Commentary

Maternal intermittent fasting during pregnancy: a translational research challenge for an important clinical scenario

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In volume 135, issue 11 of Clinical Science, Alkhalefah et al. report that, in pregnant rats, repeated, cyclic fasting, mimicking the fasting experienced by observant Muslim pregnant women during Ramadan, alters placental amino acid transport and increases the incidence of low birth weight. Though Muslim women are exempt, many observe Ramadan: >500 million fetuses worldwide may be exposed to Ramadan fasting in each generation, and low birth weight increases the risk of developing chronic disease in the future adult. Several mechanisms, including altered circadian rhythm, maternal stress, undernutrition or compensatory overeating at the breaking of fast, could, in theory, impact fetal growth during Ramadan. Limitations of the experimental model obviously prevent direct extrapolation to humans. Whether Ramadan fasting indeed affect fetal growth therefore remains unclear, as there is no clear-cut evidence from epidemiological studies. The paper illustrates the need to design further case-controlled studies in large cohorts of women who fasted at various stages of pregnancy, compared to appropriately matched women who did not fast, as well as more experimental studies focused on this issue of public health relevance.

Introduction

In volume 135, issue 11 of the journal [1], Alkhalefah et al. report on the effect of repeated, cyclic fasting—termed intermittent fasting (IF)—mimicking the fasting experienced by observant Muslim pregnant women during Ramadan, on fetal growth and metabolism in rats. They found that IF resulted in a higher incidence of low birth weight pups, impaired placental efficiency, along with decreased in vivo maternal-fetal transfer of 14C-labeled amino-isobutyrate (14C-AIB), an amino acid analogue transported by system A, and up-regulated the gene expression of this placental amino acid transport. The authors conclude that fasting through the month of Ramadan may expose pregnant women to intrauterine growth restriction (IUGR).

Why is it important?

Low birth weight—whether it is due to maternal undernutrition (predominantly in the developing world) or to impaired placental blood flow (predominantly in industrialized world)—has long been known to be associated with increased perinatal morbidity and mortality [2]. In addition, evidence accumulated over the last 3 decades suggests infants with a low birth weight are exposed to a higher risk of developing chronic disease such as obesity, type 2 diabetes, hypertension and cardiovascular disease in later, adult life [3]. Whether the cyclic fasting associated with Ramadan affects fetal growth remains debated. Assuming the number of Muslim women of childbearing age exceeds 200 million worldwide, with a fertility rate
averaging 3.1 children per woman, Glazier et al. estimated that up to 535 million babies in each generation were potentially exposed *in utero* to maternal intermittent fasting during Ramadan [4]. Should exposure to Ramadan during fetal life impact fetal outcome, this would potentially represent a tremendous public health burden.

**How could Ramadan fasting impact fetal outcome?**

From a theoretical standpoint, Ramadan fasting may impact fetal health through several mechanisms (Figure 1), including disruption of circadian rhythms, maternal sleep deprivation and stress, altered feeding pattern or water deprivation.

Disruption of circadian rhythm, is commonly encountered in women submitted to shift work or jetlag. Smarr et al examined the effect of developmental chronic circadian disruption (DCCD) in pregnant mice. Though neither litter size nor birth weight were affected, pups born to DCCD dams exhibited altered behavior at adulthood, e.g. hyperactivity and social avoidance, phenotypes not abrogated by cross-fostering to control mothers [5].

Mothers fasting for Ramadan may also experience shorter sleep duration, and lack of sleep can produce stress [6]. Though increased maternal secretion of cortisol occurs physiologically during pregnancy, fetus is normally protected from cortisol excess by 11-β-ol-dehydrogenase (β-HSD2), a placental enzyme that inactivates glucocorticoids. Underexpression of β-HSD2 [7] was proposed to account for many of the long-term adverse effects of low birth weight, e.g. higher risk of cardiometabolic disease at adulthood [8]. To our knowledge, the effect of Ramadan on fetal cortisol secretion has not been explored.

The daily alternance of a diurnal, fed period, and an unfed nocturnal period—or the reverse in rodents—is physiologic in humans. Disruption of such alternance is now felt to have detrimental effect in adults, as there is increasing evidence connecting disturbances in circadian rhythm with an increased risk of metabolic syndrome [9]. Yet time-restricted eating, i.e. restricting the timing of meals to an ≈12-h diurnal period, has been found to improve insulin sensitivity, β-cell responsiveness, blood pressure and oxidative stress in men with prediabetes, independently of weight loss [10]. The putative effects of time-restricted eating during pregnancy remain to be explored [11].

Also, fasting during the day may be associated with "feasting" at *iftaar*, the evening meal consumed after breaking the fast, with high fat, high sugar feeding at night. In a recent meta-analysis [12], a healthy maternal diet—with high intake of vegetables, fruits, wholegrains, low-fat dairy and lean protein foods—was associated with lower risk of preterm birth and a weak trend toward a lower risk of small, for gestational, age (OR: 0.86; 95% CI: 0.73, 1.01; $I^2 =$
34%), whereas unhealthy dietary patterns—with a predominant intake of refined grains, processed meat, foods high in saturated fat or sugar—were associated with lower birth weight and a trend towards higher risk of preterm birth.

