

Prophylaxis of *Striae gravidarum* with a topical formulation. A double blind trial

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Synopsis

A prophylactic antistriae cream (*Centella asiatica* extract, α -tocopherol, and collagen-elastin hydrolysates) was assessed by a double blind trial in 80 pregnant women.

In the placebo group 22 women (56%) presented striae, whereas in the treated group only 14 women (34%) developed striae in this pregnancy; this difference was significant ($p < 0.05$; χ^2 test). An arbitrary score was designed to assess the intensity of striae (from 0 to 3); this score was 1.42 (sd 0.5) in the treated group and 2.13 (sd 1.32) in the placebo group and this difference was also significant ($p = 0.014$; Mann-Whitney test).

In women with a history of striae during puberty, the active cream induced a significant absolute prevention in 89% of the cases whereas in the placebo group all the women developed striae ($p = 0.00014$; χ^2 test).

Résumé

Prévention des vergetures par application topique. Un essai pratique à l'insu de patient et du médecin

Nous avons testé une crème préventive contre les vergetures en effectuant un test à l'insu du patient et du médecin sur 100 femmes enceintes (50 ont été traitées par un placebo et 50 par la crème active).

La crème active contenait: de l'extrait de *Centella asiatica*, de l' α -tocophérol et du collagène/élastine hydrolysé.

Les crèmes ont été appliquées quotidiennement, à partir du 3ème mois de grossesse sur la poitrine, le ventre, les fesses et les hanches. L'étude a été réalisée sur une période de 30 mois au bout de laquelle nous avons obtenu 80 cas analysables (39 pour le groupe 'placebo' et 41 pour le groupe 'crème active', les 2 groupes ne présentant pas de différences significatives au niveau des paramètres considérés: âge, prise de poids durant la grossesse, grandeur, nombre d'accouchements, biotype, couleur de la peau et des cheveux, groupe sanguin et antécédents familiaux (mère ayant des vergetures), poids et sexe de l'enfant.

Dans le groupe placebo 22 femmes (56%) présentaient des vergetures tandis que dans le groupe traité, seulement 14 femmes (34%) ont eu des vergetures pendant leur grossesse. Cette différence était significative ($p < 0.05$; test χ^2).

Une note arbitraire a été attribuée pour mesurer l'intensité des vergetures (sur une échelle de 0 à 3). Cette note était de 1.42 (sd 0.5) dans le groupe traité et 2.13 (sd 1.32) dans le groupe placebo et cette différence était également significative ($p = 0.014$; test Mann-Whitney).

Sur les femmes ayant des antécédents de vergetures durant la puberté, la crème active a produit une prévention absolue dans 89% des cas alors que dans le groupe placebo, toutes les femmes avaient des vergetures ($p = 0.00014$; test χ^2).

Introduction

Cutaneous striae are characterized by superficial linear depressions of the skin [1] and may appear at any moment during human life, but according to Sisson [2] their incidence is 35% in adolescents (between 10 and 16 years) with a predominance in girls of about 2.5 fold; more recently Larsson and Lidén [3] have found an incidence of 27% in adolescents (between 12 and 17 years), the predominance in girls being two fold. Striae also appear during pregnancy and other physiological and pathological conditions.

It is well accepted that cutaneous striae are secondary to one or both of two factors: 1. mechanical and 2. biochemical. The mechanical factor involves skin stretching, secondary to the development of subcutaneous structures: adipose and interstitial tissue, as happens in obesity, pregnancy and muscle development in athletes.

The biochemical factor is mainly represented by glucocorticoids which inhibit proliferation and many functions of fibroblasts, this in turn leads to the defective production of specific fibrous proteins. This is a typical situation in the Cushing syndrome, topical corticosteroid therapy and during pregnancy [4].

Spontaneously, striae tend to become less visible in the course of time and their unaesthetic effects are better accepted by the patient [1, 4]. Strictly speaking, striae are not a true disease, but this unaesthetic effect has a strongly negative psychological impact in many persons and they are a permanent source of distress in women. There is no effective treatment to eliminate skin striae once they have appeared, but in contrast it seems possible to prevent their formation when this is predictable, i.e. during pregnancy. In this sense, some OTC formulations make claims for their effectiveness because they contain active substances which can stimulate the fibroblast activity and the synthesis of collagen and elastin fibres are thus increased.

Pregnant women who are influenced by the negative consequences of the appearance of striae, tend to use such products to prevent the problem but a rigorous study to demonstrate their true efficacy does not appear to have been carried out. It is perhaps for this reason that when the gynaecologist or the midwife suggest their use to pregnant women, they act merely in compliance with the patient rather than because they are convinced of their efficacy. Moreover, very frequently pregnant women use them without medical consent. We have reviewed the medical literature on the incidence of *striae gravidarum* in the whole population or in obstetric consultation, their correlations with some biological parameters, etc., in order to have a starting point to evaluate interest in prevention of striae, but we have no knowledge of such a study.

In order to remedy this gap we developed a double-blind study which allowed us to record new data and to evaluate the true efficacy of a preventive anti-striae cream during pregnancy.

