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The Aetiology of Premenstrual Syndrome is with the Progesterone Receptors

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Abstract — Recent work by molecular biologists into the behaviour of progesterone receptors (PR) has suggested an aetiological hypothesis for premenstrual syndrome (PMS). The proposition is that PMS is related to the transport by PR of sufficient progesterone (P) molecules into the cell nuclei during menstruating years. PR are widely distributed in target cells throughout the body (1, 2, 3, 4,·5, 6, 7). It suggests also why measuring P blood levels is of no value in PMS (8, 9, 10, 11); why pharmacological doses of P are required (8); and explains the failure of current double blind trials using low dose P (12, 13, 14, 15, 16).

Introduction

PMS is the presence of recurrent premenstrual symptoms with complete absence in the postmenstruum (8), and is limited to menstruating women. Patients benefit from high dose P (8, 17, 18, 19, 20, 21), even though other studies have shown that neither the disease nor its severity is related to P blood levels (9, 10, 11), and double blind controlled studies show low dose P to be no more effective than placebo (12, 13, 14, 15, 16). PMS has a high placebo response rate (22), and others suggest PMS represents not one but many syndromes (23). Recent work on PR suggests a possible explanation of these confounding results.

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Reasons for implication progesterone

P was first used for PMS because PMS symptoms are present in the luteal phase and absent after menstruation (8). Thus symptoms occur in the luteal phase when P blood level is raised, and symptoms are absent in the follicular phase when blood P is absent. PMS is also absent during pregnancy, when a massive increase in P blood level is present, but severe attacks occur following the precipitous drop of P in the puerperium. In 1953, using P injections, successful treatment of PMS was reported in 87% of carefully diagnosed women (17).

Progesterone levels

Adrenal P present in men, women and children is converted into various steroids. During childbearing years, overian P is present from ovulation to menstruation, and in pregnancy

from the placenta. Following ovulation there is an increase in the P level in peritoneal fluid (24). PMS is not related to the blood levels of P (9, 10, 11, 25), oestradiol (11, 25), follicle stimulating hormone (11), luteinising hormone (11), testosterone (11, 26), prolactin (11, 26, 27), cortisol, aldosterone (7) nor serotonin (28). However, Backstroom et al (29, 30) and Munday et al (31) showed lower plasma P and altered oestrogen levels in PMS subjects. P has a hypotensive action (32). Following tubal sterilisation blood P level drops (33).

Progesterone therapy

PMS benefits from P administered intramuscularly (8, 17, 18, 20, 21), rectally or vaginally (8, 19, 21, 34). Micronised oral P relieves mild psychological symptoms (35). Differences in suppository base affect absorption (36, 37, 38, 39). Nasal absorption of P increases with the area of mucosa covered (40, 41). After intramuscular P, serum levels of deoxycorticosterone were two to three times higher than after oral P administration (42, 43). There is an individual variation in the absorption of P, both in time taken to reach peak level and in duration of effectiveness (36, 37). P therapy is from ovulation to menstruation (8).

The therapeutic doses of P used for PMS reach a P blood level normally found at the third month of pregnancy (8). Among 1,096 PMS women the most frequent dose used by 33% was 800 mg supppository daily, with 30% requiring a higher dose (8). Individuals vary in the dose required. P is safe in pregnancy and enhances intelligence (44, 45). Synthetic progestogens do not benefit PMS (46, 47) and have side effects, especially in pregnancy. They also lower P blood level (48). Abolition of cyclical ovarian activity by oestrogen implant, followed by cyclical progestogens to allow endometrial bleeding, has proved effective in some cases of PMS (22), but is not uniformly successful, and the severity of PMS increases when cyclical ovarian activity is resumed after an interval of amenorrhoea (8).

Low levels of the binding capacity of sex hormone binding globulin (SHBG) to dihydrotestosterone were are found in women with severe somatic and psychological PMS symptoms, who were free from medication, were neither obese, hirsute nor suffering from thyroid or liver disease (49). P adminstered to PMS subjects with low SHBG raises the level and provides symptomatic relief (50). However, Backstroom et al (25) employing a different method of estimation and not screening subjects for medication, obesity, hirsutism, thyroid or liver disease, noted no difference in SHBG levels when studying women with mild PMS anxiety. Testosterone and P both compete for SHBG, so if P is not used by PR it will lower SHBG even in the presence of low testosterone. When progestogens are given SHBG levels drop (51) and PMS increases in severity (8, 17).

