The Role of Placental Hormones in Mediating Maternal Adaptations to Support Pregnancy and Lactation

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During pregnancy, the mother must adapt her body systems to support nutrient and oxygen supply for growth of the baby in utero and during the subsequent lactation. These include changes in the cardiovascular, pulmonary, immune and metabolic systems of the mother. Failure to appropriately adjust maternal physiology to the pregnant state may result in pregnancy complications, including gestational diabetes and abnormal birth weight, which can further lead to a range of medically significant complications for the mother and baby. The placenta, which forms the functional interface separating the maternal and fetal circulations, is important for mediating adaptations in maternal physiology. It secretes a plethora of hormones into the maternal circulation which modulate her physiology and transfers the oxygen and nutrients available to the fetus for growth. Among these placental hormones, the prolactin-growth hormone family, steroids and neuropeptides play critical roles in driving maternal physiological adaptations during pregnancy. This review examines the changes that occur in maternal physiology in response to pregnancy and the significance of placental hormone production in mediating such changes.

Keywords: pregnancy, placenta, hormones, maternal adaptations, metabolism, fetal growth, endocrine, cardiovascular

INTRODUCTION

Pregnancy is a dynamic and precisely coordinated process involving systemic and local changes in the mother that support the supply of nutrients and oxygen to the baby for growth in utero and in the subsequent lactation. Inappropriate adaptation of maternal physiology may lead to complications of pregnancy, such as gestational diabetes, preeclampsia, fetal growth restriction, fetal overgrowth and pre-term birth; which can have immediate consequences for fetal and maternal health. Furthermore, these pregnancy complications can also lead to long-term health consequences for the mother and infant. Altered fetal growth is associated with an increased risk of the offspring developing obesity, type-2 diabetes and cardiovascular disease in adulthood (Hales and Barker, 2001; Barker, 2004; Fowden et al., 2006). Moreover, women who develop gestational diabetes or preeclampsia are more likely to develop type-2 diabetes or cardiovascular disease in later life (Kim et al., 2002; Petry et al., 2007). Maternal adaptations to pregnancy are largely mediated by the placenta; the functional interface between the mother and fetus that secretes hormones and growth factors into the mother with physiological effects. This review aims to provide an overview of the physiological changes that occur in the mother in response to pregnancy and to discuss the role of key placental hormones in mediating such adaptations. In particular, this review focuses
on the importance of the prolactin-growth hormone family (e.g., prolactin, placental lactogen and growth hormone), steroids (estrogens and progesterone) and neuropeptides (serotonin, melatonin and oxytocin) in adaptations of maternal physiology during pregnancy. Where possible, this review draws upon findings in women and animal models, including rodents and sheep. However, differences exist between species in the specific hormones produced by the placenta, the access of these hormones to the maternal circulation, and the relative proportion of conceptus mass to maternal size (hence constraint on the mother to provide resources for fetal growth; Haig, 2008; Carter, 2012; Fowden and Moore, 2012). Where such differences between species exist, these have been highlighted and discussed as necessary in the relevant sections. Nevertheless, although some effects described may not be applicable to all species, the different animal models of pregnancy still provide novel insight into the fundamental mechanisms of maternal adaptation during gestation.

ADAPTATIONS IN MATERNAL PHYSIOLOGY DURING PREGNANCY AND LACTATION

Most tissues and organs in the mother respond to the pregnant state. Changes include alterations in size, morphology, function and responsiveness of tissues and organs to hormonal and metabolic cues. These changes arise in the cardiovascular, pulmonary, immune, and metabolic systems of the mother (Figure 1). Some of these changes are seen from very early in pregnancy, prior to the establishment of a fully functional placenta, highlighting that non-placental factors may also be important (Paller et al., 1989; Drynda et al., 2015). The specific nature of changes in maternal physiology depends on the stage of the pregnancy and appears to track with alterations in the metabolic requirements of the mother versus the developing fetus.

Alterations in the maternal cardiovascular system begin very early in gestation (Chapman et al., 1998) and ultimately lead to systemic vasodilation and increased blood perfusion of maternal organs, including the gravid uterus. Systemic vascular resistance is reduced by 25–30% and accompanied by a 40% increase in cardiac output during human pregnancy; while in mice, blood pressure decreases by 15% and cardiac output is increased by 48% (Bader et al., 1955; Kulandavelu et al., 2006; Soma-Pillay et al., 2016). Renal blood flow and glomerular filtration rates are also increased (Davison and Dunlop, 1980; Soma-Pillay et al., 2016). The renin-angiotensin-aldosterone system (RAAS) which is a major determinant for sodium balance during gestation, is progressively upregulated toward term with associated plasma volume expansion (Elsheikh et al., 2001; Tkachenko et al., 2014). This rise in blood volume, which is required to cope with the oxygen requirements of the maternal organs and the conceptus growth, plateaus by the late gestation, resulting in an increase in total blood volume by approximately 30% at the end of pregnancy (Chang and Streitman, 2012). There is also an increase in the numbers of red blood cells in the mother during pregnancy, due to proliferation of erythroid progenitors in the spleen (Bustamante et al., 2008). Pulmonary function is also altered and encompasses changes in ventilation rates and blood gases. For instance, lung tidal volume and minute ventilation increases by 30–50% (Hegewald and Crapo, 2011). As a result of increased oxygen consumption during hyperventilation, there is greater carbon dioxide production, which leads to chronic respiratory alkalosis that is compensated by an increased renal excretion of bicarbonate (Weinberger et al., 1980). Overall, these adaptations ensure the well-being of the mother, while also providing an adequate blood flow to the placenta for fetal nutrition, oxygenation and maturation.

There are also alterations in maternal metabolic and endocrine state during gestation. In early pregnancy, the maternal pancreatic β-cell mass expands due to both hyperplasia and hypertrophy of islets, which for example in rats, results in a >50% increase (Ackermann and Gannon, 2007; Rieck and Kaestner, 2010). The threshold for glucose-stimulated insulin production is also lowered and maternal circulating insulin concentration is greater compared to the non-pregnant state. In early pregnancy, when fetal demands are relatively low, whole body maternal insulin sensitivity is unchanged or increased and there is accumulation of energy reserves in the mother. In particular, early pregnancy is associated with adipocyte hypertrophy, increased lipogenesis and lipid storage and relates to improved insulin sensitivity of white adipose tissue in the mother (Hadden and McLaughlin, 2009; Mcilvride et al., 2017). Interestingly, in pregnant mice, brown adipose stores of the dam also switch to a white adipose tissue-like phenotype in early gestation (Mcilvride et al., 2017). Additionally, glycogen accumulates in the liver, which also increases in size from early gestation (Bustamante et al., 2010). In contrast, late pregnancy is associated with diminished maternal tissue insulin sensitivity and a concomitant increase in lipolysis and hepatic gluconeogenesis (Freemark et al., 2002; Lain and Catalan, 2007; Musial et al., 2016). Despite the pregnancy-related rise in leptin and insulin concentrations, maternal appetite increases in pregnancy (Villar et al., 1992; Douglas et al., 2007; Hadden and McLaughlin, 2009; Diaz et al., 2014). Together, these metabolic and endocrine alterations increase lipid and glucose availability for the rapidly growing fetus in late gestation. Intriguingly in rodents, whole body responsiveness to insulin starts to improve near term, which may be important for conserving nutrients for maternal use, as parturition and lactation approach (Musial et al., 2016). There are also notable changes in maternal bone metabolism during pregnancy. In particular, intestinal calcium absorption is enhanced in the mother during pregnancy via upregulation of 1,25-dihydroxyvitamin D levels, improved renal conservation and increased calcium mobilization from the maternal skeleton (Hellmeyer et al., 2006). These processes support the supply of calcium for the formation, growth and mineralization of the fetal skeleton (King, 2000; Kalkwarf and Specker, 2002).

The immune system of the mother during pregnancy is tightly regulated to prevent an unwanted immune response against the maternal antigens present in the developing conceptus (Racicott et al., 2014; Groen et al., 2015; Zöllner et al., 2017). As gestation progresses, there is suppression of the pro-inflammatory Th1
FIGURE 1 | Schematic diagram highlighting the main physiological modifications in the maternal physiology in response to pregnancy. Many of the changes described in the figure for women during pregnancy also occur in other species, including mice. Respiratory system (Macrae and Palavradji, 1967; Weinberger et al., 1980; Contreras et al., 1991; Hegewald and Crapo, 2011; Frise et al., 2013; Lomauro and Aliverti, 2015; Soma-Pillay et al., 2016); cardiovascular system (Adamova et al., 2009; Li et al., 2012; Pieper, 2015; Soma-Pillay et al., 2016); hematological system (Shakhmatova et al., 2000; Chang and Streitman, 2012; Rodger et al., 2015; Soma-Pillay et al., 2016); spleen (Maroni and De Sousa, 1973; Sasaki et al., 1981; Norton et al., 2009); renal system (Davison and Dunlop, 1980; Atherton et al., 1982; Elsheikh et al., 2001; Cheung and Lafayette, 2013; Lumbers and Pringle, 2014; Pieper, 2015; Soma-Pillay et al., 2016); pancreas (Ziegler et al., 1985; Ernst et al., 2011; Chara-Imaizumi et al., 2013; Baeyens et al., 2016); adipose tissue (Catalano et al., 2006; Hauguel-De Mouzon et al., 2006; Valsamakis et al., 2010; Musial et al., 2016); skeletal muscle (Alperin et al., 2015, 2016; Musial et al., 2016); bone (Shahtaheri et al., 1999; Ulrich et al., 2003; Hellmeyer et al., 2006; Salles, 2016); digestive tract (Everson, 1992; Fudge and Kovacs, 2010; Pieper, 2015); liver (Munnell and Taylor, 1947; Van Bodegraven et al., 1998; Ando et al., 2012; Bacci, 2013; pancreas (Ziegler et al., 1985); neuroendocrine (Shahtaheri et al., 1999; Ulrich et al., 2003); reproductive (Clarke and Kendall, 1994; Kendall and Clarke, 2000); mammary (Elling and Powell, 1997; Neville et al., 2002; Sternlicht, 2006; Pang and Hartmann, 2007); immune system (Clarke and Kendall, 1994; Kendall and Clarke, 2000; Veenstra Van Nieuwenhoven et al., 2002; Norton et al., 2009; Mor and Cardenas, 2010; Saito et al., 2010; Racicot et al., 2014; Groen et al., 2015; Zöllner et al., 2017; Edey et al., 2018); nervous system (Shingo et al., 2002; Gregg, 2009; Roos et al., 2011; Hoekzema et al., 2017).

Type of immunity and a shift toward a more anti-inflammatory, Th2 immune state in the mother (Saito et al., 2010), which supports fetal growth and maternal well-being (Mor and Cardenas, 2010). In particular, the total abundance of circulating leukocytes, monocytes, granulocytes and T lymphocytes increase in the mother in response to pregnancy (Groen et al., 2015). However, expression of major histocompatibility complex class II by circulating monocytes is reduced in the mother, which would decrease antigen presentation and stimulation of T cells during pregnancy and prevent the maternal immune system from mounting an unwanted response against fetal antigens (Groen et al., 2015). The total number of circulating natural killer cells and secretion of pro-inflammatory cytokines (IFN-gamma) is also reduced in the pregnant state (Veenstra Van Nieuwenhoven et al., 2002). However, close to parturition, the maternal immune system shifts to a pro-inflammatory state, particularly locally within the uterus, to promote labor (Mor and Cardenas, 2010; Edey et al., 2018). There are also specific changes in the numbers of different leukocyte populations in the maternal thymus and spleen during pregnancy (Clarke and Kendall, 1994; Kendall and Clarke, 2000; Norton et al., 2009). The spleen, which also has functions in hematopoiesis, enlarges due to an expansion of the splenic red pulp during pregnancy (Maroni and De Sousa, 1973; Norton et al., 2009). Neurological changes must also occur during pregnancy to increase maternal nursing behavior and enable the mother to properly care for her newborn infant (Bridges et al., 1997; Bridges, 2015; Kim, 2016; Kim et al., 2016). For instance, there is increased activation of the prefrontal cortex and neurogenesis of the forebrain olfactory bulb (Shingo et al., 2003), which are important in regulating...
behavior. In addition, formation of lobulo-alveolar units in the mammary gland commences during pregnancy, in preparation for lactational support of the neonate.

