HORMONAL CONTRACEPTIVES AND DERMATOLOGY

M. Prenen, M.D.
M. Ledoux-Corbusier, M.D.

Clinic of Dermatology
University of Brussels
Brussels, Belgium

ABSTRACT

The effects of oral contraceptives on various dermatologic aspects are discussed. A pigmentary complication, chloasma, may occur after administration of any type of estrogen-progestogen combination oral contraceptives. Individual sensibility and ultraviolet irradiation are determinant factors. Pilosebaceous complications (facial hypertrichosis, seborrheic alopecia and acne) may be attributed to the androgenic potential of progestogens derivated from 19-nor-testosterone. By contrast, combination estrogen-progestogens with estrogenic predominance, with non-androgenic progestogens, or sequential contraceptive steroids may be beneficial for the treatment of idiopathic hirsutism, resistant seborrheic alopecia, and some acne. The complications of yeast vulvo-vaginitis and porphyria **cutanea** tarda are discussed.

Accepted for publication July 12, 1971.

CONTRACEPTION

INTRODUCTION

From the dermatological viewpoint, hormonal contraceptives have advantages as well as disadvantages.

However, if we consider their large consumption by women, side-effects associated with their use appear to be relatively infrequent. We have also noticed that some of the cutaneous problems attributed to hormonal contraceptives, such as allergic eruptions (urticaria, fixed erythema, erythema multiforme) are not specific to their use and are described as appearing after other drugs have been taken (1-3).

We will consider particularly the cutaneous reactions which depend upon the hormonal activity of contraceptives. Estrogens and progestogens which are the components of anovulants act chiefly upon two cutaneous structures: the pigmentary system and the pilosebaceous system. Also included in this review are cutaneous disorders described by various authors as being produced by contraceptives, such as vulvo-vaginitis and porphyria.

1. Effects on the Pigmentary System

The physiology of the pigmentary system under the action of the hormone MSH (melanocyte stimulating hormone), from the pituitary gland, as well as estrogenic and progestogenic hormones from steroid producing glands and its pathology under the influence of hormonal contraceptives (Figure 1) will allow a better understanding of the pathogenesis of the cutaneous modification seen after taking contraceptives.

The melanocyte is an epidermic cell specializing in the synthesis of melanin. It responds to various hormonal stimulating actions (4), the most important being that of MSH. This hormone acts on all melanocytes of the organism by increasing the synthesis of melanin and by dispersing the melanin granules within the cytoplasm. Besides this stimulating action, some groups of melanocytes, particularly those of the face, undergo direct melanocyte stimulation by estrogens, progesterone (5,6) and androgens (7). Estrogens increase the size of melanocytes and their concentration in melanin: the clinical translation of this influence is the appearance and the development of nevi at the time of puberty and during pregnancy, as well as the sexual pigmentation of pregnant women. Progesterone has an action similar to estrogens, but of lesser intensity. It acts most probably on the dispersion of the melanin granules within melanocytes (8).

Estrogens and progestogens, consitituents of the hormonal contraceptives, are also directly responsible for the eventual development of the very unesthetic dyschromia referred to as chloasma or "mask of pregnancy". It is thought that increased levels of MSH are not a causative factor in the development of chloasma (9). This irregular pigmentation manifests itself mainly on the forehead, the malar eminences, the lower parts of the cheeks and the upper lip. Ultraviolet rays

