NJOG 2011 Nov-Dec; 6(2): 2-6

Stress and Recurrent Miscarriage

Bhandari S

Department of Obs/Gyn, KIST Medical College Hospital

Stress has long been suspected as a possible cause of unexplained recurrent miscarriage. But while a relationship has been noted, we didn't know exactly how a woman's stress could cause miscarriage. Three "Super-systems"-the endocrine, immune, and nervous systems engage in multiple interactions during the body`s response to stress. Here we briefly discuss the possible mechanisms of stress induced changes on these systems leading to miscarriage.

Keywords: Recurrent miscarriage, stress, super-systems

INTRODUCTION

Recurrent miscarriage is defined as three or more consecutive spontaneous miscarriages.[1] It is estimated that up to 1-5% of couples trying to establish a family are affected.[2] There have been numerous proposed causes of recurrent miscarriage: parental chromosomal abnormalities, uterine anatomic anomalies, endometrial infections, endocrine etiologies (luteal phase defect, thyroid dysfunction, uncontrolled diabetes mellitus), anti phospholipid syndrome, inherited thrombophilias, and alloimmune causes. However, in 50% of these women, the cause is unknown.[3]

Stress has long been suspected as a possible cause of unexplained recurrent miscarriage, but the mechanisms by which stress may lead to recurrent miscarriage have not yet been identified. The majority of research has examined the role of psychological support within this patient population. This support has been provided in a number of ways ranging from weekly interviews with a psychiatrist or gynecologist and/or visual re-assurance in the form of ultrasound scans. It has been assumed that psychological support reduces the miscarriage rate by reducing "Stress" within this patient population. In addition it provides indirect support for a role of stress in the etiology of unexplained recurrent miscarriage (Table 1). Other studies have attempted to directly assess the effect of stress exposure on miscarriage rate; these studies have yielded conflicting results (Table 2).

Table 1. Studies of psychological interventions relevant to stress and miscarriage

Authors, year	Study type	Outcome	Intervention overview
Stray Pedersen[4], 1984	Clinical guidelines and treatment evaluations: 'tender loving care' patient-centred routine clinical care	Pregnancy success after recurrent spontaneous abortions	Couples receiving antenatal counseling and psychological support in a clinical setting had 86% pregnancy success, compared to 33% in controls given no antenatal care
Clifford[5] et al, 1997			Supportive care in early pregnancy conferred a significant beneficial effect on the outcome of the pregnancy (79% success for women <40 years <6 misc. offered supportive care).
RCOG[6]-UK 2003			Women with unexplained recurrent first trimester miscarriage have an excellent pregnancy outcome without pharmacological intervention offered supportive care alone in a dedicated miscarriage clinic.

CORRESPONDENCE

Dr. Sunita Bhandari, MD
Department of Obstetrics and Gynaecology
KIST Medical College Hospital
Mobile : 9808736309
Email : nusita5@hotmail.com

