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REVIEW ARTICLE

Female acne – a different subtype of teenager acne?

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Abstract

Above all, acne is considered an adolescent affection. However, in literature as in daily life, female acne is becoming more and more common. According to the articles that cover this subject, the prevalence is estimated from 40% to 50%. The objective of our work was to make an overview of new data about female acne at the clinical and epidemiological level to be precise if female acne has to be considered as a subtype of acne different from teenager acne. This review shows that the most frequently recognized age when speaking about female acne is 25 years old. Most commonly it is a light to moderate acne that mainly affects the face. Two clinical forms can be identified: an inflammatory form, the most frequent, made up of papulo-pustules and nodules on the lower part of the face and a retentional form made up of blackheads and micro cysts with hyperseborrhoea. Concerning its evolution, it is characterized by three subtypes of which two are predominant: the most frequent form called 'continue acne' from adolescence to adult age and the less frequent form called 'late onset acne' that starts after 25 years of age. On a physiopathological level two main hypotheses can be proposed. Specific global assessment and therapeutic algorithm would be necessary for female acne, which in addition, in future would have to be considered separately from teenagers for the evaluation of a new drug.
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Conflict of interest

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Introduction

Acne is a chronic inflammatory illness of the pilosebaceous follicle.

Adolescent acne is very frequent and on average affects 80% of young people irrespective of their country of origin.[1] It is a dermatological illness that is well known in dermatology. However, over the last few years, more and more articles are discussing about adult acne and more specifically female acne. At the practical level, the dermatologists in their offices have an increasing number of female patients consulting for acne lesions. Thus, today one of the questions raised by female acne, is to determine if it has to be considered as a subtype of acne different from teenager acne based on specific clinical aspect, different evolution and finally different physiopathological mechanisms. This question is important as it opens firstly the discussion of treating differently female acne from teenager acne and secondly it could mean that there are 'several subtypes of acne' which would have to be considered. Today no difference is performed in clinical trial. Hence, to answer this question, we reviewed data of the literature concerning female acne by focusing on clinical and epidemiological aspects.

Methodology

The database used for this work was Pubmed, with articles being limited to those in French or English. All articles concerning clinical and epidemiological aspects of female acne with the exclusion of treatment were reviewed. In addition, we also discussed the data of the literature about physiopathological aspects.

The keywords for the bibliographical research were: adult acne, female acne, post-adolescent acne.

Fourteen articles from 1997, between, the date of the oldest, up to the present day were selected: Eight were prospective studies, three were retrospective studies, and three were summaries (Table 1).

Results

Age at onset of female acne

One of the first questions concerning female acne is at what age can we speak about 'adult acne'? The literature review shows that the age most frequently used to talk about female acne is 25, without knowing whether this concerns acne that starts at 25 years of

Table 1 Summary of literature studies on female acne

Reference	Study type	Main conclusions
(Capitanio, Sinagra *et al.* 2009)	Retrospective	Strong correlation between tobacco and post-puberty acne
(Capitanio *et al.* 2010)	Prospective	CPAA (comedonal post-adolescent acne) = most frequent clinical form of post-adolescent acne. CPAA intensity appears to be correlated to tobacco
(Collier, Harper *et al.* 2008)	Prospective with questionnaire	Frequency of female acne>20 years of age
(Dumont-Wallon and Dreno 2008)	Open retrospective	Female acne: persistent form of adolescent acne Influence of hormonal, stress, cosmetic and hereditary factors Very good therapeutic response with isotretinoin in the event of failure or relapse with cyclins
(Goulden, Clark *et al.* 1997)	Prospective	Light to moderate female acne with inflammatory lesions mainly affecting the face 2 forms: late onset acne and persistent acne It suggests that the latter group could be more specifically associated to ovarian or adrenal androgenic anomalies
(Goulden, Stables *et al.* 1999)	Prospective	Female acne problems: 54% 80% persistent form since adolescence
(Kane, Niang *et al.* 2007)	Prospective	Acne in black women: In Dakar, most patients consulting a doctor for acne are women with an average age of 25.6
(Knaggs, Wood *et al.* 2004)	Synthesis of literature	
(Poli, Dreno *et al.* 2001)	Prospective with questionnaire	Female acne prevalence >25: 41%
(Rivera and Guerra 2009)	Synthesis of literature	Female acne clinical characteristics >25 years of age, therapeutic options
(Schmitt, Masuda *et al.* 2009)	Prospective with questionnaire	Defines topographical clinical models and chronological models for different age groups of women with acne
(Seirafi, Farnaghi *et al.* 2007)	Prospective	DHEA sulfate plays a role in the pathogenesis of female acne appearing after 25 years of age (adult onset acne)
(Shaw and White 2001)	Retrospective	Persistent form female acne: 80% with influencing factors (stress, hormonal)
(Williams and Layton 2006)	Synthesis of literature	

age or persistent acne at 25 years of age or returning acne at 25 years of age.[2–4]

