Investigative report

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Low iron stores: a risk factor for excessive hair loss in non-menopausal women

Iron deficiency has been suspected to represent one of the possible causes of excessive hair loss in women. The aim of our study was to assess this relationship in a very large population of 5110 women aged between 35 and 60 years. Hair loss was evaluated using a standardized questionnaire sent to all volunteers. The iron status was assessed by a serum ferritin assay carried out in each volunteer. Multivariate analysis allowed us to identify three categories: "*absence of hair loss*" (43%), "*moderate hair loss*" (48%) and "*excessive hair loss*" (9%). Among the women affected by excessive hair loss, a larger proportion of women (59%) had low iron stores (< 40 µg/L) compared to the remainder of the population (48%). Analysis of variance and logistic regression show that a low iron store represents a risk factor for hair loss in non-menopausal women.

Key words: hair loss, non-menopausal women, serum ferritin

Hair loss in women is a common trait and the prevalence is age dependent [1]. When a woman consults a dermatologist about hair loss, her condition may or may not lead to alopecia, defined as a decrease in hair density. Patterned androgenic alopecia occurs in 37% of post-menopausal women [2] but only in 10-13% of non-menopausal women [2, 3]. Another hair trouble in non-menopausal women is increased hair loss or hair shedding, also known as chronic telogen effluvium (CTE) [3], affecting around 30% of women in the USA, UK and Japan [4]. Both diffuse androgen-dependent alopecia and chronic telogen effluvium are a major concern in dermatology [5]. However, it is important to remember that in clinical practice, women's complaint of hair loss is still unclear or controversial [6, 7]; other causes must be taken into consideration.

Iron deficiency has been suspected to represent one of the possible causes of excessive hair loss in women. Iron deficiency has been reported to be associated with chronic diffuse hair loss [5, 6, 8, 9]. A total iron depletion was observed when the serum ferritin was below 15 µg/L, and low iron stores with serum ferritin was between 15 and 30 µg/L [10]; Rushton [11] reported that the critical threshold of serum ferritin was 40 µg/L, a level under which increased telogen hair shedding was observed. So far, a direct relationship between ferritin levels and hair loss has not been confirmed by other studies [12, 13] and is still a matter of debate [14-16]. Some evidence was provided in a recent report [17] that decreased serum ferritin is associated with hair loss or alopecia in women; however, several parameters in this study, such as sample sizes, the ferritin thresholds and the clinical features [16, 17] need further explanation.

To further investigate the relationship between iron store and hair loss, we decided to explore this relationship by assessing hair loss and measuring serum ferritin concentration, which is closely related to iron stores [10], in a very large sample of subjects by taking the advantage of the SU.VI.MAX epidemiological study, which provided us with the opportunity to study, for the first time, a large cohort of 5110 women. The aim of the study was to evaluate a possible link between iron stores based on the assessed ferritin level, and hair loss in women.

Materials and methods

Volunteers

5110 women aged between 35 and 60 years were involved in the study. This cohort of volunteers was part of the SU.VI.MAX trial, a large French epidemiological study [18, 19] approved by the ethical Committee of Paris-Cochin. SU.VI.MAX, which stood for "SUpplementation en VItamines et Minéraux AntioXydants", was a randomized double blind, placebo-controlled, primary-prevention trial designed to test the efficiency of daily supplementation with anti-oxidant, vitamins and minerals at nutritional doses, in reducing the incidence of cancers and ischemic vascular diseases in a middle-age general population. Detailed description of the SU.VI.MAX study-design, randomization and participant characteristics have been previously reported [18, 19].

Hair loss assessment

Hair loss was assessed with the help of a set of descriptive questions extracted from a self-assessment questionnaire which had been sent to all volunteers at inclusion in the study *(table 1)*. The quantification of hair loss was estimated by quantification of the hairs lost during washing, brushing, after drying with a towel, on the pillow after a night's sleep and on clothes. Hairs that shed were quantified as none or a little, a few and a lot of hairs. Questions concerning the degree of self-perceived hair loss were also

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Table 1. Hair loss questionnaire