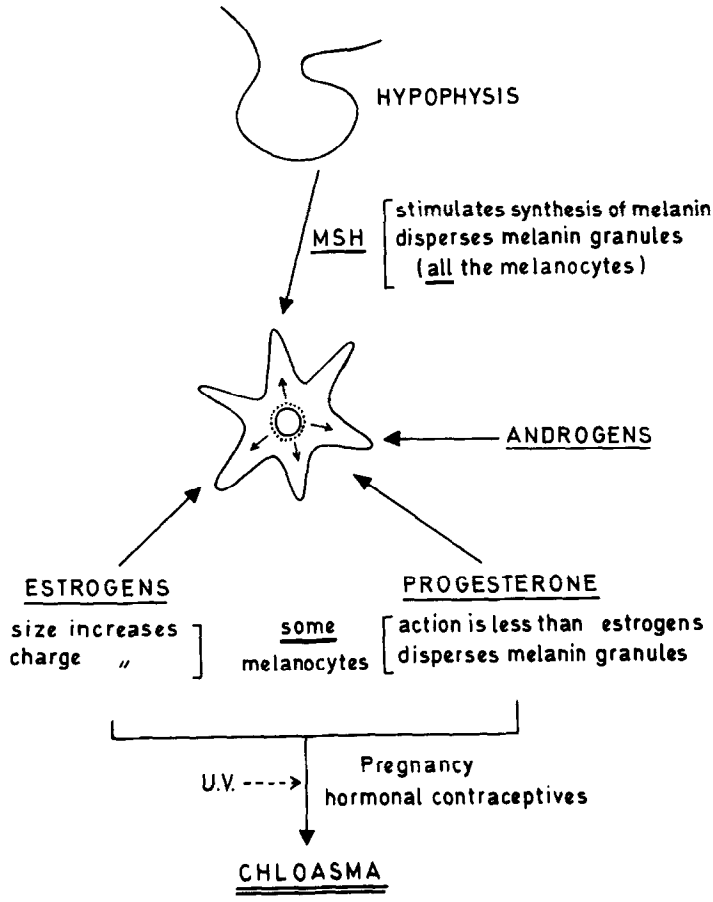

Figure 1. Physiologic responses of melanocytes to stimuli of MSH, androgens, estrogens and progesterone. Effects of estrogens and progestogens, constituents of the hormonal contraceptives, on facial pigmentation (chloasma).

promote its appearance. Chloasma has been observed to occur in 1 to 3% of French women (10-13), in 8% of Puerto Rican women (14), in 6% of Belgian women (15), and in 11.5% of Australian women (16) taking oral contraceptives. These variations of incidence can be explained by the different intensities of ultraviolet rays to which these women are exposed. Anti-"sunburn" creams can play a beneficial role in the prevention of this pigmentation. The delay in the appearance of this pigmented mask varies according to the sensitivity of the patient, ranging from 3 months to 3 years. Resnik (17) points out that chloasma resulting from oral contraceptive steroids disappear less easily than those of pregnancy. We wonder if this does not correspond to a deeper hormonal impregnation of melanocytes by the contraceptives.

It should be emphasized that all types of hormonal contraceptives could be, by their composition, responsible for the appearance of dyschromia. The individual sensitivity of the woman to these hormones seems to play an important role regarding the frequency of this complication (2,13).

2. Effects on the Pilosebaceous System

The physiology of the pilosebaceous system under the action of sexual hormones and the repercussions observed under the influence of hormonal contraceptives will now be considered (Figure 2).

Normally in women, ovarian and adrenal androgens stimulate the growth of sexual hairs and some vellus hairs (lip, chin). Moreover, they stimulate the function of sebaceous glands attached to the hair (18-26). The suppressive effect of estrogens on sebum production is not yet clearly explained. Ebling (27) showed that estrogens reduced the size of the sebaceous glands; others (22,23,28) reported that estrogens did not act directly on the glands, but did inhibit pituitary function and thus depressed the production of ovarian and adrenal androgens. Estrogens also depressed sebaceous activity by increasing the synthesis of the protein that normally binds plasma androgens (sexual binding protein) (28,29).

Natural progesterone given at physiological or even higher doses does not change the size or function of sebaceous glands (19,28). However, some synthetic derivatives of progesterone, for example medroxyprogesterone acetate, have a proven androgenic action (30).

In view of these effects, we can better understand the pathogenesis of pilosebaceous complications of contraceptives and appreciate their possible therapeutic role (Figure 2).