Table 2. Studies of stress exposure and miscarriage

Authors, year	Stress exposure	Study, design	Results
O'Hare[7] et al, 1995	Stressful life events: LEDS life event inventory/past 3 months	Retrospective case control	Psychosocial stress may be a factor in the etiology of miscarriage. Alternatively, there may be a common determinant (e.g. personality, lifestyle or environmental) predisposing to both stress and miscarriage.
Fenster[8] et al, 1995	Psychologic work stress+social support stressful life events/ past 6 months; stressful job by strain+demands/ control	Prospective case control	Overall, stressful work was not associated with an increased risk of spontaneous abortion. However, interactions were observed between stressful work and maternal age over 32 years (p = 0.04), cigarette smoking (p = 0.02), and primigravidity (p = 0.06). Relative to the odds ratio for stressful work in young, nonsmoking, multigravid women without a history of two or more spontaneous abortions, the odds ratios for spontaneous abortion given stressful work were higher by 2.45 (95% confidence interval (Cl) 1.03–5.81) for older women, 2.96 (95% Cl 1.16–7.52) for smokers, and 2.27 (95% Cl 0.97–5.27) for primigravid women.
Neugebauer[9] et al, 1996	Stressful life events/ past 4–5 months	Retrospective case control	70% of the women with chromosomally normal losses reported having had one or more negative life events in the months preceding loss, compared with 52% of the women with chromosomally abnormal losses (adjusted odds ratio = 2.6, 95% confidence interval (Cl) 1.3–5.2)
Hjollund[10], 2000	Work stress and strain: daily diary kept	Prospective cohort	Physical strain around the time of implantation was associated with later spontaneous abortion. The adjusted risk ratio for women who reported physical strain higher than average at day 6 to 9 after the estimated date of ovulation was 2.5 (95% CI = 1.3-4.6).
Hamilton Boyles[11] et al, 2000	Stressful life events: life event inventory	Retrospective case control	Spontaneous abortion at 11 weeks or greater was associated with more life event stress (adjusted odds ratio 2.9, 95% confidence interval 1.4–6.2), whereas spontaneous abortion at any gestational age was not, implying that life event stress increases the risk of chromosomally normal spontaneous abortion.
Arck[12] et al, 2001	High stress perception, cytokine profile (PSQ, SOZU; tissue biopsy)	Retrospective cross sectional	In the decidua of women with high stress scores observed significantly higher numbers of MCT+, CD8+ T cells and TNF- α + cells per mm2 tissue (P ≤ 0.05). No significant differences between individuals with lower or higher stress scores could be observed with respect to decidual CD56+ NK and CD3+ T cells. Stress-triggered abortion in humans, identified by a questionnaire, can be linked to immunological imbalances.
Sugiura-Ogasawara[13] et al, 2002	Psychological factors and personality traits: interview, extensive screening; Symptom Checklist 90-R; NEO 5 Factor Index	Prospective cross sectional	A high depression scale is associated with a high miscarriage rate in those patients suffering recurrent miscarriage.
Nelson[14] et al, 2003	Psychosocial stress: perceived stress scale, prenatal social environment inventory, index of spousal abuse	Case control, mixed prospective and retrospective	No relationship was found between psychosocial stress, as determined by the three stress scales or cortisol level, and the risk for spontaneous abortion. Women with high stress, as measured by the PSE, were more likely to use cigarettes and marijuana during pregnancy. High psychosocial stress during early pregnancy was not related to spontaneous abortion but high stress was associated with substance use during pregnancy.
Neponmaschy[15] et al, 2006	Stress biomarker: cortisol (daily flux, peaks from urine samples 3 times per week, medical exam 1 time per month)	Prospective, cross sectional	Pregnancy exposed to increased cortisol were 2.7 times (95%confidence interval=1.2-6.2)more likely to be unsuccessful than those exposed to normal cortisol levels(p=0.03).

Presently, the mechanisms by which psychological stress may lead to pregnancy loss have not yet been identified. A well-balanced network of endocrine, nervous and immune system is essential for the maintenance of pregnancy. The effect of stress on these three "super-systems" are discussed below.

