

BMJ Open Lactogenic hormones in relation to maternal metabolic health in pregnancy and postpartum: protocol for a systematic review

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ABSTRACT

Introduction Maternal metabolic disease states (such as gestational and pregestational diabetes and maternal obesity) are reaching epidemic proportions worldwide and are associated with adverse maternal and fetal outcomes. Despite this, their aetiology remains incompletely understood. Lactogenic hormones, namely, human placental lactogen (hPL) and prolactin (PRL), play often overlooked roles in maternal metabolism and glucose homeostasis during pregnancy and (in the case of PRL) postpartum, and have clinical potential from a diagnostic and therapeutic perspective. This paper presents a protocol for a systematic review which will synthesise the available scientific evidence linking these two hormones to maternal and fetal metabolic conditions/outcomes.

Methods and analysis MEDLINE (via OVID), CINAHL and Embase will be systematically searched for all original observational and interventional research articles, published prior to 8 July 2021, linking hPL and/or PRL levels (in pregnancy and/or up to 12 months postpartum) to key maternal metabolic conditions/outcomes (including pre-existing and gestational diabetes, markers of glucose/insulin metabolism, postpartum glucose status, weight change, obesity and polycystic ovary syndrome). Relevant fetal outcomes (birth weight and placental mass, macrosomia and growth restriction) will also be included. Two reviewers will assess articles for eligibility according to prespecified selection criteria, followed by full-text review, quality appraisal and data extraction. Where possible, meta-analysis will be performed; otherwise, a narrative synthesis of findings will be presented.

Ethics and dissemination Formal ethical approval is not required as no primary data will be collected. The results will be published in a peer-reviewed journal and presented at conference meetings, and will be used to inform future research directions.

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INTRODUCTION

Pregnancy entails profound maternal physiological and metabolic adaptations to accommodate the needs of the growing fetus and to prepare for lactation. An increase in insulin resistance of 50%–60% between prepregnancy and the late third trimester is a physiological

Strengths and limitations of this study

- Novel and relevant research area linking lactation hormones to maternal metabolic health, with particular relevance to pregnancies affected by obesity and/or diabetes.
- Protocol is for the first systematic review in this area.
- Employs rigorous, standardised methodology and will involve an exhaustive literature search and quality appraisal.
- Limitations include the anticipated heterogeneity in study designs, most of which will likely be observational in nature and hence unable to establish causality.

change in every pregnancy (regardless of glucose tolerance) and is essential to prioritise the delivery of glucose across the placenta for fetal development.¹ This is paralleled—in a normal pregnancy—by adaptive changes in the islets of the maternal endocrine pancreas to allow increasing insulin synthesis and secretion, including an increased beta-cell mass. Overall, this results in maintenance of maternal glucose homeostasis.¹

Gestational diabetes mellitus (GDM) may develop when there is failure to balance insulin secretion with the composite of prepregnancy and pregnancy-induced insulin resistance, and is an increasingly prevalent condition (affecting between 2% and 38% of pregnant women worldwide).² GDM is associated with multiple adverse maternal and fetal outcomes, including macrosomia, pre-eclampsia and gestational hypertension, polyhydramnios, stillbirth and neonatal hypoglycaemia, as well as an increased lifetime risk of obesity and dysglycaemia in the offspring.³ In women with pre-existing diabetes mellitus (type 1 or type 2), superimposed pregnancy-induced insulin resistance exacerbates



established pregestational insulin resistance and/or deficiency, with similar potential complications.

Lactogenic hormones, chiefly human placental lactogen (hPL) and prolactin (PRL), are well recognised for their roles in the antenatal preparation of the breast for lactation, and—in the case of PRL—in establishing and maintaining lactation after delivery. However, these hormones also have central roles in maternal metabolism: during gestation, both contribute to insulin resistance but are also likely to act as stimuli for the adaptation of maternal pancreatic islet function. Postpartum, the hormonal control of lactation (primarily mediated by PRL) may fundamentally alter carbohydrate and lipid metabolism and adipocyte biology, guarding lactating postpartum women against progression to type 2 diabetes.⁴