• Do you feel involved by hair loss?	☐ Yes	☐ No	
• If you feel involved by hair loss, do you estimate that your hair loss corresponds to a transient hair loss?	☐ Yes	☐ No	
do you estimate that your hair loss corresponds to a persistent hair loss?	☐ Yes	☐ No	
• Currently, during hair washing, how much do you estimate your hair loss?	☐ Many hairs	☐ Few hairs	☐ Very few or None
• Currently, drying your hair with a bath towel, how much do you estimate your hair loss?	☐ Many hairs	☐ Few hairs	☐ Very few or None
• Currently, during hair brushing, how much do you estimate your hair loss?	☐ Many hairs	☐ Few hairs	☐ Very few or None
• Currently, after a night sleep, how much do you estimate your hair loss on the pillow?	☐ Many hairs	☐ Few hairs	☐ Very few or None
• Currently, during a day how much do you estimate your hair loss on your clothes?	☐ Many hairs	☐ Few hairs	☐ Very few or None

provided to establish if the volunteers consider themselves to be concerned by hair loss (non existent, normal, abnormal) and were included in the data analysis. Multiple correspondence analysis and hierarchical cluster analysis (HCA) [20] were used to group the answers with similar expression patterns. This allowed us to identify three distinct groups of volunteers characterized by "*absence of hair loss*", "*moderate hair loss*" and "*excessive hair loss*" *(table 2)*.

Biochemical measurements

The iron status was assessed by measuring the serum ferritin level and haemoglobin levels in each volunteer. At entry in the study, a 35 mL venous blood sample was collected. After collection (Becton Dickinson tubes), haemoglobin was measured immediately (cyanmethemoglobin method) and kept at + 4 °C in the dark until centrifugation and preparation of the aliquots. Serum ferritin levels were measured using a nephelometric assay (BNII Berhing) [21].

Statistical analysis

Descriptive and inferential analyses were performed using SPSS 11.0, SPAD 5.1 and SAS 8.2 statistical softwares. The detection limit of the serum ferritin assay caused some departure from normality even for log-transformed data. Therefore analyses based on ranks have been preferred. Analysis of variance (ANOVA) of serum ferritin level based on ranks has been carried out independently in postmenopausal and non-menopausal women, taking into account the age factors, "hemoglobin" and "hair loss classes" *(table 2)*. For non-menopausal women, the use of intrauterine devices or contraceptives was also taken into consideration. Comparisons of mean ranked serum ferritin levels relative to the hair loss classes were carried out using the Tukey-Kramer procedure for pairwise comparisons [22]. The relationship between the hair loss classes and serum ferritin levels were fitted using generalized logits [23] controlled for age, haemoglobin, and contraceptives or intra-uterine devices. The "*excessive hair loss*" class was chosen as the reference class; the significance level was set up at 0.05.

Results

Hair loss quantification

Based on the questionnaire, hierarchical cluster analysis (HCA) using Ward's criteria clearly identified three well-defined classes of women [20]. The planar projection of individuals *(figure 1)* displays the three clusters on the first factorial plan. The clusters are stretched along the first component, corresponding to an intensity hair loss axis. The U-shape representation of the clusters is characteristic of a Guttman effect [20] which opposes the classes "*absence of hair loss*" and "*excessive hair loss*" classes to "*moderate hair loss*" class on the second factorial axis. The three classes were characterized using modalities overexpressed in respect to the whole population *(table 2)*. The ellipsoids displays the classes "*absence of hair loss*", "*moderate hair loss*", and "*excessive hair loss*" which correspond to 43%, 48%, and 9% of the 5110 women, respectively. Each point on this figure corresponds to a particular profile and is sized proportionally to the frequency of the profile in the studied population.

Table 2. Hair loss classification according to descriptive questions on hair loss signs and hierarchical cluster analysis

Cluster 1"Absence of Hair Loss"	Cluster 2 "Moderate Hair Loss"	Cluster 3 "Excessive Hair Loss
"not concerned by hair loss"	*"hair loss self-perceived as normal hair loss"*	*"hair loss self-perceived as abnormal hair loss"*
"no hair loss or a little during the washing"	*"lose a few hairs during the washing"*	*"lose a lot of hairs during the washing"*
"no hair loss or a little during hair brushing"	*"lose a few hairs during hair brushing"*	*"lose a lot of hairs during hair brushing"*
"no hair loss or a little on the bath towel"	*"lose a few hairs on the bath towel"*	*"lose a lot of hairs on the bath towel"*
"no hair loss or a little on the pillow"		*"lose a few or a lot of hairs: on the pillow"*
"no hair loss or a little on the clothes"		*"lose a few or a lot of hairs on the clothes"*