Stress and Endocrine System

Corticotropin releasing hormone (CRH): When a situation is perceived as stressful, the Hypothalamic-Pituitary -Adrenal (HPA) axis becomes activated, causing a cascade of hormones to be produced that may (in turn) negatively impact reproduction. The paraventricular nucleus of the hypothalamus releases corticotropin-releasing factor (CRF), which stimulates the pituitary gland. In response to this stimulation, the pituitary gland releases adrenocorticotropic hormone (ACTH). Finally, the release of ACTH results in the secretion of glucocorticoids from the adrenal cortex. Stress is a potent activator of CRH release from the hypothalamus and extrahypothalamic sites. [16] A direct neural connection between CRH and GnRH has been documented.[17] CRH, the major regulator of the HPA axis and the CRH-induced proopiomelanocortin peptide, such as β-endorphin reduce the hypothalamic GnRH pulse generator activity and concurrently inhibit GnRH secretion.[18] The resulting decrease in pulsatile release of LH subsequently leads to anovulation, interruption of endometrial decidualisation and pregnancy wastage.[19] Receptors for CRH are identified in most of the female reproductive tissues including the ovary, uterus and placental trophoblast.[20] CRH in the ovarian theca and granulosa cells is found to reduce ovarian steroidogenesis in a dose-dependent manner which suggests that the ovarian CRH may lead to ovarian failure in women exposed to high psychological stress.[21] At the uterine level, an excess of CRH may induce infertility and at the placental level it may induce premature labor, because stress-induced premature labor due to an excess placental CRH is reversed by CRH antagonist.[22-23] However, locally produced normal concentration of CRH is proposed to be essential in promoting endometrial decidualisation and implantation.[24]

Glucocorticoids: Persistent increase in serum concentration of glucocorticoids in humans and rhesus monkeys evidently suppresses the hypothalamic-pituitary-ovarian (HPO) axis.[25] Glucocorticoids receptors are found in the hypothalamic GnRH neurons and in the pituitary gonadotrophs.[26] Stress-like glucocorticoid concentration blocks pituitary tissue concentration of GnRH[25] and the responsiveness of the gonadotrophs to GnRH[27] with a resulting attenuation of LH pulse frequency. An impaired generation of LH surge subsequently results in anovulation as well as menstrual disorders. Glucocorticoids receptors have been demonstrated in the ovaries and ovarian granulosa cell cytosol.[28] A direct effect of glucocorticoids could possibly result in follicular atresia by suppressing the action of LH at the receptor level.[29] Glucocorticoids also induce estrogen deficiency by suppressing granulosa cell aromatase activity.[30] As a result, estrogen deficiency is found in anxiety and depression-related stress.[31] Glucocorticoids also reduce blood flow, protein synthesis, IGF-1 m-RNA expression and prostaglandins synthesis in the uterus. Most of these estrogen-induced uterine profiles are essentially important for blastocyst implantation, endometrial decidualization and pregnancy maintenance. Estrogen deficiency not only impairs luteal steroidogenesis, it also jeopardizes receptor expression of estrogen and progesterone in the uterus[32] which may subsequently result in pregnancy wastage.[33]

Prolactin(PRL): During pregnancy, the development of increased luteinizing hormone/chorionic gonadotropin (LH/CG) receptor binding in the corpus luteum is under hormonal influence of PRL. Inhibition of pituitary PRL secretion in the rat by bromocriptine during early pregnancy decreased LH/CG receptor mRNA levels and decreased progesterone secretion leading to abortion.[33] In human, chronic and transient hyperprolactinemia has also been associated with luteal phase dysfunction. An increase in plasma PRL due to stress is well known. Elevated PRL may exert its antigonadal effects through reducing available ovarian LH receptors.[34]

Progesterone: Progesterone is essential during pregnancy in allowing implantation to occur and for continued maintenance of pregnancy.[35] Stress has been linked to decreased levels of progesterone in human.[36] Progesterone replacement abrogates effects of stress exposure by decreasing the levels of the abortogenic proinflammatory cytokines.[37] As progesterone may stimulate the production of progesterone-induced blocking factor (PIBF) by $CD8^{+}$T cells, pregnancy loss in the setting of reduced plasma progesterone could be due to decreased inhibition of LAK cells by PIBF.[38]

Stress and Immune System

During pregnancy, a Th1 (type 1 T helper) to Th2 shift has been postulated. Recent published data have elucidated that cytokines produced by Th1 cells, namely tumor necrosis factor-α (TNF-α) and γ-interferon (γ-IFN), mediate abortion by targeting vascular endothelial cells, ultimately resulting in ischemic death of the embryo by increased procoagulant secretion.[39]