**PLACENTAL HORMONES THAT MEDIATE MATERNAL ADAPTATIONS TO PREGNANCY, PARTURITION AND LACTATION**

The placenta is a highly active endocrine organ during gestation; secreting a variety of hormones with physiological effects in the mother. Placental hormones include members of the prolactin and growth hormone family, steroid hormones and neuroactive hormones. The function of these hormones in driving physiological changes during pregnancy has been assessed in two main ways. First, the expression and activity of the hormones have been manipulated in vivo by either exogenously administering or genetically manipulating the expression of hormones and hormone receptors to study the physiological consequences for the animal. Secondly, hormones have been manipulated similarly in cultured cells and tissue explants to inform on the cellular and molecular mechanisms by which they modulate function. The effects of hormones in non-pregnant animals have been included as they provide information on the baseline of physiological changes that occur in the absence of hormone expression/activity, which is especially important in the case of some placental-derived hormones, where analyses in the pregnant state have not been conducted.

**Prolactin (PRL)-Growth Hormone (GH) Family**

The PRL-GH family is one of the main families of hormones secreted by the placenta during gestation. Members of this family consist of prolactin (PRL) (Handwerger et al., 1992), placental lactogens (PLs) (Wiemer et al., 2003), PRL-like hormones (Wiemer et al., 2003), proliferins (PLF) (Lee et al., 1988), proliferin-related proteins (PRP) (Jackson et al., 1994) and growth hormone (GH). Between mammalian species, there are differences in the number and type of family members expressed by the placenta [reviewed elsewhere (Linzer and Fisher, 1999; Soares, 2004; Soares et al., 2007)]. For instance, in the mouse and rat, the placenta expresses all these members except for PRL and GH whereas the human placenta only expresses GH and PL genes. In mice and rats, expression of the individual PRL-GH family members vary spatially and temporally in the placenta (Dai et al., 2002; Simmons et al., 2008; Urbanek et al., 2015). The anterior pituitary also produces PRL and GH; however this is diminished by mid-pregnancy, when placental hormone production predominates (Bridges, 2015). In several species including rodents and humans, PRL is additionally produced by the decidua during pregnancy. The family members share structural similarity to one another and may bind, with varying affinity to PRL and GH receptors (PRLR and GHR, respectively), which are widely expressed by tissues in the body (Haig, 2008; Trott et al., 2008; Ben-Jonathan and Hugo, 2015). As the PRL-GH members also exert similar functions, these have been presented in a grouped fashion in the text and tables (Tables 1, 2). However, where possible, the roles of individual family members of the PRL-GH in physiological changes have been described.

Studies performed both in vivo and in vitro support a role for the PRL-GH family in mediating maternal metabolic adaptations to pregnancy (Tables 1, 2). PRL, PRL-like proteins and PL, principally via the PRL receptor, induce β-cell mass expansion by both increasing β-cell proliferation and reducing apoptosis of islets in vivo and in vitro (Table 2; PRL/PL/GH; Brejle et al., 1993; Huang et al., 2009). PRL and PL also increase insulin secretion during pregnancy, particularly in response to glucose, by enhancing the expression of glucose sensors (glucokinase, hexokinase and glucose transporter-2) and activating the serotonin biosynthesis pathway in pancreatic islets (Table 2; PRL/PL/GH; Nielsen, 1982; Brejle et al., 1989, 1993; Weinhaus et al., 1996; Sorensen and Brejle, 1997; Arumugam et al., 2014). Moreover, PL protects β-cells against streptozotacin-induced cell death in mice (Fujinaka et al., 2004). GH may also be important for modulating pancreatic insulin production (Billestrup and Nielsen, 1991; Brejle et al., 1993). However, GH from the placenta appears to be primarily important in the acquisition of insulin resistance and shifting metabolic fuel use from glucose to lipid in the mother during pregnancy (Table 1; PRL/PL/GH; Horber and Haymond, 1990; Goodman et al., 1991; Galosy and Talamanes, 1995; Barbour et al., 2002; Dominici et al., 2005; Boparai et al., 2010; Liao et al., 2016b; Sairenji et al., 2017). Placental GH reduces insulin receptor expression and signaling, as well as, diminishes the abundance of the insulin-sensitive glucose-transporter, GLUT-4, in the skeletal muscle (Barbour et al., 2004; Kirwan et al., 2004). Insulin receptor abundance and signaling in the liver is also reduced in response to increased GH abundance in transgenic mice (Dominici et al., 1999). In white adipose tissue, GH also disrupts the insulin signaling pathway, and inhibits insulin action on glucose uptake and lipid accumulation (Del Rincon et al., 2007). In part, the effects of GH may be mediated through insulin-like growth factor-1 (IGF1), which is primarily secreted from the liver in response to GH and exerts lipolytic effects during pregnancy (Randle, 1998; Sferruzzi-Perri et al., 2006; Del Rincon et al., 2007). Insulin-like growth factor-2 (IGF2), which is not directly regulated by GH, but is secreted by the placenta is also important for modulating the sensitivity of β cells to glucose (Tables 1, 2; IGF2; Casellas et al., 2015; Modi et al., 2015) and maternal insulin and glucose concentrations during pregnancy (Petry et al., 2010; Sferruzzi-Perri et al., 2011). Polymorphisms/mutations in the PRL-GH family of genes and receptors have been reported in human pregnancies associated with gestational diabetes and fetal growth restriction (Rygaard et al., 1998; Le et al., 2013). Moreover, loss of PRLR signaling in β-cells causes gestational diabetes mellitus (GDM) in mice (Banerjee et al., 2016). Taken together, the production of PRL-GH family of hormones by the placenta appears to be important in regulating both insulin production and sensitivity of the mother in response to pregnancy.

The PRL-GH family is also implicated in the regulation of appetite and body weight. For instance, exogenous PRL increases food intake through inhibiting the action of leptin
| Hormone                                                                 | Expression level | In vivo effects                                                                                                                                                                                                 | References                                                                 |
|------------------------------------------------------------------------|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Prolactin, Placental lactogen, Prl-like hormones, Growth hormone        | Low              | Prl knockout Prl<sup>−/−</sup> (mouse): ↓ fertility; blood prolactin; mammary gland development (ductal branching, alveolar budding); oocyte maturation ↔ weight; body composition; blood lipids, adiponectin, leptin, glucose tolerance | Horseman et al., 1997; Gallego et al., 2001; Lapensee et al., 2006 |
|                                                                        |                  | Prl receptor knockout Prlr<sup>−/−</sup> (mouse): ↓ fertility; weight; abdominal fat content; glucose tolerance; pancreatic β cell mass; GSIS; blood leptin, progesterone ↑ blood glucose and prolactin | Freemark et al., 2001, 2002; Rawn et al., 2015 |
|                                                                        |                  | Heterozygous Prl receptor knockout Prlr<sup>+/−</sup> (mouse): ↔ body weight; glucose and insulin tolerance; GSIS; blood insulin and glucose | Binart et al., 2000 |
|                                                                        |                  | GH receptor knockout GHR/BP<sup>−/−</sup> (human/mouse): ↓ body size (weight and height); postnatal growth rate; blood glucose and IGF1; sexual maturation ↑ proportional dwarfism (human), abdominal adiposity; blood GH | Zhou et al., 1997 |
|                                                                        |                  | Injection with GHRH antisera (rat): ↓ growth rate; blood growth hormone | Vaccarello et al., 1993 |
|                                                                        |                  | GHRH knockout GHRH<sup>−/−</sup> (mouse): ↓ weight, blood and liver IGF1, pituitary growth hormone; pituitary size; adipose tissue expression of adiponectin and visfatin; hypothalamic expression of CRH, norepinephrine; anxiety and depression related behavior ↑ adiposity; food intake, blood adiponectin, ghrelin, hypothalamic expression of AgRP, NPY; exploratory activity ↔ blood leptin | Farmer et al., 1991, 1992 |
| Pregnancy and lactation                                                | High             | Heterozygous PRL receptor knockout Prlr<sup>+/−</sup> (mouse): ↓ pup-induced maternal behavior; post-partum nurturing behavior (pup retrieval); glucose tolerance; blood insulin; GSIS, pancreatic β cell proliferation and mass; olfactory bulb interneuron proliferation; mammary gland differentiation; milk protein expression (β-casein, whey acidic protein) ↑ blood glucose, serum metabolites ↔ body weight; insulin tolerance; blood pressure; fertility; pup weight | Horseman et al., 1997; Lucas et al., 1998; Huang et al., 2009; Rawn et al., 2015 |
|                                                                        |                  | Bromocriptine inhibition of Prl secretion (mouse): ↓ milk production (↓pSTAT5) ↑ Cldn3 and Cldn4 | Weinhaus et al., 1996 |
|                                                                        |                  | GH knockout GHR/BP<sup>−/−</sup> (mouse): ↓ lactation (mouse) | Zhou et al., 1997 |
|                                                                        |                  | PRL overexpression (mouse): ↑ IGF1 | Wennbo et al., 1997 |
|                                                                        |                  | Exogenous PRL (rats): ↓ GSIS ↑ food intake (↓ability of leptin to suppress food intake), fat deposition, blood insulin, β cell coupling | Sorenson et al., 1987; Ladyman et al., 2010 |
|                                                                        |                  | Exogenous GH (human): ↓ insulin sensitivity ↑ protein synthesis; lipolytic effect of catecholamines ↔ proteolysis | Horber and Haymond, 1990 |
|                                                                        |                  | Exogenous PRL (mouse): ↑ mammary gland lymphocytes | Dill and Walker, 2017 |
|                                                                        |                  | PLP-E overexpression (mouse): ↑ thrombocytopenia recovery; neutropenia recovery ↔ platelet, erythrocyte, total white blood cell levels | Zhou et al., 2005 |
|                                                                        |                  | Pancreatic islet-specific PL-I overexpression (mouse): ↓ blood glucose ↑ pancreatic β cell mass (islet proliferation and size) and insulin content; blood insulin ↔ GSIS | Vasavada et al., 2000 |
|                                                                        |                  | Exogenous PRL (ovariectomized rat): ↑ induction of maternal behavior (nurturing, retrieval, nursing and crouching) | Sairenji et al., 2017 |

(Continued)
### TABLE 1 | Continued

| Hormone Expression level | In vivo effects | References |
|--------------------------|----------------|------------|
| Low                      | Pancreatic β-cell specific Igf2 inactivation (mouse): | Modi et al., 2015 |
|                          | ↓ GSIS (aged female) | | |
|                          | ↑ insulin sensitivity | | |
|                          | ↔ glucose tolerance | | |
| Non-pregnant             | Pancreatic β-cell specific Igf2 knockout with high-fat diet (mouse): | Modi et al., 2015 |
|                          | ↓ GSIS; pancreatic β-cell mass (only in females) | | |
| Pregnancy and lactation | Placental-specific Igf2 knockout Igf2P0 (mouse): | Mikaelsson et al., 2013 |
|                          | ↓ blood alpha-amino nitrogen; fetal and placental weight | | |
|                          | ↑ body weight; blood insulin, cortisol, leptin | | |
|                          | ↔ blood glucose | | |
| High                     | No known physiological changes | Sferuzzi-Perri et al., 2007 |
| Non-pregnant             | Exogenous (guinea pig): | | |
| Pregnancy and lactation | ↑ visceral tissue amino acid uptake, fetal weight; placental structural and functional capacity | | |
|                          | ↔ lean mass; adiposity; blood glucose, alpha-amino nitrogen, FFA, triglycerides and cholesterol | | |

AgRP, Agouti-related peptide; CRH, Corticotropin-releasing hormone; FFA, Free fatty acids; GSIS, Glucose-stimulated insulin secretion; NEFA, Non-esterified fatty acids; NPY, Neuropeptide Y.
TABLE 2 | Effects of the prolactin-growth hormone family in vitro.

