Universal screening of thyroid dysfunction in the pregnant population☆

Cribado universal de la disfunción tiroidea en la población gestante

Sir,

Universal screening for thyroid dysfunction in pregnant women is an extremely complex subject which has stirred up broad debate and opposing positions regarding the convenience or inconvenience of performing universal versus selective screening. The recently published consensus document advocates universal screening because adequate evidence to justify it is considered to be available.[1] Some of our arguments are debated in the letter of G. Giménez-Pérez published in this issue. As regards the prevalence of hypothyroidism, the values given under the Stagnaro et al. reference (0.3–0.5%)[2] are based on studies by Casey et al.[3] and Allan et al.[4] In both these studies, prevalence was estimated based on previously calculated or established reference values (RVs) for TSH. In the Casey study, clinical hypothyroidism was defined as a TSH level above the 97.5th percentile and a free thyroxine value below the 2nd percentile. These criteria were met by 0.2% of the total sample. In the Allan et al. study, pregnant women with TSH levels higher than 10 mU/mL (0.4% of all study patients) were considered to have clinical hypothyroidism. Thus, the prevalence estimated in both studies corresponded to women who were hypothyroid at the time of the control. The document discusses the possibility that prevalence may be higher and, actually, Blatt et al.[5] (the first edition, in an electronic version, was published in 2011) found a 2.4% prevalence of clinical hypothyroidism using a TSH cut-off point of 2.5 μIU/mL, based on specific RVs for each trimester of pregnancy. Very few studies are available in Spain on the prevalence of thyroid dysfunction in pregnant women. This is why mention is made of the results of the study conducted in Asturias of more than 2,000 women.[6] While it is true that the study has not been published and the reference is to the abstract of a conference, its relevance lies in the fact that, in addition to recruiting a large population, the prevalence of hypothyroidism was calculated based on their own RFs and was found to be 1.96%. G. Giménez-Pérez states that the most adequate estimate of the prevalence of clinical hypothyroidism in this population is 0.23%, as reported by Lazarus.[7] In accordance to the American Thyroid Association (ATA) recommendations for thyroid dysfunction screening in pregnancy and using this latter prevalence figure, in 2010 there may have been in Spain approximately 290 women with clinical hypothyroidism younger than 30 years who did not meet other criteria for screening.

Regarding the screening test. The document discusses in depth the limitations of immunoassays for measuring free thyroxine (FT_4) during pregnancy, caused by changes in transporter proteins. The sentence ''there could be no absolute FT_4 value that may define hypothyroxinemia with these techniques'' is taken literally from the opinion of Soldin et al.[8] However, it is also stated that some authors have found that some immunoassay techniques may provide a good approximation to the standard provided by tandem mass spectrometry,[9] which has in turn be shown to have a good correlation to the gold standard in the different trimesters of pregnancy. Our document also widely discusses the significance of detecting isolated hypothyroxinemia, because of its relationship to moderate neurodevelopmental delay according to various studies.[10] When hypothyroxinemia is not isolated, but associated with elevated TSH, we think that treatment should be considered. It is undoubtedly very important that each center has its own RVs, but if these are not available, the ATA recommends a cut-off point of 2.5 μU/mL in the first trimester. It is true that this figure may overestimate the prevalence of hypothyroidism in certain populations, as stated by Allan et al. Our document mentions this possibility, and explicitly states in the recommendations that ''the availability of RVs for these hormones for each population, measured using the laboratories own procedures, is indispensable''. It should be noted, however, that different studies, such as the one conducted by Negro et al. in Italy, showed a greater obstetric morbidity in women with TSH levels above 2.5 μU/mL,[11] and that the situation worsened in the presence of positive anti-peroxidase antibodies (TPO Ab). On the other hand, the use of RVs for the general population may underestimate the number of cases with hypothyroidism. Laboratories should make an effort to establish their own RVs.