The concept of cytokine patterns determining the failure or success of pregnancy leads to the still unanswered question as to which factors mediate the switch to a Th1 cytokine response resulting in abortion. Various factors have been shown to promote a shift of the pregnancy-protective Th2 cytokine pattern towards a Th1 cytokine response. Endotoxin, a potent abortogenic substance, stimulates macrophages to release TNF-α and IFN-γ in mice.[40] One study revealed a positive correlation between increasing stress scores and number of decidua basalis mast cells, CD8+T cells and TNF-α expression.[12] Besides the production of inflammatory cytokines, the secretion of decidual mast cell tryptase might imply an additional threat to pregnancy maintenance. It has recently been

shown that mast cell tryptase cleaves proteinase-activated receptor 2 (PAR-2) and, by unknown mechanisms, induces wide spread inflammation.[41] A large proportion of primary spinal afferent neurons, which express PAR-2, have been shown to also contain the proinflammatory neuropeptide substance P. Tryptase directly signals to neurons to stimulate release of these neuropeptides, which mediate inflammatory edema. This new mechanism of protease-induced neurogenic inflammation may contribute to the stress-triggered proinflammatory effects of mast cells in human miscarriage decidua.

Increased numbers of natural killer (NK) cells have been found in the peripheral blood of women with recurrent miscarriage.[42] Moreover, NK cells have been described to be up-regulated during stress. Even mild psychological stress and moderate physical activity rapidly recruit large numbers of NK cells into the circulation, an effect which subsides shortly after the stress ceases.[43] NK cells express high levels of β-adrenergic receptors, and their adherence to endothelium and migration into the blood are affected by catecholamine levels.[44] The increased NK number and activity previously observed in recurrent miscarriage (RM) patients may results from mobilization of NK cells in response to stress of venepuncture which is more pronounced in patients with primary recurrent miscarriages than secondary recurrent miscarriages.[45] Stress elevation of NK activity and NK cell mobilization support a known pathophysiological link between NK cells and reproductive failure. However, data on NK cells underlying the influence of stress, as published by various groups, are still contradictory; most results were acquired by flow cytometry using peripheral blood lymphocytes. Decidual NK cells have an unusual phenotype, CD3−CD16−CD56+++, distinguishing them from peripheral blood NK cells, which might explain the different observations on stress and NK cells in different experimental settings.

Stress and Nervous System

The hormonal regulation of female reproductive function has been studied in great detail, but the neural innervation of the reproductive organs has received less attention. A number of peptide neurotransmitters in the autonomic and peripheral nerves contain substance P (SP), vasoactive intestinal polypeptide (VIP), enkephalin and neuropeptide tyrosine. SP shows direct effects on vasculature and contracts smooth muscles of airways and gut.[46] SP-containing nerve fibers have been observed in the reproductive organs of female mammalian species.[47] The functions of these peptide-containing nerves in reproduction have not yet been elucidated. However, some evidence suggests that SP and VIP play an important role in hemodynamics, and influence smooth muscle contraction. It is highly probable that these interactions could effect coordination of muscular activity, important for the transport of sperm and ova in the fallopian tubes, and subsequently, the uterine implantation of the conceptus. Besides its ability to induce smooth-muscle contraction, vasodilatation or ion secretion, SP is seen as a potential immunomodulating peptide. SP modulates a variety of immune responses, such as T cell proliferation, immunoglobulin synthesis, lymphocyte traffic, macrophage activation, mast cell degranulation, and release of histamine and mast cell dependent granulocyte infiltration.[48] In murine pregnancy, blocking the SP specific NK1 receptor completely abrogated the effect of stress in boosting the abortion rate by reducing decidual levels of TNF-α. [49] Moreover, the activation of the stress hormone cascade CRH-ACTH-cortisol in response to different modes of somatosensory stimuli is signalled by SP containing afferent nerve fiber. Catecholamine release from the adrenal medulla is induced by hypothalamic centres when these receive relevant stimuli from the periphery by SP afferents, i.e., in hypoglycemia and stress.[50] Observations on the presence of neurotransmitter SP in normal tissues, as well as the very high concentrations of SP in tissues undergoing pathologic processes, support the hypothesis that pregnancy failure may be the result of a deregulated complex system between neurotransmitters, cytokines and hormones.

