type 2 diabetes. After review of these data and modelling of the tolerability profiles of gastrointestinal adverse events, exposure, and comparisons to studies with weekly administration of semaglutide,[3,4] no difference in gastrointestinal adverse events resulting from daily versus weekly dosing regimens was noted. Results from our study showed that a 0·4 mg once-daily dose of subcutaneous semaglutide was most effective in terms of weight loss, while displaying an acceptable tolerability profile.[1] Estimates from population pharmacokinetic modelling indicate that the steady-state maximum serum concentration achieved with a 2·4 mg once-weekly maintenance dose of subcutaneous semaglutide would not exceed that of a 0·4 mg once-daily dose.[1] As a result, ongoing studies of semaglutide for the treatment of people with obesity (NCT03548935, NCT03552757, NCT03611582, NCT03548987, NCT03693430, and NCT03574597) are using a weekly subcutaneous 2·4 mg dose.

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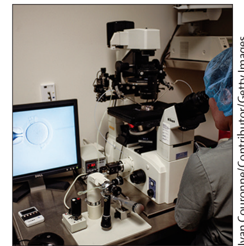
1 O'Neil PM, Birkenfeld AL, McGowan B, et al. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. *Lancet* 2018; **392:** 637–49.
2 Lingvay I, Desouza CV, Lalic KS, et al. A 26-week randomized controlled trial of semaglutide once daily versus liraglutide and placebo in patients with type 2 diabetes suboptimally controlled on diet and exercise with or without metformin. *Diabetes Care* 2018; **41:** 1926–37.
3 Petri KCC, Ingwersen SH, Flint A, Zacho J, Overgaard RV. Exposure-response analysis for evaluation of semaglutide dose levels in type 2 diabetes. *Diabetes Obes Metab* 2018; **20:** 2238–45.
4 Overgaard RV, Delff PH, Petri KCC, Anderson TW, Flint A, Ingwersen SH. Population pharmacokinetics of semaglutide for type 2 diabetes. *Diabetes Ther* 2019; **10:** 649–62.

Fresh versus frozen blastocyst transfer



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We read with interest the report by Daimin Wei and colleagues,[1] in which they concluded that frozen blastocyst transfer resulted in a higher livebirth rate than fresh blastocyst transfer in ovulatory women with good prognosis. However, we consider that the use of the livebirth rate after the first transfer in each arm of the study is problematic in this evaluation. Although biologically interesting, from a patient's perspective this comparison is not relevant when evaluating livebirths. At the time when women in the frozen blastocyst group received their first transfer, women in the fresh blastocyst group had already received their second transfer (of a frozen-thawed embryo) if the fresh transfer had been unsuccessful. The result of the first embryo transfer in the frozen transfer group should be considered against the combined outcomes of the fresh transfer and the first frozen-thawed transfer in the fresh transfer group, which would have favoured the fresh transfer strategy. Frozen transfer could still have been superior to fresh transfer, as a higher number of frozen-thawed transfers per started treatment could have resulted in a higher cumulative livebirth rate. However, no evidence of a difference in cumulative livebirth rate was found between groups. Thus, a similar cumulative livebirth rate is always accompanied by a reduced time to pregnancy in the fresh transfer group (per start of treatment) when comparing fresh and frozen transfers with frozen transfers only in in-vitro fertilisation. Taken together with the finding of no difference in ovarian hyperstimulation syndrome between groups and the increased reported risk of pre-eclampsia after frozen transfer, these findings actually suggest that fresh transfer should be the treatment of choice for these women.

We declare no competing interests.

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1 Wei D, Liu J-Y, Sun Y, et al. Frozen versus fresh single blastocyst transfer in ovulatory women: a multicentre, randomised controlled trial. *Lancet* 2019; **393:** 1310–18.

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Daimin Wei and colleagues[1] coordinated the largest randomised controlled trial on elective frozen-thawed versus fresh single blastocyst transfer in normogonadotropic healthy young women undergoing in-vitro fertilisation. The investigators reported a substantially higher singleton livebirth rate in women in the elective frozen transfer group than in those in the fresh transfer group. However, elective frozen transfer increased the risk of maternal pre-eclampsia and the birth of neonates too large for their gestational age, thus corroborating other new meta-analyses.[2,3]

Adverse obstetric and perinatal outcomes after elective frozen transfer are likely to be multifactorial, but the corpus luteum seems to have a crucial role in maternal circulatory adaptation during pregnancy.[4] Indeed, two new studies[4,5] showed an increased risk of hypertensive disorders and macrosomia in women who received elective frozen transfers under artificial endometrial preparation. Notably, such unfavourable outcomes are not apparent after elective frozen transfer under natural or stimulated cycles, as well as after fresh embryo transfer or natural conception. A common

feature among the latter scenarios is the presence of a functioning corpus luteum.[4,5]