Progesterone receptors

PR were isolated in rat brain in 1978 (52) and in human ovary in 1980 (1). PR are found in most vertebrates, and are not limited to menstruating species. Recent work on chick oviduct and rodent uterus suggests that molecules of P pass freely through the cell membrane to the cytoplasm (53). In target cells PR in cytoplasm bind molecules of P, forming a hormone-receptor complex. This binding causes a conformational change in the receptor resulting in its translocation to the cell nucleus and changes in gene expression, which leads to protein synthesis and consequently to altered cellular function (53).

PR are widespread in humans, including all areas subject to PMS symptoms. Most occur in the limbic area, hypothalamus, preoptic area (53) and meninges (54), where they may be responsible for psychological symptoms (8, 9, 10, 11, 12, 17), epilepsy (8, 17, 17, 55, 56) and headaches (8, 17, 19). PR are present in nasopharangeal passages (3) and lungs, which may account for rhinitis, sore throat, sinusitis, pharyngitis, laryngitis and asthma (8, 17, 20, 57, 58, 59), also in skin (2), eyes and breast (4) accounting for dermatological (8, 17, 60, 61), ocular (62), and breast lesions (4, 8). Human biopsy specimens of uterus (5), breast tissue (4), fallopian tubes (6), skin (2) and nasal mucosa (3) have revealed PR, but studies on their behaviour, particularly in the brain, have been limited to animals.

In most parts of rat brain PR levels are unaffected by oestrogen, but in the hypothalamus, preoptic areas, pituitary and uterus the situation is different and oestrogen increases the concentration of PR (63). Studies in rats and guinea pigs suggest the initial dose of P causes an increase of nuclear PR, but PR are then hyposensitive to a second injection and require a dose some forty times greater to stimulate their receptivity (53). During pregnancy placental P production results in daily increasing blood

levels, rising to 40 times the level at the peak of the luteal phase, and is presumably intended primarily for the fetus. Could it be that this relative insensitivity of PR is to ensure that the fetus gets adequate supplies of P during pregnancy, only allowing excess P to pass to the mother? However, if the blockade of PR continued into the premenstruum or puerperium, or occurred during the premenstruum, it could result in an insufficient metabolism of P resulting in PMS or postnatal depression. This insensitivity phase may also explain the need for pharmacological doses of P in treatment.

Studies have shown that nuclear PR are blocked by noradrenergic agents (64). These neurotransmitter-induced changes in sensitivity of PR may explain increased severity of PMS in times of stress. The controlling mechanism for prevention of hypoglycaemia is adrenalin secretion which mobilises cellular glucose, transferring it to the blood. In the presence of adrenalin PR are blocked and unable to bind to P molecules. PR are only activated when P is present in peripheral blood, during the premenstruum and pregnancy. PR do not bind to progestogens (65).

Conclusion

Recognition of the role of PR suggests an aetiology and explanation for the known facts of PMS. PMS occurs only during childbearing years, during luteal phase with absence in follicular phase, occuring only when P is present in peripheral blood. Attacks in the premenstruum and puerperium occur when PR are requiring a higher level of P than is available. PMS can occur in ovular, anovular cycles, luteal phase defect (66) and following hysterectomy or oophorectomy (8, 67), because PMS does not depend solely on P blood levels. In PMS the dosage of P required to stimulate PR is pharmacological, accounting for the failure of double blind controlled trials in PMS using low dose P (12, 13, 14, 15, 16). PMS starts and increases in severity at times of altered menstrual hormones e.g. puberty, after amenorrhoea, pregnancy (8), pre-eclampsia (18), and postnatal depression (8), all times when there may be insufficient oestrogen to activate PR, for some PR only act in the presence of oestrogen (63), which may explain the apparent benefit from oestrogen implants (22). The wide distribution of PR may account for the wide variety of PMS symptoms. PMS starts or increases after sterilisation (8) when P blood level is reduced (33) and PR in fallopian tubes (6) are damaged.

PMS increases with stress, when PR are inactivated by adrenalin (64). Adrenalin released by the regulating mechanism in blood glucose control would inactivate PR, and explain why PMS subjects have food binges and are unable to go long intervals without carbohydrates (8). A genetic factor in PMS suggested by the twin study (68) may be expected with nuclear involvement of PR. PR do not bind to progestogens (69) and progestogens do not relieve PMS (8, 21, 46, 47).

This aetiological hypothesis of PMS vindicates the use of individually tailored pharmacological doses of P in treatment; explains negative double blind controlled trials of low dose P; confirms the irrelevance of testing P blood levels; and suggests why frequent snacks benefit PMS subjects.