CONCLUSIONS

Evidence continues to accumulate indicating that stress can lead to miscarriage. Pathophysiological changes in response to stress involve various systems. Animal research is revealing some of the neuroendocrine-immune pathways linking stress and miscarriage. Translation of those results to human application is, however, a complex process. More population-based prospective studies will be needed to further explore the impact of stress on human reproduction.

REFERENCES

1. Stirrat GM. Recurrent miscarriage. Lancet. 1990;336:673-5.
2. Stephenson M, Kutteh W. Evaluation and management of recurrent early pregnancy loss. Clin Obstet Gynecol. 2007;50(1):132-45.
3. Lee RM, Silver RM 2000, Recurrent pregnancy loss: Summary and clinical recommendations. Semin Reprod Med. 18(4):433-40
4. Stray Pedersen B, Stray Pedersen S. Etiologic factors and subsequent reproductive performance in 195 couples with a prior history of habitual abortion. Am J Obstet Gynecol.1984;148: 140–6.
5. Clifford K, Rai R, Regan L. Future pregnancy outcome in unexplained recurrent first trimester miscarriage. Hum Reprod.1997;12:387–9
6. Royal College of Obstetricians and Gynecologists. The Investigation and treatment of couples with recurrent miscarriage.Guideline No. 17, RCOG-UK: London; 2003.
7. O'Hare T, Creed F. Life events and miscarriage. Br J Psychiatry.1995; 167:799–805.
8. Fenster L, Schaefer C, Mathur A, Hiatt RA, Pieper C, Hubbard AE. Psychologic stress in the workplace and spontaneous abortion. Am J Epidemiol. 1995;142:1176–83.
9. Neugebauer R, Kline J, Stein Z, Shrout P, Warburton D, Susser M. Association of stressful life events with chromosomally normal spontaneous abortion. Am J Epidemiol. 1996;143:588–96.
10. Hjollund NH. Spontaneous abortion and physical strain around implantation: A follow-up study of first-pregnancy planners. Epidemiology. 2000;11:18–23.
11. Hamilton BS, Ness RB, Grisson AJ, Marcovic N, Bromberger J, CiFellie D. Life events stress and the association with spontaneous abortion in gravid women at an urban emergency department. Health Psychol.2000;19:510–4.

12. Arck PC, Rose M, Hertwig K, Hagen E, Hildebrandt M, Klapp BF. Stress and immune mediators in miscarriage. Hum Reprod .2001;16:1505–11.

13. Sugiura-Ogasawara M, Furukawa TA, Nakano Y, Hori S, Aoki K, Kitamura T. Depression as a potential causal factor in subsequent miscarriage in recurrent spontaneous aborters. Hum Reprod.2002; 17:2580–4.

14. Nelson DB, Grisso JA, Joffe MM, Brensinger C, Shaw L, Datner E. Does stress influence pregnancy loss. Ann Epidemiol.2003;13: 223–9.

15. Nepomnaschy PA, Welch KB, McConnell DS, Low BS, Strassmann BI, England BG. Cortisol levels and very early pregnancy loss in humans. Proc Natl Acad Sci.2006;103:3938-3942.

16. Horrocks PM, Jones AF, Ratcliffe WA, Holder G, White A, Holder R, Ratcliffe JG, London DR. Pattern of ACTH and cortisol pulsatility over twenty-four hours in normal males and females. Clin Endocrinol.1990;32:127-134.

