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An endocrine hypothesis to explain obesity-related lactation insufficiency in breastfeeding mothers

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Research Reflection

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Abstract

In this Research Reflection I shall develop and validate the hypothesis that lactation insufficiency in obese breastfeeding mothers has an endocrine explanation. I shall not present data, but I shall review pertinent literature to show that obesity is associated with a partial or sometimes complete failure to initiate and maintain lactation, and critically examine the belief that this is due to psychosocial factors, a failure of prolactin secretion or both. Since progesterone is inhibitory to lactogenesis and oestrogens are inhibitory to milk secretion, I shall then explore the possibility that these steroids are linked to lactation failure, through sequestration of progesterone and aromatization of oestrogen in mammary adipose tissue. I shall conclude by describing experimental approaches in animal models that could be used to test this hypothesis.

Introduction

I present the following case in support of the hypothesis that lactation insufficiency in obese breastfeeding mothers has an endocrine explanation:

There is increasing evidence to show that both the initiation and the duration of breastfeeding are adversely affected by obesity (reviewed by Garcia *et al*., 2016, and see online Supplementary File for earlier references). Gestational obesity in itself is not necessarily a problem (Michaelsen *et al*., 1994), and it is likely that the effects of obesity are exerted earlier in life. One of several 'critical windows' in mammary development occurs around puberty (Knight, 2001) and in dairy cattle, overweight at this time can cause a permanent impairment of mammary development and milk production (Sejrsen and Purup, 1997). If the same is true in man, lactation insufficiency may increase particularly dramatically in the next few years, as those who were obese as young girls reach childbearing age.

For many years it was difficult to exclude sociocultural reasons for the poor breastfeeding success of obese mothers, and it has been suggested that additional support and encouragement will overcome the problem (Mok *et al*., 2008). However, an analysis of data from the Danish National Birth Cohort not only confirmed the negative effect of obesity but also showed it to occur in a supportive social context (Baker *et al*., 2007), leading the authors to propose a biological basis for the association. This agrees with a number of observations in animal models. Genetically-obese (leptin deficient) mice exhibit a marked inhibition of mammary development and delay of lactogenesis (Knight *et al*., 2002), normal mice rendered obese by dietary means also suffer impaired lactogenesis (Flint *et al*., 2005), and milk yield is reduced in obese dairy cattle (Sejrsen and Purup, 1997).

Lactogenesis, the establishment of lactation, occurs in two distinct stages. Stage I is the acquisition of secretory capability some time pre-partum, whereas Stage II is the onset of copious secretion at or soon after parturition. Prolactin is essential to a successful establishment of lactation in most species, including man. Prolactin secretion is pulsatile and is stimulated by suckling. It has been suggested that suckling-related prolactin secretion is compromised in obese breastfeeding mothers (Rasmussen and Kjolhede, 2004). However, this conclusion was based on a very restricted sampling schedule (one sample pre-suckling and one 30 min post-suckling) which would not be sufficient to properly characterize the prolactin response. There is no reason to believe that obesity would negatively affect baseline prolactin secretion, indeed a positive relationship between prolactin and obesity has been demonstrated in post-menopausal women (McTiernan *et al*., 2006).

Stage II lactogenesis is specifically triggered by progesterone withdrawal, hence if for any reason progesterone remains elevated, full lactation will not ensue. In women, progesterone levels typically do not fall until the second day postpartum, accounting for the relatively-late 'coming in' of milk, usually around 30–40 h after delivery. Progesterone concentration was measured at 48 h and 7 d postpartum in the same study as before (Rasmussen and Kjolhede, 2004), and since there was no difference between obese and non-obese individuals

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it was concluded that inappropriate progesterone secretion was not a factor in obesity-mediated lactation insufficiency. However, the time of the post-partum fall in progesterone was not detected (progesterone was high at 48 h and low at 7 d irrespective of BMI) and may have been delayed in obese women. There is evidence of enhanced progesterone clearance in obese women (Azziz, 1989), but the mechanism is through sequestration in adipose tissue. If the breast is only responsive to serum levels of progesterone then this sequestration is immaterial. However, a local inhibitory effect of progesterone sequestered within the mammary fat pad cannot be discounted.

Oestrogens are produced in adipose tissue and are inhibitory to milk secretion, so one can hypothesize that obesity exerts its inhibitory effect through local oestrogen production within the mammary fat pad. The lactation-inhibiting properties of systemic oestrogens are well known (Agenäs *et al*., 2019 and see online Supplementary File for earlier references) and the role that local oestrogen production might play in the mammary gland has been reviewed (Simpson, 2000). Mammary aromatase has received attention because of its possible role in breast cancer (Tekmal and Santen, 1999) and there is evidence of aromatase activity in mammary tumors, but also in healthy mammary glands of goats, cows, mice, primates and dogs (Peaker and Taylor, 1990 and see online Supplementary File for additional references). Whilst adipose tissue is quantitatively the major extragonadal site of oestrogen biosynthesis (Simpson, 2000) and as a result is a significant modulator of reproductive function (Norman and Clark, 1998), the relationship between adiposity, intramammary oestrogen biosynthesis and lactation has not been investigated. It is likely that effects would be greater in breastfeeding women than in dairy animals, due to the more variable composition and greater fat content of the human breast.