The pilosebaceous complications caused by combination estrogen-progestogen contraceptives are attributed to their progestogenic part. The majority of synthetic progestogens are actually derivatives of 19-nor-testosterone and have androgenic effects (23,30). The pilosebaceous complications consist mainly of facial hypertrichosis, seborrheic alopecia and acne. Cohen (31) observed facial hypertrichosis

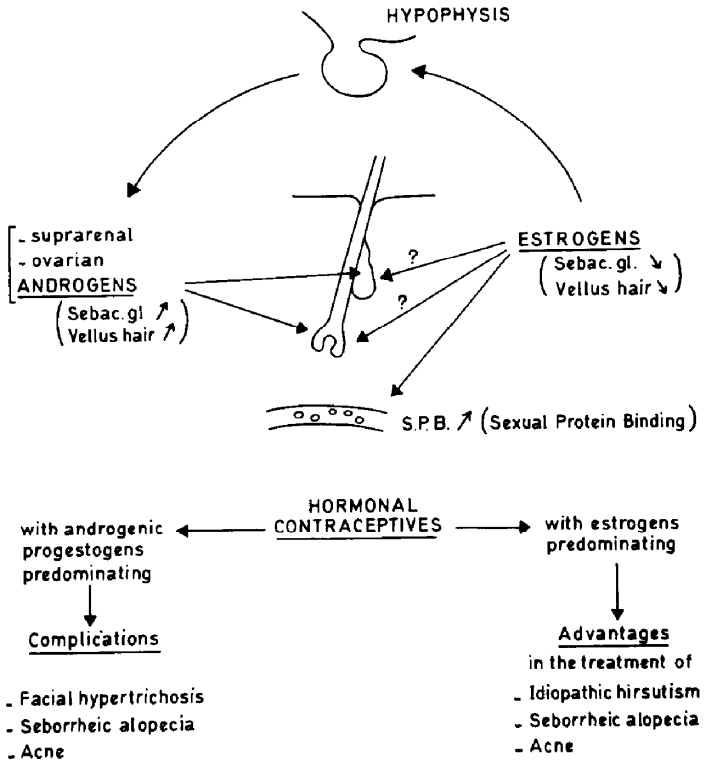

Figure 2. Hormonal influences on the physiological activity of the pilosebaceous system. Pilosebaceous effects of the hormonal contraceptives.

in 0.1% of women receiving oral contraceptive steroids. This hypertrichosis is characterized by the development of soft hair at the chin and at the upper lip and affects women under thirty years of age (32,33). According to a statistic reported by Cohen (31), 3 to 4% of women taking anovulatory compounds suffer from seborrheic alopecia characterized by seborrhea, hair loss at the vertex and at frontotemporal regions (2). Other authors have reported cases of diffuse alopecia which they attributed to oral contraceptives (15,34,35). Three types of acne have been described in some of these patients: acne vulgaris, phlegmonous acne of the chin and microcystic acne of the temporal regions and forehead (2). This acneic complication can be compared with steroid acne.

These side-effects are attributed mainly to the chemical nature of those progestogens which are derivatives of 19-nor-testosterone, the progestogen occuring in nearly all oral contraceptive steroids (20,28,30), as these progestogens have androgenic effects. Moreover, the doses of the various components and their relative quantitative ratio are important factors (11,24,25,30).

On the other had, some combination estrogen-progestogens can be of therapeutic value for the same pilosebaceous effects previously described as side-effects. Here the therapeutic virtue of the pill is to be attributed to its estrogenic component. Thus, in treating acne, the choice of contraceptive is very important. Indeed some anovulatory compounds have an estrogenic dominance and their progestogenic component is not very androgenic (e.g., norethynodrel and chlormadinone acetate). The sequential types of oral contraceptives have the same characteristics. One can use this therapy for idiopathic hirsutism (36,37), for resistant seborrheic alopecia (38) and for some forms of acne (23), mainly those with premenstrual exacerbations, those improved by pregnancy and also microcystic acne of the adult women (13,15, 39).

