17 **Katz N**, Mazer NA. The impact of opioids on the endocrine system. *Clin J Pain* 2009; **25**: 170-175 [PMID: 19333165 DOI: 10.1097/AJP.0b013e3181850df6]
- 18 **Brennan MJ**. The effect of opioid therapy on endocrine function. *Am J Med* 2013; **126**: S12-S18 [PMID: 23414717 DOI: 10.1016/j.amjmed.2012.12.001]
- 19 **Rasheed A**, Tareen IA. Effects of heroin on thyroid function, cortisol and testosterone level in addicts. *Pol J Pharmacol* 1995; **47**: 441-444 [PMID: 8868137]
- 20 **Yee A**, Loh HS, Hisham Hashim HM, Ng CG. The prevalence of sexual dysfunction among male patients on methadone and buprenorphine treatments: a meta-analysis study. *J Sex Med* 2014; **11**: 22-32 [PMID: 24344738 DOI: 10.1111/jsm.12352]
- 21 **Roberts LJ**, Finch PM, Pullan PT, Bhagat CI, Price LM. Sex hormone suppression by intrathecal opioids: a prospective study. *Clin J Pain* 2002; **18**: 144-148 [PMID: 12048415 DOI: 10.1097/0002508-200205000-00002]
- 22 **Rhodin A**, Stridsberg M, Gordh T. Opioid endocrinopathy: a clinical problem in patients with chronic pain and long-term oral opioid treatment. *Clin J Pain* 2010; **26**: 374-380 [PMID: 20473043 DOI: 10.1097/AJP.0b013e3181d1059d]
- 23 **Fraser LA**, Morrison D, Morley-Forster P, Paul TL, Tokmakejian S, Larry Nicholson R, Bureau Y, Friedman TC, Van Uum SH. Oral opioids for chronic non-cancer pain: higher prevalence of hypogonadism in men than in women. *Exp Clin Endocrinol Diabetes* 2009; **117**: 38-43 [PMID: 18523930 DOI: 10.1055/s-2008-1076715]
- 24 **Bawor M**, Bami H, Dennis BB, Plater C, Worster A, Varenbut M, Daiter J, Marsh DC, Steiner M, Anglin R, Coote M, Pare G, Thabane L, Samaan Z. Testosterone suppression in opioid users: a systematic review and meta-analysis. *Drug Alcohol Depend* 2015; **149**: 1-9 [PMID: 25702934 DOI: 10.1016/j.drugalcdep.2015.01.038]
- 25 **Pfaus JG**, Gorzalka BB. Opioids and sexual behavior. *Neurosci Biobehav Rev* 1987; **11**: 1-34 [PMID: 3554038 DOI: 10.1016/S0149-7634(87)80002-7]
- 26 **Cicero TJ**, Wilcox CE, Bell RD, Meyer ER. Acute reductions in serum testosterone levels by narcotics in the male rat: stereospecificity, blockade by naloxone and tolerance. *J Pharmacol Exp Ther* 1976; **198**: 340-346 [PMID: 948030]
- 27 **Graves GR**, Kennedy TG, Weick RF, Casper RF. The effect of nalmefene on pulsatile secretion of luteinizing hormone and prolactin in men. *Hum Reprod* 1993; **8**: 1598-1603 [PMID: 8300813 DOI: 10.1093/oxfordjournals.humrep.a137898]
- 28 **Agirregoitia E**, Subiran N, Valdivia A, Gil J, Zubero J, Irazusta J. Regulation of human sperm motility by opioid receptors. *Andrologia* 2012; **44** Suppl 1: 578-585 [PMID: 21919945 DOI: 10.1111/j.1439-0272.2011.01230.x]
- 29 **Sathe RS**, Komisaruk BR, Ladas AK, Godbole SV. Naltrexone-induced augmentation of sexual response in men. *Arch Med Res* 2001; **32**: 221-226 [PMID: 11395188 DOI: 10.1016/S0188-4409(01)00279-X]
- 30 **de Catanzaro D**, Douglas A, Griffiths J, Muir C. Differential sexual activity of isolated and group-housed male mice: lack of substantial influence of acute or chronic naloxone administration. *Pharmacol Biochem Behav* 1996; **55**: 169-174 [PMID: 8870054 DOI: 10.1016/0091-3057(95)02212-0]
- 31 **Goldstein A**, Hansteen RW. Evidence against involvement of endorphins in sexual arousal and orgasm in man. *Arch Gen Psychiatry* 1977; **34**: 1179-1180 [PMID: 199128 DOI: 10.1001/archpsyc.1977.01770220061006]
- 32 **Gillman M**, Lichtigfeld F. The effects of nitrous oxide and naloxone on orgasm in human females: A preliminary report. *J Sex Research* 1983; **19**: 49-57 [DOI: 10.1080/00224498309551168]
