

# Endocrine dysfunction and recurrent spontaneous abortion: An overview

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## ABSTRACT

Miscarriage is the spontaneous loss of a fetus before it is viable, occurring at a rate of 15–20%. Recurrent spontaneous abortion (RSA) or habitual miscarriage is defined as repeated occurrence of 3 or more miscarriages before 20<sup>th</sup> week of gestation accounting for the most common complication of early pregnancy in humans. Various etiological factors responsible for recurrent miscarriage are anatomical, genetical, endocrinological, immunological, and infectious. The endocrinological abnormalities may be polycystic ovarian syndrome, hyperprolactinemia, luteal phase defect, thyroid dysfunction, diabetes, or hyperandrogenism contributing to recurrent pregnancy loss. In the present article, the role of endocrinological disorders in patients with RSA has been reviewed. The article search was done using electronic databases, Google scholarly articles, and PubMed based on different key words. We have further combined the searches and made grouping as per various endocrine abnormalities, which might be responsible to cause spontaneous loss of fetus.

**Key words:** Hyperandrogenism, hyperprolactinemia, luteal phase defect, polycystic ovarian disease, recurrent spontaneous abortion, thyroid dysfunction

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## INTRODUCTION

Miscarriage or spontaneous abortion is defined as expulsion or extraction of the embryo or fetus weighing <500 g, which is equivalent to approximately 20–22 weeks of gestation. It is the most common complication of early pregnancy.<sup>[1]</sup> Recurrent spontaneous abortion (RSA) or habitual abortion means three or more clinically recognized pregnancy losses before 20<sup>th</sup> week of gestational age affecting about 2–4% of reproductive age couples.<sup>[2]</sup> A pregnancy loss that occurs after a positive human chorionic gonadotropin (hCG) or a raised serum  $\beta$ -hCG, but before ultrasound or histological verification is defined as a biochemical loss occurring before

6 weeks of gestation, whereas the clinical miscarriage is the loss of positive ultrasound examination or histological evidence for intrauterine pregnancy.<sup>[3]</sup> The rate of pregnancy loss among clinically diagnosed pregnancies is 8–15%. The 80% of miscarriages occur before 12 weeks of gestation, with miscarriage rates decreasing sharply after the first trimester.<sup>[4]</sup>

RSA is a multifactorial disorder resulting from genetic factors, anatomic factors, autoimmune disorders, endocrine dysfunction, thrombophilia, life style factors, and maternal infections. However, the underlying cause remains undetermined in up to 50% of cases.<sup>[5,6]</sup>

The endocrinology of human pregnancy involves endocrine and metabolic changes that result from physiological alterations at the boundary between mother and fetus; which

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results in growth and development of the fetus.<sup>[7]</sup> Although vast majority of pregnant women have no preexisting endocrine abnormalities, a small percentage of women (8–12%)<sup>[8]</sup> may develop endocrine alterations that could potentially lead to sporadic or recurrent miscarriage.<sup>[9]</sup>

Literature search was performed using electronic databases, Google scholarly articles, and PubMed (1990–2013). We have included all studies in English found in literature focusing on endocrine abnormalities and its association with spontaneous abortion and RSA. We have used different key words such as endocrine abnormalities, polycystic ovary disease, obesity, hyperinsulinemia, hyperandrogenism, thyroid dysfunction, hyperprolactinemia, luteal phase defect, and these words were combined with spontaneous abortion, miscarriage, recurrent miscarriage, or RSA to generate a set of results. These search results were combined to generate most relevant results for critical appraisal.

The major endocrinal causes of recurrent abortions are polycystic ovarian syndrome (PCOS), obesity, hyperinsulinemia, and insulin resistance (IR) among others [Table 1].