Thus this criterion was used in three studies for which the average age was 36 in the study by Shaw and White,[5] 31.8 years in that of Dumont-Wallon[4] and 26.5 years in that of Williams.[3]

Concerning the average age at the start of symptoms, it was reported at 16.1 years in a Brazilian study,[6] 16.3 years in an American study[5] and 16.6 years in a third French study, respectively,[4] which suggests a high level of persistent acne from adolescence.

Prevalence of female acne

Concerning the prevalence of female acne, five articles cover this subject. In Poli *et al.*'s article based on a questionnaire filled in by women, prevalence was evaluated at 41%. This study concerned 3305 women aged between 25 and 40 years.[2] Two others studies have identified greater prevalence: 54% in 749 people examined by Goulden *et al.* with 40% being women,[7] 51% of women between 20 and 29 years of age were questioned on a university campus and medical complex.[8]

The methods used were based either on a questionnaire sent to the women, the most frequent method (three articles of five)) or on a clinical examination carried out by a doctor (two articles of five). Thus, Poli *et al.*[2] use a standardized questionnaire sent by e-mail and filled in by patients. Similarly in Brazil, 103 women seen during a dermatological consultation were contacted by telephone and questioned by the authors using a standardized

questionnaire.[6] For Collier *et al.*, a questionnaire was distributed at different sites of a university campus and a medical complex of the University of Alabama.[8] Interestingly, there was no difference between the two methods concerning the evaluation of the frequency of female acne.

Adult female acne is also present in black people. A study carried out in Dakar on 93 women seen during dermatological consultations shows that 75% were young women with an average age of ~25.6.[9]

Specificities at clinical level

Most often, female acne is a light to moderate acne[3,10,11] with lesions that tend to be less numerous compared with adolescent acne. The severe forms with a high number of lesions are rare. In the future, this point has to be taken into consideration using a global assessment for evaluating female acne in a trial.

In all the studies, female acne mainly affect the face [3,5,10] and notably the chin and the mandibular region[2,6,10,11] as well as the peri-oral region frequently described.[2,11] However, the torso and shoulders can also be affected[4] although there are only mentioned in two studies. Frequency of this in the Dumont-Wallon[4] study is evaluated at 41% and the Brazilian study identified a statistically significant predilection for lesions in the chest/neck in adult women.[6]

Two clinical forms are described:[2,4,10,11]

1 The inflammatory form, most frequently made up of papulo-pustules and deep inflammatory nodules that lead to scarring. Hyper-seborrhoea is not always present. This clinical form represents 58% of women in the studies of Goulden V[12] and Dumont-Wallon[4] (Fig. 1).
2 The retentional form, which includes numerous blackheads and micro cysts with a small number of inflammatory lesions. Hyper-seborrhoea is always present and lesions are more often spread across the face notably reaching the forehead[2] (Fig. 2).

Interestingly, both forms are described in the literature as non-responding or low responding to local or systematic antibiotic treatment:[10,12] 82% of women studied by Rivera and Guerra did not respond to antibiotic.[11]

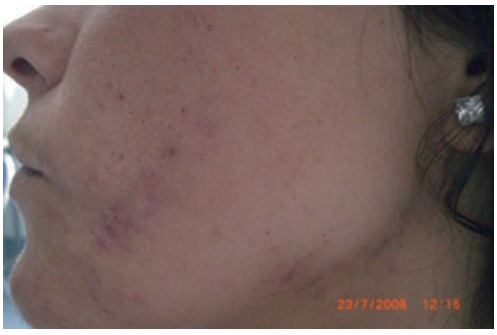

Figure 1 Inflammatory acne with mandibular localization.