About effective treatment. It is true that further controlled studies are required to confirm the level of evidence concerning the effectiveness of the treatment of clinical hypothyroidism in pregnant women. However, we think that total agreement exists on the need to treat clinical hypothyroidism in any patient and even more in pregnant women. In any case, the question is how to define hypothyroidism in pregnant women, and with which hormone values. A level of maximum evidence is not needed to treat a pregnant woman with high TSH levels and low thyroxine levels. The risks of clinical hypothyroidism during pregnancy are well known. The evidence concerning treatment benefits is sufficient for treating women in this situation, as recommended by the extensive review by Vissenberg[12] and by the ATA.[2] On the other hand, the risk of thyroxine treatment is virtually nil. Placental type 3 deiodinase neutralizes a hypothetical excess while, conversely, the fetus is put at risk if it does not receive sufficient thyroxine, especially in the first trimester of pregnancy. The Männistö et al. study[13] is one of the few reporting greater obstetric morbidity in cases of clinical hypothyroidism, but the study also predicted an odds ratio of 3.2 for fetal mortality in women with positive TPO Ab.

In studies by Negro et al. and Lazarus et al.,[7,14] blood samples of the respective control groups were frozen and tested after delivery. Thus, all women diagnosed with hypothyroidism in screening groups from both studies and those diagnosed among women considered to be at risk, in the Negro study, were treated with thyroxine. In the Lazarus study, no benefit was seen in the cognitive function

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of children born to treated hypothyroid mothers, probably because treatment was started in the second trimester of pregnancy. This would support the importance of early diagnosis and treatment, preferably even before conception. The Lazarus study did not assess potential changes in obstetric morbidity. The Negro study, conducted in women at low risk of thyroid dysfunction, found a very significant decrease in obstetric complications in treated as compared to untreated women (women in whom diagnosis was known after delivery). As regards subclinical hypothyroidism, no guidelines directly recommend treatment. The systematic review by Vissenberg concluded that inadequate evidence is available to recommend whether to treat or not.[12] When faced with this dilemma, only the clinical criterion remains, but it is very clear if, in addition to subclinical hypothyroidism, associated positive thyroid autoimmunity exists, or if an obstetric history that may be related to thyroid dysfunction, such as delayed fetal growth, pre-eclampsia, or recurrent abortion is found. The criteria for the clinical diagnosis of hypothyroidism are very clear, and the purpose of the recommendation to screen is the early detection and treatment of the pregnant population affected by this disease. On the other hand, it is also indispensable to assess the results of any screening. The evidence for a favorable benefit/risk ratio that some studies may provide should be confirmed in practice. Screening programs should therefore be assessed.[15] In this regard, protocols are being designed to assess the results of screening in some of the areas where it is implemented, in order to provide additional evidence to our current understanding of the subject. Clinical hypothyroidism is easy to diagnose, even in pregnant women, may affect a significant number of pregnant women, is easily treated, and its treatment poses little risk and, when adequate, may provide benefits. Our document also supports the need for implementing training programs for non-endocrinologists (family physicians, gynecologists, and midwives). In this regard, quite a number of hospitals teaching basic courses on thyroid disease for general practitioners include sessions on the importance of the thyroid gland in pregnancy. On the other hand, it should not be forgotten that active screening for gestational diabetes, more complex from the organizational viewpoint and involving a greater therapeutic difficulty, started more than 30 years ago, and nobody questions today that this type of program, coordinated with other professionals and targeting the pregnant population, may achieve reliable results in clinical practice. The culture for this type of action already exists in medical practice. In the setting of thyroid function screening in pregnant women, this represents an intense work plan which our group (iodine deficiency disorders and thyroid dysfunction) is already implementing. We therefore think that the screening of pregnant women to detect clinical hypothyroidism is justified and feasible.

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Lluís Vila[a,*], Inés Velasco[b], Stella González[c], Francisco Morales[d], Emilia Sánchez[e], José Maria Lailla[f], Txanton Martinez-Astorquiza[g], Manel Puig-Domingo[h]

[a] *Servicio de Endocrinología y Nutrición, Hospital de Sant Joan Despí Moisés Broggi, Barcelona, Spain*
[b] *Servicio de Ginecología y Obstetricia, Hospital de Río Tinto, Huelva, Spain*
[c] *Servicio de Endocrinología y Nutrición, Hospital Carlos Haya, Málaga, Spain*

[d] *Endocrinología y Nutrición, UGEN, Hospital Universitario Virgen del Rocío, Sevilla, Spain*
[e] *Facultad de Ciencias de la Salud Blanquerna, Universitat Ramon Llull, Barcelona, Spain*
[f] *Servicio de Ginecología y Obstetricia, Hospital de Sant Joan de Déu, Barcelona, Spain*
[g] *Servicio de Ginecología y Obstetricia, Hospital de Cruces, Bilbao, Spain*
[h] *Servicio de Endocrinología y Nutrición, Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain*

* Corresponding author.
E-mail address: lluis.vila@sanitatintegral.org (L. Vila).

