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HYPERPIGMENTATION ASSOCIATED WITH HORMONAL CONTRACEPTIVE USE

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Abstract

Introduction: Melanocytes are cells which are present in the human skin and they are responsible for the melanin production. They can be found in the basal stratum of the epidermis and they have some prolongations extending until the stratum corneum. Melanin synthesis may increase in the presence of some factors and some irregular brownish spots – hyperpigmentations – may appear. Factors which can trigger melanogenesis are excessive sun exposure, hormonal contraception, hormonal reposition therapy, pregnancy, medicines, cosmetics, stress or genetics.
Aim: Understanding of the relationship between hormonal contraceptives and hyperpigmentation.
Material and Methods: A bibliographic review through a research in diverse databases (PubMed, Google Scholar, ScienceDirect and Wiley Online Library).
Results/Discussion: According to some authors, estrogenic components found in hormonal contraceptives are associated with hyperpigmentation situations. In the case of progestagenic components, opinions diverge: some studies substantiate that progesterone has the ability to increase melanogenesis and others that it may have the opposite effect of estrogen. In a general way, most researchers say that hormonal contraceptives affect melanin synthesis; however others reject that fact.
Conclusion: It is verified the relationship between hormonal contraceptives and hyperpigmentation. However, this topic is not sufficiently well approached, so future investigations are needed to allow its best understanding.

Introduction

Skin is the biggest multifunctional organ of the human body and it acts as a barrier against ultraviolet (UV) radiation, microorganisms' invasions and chemical agents' penetration. It also controls body fluids loss. The skin is an organ which is really important in thermoregulation and it also plays an important role in immunological, sensational and autonomous responses.(1)

The skin is constituted by 3 main layers: the epidermis – the exterior layer, the dermis – the intermediate layer, and the hypodermis – the most interior and deep layer of the skin. In its turn, the epidermis is divided in 5 subdivisions: the stratum basale – most interior and deep, the stratum spinosum, the stratum granulosum, the stratum lucidum and the stratum corneum – the most exterior. The physic barrier is located mainly in the stratum corneum because on that stratum there are dead cells – keratinocytes -, nucleated epidermal cells and complexes formatted by keratin and proteins, evolved by a lipid matrix.(2)

Melanocytes are the cells responsible for the production of melanin. They have an important function in skin protection against the malign effects of UV radiation. They are located in the stratum basale of the epidermis and they possess extensions until the stratum corneum, where the keratinocytes are. Melanocytes descend from precursor cells – melanoblasts. Melanocytes are responsible for skin tone, which differs from individual to individual according to its density, number, size and dispersion. Within the melanocytes, melanin is produced by

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melanossomes – particles disposed in the cytoplasm of melanocytes, in which melanin is produced. After the production of melanin, it is transferred to the keratinocytes through the melanocytes' extensions, where it is stored.[3,4]

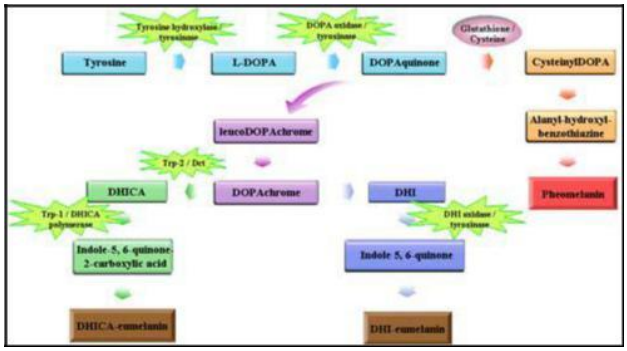
The melanin production happens inside the melanocyte through a process which requires the knowledge of basic physiology of the human cell as the structural and functional unit of all living beings:

Tyrosinase is the bottom line for all the mechanism which leads to melanin production. It is an enzymatic complex synthetized in ribosomes and it is transferred to the Golgi complex. In the presence of oxygen, tyrosinase oxidizes tyrosine (an essential aminoacid) into dihydroxyphenylalanine (DOPA) and then DOPA into dopaquinone. From this point, the process can take two distinct pathways, depending on the presence or absence of cysteine.

In the absence of cysteine (non-essential aminoacid), dopaquinone is converted into cyclodopa and then cyclodopa into dopachrome. Dopachrome is degraded by dopachrome tautomerase into dihydroxyindole (DHI), in greater proportion, and into dihydroxyindole-2-carboxylic acid (DHICA), in minor. Tyrosinase then oxidizes DHICA into eumelanin.