3. Vulvo-Vaginitis due to Yeastlike Fungi

Several statistics (40,41) point out the presence of Candida albicans in 5 to 30% of the adult women with or without symptoms. During pregnancy, this rate can reach 40 to 50% (42). Contraceptives, with the quantity of estrogens they contain, should be added to the list of factors predisposing to the development of this flora (43-46). It has been stated that estrogens increase the amount of glycogen in the vaginal mucous and so enhance the proliferation of Candida (47,48).

Nystatin, applied locally, improves this vulvo-vaginitis, but only during its administration. Catterall (49) noted an increased frequency of Candida balanitis in the male partners of women receiving oral steroid contraceptives.

4. Porphyria Cutanea Tarda

Porphyria cutanea tarda has been reported to occur after taking oral contraceptives (50,51). Cases have also been described by Walsche and Warin (52), Sourreil et al (53) and Stewart et al (54) during treatment of prostatic or mammary

carcinoma by estrogens alone. In these instances, estrogens could be harmful to the hepatic parenchyma and would reveal a hidden genetic defect of porphyrin metabolism (55).

CONCLUSION AND SUMMARY

The physiological characteristics of the pigmentary and pilosebaceous systems aid in a better understanding of the cutaneous side-effects of hormonal contraceptives. The frequency of these side-effects is relatively low.

A pigmentary complication, chloasma, may occur after administration of any type of estrogen-progestogen combination oral contraceptives. Individual sensibility and ultraviolet irradiation are determinant factors. Pilosebaceous complications (facial hypertrichosis, seborrheic alopecia and acne) may be attributed to the androgenic potential of progestogens derivated from 19-nor-testosterone. By contrast, combination estrogen-progestogens with estrogenic predominance or with non-androgenic progestogens or sequential contraceptive steroids may be beneficial for treatment of idiopathic hirsutism, resistant seborrheic alopecia and some acne. Therefore, they can be recommended for treatment from the dermatological point of view without taking into account other medical considerations. The appearance of yeast vulvovaginitis and porphyria cutanea tarda is mentioned.

It might be added that the disfiguring side-effects of contraceptives occur only in some patients. The patients themselves and their environment will aid in choosing whether the benefits of the pill outweigh possible dermatologic side-effects.

REFERENCES

1. Ortiz, Y.: Anovulatorios un nuevo factor pathogeno en dermatologia. Dermatologia (Mexico) 9:63, 1965.

2. Merklen, F. and Melki, G.R.: Incidences dermatologiques des contraceptifs oraux. Acad. Nation. de Med. 150:624, 1966.

3. Melki, G.R.: Incidents et accidents dermatologiques de la contraception orale. Nouv. Arch. Hosp. 5:204, 1967.

4. Johnsson, S. and Hogbern, B.: The occurrence of the melanophore hormone in serum from human subjects in different pathological condition and its relation to corticotrophine. Acta Endocrin. 13:325, 1953.

5. Snell, R.S. and Bischitz, P.G.: The effect of large dose of oestrogen and progesterone on melanine pigmentation. J. Invest. Derm. 35:73, 1960.

6. Snell, R.S. and Bischitz, P.G.: The melanocytes and melanine of human abdominal wall skin: a survey made on different stages in both sexes and during pregnancy. J. Anat. Lond. 97:361, 1963.

7. Rook, A., Wilkinson, D.S. and Ebling, F.: The Ages of Man and Their Dermatoses, Textbook of Dermatology, vol. 2, ed. Blackwell Scientific Publications, Oxford, England 1:138, 1968.

8. Lerner, A.B. and Case, J.D.: Pigment cell regulatory factors. J. Invest. Derm. 32:211, 1959.

9. Carruthers, R.: Chloasma and oral contraceptives. Med. J. Aust. 2:17, 1966.

10. Thiers, H., Villedieu, P. and Moulin, G.: Le chloasma, une complication des traitements par les progestatifs de synthèse (7 observations). J. Méd. Lyon 47:1815, 1966.