| Hormones | Expression level | In vitro effects | References |
|----------|-----------------|-----------------|------------|
| Prolactin, Placental lactogen, Prl-like hormones, Growth hormone | Low | siRNA knockdown of PRL receptor (rat pancreatic β-cells): ↓ DNA synthesis (β-cyclin B2 and D2, IRS-2, Tph1) ↑ apoptosis (anti-apoptotic proteins PTTG1, p21 and BCL6) → β-cell replication or survival related genes (p18, p19, Cyclin D3, CDK2, CDK4, CDK6, IGFF2, BAX, or TLR4) | Arumugam et al., 2014 |
| | | | |
| | High | siRNA knockdown of GH (hen granulosa cells primary culture): ↓ proliferation | Ahumada-Solórzano et al., 2016 |
| | | Exogenous PRL, PLP, GH (human, rat and mouse islets): ↓ apoptosis (anti-apoptotic proteins; p21 and BCL6) ↑ β-cell mass; GSIS; DNA synthesis, β-cell replication or survival related genes (cyclins A2, B1, B2 and D2, IRS-2, Tph1, FoxM1, BCLxL and PTTG1); insulin secretion and glucose oxidation (only PRL↑glucokinase, hexokinase and GLUT2 expression); serotonin biosynthesis (Tph1, Tph2, Jak2, STAT5) → β-cell replication or survival related genes (p18, p19, Cyclin D3, CDK2, CDK4, CDK6, IGFF2, BAX, or TLR4). | Ahumada-Solórzano et al., 2016; Nielsen, 1982; Breile et al., 1989, 1993; Weinhaus et al., 1996; Sorenson and Breile, 1997; Arumugam et al., 2014 |
| | | Exogenous PRL (mouse alveolar mammary epithelial cells): ↓ milk protein expression (β-casein) ↓ leaky tight junctions (α-T transmembrane proteins; Cldn3, Cldn4) | Kobayashi et al., 2016 |
| | | Exogenous PRL (human fetal membranes-LPS): ↓ TNF-α, IL-1β ↑ IL-6, IL-10 | Flores-Espinosa et al., 2017 |
| | | Exogenous PRL (rat uterine stromal cells): ↓ decidualization (PGE2, PGF2α); cytolytic activity → cell viability; proliferation | Prigent-Tessier et al., 1996 |
| | | Exogenous PL (mouse ovarian cells): ↑ progesterone secretion | Galosy and Talamantes, 1995 |
| | | Exogenous PRL (mouse uterine NK cells): ↓ cytolytic activity → cell viability; proliferation | Müller et al., 1999 |
| | | PLPE transfection (human and murine erythroid cells): ↑ proliferation; differentiation (hemoglobin production) | Bittorf et al., 2000 |
| | | Exogenous PLF (bovine capillary endothelial cells): ↑ angiogenesis- endothelial cell migration (through MAPK activation and IGF-II/mannose 6-phosphate receptor interaction) | Groskopf et al., 1997 |
| | | PLP-E/F exogenous (mouse bone marrow): ↑ megakaryocyte differentiation, progenitor growth (colony formation) | Zhou et al., 2002 |
| | | Exogenous PLF (mouse neuroblastoma cells): ↑ microvilli formation; proliferation | Wang et al., 2006 |
| | | Exogenous GH (hen granulosa cells primary culture): ↑ proliferation; IGF1 secretion | Ahumada-Solórzano et al., 2016 |
| | | Exogenous GHRH (sheep and rat pituitary cells): ↑ GH secretion; IGF1 secretion | Blanchard et al., 1991 |
| | | Exogenous GH (rat ovarian granulosa cells): ↓ LH-stimulated progesterone production ↑ progesterone production; cAMP accumulation | Apa et al., 1995 |
| Insulin-like growth factor 2 (Igf2) | Low | Treatment with Igf2 mutant + prolactin (bovine capillary endothelial cells): ↓ motility; MAPK activity | Groskopf et al., 1997 |
| | | IGF2R siRNA knockdown (BeWo and human placental villous explants): ↓ apoptosis ↑ IGF2-stimulated mitosis | Harris et al., 2011 |
| | | IGF2R knockdown (human hemangioma stem cells): ↓ cell differentiation; leptin induction → proliferation | Kleinman et al., 2013 |
| | | Exogenous (human endothelial cells): ↑ migration; angiogenesis | Lee et al., 2000 |
| | | Exogenous (chick chorioallantoic membrane): ↑ angiogenic activity; migration | Bae et al., 1998 |

(Continued)
TABLE 2 | Continued

| Hormones | Expression level | In vitro effects | References |
|----------|-----------------|-----------------|------------|
| Exogenous (human keratinocyte cell line, human liver carcinoma cell line): | | | Bae et al., 1998 |
| ↑ VEGF | | | |
| Adenoviral-mediated overexpression (mouse pancreatic β cells): | ↓ β cell differentiation; insulin function (↑ glucose intolerance and ↓ insulin release) | | Casellas et al., 2015 |
| Exogenous (bovine granulosa cells): | ↑ proliferation; estradiol and progesterone production; aromatase (CYP19A1) mRNA | | Spicer and Aad, 2007 |
| Exogenous (mouse primary hepatocytes): | ↑ proliferation | | Bae et al., 1998 |

BAX, BCL2 associated X; CDK, Cyclin dependent kinases; GSIS, Glucose-stimulated insulin secretion; IRS2, Insulin receptor substrate 2; LPS, Lipopolysaccharide; MAPK, Mitogen-activated protein kinase; PGE, Prostaglandin E synthase; PGF2α, Prostaglandin F2α; PTTG1, Pituitary tumor-transforming 1; siRNA, short interfering RNA; TLR4, Tolllike receptor; VEGF, Vascular endothelial growth factor.

in non-pregnant rats (Table 1; PRL/PL/GH; Sorenson et al., 1987; Farmer et al., 1991, 1992; Ladyman et al., 2010). In contrast, GH appears to decrease food intake in rodents through reducing ghrelin production and hypothalamic expression of appetite-stimulating neuropeptides, AgRP and NPY (Table 1; PRL/PL/GH; Farmer et al., 1991, 1992). In non-pregnant animals, GH is important for controlling body weight and composition (such as adiposity; Farmer et al., 1991, 1992; Zhou et al., 1997). However, in pregnancy, exogenous GH or GH releasing hormone (GHRH) does not appear to affect maternal weight gain in mice, although increases it in pigs (Table 1; PRL/PL/GH; Brown et al., 2012). The effect of PRL on weight gain and body adiposity is even less clear; with both no effect and an increase reported for non-pregnant and pregnant rodents.

The PRL-GH family also plays an important role in lactation and maternal behavior. In mice, a deficiency in PRLR or inhibition of PRL secretion in vivo compromises mammary gland development, differentiation and milk production; the latter of which is associated with loss of STAT5 signaling and fewer leaky tight junctions (Table 1; PRL/PL/GH; Weinhaus et al., 1996; Zhou et al., 1997). In contrast, exogenous GHRH in sheep and cows increases mammary gland milk production (Hart et al., 1985; Enright et al., 1988). There is also evidence that PRL induces maternal behaviors, such as nurturing, nursing and pup retrieval in non-pregnant rodents (Table 1; PRL/PL/GH; Bridges and Millard, 1988). Taken together, members of the PRL-GH family appear to promote changes in maternal glucose metabolism, behavior and mammary gland function which are expected to be important for supporting the growth of offspring during pregnancy and lactation.

Steroid Hormones

The placenta is a primary source of steroid hormones during pregnancy. Placental steroid hormones include estrogens and progesterone (Costa, 2016; Edey et al., 2018). In species like rodents, the corpus luteum continues to contribute to the circulating pool of steroid hormones during pregnancy, whereas in other species such as humans and ruminants, the placenta serves as the main source (Costa, 2016). Physiological effects of progesterone are mediated predominantly by nuclear receptors (PR-A, PR-B) although membrane bound-type receptors (mPR) enable non-genomic actions. Steroid hormones are implicated in pregnancy complications such as gestational diabetes and preeclampsia. High progesterone and estrogen concentrations have been reported for women with gestational diabetes (Branisteau and Mathieu, 2003; Qi et al., 2017). Moreover, placental estrogen and progesterone levels are reduced in preeclamptic patients compared with healthy pregnant women (Açıkgöz et al., 2013).

Studies performed in vivo, suggest placental steroid hormones may be important in driving the changes in insulin sensitivity and glucose metabolism of the mother during pregnancy (Table 3). Hyperinsulinemic-euglycemic clamp studies in women and rodents highlight a role for progesterone in reducing maternal insulin sensitivity during pregnancy. Progesterone administration decreases the ability of insulin to inhibit glucose production by the liver, and diminishes insulin-stimulated glucose uptake by skeletal muscle and to a lesser extent in the adipose tissue of non-pregnant animals (Table 3; Progesterone; Leturque et al., 1984; Ryan et al., 1985; Kim, 2009). In contrast, exogenous estrogen increases whole body insulin sensitivity in non-pregnant state (Table 3; Estrogen; Ahmed-Sorour and Bailey, 1980). Similarly, genetic deficiency of ERα or aromatase (Cyp19), which is involved in estrogen production, reduces hepatic and whole body insulin sensitivity and impairs glucose tolerance in non-pregnant mice (Takeda et al., 2003; Bryzgalova et al., 2006). Loss of the estrogen receptor or estrogen production is also associated with increased body weight, adiposity and hepatic lipogenesis (Table 3; Estrogen; Takeda et al., 2003; Bryzgalova et al., 2006). Progesterone and estrogen also exert opposite effects on food intake in vivo (Table 3). In particular, estrogen depresses food intake in part via induction of leptin production by adipose tissue, whereas progesterone increases food intake by enhancing NPY and reducing CART expression by the hypothalamus (Table 3; Fungfuang et al., 2013; Stemanska and Sucajtys-Szulc, 2014). Estrogen and progesterone however seem to have similar effects on the pancreas; they both appear to induce islet hypertrophy and/or increase pancreatic insulin levels and glucose-stimulated secretion in vivo (Table 3; Costrini and Kalkhoff, 1971; Bailey and Ahmed-Sorour, 1980). Nevertheless, there is some evidence that progesterone may inhibit the PRL-induced proliferation...
### TABLE 3 | In vivo effects of steroid hormones in vivo.

| Hormones | Expression level | In vivo effects | References |
|----------|------------------|----------------|------------|
| **Estrogen** | **Low** Non-pregnant | **Estrogen receptor knockout ER<sup>−/−</sup> (ERKO, BERKO or viral-mediated ER suppression mouse):**  
↓ glucose tolerance; whole body and hepatic insulin sensitivity; insulin-stimulated glucose uptake by skeletal muscle; blood adiponectin, testosterone; sexual behavior  
↑ body weight; abnormalities in vascular smooth muscle cells (ion channel function); systolic and diastolic blood pressure; arterial pressure; heart failure; hepatic lipid biosynthesis; adipose tissue mass; blood glucose, insulin, leptin  
**Aromatase knockout CYP19–/– (mouse):**  
↓ glucose and insulin tolerance; glucose oxidation; lean body mass  
↑ body weight; adipocyte volume; blood glucose and testosterone | Zhu et al., 2002; Bryzgalova et al., 2006; Ribas et al., 2011 |
| **High** Non-pregnant | **Exogenous estrogen in T1DM, T2DM model (mouse):**  
↓ oxidative stress (β cells); apoptosis; amyloid polypeptide toxicity; lipotoxicity  
**Exogenous (ovariectomized rat or mouse):**  
↓ hepatic glucose production; blood glucose; TNF-α macrophage synthesis; gluconeogenesis; food intake (via ↑ leptin)  
↑ insulin sensitivity; glycogen storage; VEGF, PGF (angiogenesis); eNOS production; arterial vasodilatory responses  
↔ body weight | Tiano and Mauvais-Jarvis, 2012, Ahmed-Sorour and Bailey, 1980, 1981; Zhang et al., 1999; Fungfuang et al., 2013 |
| **Pregnancy and lactation** | **Exogenous (ovariectomized mouse):**  
↓ litter size; maternal nurturing behavior (time spent nursing pups)  
↔ maternal aggression toward a male intruder | Ribeiro et al., 2012 |
| **Exogenous antagonist (guinea pig):**  
↓ NOS activity in the cerebellum | Weiner et al., 1994 |
| **Progesterone** | **Low** Non-pregnant | **Progesterone receptor knockout PR<sup>−/−</sup> (mouse):**  
↓ reproductive tissue development; mammary gland development; sexual behavior  
↑ uterine mass, inflammation | Lydon et al., 1995 |
| **High** Non-pregnant | **Exogenous antagonist (rat):**  
↓ oxytocin production; oxytocin receptor synthesis  
**Exogenous antagonist (mouse):**  
↑ premature birth; blood estrogen; oxytocin receptor synthesis  
↑ preterm parturition; myometrial monocytes near parturition (Cx-43) | Fang et al., 1997; Edey et al., 2018 |
| **Pregnancy and lactation** | **Exogenous (mice):**  
↑ mammary gland lateral branching and number of stem cells  
**Exogenous (ovariectomized rat):**  
↓ insulin-dependent suppression of endogenous hepatic glucose production  
↑ insulin resistance in the liver, skeletal muscles and adipose tissue; eNOS expression in the abdominal aortas, food intake (via ↑ NPY, ↓ CART)  
↔ insulin-mediated glucose uptake (peripheral tissues), body weight  
**Exogenous (mink):**  
↑ uterine glycogen catabolism, glucose release  
**Exogenous (mouse):**  
↓ myometrial monocyte numbers  
↔ myometrial neutrophil numbers  
**Exogenous (ovariectomized mice):**  
↓ intimal proliferation in response to vessel injury  
‖ anti-anxiety behavior (↑ hippocampal and prefrontal cortex 3α,5α-THP) | Edey et al., 2018; Koonce and Frye, 2013; Dean et al., 2014 |