## POLYCYSTIC OVARIAN SYNDROME

PCOS is the most common cause of anovulatory infertility in the developed countries<sup>[10]</sup> and most commonly identified abnormality among women with recurrent miscarriage.<sup>[11]</sup> Spontaneous loss of fetus occurs in 40% women with PCOS<sup>[12]</sup> and the underlying cause may include obesity, hyperinsulinemia, IR, hyperandrogenemia, hyperhomocysteinemia, high levels of plasminogen activator inhibitor-1 factor, poor endometrial receptivity, and elevated levels of luteinizing hormone (LH).<sup>[13]</sup>

## OBESITY

Obesity is believed to act on female reproductive function through hyperinsulinemia and on the production of androgen. Maternal obesity has been reported as an independent risk

**Table 1: Major endocrinal causes of recurrent spontaneous abortions**

Polycystic ovarian syndrome
Obesity
Hyperinsulinemia and insulin resistance
Hypersecretion of luteinizing hormones
Hyperandrogenism
Hyperprolactinemia
Luteal phase defect
Hyperthyroidism and hypothyroidism
Thyroid autoimmunity
Low serum human chorionic gonadotropin levels

factor for miscarriage,<sup>[14]</sup> leading to sudden and unexplained intrauterine death<sup>[15]</sup> with increased risk in PCOS women receiving infertility treatment.<sup>[16]</sup> IR may play a key role in explaining the association among obesity, PCOS, and recurrent miscarriages.<sup>[17]</sup>

## HYPERINSULINEMIA AND INSULIN RESISTANCE

Pregestational diabetes, including Type 1 and Type 2 diabetes, complicate up to 1% of all pregnancies.<sup>[18]</sup> It increases the risk of spontaneous abortion, preterm labor, hypertensive disorders, and operative deliveries.<sup>[19]</sup> The main underlying cause is lethal embryonic malformations, the prevalence of which increases in the case of poorly controlled diabetes during the periconceptual period.<sup>[20]</sup>

Women with idiopathic RSA have high fasting insulin and IR.<sup>[21]</sup> IR is known to play a critical role in the ovarian androgen excess and might promote miscarriage by increasing circulating testosterone concentration, hyperhomocysteinemia, and the increased risk of PCOS.<sup>[22]</sup> Hyperhomocysteinemia interferes with endometrial blood flow and vascular integrity<sup>[23]</sup> resulting in increased oxidative stress in vascular endothelium and so early pregnancy loss.<sup>[24]</sup> The well-controlled diabetes mellitus is not a risk factor for RSA and attention should first be given to optimal metabolic control of diabetic women during the preconceptional period.<sup>[25]</sup> Treatment of PCOS patients with metformin decreases IR, thus helps in improving ovulation cycles and therefore conception rates in infertile women.<sup>[26]</sup> Metformin is also helpful in reducing the risk of miscarriage in women with a history of RSA and abnormal results of glucose tolerance test.<sup>[27]</sup> Whether metformin is helpful in reducing the risk of miscarriage in PCOS women is yet unclear.

## HYPERSECRETION OF LUTEINIZING HORMONE

It has been reported that hypersecretion of basal LH with or without polycystic ovaries is a risk factor for miscarriage.<sup>[12]</sup> Raised follicular phase serum LH levels increase the risk of miscarriage following either spontaneous conception<sup>[28]</sup> or assisted conception.<sup>[29]</sup> Elevated urinary LH excretion has been reported in 57% of women with recurrent miscarriage.<sup>[11]</sup> Deleterious effects of high LH can be reversed by LH suppression using gonadotropin-releasing hormone analogs.<sup>[30]</sup>

## HYPERANDROGENISM

Elevated androgens levels are associated with the retardation of endometrial development in luteal phase.<sup>[31]</sup> An elevated free androgen index (FAI) appears to be a prognostic factor

for miscarriage in women with earlier miscarriage and risk increases significantly (FAI >5) during follicular phase,<sup>[32]</sup> indicating the sensitivity of assessment in this phase.<sup>[33]</sup>