11. Grupper, Ch.: Le traitement de l'acné féminine par les oestroprogestatifs. Indications, modalites et limites. Bull. Soc. Franç. Derm. Syph. 73:862, 1966.

12. Rivoire, M.: A propos de l'apparition de chloasmas au cours des traitements par les progestatifs de synthèse. Bull. Soc. Franç. Derm. Syph. 73:353, 1966.

13. Aron-Brunetiere, R. and Robin, J.: Données nouvelles sur le traitement de la séborrhée et de l'acné vulgaire féminines par les inhibiteurs d'ovulation. Rev. Med., Paris 2:85, 1969.

14. Esoda, E.C.: Chloasma from progestational oral contraceptives. Arch. of Derm. 87:626, 1963.

15. Prenen, M. and Ledoux-Corbusier, M.: Contraceptifs hormonaux et dermatologie. Arch. Belg. Derm. Syph. (In press).

16. Carruthers, R.: Chloasma and the "pill". Brit. Med. J. 3:307, 1967.

17. Resnik, S.: Melasma induced by oral contraceptive drugs. J. Am. Med. Assoc. 199:601, 1967.

18. Strauss, J.S.: The development of the pilosebaceous units of the human cheek at puberty: Anatomical and hormonal studies. Proc. XIIe Intern. Congress Derm. 2:945, 1962.

19. Strauss, J.S. and Kligman, A.M.: The effect of progesterone and progesterone-like compounds on the human sebaceous gland. J. Invest. Derm. 36:309, 1961.

20. Strauss, J.S. and Kligman, A.M.: Androgenic effects of a progestational compound, 17α-ethynyl-19-nortestosterone (Norlutin) on the human sebaceous gland. J. Clin. Endocrin. 21:215, 1961.

21. Strauss, J.S. and Pochi, P.E.: The quantitative gravimetric determination of sebum production. J. Invest. Derm. 36:293, 1961.

22. Strauss, J.S., Kligman, A.M. and Pochi, P.E.: The effect of androgens and estrogens on human sebaceous glands. J. Invest. Derm. 39:139, 1962.

23. Strauss, J.S. and Pochi, P.E.: Effect of cyclic progestin-estrogen therapy on sebum and acne in women. J. Am. Med. Assoc. 190:815, 1964.

24. Pochi, P.E. and Strauss, J.S.: Lack of androgen effect on human sebaceous glands with low-dosage norethindrone. Am. J. Obstet. Gynec. 93:1002, 1965.

25. Pochi, P.E. and Strauss, J.S.: Sebaceous gland response in man to the administration of testosterone, Δ4-androstenedione, and dehydroisoandrosterone. J. Invest. Derm. 52:32, 1969.

26. Milne, J.A.: The metabolism of androgens by sebaceous glands. Brit. J. Derm. 81:23, 1969.

27. Ebling, F.: Sebaceous glands. I. The effect of sex hormones on the sebaceous glands of the female albino rat. J. Endocrin. 5:297, 1948.

28. Bercovici, J.P. and Mauvais-Jarvis, P.: Physiologie et pathologie du récepteur pilo-sébacé. La Presse Médicale 78:2229, 1970.

29. Mauvais-Jarvis, P.: Comment peut-on concevoir l'approche clinique et hormonale des hirsutismes en 1969? La Revue du Praticien 19:4015, 1969.

30. Simon, P.: Précis de contraception. Ed., Masson, Paris, France, vol. I, 119, 1968.

31. Cohen, J.: Bilan des effets biologiques et cliniques des inhibiteurs de l'ovulation utilisés en administration prolongée aux USA. Rev. Med. Paris 18:993, 1965.

32. Gomez, D.F., Abalos, J.C., Barcas, R. and Coll, A.: Trastornos de conducta y modificaciones somaticas determinades por la administracion do androgenos, solos o combinados con estregenos. La Prensa Medica Argentina 49:2554, 1962.