Human placental lactogen (HPL) is a peptide hormone produced by the placenta. It is detectable as early as 6 weeks' gestation and increases across gestation, peaking at around 30 weeks. The secretion rate of hPL near term is about 1 g/day (a rate considerably greater than that of any other protein hormone),⁵ and the peak concentration of hPL is at least 25-fold that of PRL.⁴ hPL binds with high affinity to the PRL receptor and is increasingly recognised as playing a major role in the modulation of maternal metabolism to meet the energy requirements of the growing fetus.⁶ It is also involved in lactogenesis I (secretory initiation), supporting alveolar and ductal growth in the breast in preparation for milk production.⁵

As one of the major 'diabetogenic' hormones of pregnancy (alongside placental growth hormone, progesterone, cortisol and PRL), hPL increases maternal insulin resistance and reduces maternal glucose utilisation, elevating maternal blood glucose levels (supporting transplacental glucose transfer and adequate fetal nutrition).⁴ However, this appears to be matched by parallel upregulation of insulin secretory capacity. In rodent models, placental lactogens significantly increase glucose-induced insulin secretion, beta-cell proliferation and survival in isolated pancreatic islets.^{7–9} In humans, *in vitro* evidence using human islet cell tissue suggests that hPL also acts (likely via the PRL receptor) on the endocrine pancreas to promote maternal beta-cell function, enhancing insulin synthesis and glucose-stimulated insulin secretion.⁹ The net effect of this is—in a healthy pregnancy—maintenance of maternal normoglycaemia.

hPL also increases lipolysis and release of free fatty acids (FFAs). With maternal fasting, hPL release increases the availability of FFAs to the mother for use as fuel, sparing glucose and amino acids for placental transport and fetal nutrition.¹⁰ hPL is also likely to play a role in inducing and maintaining the state of physiological hyperleptinaemia but relative leptin resistance seen in pregnancy, which provides maternal appetite stimulus even with increasing adipose deposition.⁴ hPL (and PRL) also seems to increase appetite and food intake via other mechanisms, with widespread distribution of PRL receptors in the hypothalamus and induction of hyperphagia

after intracerebroventricular administration, suggesting a central mode of action.¹¹

Being placentally derived, hPL is also positively correlated with birth weight and placental mass, with potential clinical application in the antenatal prediction of macrosomia and/or fetal growth restriction in both metabolically normal and abnormal pregnancies.¹²

Prolactin (PRL) is a peptide hormone produced by lactotrophs in the anterior pituitary gland and has close structural homology to hPL. Basal serum PRL increases progressively during normal pregnancy, with peak values in late gestation approximately 10-fold higher than preconception.⁴ While best known for its lactogenic effect on the female mammary gland, PRL also alters insulin sensitivity and lipid metabolism. PRL may induce insulin resistance outside of pregnancy (as demonstrated in non-pregnant patients with prolactinoma and pathological PRL elevation)¹³ and, like hPL, is likely to contribute to the insulin-resistant state of pregnancy, ensuring the availability of glucose for the fetal–placental compartment. However, the physiological contribution of PRL to glucose tolerance in pregnancy and postpartum is thought to differ from other states of relative or absolute hyperprolactinaemia.⁴ *In vitro* evidence suggests that PRL (like hPL) can directly enhance insulin secretion from human islets, although the latter hormone may have the dominant effect during human pregnancy due to its higher concentrations.⁹ It is worth noting that rodent evidence for the effect of PRL on maternal beta-cell function during pregnancy is striking: knockout mice specifically lacking PRL receptors on pancreatic beta cells have normal glucose tolerance outside of pregnancy but become progressively glucose intolerant with gestation due to corresponding failure of beta-cell proliferation, essentially developing GDM.^{14 15}

Postpartum, physiological hyperprolactinaemia is the key endocrine change responsible for the initiation and maintenance of lactation. PRL concentrations during lactation are intermediate between those in the non-pregnant state and those in late pregnancy, and the pulsatile nature of secretion (lost during pregnancy) is restored. PRL surges occur following nursing, and peaks are higher in women who exclusively breast feed their infants than in those who supplement with formula or only feed formula. In women who do not breast feed, PRL falls to non-pregnant concentrations within 3 weeks postpartum.⁴