- 33 **Argiolas A**, Melis MR. Neuropeptides and central control of sexual behaviour from the past to the present: a review. *Prog Neurobiol* 2013; **108**: 80-107 [PMID: 23851261 DOI: 10.1016/j.neurobio.2013.06.006]
- 34 **Melis MR**, Succu S, Spano MS, Argiolas A. Morphine injected into the paraventricular nucleus of the hypothalamus prevents noncontact penile erections and impairs copulation: involvement of nitric oxide. *Eur J Neurosci* 1999; **11**: 1857-1864 [PMID: 10336653 DOI: 10.1046/j.1460-9568.1999.00603.x]
- 35 **Dornan W**, Malsbury C. Neuropeptides and male sexual behavior. *Neurosci Biobehav R* 1989; **13**: 1-15 [DOI: 10.1016/S0149-7634(89)80046-6]
- 36 **Myers BM**, Baum MJ. Facilitation of copulatory performance in male rats by naloxone: effects of hypophysectomy, 17 alpha-estradiol, and luteinizing hormone releasing hormone. *Pharmacol Biochem Behav* 1980; **12**: 365-370 [PMID: 6994127 DOI: 10.1016/0091-3057(80)90038-6]
- 37 **Sirinathsinghi DJ**, Whittington PE, Audsley A, Fraser HM. beta-Endorphin regulates lordosis in female rats by modulating LH-RH release. *Nature* 1983; **301**: 62-64 [PMID: 6296683 DOI: 10.1038/301062a0]
- 38 **Pfeiffer A**, Herz A. Endocrine actions of opioids. *Horm Metab Res* 1984; **16**: 386-397 [PMID: 6088380 DOI: 10.1055/s-2007-1014801]
- 39 **Fraioli F**, Fabbri A, Gnassi L, Moretti C, Bonifacio V, Isidori A, Dufau M. Naloxone increases bioactive LH in man: evidence for selective release of early LH pool. *J Endocrinol Invest* 1985; **8**: 513-517 [PMID: 3914504 DOI: 10.1007/BF03348550]
- 40 **Csaba G**, Knippel B, Karabélyos C, Inczeffi-Gonda A, Hantos M, Tóthfalusi L, Tekes K. Effect of neonatal beta-endorphin imprinting on sexual behavior and brain serotonin level in adult rats. *Life Sci* 2003; **73**: 103-114 [PMID: 12726891 DOI: 10.1016/S0024-3205(03)00254-6]
- 41 **Bacigalupo G**, Riese S, Rosendahl H, Saling E. Quantitative relationships between pain intensities during labor and beta-endorphin and cortisol concentrations in plasma. Decline of the hormone concentrations in the early postpartum period. *J Perinat Med* 1990; **18**: 289-296 [PMID: 2262873 DOI: 10.1515/jpme.1990.18.4.289]
- 42 **Sundblad C**, Eriksson E. Reduced extracellular levels of serotonin in the amygdala of androgenized female rats. *Eur Neuropsychopharmacol* 1997; **7**: 253-259 [PMID: 9443656 DOI: 10.1016/S0924-977X(97)00031-X]
- 43 **Keverne EB**, Martensz ND, Tuite B. Beta-endorphin concentrations in cerebrospinal fluid of monkeys are influenced by grooming relationships. *Psychoneuroendocrinology* 1989; **14**: 155-161 [PMID: 2525263 DOI: 10.1016/0306-4530(89)90065-6]
- 44 **Veening JG**, Barendregt HP. The effects of beta-endorphin: state change modification. *Fluids Barriers CNS* 2015; **12**: 3 [PMID: 25879522 DOI: 10.1186/2045-8118-12-3]
- 45 **Corrêa BB**, Xavier M, Guimarães J. Association of Huntington's disease and schizophrenia-like psychosis in a Huntington's disease pedigree. *Clin Pract Epidemiol Ment Health* 2006; **2**: 1 [PMID: 16480508 DOI: 10.1186/1745-0179-2-1]
- 46 **Meston CM**, Levin RJ, Sipski ML, Hull EM, Heiman JR. Women's orgasm. *Annu Rev Sex Res* 2004; **15**: 173-257 [PMID: 16913280]

- DOI: 10.1080/10532528.2004.10559820]
- 47 **Gordon I**, Martin C, Feldman R, Leckman JF. Oxytocin and social motivation. *Dev Cogn Neurosci* 2011; **1**: 471-493 [PMID: 21984889 DOI: 10.1016/j.dcn.2011.07.007]