*eNOS, Endothelial nitric oxide synthase; PGF, Placental growth factor; T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus; THP, Tetrahydroprogesterone; TNF, Tumor necrosis factor; VEGF, Vascular endothelial growth factor.*

and insulin secretion of β cells in vitro (Table 4; Progesterone; Sorenson et al., 1993). Furthermore, in rodent models of type 1 and 2 diabetes mellitus, estrogen supplementation protects pancreatic β-cells from oxidative stress, lipotoxicity and apoptosis (Table 3; Estrogen; Tiano and Mauvais-Jarvis, 2012). Therefore, both estrogen and progesterone play roles in regulating insulin and glucose homeostasis, lipid handling and appetite regulation, which may be important in promoting metabolic changes in the mother during pregnancy.
Work conducted both in vitro and in vivo indicate that estrogen and progesterone may also facilitate some of the cardiovascular changes that accompany pregnancy (Tables 3, 4). Estrogen attenuates the vasoconstrictor responses of blood vessels, impairs vascular smooth muscle cell proliferation and calcium influx, and increases vasodilatory nitric oxide synthase activity in vitro (Table 4; Estrogen; Takahashi et al., 2003). It also increases uterine artery angiogenesis and amplifies the vasodilatory impact of vascular endothelial growth factor on coronary relaxation (calcium influx dependent) (Table 4; Estrogen; Takahashi et al., 2003). Estrogen also exerts cardiovascular effects. It stimulates nitric oxide synthesis by human umbilical vein endothelial cells in vitro and by rat abdominal aorta and mesenteric arteries in vivo (Tables 3, 4; Progesterone; Chataigneau et al., 2004; Simoncini et al., 2004). It also decreases blood pressure, when infused into ovariectomised ewes and protects against vascular injury in non-pregnant mice (Pecins-Thompson and Keller-Wood, 1997; Zhang et al., 1999). In culture, progesterone induces hypertrophy and inhibits apoptosis of rodent cardiomyocytes (Morrissy et al., 2010; Chung et al., 2012). Thus, via its impacts on cardiomyocytes, progesterone may mediate the pregnancy-induced growth of the mother's heart in vivo. In late pregnancy, the murine heart shifts to use fatty acids, rather than glucose and lactate, as a metabolic fuel. In part, this metabolic shift is proposed to be mediated by progesterone during pregnancy, which inhibits pyruvate dehydrogenase activity in ventricular myocytes ( Liu et al., 2017). Thus, placental-derived progesterone and estrogen may mediate part of the changes in the maternal cardiovascular system during pregnancy. In many mammalian species, progesterone levels decline just before parturition and this is associated with the initiation of labor. Indeed, in rodents, inhibition of progesterone synthesis or administration of a progesterone antagonist results in premature delivery of the neonate (Tables 3; Progesterone; Fang et al., 1997;
In humans, circulating progesterone levels continue to be high until birth. Commencement of labor is therefore proposed to be related to a functional withdrawal of progesterone activity in the myometrium of women (Brown A. G. et al., 2004; Norwitz and Caughey, 2011). In experimental animals, progesterone reduces the production of prostaglandins and decreases the expression of contraction-associated genes including oxytocin and prostaglandin receptors, gap junction proteins and ion channels in the myometrium (Table 3; Progesterone; Fang et al., 1997; Soloff et al., 2011; Edey et al., 2018). Together, these progesterone-mediated actions decrease contractility of uterine smooth muscle cells and maintain uterine quiescence until term. In contrast to progesterone, estrogen levels rise prior to term and estrogen promotes the expression of contraction-associated genes and contraction of the myometrium (Table 4; Estrogen; Nathanielz et al., 1998; Di et al., 2001; Chandran et al., 2014). Therefore, in many species, the high ratio of estrogen to progesterone in the maternal circulation is thought to contribute the onset of labor. Parturition is associated with an influx of inflammatory cells and release of pro-inflammatory cytokines, including interleukin (IL)-1β and tumor necrosis factor (TNF)-α, in the myometrium, cervix and fetal membranes (Golightly et al., 2011). In mice, progesterone reduces the expression of pro-inflammatory cytokines, including IL-1β and IL-6 by the uterus and trophoblast and may modulate the abundance of myometrial monocytes (Table 3; Estrogen; Edey et al., 2018). Progesterone also decreases the ability of LPS to induce pro-inflammatory cytokine secretion by human myometrium and placental explants (Youssef et al., 2009; García-Ruiz et al., 2015). It also diminishes the ability of estrogen to induce the infiltration of macrophages and neutrophils into the uterus, and decreases LPS-induced leukocyte adhesion to human umbilical vein cells (Simoncini et al., 2004). Thus, it is perhaps not surprising that progesterone receptor null mice demonstrate chronic uterine inflammation, particularly in response to estrogen treatment (Table 3; Estrogen; Lydon et al., 1995). There is also evidence that placental steroids participate in cervical softening, by regulating the expression of matrix remodeling enzymes as well as leukocyte infiltration and function (Chinnathambi et al., 2014; Gopalakrishnan et al., 2016; Berkane et al., 2017). In addition to regulating the events leading to parturition, recent data suggest that during the course of pregnancy, both estrogen and progesterone contribute to the maternal tolerance of the fetus by modulating proliferation and cytokine expression of CD4 and CD8 T cells and enhancing the suppressive function of T-regulatory cells (Mao et al., 2010; Robinson and Klein, 2012; Lissauer et al., 2015).

Additionally, both estrogen and progesterone are key stimulators of mammary gland development. For instance, progesterone stimulates proliferation of mammary stem cells and mammary epithelium (Tables 3, 4; Progesterone; Joshi et al., 2010; Lee et al., 2013). In mice, deficiency of the progesterone receptor restricts mammary gland development, whereas exogenous progesterone induces ductal side branching and lobuloalveolar differentiation and development (Table 3; Progesterone; Plaut et al., 1999; Joshi et al., 2010). In addition, both estrogen and progesterone may have indirect effects on mammary gland development by regulating prolactin secretion from the pituitary gland (Rezaei et al., 2016).

Maternal behavior during and after birth are regulated by the steroid hormones. Estrogen stimulates maternal nurturing behavior in numerous species, including rats, mice, sheep and primates (Bridges, 2015). In particular, maternal care is induced by estrogen treatment, whereas the converse happens when ERα expression is suppressed; deficiency of ERα increases the latency to pup retrieval and reduces the length of time dams spend nursing and licking their pups (Table 3; Estrogen; Ribeiro et al., 2012). Findings from animal models suggest that progesterone plays a role in regulating anxiety and depression-related behavior. For instance, exogenous progesterone stimulates anti-anxiety and anti-depressive actions in mouse dams (Table 3; Progesterone; Koonce and Frye, 2013). In contrast, progesterone withdrawal increases these types of behaviors (Gulinello et al., 2002). Thus, placental-derived steroids may modulate several aspects of maternal physiology which are beneficial to both pregnancy and post-partum support of the offspring.

**Neuroactive Hormones**

One major target of placental hormones is the maternal brain and related neuroendocrine organs such as the hypothalamus and pituitary glands. These neuroendocrine effects enable the mother to respond and adapt accordingly to her environment, so as to mitigate the adverse effects of stress and maintain homeostasis (Voltoolini and Petraglia, 2014). Neuroactive hormones also prepare and enable the future mother to adequately care for her young (Lévy, 2016). In addition to their impact on the maternal neuroendocrine system, these hormones have additional functions in vivo and in vitro functions as well, which are detailed in Tables 5, 6, respectively.

**Melatonin and Serotonin**

Melatonin and its precursor, serotonin, are tryptophan-derived hormones with well-known neuroendocrine impacts. In humans, circulating concentrations of melatonin and serotonin increase as pregnancy advances (Lin et al., 1996; Nakamura et al., 2001). In the non-pregnant state, melatonin and serotonin are primarily produced by the pineal gland and the brain, respectively. However, the enzymes involved in melatonin and serotonin biosynthesis are also expressed by the human placenta throughout gestation (Iwasaki et al., 2005; Soliman et al., 2015; Laurent et al., 2017). The mouse placenta similarly expresses the enzymes needed for serotonin synthesis (Wu et al., 2016), although work is required to assess if melatonin synthesizing enzymes are also expressed. The rat placenta does not produce melatonin de novo due to the lack of synthesizing enzymes (Tamura et al., 2008). However, the same study demonstrated that conditioned medium from cultured term rat placentas stimulated melatonin release by the maternal pineal gland (Tamura et al., 2008). These findings suggest that placental-derived factors may indirectly regulate melatonin levels by the mother during pregnancy. Placental expression of melatonin, serotonin and their respective enzymes, also remains to be investigated in other species such as rabbits and sheep, which are commonly used in pregnancy-related...
| Hormones     | Expression level | Non-pregnant | Pregnancy and lactation | In vivo effects                                                                 | References |
|--------------|------------------|--------------|-------------------------|--------------------------------------------------------------------------------|------------|
| Serotonin    | Low              | Non-pregnant |                         | Serotonin receptor knockout Htr3a<sup>−/−</sup> (mouse): &lt;→ glucose tolerance; GSIS; serotonin production and release; pancreatic β-cell mass | Obara-Imaizumi et al., 2013; Kim et al., 2010 |
|              |                  |              |                         | Dietary restriction of precursor – tryptophan/inhibitor of serotonin synthase or receptor/serotonin receptor knockout Htr2b<sup>−/−</sup> (mouse): &lt;→ glucose tolerance |            |
|              |                  |              |                         | Serotonin transporter knockout SERT<sup>−/−</sup> (mouse): ↓ food intake; glucose and insulin tolerance; hepatic and white adipose tissue glucose uptake and insulin sensitivity (Akt signaling); estrus cyclicity; blood 17β-estradiol; brown adipose tissue mass; lipid droplet number; lipoysis (PGC1α, PPARγ, and CPT1b); ovarian Cyp19a expression | Zha et al., 2017 |
|              |                  |              |                         | ↑ blood glucose; white adipose tissue mass; adipocyte size; lipid droplet area; lipogenesis (PPARYγ, SREBP1c, Fabp4, LPL, HSL and ATGL); adipose inflammation (IL-6 and TNF-α) |            |
|              |                  |              |                         | Administration of selective serotonin-reuptake inhibitors (mouse): ↓ glucose and insulin tolerance; blood 17β-estradiol; ovarian Cyp19a expression; ↑ weight; adiposity; adipocyte size | Aienina et al., 2009; Kane et al., 2012 |
|              |                  |              |                         | Serotonin synthesis pathway enzyme knockout Tph2<sup>−/−</sup> (mouse): ↓ postnatal survival; heart rate; blood pressure; respiration; social interaction; blood IGF1; ↑ early growth restriction; aggression; repetitive and compulsive behaviors; daytime sleep |            |
|              |                  |              |                         | Serotonin synthesis pathway enzyme Tph1<sup>−/−</sup> (mouse): ↓ blood and mammary serotonin and PTHrP; blood calcium; osteoclast activity; mammary gland epithelial cell proliferation, calcium transporters and sonic hedgehog signaling; ↑ blood glucose and insulin | Laporta et al., 2014a,b |
|              |                  |              |                         | Serotonin synthesis pathway enzyme Tph2<sup>−/−</sup> (mouse): ↓ brain serotonin; pup retrieval; nest building; offspring survival and weaning weights; lactation; lactation-induced aggression; ↑ pup killing | Angoa-Pérez et al., 2014 |
|              |                  |              |                         | Dietary restriction of precursor – tryptophan/inhibitor of serotonin synthase or receptor/serotonin receptor knockout Htr2b<sup>−/−</sup> (mouse): ↓ glucose tolerance; pancreatic β-cell expansion (proliferation); blood insulin ↔ insulin tolerance | Kim et al., 2010 |
|              |                  |              |                         | Serotonin transporter SERT<sup>−/−</sup> (mouse): ↑ blood glucose and insulin; JZ necrosis (TUNEL positive cells) and hemorrhage (fibrin deposition) | Hadden et al., 2017 |
|              |                  |              |                         | No known physiological changes |            |
|              | High             | Non-pregnant | Pregnancy and lactation | Infusion of serotonin precursor (cow): ↓ food intake; colostrum yield; urine calcium elimination | Laporta et al., 2015; Weaver et al., 2016, 2017; Hernández-Castellano et al., 2017 |
|              |                  |              |                         | ↑ blood FFAs, calcium content; colostrum serotonin; loose stools; defecation frequency; urine metabolite (deoxypyridinoline); milk calcium content; hepatic expression of serotonin; hepatic CASP3- and K67-positive cell numbers ↔ blood glucose, insulin; magnesium; prolactin, glucagon; weight; milk yields; heart rates; respiration rates; body temperatures |            |
|              |                  |              |                         | Injection of precursor – tryptophan (mouse, rat and rabbit): ↓ uterine blood flow; decidualization | Poulson et al., 1960; Robson and Sullivan, 1966; Habiger, 1975; Mitchell et al., 1983; Tomogane et al., 1992 |
|              |                  |              |                         | ↑ termination of pregnancy; placential hemorrhage; circulating PRL ↔ uterine contractility; serum progesterone |            |
|              |                  |              |                         | Dietary intake of precursor – tryptophan (mice, rats): ↓ blood glucose; milk glucose | Laporta et al., 2013a,b |
|              |                  |              |                         | ↑ blood, liver and mammary gland serotonin; blood and mammary gland PTHrP; blood and milk calcium; liver expression of gluconeogenic and glycolytic enzymes (PC, PCK, PDK4, FF1); mammary gland expression of TPH1, calcium transporters, glucose transporters; femur bone resorption ↔ body weight; mammary gland structure and milk yield; pup weights |            |