## HYPERPROLACTINEMIA

Prolactin is essential for female reproduction and commonly measured in women with RSA, as elevated prolactin levels are associated with ovulatory dysfunction. Past *in vitro* studies have shown that prolactin plays a critical role in corpus luteum maintenance and progesterone production in rodents, but not in humans.<sup>[34]</sup> Moreover, progesterone secretion by cultured granulosa cells obtained from human ovarian follicles is almost completely inhibited by high prolactin concentrations (100 ng/ml), but not by lower concentrations (10–20 ng/ml). These observations suggest that high prolactin in early follicular growth may inhibit progesterone secretion, which results in luteal phase defects.<sup>[35]</sup> Some recent researches on rodents have revealed that prolactin receptors are involved not only in generating, but also in maintaining pregnancy. It has been reported that hyperprolactinemia may occur in a transient manner, around the preovulatory phase. A rise of 200% greater than mid follicular baseline levels at the time of peak follicular maturity indicated transient hyperprolactinemia, associated with unexplained infertility and repeated miscarriages.<sup>[36]</sup> On the other hand, one study revealed that lower basal serum prolactin concentration is associated with an increased risk of miscarriage in a subsequent pregnancy in women with unexplained recurrent miscarriage.<sup>[37]</sup> Rate of successful pregnancy is higher in hyperprolactinemic women with RSA who are treated with bromocriptine during randomized control trial (4.6–15.5 ng/ml,  $P < 0.01$  or  $P < 0.05$ ).<sup>[38]</sup>

## LUTEAL PHASE DEFECT

Decreased levels of progesterone are found in women with recurrent pregnancy loss.<sup>[39]</sup> Progesterone production triggers morphological and physiological changes in the endometrium creating a suitable environment for the embryo during the implantation window.<sup>[40]</sup> Progesterone also helps in maintaining early pregnancy. It affects proliferation and differentiation of stromal cells, augments uterine receptivity through the modulation of locally acting growth factors, and regulation of cytokine production in maternal fetal interface. Studies on humans and animals suggest that progesterone maintains pregnancy by down regulation of Th1 cytokines and stimulation of Th2 cytokines as Th2 cytokines favor normal pregnancy, while excess of Th1 cytokines leads to termination of pregnancy. In the presence of progesterone, lymphocytes of pregnant women release a 35 kDa protein known as progesterone-induced blocking factor, which in turn alters the profile of cytokine secretion of activated lymphocytes and shift the balance toward Th2 dominance.<sup>[41,42]</sup>

All these changes fail to occur if progesterone production is lower than the normal minimum. In early pregnancy, the corpus luteum continuously produces progesterone until the luteal placental shift. Luteal phase defect is originally thought to derive from inadequate production of progesterone by the corpus luteum and subsequent inadequate endometrial maturation to allow proper placentation. Abnormalities of the luteal phase defect have been historically reported to occur in up to 35% of women with recurrent pregnancy loss.<sup>[9]</sup> Serum progesterone levels >10 ng/ml in the mid luteal phase are rarely associated with an abnormal luteal phase, whereas the levels below 12 ng/ml have been associated with an increased risk of miscarriage.<sup>[43]</sup>

## THYROID DYSFUNCTION

Thyroid hormones are vital for the development of the brain both during fetal and early postnatal life. Impaired maternal thyroid hormone availability may induce irreversible brain damage with consequent neurological abnormalities.<sup>[44]</sup> Thyroid hormones also have an impact on oocytes at the level of the granulosa and luteal cells that interfere with normal ovulation.<sup>[45]</sup>

## HYPERTHYROIDISM

It occurs in approximately 0.1–0.4% of pregnancies.<sup>[46]</sup> Pregnant women with untreated excess hyperthyroidism are at an increased risk for spontaneous miscarriage, congestive heart failure, thyroid storm, preterm delivery, preeclampsia, fetal growth restriction, and increased perinatal morbidity or mortality.<sup>[47]</sup> Improved pregnancy outcome has been reported in patients who are treated for overt Graves' hyperthyroidism. However, hyperthyroidism has not commonly been reported as an independent cause of RSA, although one study found that excess exogenous thyroid hormone is associated with an elevated rate of fetal loss.<sup>[48]</sup>