Relating with monographic ''Actualización terapéutica para el tratamiento de la diabetes tipo 2''☆

En relación con el monográfico «Actualización terapéutica para el tratamiento de la diabetes tipo 2»

Sir,

In mid-2012, the journal *Avances en Diabetología* published a special issue analyzing the potential advantages of insulin aspart in different clinical settings.[1] The undersigned did not consider its publication appropriate and thought it useful to express our opinion in a letter to the editor.[2] A little later, we had the unpleasant experience of finding the situation being repeated, in this case in a linagliptin monograph published in the journal ENDOCRINOLOGÍA Y NUTRICIÓN, the channel of communication of the Spanish Society of Endocrinology and Nutrition. Both papers were related to diabetes. Although we took good note of the explanation given by the editorial board of *Avances en Diabetología* in its reply to our protest letter,[3] we think we have reason on our side again.

We therefore feel obliged to take up again the final paragraph of the abovementioned letter and repeat: ''The use of the official channel of expression of a scientific society to publish the monograph of a product sponsored by the company manufacturing such a product is another question. The undersigned think that such publication—however it is justified—represents advertising. Mixing the activities of the scientific societies and the pharmaceutical companies is nothing new. It is the basis for the sponsorship of scientific meetings, and one of the reasons for their relative—but progressive—disrepute. It hurts, however, when the same systemic disease reaches the heart of a scientific society and its organ of expression because we might as well register it directly as a trading company''.

After the publication of our first letter and the abovementioned reply to it, we find this painful repetition of the same story, so consolidating a very questionable habit and the undersigned again find themselves questioning the publication of a sponsored product monograph in the official organ of expression of a scientific society. We think that when a product is not analyzed in its context or with its competitors, we are coming close to propaganda, either express or subliminal. And this is not the concept of the organ of expression of a scientific society that we wish to uphold and defend. Amongst other things, this is because it may lead to odd or spurious interpretations which we are all undoubtedly interested in avoiding. An additional reason is that, because of the social and health significance of the concerned issue, the leadership that scientific societies and their organs of expression should exercise must be beyond doubt or it will evaporate. We would not like our scientific society to end up as merely an additional link in the chain of consumption.

With specific regard to the linagliptin monograph, particular mention should be made of the approach proposed: because of the alarming prevalence of diabetes and the frequent coexistence of chronic renal failure, it is particularly appropriate to discuss the adequacy of hypoglycemic drugs in renal failure. This appears to be a planned stage in which—involuntarily, we hope—cardinal issues such as cost-effectiveness are minimized. Increased healthcare expense is too often attributed to demographic factors, ignoring the fact that the economic development of the region concerned and increased technological expense (in the widest sense of the term) are even more important factors.[4] We would like to highlight as an example that in the first three trimesters of 2012, almost 12.5 million euros were spent on hypoglycemic drugs (excluding insulins) in Extremadura. Eighty percent of this amount was accounted for by different presentations of DPP-IV inhibitors or GLP-1 analogues, and it is a fact that costs in this field have increased by 200–300% in recent years. At a time when we see cuts being made daily in budget provisions, including expenses on staff and healthcare benefits, which sometimes make access to services difficult or impossible, we must ask ourselves if this increase under the heading of pharmaceutical expense is really supported by clinically relevant results. If, as we suspect, the answer is no, what other factors have influenced this change in prescription?

In this regard, we only want to clearly show that, as stated in the monograph's introduction, the current state of well-being is ''evidently threatened''. Our own scientific society recently gave its support to the manifesto ''Debate on the risk of irreversible impairment to Spanish public health''.[5] We need to consider whether, along with some questionable political decision-making, inadequately based prescription might not be the accomplice of this process?

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