References

1. Jacobs B R, Suchocki S and Smith R G (1980) Evidence for a Human Ovarian Progesterone Receptor. *Am J Obstet Gynec*, 138, 3, 332–6.
2. Richtsmeier W, Weaver G, Streck W, Jacobson H, Dewell R and Olson J (1984) Estrogen and Progesterone Receptors in Hereditary Haemorrhagic Telangiectasia. *Otolaryngology*, 92, 5, 564–70.
3. Wilson J A, Hawkins R A, Sangster K, Von Haacke N P, Tesdale A, Leese A M, Murray J A M and Maran A G D (1986) Estimation of oestrogen and Progesterone Receptors in Chronic Rhinitis. *Otolaryngol*, 11, 213–8.
4. Hubay C A, Arafat B, Gordon N H, Guyton S P and Crowe J P (1984) Hormone Receptors: an Update and Application. *Surg. Clin. N. Amer*, 64, 6, 1155–72.
5. Gorodeski I G, Geier A, Lunenfeld B, Beery R and Bahary C M (1986) Progesterone Receptor Levels and Distribution in Different Phases of the Menstrual Cycle and Estrogen-Primed Postmenopausal Endometrium. *Obstet Gynec*, 688, 4, 513–6.
6. Helm G, Batra S and Owman C (1987) Cytoplasmic and Nuclear Progesterone Receptors in Human Fallopian Tube and Their Relationship to Plasma Steroids during the Menstrual Cycle. *Int J Fertil*, 32 (2), 162–65.
7. Law M L, Kao F T, Q Wei, Hartz J A, Greene G L, Zaruchi-Schulz T, Conneely O M, Jones C, Puck T T, O'Malley B W and Horwitz K B (1986) The progesterone receptor gene map to human chromosome band 11q13, the site of the mammary oncogene int 2. *Proc Natl Aced Sci* 84, 2877–2881.
8. Dalton K (1984) *Premenstrual Syndrome and Progesterone Therapy*, 2nd Edit Wm Heinemann Medical Books, London & Year Book Medical Publishers Inc, Chicago.
9. O'Brien P M S, Selby C and Symonds E M (1980) Progesterone, Fluid and Electrolytes in Premenstrual Syndrome. *Brit Med J*, 1, 1161–3.1.
10. Dennerstein L, Spencer-Gardner C, Brown J B, Smith M A and Burrows G D (1984) Premenstrual Tension —