Lactation—under the chief control of PRL—is a unique metabolic state associated with an elevation of plasma FFAs and with the mobilisation of lipids from diet and adipose stores to the breast for milk production. Observational evidence suggests that lactation is associated with maternal metabolic benefits, with consistent findings of lower rates of persistent postpartum dysglycaemia and progression to type 2 diabetes in women who breast feed compared with those who do not (both in the general population¹⁶ and following GDM pregnancy¹⁷). As such, PRL may link effective and sustained lactogenesis

to improved maternal metabolic status postpartum. Whether this is primarily mediated by improved insulin secretory capacity or reduced insulin resistance remains unclear, as there are putative biological mechanisms for both in the postpartum context.^{4 18 19} Regardless, lactation may present a particular window of opportunity for women with postpartum insulin resistance (relevant to many women following a GDM pregnancy) to significantly improve long-term health outcomes by improving insulin secretion and/or sensitivity. Indeed, some authors have argued that lactation (quite apart from its other benefits to mother and offspring) may be seen as a therapeutic intervention in this patient cohort, analogous to the prescription of an insulin-sensitising medication.⁴

It is also increasingly apparent that the relationship between impaired glucose/insulin metabolism and poor lactation outcomes may be bidirectional. While lactation outcomes are not the focus of this review, women with obesity and/or diabetes are at increased risk of lactogenesis delay and persistent poor milk supply,^{20 21} reasons for which may include a suboptimal PRL response to infant suckling²² and impaired insulin-receptor dynamics at the level of the lactocyte.²³ Authors linking PRL to glucose dynamics during lactation have suggested that ‘good beta-cell plasticity’ in metabolically healthy women may exert a permissive effect on lactation, allowing PRL to play its primary evolutionary role.¹⁸ As such, the women who stand to benefit most from the metabolic benefits of sustained lactation may face the most barriers to achieving it. A more complete understanding of lactogenic hormone action, as well as how it is altered in metabolically abnormal pregnancies, is essential to promote and support lactation in this population.

Narrative reviews (which constitute the majority of the existing work in this area and have produced many of the current mechanistic hypotheses) are often incomplete or reach subjective conclusions. Systematic reviews focused on key physiological questions are uncommon in contemporary endocrine literature but provide an opportunity to move toward extensive synthesis with objective, evidence-based conclusions. This review aims to systematically examine the relationship between hPL and PRL and maternal metabolism in pregnancy and postpartum, particularly in relation to common gestational metabolic conditions, as well as the association between hPL and PRL and key fetal outcomes. It also aims to provide mechanistic insights and to examine the clinical implications of these findings from both diagnostic and therapeutic perspectives.

SYSTEMATIC REVIEW QUESTION

In pregnant women (participants), what is the relationship between hPL/PRL levels (exposures) and

- ▶ Maternal gestational metabolic status/ outcomes?
- ▶ Relevant fetal outcomes?
- ▶ Maternal metabolic outcomes up to 12 months postpartum?

METHODS/DESIGN

Rigorous international gold-standard methodology will be adopted in this review, which will conform to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.²⁴ This review has been registered with the International Prospective Register of Systematic Reviews (PROSPERO). We used the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols checklist when writing this protocol paper.²⁵ Any future amendments to this protocol will be reported on PROSPERO and published with the results of the review.

Eligibility criteria

Selection criteria using a modified version of the participant, exposure, comparison, outcome and study type framework²⁶ (table 1), established *a priori*, will be used to determine the eligibility of articles to include in this review. All articles published prior to 8 July 2021 will be eligible, but only articles with full text available in English will be included.

It should be noted that the review aims to elucidate the *relationship* between maternal serum hPL/PRL levels and metabolic/fetal conditions/outcomes without assuming causality or directionality. The designation of hPL and PRL levels as ‘exposure’ and the listed outcomes as ‘outcomes’ is somewhat arbitrary and may not apply to all studies: some may work in the opposite direction. For example, studies that enrol women with pre-existing diabetes or GDM (relevant metabolic exposure) and look at PRL and hPL levels across gestation (outcome) would warrant inclusion. It is acknowledged by the reviewers that the relationship between lactogenic hormones and maternal metabolism is likely bidirectional, and the inclusion criteria will reflect this.

Search strategy

A systematic search strategy using relevant search terms, in accordance with the selection criteria (table 1), has been developed (see online supplemental material 1) in consultation with expert subject librarians. A combination of keywords and database-specific subject headings will be used. The following electronic databases will be searched:

- ▶ MEDLINE via OVID.
- ▶ MEDLINE ePub ahead of print, in-process, in-data review and other non-indexed citations via OVID.
- ▶ CINAHL Plus.
- ▶ Embase.