Our call to rethink endometrial preparation for elective frozen transfer relies on three premises. First, clinical outcomes of elective frozen transfer are either equivalent or superior (in specific patient subgroups) to those of fresh cleavage-stage embryos or fresh blastocyst transfer.[1,2] Second, obstetric and perinatal outcomes are generally poorer following fresh embryo transfers than frozen transfers.[3] Lastly, the pre-eclampsia and increased size of neonates in women who receive elective frozen transfers seem to be related to the use of endometrial preparations in these women, who do not have a functioning corpus luteum. These adverse outcomes might be mitigated through a natural or stimulated elective frozen transfer cycle, instead of an artificial endometrial preparation, a hypothesis that warrants further investigation.[4,5]

We declare no competing interests.

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1 Wei D, Liu J-Y, Sun Y, et al. Frozen versus fresh single blastocyst transfer in ovulatory women: a multicentre, randomised controlled trial. *Lancet* 2019; **393:** 1310–18.
2 Roque M, Haahr T, Geber S, Esteves SC, Humaidan P. Fresh versus elective frozen embryo transfer in IVF/ICSI cycles: a systematic review and meta-analysis of reproductive outcomes. *Hum Reprod Update* 2019; **25:** 2–14.
3 Maheshwari A, Pandey S, Amalraj Raja E, Shetty A, Hamilton M, Bhattacharya S. Is frozen embryo transfer better for mothers and babies? Can cumulative meta-analysis provide a definitive answer? *Hum Reprod Update* 2018; **24:** 35–58.
4 Ginström Ernstad E, Wennerholm U-B, Khatibi A, Petzold M, Bergh C. Neonatal and maternal outcome after frozen embryo transfer: increased risks in programmed cycles. *Am J Obstet Gynecol* 2019; published online March 22. DOI:101.016/j.ajog.20190.30.10.
5 von Versen-Höynck F, Schaub AM, Chi Y-Y, et al. Increased preeclampsia risk and reduced aortic compliance with in vitro fertilization cycles in the absence of a corpus luteum. *Hypertension* 2019; **73:** 640–49.

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Authors' reply

We appreciate the comments from Tjitske Zaat and colleagues and Matheus Roque and colleagues. We disagree that we should have compared the outcomes from two embryo transfers (ie, a fresh and a frozen one) to one embryo transfer (ie, a frozen one only) in our study.[1] Whenever time to pregnancy is evaluated as the primary outcome of infertility treatment, it will encourage the rapid use of expensive and invasive assisted reproductive technology and a willingness to tolerate increased patient risk, such as inducing ovarian hyperstimulation syndrome. However, to address Zaat and colleagues' request, we reviewed our data. We found that the frequency of livebirths in the frozen embryo transfer group after the first frozen embryo transfer was 439 (53%) of 825, whereas the proportion of livebirths in the fresh embryo transfer group after the fresh and the first frozen embryo transfer was 546 (66%) of 825 (p=0·0001). We also examined the cumulative livebirths after the first two transfers in each group. This comparison between the frozen and the fresh embryo transfer groups (587 [71%] livebirths in 825 women *vs* 546 [66%] in 825, p=0·030), showed that the frozen embryo transfer group had significantly higher cumulative livebirths after the first two transfers. We believe that this is the more clinically relevant comparison. Meanwhile, we agree with Zaat and colleagues that the cumulative number of livebirths is also an important outcome and have reported it in our previous and present trials.[1,2] The field of in-vitro fertilisation is changing, and provider and patient perception of the procedure's success are drifting from the results of the first embryo transfer to the cumulative results of a single ovarian stimulation cycle.

Roque and colleagues proposed that a programmed regimen for endometrial preparation could contribute to the increased risk of pre-eclampsia after frozen embryo transfer. In our two trials with ovulatory women,[1,3] 1283 (69%) of 1860 women in the frozen embryo transfer group had a natural ovulatory regimen and 577 (31%) had a programmed regimen. The incidence of pre-eclampsia in women who became pregnant with a programmed regimen was 14 (4%) of 328 and in those with a natural ovulatory regimen was 27 (3%) of 805 (p=0·46). We understand that our data are underpowered for this comparison. We concur with the authors that randomised trials need to compare different regimens of endometrial preparation.

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1 Wei D, Liu JY, Sun Y, et al. Frozen versus fresh single blastocyst transfer in ovulatory women: a multicentre, randomised controlled trial. *Lancet* 2019; **393:** 1310–18.
2 Chen Z-J, Shi Y, Sun Y, et al. Fresh versus frozen embryos for infertility in the polycystic ovary syndrome. *N Engl J Med* 2016; **375:** 523–33.
3 Shi Y, Sun Y, Hao C, et al. Transfer of fresh versus frozen embryos in ovulatory women. *N Engl J Med* 2018; **378:** 126–36.