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PERSPECTIVE

Clinical Research

Pharmacological interventions for weight loss before conception—putative effects on subsequent gestational weight gain should be considered

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Obesity is a well-known risk factor for adverse pregnancy outcomes. It increases the risk of pregnancy complications such as gestational diabetes, hypertension or preeclampsia and also the risk of complications during delivery and adverse outcomes for the offspring such as large for gestational age babies, congenital malformations and even stillbirths [1]. Furthermore, maternal obesity also adversely affects long-term metabolic health of the offspring through foetal programming [2]. Finally, obesity can impair fertility preventing many women to get pregnant. If successfully treated, previous infertility also represents an independent risk factor for adverse gestational outcomes. On this background, weight loss before conception is widely recommended to improve fertility as well as gestational and offspring outcomes. Of note, however, the maintenance of weight loss, i.e., keeping the weight at the reduced levels over a longer period of time, is even much harder to achieve than weight loss per se. This is one of the reasons why obesity is a chronic, relapsing disease. With this in mind, the aspect of weight loss maintenance should be taken into account when planning a weight loss intervention in women with obesity or overweight who might get pregnant in the future since the extent of weight gain or weight regain during pregnancy also impacts gestational and offspring outcomes.

Weight loss can be achieved by behavioral lifestyle interventions aiming to improve dietary habits and increase physical activity, but the effectiveness of such interventions is often limited, also due to neuroendocrine counterregulatory responses. This results in an only moderate weight loss in a limited number of women with obesity [3]. A greater amount of weight loss before conception can be achieved by bariatric surgery. While overall bariatric surgery appears to reduce the risk of obesity-related gestational complications, it was also found to be associated with an increased risk of small for gestational age babies as well as more frequent respiratory failures associated with bronchiolitis in infants. Moreover, women who have undergone bariatric surgery before pregnancy require continuous nutritional support including a regular intake of micronutrient supplements [4].

In light of these limitations of current behavioral and surgical strategies for weight loss, anti-obesity medications, that can help to reduce body weight in women prior to conception, appeared to be highly welcomed. Fortunately, substantial progress has been made during the last years in the fields of anti-obesity drug development. In particular, drugs that target the glucagon like peptide-1 (GLP-1) receptors such as liraglutide or semaglutide appear to be highly effective in reducing body weight. The effect is primarily mediated through a reduction in hunger and appetite and thus in caloric intake. However, it should also be noted that these anti-obesity drugs have not been studied during pregnancy and thus need to be stopped immediately once a woman is pregnant. From a more preventive point of view, such drugs might not be prescribed to women who wish to get pregnant in the near future or even to sexually active women in the absence of safe contraceptive measures.

The withdrawal of any anti-obesity medication has consistently been documented to be followed by a regain in body weight [5]. For instance, in the "STEP 4 trial" participants had a 10.6% weight reduction after 20-weeks of treatment with semaglutide. When then the participants in one out of two treatment arms were switched to placebo they showed a 6.6 kg increase in body weight during the subsequent 48 weeks [6]. Similar, in the "STEP 1" trial extension, participants had a 11.5 kg increase in body weight during 52 weeks following the withdrawal of semaglutide. This was preceded by a 68-week active treatment period which had led to a weight reduction of 17.3% [7]. Assuming that 1 kg of weight gain translates into a 8000 kcal energy excess it can be calculated that the participants experienced an average energy surplus of 157 kcal per day in the"STEP 4" trial and of 253 kcal in the "STEP 1" trial extension after withdrawal of the drug. Moreover, considering that the weight regain was not linear across the posttreatment observation period but was steeper during the first weeks, it might be assumed that the amount of daily positive energy balance is even greater during the early phase after an anti-obesity drug withdrawal.

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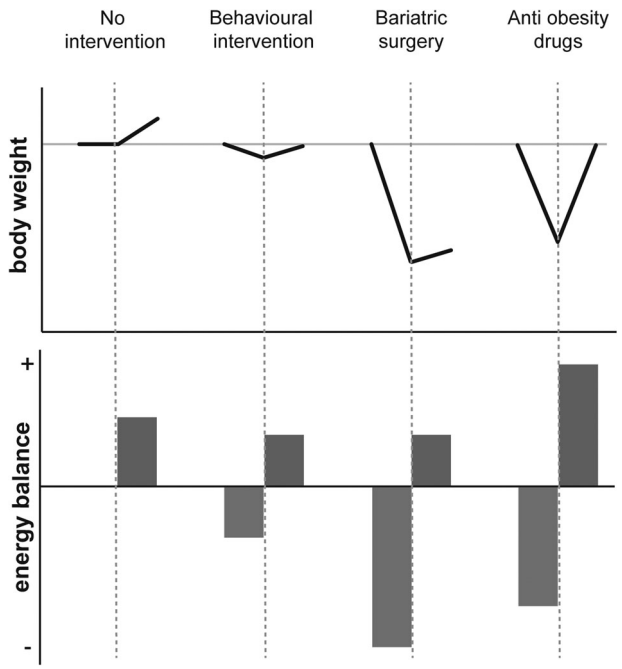