Bibliographies of relevant studies identified by the search strategy and relevant reviews/meta-analyses will also be manually searched for identification of additional eligible studies.

Given that we intend to conduct an in-depth synthesis of a large body of research spanning several decades, only peer-reviewed published data with all results available will be considered eligible for inclusion (conference abstracts will be excluded, and grey literature will not be searched).

Table 1 Modified PECOT framework for study inclusion/exclusion

| | P | E | C | O | T |
|---------------------------|--|--|--|---|--|
| Inclusion criteria | Pregnant women Women up to 12 months postpartum (regardless of lactation status) | Endogenous maternal serum hPL* (recorded at least once during pregnancy) or Endogenous maternal serum PRL (recorded at least once during pregnancy and/ or up to 12 months postpartum) | Studies with any/ multiple control groups or no control group will be included | Maternal: Diabetes status during pregnancy and up to 12 months postpartum (pre-existing diabetes (type 1 or type 2), IGT or GDM; adequately defined)† Metabolic indices (continuous measurements) related to maternal glucose/lipid metabolism (eg, glucose measurements on OGTT, insulin secretion, sensitivity/resistance indices, beta-cell function) during pregnancy or postpartum Obesity, gestational weight gain Postpartum weight change Polycystic ovary syndrome Lipid profile Infant: Birth weight (absolute/centiles, macrosomia), growth restriction or placental mass in pregnancies affected by GDM or pregestational DM† | Longitudinal cohort Case-control Cross-sectional studies Randomised controlled trials Clinical observational human trials (eg, infusion/clamp studies) if methods were used to determine a maternal metabolic outcome of interest Systematic reviews (to be examined for eligible articles) |
| Exclusion criteria | Non-pregnant populations Men Pathological/iatrogenic elevation of PRL (eg, prolactinoma, medication-induced hyperprolactinaemia) or hPL (eg, molar pregnancy) Studies focused on multiple pregnancy | hPL/PRL levels in other fluids (eg, amniotic fluid and breast milk) in fetus or infant, or in cord blood hPL/PRL administered exogenously Trials examining an intervention/procedure (eg, amniocentesis, induction of labour, drug treatment, intravenous glucose or insulin infusion and prolonged fasting) with hPL/PRL levels as outcome Trials focused on ART and ART outcomes Trials examining 'lactation' as exposure without PRL measured, or where PRL is measured but not directly analysed relative to metabolic outcomes | None | Diabetes status during pregnancy and up to 12 months postpartum inadequately defined† Birth weight, placental weight or growth restriction in pregnancies <i>not</i> affected by GDM or pregestational DM Outcomes unrelated to named key maternal metabolic or infant outcomes, for example, placental function/perfusion/ blood flow without mention of weight or FGR (eg, Doppler indices alone), pre-eclampsia, miscarriage/pregnancy loss, fetal structural abnormalities/ congenital malformations, diabetic retinopathy, lactation outcomes/parameters (milk transfer, milk production and infant weight change during breast feeding) | Animal studies In vitro/tissue culture studies Narrative reviews Commentaries/letters Case reports and case series Conference abstracts Expert opinion Protocol papers |

*Alternative name: *human chorionic somatomammotropin*, also included in search (and studies eligible for inclusion).

†Regarding classification of diabetes type: *include* studies referring clearly to type 1 or type 2 diabetes, or gestational diabetes or impaired glucose tolerance; include studies which refer to 'insulin-dependent', 'juvenile-onset' or 'insulin-requiring' diabetes (inside or outside of pregnancy) *only if* the supporting data clearly suggest type 1 diabetes; *exclude* studies which refer to 'diabetic' pregnancies, 'diabetes', 'chemical diabetes', or 'DM' in pregnancy without further definition, or 'pregestational' diabetes without further definition or 'insulin-treated' diabetes without further clarification; exclude studies which define diabetes only according to White's classification (A/B/C/D) for diabetes in pregnancy. If one group within a study is considered adequately defined and another inadequately defined, include the study but only extract data for the groups meeting definition requirements
ART, assisted reproductive technologies; DM, diabetes mellitus; FGR, fetal growth restriction; GDM, gestational diabetes mellitus; hPL, human placental lactogen; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; PECOT, participant, exposure, comparison, outcome and study type; PRL, prolactin.