(Continued)
TABLE 5 | Continued

| Hormones | Expression level | In vivo effects | References |
|----------|-----------------|----------------|------------|
| Melatonin | Low | Non-pregnant | | |
| | | | **Melatonin receptor knockout MT1**−/− (mouse):** | |
| | | | ↓ glucose and insulin tolerance; circadian rhythm of blood glucose and corticosterone; time spent resting | |
| | | | ↑ depressive-like and anxiety-like behaviors; psychomotor disturbances; time spent eating; hyperactivity; blood corticosterone and glucose; pancreatic insulin production; liver glucagon receptor expression | |
| | | | **Melatonin receptor knockout MT2**−/− (mouse):** | |
| | | | ↓ circadian rhythm of blood glucose; blood insulin; axon formation; synaptic transmission | |
| | | | ↑ liver glucagon receptor expression; pancreatic insulin production | |
| | | | **Double melatonin receptor knockout MT1/MT2**−/− (mouse):** | |
| | | | ↓ blood insulin | |
| | | | ↑ cognitive performance; hyperactivity; motor activity; liver glucagon receptor expression; pancreatic insulin production | |
| | | | | | |
| | | | **Pregnancy and lactation** | |
| | | | | | |
| | | | **Exogenous (rat):** | |
| | | | ↓ liver glucagon receptor expression | |
| | | | ↑ blood glucagon | |
| | | | **Mammary-specific melatonin MT1 receptor overexpression (mouse):** | |
| | | | ↓ mammary gland ductal growth, ductal branching, and terminal end bud formation | |
| | | | **Exogenous (cow):** | |
| | | | ↑ heart rate; pulse pressure; uterine blood flow; uterine melatonin receptor expression | |
| | | | ↔ gestation and birthweight | |
| | | | **Exogenous (sheep):** | |
| | | | ↓ pancreatic insulin-positive tissue area, size and percentage of large insulin-containing cell clusters; blood prolactin receptors; milk protein content (β-casein and whey acidic protein) | |
| | | | ↑ oxygen consumption; blood LH and progesterone; pancreas and small intestine weights; pancreatic α-amylase activity; citrate synthase activity; number of fetuses; conception and pregnancy rates | |
| | | | **Exogenous in growth restriction model – high altitude (sheep):** | |
| | | | ↓ oxidative stress (↓ blood 8-isoprostanotes); birthweight | |
| | | | ↑ blood cortisol; plasma antioxidant capacity; gestation length | |
| | | | **Exogenous (rat):** | |
| | | | ↓ food intake; weight gain; blood and pituitary LH; pituitary prolactin; litter size; birthweight | |
| | | | ↑ blood prolactin; offspring mortality | |
| | | | **Melatonin receptor MT1 overexpression (mouse):** | |
| | | | ↓ mammary gland lobulo-alveolar development; mammary epithelial cell proliferation (Akt1, phosho-Stat5, Wnt4) and estrogen and progesterone receptor expression; suckling pup weight | |
| Oxytocin | Low | Non-pregnant | | |
| | | | **Oxytocin knockout OT**−/− (mouse):** | |
| | | | ↓ glucose and insulin tolerance; bone mineral density; social memory; maternal behavior (pup retrieval and licking) | |
| | | | ↑ adiposity; sucrose solution intake; carbohydrate preference; blood glucose, leptin and adrenaline | |
| | | | ↔ food intake | |
| | | | **Oxytocin receptor knockout OTR**−/− (mouse):** | |
| | | | ↓ bone mineral density; cold-induced thermogenesis; social memory; maternal behavior (pup retrieval) | |
| | | | ↑ adiposity; aggressive behavior; blood triglycerides; brown adipose tissue lipid droplet size | |
| | | | **Oxytocin antagonist administration (rat):** | |
| | | | ↓ latency to first meal post-fast | |
| | | | ↑ food and fluid intake; time spent eating | |
| | | | **OXTR RNAi administration (prairie voles):** | |
| | | | ↓ social attachment; maternal care (grooming) | |

(Continued)
TABLE 5 | Continued

| Hormones | Expression level | In vivo effects | References |
|----------|-----------------|----------------|------------|
| Pregnancy and lactation | Oxytocin knockout OT<sup>−/−</sup> (mouse): | ↓ milk release; post-partum mammary development | Nishimori et al., 1996; Young et al., 1996; Wagner et al., 1997 |
| | † mammary gland milk accumulation | | |
| | Oxytocin receptor knockout OTR<sup>−/−</sup> (mouse): | ↓ milk release; maternal behavior (pup retrieval) | Takayanagi et al., 2005; Lee et al., 2008 |
| | † mammary gland milk accumulation | | |
| | Oxytocin antagonist administration (rat): | † latency to display maternal behaviors (nest building, pup retrieval) | Van Leengoed et al., 1987 |
| High Non-pregnant | Exogenous (rat): | ↓ food and fluid intake; blood pressure; blood calcium | Arletti et al., 1989, 1990; Pettersson et al., 1996; Elabd et al., 2007 |
| | † latency to first meal post-fast; bone formation | | |
| | Exogenous (diet-induced obese rats): | ↓ weight gain | Deblon et al., 2011 |
| | † glucose and insulin tolerance; adipose tissue lipolysis and fatty acid β-oxidation | | |
| | Exogenous (mouse): | † body temperature; bone mineral density | Mason et al., 1986; Tamma et al., 2009 |
| | Exogenous (rat): | † delivery induction (via induced Fos expression in supraoptic nucleus and brain stem neurons) | Antonijevic et al., 1995 |
| Pregnancy and lactation | Injection of oxytocin antagonist (Syrian hamster): | † aggression to intruder (number of bites and contact time) | Ferris et al., 1992 |

| ATGL, Adipose triglyceride lipase; CASP, Caspase; CPT1b, Carnitine palmitoyltransferase 1B; GSIS, Glucose-stimulated insulin secretion; HSL, Hormone-sensitive lipase; IL, Interleukin; JZ, Junctional zone; PC, Pyruvate carboxylase; PDK4, Pyruvate dehydrogenase kinase 4; PFK1, 6-phosphofructokinase subunit alpha; PGC1, PPAR G Coactivator 1; PPAR, Peroxisome proliferator-activated receptor; SREBP1, Sterol regulatory element-binding transcription factor 1; LPL, Lipoprotein lipase; TNF, Tumor necrosis factor. |

studies. Mouse models that result in deficiencies or reduced bioactivity of these hormones demonstrate altered sleep patterns, melancholic behavior, hyperactivity and aggression in the non-pregnant state (Table 5; Serotonin and Melatonin; Weil et al., 2006; Alenina et al., 2009; Kane et al., 2012; Adamah-Biassi et al., 2014; O’neal-Moffitt et al., 2014; Comai et al., 2015). Serotonin is thus a major regulator of maternal mood and behavior (Angoa-Pérez and Kuhn, 2015). For instance, genetically-induced serotonin deficiency leads to increased maternal aggression, lower pup retrieval and greater pup cannibalization, which reduces postnatal survival of offspring in mice (Angoa-Pérez et al., 2014). There is some evidence that serotonin and melatonin may also impact maternal feeding behavior. For example, increased serotonin signaling reduces food intake in pregnant cows (Laporta et al., 2015; Weaver et al., 2016, 2017; Hernández-Castellano et al., 2017). Similarly, exogenous melatonin lowers food intake in pregnant rats (Nir and Hirschmann, 1980; Jahnke et al., 1999; Singh et al., 2013). These negative effects on maternal food intake suggest that peak serotonin and melatonin concentrations in late pregnancy may serve to control the maternal appetite and prevent excessive weight gain.

Another key function of melatonin and serotonin is glucose homeostasis and the regulation of steroid synthesis (Table 5; Serotonin and Melatonin). In mice, loss of melatonin or serotonin signaling leads to glucose intolerance and insulin resistance, with consequences for blood glucose and insulin concentrations in both the non-pregnant and pregnant state (Contreras-Alcantara et al., 2010; Kim et al., 2010; Owino et al., 2016). However, these neuroactive hormones appear to have differential effects on the pancreas (Table 6; Serotonin and Melatonin). Serotonin promotes pancreatic β-cell proliferation in vitro (Kim et al., 2010), and is thus important for pancreatic β-cell mass expansion during pregnancy in mice (Goyvaerts et al., 2016). In contrast, melatonin reduces insulin release by rodent pancreatic islets in vitro (Mühlbauer et al., 2012). Non-pregnant mice with deficient serotonin signaling have impaired lipid handling and excessive lipid accumulation in association with reduced adipose aromatase expression and circulating estrogen (Zha et al., 2017). Similarly, treating placental-derived trophoblast cells with norfluroxetine, a selective serotonin-reuptake inhibitor, inhibits aromatase activity and estrogen secretion in vitro (Hudon Thibeault et al., 2017). Supplementation of melatonin in non-pregnant humans reduces circulating triglycerides and cholesterol levels, but effects of lipid handling in pregnancy are unknown (Mohammadi-Sartang et al., 2017). Melatonin also modulates steroid production. For instance, melatonin treatment in pregnant cows reduces circulating estrogen and progesterone (Brockus et al., 2016), while lack of melatonin signaling raises blood corticosterone in mice (Comai et al., 2015).