Methods

I propose the following approaches to test the hypothesis that lactation insufficiency in obese breastfeeding mothers has an endocrine explanation. References to the individual techniques are given in the online Supplementary File.

Animal models: These would be used to establish the chronology of the relationship between obesity and lactation insufficiency and then be the basis of subsequent investigations of endocrine regulation. Two obese mouse models could be used, namely dietary induced (moderate obesity) and genetically programmed (severe obesity). For the first model, a cafeteria diet known to induce obesity would be offered to normal mice either from weaning age onwards, or introduced at 6 weeks of age (post-puberty) or from weaning until 6 weeks of age. Obese mice and lean controls would be mated such that at the end of pregnancy groups would either have been obese since they were juveniles, have been obese only as adults, have been obese as juveniles but would no longer be obese or would never have been obese. For the second model, leptin deficient ob/ob mice (which are infertile) would be treated with leptin to restore fertility and then mated, at which time leptin treatment could be discontinued. The extent of lactation inhibition in these mice is such that regular twice-daily litter swapping is essential for the first few days post-partum, both to ensure the young are fed and to maintain a strong suckling stimulus to the mother. Once lactation is established it is quantitatively normal and both the inhibition and the recovery occur irrespective of leptin treatment. The model is thus reflective of extreme adiposity, not leptin deficiency per se.

Three large animal models could also be used. Pregnant beef-suckler cows would be fed to achieve low ($\leq$2) and high ($\geq$4) body condition scores (BCS: measured using a 5 point score where 1 is very lean and 5 is very obese) at calving. Pregnant sheep would be overfed during late gestation and lactation to become obese and compared with normally fed lean controls. Overfed obese pigs and normal lean pigs would be mated and studied during lactation. Standard protocols are available for creating different degrees of obesity in all three species.

In breastfeeding mothers it would be possible to collect samples of human milk (minimum 2.5 ml foremilk and 2.5 ml hindmilk) by expression from mothers of different body mass index (BMI) during early lactation (weeks 1 to 3) and later lactation (weeks 8 to 10) for analysis of oestrogen content. An appropriate approach could be to collect from at least 15 normal mothers (body mass index 18–25) and 15 obese mothers (BMI >30).

Putative endocrine deficiencies: The same protocol could be used to test whether defects in prolactin or oxytocin secretion are responsible for poor lactation outcome in obesity. The prolactin and oxytocin response to suckling would be measured in lean and obese pigs, sheep and cattle using standardized suckling regimes and sampling intervals appropriate to the species. Measurements would be made within 24 h of parturition and again 1 week and 2 weeks later. Additional measurements would be made in cattle and sheep in late lactation; 2 weeks is late lactation for pigs. The choice of species is guided by the different mammary anatomy and physiological suckling strategies adopted. Pigs have very little intramammary milk storage capacity and suckle often and very briefly. Cattle have abundant storage capacity and suckle less often and for longer. Sheep are intermediate.

Putative steroid excesses: A number of approaches could be used to identify whether progesterone sequestration and/or oestrogen aromatization within the mammary fat pad is responsible for the inhibition of lactation. Progesterone experiments would target the periparturient period, since progesterone is a specific inhibitor of lactogenesis, not of established lactation. Oestrogen experiments would include different stages of lactation. To establish whether excess adiposity within the fat pad has a role of any sort, we would perform unilateral lipidectomy (liposuction) during late pregnancy in obese mice and compare the establishment of lactation in the 'lean' gland with that in the contra-lateral 'obese' gland. Expression of a panel of genes involved in mammary differentiation and functionality would be determined at different times after parturition using quantitative rt-PCR according to established methods. To establish whether progesterone is sequestered within the mammary fat pad of obese animals we would take mammary biopsies from normal and obese cattle, pigs and sheep within 12 h of parturition and determine progesterone content for comparison with plasma concentration. Plasma concentration would be determined twice daily from 2 d before expected parturition until a fall is detected, to establish whether the fall is delayed in obese individuals. Groups of normal and obese mice would be killed at parturition for the same analysis. Additional groups of mice would be treated with a progesterone antagonist at parturition and the effects on establishment of lactation measured using litter weight gain and mammary analysis as above. Finally, groups of normal mice would receive locally-active intramammary silastic implants containing amounts of progesterone calculated to mimic the previously observed mammary content, and effects on lactation establishment measured as before. A unilateral-comparison (within-animal) design would be employed.