33. Gomez, D.F., Abalos, J.C., Barcas, R. and Coll, A.: Summary. Ann. Soc. Franç. Derm.Syph. 91:350, 1964.

34. Cormia, F.E.: Alopecia from oral contraceptives. J. Am. Med. Assoc. 201:635, 1967.

35. Eckert, J.,Church, R., Ebling, F.J. and Munro, D.S.: Hair loss in women. Brit. J. Derm. 97:543, 1967.

36. Greenblatt, R.B. and Mahesh, V.B.: Clinical evolution and treatment of the hirsute female. Clin. Obstet. Gynec. 7:1109, 1964.

37. Greenblatt, R.B. and Audebert, A.: La femme hirsute. L'Union Med. du Canada 98:85, 1969.

38. Chanial, G.: Oestro-progestatifs acné et séborrhée féminine. Bull. Soc. Franç. Derm. Syph. 73:163, 1966.

39. Aron-Brunetiere, R. and Robin, J.: Essai d'estimation de la valeur thérapeutique des contraceptifs oraux dans la séborrhée et l'acné vulgaire féminines. Rev. Med. Paris, 18:913, 1967.

40. Gray, L.A. and Barnes, M.L.: Vaginitis in women. Diagnosis and treatment. Am. J. Obstet. Gynec. 92:125, 1965.

41. Rohatiner, J.J.: Relationship of Candida albicans in the genital and ano-rectal tracts. Brit. J. Vener. Dis. 42:197, 1966.

42. Jackson, J.L. and Spain, W.T.: Comparative study of combined and sequential antiovulatory therapy on vaginal moniliasis. Am. J. Obstet. Gynec. 101:1134, 1968.

43. Porter, P.S. and Lyle, J.S.: Yeast vulvo-vaginitis due to oral contraceptives. Arch. Derm. 93:402, 1966.

44. Rieth, H.: Candida-Balanitis und Candida-Fluor nach längeren Einnehmen oraler Kontrazeptiva. Mykosen 10:151, 1967.

45. Walsh, H., Hildebrandt, R.J. and Prystowsky, H.: Oral progestational agents as a cause of Candida albicans. Am. J. Obstet. Gynec. 101:991, 1968.

46. Catterall, R.D.: Influence of gestogenic contraceptive pills on vaginal candidosis. Brit. J. Vener. Dis. 47:45, 1971.

47. Wynn, V. and Doar, J.W.: Some effects of oral contraceptives on carbohydrate metabolism. Lancet 2:715, 1966.

48. Wynn, V. and Doar, J.W.: Oral contraceptives and glucose tolerance. Lancet 1:1156, 1969.

49. Catterall, R.D.: Candida albicans and the contraceptive pill. Lancet 468: 830, 1966.

50. Wetterberg, L.: Oral contraceptives and acute intermittent porphyria. Lancet 2:1178, 1964.

51. Degos, R., Touraine, R., Kalis, J., Delort, J. and Mme. Bonvalet, D.: Porphyrie cutanée tardive après prise prolongée de contraceptifs oraux. Ann. Derm. Syph. Paris 96:5, 1969.

52. Walshe, M. and Warin, R.P.: Porphyria cutanea tarda associated with oestrogen therapy for prostatic carcinoma. Brit. J. Derm. 75:298, 1963.

53. Sourreil, M.T., Mme Beylot, C. and Marc, Y.: Porphyrie cutanée tardive. Bull. Soc. Franç. Derm. Syph. 75:397, 1968.

54. Stewart, W.M., Lecroq, C. and Fondimare, A.: Porphyrie cutanée tardive de l'adulte révélée par les oestrogènes. Bull. Soc. Franç. Derm. Syph. 75:294, 1968.

55. Thivolet, J., Perrot, H. and Arcadio, F.: Le rôle révélateur des oestrogènes dans les porphyries cutanées tardives. Dermatologica 135:455, 1967.