## HYPOTHYROIDISM

In contrast to hyperthyroidism, hypothyroidism is common in pregnancy. It is more prevalent (7%) during pregnancy and there is a statistical significant relationship of hypothyroidism with recurrent pregnancy loss in < 20 weeks of gestation.<sup>[49]</sup> The most prevalent cause of hypothyroidism in pregnant women, affecting approximately 0.5% of patients is chronic autoimmune thyroiditis. The TSH levels above 6 mIU/ml are significantly associated with higher frequency of still birth<sup>[50]</sup> and risk increases by 15% for each 1 mIU/ml elevation.<sup>[51]</sup> Other causes include endemic iodine deficiency, prior radioactive iodine therapy, and thyroidectomy. Untreated hypothyroidism in pregnancy is associated with an increased

risk for adverse pregnancy complications, detrimental effects on fetal neurocognitive development, and decreased fertility.<sup>[52]</sup> Both overt hypothyroidism and subclinical thyroid dysfunction can have adverse effects on fetal and maternal outcome, but in women with subclinical hypothyroidism, gestational age is low at the time of abortion.<sup>[53]</sup>

## THYROID AUTOIMMUNITY

Autoimmune thyroid disease is the most frequent cause of hypothyroidism in women of reproductive age, with an overall prevalence of 10–15%.<sup>[54]</sup> There has been found an association between thyroid autoimmunity (TA) and recurrent abortions, as women with TA has higher prevalence of recurrent miscarriage.<sup>[55]</sup> Therefore, it has been suggested that thyroid auto antibodies may be employed as a marker for at-risk pregnancies.<sup>[56]</sup> TA has a positive association with preterm delivery and neonatal respiratory distress syndrome in euthyroid women.<sup>[57]</sup> Although the mechanism is not completely understood, it is postulated that TA results in early pregnancy loss because of activation of immune system<sup>[58]</sup> or act as an infertility factor and results in delayed conception.<sup>[59]</sup>

## LOW SERUM HUMAN CHORIONIC GONADOTROPIN LEVELS

hCG is a glycoprotein produced primarily by placenta and peaks at the end of the first trimester of pregnancy. hCG can stimulate the thyroid gland by binding with thyrotropin (TSH) receptor of the thyroid cell membrane during pregnancy due to its structural similarity to TSH,<sup>[60]</sup> resulting in increased secretion of T4 and T3 and partial suppression of serum TSH.<sup>[61]</sup> The higher serum hCG concentration is seen in multiple gestation pregnancies and associated with an even greater decrease in TSH. hCG levels are used as a marker for miscarriage; women with low hCG levels are at much higher risk of child loss. On contrary, one study reported that there is no correlation between TSH and hCG levels.<sup>[62]</sup>

## CONCLUSION

Factors responsible for recurrent pregnancy loss are multiple, and endocrine dysfunction is one of them. Altered endocrine profile results in loss of pregnancy, especially in the early stages of gestation. There is need of the hour that women expecting a pregnancy must be screened to assess the endocrine profile even before conception to avoid loss of otherwise wanted pregnancy and to improve the health and social well-being of the females.