In the presence of cysteine, dopaquinone reacts with it and forms cysteynildopa, which is oxidized into benzothiazinic intermediates, which produce pheomelanin. This process goes on while cysteine is present. When it finishes, it starts the process of production of eumelanin.[3,5]

Figure 1.



Melanin production process (L-DOPA – L-3,4-dihydroxyphenylalanine; Trp-2 –tyrosinase-related protein-2; Trp-1 – tyrosinase-related protein-1; DHICA – dihydroxyindole-2-carboxylic acid; DHI – dihydroxyindole) Source: Uyen et al, 2005

Individual with a darker skin have a bigger production of eumelanin (darker pigment); those with a lighter skin have a bigger production of pheomelanin (lighter pigment). Eumelanin diffuses UV radiation, attenuates its penetration on skin and reduces its harmful effects, so people with darker skins can get tanner without getting burned. Pheomelanin generates free radicals in response to UV radiation and it is capable of causing damage in deoxyribonucleic acid (DNA), so people with lighter skins present higher risk of epidermal damage induced by UV radiation. Skin and hair colour result from the mixture of both melanins.[3,4]

As a response to diverse stimulus, melanin synthesis may increase so there may appear some irregular brownish marks, especially in the areas exposed to sun radiation. Those areas are called hyperpigmented areas. Two common problems are melasma and post-inflammatory hyperpigmentation. The most prevalent situation is melasma, which is characterized by marks which appear on the face. Within other pathologies that consist on hyperpigmentations, there

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can be found the following: periorbital hyperpigmentation, Riehl's melanosis, exogenous ochronosis, dermatosis papulosa nigra, lentigo, lichen planus pigmentosus and freckles.[6,7]

The most affected areas ate the forehead, the temples and the cheeks. This phenomenon affects mainly women on fertile age. Meanwhile, it can also affect men, although they represent 10% of all cases. The appearance of these cutaneous manifestations happens due to excessive sun exposure, hormonal contraception, hormonal reposition therapy, pregnancy, medicines, cosmetics or stress, and there is also a genetic component associated with this outcoming, with a probability around 40-60%.[3,8-12]

Among the medicines that can cause hyperpigmentation there are antimalarial, amiodarone, cytotoxic, minocycline, chlorpromazine, tricyclic antidepressives and anticonvulsants. Hyperpigmentation develops slowly. The first marks and visible only months or even years after the taking.[11]

The responsible genes for human pigmentation differ from population to population and inside the population, resulting on a different production of melanin and, consequently, on a bigger or smaller manifestation of cutaneous hyperpigmentations.[13]

Deep down, melanin confers some protection to the skin because of its ability to absorb UV radiation and it also has antioxidant properties once it eliminates free radicals. Besides UV radiation, nowadays it is known that visible spectrum light may also have potential to cause hyperpigmentations, at least on the individuals with darker skin.[14,15] In the case of hormonal contraception, it is used for about 60% of women with ages between 16 and 30 years old. At first, contraceptives contained only progesterone; however, as time went by, there were seen a few undesirable androgenic effects, so it was introduced estrogen to the contraceptives. Nowadays, combined hormonal contraceptives are a very effective method of undesirable pregnancy prevention when used properly.[12,16]

There are some hormonal contraceptive methods like oral contraception, vaginal ring, transdermal patch, intra uterine device, subcutaneous implant and injectable contraceptive. It is estimated that around 10 to 20% of women who use contraceptives develop this kind of marks. There are several studies about the area and it appears that the cause of this cutaneous expressions derives from the fact that most contraceptives contain estrogen in its composition. There are two types of estrogenic receptors which measure the biologic responses of estrogen in the human body. One of its responses may be the increase of melanogenesis.[12,16-18]

So, the problem to approach is the possibility that the hormones contained in the hormonal contraceptives may be or may not be a potential cause of hyperpigmentations.

Materials and methods

This study is a bibliographic review, effectuated between September 2017 and May 2018. For this research, there were analysed free-access articles retrieved from online databases (PubMed, Google Scholar, ScienceDirect and Wiley Online Library), with the support of software and computer equipment. The articles had language restriction for Portuguese, English, Spanish and Polish and the keywords searched were "hormonal contraceptives", "hyperpigmentation", "estrogen", "progesterone", "melanin" and "pigmentation".

Inclusion criteria to use the articles found were:

-Study of the relationship between the use of hormonal contraceptives and the emergence and/or aggravation of hyperpigmentation situations;

-Date of publication in the last 10 years (2008-2017).