17. Rivest S, Rivier C. The role of corticotrophin-releasing factor and interleukin-1 in the regulation of neurons controlling reproductive functions. Endocr Rev. 1995;16:177-199.

18. Petraglia F, Sutton S, Vale W, Plotsky P. Corticotropin releasing factor decreases plasma luteinizing hormone levels in female rats by inhibiting gonadotropin releasing hormone release into hypophysial-portal circulation. Endocrinology.1987;120:1083-8.

19. Chatterjee A, Harper MJK. Interruption of implantation and gestation in rats by reserpine, chlorpromazine and ACTH: possible mode of action. Endocrinology. 1970;87:966-9.

20. Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. N Eng J Med.1995;332:1351-62.

21. Bromberger JT, Matthews KA, Kuller LH, Wing RR,laine N. Meilahn EN,Plantinga P. Prospective study of the determinants of age at menopause. Am J Epidemiol. 1997;145:124-133.

22. Makrigiannakis A, Zoumakis E, Margioris AN et al. Regulation of the promoter of the corticotrophin releasing hormone gene in transfected human endometrial cells. Neuroendocrinology 1996; 64: 85-92

23. Webster EL, Lewis DB, Torpy DJ et al. In vivo and in vitro characterization of antalarmin, a nonpeptide corticotrophin-releasing hormone (CRH) receptor antagonist: suppression of pituitary ACTH release and peripheral inflammation. Endocrinology. 1996;137:5747-50.

24. Zoumakis E, Chatzaki E, Charalampopoulos I et al. Cycle and age-related changes in corticotrophinreleasing hormone level in human endometrium and ovaries. Gynecol Endocrinol.2001;15:98-102.

25. Dubey AK, Plant TM. A suppression of gonadotropin secretion by cortisol in castrated male Rhesus monkeys (Macaca mulatta) mediated by the interruption of hypothalamic gonadotropin-releasing hormone release. Biol Reprod.1985;33:423-431.

26. Breen KM, Stackpole CA, Clarke IJ et al. Does the type II glucocorticoid receptor mediate cortisol-induced suppression in pituitary responsiveness to gonadotropin-releasing hormone? Endocrinology.2004;145:2739-46.

27. Breen KM, Oakley AV, Pytiak AV et al. Does cortisol acting via the type II glucocorticoid receptor mediate suppression of pulsatile LH secretion in response to psychosocial stress? Endocrinology.2007; 148:1882-90.

28. Louvet JP, Baislic M, Bayard F et al. Glucocorticoid receptors in rat ovarian granulosa cell cytosol. 59th Annual Meeting of the Endocrine Society:Chicago IL,1977;p 601 (Abstract).

29. Meurer KA, Cox NM, Matamoros IA et al. Decreased follicular steroids and insulin-like growth factor-1 and increased atresia in diabetic gilts during follicular growth stimulated with PMSG. J Reprod Fert.1991;91:187-196.

30. Hsueh AJW, Erickson GF. Glucocorticoid inhibition of FSH-mediated estrogen production of cultured rat granulosa cells. Steroids.1983; 32:639-43.

31. Andrade TG Nakamuta JS, Avanzi V, Graeff RG. Anxiolytic effect of estradiol in the median raphe nucleus mediated by 5 HT1A receptors. Behav Brain Res.2005;163:18-25.

32. Bergman MD, Schachter BS, Karelusk CEP et al. Upregulation of uterine estrogen receptor and its messenger ribonucleic acid during the mouse oestrous cycle: The role of oestradiol. Endocrinology. 1992;130:1923-30.

33. Gafvels M, Bujurulf E, Seltsam G: Prolactin stimulates the expression of luteinizing hormone/chorionic gonadotropin receptor messenger ribonucleic acid in the rat corpus luteum and rescues early pregnancy from bromocriptine-induced abortion.Biol Reprod.1992;47:534–40.