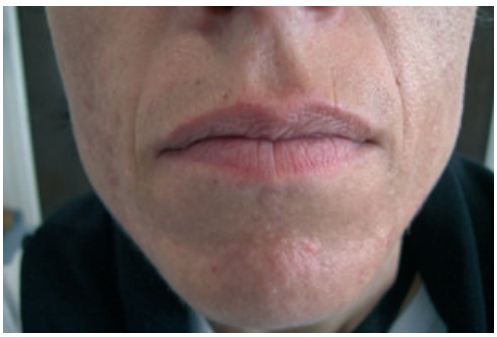

Figure 2 Retentional acne with hyper-seborrhoea.

The notion of a premenstrual increase is found in both forms indicating that the hormonal factor is not the discriminating factor:[5,10] 85% of women report an increase in acne symptoms during the premenstrual period.[11]

Specificities of the evolution

Three subtypes of evolution of female acne are identified when analysing literature.

1 The 'continuous' subtype where acne is a continuum from adolescence to adult age, also called 'persistent acne'. It is the most frequent subtype by far. It is described in 80% of women by Goulden *et al.*,[7] as well as Shaw,[5] or in the Brazilian study.[6]
2 The 'late start' subtype, appearing after 25 years, called 'late onset acne'. Dumont-Wallon described it as representing 20% of women examined[4] and Poli *et al.* found it in 41% of women questioned.[2]
3 The 'relapse' subtype in women having had adolescent acne that disappeared for a few years and then returned as adult acne This form is poorly described in literature and to date there is no accurate data.

We did not find works specifically looking at acne at menopause and notably the role of hormone replacement therapy, nor acne in pregnant women.

The factors triggering or aggravating outbreaks in female acne

The review of the literature did not permit to identify specific factors for explaining aggravating outbreaks in female acne. At the moment the factors remain similar to those implicated in teenager acne.

Internal factors

Two main internal factors triggering or aggravating female acne are suggested in literature.

Hormonal factors. A well known phenomenon is the link between female acne and the use of pro-androgenic progestin.[7] In

the Brazilian study, the use of oral contraception was strongly associated with an increase in the frequency of acne.[6] But they compared the use of oral contraception between adult and adolescent and we well know that sexual activity is much more prevalent in adult women and could be an explanation for the association found. It has also been suggested that its use could play a role in the persistence of female acne but other investigations are required.[7] Progesterone and implanon coils are also a source of outbreaks in female acne. Approximately 80% of women report exacerbation of acne before menstrual cycles.[2,5,11,12] Furthermore, in the study carried out by Goulden V in 2008, 37% of women had at least one sign of hyperandrogenism characterized by hirsutism, an alopecia and disturbances of the menstrual cycle and 12% had more than one clinical sign of hyperandrogenism. The same study suggests that the subgroup of late onset acne patients could be more specifically the subgroup associated to ovarian or adrenal androgenic anomalies.[12] Acne would then be one of the signs of an endocrine disease.

Concerning the frequency of pre-puberty in acne in the adult female acne sufferer, it is evaluated at 13% in the Dumont-Wallon study, which is the only one to have studied this factor.[4]

Genetic predisposition. This is a factor that appears frequently in female adult acne. Thus, three studies speak about family forms, that of Knaggs,[10] that of Goulden V where 50% of patients had a first degree family history,[12] and 53% in the Dumont-Wallon study.[4] To date, the family factor has not been demonstrated linked to a specific clinical subtype or a specific subtype of evolution.

External factors

Cosmetics. This factor remains controversial. Several studies[2–4,9,10] have shown that cosmetics play an aggravating role. However, other studies note that stopping using cosmetics is not associated to regression of post-adolescent acne.[3] In both studies by Goulden,[7,12] the cosmetic factor is not shown as an aggravating factor for acne in adult female patients, (only 16% of women reported the use of cosmetics more than twice a week). On the other hand, for Dumont-Wallon, the use of cosmetics was amongst the four most frequently described factors (62%).[4] This could be explained notably by the wide variety of products grouped together under the term 'cosmetics', certain cosmetics being more involved than others in the development of acne lesions (sun powder, creams not tested as being non-blackhead creating, masks). The quality of cosmetic products is furthermore very variable depending on the brand.

Stress. Stress is often reported as a factor triggering female acne. In the study of Poli *et al.*, it was present in 50% of women.[2] For Goulden V, 71% of patients estimated that their acne got worse during periods of stress but only 12% admitted that their acne was due to stress.[12] For Dumont-Wallon, stress is part of the four most frequently described factors promoting acne (34% of women).[4] The link between stress and acne outbreaks of today is explained by the production of neuromediators such as the substance P in sebaceous glands which are receptors that stimulate the sebaceous gland[3] and thus the production of sebum.

