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LETTER

Response: in reference to 'Strategies to manage refractory endometrium: state of the art 2016'

To the Editor

We thank Dr Gleicher and colleagues for their letter (Gleicher et al., 2016) regarding our review on the management of refractory endometrium (Garcia-Velasco et al., 2016) and appreciate their comments on their published studies concerning G-CSF and thin refractive endometrium. The aim of our review was to evaluate critically the most recent evidence regarding the many different interventions that claim to benefit endometrial development, including treatment with G-CSF. We apologize if one of our conclusions was interpreted erroneously, but according to their randomized trial in normal IVF patients – not thin endometrium patients – the intrauterine administration of G-CSF did not affect endometrial thickness, implantation rates, or clinical pregnancy rates.

As we show in our review, most of the published studies suffer from some problems such as very limited sample size – the so-called 'miniature studies' – and are thus subject to type II error and underpowered to support a hypothesis, and the type of study design – being retrospective, case series, or observational cohorts – which again may bias the results (for example, the patient being her own control is far from ideal, as those who conceive will not try the alternate treatment, creating a huge selection bias). Also not all cycles are equal – just as there is cycle-to-cycle variation regarding follicular recruitment, similar cycle-specific variation in the growth of the endometrium also occurs. But most importantly, what constitutes a thin endometrium and why focus only on thickness for diagnosis and for the evaluation of any benefit of intervention? Perhaps we should start looking at the endometrium from a new perspective, focusing on functionality rather than thickness. Obviously, endometrial thickness is does play a role – there is sufficient evidence in the literature to show that when it falls below 5 mm there should be concern (Cai et al., 2011) – but an exclusive focus on this feature may not be helpful beyond the 5 mm threshold when sonographic pattern as well as functional tests can show us whether the endometrium is competent to support successful implantation.

The recent campaign of 'Choosing Wisely' (www.choosingwisely.org) has increased efforts to reduce inappropriate use of medical treatments. When treating patients, we as doctors sometimes tend to overestimate the effects of our interventions, resulting in what is known as 'therapeutic illusion' or 'illusion of control' (Casarett, 2016). In reproductive medicine there are several recent examples such as the use of low-molecular-weight heparin (LMWH), endometrial scratching or intra-venous immunoglobulin therapy (IVIg) to improve implantation. The aim of our recent review was to evaluate many of these interventions in the management of thin endometrium. Based on the best available evidence, we cannot conclude that the administration of intrauterine G-CSF – while a promising treatment in a specific category of patients, as demonstrated by Professor Gleicher and colleagues – should be used generally to expand endometrial thickness and increase clinical outcome. Adequately powered RCT are clearly needed.

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