Given melatonin’s additional effects on regulating the circadian rhythm (Mühlbauer et al., 2009), there is some weak evidence for its role in the timing of parturition (Yellon and Longo, 1988; González-Candia et al., 2016). Melatonin can either enhance or reduce uterine myometrial contractility depending on the species (Table 6; Melatonin; Ayar et al., 2001; Sharkey et al.,
### TABLE 6 | Effects of neuropeptides in vitro.

| Hormones | Expression level | In vitro effects | References |
|----------|------------------|------------------|------------|
| Serotonin | Low | Exposure to selective serotonin-reuptake inhibitors (BeWo trophoblast cell and H295R adrenocortical cell co-culture): ↓ serotonin transporter activity; estrogen secretion ↑ aromatase CYP19 activity | Hudon Thibeault et al., 2017 |
|          | High | Exogenous (human third trimester placental arteries and veins): ↑ vessel vasoconstriction; cotyledon; perfusion pressure and thromboxane release Exogenous (bovine placenta cells): ↑ proliferation Exogenous (human adipocytes): ↑ lipid-binding proteins, glucose carriers, triacylglycerol synthesis enzymes Exogenous (mouse adipocytes): ↓ brown fat differentiation ↑ fat storage and white fat differentiation; lipid-binding proteins, glucose carriers, triacylglycerol synthesis enzymes Exogenous (mouse pancreatic β cells): ↑ proliferation Exogenous (rat osteoblast): ↓ proliferation; differentiation; mineralization | Bjoro and Stray-Pedersen, 1986; Cruz et al., 1997 Fecteau and Eiler, 2001 Sonier et al., 2005 Grès et al., 2013; Rozenblit-Susan et al., 2017 |
|          | Low | Melatonin receptor MT1 siRNA administration (rat insulinoma): ↑ insulin production and secretion | Wang et al., 2017 |
|          | High | Exogenous (human trophoblast cells): ↑ hCG secretion; syncytialization ↓ hypoxia-induced oxidative stress and apoptosis; mitochondrial lipid peroxidation Exogenous (human myometrial cells): ↑ oxytocin-induced contractility; oxytocin sensitization Exogenous (rat myometrial cells): ↓ spontaneous and oxytocin-induced contractility Exogenous (rat uterine and hypothalamic explants): ↓ prostaglandin release Exogenous (seal uterine artery): ↓ noradrenaline-induced vasoconstriction Exogenous (rat insulinoma and mouse pancreatic islets): ↓ insulin release; expression of glucagon-like peptide 1; glucagon-stimulated insulin release Exogenous (mouse pancreatic α-cells): ↑ glucagon production | Iwasaki et al., 2005; Milczarek et al., 2010; Lanoix et al., 2013; Soliman et al., 2015 Ayar et al., 2001; Sharkey et al., 2009, 2010 Abd-Allah et al., 2003 Gimeno et al., 1980 Stokkan and Aarseth, 2004 Mühlbauer et al., 2012 Bähr et al., 2011 |
|          | Low | Oxytocin knockout OT−/− (mouse osteoblast and osteoclast cells): ↓ proliferation; maturation; differentiation | Tamma et al., 2009 |
|          | High | Exogenous (human third trimester primary trophoblast cells): ↓ nitric oxide production Exogenous (human decidual cells in labor): ↑ prostaglandin synthesis; release of free arachidonic acid Exogenous (guinea pig placenta perfusion): ↓ uptake of glucose and alanine (related to changes in placental flow) Exogenous (rat myometrial strips): ↑ contractility Exogenous (rat mammary gland slice): ↑ release of triglycerides and protein Exogenous (human umbilical vein endothelial cells): ↑ migration; invasion Exogenous (mouse osteoblast and osteoclast): ↑ proliferation; differentiation | Nanetti et al., 2015 Wilson et al., 1988 Rybakowski et al., 2000 Ayar et al., 2001 Da Costa et al., 1995 Cattaneo et al., 2008 Tamma et al., 2009 |

Both melatonin and serotonin are also important for lactation, specifically for mammary gland development and milk nutrient content (Okatani et al., 2001; Xiang et al., 2012; Laporta et al., 2009, 2010). For instance, mammary gland proliferation and calcium transport is impaired in pregnant mice with genetically-induced serotonin deficiency (Laporta et al., 2014a,b).
Conversely, supplementation of a serotonin precursor increases mammary calcium transporter expression and milk calcium content in lactating mice and cows (Laporta et al., 2013a,b, 2015; Weaver et al., 2016, 2017; Hernández-Castellano et al., 2017). In contrast to serotonin, increased melatonin signaling is associated with reduced ductal growth and branching, as well as impaired terminal end bud formation in the non-pregnant state (Xiang et al., 2012). Thus, during lactation, these mice with increased melatonin signaling have impaired mammary gland lobulo-alveolar development and reduced milk protein content, which reduces the weight of suckling pups (Xiang et al., 2012). Indeed, a recent study showed antennal melatonin supplementation further exacerbated the growth restriction of offspring and raised circulating maternal cortisol in a sheep model of fetal growth restriction (González-Candia et al., 2016). Nevertheless, melatonin supplementation during pregnancy confers significant beneficial neuroprotective effects on the fetus and enhances maternal antioxidant capacity (Miller et al., 2014; González-Candia et al., 2016; Castillo-Melendez et al., 2017). Therefore, while melatonin supplementation shows promise for use in the clinic, particularly for enhancing the neurodevelopmental outcomes of offspring in growth compromised pregnancies, the potential adverse outcomes for both mother and child must also be considered and should be assessed in further studies.

**Oxytocin**

Another key neuroendocrine factor is oxytocin. Oxytocin is widely known for its role in triggering maternal nursing behavior (Bosch and Neumann, 2012). This is mediated by oxytocin’s actions on the maternal brain, as well as, the mammary glands. Indeed, a greater rise in circulating oxytocin concentrations from early to late pregnancy in pregnant women, is associated with a stronger bond between a mother and her infant (Levine et al., 2007). Concurrently, placental expression of oxytocin also peaks at term in humans (Kim S. C. et al., 2017). The rat placenta also produces oxytocin (Lefebvre et al., 1992), while placental expression in other species remains unclear. Reduced oxytocin signaling decreases maternal nurturing behavior such as pup retrieval in rats (Van Leengoed et al., 1987). It also decreases the willingness of female voles to care for, groom and lick unrelated pups (Keenbaugh et al., 2015). Low oxytocin signaling can additionally impair social bonding in voles and mice (Ferguson et al., 2000; Takayanagi et al., 2005; Lee et al., 2008; Keenbaugh et al., 2015), while high levels builds trust and cooperation in a group setting to facilitate group survival in humans (Declerck et al., 2010; De Dreu et al., 2010). Moreover, a lack of oxytocin disrupts mammary gland proliferation and lobuloalveolar development, which impairs milk release from the mammary tissues in mice (Nishimori et al., 1996; Wagner et al., 1997). Therefore, high oxytocin levels enable the mother to bond better and protect her newborn, when it is most vulnerable.

Oxytocin is also important in the process of parturition (Table 6; Oxytocin); it stimulates the contraction of smooth muscle cells in the myometrium (Ayar et al., 2001; Arrowsmith and Wray, 2014), by inducing calcium influx and stimulating prostaglandin release (Wilson et al., 1988; Volotolin and Petraglia, 2014; Kim S. H. et al., 2017). Cardiovascular effects of oxytocin include its ability to significantly lower blood pressure in non-pregnant rats (Petersson et al., 1996). There is also some evidence that oxytocin induces anti-inflammatory and antioxidative effects in the heart under hypoxic conditions in non-pregnant rats (Gutkowska and Jankowski, 2012). Nevertheless, the specific cardiovascular effects of oxytocin in pregnancy remain to be explored.

Studies performed in non-pregnant rodents show that oxytocin also affects metabolic function in vivo (Table 5; Oxytocin). In particular, loss of oxytocin reduces glucose and insulin tolerance and increases adiposity (Camerino, 2009), whereas exogenous oxytocin has the reverse effect (Deblon et al., 2011). Studies are however, required to determine whether the rise in oxytocin in late pregnancy (Levine et al., 2007) may serve to improve insulin sensitivity in the mother in preparation for the metabolic requirements of delivery and lactation. There is some evidence that oxytocin may additionally play a role in controlling energy expenditure and thermoregulation during pregnancy. Even with a similar diet and activity level to control mice, oxytocin-deficient mice become obese due to reduced energy expenditure from poor thermoregulation in the non-pregnant state (Chaves et al., 2013). Furthermore, exogenous oxytocin in non-pregnant mice causes a rise in body temperature (Mason et al., 1986; Tamma et al., 2009). Nevertheless, whether oxytocin may play a role in controlling heat dissipation due to the increased maternal energy expenditure during pregnancy requires exploration. Exogenous oxytocin also reduces food intake in non-pregnant rats (Arletti et al., 1989, 1990). However, the role of oxytocin in appetite regulation during pregnancy remains to be explored. There is also evidence for oxytocin’s possible involvement in maternal bone metabolism and calcium homeostasis during pregnancy and lactation. For instance, oxytocin stimulates both bone resorption and bone formation by osteoclasts and osteoblasts respectively in vitro (Tamma et al., 2009). Moreover, oxytocin administration in rats reduces circulating calcium with an overall skew toward bone formation (Elabd et al., 2007). These findings may suggest that the peak in circulating oxytocin toward term promote the restoration of depleted maternal skeletal calcium stores.

**Other Neuroactive Hormones**

In addition to the aforementioned melatonin, serotonin and oxytocin, the human placenta also produces neuroactive hormones such as kisspeptin and thyrotropin-releasing hormone (TRH), which may function in adapting maternal physiology to support pregnancy (Bajoria and Babawale, 1998; De Pedro et al., 2015). In humans, circulating kisspeptin rises throughout pregnancy to concentrations 10,000-fold that of the non-pregnant state, with the placenta speculated as a major source (Horikoshi et al., 2003). In the non-pregnant state, kisspeptin can both stimulate and impede glucose stimulated insulin secretion in mice (Bowe et al., 2009; Song et al., 2014). The nature of the effect may partly relate to differences in the actions of kisspeptin isoforms on pancreatic islets (Bowe et al., 2012). Kisspeptin may also have effects on the maternal cardiovascular system,
given its reported vasoconstrictive effects on vascular smooth muscle cells and fibrotic effects on the heart in non-pregnant rats (Mead et al., 2007; Zhang et al., 2017). Studies in humans highlight the importance of regulating kisspeptin production during gestation; increased placental kisspeptin is associated with pre-eclampsia (Whitehead et al., 2013; Matjila et al., 2016) and reduced circulating kisspeptin is observed in women with hypertension and diabetes during pregnancy (Cetković et al., 2012; Matjila et al., 2016). Like the human, the murine placenta produces kisspeptin. Although a kisspeptin-deficient mouse has been established, previous work has been focused on fetoplacental outcomes, with no examination of maternal physiology (Herreboudt et al., 2015). Studies are required to determine the consequences of abnormal placental kisspeptin on the maternal physiology during pregnancy.

In the non-pregnant state, hypothalamic TRH stimulates release of thyroid-stimulating hormone and PRL from the pituitary (Hershsan et al., 1973; Vale et al., 1973; Askew and Ramsden, 1984). However, during pregnancy, the placenta serves as an additional source of TRH (Bajoria and Babawale, 1998). Excess TRH in pregnancy raises blood concentrations of thyroid-stimulating hormone and PRL in human, rhesus monkey, sheep and rats (Thomas et al., 1975; Azukizawa et al., 1976; Roti et al., 1981; Moya et al., 1986; Lu et al., 1998). Conversely, a lack of TRH reduces blood PRL in mice (Rabler et al., 2004; Yamada et al., 2006). Thyroid hormones are necessary for optimal brain development as well as thyroid function (Miranda and Sousa, 2018). Impaired TRH signaling is associated with anxiety-like and depressive-like behavior in non-pregnant mice (Zeng et al., 2007; Sun et al., 2009) and there is some evidence which suggests a link between thyroid dysfunction and poor maternal mood during pregnancy in humans (Basraon and Costantine, 2011). However, whether any direct causal relationship between placental hormones, like TRH and perinatal depression remains unclear. Additionally, TRH is implicated in glucose homeostasis and appetite regulation. For example, mice with TRH deficiency are hyperglycaemic, due to an impaired insulin response to glucose (Yamada et al., 1997). Reduced TRH signaling also impedes leptin production and ghrelin acylation, which results in less energy conservation during fasting and a lower body mass in the non-pregnant state (Groba et al., 2013; Mayerl et al., 2015). Investigations are warranted to identify whether TRH may contribute to the regulation of glucose handling and appetite in the mother during pregnancy.