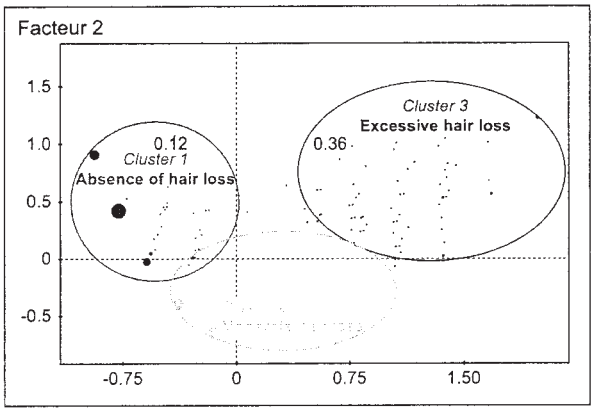

Figure 1. Diagram representing the 3 classes of Non-Menopausal Women according to their hair loss data: *absence of hair loss*: 43%, *moderate hair loss*: 48%, *excessive hair loss*: 9%. This representation is obtained by Principal Component Analysis; it corresponds to the projection of the individuals in the mathematical space done by the variables. The classes ("clusters") are represented here on the factorial plan defined by the first two principal components *(The abscissa axis represents "the first Principal Component" and the ordinate axis represents the "second Principal Component").*

Link between hair loss and serum ferritin levels

In non-menopausal women, 41.5%, 48.6% and 10% displayed *absence*, *moderate* and *excessive hair loss*, respectively *(table 3A)*. Among them, 23% (881/3759) presented iron depleted stores (serum ferritin levels < 15 µg/L). In addition, 57% [(881+1269)/3759] of non-menopausal women presented low iron stores (serum ferritin < 40 µg/L) *(table 3A, figure 2)*.

In post-menopausal women, the iron loss caused by bleeding during menstruation does not occur anymore. Among them, 47.4%, 46% and 6.6% display *absence*, *moderate* and *excessive hair loss* respectively *(table 3B)*. At that time, only 5% (67/1351) had depleted iron stores (serum ferritin < 15 µg/L) *(table 3B)*. Similarly, the low iron stores (serum ferritin < 40 µg/L) affected only 23% [(67+243)/1351] of post-menopausal women *versus* 57% of non-menopausal women.

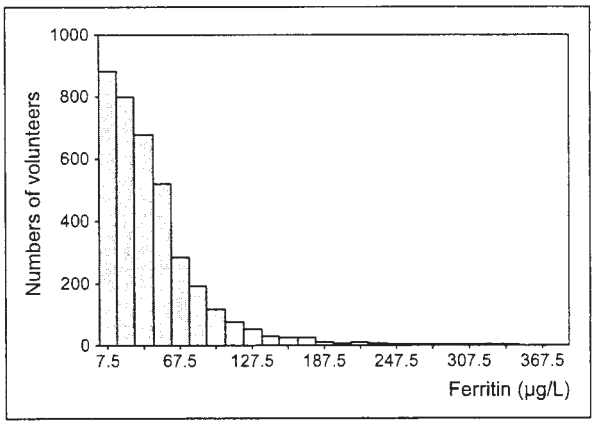

Figure 2. Distribution frequency of Non-Menopausal Women as a function of serum ferritin levels (µg/L) (n = 3759). Note that women with serum ferritin levels ≤ 15 µg/L and ≤ 40 µg/L represent 23% and 57% respectively, of total non-menopausal population.

The detection limit of the serum ferritin assay caused some deviation from normality, even for log-transformed data. Since the parametric analyses could thus be biased, we decided to perform analyse based on ranks, The ANOVA based on ranks showed a significant effect of the mean serum ferritin level on hair loss (p = 0.01) only in non-menopausal women. The Tukey-Kramer test for pairwise comparisons showed significant differences between *excessive hair loss* and both *absence* (p = 0.01) and *moderate* (p = 0.02) *hair loss (figure 3)*.

In non-menopausal women, with serum ferritin levels below 40 µg/L or below 15 µg/L, *excessive hair loss* was significantly more frequent (11.4% [(90+156)/(881+1269)] and 10.2%, respectively), compared to women with optimal levels of ferritin, above 70 µg/L (6.8%) *(table 3A)*. Anemia (defined as hemoglobin < 120 g/L) concerned 10% [(173+43)/(881+1269)] and 19.6% of women presenting a serum ferritin level lower than 40 µg/L or 15 µg/L, respectively. With a serum ferritin level above 40 µg/L, only 1.8% [(23+7)/(937+672)] of the women showed anemia *(table 4)*. Thus, a relationship between hair loss and anemia was noticed only when the body's iron stores was below 40 µg/L.