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Results and discussion

Given the theme under study, the research focused on bibliographical sources which debate the hypothesis that steroid hormones contained in the hormonal contraceptives constitute a potential to emerge and/or aggravate hyperpigmentations. Therefore, the presented review is focused on the demystification of that conjecture.

1. Estrogenic components

Sun *et al*., in 2017, determined through an *in vitro* study that estrogen promotes melanogenesis both in the skin and in the hair. This study allowed to conclude that women who take oral contraceptives which contain estrogen are more disposed to the development of cutaneous hyperpigmentations. It was discovered that UV radiation increases the proliferation of melanocytes, so it is a factor which upholds the effect of estrogen.[19]

According to Tamega *et al*., estradiol present in the hormonal contraceptives causes, in a dose-dependent way, the increase of the activity of tyrosinase and dopachrome tautomerase, with the subsequent decrease of the proliferation of the melanocytes. This study *in vitro* was carried in the year of 2015, using samples of healthy cutaneous tissue and tissue affected by hyperpigmentations. The authors discovered that estradiol increases ribonucleic acid (RNA) levels of the melanocortin receptors type 1 (MCR-1), which is evolved in the regulation of melanin synthesis. The increase of MCR-1 expression is responsible for a higher activity of the keratinocytes, leading to a bigger production of melanin. These authors try to approach the way progesterone acts by the level of melanogenesis; however, the research is inconclusive so they appeal to the need of more studies.[20]

Following Cohen, in 2017, estrogenic receptors - α and β - are both over-expressed in a hyperpigmented skin when compared to a normal skin. This fact happens due to the presence of high levels of estrogen. Estrogen, as referred by other authors, increases melanogenesis through stimulation of some proteins: tyrosinase, tyrosinase-related protein-1 (TRP-1), tyrosinase-related protein-2 (TRP-2) and melanogenesis associated transcription factor (MITF). On a microscopic exam performed on a hyperpigmented skin, it was possible to verify that the melanocytes were bigger and more prominent; yet, there weren't more than before. Meanwhile, Asian women with hyperpigmentations in the face were evaluated as its lesions showed that melanin was more dispersed for all the epidermis but also a numeric increase of melanocytes, melanin and melanossomes.[21]

As studied by Kim *et al*. in 2012, estrogen may induce the expression of PDZ domain containing 1 (PDZK1). This protein is clinically related to melasma. In this study there were used monocultures and co-cultures of melanocytes and keratinocytes with and without over-expression of PDZK1 form 15 individuals. The administered estrogen caused an increase of PDZK1 expression. This protein increases tyrosinase's activity and the transfer of melanin from melanossomes to keratinocytes. PDZK1 inhibition reduced tyrosinase's expression through regulation of the activity of α and β estrogen receptors. The authors also verified that hyperpigmented cells had a higher expression of PDZK1 in comparison to normal cells.[22]

According to Lee, on a systematic review from 2015, melanogenesis induction by estrogen may occur through PDZK1 expression and may be associated to cyclic adenosine monophosphate (cAMP) cascade activation, once estrogen increases cAMP levels and the expression of tyrosinase and MITF.[23]

Mahmood *et al*., on their research from year 2011, quote some studies *in vitro* which prove that melanocytes express estrogenic receptors and that estrogen increases levels of tyrosinase, TRP-1 and TRP-2 (Figure 2). The connection of melanocytes stimulation hormone (MSH) to MCR-1 receptors mediates melanogenesis which occur naturally in the human being. In the presence of estrogen, the expression of MCR-1 and tyrosinase increase, leading to an augmented melanogenesis.[24]

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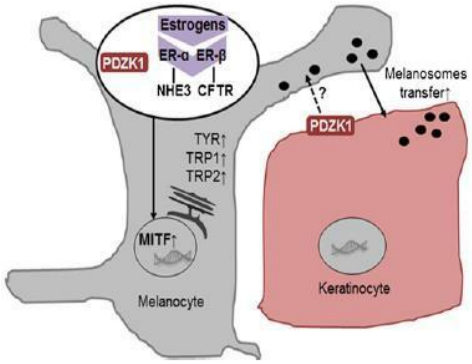
Figure 2.