### Additional Hormones

The placenta also produces numerous other hormones with pleiotropic effects. Several key ones, which have been implicated in pregnancy failure or disorders of pregnancy such as hypertension, hyperglycemia and hypercalcemia, are discussed here. The hormones presented here are by no means exhaustive and were selected primarily on their major associations with abnormal maternal physiology during pregnancy. The gonadotropin, chorionic gonadotropin (CG); transforming growth factor β (TGF β) family member, activin; angiogenic factor, relaxin; bone metabolism-associated parathyroid hormone-related protein (PTHrP) and energy homeostasis regulator, leptin are reviewed (Tables 7, 8).

### Chorionic Gonadotropin (CG)

CG, is secreted by the human (hCG) and equine (eCG) placenta, although hCG has been more extensively studied. hCG is a large glycoprotein composed of α and β subunits, of which the α subunit identical to luteinizing hormone (LH), follicle stimulating hormone (FSH) and thyroid stimulating hormone (TSH). As a result, hCG can interact with LH, FSH and TSH receptors. In women, hCG is secreted from the trophoblast from very early in gestation and is thought to be the first placental hormone to act on the mother (Ogueh et al., 2011). Indeed, maternal circulating hCG concentrations peak in the first trimester and then decline toward term (Ogueh et al., 2011). In early pregnancy, hCG maintains corpus luteum allowing the continued secretion of ovarian progesterone and estrogens until the steroidogenic activity of the fetal-placental unit can compensate for maternal ovarian function (Fournier et al., 2015). In particular, hCG increases the abundance of low-density lipoprotein receptor and thus uptake of cholesterol for steroidogenesis. It also enhances the expression and/or activity of steroidogenic enzymes including 3β-hydroxysteroid and aromatase. There is also some evidence which suggests hCG may inhibit factors that promote luteal demise, such as the prostaglandins. The high levels of hCG in early pregnancy are also sufficient to bind to the TSH receptor and may act to increase maternal thyroid hormone production, which as mentioned previously, may exert effects in the mother and fetus.

CG may also play important autocrine and paracrine roles at the maternal-fetal interface. Administration of hCG antisera prevents implantation in vivo (Hearn et al., 1988). Recent proteomic analysis of estrogen and hCG treated human endometrial epithelial cells demonstrates that hCG targets pathways involved in metabolism, basement membrane and cell connectivity, proliferation and differentiation, cellular adhesion, extracellular-matrix organization, developmental growth, growth factor regulation and cell signaling (Greening et al., 2016). Such pathways are likely to be important for placental development, as attenuating hCG signaling disrupts trophoblast differentiation in vitro (Shi et al., 1993). In contrast, supplementing human trophoblast cells with hCG increases their differentiation, migration, invasion and adhesion to uterine epithelial cells, and decreases their leptin secretion in vitro (Table 8, hCG; Shi et al., 1993; Prast et al., 2008; Lee C. L. et al., 2013; Chen et al., 2015). hCG also promotes angiogenic vascular endothelial growth factor secretion by both trophoblast and endometrial epithelial cells (Islami et al., 2003a; Berndt et al., 2006) and enhances endothelial tube formation and migration (Zygmun et al., 2002). Furthermore, hCG is key in suppressing the maternal immune system from mounting a response against paternal antigens carried by the allogenic conceptus. Administration of hCG in a mouse model of spontaneous abortion significantly reduces the number of fetal resorptions due to improved immune tolerance of the fetus (Schumacher et al., 2013). In vitro, hCG enhances proliferation of immunosuppressive uterine natural killer cells (Kane et al., 2009), and the production of immunosuppressing
| Hormones        | Expression levels | **In vivo effects** | References |
|-----------------|-------------------|--------------------|------------|
| Activins        | Low               | Dysfunction activin receptor ACVR1C (mouse): | Yogosawa et al., 2013 |
|                 |                   | ↓ fat accumulation |            |
|                 |                   | ↑ adipocyte lipolysis |            |
|                 |                   | Truncated activin receptor ACVR2A (mouse): | Maeshima et al., 2000 |
|                 |                   | ↑ number and area of renal glomeruli |            |
|                 |                   | ↓ size of renal glomeruli |            |
|                 |                   | Bone-specific activin receptors ACVR2A and/or ACVR2B deletion (mouse): | Goh et al., 2017 |
|                 |                   | ↑ femoral trabecular bone volume |            |
|                 |                   | Pregnancy and lactation | No known physiological effects |
|                 | High              | Induced endogenous overexpression (mouse): | Kim et al., 2008 |
|                 |                   | ↑ estrus stage in cycle; blood activin A and FSH; numbers of corpora lutea; granulosa cell layer thickness; ovary size |            |
| PTHrP           | Low               | PTHRP knockout PTHRP −/− (mouse): | Karaplis et al., 1994 |
|                 |                   | ↓ height; chondrocyte proliferation |            |
|                 |                   | ↑ premature chondrocyte maturation; bone mineralization |            |
|                 |                   | - Lethal at birth |            |
|                 |                   | Pregnancy and lactation | Infusion of PTH/PThrP receptor antagonist or antibody against PThrP: | Vanhouten et al., 2003 |
|                 |                   | ↓ decidual apoptosis |            |
|                 |                   | ↑ decidualization; uterine weight |            |
|                 |                   | Mammary-specific PTHrP deletion (mouse): | Williams et al., 1998 |
|                 |                   | ↓ blood and milk PTHrP; blood vitamin D; urinary cAMP; bone turnover; lactation-associated bone loss |            |
|                 |                   | ↑ bone mass |            |
|                 | High              | Mammary-specific PTHrP overexpression (mouse): | Wysolmerski et al., 1995; |
|                 |                   | ↓ mammary ductal branching and elongation | Dunbar et al., 2001; |
|                 |                   | Pancreatic β cell-specific PTHrP overexpression (mouse): | Vasavada et al., 1996; |
|                 |                   | ↓ diabetogenic effects of streptozotocin; blood glucose | Porter et al., 1998 |
|                 |                   | Bone-specific PTHrP overexpression/constitutively active PTHrP receptor (mouse): | Weir et al., 1996; |
|                 |                   | ↓ bone ossification, mineralization and length; chondrocyte differentiation | Schipani et al., 1997 |
|                 |                   | Kidney-specific PTHrP overexpression (mouse): | Izquierdo et al., 2006; |
|                 |                   | ↑ renal hypertrophy; urinary albumin excretion | Romero et al., 2010 |
| Relaxin         | Low               | Exogenous (goat): | Barlet et al., 1992 |
|                 |                   | ↑ mammary gland uptake of calcium, phosphorous, magnesium; milk calcium, phosphorous, magnesium content |            |
|                 |                   | Mammary-specific PTHrP overexpression (mouse): | Wysolmerski et al., 1995; |
|                 |                   | ↓ mammary lobuloalveolar and terminal duct development |            |
|                 | High              | Relaxin knockout Rin−/− (mouse): | Samuel et al., 2003; |
|                 |                   | ↓ renal smooth muscle cell density | Lekgaba et al., 2006; |
|                 |                   | ↑ mean arterial pressure; lung function (airway fibrosis and smooth muscle thickening); heart weight (expression of cardiac hypertrophy associated genes); renal collagen content | Debrah et al., 2011; |
|                 |                   | Pregnancy and lactation | Relaxin knockout Rin−/− (mouse): | Zhao et al., 1999, 2000; |
|                 |                   | ↓ gestational weight gain; lactation; blood sFlt-1; mammary gland development; reproductive tissue growth and remodeling (e.g., cervix, vagina); litter size | Marshall et al., 2016a,b; |
|                 |                   | ↑ labor length; mean arterial pressure; plasma osmolality; urinary albumin/creatinine ratio; vascular vasosclerosis; expression of angiogenic markers (Vegfa, Esr1, Pgr, Rdp1, Eg1n1, Hif1a, MMP14, Ankrd37); blood progesterone; mammary duct dilation | Mirabito Colafella et al., 2017; O’Sullivan et al., 2017 |

(Continued)
| Hormones | Expression levels | In vivo effects | References |
|----------|------------------|----------------|------------|
| Relaxin receptor knockout RXFP1 −/− (mouse): | ↓ mammary gland development; lactation ↑ obstructed delivery; lung fibrosis and collagen accumulation | Kamat et al., 2004; Krajnc-Franken et al., 2004 |
| Smooth muscle-specific relaxin receptor RXFP1 deletion (mouse): | ↓ cervical and vaginal epithelial development ↑ collagen content in reproductive tract organs and uterine artery | Kftanovskaya et al., 2015 |
| Administration of relaxin antibody (rat): | ↓ stroke volume; cardiac output; global arterial compliance ↑ systemic vascular resistance | Debrah et al., 2006 |
| Exogenous (rhesus monkeys): | ↓ endometrial expression of MMP1 and MMP3; endometrial progesterone production↑ blood GH and prolactin; endometrial angiogenesis (endothelial proliferation and dilatation); uterine weight; endometrial expression of TIMP1, estrogen receptor alpha; endometrial resident lymphocyte number | Hisaw et al., 1967; Bethea et al., 1989; Goldsmith et al., 2004 |
| Exogenous (rat): | ↓ systemic and renal vascular resistance; angiotensin-induced renal vasoconstriction; plasma osmolality; haematocrit; vascular smooth muscle tone↑ renal plasma flow; glomerular filtration rate; urinary sodium excretion; water intake; cardiac output; global arterial compliance; uterine artery blood flow velocity | Weisenger et al., 1993; Danielson et al., 1999; Conrad et al., 2004; Vodstrcil et al., 2012 |
| Exogenous (mouse): | ↓ cervical and vaginal apoptosis of stroma and epithelium; renal collagen content ↑ decidualization; decidual expression of laminin; cervical and vaginal proliferation of stroma and epithelium; renal vascular remodeling; renal smooth muscle cell density | Bani et al., 1995; Yao et al., 2008; Debrah et al., 2011 |
| Overexpression (mouse): | ↑ nipple hypertrophy | Feng et al., 2006 |
| Exogenous (rhesus monkeys): | ↑ blood prolactin | Bethea et al., 1989 |
| Exogenous (marmoset): | ↓ gestation length ↑ uterine expression of estrogen-associated factors; uterine macrophage infiltration; endometrial angiogenesis; uterine growth; placental growth | Einspanier et al., 2009 |
| Dysfunctional leptin Lepob/ob (mouse): | ↓ activity; oxygen consumption; body temperature↑ food intake; weight; weight gain; adiposity; blood glucose and insulin | Pelleymounter et al., 1995 |
| Heterozygous for dysfunctional leptin Lepob/+ or leptin receptor Leprdb/+ (mouse): | ↑ adiposity; adipose tissue mass | Chung et al., 1998 |
| Dysfunctional leptin Lepob/ob (mouse) with pre to mid pregnancy leptin treatment to initiate pregnancy | ↓ lactation; mammary gland development↑ food intake; gestation length | Chehab et al., 1996; Mouznih et al., 1998; Malik et al., 2001 |
| Heterozygous for dysfunctional leptin receptor Leprdb/+ (mouse): | ↑ food intake; weight gain; GSIS; blood leptin; fasting blood glucose; adipose tissue mass; hepatic glucose production; fetal weight ↔ fed and fasting blood insulin | Ishizuka et al., 1999; Yamashita et al., 2001 |
| Exogenous (rat): | ↓ food intake; blood glucose and insulin↑ blood pressure; heart rate; oxygen consumption; energy expenditure (brown adipose thermogenesis) | Scarpaces et al., 1997; Shek et al., 1998 |
| Overexpression (mouse): | ↓ time to puberty and menopause onset; liver; white and brown adipose tissue mass; hepatic glycogen and lipid storage↑ glucose metabolism; insulin sensitivity (skeletal muscle and hepatic insulin signaling); blood pressure; sympathetic nervous system activation; urinary catecholamine content | Ogawa et al., 1999; Aizawa-Abe et al., 2000; Yura et al., 2000 |
| Exogenous (mouse): | ↓ food intake; weight; weight gain; time to puberty onset; blood LH↑ lean mass percentage; ovarian and uterine weight | Pelleymounter et al., 1995; Chehab et al., 1997 |

(Continued)
TABLE 7 | Continued

| Hormones | Expression levels | In vivo effects | References |
|----------|------------------|-----------------|------------|
| Pregnancy and lactation | Overexpression (mouse): | ↓ food intake; fetal weight | Sagawa et al., 2002 |
| | ↑ blood pressure; pregnancy-associated rise in blood leptin | | |
| | Exogenous (mouse): | ↓ food intake; weight gain; GSIS; fed blood insulin; fasting blood insulin and leptin; adipose tissue mass; fetal and placental weights; placental leptin | Kukkarni et al., 1997; Yamashita et al., 2001 |
| | ↑ fed blood glucose | | |
| | Exogenous (rat): | ↑ blood pressure; proteinuria; blood markers of endothelial activation (E-selectin and ICAM-1) | Ibrahim et al., 2013 |
| | ↔ food intake; weight | | |

cAMP, Cyclic adenosine monophosphate; FSH, Follicle stimulating hormone; GSIS, Glucose-stimulated insulin secretion; ICAM-1, Intercellular adhesion molecule 1; LH, Luteinizing hormone; MMP, Matrix metalloproteinase; TIMP, Tissue inhibitor of metalloproteinase.