Adjusted for age, haemoglobin, and the use of contraceptives or intra-uterine devices [21], generalized logits based on ranks for the *absence* versus *excessive hair loss* and *moderate* versus *excessive hair loss* were performed. A generalized logits model was preferred over a conventional polytomic logistic regression, since the assumption of proportional odds was rejected (score test for the proportional assumption, p = 0.009). The results showed that low serum ferritin levels appeared to be highly significantly linked to the presence of *excessive hair loss* in non-menopausal women (p = 0.005 for *excessive hair loss* versus *absence of*

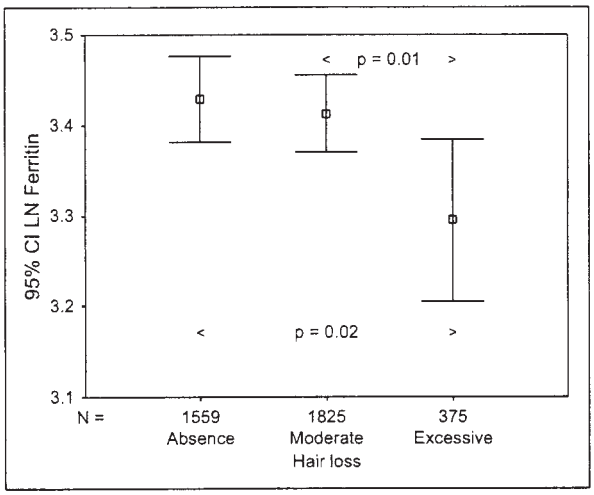

Figure 3. Variation in serum ferritin levels (µg/L) as a function of severity of hair loss in women before menopause (non-menopausal women). Note that Tukey-Kramer test for pair wise comparisons showed significant differences between *excessive hair loss* versus *absence* or *moderate hair loss* classes (p = 0.02, p = 0.01 respectively). CILN: Confidence Interval of Log $_N$.

Table 3A. Impact of iron store levels on hair loss status in non-menopausal women (n = 3759)

Ferritin (µg L^{-1})		Hair loss			Total
		Absence of hair loss	Moderate hair loss	Excessive hair loss	
< 15	Count	365	426	90	881
	% within ferritin	41.4%	48.4%	10.2%	100.0%
[15-40]	Count	512	601	156	1269
	% within ferritin	40.3%	47.4%	12.3%	100.0%
[40-70]	Count	385	469	83	937
	% within ferritin	41.1%	50.1%	8.9%	100.0%
≥ 70	Count	297	329	46	672
	% within ferritin	44.2%	49.0%	6.8%	100.0%
Total	Count	1559	1825	375	3759
	% within ferritin	41.5%	48.6%	10.0%	100.0%

Table 3B. Impact of iron store levels on hair loss status in post-menopausal women (n = 1351)

Ferritin (µg L^{-1})		Hair loss			Total
		Absence of hair loss	Moderate hair loss	Excessive hair loss	
< 15	Count	30	30	7	67
	% within ferritin	44.8%	44.8%	10.4%	100.0%
[15-40]	Count	106	117	20	243
	% within ferritin	43.6%	48.1%	8.2%	100.0%
[40-70]	Count	175	142	21	338
	% within ferritin	51.8%	42.0%	6.2%	100.0%
≥ 70	Count	330	332	41	703
	% within ferritin	46.9%	47.2%	5.8%	100.0%
Total	Count	641	621	89	1351
	% within ferritin	47.4%	46.0%	6.6%	100.0%

hair loss; p = 0.005 for *excessive hair loss* versus *moderate hair loss*). Model adequacy was supported by Hosmer and Lemeshow Goodness-of-Fit test [23]. In addition, the model based on the log transformed ferritin data *(figure 4)* shows similar results.

Table 4. Impact of iron store levels on hemoglobin level in non-menopausal women (n = 3759)

Ferritin (µg /L)		Hemoglobin		Total
		< 120 g/L	≥120 g/L	
< 15	number	173	708	881
	%	19.6%	80.4%	100.0%
[15-40]	number	43	1226	1269
	%	3.4%	96.6%	100.0%
[40-70]	number	23	914	937
	%	2.5%	97.5%	100.0%
≥ 70	number	7	665	672
	%	1.0%	99.0%	100.0%
Total	number	246	3513	3759
	%	6.5%	93.5%	100.0%

Discussion

This study, carried out for the first time on a very large cohort of women, provides strong arguments in favor of an association between depleted iron stores and hair loss, particularly excessive hair loss in women before menopause. It is likely that women classified in the present study under "*excessive hair loss*" were mainly women with androgenetic alopecia [17], however considering their large number, women with CTE [3] might also be included. Since serum ferritin measurement has been reported to be the most sensitive assay for estimating the iron status in an adult population [24], we used this assay to verify a possible link between iron status and hair loss.