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## REFERENCES

1. Baek KH, Lee EJ, Kim YS. Recurrent pregnancy loss: The key potential mechanisms. *Trends Mol Med* 2007;13:310-7.
2. Stephenson M, Kutteh W. Evaluation and management of recurrent early pregnancy loss. *Clin Obstet Gynecol* 2007;50:132-45.
3. Jauniaux E, Farquharson RG, Christiansen OB, Exalto N. Evidence-based guidelines for the investigation and medical treatment of recurrent miscarriage. *Hum Reprod* 2006;21:2216-22.
4. Chen BA, Creinin MD. Contemporary management of early pregnancy failure. *Clin Obstet Gynecol* 2007;50:67-88.
5. Wang X, Chen C, Wang L, Chen D, Guang W, French J. Conception, early pregnancy loss, and time to clinical pregnancy: A population-based prospective study. *Fertil Steril* 2003;79:577-84.
6. Ford HB, Schust DJ. Recurrent pregnancy loss: Etiology, diagnosis, and therapy. *Rev Obstet Gynecol* 2009;2:76-83.
7. Feldt-Rasmussen U, Mathiesen ER. Endocrine disorders in pregnancy: Physiological and hormonal aspects of pregnancy. *Best Pract Res Clin Endocrinol Metab* 2011;25:875-84.
8. Smith ML, Schust DJ. Endocrinology and recurrent early pregnancy loss. *Semin Reprod Med* 2011;29:482-90.
9. Arredondo F, Noble LS. Endocrinology of recurrent pregnancy loss. *Semin Reprod Med* 2006;24:33-9.
10. Asunción M, Calvo RM, San Millán JL, Sancho J, Avila S, Escobar-Morreale HF. A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. *J Clin Endocrinol Metab* 2000;85:2434-8.
11. Clifford K, Rai R, Watson H, Regan L. An informative protocol for the investigation of recurrent miscarriage: Preliminary experience of 500 consecutive cases. *Hum Reprod* 1994;9:1328-32.
12. Rai R, Backos M, Rushworth F, Regan L. Polycystic ovaries and recurrent miscarriage – A reappraisal. *Hum Reprod* 2000;15:612-5.
13. Glueck CJ, Wang P, Goldenberg N, Sieve-Smith L. Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin. *Hum Reprod* 2002;17:2858-64.
14. Bellver J, Rossal LP, Bosch E, Zúñiga A, Corona JT, Meléndez F, *et al.* Obesity and the risk of spontaneous abortion after oocyte donation. *Fertil Steril* 2003;79:1136-40.
15. Frøen JF, Arnestad M, Frey K, Vege A, Saugstad OD, Stray-Pedersen B. Risk factors for sudden intrauterine unexplained death: Epidemiologic characteristics of singleton cases in Oslo, Norway, 1986-1995. *Am J Obstet Gynecol* 2001;184:694-702.
16. Wang JX, Davies M, Norman RJ. Body mass and probability of pregnancy during assisted reproduction treatment: Retrospective study. *BMJ* 2000;321:1320-1.
17. Tian L, Shen H, Lu Q, Norman RJ, Wang J. Insulin resistance increases the risk of spontaneous abortion after assisted reproduction technology treatment. *J Clin Endocrinol Metab* 2007;92:1430-3.
18. Gabbe SG, Graves CR. Management of diabetes mellitus complicating pregnancy. *Obstet Gynecol* 2003;102:857-68.
19. Melamed N, Hod M. Perinatal mortality in pregestational diabetes. *Int J Gynaecol Obstet* 2009;104 Suppl 1:S20-4.
20. Gutaj P, Zawiejska A, Wender-Ozegowska E, Brazert J. Maternal factors predictive of first-trimester pregnancy loss in women with pregestational diabetes. *Pol Arch Med Wewn* 2013;123:21-8.