Fig. 1 Schematic illustration of hypothetical body weight trajectory (upper panel) and concurrent energy balance (deficit and excess) during various weight loss interventions before conception: no intervention, behavioral intervention, bariatric surgery, and anti-obesity drug therapy, as well as the subsequent pregnancy. The horizontal solid line indicates the baseline body weight; the vertical dashed lines indicate conception with the preconceptional period presented on the left side and the gestational period on the right side.

What do these considerations on the weight regain after an anti-obesity drug withdrawal mean in the context of pregnancy? Irrespectively of whether the prescription of an anti-obesity drug is intended to reduce body weight before conception or whether a pregnancy occurs unintendedly during the treatment, the medication needs to be stopped immediately after the pregnancy is confirmed to avoid any potential teratotoxic effect [8–10]. Based on previous observations in non-pregnant people with obesity mentioned above, we hypothesize that the extent of gestational weight gain will be accelerated after such a drug withdrawal. This is important as the risk of adverse maternal and offspring outcomes is not only determined by the degree of preconceptional obesity, but also by the extent of gestational weight gain [1]. Therefore, it might even be that a forced weight loss before conception by using anti-obesity drugs could be rather harmful than beneficial regarding pregnancy and offspring outcomes. While for ethical reasons this hypothesis can likely not be systematically tested in randomized control trials, we think that it is mandatory to at least gather observational data on the use of anti-obesity drugs shortly before pregnancy onset and related gestational and offspring outcomes.

To provide a more comprehensive conceptual overview on the issue we set up Fig. 1 which illustrates the hypothetical effects of distinct weight loss interventions before pregnancy on subsequent gestational gain and on the concurrent body energy balance in women with obesity or overweight. As can be seen, without any intervention we expect the body weight to remain relatively stable in the absence of any intervention in the preconceptional phase meaning that conception takes place at a rather high body weight and that these women show a "habitual" gestational weight gain (which is frequently higher than recommended). A behavioral weight loss programme carried out before conception can be expected to result in a moderate preconceptional weight loss and putatively also blunts gestational weight gain provided that it is continued during pregnancy. However, it might also be that gestational weight gain is even accelerated in such a setting since previously established behavioral changes such as dietary restriction and increased physical activity might not be maintained at the same level during pregnancy. Bariatric surgery before pregnancy will lead to an extensive weight loss and may also limit the increase of gestational weight gain. As outlined above, we expect that anti-obesity drugs can also lead to a substantial amount of weight loss. However, due to their mandatory withdrawal the subsequent gestational weight gain will be most likely accelerated in the setting of a markedly positive energy balance and a maternal and foetal caloric overload.

To summarize, in the light of the increasing use of anti-obesity drugs we believe that there is an urgent need to gather data on the effects of anti-obesity drugs used before conception on gestational weight gain as well as on pregnancy and offspring outcomes. Such data will hopefully inform clinicians on whether it is beneficial to describe such drugs to women with overweight/obesity who might became pregnant in the future and to define the best preconceptional timing to start drug treatment. Meanwhile, such anti-obesity drugs might only be prescribed with caution in women who might to get pregnant. In addition, women should be informed about the expected body weight regain after drug withdrawal and the associated potential pregnancy risks.

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AUTHOR CONTRIBUTIONS

Conceiving the work that led to the submission: BS, BE, KT, JP, GR. Drafting the paper: BS, BE, KT, JP, GR. Revising paper: BS, BE, JP, KT. All authors read and approved the final version of the paper.

COMPETING INTERESTS

Dr BS has received presentation fees from and compensation as a member of a scientific advisory board of Novo Nordisk and Eli Lilly as well as for serving as a study investigator for Novo Nordisk. Dr BE has nothing to declare. Dr KT has received presentation fees from and compensation as a member of a scientific advisory board

of Novo Nordisk. She also received a restricted research grant from Novo Nordisk. Dr JP has received compensation as a member of a scientific advisory board of Eli Lilly and received a unrestricted educational grant from Novo Nordisk. Dr GR has received presentation fees from and compensation as a member of a scientific advisory board of Novo Nordisk and Eli Lilly as well as for serving as a study investigator for Novo Nordisk.

ADDITIONAL INFORMATION

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