Our results fully agreed with previous reports [5, 6, 8, 9] and provide further evidence that the iron status has to be taken into consideration when studying hair loss in women [5] and contrasts with some previous studies where no link between iron deficiency and hair loss was detected. This discrepancy could be explained by differences in the design of the studies. None of the previous studies was performed on an important sample of the general population nor did they take into consideration parameters such as age and haemoglobin concentration in post-menopausal women,

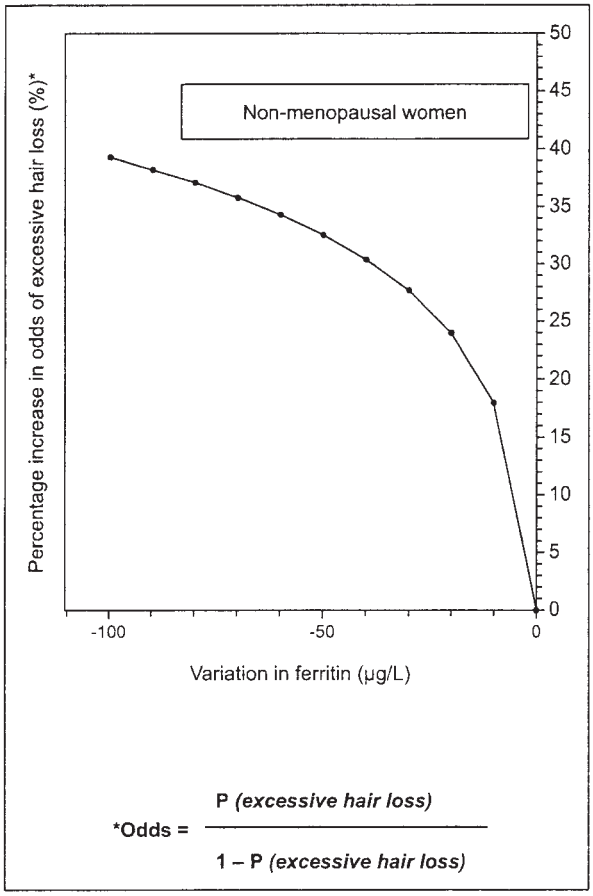

Figure 4. Logistic regression model describing the percentage variation in odds of *excessive hair loss* [(Probability of *excessive hair loss*) / 1-(Probability of *excessive hair loss*)] as a function of the variation of serum ferritin level. Note that it is adjusted for age, hemoglobin, and use of contraceptives or intra-uterine devices.

and also neglecting the adjustment of the results with the use of contraceptives or intra-uterine devices in non-menopausal women. It is known that menstruating women using intra-uterine devices have significantly lower serum ferritin levels than those without contraception, or using oral contraception [21]. A potential weakness of our study, based on the way the data on hair loss were collected, was compensated by the successful logistic regression model, establishing a link between serum ferritin level and *excessive hair loss* in non-menopausal women.

According to these results, a decrease in ferritin levels might be considered as a potential risk factor for *excessive hair loss*. For example, a decrease in 30 units of serum ferritin level in non-menopausal women presenting an initial serum ferritin concentration of 70 µg/L (reference mean value of serum ferritin) would lead to a 28% increase in the odds of *excessive hair loss*.

Our results support the "threshold hypothesis" [17], which states that decreased iron stores lower the threshold for developing different types of alopecia. Nevertheless, additional studies are required to better understand the biological significance of the critical iron status level of 40 µg/L in the etiology of hair loss.

In hair follicles, iron is implicated as a metabolic factor. Iron is also a main constituent for hemoglobin, and iron depletion leads to anemia. The present study indicates that anemia appears for a ferritin threshold much lower than for hair loss. Consequently in clinical practice, an *excessive hair loss* supports the need to check serum ferritin levels. The optimum serum ferritin levels to reach for effectiveness on hair loss are higher than those usually recommended for treatment of anemia. ■

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