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To establish whether the mammary fat pad is capable of oestrogen production through aromatization, the same biopsy samples and tissue samples used for the progesterone work would also be subject to further rt-PCR analysis for CYP19 (aromatase cytochrome P450) mRNA. The effect of aromatase inhibitors would be assessed. In all of these experiments comparison would be drawn between the mammary fat and visceral fat. We would attempt to create lactation insufficiency in lean mice using silastic implants containing oestrogen in the same way as before for progesterone. Finally, we would also collect milks from lean and obese women and animal models and analyze oestrogen content.

Discussion

No species is more prone to obesity than our own. In the USA almost 60% of reproductive-age women and one-third of children aged 2–19 are overweight or obese (Bever Babendure *et al.*, 2015). The same study reported that pre-pregnancy obesity was associated with a 13% reduction in successful initiation of breastfeeding and a 20% decrease in any breastfeeding at 6 months *postpartum,* and reviewed evidence showing that breastfeeding decreases childhood obesity (by up to one-third) and reduces obesity-associated co-morbidities (diabetes, high blood pressure, elevated cholesterol) in both mother and young (Bever Babendure *et al.*, 2015). Expressed simply, obesity starting early in life makes later breastfeeding less likely (Garcia *et al.*, 2016), absence of breastfeeding compounds the mother's obesity (Janney *et al.*, 1997) and makes the baby more prone to juvenile obesity (Gillman *et al.*, 2001) hence the problem becomes self-sustaining in what amounts to an obesity cycle (Fig. 1). The benefits of breastfeeding to mother and baby are well recognized (Knight, 2010), leading WHO to recommend 6 months of exclusive breastfeeding. At a global level, suboptimal breastfeeding is a significant cause of infant mortality and accounts for some 8% of the global burden of disease (Garcia *et al.*, 2016). Despite the scale of the problem, little has been done to address the recognized adverse effect of obesity on breastfeeding outcome. This is perhaps not surprising given that the mammary gland is the only major organ in the body that does not have a medical specialism associated with its functioning and dysfunction. The relative lack of knowledge in the field is exemplified by the fact that an early hypothesis for the biological basis of obesity-related lactational insufficiency was inadequate glucose uptake by the mammary cell as a consequence of insulin deficiency (Lovelady, 2005): this is untenable since mammary glucose uptake is recognized to be insulin-independent.

Counseling and advice is sometimes offered to obese mothers wishing to breastfeed, but the sources of such advice are varied, with few recognized international standards and considerable variability between national support structures. The value of counseling for the obese mother has been questioned: of four intervention studies involving face to face or telephone advice, only one (Carlsen *et al.*, 2013, and see online Supplementary File for additional references) reported a positive outcome, and this was in a selected population of mothers who had previously committed to weight reduction. In reviewing the evidence, Bever Babendure *et al.* (2015) concluded that 'further research is needed to identify modifiable behavioral and physiological variables that may lead to increased breastfeeding'.

If the evidence supported the hypothesis that lactation insufficiency in obese breastfeeding mothers has an endocrine explanation, further work would be necessary in order to devise prevention or mitigation strategies based on the research findings. The exact nature of such strategies cannot be predicted with certainty, but progesterone antagonists with proven efficacy in humans are available, as are aromatase inhibitors. It should be evident from the introduction that both interventions might be needed, since progesterone sequestration might account for delayed lactogenesis whilst local oestrogen production by aromatization might be responsible for the shorter than normal lactations.

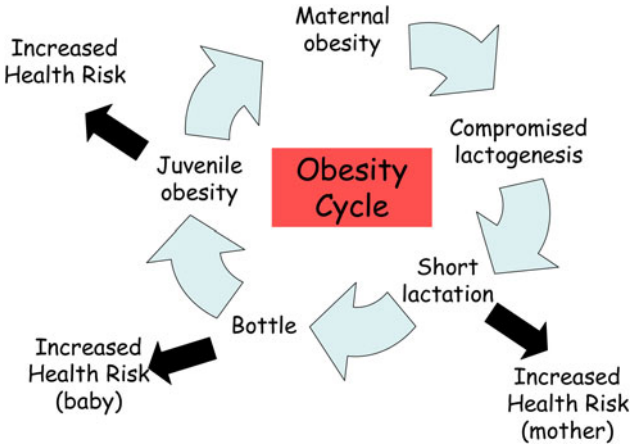

Fig. 1. Schematic to show the obesity cycle: consequences of obesity for lactation outcome and health of mother and baby. Recent evidence indicates that maternal obesity compromises lactogenesis (the establishment of lactation) and reduces the duration of lactation. Absence of breastfeeding increases the risk of continued maternal obesity and babies who are not breastfed are at greater risk of juvenile obesity.

In conclusion, I hypothesize that obesity impairs lactation in women through an endocrine mechanism and propose a series of experiments to test that hypothesis.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0022029920000047.

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