Mechanism evolved on melanogenesis induced by estrogen (ER – estrogen receptor; PDZK1 – PDZ domain containing 1; NHE3 – sodium-hydrogen antiporter 3; CFTR - Cystic fibrosis transmembrane conductance regulator; TYR - tyrosinase; TRP1 – tyrosinase-related protein-1; TRP1 – tyrosinase-related protein-2; MITF – melanogenesis associated transcription factor)

Source: Lee, 2015

In short: All the previously quoted authors associate estrogenic components in hormonal contraceptives with hyperpigmentation situations. Sun *et al*. also allege that UV radiation is an aggravating factor. Tamega *et al*. and Mahmood *et al*. studied the evolvement of MCR-1 receptors in melanogenesis. PDZK1 is over-expressed in hyperpigmented cells, as described for Lee and Kim *et al*. The implication of TRP-1 and TRP-2 is also evident, as studied for Cohen.

2. Estrogenic and progestagenic components

A cross-sectional study accomplished by Damayanti *et al*. in 2017, with a sample of 17 female individuals, allowed to associate the continuous use of oral combined contraceptives with the appearance of hyperpigmentations. They have concluded that women who took those contraceptives for at least 2 years have suffered the adverse effect on approach: hyperpigmentations. The authors determine that a period of three months of oral combined contraceptives may be enough to start mechanisms which can lead to hyperpigmentation.[25]

A review study done by Gardini *et al*. in the year of 2011 allowed to associate the progression of a hyperpigmentation situation to an oncological situation of melanoma. The authors close the article concluding that the use oral contraceptives only containing estrogen or containing a combination of estrogen and progesterone increase melanin production and the number of melanocytes. However, those don't increase the risk for developing melanoma.[26]

Following Wiedemann *et al*., on a study *in vitro* on melanocytes in 2009, estrogen and progesterone caused its multiplication and increased tyrosinase' activity on three from eight cell cultures. Still, when they studied the effects of progesterone isolated, there wasn't any increase of tyrosinase but there was a decrease of the amount of melanin. Therefore, the authors conclude that progesterone present in hormonal contraceptives may have an inhibitory effect on the proliferation of melanocytes.[12]

An *in vitro* study realized in 2016 allowed to Natale *et al*. to associate ethinylestradiol which is present in hormonal contraceptives with melanin production. The process that occurs naturally to form melanin is regulated by MSH. As referred by other authors, MSH links to MCR-1, activating adenylcyclase and increasing cAMP. This molecule triggers a cascade of events required to melanin synthesis. Women who use hormonal contraceptives keep this process dependent of MSH. Nevertheless, after *in vitro* evaluation of the behaviour of melanocytes which had been

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treated with estrogen, melanin synthesis increased in about 208%, without affecting the number or density of melanocytes. The authors also evaluate the production of melanin when progesterone was administered. They concluded that progesterone has the opposite effect of estrogen, diminishing melanin production in about 58%. So, the conclusion of this study leaves the possibility that, in the case of use of hormonal combined contraceptives, the stimulatory effects of estrogen can be antagonized by the presence of progesterone.(27)

According to Hyun Jang *et al.*, in 2012, estrogen and progesterone are related to hyperpigmentation. Estrogen interacts and activates α and β estrogenic receptors. The expression of β-estrogenic receptor is predominant in case of lesion of melanocytes. This discover suggests that estrogen and its analogues, by interacting with this receptor, play an important role on physiology and physiopathology of the melanocyte. As for progesterone, the researchers assume that it stimulates melanogenesis in the melanocytes, although they say that its function, as said for other studies, inhibits melanogenesis.(28)

An *in vitro* study conducted by Jang *et al*. in 2010 consisted in comparing the expression of estrogenic and progestagenic receptors between hyperpigmented areas and non-affected areas from the faces of individuals with melasma. All the participants were female and had been suffering from the problem for at least 8 years. Although the protective effects of estrogen against skin aging, the authors allege that estrogen increases melanin activity, inducing skin pigmentation. Between the two estrogen receptors already mentioned, the β-estrogenic receptor is the predominant one on the lesions of melanocytes. Results indicate a higher activity of those receptors in skins affected by melasma on the epidermis, essentially on stratum basale and stratum spinosum, on which β-estrogenic receptors present a greater immunoreactivity than those on stratum granulosum. There wasn't found any specific expression of receptors in affected skin, neither in the surrounding healthy tissues. As for progesterone receptors, its expression was also higher in skin with lesions. Therefore, investigators prove that the melanin amount present in skin affected by melasma was superior in comparison to non-affected skin and they associate positively hormonal receptors like estrogenic and progestagenic with skin lesions derived from melasma.(29)

In short: Through the analysis of precious data, it is understandable that according to Damayanti *et al*., Gardini *et al*., Hyun Jang *et al*. and Jang *et al*. estrogen and progesterone both possess ability to increase melanogenesis. However, Wiedemann *et al*. and Natale *et al*. say that only estrogen presents stimulatory effects of melanogenesis and that progesterone could have the opposite effect of estrogen.