Inclusion of studies

References will be screened and managed using EndNote V.x9 and Covidence software. Two reviewers will scan the titles, abstracts and keywords of every record retrieved by the search strategy, assessing eligibility according to the inclusion and exclusion criteria in [table 1](#) (and in consultation with a third reviewer where required). A pilot test of the selection criteria will be conducted on 20–30 article titles and abstracts in order to refine and clarify the criteria prior to the formal commencement of screening.

If initial information suggests that an article meets the selection criteria for eligibility, the full text will be retrieved for further assessment by two reviewers. Disagreement between reviewers as to whether a study meets the inclusion criteria will be resolved by discussion, with referral to a third reviewer if consensus cannot be reached. Studies excluded based on full-text review will be tabulated, along with reasons for their exclusion. Following PRISMA guidelines,²⁴ a flow diagram will be created to illustrate the selection process.

Quality appraisal of the evidence

Methodological quality of the included studies will be assessed by two independent reviewers using criteria established *a priori*, outlined in the Monash Centre for Health Research and Implementation Evidence Synthesis Programme critical appraisal template²⁷ (see online supplemental material 2). Individual quality items will be investigated using a descriptive component approach. Assessment will be based on criteria relating to external validity (population, setting, clarity of study objectives, inclusion and exclusion criteria, appropriateness of study design and follow-up) and internal validity (selection, performance and detection bias, attrition, exposure and outcome measurement, reporting bias and potential confounders). Other domains for assessment will include potential conflicts of interest, study power and appropriateness/quality of statistical methodology. Any disagreement or uncertainty will be resolved by discussion among review authors. Using this approach, we will allocate a risk of bias rating for each study.

Data extraction

Data will be extracted from all included studies by two independent reviewers using a specifically developed data extraction form. Pilot testing of the form will be conducted using three to five studies of different formats to ensure all required data are captured, particularly given the anticipated heterogeneity in study design. Key anticipated domains for extraction are shown in [table 2](#). Relevant data which are not reported in published studies will be requested from corresponding authors.

Statistical analysis

Analysis for the two lactogenic hormones of interest, hPL and PRL, will be undertaken separately. Key exposure/outcome associations for each hormone will be determined based on the number of studies available. It is anticipated that hPL will be analysed primarily in relation to maternal metabolic/glycaemic status during pregnancy and to fetal outcomes (birth weight, macrosomia, growth restriction and placental mass) in pregnancies affected by diabetes. For PRL, it is anticipated that key outcomes will be maternal metabolic/glycaemic status and related maternal metabolic indices (measures of insulin secretion, sensitivity and beta-cell function) during both pregnancy and postpartum. After data extraction, the reviewers will determine whether meta-analysis is appropriate (based on the number of studies for each hormone/outcome relationship and the heterogeneity of their designs and participant groups). If meta-analysis is possible, Review Manager statistical software will be used for analysis with random effects models employed to generate weighted mean differences. Statistical heterogeneity will be assessed using the I^2 test, with I^2 values of $>50\%$ indicating moderate to high heterogeneity. Sensitivity analyses will be performed where applicable to explore the effects of studies with high risk of bias on the overall results. Subgroup analyses will also

be performed where possible (eg, by type of diabetes). Where meta-analysis is not possible, a narrative synthesis of results will be performed.

Data will be presented in summary tables and in narrative format to describe the populations, exposures and key outcomes of the included studies. Forest plots and funnel plots will be used to present results from meta-analyses (where applicable) and publication bias assessments, respectively. Meta-analysis results will be reported according to PRISMA guidelines.²⁴

Ethics and dissemination

This project will collate aggregate data from published studies (or aggregate data provided by study investigators on request), and thus ethical approval will not be required.

Findings will be disseminated via publications in peer-reviewed journals and presentations at scientific meetings. If deemed appropriate, findings will also be communicated to relevant stakeholders to guide clinical practice and public health actions in this area.

Data availability statement

No data have been generated or analysed in this paper.

Patient and public involvement statement

It was not feasible or appropriate to involve patients or members of the public in the design, planning or conduct of the planned research.