Material and methods

In this study we used an anti-striae cream and a placebo cream which contained only the excipient matter of the active cream (both creams were identical in colour, flavour and texture). The active cream (Trofolastin[®]) was a marketed product and contained: *Centella asiatica* extract, α -tocopherol and collagen-elastin hydrolisates. Creams were distributed in sets, large enough for the complete treatment of each individual, and marked with a randomized code number. The assay was carried out in 100 pregnant women attending

obstetric consultation, with their consent and that of the ethics committee of the institution in which the study was carried out. All of them were healthy and we included in the study only those whose pregnancy was in the first 12 weeks. At the beginning of the study an application form was completed for each subject. This form contained all the data for each subject, and at the same time, the woman was instructed about the mode of use for the cream. The product was applied daily from the end of 12th week of pregnancy to the day of labour on abdomen, breasts, buttocks and hips.

Five checks were performed during pregnancy: the first at the moment of inclusion in the study, three during pregnancy and the last in the puerperal period. In each check the obstetrical parameters were registered as well as the possible incidence of striae. If striae appeared, they were registered and drawn on the personal card of each woman. To evaluate the degree of the striae an arbitrary score was designed: 0 = no striae; 1 = few and thin striae; 2 = many thin striae or few thick striae, and 3 = many thick striae. This score was registered independently for each area studied (abdomen, breasts and buttocks-hips). The presence of previous striae developed either during puberty or in previous pregnancies was also registered.

The codes for placebo and active cream were opened at the end of the study, when all cases were terminated. The whole study was carried out over a period of 30 months and some cases were eliminated (one abortion and several changes of residence). The total valid cases were: 41 treated with active cream and 39 treated with placebo.

The statistical study was divided in three parts: 1. Description of the characteristics of the whole population. This allowed us to measure the homogeneity of the samples and the normality of the distribution. 2. Analysis of the statistical significance of the possible protective effect observed. In this case, the evaluation was done in the whole sample and in representative groups of the sample. 3. Study of the correlation between striae and some parameters of the sample (anthropomorphic features, weight gain, weight of newborn, etc.).

The statistical analysis was performed with the aid of an SPSS program. The different tests used will be detailed together with the results presented in the next paragraph. When the χ^2 test was used, the Yate's correction was applied if expected frequencies were between 3 and 5.

Results

DESCRIPTIVE STATISTICS

Both groups of subjects (treated and placebo) present a normal distribution for the following parameters (Kolmogorov-Smirnov test for normality at 95% confidence level): age, weight increase during pregnancy, height and weight of the newborn.

Parity did not follow the normal distribution because for most women this was their first child. Using parametric tests for those parameters which follow the normal distribution and the Mann-Whitney 'U' test for parity there were no statistically significant differences between the two groups of subjects. Table I describes such values for each group and for the whole population.

The remaining parameters (results not shown) were compared by the χ^2 test and no differences were observed between the two groups: biotype, skin colour, hair colour, child's sex and blood group. We also compared the existence of previous striae (during

Table I. Quantitative parameters in the population studied. Mean values \pm sd. For placebo vs treated, $p > 0.05$.

Parameter	Placebo	Treated	Whole sample
Mother's age (years)	24.62 \pm 4.63	26.44 \pm 5.03	25.55 \pm 4.89
Parity ^a	1.39 \pm 0.68	1.54 \pm 0.81	1.47 \pm 0.75
Weight gain (%)	18.36 \pm 5.57	18.59 \pm 6.12	18.47 \pm 5.82
Mother's height (m)	1.61 \pm 0.06	1.59 \pm 0.05	1.60 \pm 0.056
Son's weight (kg)	3.24 \pm 0.49	3.28 \pm 0.44	3.26 \pm 0.47

^a Including present pregnancy

puberty and previous pregnancies) in both groups by the χ^2 test and no differences were observed (results not shown).

PROTECTIVE EFFECT OF THE ANTI-STRIAE CREAM

In the placebo group 22 (56%) women developed striae in the present pregnancy whereas the treated group presented striae in only 14 women (34%). This difference was significant by the χ^2 test with $p < 0.05$ (Table II). When we compare the development of striae in the present pregnancy in both groups in relation to the previous existence of striae (puberty or previous pregnancies), the χ^2 test gives the following conclusions (Table II): In women without previous striae the development of striae in the present pregnancy is similar in

Table II. Striae in the present pregnancy. Whole sample and subgroups accordingly with the existence of previous striae.

Sample	Placebo	Treated	
Whole sample			
Striae yes	22	14	
Striae no	17	27	$p = 0.045$
Without previous striae			
Striae in act. preg. yes	12	11	
Striae in act. preg. no	11	12	$p > 0.05$
With previous striae (all)			
Striae in act. preg. yes	10	3	
Striae in act. preg. no	6	15	$p = 0.006$
With striae during puberty			
Striae in act. preg. yes	9	1	
Striae in act. preg. no	0	8	$p = 0.00014$
With striae in previous pregnancies			
Striae in act. preg. yes	0	2	
Striae in act. preg. no	7	7	$p > 0.05$

both groups and no statistical differences were observed. Women having previous striae developed during puberty were strongly protected by the active cream in contrast with women who used the placebo cream; this difference was highly significant ($p = 0.00014$). Finally, there was no statistical difference between the two groups in women having previous striae coming from preceding pregnancies. The degree of intensity of striae appearing in the present pregnancy was significantly lower ($p = 0.014$) in women treated with the active cream with a mean value of 1.42 (SD 0.5) than in women treated with the placebo cream with a mean value of 2.13 (SD 1.32) using the Mann-Whitney test.