21. Ispasoiu CA, Chicea R, Stamatian FV, Ispasoiu F. High fasting insulin levels and insulin resistance may be linked to idiopathic recurrent pregnancy loss: A case-control study. *Int J Endocrinol* 2013;2013:576926.
22. Schachter M, Razieli A, Friedler S, Strassburger D, Bern O, Ron-El R. Insulin resistance in patients with polycystic ovary syndrome is associated with elevated plasma homocysteine. *Hum Reprod* 2003;18:721-7.
23. Meigs JB, Jacques PF, Selhub J, Singer DE, Nathan DM, Rifai N, *et al.* Fasting plasma homocysteine levels in the insulin resistance syndrome: The Framingham offspring study. *Diabetes Care* 2001;24:1403-10.
24. Quéré I, Mercier E, Bellet H, Janbon C, Marès P, Gris JC. Vitamin supplementation and pregnancy outcome in women with recurrent early pregnancy loss and hyperhomocysteinemia. *Fertil Steril* 2001;75:823-5.
25. Nicholson W, Baptiste-Roberts K. Oral hypoglycaemic agents during pregnancy: The evidence for effectiveness and safety. *Best Pract Res Clin Obstet Gynaecol* 2011;25:51-63.
26. Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. *Cochrane Database Syst Rev* 2012;5:CD003053.
27. Zolghadri J, Tavana Z, Kazerooni T, Soveid M, Taghieh M. Relationship between abnormal glucose tolerance test and history of previous recurrent miscarriages and beneficial effects of metformin in these patients: A prospective clinical study. *Fertil Steril* 2008;90:727-30.
28. Regan L, Owen EJ, Jacobs HS. Hypersecretion of luteinising hormone, infertility, and miscarriage. *Lancet* 1990;336:1141-4.
29. Homburg R, Armar NA, Eshel A, Adams J, Jacobs HS. Influence of serum luteinising hormone concentrations on ovulation, conception, and early pregnancy loss in polycystic ovary syndrome. *BMJ* 1988;297:1024-6.
30. Madani T, Ashrafi M, Yeganeh LM. Comparison of different stimulation protocols efficacy in poor responders undergoing IVF: A retrospective study. *Gynecol Endocrinol* 2012;28:102-5.
31. Okon MA, Laird SM, Tuckerman EM, Li TC. Serum androgen levels in women who have recurrent miscarriages and their correlation with markers of endometrial function. *Fertil Steril* 1998;69:682-90.
32. Cocksedge KA, Saravelos SH, Wang Q, Tuckerman E, Laird SM, Li TC. Does free androgen index predict subsequent pregnancy outcome in women with recurrent miscarriage? *Hum Reprod* 2008;23:797-802.
33. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod* 2004;19:41-7.
34. Frasier J, Park K, Byers M, Telleria C, Kitamura T, Yu-Lee LY, *et al.* Differential roles for signal transducers and activators of transcription 5a and 5b in PRL stimulation of ERalpha and ERbeta transcription. *Mol Endocrinol* 2001;15:2172-81.
35. Porter MB, Brumsted JR, Sites CK. Effect of prolactin on follicle-stimulating hormone receptor binding and progesterone production in cultured porcine granulosa cells. *Fertil Steril* 2000;73:99-105.
36. Bussen S, Sütterlin M, Steck T. Endocrine abnormalities during the follicular phase in women with recurrent spontaneous abortion. *Hum Reprod* 1999;14:18-20.
37. Li W, Ma N, Laird SM, Ledger WL, Li TC. The relationship between serum prolactin concentration and pregnancy outcome in women with unexplained recurrent miscarriage. *J Obstet Gynaecol* 2013;33:285-8.
38. Hirahara F, Andoh N, Sawai K, Hirabuki T, Uemura T, Minaguchi H. Hyperprolactinemic recurrent miscarriage and results of randomized bromocriptine treatment trials. *Fertil Steril* 1998;70:246-52.
39. Dante G, Vaccaro V, Facchinetti F. Use of progestagens during early pregnancy. *Facts Views Vis Obgyn* 2013;5:66-71.
40. Graham JD, Clarke CL. Physiological action of progesterone in target tissues. *Endocr Rev* 1997;18:502-19.