Hormone Profiles. *J Psychosomat Obstet Gynaec*, 3, 37–51.
11. Rubinow D R, Hoban M C, Grover G N, Galloway D S, Roy-Byrne P, Andersen R and Merriam G R. (1988) Changes in Plasma Hormones across the Menstrual Cycle in Patients with Menstrually related Mood Disorders and in Control Subjects. *Am J Obstet Gynec*, 158, 1, 5–11.
12. Sampson G A (1979) Premenstrual Syndrome: A double blind controlled trial of progesterone and placebo. *Brit J Psychiat*, 135, 209.
13. Van der Meer Y G, Benedek-Jaszmann L J and Van Loenen A C (1983) Effect of High Dose Progesterone on the Premenstrual Syndrome: a double blind cross-over trial. *J Psychosomat Obstet Gynaec*, 2–4, 220–1.
14. Andersch B and Hahn L (1985) Progesterone Treatment of Premenstrual Tension — A double blind study. *J Psychosomat Res*, 29, 5, 489–93.
15. Maddocks S, Hahn P, Moller F and Reid R L (1986) A double blind placebo-controlled trial of vaginal suppositories in the treatment of Premenstrual Syndrome. *Am J Obstet Gynec*, 154, 3, 573–81.
16. Rapkin A, Chang L H and Reading A E (1987) Premenstrual syndrome: a double blind placebo controlled study of treatment with progesterone suppositories. *Obstet Gynec*, 7, 3, 217–20.
17. Greene R and Dalton K (1953) The Premenstrual Syndrome. *Brit Med J*, 1, 1007–11.
18. Dalton K (1954) Similarity of Premenstrual Syndrome and Toxaemia of Pregnancy and their Response to Progesterone. *Brit Med J*, 2, 1070–2
19. Dalton K (1973) Progesterone Suppositories and Pessaries in the Treatment of Menstrual Migraine. *Headache* 12, 4, 151–9.
20. Beynon H L C, Garbett N D and Barnes P J (1988) Severe Premenstrual Exacerbations of Asthma Effect of Intramuscular Progesterone. *Lancet*, 370–1.
21. Norris R V (1983) Progesterone for Premenstrual Syndrome. *J Repro Med*, 28, 8, 509–16.
22. Magos A L, Brincat M and Studd J W W (1986) Treatment of Premenstrual Syndrome by subcutaneous oestradiol implants and cyclical norethisterone: placebo controlled study. *Brit Med J* 292, 1629–33.
23. Abraham G E (1984) Nutrition and the Premenstrual Tension Syndromes. *J Appl Nutrit, 36, 2, 103–23.*
24. Kruitwagon R F P M, Janssen-Caspers H A B, Wladimiroff J W, Schats R, De Jong F H and Drogendijk A C. (1987) Oestradiol-17B and Progesterone level changes in peritoneal fluid around the time of ovulation. *Brit J Obstet Gynaec*, 94, 548–53.
25. Backstrom T, Wide L, Sodergard R and Cartensen H (1975) FSH, LH, TeBG Capacity, Oestrogen and Progesterone in Women with Premenstrual Tension during the Luteal Phase. *J. Ster Biochem*, 7, 473–6.
26. Backstrom T and Aakvaag A (1981) Plasma Prolactin and Testosterone during the Luteal phase in Women with Premenstrual Tension Syndrome. *Psychoneuroendo*, 6, 3, 245–51.
27. Jeske W, Klos J, Perkowicz J and Stopinska U (1980) Serum Prolactin in Women with Premenstrual Syndrome. *Materio Medica*, 1–2, 42.
28. Rapkin A J, Edelmuth E, Chang L C, Reading A E, McGuire M T and Su T (1987) Whole-blood Serotonin in Premenstrual Syndrome. *Obstet Gynec*, 70, 4, 533–37.
29. Backstrom T and Cartensen H (1973) Estrogen and Progesterone in Plasma in relation to Premenstrual Tension. *J Ster Biochem* 5, 257–60.
30. Backstrom T and Mattsson B (1975) Correlation of Symptoms in Pre-Menstrual Tension to Oestrogen and Progesterone Concentrations in Blood Plasma. *Neuropsychobiol*, 80–6.
31. Munday M R, Brush M G and Taylor R W (1981) Correlations between Progesterone, Oestradiol and Aldosterone levels in the Premenstrual Syndrome. *Clin Endocrin* 14, 1–9. 32 Rylance P B, Brincat M, Lafferty K, De Trafford J C, Brincat S and Parsons V (1985) Natural Progesterone and Antihypertensive Action, *Brit Med J*, 290, 13–13–4.
33. Radwanska E, Berger G S and Hammond J (1979) Luteal Deficiency among Women with Normal Menstrual Cycles Requesting Reversal of Tubal Sterilization. *Obstet Gynec*, 54, 2, 189–92.
34. Dalton K (1973) Progesterone Suppositories and Pessaries in the Treatment of Menstrual Migraine. *Headache*, 12, 4, 151–9.
35. Dennerstein L, Spencer-Gardner A, Gotts G, Brown J B and Smith M A (1985) Progesterone in the Premenstrual Syndrome: a double blind crossover trial. *Brit Med J*, 290, 1617–21.
36. Van der Meer Y G, Van Loenen A C, Loendersloot E W and Jaszmann L J B (1982) Plasma Progesterone Levels after using High Dose Suppositories: a preliminary report. *Pharma Weekblad Sci Ed*, 4, 135–6
37. Chakmakjian Z H and Zachariah N Y (1987) Bioavailability of Progesterone with Different Modes of Administration. *J Reprod Med*, 32, 443–8.
39. Price J H, Ismail H, Gorwill R H and Sarda I R (1983) Effect of the suppository base on Progesterone delivery from the vagina. *Fertil Steril*, 39, 4, 490–3.
40. Steege J F, Rupp S, Stout A and Bernhiusel M (1986) Bioavailability of Nasally Administered Progesterone. *Fertil Steril*, 46, 4, 727–9.
41. Dalton M E, Bromham D R, Ambrose C L, Osborne J and Dalton K. (1987) Nasal Absorption of Progesterone in Women. *Brit J Obstet Gynaec*. 94, 84–8.
42. Ottoson U B, Carlstrom K, Damber J E and Von Schoultz B (1984) Serum Levels of Progesterone and some of its Metabolites including Deoxycorticosterone after Oral and Parental Administration. *Brit J Obstet Gynaec*, 91, 1111–9.
43. Maxson W S and Hargrove J T (1985) Bioavailability of Oral Micronized Progesterone. *Fertil Steril*, 44, 8, 622–6.44 Dalton K (1968) Antenatal progesterone and intelligence. *Brit J Psychiat*, 1114, 1377–82.
44. Dalton K (1968) Ante-natal progesterone and intelligence. *Brit J Psychiat*, 114, 1377–1382.
45. Dalton K (1976) Prenatal progesterone and educational attainments. *Brit J Psychiat*. 129, 438–442.
46. Dalton K (1959) Comparative Trials of New Oral Progestogenic Compounds in the Treatment of Premenstrual Syndrome. *Brit Med J* 2, 1307–9.
47. Magos A L, Brewster E, Singh R, O'Dowd T, Brincat M and Studd J W W. (1986) The effect of norethisterone in postmenopausal women on oestrogen replacement therapy: a model for the premenstrual syndrome. *Brit J Obstet Gynaec*, 93, 1290–1296.
48. Johanson E D B (1971) Depression of progesterone levels in women treated with synthetic gestogens after ovulation. *Amer J Obstet Gynecol*, 110, 4, 470.
49. Dalton M E (1981) Sex Hormone Binding Globulin Concentrations in Women with Severe Premenstrual Syndrome. *Postgrad Med J*, 57, 560–1.
50. Dalton M E (1984) The Effect of Progesterone Ad-