CORRELATIONS BETWEEN STRIAE AND OTHER PARAMETERS

All the women who had developed striae during puberty also presented striae during pregnancy in the placebo group (Table II). This co-incidence was not possible to establish in the treated group because of the protective effect of the cream in this subgroup.

Finally there were no positive correlations between striae and the following parameters (χ^2 test): biotype (athletic, pyknic, asthenic), skin colour, hair colour and child's sex, blood group, mother's height, child's weight and mother's weight gain (results not shown).

Discussion

The descriptive analysis of the population studied demonstrates that both groups of women (placebo and treated) are similar and no differences can be established between them. For this reason, we can conclude that any difference observed should be due to the effect of the active cream and not due to possible differences between the groups. The incidence of striae in the placebo group was 56%; we cannot evaluate this incidence because there are no statistical studies available in the literature concerning this aspect. In any case, the 'absolute' protective effect of the anti-striae cream is clear, with an incidence of striae of only 34% in the treated group. On the other hand, the protective effect has been observed not only preventing the appearance of striae but also in the degree of striae formed. So, the mean score of striae in the treated group was 1.42, significantly lower than that observed in the placebo group, with a mean value of 2.13. This would indicate that in such cases in which striae were not absolutely prevented, their intensity was lower under the protective effect of the cream. The existence of striae during puberty determines the development of striae during pregnancy. In the placebo group this was confirmed in 100% of the cases. What might have happened in previous pregnancies is impossible to say because all of these women were in their first pregnancy. If we pool together those women having had striae during puberty and/or previous pregnancies, the protective effect of the active cream is evident (Table II). If we differentiate these two groups, we observe that the cream prevents striae formation only in the women with striae during puberty but not in those women having striae from previous pregnancies (Table II). Finally, the absolute incidence of striae is similar in those women which have not had striae previously either in puberty or in previous pregnancies.

To understand this protective effect we must consider the two factors previously mentioned: endocrinological and mechanical factors. It clearly appears that women with a suspected previous history of hypercorticism (striae during puberty) are protected in almost 100% of the cases by the active cream. On the other hand, in those women without this antecedent (we don't know if there was hypercorticism during the present pregnancy) the appearance of striae is not prevented, but their intensity was diminished. If we accept

that hypercorticism strongly determines the formation of skin striae we can conclude that the cream selectively neutralizes the negative effect of corticosteroids and, with less efficacy, the mechanical factor. From these results it is worth considering some aspects of the active principles contained in the cream.

The main component is the *Centella asiatica* extract which contains asiaticoside as the major active principle. This is a triterpenic compound which has long been known for its properties: stimulation of mitosis, wound healing action and facilitation of scar formation and is successfully employed in dermatology to accelerate the reparative processes in several kinds of wounds. Its mechanism of action would be the stimulation of fibroblastic activity and/or enhancement of fibre production [5-10], but an antagonistic effect upon glucocorticoids has also been reported [7, 10] probably because asiaticoside has chemical similarity with steroids [11]. Finally in a recent work, Tenni *et al.* [12] reported a stimulatory effect of asiaticoside on collagen and fibronectin production in cultures of fibroblasts when concentrations of $25 \mu\text{g ml}^{-1}$ were used. Our results demonstrate that the asiaticoside-containing cream exhibits maximal efficacy in those women with antecedents of puberal striae. These striae are due to the presence of an excess of glucocorticoids and other steroidal hormones during puberty. If we also consider the fact that all the women of the placebo group having had striae during puberty also presented striae during the present pregnancy, it is possible to speculate that asiaticoside may possess some well defined mechanism of action closely related with the corticoid receptor in target cells or with the cellular mechanisms of these hormones.

On the other hand, the lower (but significant) protective effect observed in the rest of the treated women should be attributed to the stimulatory effects of asiaticoside on the fibroblasts, increasing the synthesis of collagen, fibronectin and cell replication.

Concerning the rest of the components which are present in the formula, protein hydrolysate may contain the number of amino acids necessary to facilitate the increased protein synthesis under the effects of asiaticoside, whereas α -tocopherol has a protective action from the cytotoxic effects of oxygen free radicals [13] which are formed during enhanced metabolism. Such active forms of oxygen are produced during oxidative processes, including those which may affect the steroidal hormones [14].

From our results we cannot conclude that all the components of the active cream penetrate the intact skin or to what extent, and this is especially doubtful for protein hydrolysate. In this sense, we do not know whether the positive results observed are due only to the presence of asiaticoside in the formula or also to the rest of the components.

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