34. Hirakawa T, Minegishi T, Tano M, Kameda T, Kishi H,Ibuki Y, Mizutani T, Miyamoto K. Effect of prolactin on the expression of luteinizing hormone receptors during cell differentiation in cultured rat granulosa cells.Endocrinology.1999;140:3444–51.

35. MacNiven E, De Catanzaro D. Reversal of stress-induced pregnancy blocks in mice by progesterone and metyrapone. Physiol Behav. 1990; 47:443–8.

36. Nepomnaschy PA, Welch K, McConnell D, Strassmann BI, England BG. Stress and female reproductive function: A study of daily variations in cortisol, gonadotrophins, and gonadal steroids in a rural Mayan population. Am J Hum Biol. 2004;16:523–532.

37. Blois SM, Joachim R, Kandil J et al. Depletion of CD8+ cells abolishes the pregnancy protective effect of progesterone substitution with dydrogesterone in mice by altering the Th1/Th2 cytokine profile. J Immunol.2004;172:5893–9.

38. Faust Z, Laskarin G, Rukavina D, Szekeres-Bartho J. Progesterone-induced blocking factor inhibits degranulation of natural killer cells. Am J Reprod Immunol.1999;42:71–5.

39. Clark DA, Ding JW, Chaouat G, Levy GA. The emerging role of immunoregulation of fibrinogen-related procoagulant Fgl2 in the success or spontaneous abortion of early pregnancy in mice and humans. Am J Reprod Immunol.1999;42:37–43.

40. Silver RM, Lohner WS, Daynes RA, Mitchell MD, Branch DW. Lipopolysaccharide-induced fetal death: The role of tumor-necrosis factor? Biol Reprod. 1994; 50:1108–14.

41. Steinhoff M, Vergnolle N, Young SH et al. Agonists of proteinase-activated receptor 2 induce inflammation by a neurogenic mechanism. Nat Med.2000;6:151–8.

42. Yamada H, Kato HE, Kobashi G et al. High NK cell activity in early pregnancy correlated with subsequent abortion with normal chromosomes in women with recurrent abortion. Am J reprod Immunol.2001;46:132-6.

43. Dhabhar FS, Miller AH, McEwen BS, Spencer RL. Effects of stress on immune cell distribution dynamics and hormonal mechanisms. J Immunol.1995;154:5511–27.

44. Benschop R, Rodriguez-Feuerhahn M, Schedlowski M. Catecholamine-induced leukocytosis: Early observations, current research, and future directions. Brain Behav Immun.1996;10:77–91.

45. Shakar K, Rosenne E, Loewenthal R, Shakhar G, Carp H and Ben-Eliyahu S. High NK cell activity in recurrent miscarriage: What are we really measuring? Human Reproduction.2006;21(9):2421-5.

46. Kowalski ML, Kaliner MA. Neurogenic inflammation, vascular permeability, and mast cells. J Immunol.1988;140:3905–11.

47. Papka RE, Cotton JP, Taurig HH. Comparative distribution of neuropeptide tyrosine-vasoactive intestinal polypeptide-, substance P-immunoreactive, acetylcholinesterase-positive and noradrenergic nerves in the reproductive tract of the female rat. Cell Tissue Res.1985;242:475–90.

48. Stead RH, Bienestock J. Cellular interactions between the immune and peripheral nervous system: A normal role for mast cells? In: Burger MM, Sordat B, Zinkernagel RM (Eds.), Cell to Cell Interaction:Kargel, Basel;1990:170-87.

49. Arck P, Merali F, Stanisz A, Manuel J, Clark DA. Stress-induced murine abortion associated with substance P-dependent alteration in cytokines in maternal uterine decidua. Biol Reprod.1995;53: 814–9.

50. Donnerer J, Amann R, Skofitsch G, Lembeck F. Substance P afferents regulate ACTH-corticosterone release. Ann NY Acad Sci.1991;632: 296–30.