DISCUSSION

The proposed review will be the first, to our knowledge, to systematically collate and synthesise the existing scientific literature linking two key lactogenic hormones, hPL and PRL, to maternal metabolic health in pregnancy and postpartum (and, by extension, to infant outcomes). Systematic reviews which evaluate biomarkers or aim to explore physiological questions are rare in the endocrine literature, and represent an opportunity to move beyond subjective, narrative work towards inclusive, extensive reviews with the potential for objective and evidence-based conclusions.

While these hormones have long been recognised for their roles in the antenatal preparation of the breast for lactation and (in the case of PRL) for the postnatal initiation and maintenance of lactation, their metabolic roles have been relatively underappreciated. Both hormones contribute to the insulin resistance associated with the pregnant state, but also potentially have central roles in the adaptation of the maternal pancreas during gestation, stimulating beta-cell adaptation and increasing beta-cell mass and insulin secretion.^{1 9} During a normal pregnancy, this may allow compensation for pregnancy-induced insulin resistance, resulting in overall maintenance of euglycaemia.

Despite likely playing a key role in the regulation of glucose and insulin dynamics during pregnancy, the

**Table 2** Key domains for data extraction

| | |
|---|--|
| Study | <ul style="list-style-type: none"> First author Journal Country and year of publication Study design Follow-up duration |
| Participants | <ul style="list-style-type: none"> Number of participants Participant characteristics (at baseline) <ul style="list-style-type: none"> ▶ Baseline (prepregnancy) metabolic conditions, if present. ▶ Mean age. ▶ Parity. ▶ Ethnicity. ▶ Singleton/multiple pregnancy. ▶ Gestation at enrolment/recruitment. ▶ Mean BMI. ▶ Delivery mode ▶ Breastfeeding status. If control group is present, control characteristics (at baseline) include <ul style="list-style-type: none"> ▶ Mean age. ▶ Parity. ▶ Ethnicity. ▶ Singleton/multiple pregnancy. ▶ Gestation at enrolment/recruitment. ▶ Mean BMI. ▶ Delivery mode. ▶ Breastfeeding status. |
| Exposure* (lactogenic hormone) | <ul style="list-style-type: none"> Hormone measured (hPL/PRL/both) Number of time points Time points (pregnancy), with concentration and units of hormone at each time point Time points (postpartum), with concentration and units of hormone at each time point Assay methodology used |
| Key maternal metabolic outcomes* of interest | <ul style="list-style-type: none"> Key maternal “outcomes” assessed (from list)* For diabetes in pregnancy <ul style="list-style-type: none"> ▶ Pre-existing (T1DM/T2DM) or gestational. ▶ Gestation at diagnosis. ▶ Method used for diagnosis (eg, OGTT). ▶ Diagnostic criteria, if stated. ▶ Treatment (diet/oral medications/insulin) and treatment commencement time point. For postpartum glucose status <ul style="list-style-type: none"> ▶ Time point. ▶ Method used for diagnosis (eg, OGTT). ▶ Diagnostic criteria, if stated. ▶ Prevalence of persistent dysglycaemia postpartum. Relationship of said outcomes to hPL/PRL levels (as t-test result, OR, regression coefficient, etc) <ul style="list-style-type: none"> ▶ Unadjusted. ▶ After adjustment (with list of covariates included in models). Conclusions regarding the aforementioned |
| <ul style="list-style-type: none"> Glucose status in pregnancy (pre-existing diabetes mellitus of any type or gestational diabetes) Postpartum glucose status Continuous metabolic indices related to maternal glucose/lipid metabolism, for example, measures of <ul style="list-style-type: none"> ▶ Fasting glucose. ▶ OGTT glucose of 1 and 2 hours. ▶ Insulin secretion. ▶ Insulin sensitivity. ▶ Insulin resistance. ▶ Beta-cell function (during pregnancy or postpartum). Gestational weight gain Obesity Postpartum weight change Polycystic ovary syndrome Lipid profile (total cholesterol, HDL and LDL cholesterol, and triglycerides) | |
| Key infant metabolic outcomes* of interest (for pregnancies affected by GDM or pre-existing diabetes) | <ul style="list-style-type: none"> Key infant outcomes assessed (from list) Relationship of said outcome to hPL/PRL levels (as t-test result, OR, regression coefficient, etc) <ul style="list-style-type: none"> ▶ Unadjusted. ▶ After adjustment (with list of covariates included in models). Conclusions regarding the aforementioned |
| <ul style="list-style-type: none"> Birth weight (absolute/centiles) Macrosomia Growth restriction Placental mass | |

*Due to the likely bidirectional nature of the lactogenic hormone/maternal metabolism relationship, some studies will consider hPL/PRL as ‘exposure’ and a metabolic parameter (eg, postpartum glucose tolerance) as ‘outcome’. Others may consider a metabolic parameter (eg, maternal pregestational diabetes) as exposure with hPL/PRL levels during pregnancy, in comparison to healthy controls, as outcome. The extraction template will accommodate both.