 - 48 **Levin R**, Meston C. Nipple/Breast stimulation and sexual arousal in young men and women. *J Sex Med* 2006; **3**: 450-454 [PMID: 16681470 DOI: 10.1111/j.1743-6109.2006.00230.x]
 - 49 **Dumont GJ**, Sweep FC, van der Steen R, Hermesen R, Donders AR, Touw DJ, van Gerven JM, Buitelaar JK, Verkes RJ. Increased oxytocin concentrations and prosocial feelings in humans after ecstasy (3,4-methylenedioxymethamphetamine) administration. *Soc Neurosci* 2009; **4**: 359-366 [PMID: 19562632 DOI: 10.1080/17470910802649470]
 - 50 **Rosenbaum TY**. Musculoskeletal pain and sexual function in women. *J Sex Med* 2010; **7**: 645-653 [PMID: 19751383 DOI: 10.1111/j.1743-6109.2009.01490.x]
 - 51 **Pfaus J**, Scepkowski L. The biologic basis for libido. *Current Sexual Health Rep* 2005; **2**: 95-100 [DOI: 10.1007/s11930-005-0010-2]
 - 52 **Connolly A**, Thorp J, Pahel L. Effects of pregnancy and childbirth on postpartum sexual function: a longitudinal prospective study. *Int Urogynecol J Pelvic Floor Dysfunct* 2005; **16**: 263-267 [PMID: 15838587 DOI: 10.1007/s00192-005-1293-6]
 - 53 **Khajehei M**, Doherty M, Tilley PJ, Sauer K. Prevalence and risk factors of sexual dysfunction in postpartum Australian women. *J Sex Med* 2015; **12**: 1415-1426 [PMID: 25963126 DOI: 10.1111/jsm.12901]
 - 54 **Khajehei M**. Prevalence and Risk Factors of Relationship Dissatisfaction in Women During the First Year After Childbirth: Implications for Family and Relationship Counseling. *J Sex Marital Ther* 2016; **42**: 484-493 [PMID: 26168298 DOI: 10.1080/0092623X.2015.1069433]
 - 55 **Acevedo BP**, Aron A, Fisher HE, Brown LL. Neural correlates of long-term intense romantic love. *Soc Cogn Affect Neurosci* 2012; **7**: 145-159 [PMID: 21208991 DOI: 10.1093/scan/hsq092]
 - 56 **Weisman O**, Feldman R, Goldstein A. Parental and romantic attachment shape brain processing of infant cues. *Biol Psychol* 2012; **89**: 533-538 [PMID: 22138365 DOI: 10.1016/j.biopsycho.2011.11.008]
 - 57 **Botros SM**, Abramov Y, Miller JJ, Sand PK, Gandhi S, Nickolov A, Goldberg RP. Effect of parity on sexual function: an identical twin study. *Obstet Gynecol* 2006; **107**: 765-770 [PMID: 16582110 DOI: 10.1097/01.AOG.0000207677.03235.76]
 - 58 **Leibenluft E**, Gobbi MI, Harrison T, Haxby JV. Mothers' neural activation in response to pictures of their children and other children. *Biol Psychiatry* 2004; **56**: 225-232 [PMID: 15312809 DOI: 10.1016/j.biopsych.2004.05.017]
 - 59 **Rupp HA**, James TW, Ketterson ED, Sengelaub DR, Ditzen B, Heiman JR. Lower sexual interest in postpartum women: relationship to amygdala activation and intranasal oxytocin. *Horm Behav* 2013; **63**: 114-121 [PMID: 23085496 DOI: 10.1016/j.yhbeh.2012.10.007]
 - 60 **Khajehei M**, Doherty M, Tilley PJ. An update on sexual function and dysfunction in women. *Arch Womens Ment Health* 2015; **18**: 423-433 [PMID: 25934058 DOI: 10.1007/s00737-015-0535-y]
 - 61 **Khajehei M**, Ziyadlou S, Safari RM, Tabatabaee H, Kashefi F. A comparison of sexual outcomes in primiparous women experiencing vaginal and caesarean births. *Indian J Community Med* 2009; **34**: 126-130 [PMID: 19966959 DOI: 10.4103/0970-0218.51237]
 - 62 **Khajehei M**, Doherty M, Tilley P. Assessment of postnatal depression among Australian lesbian mothers during the first year after childbirth: A pilot study. *Inter J Childbirth Ed* 2012; **27**: 49-51
 - 63 **Gamer M**, Zurowski B, Büchel C. Different amygdala subregions mediate valence-related and attentional effects of oxytocin in humans. *Proc Natl Acad Sci USA* 2010; **107**: 9400-9405 [PMID: 20421469 DOI: 10.1073/pnas.1000985107]