41. Kalinka J, Szekeres-Bartho J. The impact of dydrogesterone supplementation on hormonal profile and progesterone-induced blocking factor concentrations in women with threatened abortion. *Am J Reprod Immunol* 2005;53:166-71.
42. Szekeres-Bartho J, Balasch J. Progestagen therapy for recurrent miscarriage. *Hum Reprod Update* 2008;14:27-35.
43. Arck PC, Rütcke M, Rose M, Szekeres-Bartho J, Douglas AJ, Pritsch M, *et al.* Early risk factors for miscarriage: A prospective cohort study in pregnant women. *Reprod Biomed Online* 2008;17:101-13.
44. Glinoe D. The regulation of thyroid function during normal pregnancy: Importance of the iodine nutrition status. *Best Pract Res Clin Endocrinol Metab* 2004;18:133-52.
45. Wakim AN, Polizzotto SL, Buffo MJ, Marrero MA, Burholt DR. Thyroid hormones in human follicular fluid and thyroid hormone receptors in human granulosa cells. *Fertil Steril* 1993;59:1187-90.
46. Glinoe D. Thyroid hyperfunction during pregnancy. *Thyroid* 1998;8:859-64.
47. Millar LK, Wing DA, Leung AS, Koonings PP, Montoro MN, Mestman JH. Low birth weight and preeclampsia in pregnancies complicated by hyperthyroidism. *Obstet Gynecol* 1994;84:946-9.
48. Anselmo J, Cao D, Karrison T, Weiss RE, Refetoff S. Fetal loss associated with excess thyroid hormone exposure. *JAMA* 2004;292:691-5.
49. Masand D, Patel J. Prevalence of hypothyroidism in unexplained recurrent miscarriages. *J Evol Med Dent Sci* 2014;3:767-77.
50. Allan WC, Haddow JE, Palomaki GE, Williams JR, Mitchell ML, Hermos RJ, *et al.* Maternal thyroid deficiency and pregnancy complications: Implications for population screening. *J Med Screen* 2000;7:127-30.
51. 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:E44-8.
52. Wasserstrum N, Anania CA. Perinatal consequences of maternal hypothyroidism in early pregnancy and inadequate replacement. *Clin Endocrinol (Oxf)* 1995;42:353-8.
53. De Vivo A, Mancuso A, Giacobbe A, Moleti M, Maggio Savasta L, De Dominicis R, *et al.* Thyroid function in women found to have early pregnancy loss. *Thyroid* 2010;20:633-7.
54. Poppe K, Velkeniers B, Glinoe D. Thyroid disease and female reproduction. *Clin Endocrinol (Oxf)* 2007;66:309-21.
55. Lata K, Dutta P, Sridhar S, Rohilla M, Srinivasan A, Prashad GR, *et al.* Thyroid autoimmunity and obstetric outcomes in women with recurrent miscarriage: A case-control study. *Endocr Connect* 2013;2:118-24.
56. Marai I, Carp H, Shai S, Shabo R, Fishman G, Shoenfeld Y. Autoantibody panel screening in recurrent miscarriages. *Am J Reprod Immunol* 2004;51:235-40.
57. Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Thyroid antibody positivity in the first trimester of pregnancy is associated with negative pregnancy outcomes. *J Clin Endocrinol Metab* 2011;96:E920-4.
58. Stagnaro-Green A, Roman SH, Cobin RH, el-Harazy E, Alvarez-Marfany M, Davies TF. Detection of at-risk pregnancy by means of highly sensitive assays for thyroid autoantibodies. *JAMA* 1990;264:1422-5.
59. Lejeune B, Grun JP, de Nayer P, Servais G, Glinoe D. Antithyroid antibodies underlying thyroid abnormalities and miscarriage or pregnancy induced hypertension. *Br J Obstet Gynaecol* 1993;100:669-72.
60. Fantz CR, Dagogo-Jack S, Ladenson JH, Gronowski AM. Thyroid function during pregnancy. *Clin Chem* 1999;45:2250-8.
61. Glinoe D, De Nayer P, Robyn C, Lejeune B, Kinthaert J, Meuris S. Serum levels of intact human chorionic gonadotropin (HCG) and its free alpha and beta subunits, in relation to maternal thyroid stimulation during normal pregnancy. *J Endocrinol Invest* 1993;16:881-8.
62. la Marca A, Morgante G, De Leo V. Human chorionic gonadotropin, thyroid function, and immunological indices in threatened abortion. *Obstet Gynecol* 1998;92:206-11.