Tobacco. Recent studies[3,11,13,14] have highlighted the role of tobacco in female acne: It was noted that female smokers had more frequent and more severe acne than non-smokers and that there was a dose-dependent correlation. Two recent studies that were published in 2009 and 2010 suggest that tobacco is perhaps a major contributing factor in a non-inflammatory type of post-adolescent female acne.[13,14] They show a strong correlation between cigarettes and the type of non-inflammatory post-adolescent acne through an increase in the production of sebum induced by nicotine and a reduction in the production of vitamin E.

Other factors described. Certain factors such as the sun,[1,10] the consumption of medication (benzodiazepin, lithium, ciclosporin, cortisone treatment, ramipril, isoniazide),[2–4] have been described as possibly playing a role but the level of proof remains low. No article mentions the influence of diet on adult acne.

Physiopathological hypotheses for female acne

Acne is a chronic inflammatory illness of the pilosebaceous follicle that brings three factors into play: hyper-seborrhoea linked to an increase in sebum production by the sebaceous gland,[3] clogging of the pilo sebaceous follicle orifice through an anomaly in the proliferation and differentiation of keratinocytes that make up the epithelium of this canal,[3,15] a proliferation within the follicle of an anaerobic Gram positive bacteria, *Propionibacterium acnes,* that induces and maintains the inflammatory reaction by the stimulation of innate immunity (TLRs, pro-inflammatory cytokines, Beta-defensins, Metalloproteases).[10,15–17]

From the review of the literature, two main physiological factors seem to predominate in the development of female acne: a peripheral hormonal factor and a chronic stimulation of innate immunity.

Female acne: a peripheral hormonal illness[12] The hypothesis is that female acne would be a peripheral hormonal illness related to a hyperactivity or abnormal activity of enzymes implicated in the metabolism of hormones (androgen and progestin), as 5 alpha reductase expressed in the skin both in sebocytes and keratinocytes (Fig. 3). In addition, a hypersensitivity of hormonal receptors which have also been identified in sebocytes and keratinocytes could play a role.[10,12] This hypothesis is based at the clinical level, notably on the flares up described before menstruations, the aggravation of acne following the use of contraception with a pro-androgenic progestin. In addition, abnormalities of hormonal dosages in the blood are rarely identified in idiopathic female acne (excluding secondary acne as polycystic ovary syndrome, ovarian and adrenal tumour associated with virility signs as hirsutism). However, in the blood a decrease of Sex-Binding Globulin protein