 - 64 **Bakermans-Kranenburg MJ**, van Ijzendoorn MH, Riem MM, Tops M, Alink LR. Oxytocin decreases handgrip force in reaction to infant crying in females without harsh parenting experiences. *Soc Cogn Affect Neurosci* 2012; **7**: 951-957 [PMID: 22037689 DOI: 10.1093/scan/nsr067]
 - 65 **Anderson-Hunt M**, Dennerstein L. Increased female sexual response after oxytocin. *BMJ* 1994; **309**: 929 [PMID: 7950665 DOI: 10.1136/bmj.309.6959.929]
 - 66 **Guastella AJ**, Mitchell PB, Dadds MR. Oxytocin increases gaze to the eye region of human faces. *Biol Psychiatry* 2008; **63**: 3-5 [PMID: 17888410 DOI: 10.1016/j.biopsych.2007.06.026]
 - 67 **Ditzen B**, Schaer M, Gabriel B, Bodenmann G, Ehler U, Heinrichs M. Intranasal oxytocin increases positive communication and reduces cortisol levels during couple conflict. *Biol Psychiatry* 2009; **65**: 728-731 [PMID: 19027101 DOI: 10.1016/j.biopsych.2008.10.011]
 - 68 **Burri A**, Heinrichs M, Schedlowski M, Kruger TH. The acute effects of intranasal oxytocin administration on endocrine and sexual function in males. *Psychoneuroendocrinology* 2008; **33**: 591-600 [PMID: 18375074 DOI: 10.1016/j.psyneuen.2008.01.014]
 - 69 **Gonzaga GC**, Turner RA, Keltner D, Campos B, Altemus M. Romantic love and sexual desire in close relationships. *Emotion* 2006; **6**: 163-179 [PMID: 16768550 DOI: 10.1037/1528-3542.6.2.163]
 - 70 **Holt-Lunstad J**, Birmingham WA, Light KC. Influence of a "warm touch" support enhancement intervention among married couples on ambulatory blood pressure, oxytocin, alpha amylase, and cortisol. *Psychosom Med* 2008; **70**: 976-985 [PMID: 18842740 DOI: 10.1097/PSY.0b013e318187aef7]
 - 71 **Tabak BA**, McCullough ME, Szeto A, Mendez AJ, McCabe PM. Oxytocin indexes relational distress following interpersonal harms in women. *Psychoneuroendocrinology* 2011; **36**: 115-122 [PMID: 20688437 DOI: 10.1016/j.psyneuen.2010.07.004]
 - 72 **Skuse DH**, Gallagher L. Dopaminergic-neuropeptide interactions in the social brain. *Trends Cogn Sci* 2009; **13**: 27-35 [PMID: 19084465 DOI: 10.1016/j.tics.2008.09.007]
 - 73 **Borrow AP**, Cameron NM. The role of oxytocin in mating and pregnancy. *Horm Behav* 2012; **61**: 266-276 [PMID: 22107910 DOI: 10.1016/j.yhbeh.2011.11.001]
 - 74 **Dhuria SV**, Hanson LR, Frey WH 2nd. Intranasal delivery to the central nervous system: mechanisms and experimental considerations. *J Pharm Sci* 2010; **99**: 1654-1673 [PMID: 19877171 DOI: 10.1002/jps.21924]
 - 75 **Chang SW**, Barter JW, Ebitz RB, Watson KK, Platt ML. Inhaled oxytocin amplifies both vicarious reinforcement and self-reinforcement in rhesus macaques (*Macaca mulatta*). *Proc Natl Acad Sci USA* 2012; **109**: 959-964 [PMID: 22215593 DOI: 10.1073/pnas.1114621109]
 - 76 **Uvnäs-Moberg K**. Antistress Pattern Induced by Oxytocin. *News Physiol Sci* 1998; **13**: 22-25 [PMID: 11390754 DOI: 10.1152/physiologyonline.1998.13.1.22]
 - 77 **Uvnäs-Moberg K**. Oxytocin may mediate the benefits of positive social interaction and emotions. *Psychoneuroendocrinology* 1998; **23**: 819-835 [PMID: 9924739 DOI: 10.1016/S0306-4530(98)00056-0]
 - 78 **Bales KL**, Perkeybile AM, Conley OG, Lee MH, Guaynes CD, Downing GM, Yun CR, Solomon M, Jacob S, Mendoza SP. Chronic intranasal oxytocin causes long-term impairments in partner preference formation in male prairie voles. *Biol Psychiatry* 2013; **74**: 180-188 [PMID: 23079235 DOI: 10.1016/j.biopsych.2012.08.025]

P- Reviewer: Zhang XQ S- Editor: Cui LJ

L- Editor: A E- Editor: Wu YXJ





Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>