Finally, women observing Ramadan would be expected to abstain not only from eating but drinking as well between dawn and sunset. In a case-control study performed in the US drinking less than 1 glass of water per day during pregnancy was associated with an increased risk of low birth weight (OR 1.4; CI 0.9–2.2) [13]. In theory, decreased water intake could be detrimental as a successful pregnancy requires a significant expansion of maternal plasma volume. A prospective, observational study exploring the relationship between water intake during pregnancy and pregnancy outcome is currently carried out [14].

Is there evidence from epidemiological surveys?

Many religions edict precepts regarding food intake. When applied according to the rules, such precepts do not seem detrimental to health, as suggested by the fact that they have been followed for centuries [15]. Although exonerated, many pregnant Muslim women fast during Ramadan. A meta-analysis of 22 studies including 31,374 pregnancies, of which 60% were exposed to Ramadan fasting, showed that neither birth weight nor the rate of preterm delivery (odds ratio: 0.99, 95% CI: 0.72–1.37) were affected by maternal fasting, but placental weight was significantly lower in fasting mothers (SMD: -0.94, 95% CI: -0.97 to -0.90). The authors concluded that there was insufficient evidence regarding other outcomes and suggested further studies were needed [4].

The study by Alkhalfalah et al. therefore is timely and relevant

Yet it has to be borne in mind that limitations inherent to animal models cannot be underestimated. Some limitations of the model used are obvious. For instance, the duration of IF chosen (3 weeks) spans the entire duration of gestation in rats rather than one ninith of the duration of pregnancy in humans. The timing of intermittent fasting, i.e., whether it coincides with early or late pregnancy, may matter as well, since fetal weight is expected to triple in the third trimester. An experimental design with timed IF—e.g., through the last week of gestation in dams—would have been more appropriate. Also, in northern latitudes, in the winter Ramadan lasts only 10–11 h, a duration that does not exceed that of the fast experienced by ladies eating an early dinner and a late breakfast, or skipping lunch for example. Thus, the number of women who actually undergo a fast long enough to be of clinical concern may be overestimated.

The animals studied presumably were primiparous rats who were normally nourished prior to pregnancy and were not exposed to either over- or undernutrition. This experimental setting obviously differs from 'real life' when over a third of women of reproductive age overweight or obese [16], and 10–32% suffer from iron deficiency [17].

Also, whereas the end of each fasting cycle (at sunset) often is accompanied by feasting and overconsumption of high energy, palatable food in humans, this did not happen in the rat model, since dams in the IF group consumed, on average, 30% less food than control dams, despite having free access to food daily over a 8 h period (from 09:00 to 17:00).

Besides, dams were allowed free access to water, and daily water consumption was comparable between diet groups, whereas observant mothers might refrain from drinking throughout the day.

It also remains unclear whether dams were in a state of stress, as neither corticosterone, nor placental β-HSD2 expression were determined.

Although plasma was obtained from both groups of dams around 9 am, at that time of the day, the IF group had been fasted for 16 h versus only a few minutes or hours for the control group. So differences between groups regarding glucose and hormone concentrations can simply reflect the difference between postprandial and postabsorptive period rather than the effect of IF per se. Blood sampling after 16 h of fasting in the control group would have been more informative.

Interestingly, the authors observed a lower system-A amino acid transport activity in IF fetuses; accordingly, the concentration of alanine was lower as lower in fetal plasma in fetuses exposed to intermittent fasting. Such decline is of concern, as decreased system A activity is known to reflect placental adaptation to maternal undernutrition in other models [18]. The decrease in four essential amino acids (histidine, isoleucine, valine, methionine), as well as one semi-essential amino acid (arginine), particularly in male fetuses, also suggests those fetuses indeed suffered undernutrition. Regrettably, long term offspring outcome was not addressed.

In conclusion, despite limitations intrinsic to the chosen model, the study by Alkhalefah et al clearly provides 'food for thought' on the potential impact of Ramadan fasting in pregnant women, and may inform health professionals when asked for dietary guidance. The study suggests experimental studies focusing on the timing of fasting, with precise monitoring of feeding behavior, water intake, energy expenditure, and the long-term effects in the offspring.
may be warranted. The paper also illustrates the need to design further observational studies in large cohorts of women who fasted at various stages of pregnancy, taking into account maternal/parental educational level to remove confounding genetic/familial/heritable factors. Prospective case–control studies, with the controls being mothers who do not fast, may be of value. So would studies in women deciding to observe Ramadan fasting in spite of a preexisting condition such as undernutrition or diabetes.

Competing Interests
The authors declare that there are no competing interests associated with the manuscript.

Abbreviations
β-HSD2, 11-β-ol-dehydrogenase; 14C-AIB, 14C-labeled amino-isobutyrate; DCCD, developmental chronic circadian disruption; IF, intermittent fasting; IUGR, intrauterine growth restriction.

References
5 Smarr, B.L. et al. (2017) Maternal and early-life circadian disruption have long-lasting negative consequences on offspring development and adult behavior in mice. Sci. Rep. 12, 3326, https://doi.org/10.1038/s41598-017-03406-4