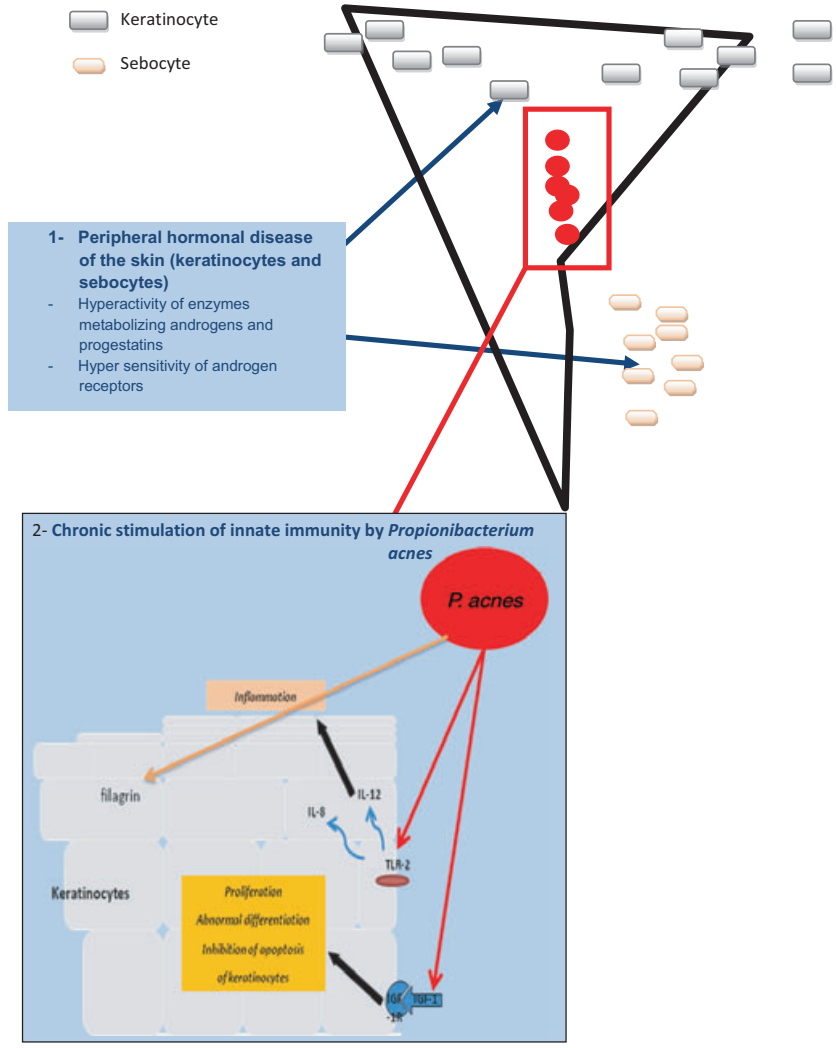

Figure 3 The two main physiopathological mechanisms in female acne: peripheral hormonal factor and innate immunity.

associated with an increase of free testosterone has been reported. The free testosterone could stimulate both hormonal enzymes and receptors in the skin.[15] In addition, androsterone glucuronide which is a metabolite of circulating androgens under the influence of 5 alpha-reductase has been shown to significantly increase in women with moderate acne and significantly reduce under oral contraceptive treatment and was correlated with the number of inflammatory lesions.[18]

Also at the therapeutic level, in favour of this hypotheses is the efficiency in adult female acne of two anti-androgens, firstly the acetate of cyproterone, and secondly the spironolactone, an inhibitor of 5 alpha reductase. Their effects are essentially suspending.[3,15,19] A high level of Dihydroepiandrostenedione-Sulfate especially in patients presenting with hirsutism could be an argument for using hormonal therapy.[15]

Female acne: an illness of innate immunity resulting in resistant Propionibacterium acnes *strains*[12] *Propionibacterium acnes* is a bacterium that secretes numerous pro-inflammatory substances activating different cells implicated in innate immunity as polynuclears, monocytes and Langerhans cells. In addition it has been shown that *Propionibacterium acnes* is able to activate TLRs expressed on the keratinocytes with the production of proinflammatory cytokines as IL-8 and metalloproteases.[17,20] It is also able to induce the expression of beta-defensins by epidermis and very recently, it has been shown that this bacteria can activate the IGF/IGF-R1system on keratinocytes in a similar manner as insulin.[16] *Propionibacterium acnes* thus has a high pro-inflammatory power notably greater than that of *Staphylococcus aureus* or *Streptococcus*. In addition, it has also been shown that it increases *in vitro* the proliferation of keratinocytes and induces the production of fillagrin.[21] Thus, modulating the differentiation of the keratinocytes and participating in the formation of acne lesion as soon as the step-up of the micro comedon.

In female acne, one hypothesis would be that the development of acne lesions would be linked to an abnormal activity of one

or several molecules involved in innate immunity as TLRs or defensins inducing a chronic inflammation of some sebaceous glands. This chronic inflammation would be kept by the development of resistant *Propionibacterium acnes* strains in pilosebaceous follicle. In this context, a recent article demonstrates that the inflammatory profile of *Propionibacterium acnes* strains is variable according the acne patients and even the controls.[22]

The development of a high percentage in female acne of resistant strains with a strong pro-inflammatory activity could chronically stimulate the innate immunity (Fig. 3). The high frequency of family forms (≥50%) is an argument supporting also the potential role of a genetic factor in the abnormalities of innate immunity. This hypothesis still needs to be confirmed by further works.

Finally these two pathophysiological factors could be modulated by both genetic and external factors.

In conclusion, this review of the literature shows that adult female acne differentiates itself from adolescent acne by its specific clinical aspects and evolution. Two pathogenic factors (hormonal and innate immunity) could play a central role. Today this leads us to consider female acne as being different to adolescent acne implicating different clinical scale, different therapeutic algorithm and finally to separate acne teenager and female acne in clinical trials for having an objective evaluation of the efficacy of a drug.

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