ministration on Sex Hormone Binding Globulin Binding Capacity in Women with Severe Premenstrual Syndrome. *J Steroid Biochem*, 20, 1, 437–9.
51. Victor A, Wiener E and Johansson E D B (1970) Relation between sex hormone binding globulin and D Norgestrel levels in plasma. *Acta Endocrin Copenh*, 84, 430–6.
52. Greenstein B D (1979) Evidence for specific Progesterone Receptors in Rat Brain Cytosol. *J Endocrin*, 79, 327–38.
53. Blaustein J D (1986) Steroid Receptors and Hormone Action in the Brain. *Reproduction: A Behavioural and Neuroendocrine Perspective*. Ed Komusaruk B R et al, Annals New York Acad Sci, New York, 474, 400–14.
54. Schlesinger S and Boop W (1985) Steroid Hormone Receptors in Human Meningiomas: a Look at the Past, Present and the Future. Minnesota Med, 68, 544–5.
55. Backstrom T (1976) Epileptic Seizures in Women related to Plasma Oestrogen and Progesterone during the Menstrual Cycle. *Acta Neurol Scand*, 54, 321–47.
56. Herzog A G (1986) Intermittent Progesterone Therapy and frequency of complex partial siezures in women with menstrual disorders. *Neurology*, 36, 1607–10.
57. Hanley S P (1981) Asthma Variations with Menstruation. *Brit J Dis Chest*, 75, 306–8.
58. Eliasson O and Scherzer H H (1984) Recurrent Respiratory Failure in Premenstrual Asthma. *Connecticut Med*, 48, 12, 777–8.
59. Gibbs C J, Coutts I I, Lock R, Finnegan O S and White R J (1984) Premenstrual Exacerbation of Asthma. *Thorax* 39, 833–36.
60. Dalton K (1985) Erythema Multiforme associated with Menstruation. *J Roy Soc Med*, 78, 787–8.
61. Wojnarowska F, Greaves M W, Peachey, Drury P L and Besser G M (1985) Progesterone-induced Erythema Multiforme. *J Roy Soc Med*, 78, 407–81.
62. Dalton K (1967) Influence of Menstruation on Glaucoma. *Brit. J Ophthal*, 51, 10, 692–5.
63. MacLusky N J and McEwen B S (1978) Oestrogen modulates progestin receptors concentration in some rat brain regions but not in others. *Nature*, 274, 276–8.
64. Nock B, (1986) Noradrenergic Regulation of Progestin Receptors: New Findings, New Questions. *Reproduction: A Behavioural and Neuroendocrine Perspective*. Ed Komusaruk B R et al, Annals New York Acad Sci, New York, 415–22.
65. Al-Kouri H and Greenstein B D (1980) Role of Corticosteroid-binding Globulin in interaction with Uterine and Brain Progesterone Receptors. *Nature*, 287, 5777, 58–60.
66. Ying Y K, Soto-Albors C E, Randolph J F, Walters C A and Riddick D H. (1987) Luteal phase defect and Premenstrual Syndrome in an Infertile Population. *Obstet & Gynec*, 69, 1 96–9.
67. Dalton K (1957) The Aftermath of Hysterectomy and Oophorectomy. *Proc Roy Soc Med* 48, 5, 337–47.
68. Dalton K, Dalton M E and Guthrie K (1987) Incidence of the Premenstrual Syndrome in Twins. *Brit J Med*, 295, 1027–8.