3. Unknown components

In 2015, Pietrzak *et al*. observed that long term use of hormonal contraceptives increases the amount of melanossomes in melanocytes, increases its metabolism and, as a consequence, increases melanin production. The authors suggest that exposure to UV radiation may rise the risk of development of hyperpigmentations.(30)

As studied by Krupashankar & Somani in the year of 2014, with the aim of evaluating the epidemiology of melasma associated with diverse factors (including oral contraceptive use), 266 women with melasma were evaluated, from which only 23 (8,6%) had taken oral contraceptives. 7 of them took it for 1 to 3 years. This way, the authors conclude that there is no statistically significant relationship; meanwhile, they appeal to the need for more studies around the subject.(31)

A case-control study performed in women in 2009 by Applebaum *et al*. allowed to make an association between oral contraceptive use and the prevalence of squamous cell carcinoma (SCC). In this study, the authors recognize that oral contraceptive taking changes cell response to exposure to UV radiation, making it more susceptible to its effects. From 261 cases and 298 controls, only 7 cases and 4 controls had experienced melasma and the duration of oral contraceptive use was equal in women who had not had that experience. In other words, from women who took oral contraceptives for the same time, only a few developed hyperpigmentations. This fact lead the investigators to conclude that hormonal contraceptive use is not statistically related to hyperpigmentation.(32)

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In a case-control study 312 individuals with hyperpigmentation in the face were evaluated, in the year of 2011. 250 individuals were female and 62 were male. From all women included in the study, only 18,4% took oral contraceptives during the follow-up period. Results show that there is no significant relationship between taking oral contraceptives and the appearance or aggravation of hyperpigmentation. However, this study only had a follow-up period of one year (January 2009 to December 2009), so the effects of estrogen may not have been perceptible within this range.(33)

According to an observational study of Guinot *et al*. from year 2010, with a sample of 197 individuals, from which 188 were female, oral contraceptives are effectively a factor which interferes with the appearance of hyperpigmentations in the face. 135 women had never used oral contraceptives, 40 had used but discontinued its use and the other 13 were still taking it. The authors conclude that oral contraceptives constitute a triggering factor in 26% of all cases and aggravating factor in 38%. Yet, the severity level of lesions varies according to ethnic group. Melasma arises 1 to 3 years after the first taking and disappears slower than marks triggered by pregnancy (some marks never disappear totally). In this study, the investigators say that melasma represents about two thirds of all cutaneous secondary effects of oral contraceptives.(34)

In short: Most studies in this category reject the hypothesis that hormonal contraceptives implicate hyperpigmentation situations, as described by Krupashankar & Somani, Applebaum *et al*. and Rathi & Achar. On other hand, Pietrzak *et al*. and Guinot *et al*. found a relationship between hormonal contraceptives use and the appearance and/or aggravation of hyperpigmentations. One aspect to point in these studies conducted by Krupashankar & Somani and Rathi & Achar is the low number of women who took hormonal contraceptives in comparison to the total of women in the sample.

Conclusion

After the present research, it is concluded that hormonal contraceptives use is related to the appearance and/or aggravation of hyperpigmentation situations.

Although some authors conclude that estrogen present in hormonal contraceptives doesn't have a statistically significant relationship with the object of study, most studies substantiate that there is a cause-effect relationship. The role of progesterone is not yet entirely clarified, once there are some studies which point its synergic potential with estrogen while others mention its antagonist and protective action from the cutaneous effects of estrogen. About the population studies, it is important to remark that tiny samples and/or restricted follow-up periods will not allow the obtaining of reliable results.

Another limit on the found studies was the fact that the main problem of hyperpigmentation is melasma. As for the remaining pathologies associated to hyperpigmentations, the information is quite reduced.

Therefore, it is verified the positive association between hormonal contraceptive use and hyperpigmentation. However, the achievement of profitable articles for this study was an arduous task because the existing studies are still rare. It becomes necessary to deepen studies about the role of progesterone and other diseases caused by hyperpigmentations. The relationship between hormonal contraceptives and hyperpigmentation is a subject which needs future investigations so that it can be fully demystified.

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