BMI, body mass index; GDM, gestational diabetes mellitus; HDL, high-density lipoprotein; hPL, human placental lactogen; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test; PRL, prolactin; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

relationship between hPL levels and the pathophysiology of GDM remains unclear. Several studies have investigated possible links, with some reporting no association between maternal hPL levels and GDM status^{28–31} and others reporting higher hPL in GDM subjects than controls,^{32–33} particularly if insulin-treated.³⁴ For hPL levels during pregnancies affected by pre-existing diabetes (type 1 diabetes mellitus (T1DM)/type 2 diabetes mellitus), the majority of authors report serially higher hPL throughout gestation in diabetic women compared with controls,^{29–32–35–37} although other studies in T1DM have shown lower levels in the setting of poor control.³⁸ Furthermore, higher hPL levels are clearly related to increased placental weight and macrosomia, and several authors have suggested that increased levels of hPL in many diabetic pregnancies may simply reflect higher placental mass.^{4–32–35} This does not suggest it is aetiologically unimportant; however, as it is possible that the placentomegaly seen in maternal diabetes causes higher hPL levels, stimulating maternal and fetal beta-cell expansion and increasing fetal insulin production, thus promoting glycogenesis, fat deposition and further fetal growth.⁶

Importantly, however, this area of the literature is particularly dated, with many studies performed well prior to the 21st century and prior to contemporary diagnostic definitions of diabetes in pregnancy. As such, the exact type of maternal diabetes among study participants is often unclear (they are simply deemed to be ‘diabetic’, are defined according to the now-historical White classification of diabetes in pregnancy³⁹ or are termed ‘insulin-dependent’).^{30–32–35–38} Such studies provided valuable basic insights into the pathophysiology of the lactogen–maternal metabolism relationship, but comparison to the available better-described contemporary cohorts²⁸ is not possible. In this systematic review, a sufficiently clear definition of diabetes type (or adequate detail for this to be confidently deduced) is thus mandated for inclusion, as we believe this is a minimum requirement if our review findings are to be applicable to modern obstetric populations.

Acknowledging these challenges, a better understanding of the role of hPL in metabolically abnormal pregnancies has potential clinical application. For example, accurate antenatal prediction of fetal macrosomia remains challenging, and current macrosomia prediction strategies (including physical examination and ultrasound assessment) are both resource-intensive and imprecise. There is thus a clear requirement for maternal serum biomarkers in improving antenatal macrosomia prediction, particularly in women at high risk of the outcome (such as those with pregestational diabetes or GDM). While several candidate maternal biomarkers have been assessed for their association with birth weight or macrosomia (both in diabetic and non-diabetic pregnancies), evidence is mixed and uncertainties around clinical utility persist.⁴⁰ hPL (which was used clinically in some settings to assess the well-being of the fetoplacental unit in the 1970s and 1980s, prior to the widespread availability of obstetric

ultrasound)⁴¹ has recently been largely overlooked as a candidate biomarker in this capacity, but previous work suggests it may have significant potential if revisited. For instance, one 1998 study measured hPL at the time of GDM screening (n=257) and found that among the subset of women with a normal glucose challenge test but whose infants ultimately weighed >4000 g (n=11), mean hPL at the time of testing had in fact been similar to the mean hPL found in women with GDM.⁴² This suggests that hPL may warrant evaluation as a biomarker for macrosomia prediction, both in women with diagnosed diabetes and those without. Such an application would require the marker to be validated in modern cohorts where the underlying aetiology of maternal diabetes was adequately understood and described.

Unlike hPL (which, as a placentally derived hormone, is washed from the circulation following delivery), PRL has probable influence in maternal metabolism during both pregnancy and postpartum, particularly if lactation ensues. The literature here is similarly conflicting. For example, maternal serum PRL levels during GDM pregnancy have been examined by several groups, with the majority reporting levels similar to those of normal pregnancies.^{28–31–43} However, more recent studies have directly contradicted this. Two groups have shown that higher PRL levels in the first⁴⁴ and third⁴⁵ trimesters of pregnancy are associated with reduced glucose tolerance on OGTT, with both groups suggesting that PRL may be independently involved in GDM pathogenesis. A third study has demonstrated an opposite result, showing an inverse association between third-trimester PRL and GDM risk.⁴⁶ This lack of consensus highlights the need for effective evidence synthesis followed by further research.

Postpartum, lactation (under the chief control of PRL) appears to confer maternal metabolic benefits, but the mechanism by which this occurs is unclear. One group found that maternal serum PRL in late pregnancy was significantly higher in women who progressed to normal glucose tolerance postpartum than in those who progressed to postpartum pre-diabetes/diabetes; and that higher antepartum PRL independently predicted improved postpartum insulin secretion capacity. That group suggested that these findings may reflect a postpartum extension of the beneficial effects of PRL on beta-cell mass and islet adaptation that are thought to occur during gestation. Another group which measured PRL postpartum presented different findings and discussion: women with higher circulating PRL in the context of lactation in their study had reduced beta-cell function and lower insulin secretion indices but were less insulin resistant.¹⁸ Authors have suggested that this improvement in insulin resistance may result from the mobilisation of muscle and liver lipids into breast milk under the control of PRL,⁴ an action that may be particularly beneficial in women who are insulin resistant at baseline (women with recent GDM are known to have increased intramyocellular lipid content at 4–6 months postdelivery compared with controls).⁴⁷



There is thus a clear need for a systematic review of the literature in this field—both lactogenic hormones clearly have central roles in the regulation of maternal metabolism (both during pregnancy and postpartum, and for women with normal and abnormal pregnancies). However, to date, the evidence has not, to our knowledge, been effectively synthesised.

Some limitations of the review process should be noted. First, owing to the intentionally broad scope of the review, included studies will be heterogeneous in their design, methodology and research questions. In the analysis phase, hPL and PRL will thus be considered separately and studies will be grouped according to similar outcomes, but it is possible that marked heterogeneity will preclude meaningful conclusions and/or statistical meta-analysis. Second, some of the basic clinical work on hPL and PRL levels in normal and diabetic pregnancies is now very dated, extending back to the 1970s and 1980s. While robust and worthy of inclusion, differences in experimental design and (in particular) the classification and treatment of maternal diabetes will present challenges when comparing such studies to modern cohorts. As such, clear requirements for the adequacy of maternal diabetes definitions have been stipulated in our inclusion and exclusion criteria. Where possible, we will endeavour to conduct a subgroup analysis by publication year range or otherwise perform a narrative comparison between older and newer studies. We will also extract and tabulate variables such as the exact GDM diagnostic criteria used and the assay methodology employed in each case, as such details are likely to vary according to era of publication (in particular, many older studies involve the routine use of radioimmunoassay, now largely superseded by modern enzyme-linked immunoassay techniques). Finally, as previously described, the relationship between lactogenic hormones and maternal metabolism is almost certainly bidirectional, whereby some studies examine the effects of lactogenic hormones (exposure) on metabolic conditions (outcome), while in others, exposure and outcome are reversed. The review is designed to capture both, but—particularly in the postpartum context—the bidirectional nature of the relationship can bias observational studies. While this cannot be directly addressed in our review methodology, it will be acknowledged in the synthesis and interpretation of the findings.

CONCLUSION

In summary, this systematic review will rigorously and systematically collate and synthesise current evidence linking the key lactogenic hormones hPL and PRL to maternal metabolic health in pregnancy and postpartum. Both hormones have key roles in the maintenance of glucose homeostasis during pregnancy, including direct actions on the beta cells of the maternal endocrine pancreas. However, the exact roles of these hormones—particularly in metabolically abnormal pregnancies—remain unclear, and evidence is conflicting. Further,

hPL may have untapped potential clinical application in the antenatal prediction of macrosomia; whilst lactation, under the hormonal control of PRL, may regulate glucose and lipid metabolism and help to guard postpartum women against persistent dysglycaemia. Through this review process, the available scientific evidence will be synthesised to clarify these relationships and to inform future research in the field of maternal metabolic and endocrine health.

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