IL-10 by B cells (Fettke et al., 2016). hCG can also modulate the immune system even in a non-pregnant state, as shown by its efficacy in preventing the development of autoimmune diabetes in a mouse model (Khil et al., 2007). In pregnancy, hCG additionally inhibits the contractile function of smooth muscle cells in the uterus to help sustain myometrial quiescence (Ambrus and Rao, 1994; Eta et al., 1994), so as to prevent premature expulsion of the fetus. Glycosylation of hCG affects its biological activity and half-life (Fournier et al., 2015). Given its involvement with multiple systems, it is perhaps unsurprising that abnormal concentrations of hCG and hCG glycoforms have been linked with pregnancy complications such as fetal growth restriction and preeclampsia (Chen et al., 2012). However, whether the abnormal concentrations of hCG are cause or consequence of the disorders remains to be determined.

Activins

Activins are members of the TGFβ family and were first discovered for their role in stimulating FSH production and determining estrus cyclicity and fertility in mice (Ahn et al., 2004; Sandoval-Guzmán et al., 2012). Activin signaling promotes the decidualization, as well as, apoptosis of endometrial stroma cells (Table 8; Activins; Tessier et al., 2003; Clementi et al., 2013; Yong et al., 2017); processes that accommodate implantation and conceptus development (Peng et al., 2015). Additionally, activin A enhances steroid production, invasion and apoptosis of human trophoblast in vitro (Ni et al., 2000; Yu et al., 2012; Li et al., 2015). However, activins may also be of importance in modulating the physiology of the mother during pregnancy (Table 7; Activins). In normal human pregnancy, activin A concentrations gradually rise during gestation and peak at term (Fowler et al., 1998). The placenta is thought to be the main source of activin A in the maternal circulation during pregnancy, given the rapid clearance after delivery of the placenta (Muttkrishna et al., 1997; Fowler et al., 1998). A similar rise of activin in the maternal circulation is observed in pregnant ewes (Jenkin et al., 2001), while the circulating profiles in other species remain undetermined. Nevertheless, in mice, impaired activin signaling leads to poor pregnancy outcomes such as fewer viable pups (Clementi et al., 2013; Peng et al., 2015). However, there is evidence that an increase in activin may also be pathological and detrimental to pregnancy outcome. For instance in pregnant mice, infusion of activin A or plasmid overexpression of activin A results in the development of a preeclamptic phenotype; dams display hypertension and proteinuria, in addition to growth restriction and greater in utero deaths (Kim et al., 2008; Lim et al., 2015). The maternal hypertension observed likely results from pathological concentrations of activin A inducing vascular endothelial dysfunction (Yong et al., 2015). In the non-pregnant state, activins are also important for renal glomeruli development (Maeshima et al., 2000), as well as, for bone, fat and muscle metabolism (Yogosawa et al., 2013; Ding et al., 2017; Goh et al., 2017). The possible contributions of activin to these latter functions in pregnancy are currently unclear. Therefore, the impact of activin signaling on these other body systems during pregnancy remains to be determined.

Relaxin

Relaxin is a potent vasodilator (Danielson et al., 1999), and regulates hemodynamics in both the non-pregnant and pregnant state (Table 7; Relaxin; Conrad et al., 2004). In pregnant women, circulating relaxin concentration peaks in the first trimester, declines in the second trimester and is maintained until delivery in the third trimester (Quagliarello et al., 1979; Seki et al., 1985). In contrast, circulating relaxin peaks toward term in mice, rats, guinea pigs and hamsters (O’byrne and Steinetz, 1976; O’byrne et al., 1976; Renegar and Owens, 2002). In pregnant mice, relaxin deficiency leads to proteinuria, suggesting a particular role of relaxin in modulating renal function during pregnancy (O’sullivan et al., 2017). In addition, relaxin-deficient mice remain sensitive to vasoconstrictors such as angiotensin and endothelin, and are hypertensive during pregnancy (Marshall et al., 2016a; Mirabito Colafella et al., 2017). During pregnancy, relaxin-deficient mice also display stiffer uterine vessels and fetal growth is retarded (Gooi et al., 2013). Relaxin also enhances capillarisation and glucose uptake of skeletal muscles in non-pregnant mice (Bonner et al., 2013). Taken together, these data highlight the importance of relaxin in mediating changes in
### TABLE 8 | Effects of additional hormones in vitro.

| Hormones | Expression level | In vitro effects | References |
|----------|------------------|------------------|------------|
| Activins | Low | **Exogenous low physiological concentrations (human endothelial cells):**<br>↑ proliferation and migration | Yong et al., 2015 |
|          |      | **Activin receptor ACVR2A siRNA knockdown (human endometrial stromal cells):**<br>↓ decidualization | Yong et al., 2017 |
|          |      | **Activin receptor knockout ACVR2A^−/− (mouse osteoblast cells):**<br>↑ differentiation; mineral deposition; expression of osteixin, osteocalcin, and dentin matrix acidic phosphoprotein 1 | Clementi et al., 2013; Goh et al., 2017 |
|          |      | **High**<br>Exogenous (human first trimester and third trimester primary trophoblast, JEG-3 and HTR-8/SVneo cells):<br>↓ inhibin secretion<br>↑ apoptosis, invasion (SNAIL, SLUG, MMP2); hCG production; oxytocin secretion; aromatase activity (estrogen production); progesterone production | Qu and Thomas, 1993; Steele et al., 1993; Florio et al., 1996; Song et al., 1996; Ni et al., 2000; Bearfield et al., 2005; Jones et al., 2006; Yu et al., 2012; Li et al., 2014, 2015 |
|          |      | **Exogenous (mouse placental cells):**<br>↑ growth hormone releasing hormone secretion<br>↓ proliferation; differentiation | Yamaguchi et al., 1995 |
|          |      | **Exogenous (rat decidual stromal cells):**<br>↑ apoptosis (DNA degradation; caspase 3 activity) | Tessier et al., 2003 |
|          |      | **Exogenous (human endometrial stromal cells):**<br>↑ decidualisation; production of MMP2, MMP3, MMP7, MMP9 | Jones et al., 2006 |
|          |      | **Exogenous high pathological concentrations (human endometrial cells):**<br>↑ oxidative stress, permeability and endothelium production | Lim et al., 2015; Yong et al., 2015 |
|          |      | **Exogenous (mouse myoblast cells):**<br>↑ atrophy; myofibrillar protein loss; autophagy activation | Ding et al., 2017 |
|          | High | **PTHrP**<br>Low<br>Parathyroid hormone-related protein knockout PTHrP^−/− (mouse ectoplacental cone explant):<br>↑ apoptosis<br>↓ proliferation; differentiation | Duval et al., 2017 |
|          |      | **PTHrP antibody, siRNA or receptor antagonist administration (rat and mouse vascular smooth muscle cells):**<br>↑ proliferation<br>↓ PTH1R expression | Song et al., 2009 |
|          |      | **PTHrP antibody or siRNA administration (mouse podocytes):**<br>↓ high glucose induced hypertrophy | Romero et al., 2010 |
|          |      | **High**<br>Exogenous (human third trimester cytotrophoblast cells):<br>↑ apoptosis | Crocker et al., 2002 |
|          |      | **Exogenous (rat choriocarcinoma cells):**<br>↑ calcium uptake | Hershberger and Tuan, 1998 |
|          |      | **Exogenous (mouse ectoplacental cone cells):**<br>↑ trophoblast giant cell differentiation | El-Hashash and Kimber, 2006 |
|          |      | **Exogenous (human, baboon and rat myometrium):**<br>↓ spontaneous contraction; oxytocin-induced contraction | et al., 1994; Pitera et al., 1998; Slattery et al., 2001 |
|          |      | **Exogenous (rat uterine artery):**<br>↑ relaxation | Meziani et al., 2005 |
|          |      | **Exogenous (mouse podocytes):**<br>↑ high glucose-induced hypertrophy | Romero et al., 2010 |
|          |      | **Exogenous (human lung epithelial cell):**<br>↓ proliferation<br>↑ surfactant production | Sasaki et al., 2000 |
|          |      | **Exogenous (mouse osteoblast):**<br>↑ growth arrest (↓ cyclin D1 expression; CDK1 kinase activity) | Datta et al., 2005 |
|          |      | **Exogenous (rat and mouse vascular smooth muscle cells):**<br>↓ proliferation | Song et al., 2009 |
|          | High | **hCG**<br>Low<br>hCG antibody administration (human third trimester cytotrophoblast cells):<br>↑ syncytiotrophoblast differentiation | Shi et al., 1993 |
|          |      | **hCG receptor antibody administration (human third trimester cytotrophoblast cells):**<br>↑ syncytiotrophoblast differentiation; hCG release (*autocrine, self-stimulatory effects) | Shi et al., 1993 |
|          |      | **High**<br>Exogenous (human trophoblast cells):<br>↓ leptin secretion<br>↑ VEGF secretion; adhesion to uterine epithelial cells; invasion; migration; differentiation | Shi et al., 1993; Islami et al., 2003a; Prast et al., 2008; Lee C. L. et al., 2013; Chen et al., 2015 |

(Continued)
### TABLE 8 | Continued

| Hormones                                      | Expression level | In vitro effects                                                                 | References |
|-----------------------------------------------|------------------|-----------------------------------------------------------------------------------|------------|
| Exogenous (human myometrial strips/smooth muscle cells): |                  | ↓ oxytocin-induced contractions; gap junctions (connexin43)                      |            |
| Exogenous (human endometrial epithelial cells): |                  | ↑ VEGF secretion                                                                  |            |
| Exogenous (human uterine microvascular/umbilical vein endothelial cells): |                  | ↑ proliferation; capillary formation; migration                                   |            |
| Exogenous (rat aorta explant/chicken chorioallantoic membrane): |                  | ↑ vessel outgrowth and network complexity                                         |            |
| Exogenous (human uterine natural killer cells): |                  | ↑ proliferation                                                                  |            |
| Exogenous (mouse B cells):                    |                  | ↑ proliferation of specific cell populations; IL10 production; glycosylated antibody synthesis |            |
| Relaxin Low                                   |                  | Relaxin antibody administration (pregnant mouse uterine arteries):               |            |
| Exogenous (human first trimester extravillous, third trimester cytotrophoblast and HTR-8/SVneo cells): |                  | ↓ apoptosis (↓ caspase 3 and cleaved PARP; ↑ BCL2)                                   |            |
| Exogenous (human lower uterine segment fibroblast cells): |                  | ↑ matrix remodeling (↑ MMP1 and MMP9; ↓ TIMP1)                                  |            |
| Exogenous (rat uterine artery):               |                  | ↑ relaxation                                                                    |            |
| Exogenous (human endometrial/decidual stromal cells): |                  | ↑ expression of VEGF, IGBPBP1, RXFP1                                            |            |
| Exogenous (human, pig and rat myometrial strips): |                  | ↓ spontaneous contraction                                                         |            |
| Leptin Low                                    |                  | Leptin antisense oligonucleotide (human third trimester placental explants):     |            |
| Exogenous (human third trimester placental explants): |                  | ↑ immunosuppression (HLA-G)                                                      |            |
| Exogenous (human JEG-3 and BeWo cytrophoblast cells): |                  | ↑ apoptosis                                                                      |            |
| Exogenous (human primary first and third trimester trophoblast, JEG-3 and BeWo cells): |                  | ↓ apoptosis (caspase 3 activation and p53); VEGF, estradiol and progesterone release |            |
| Exogenous (mouse trophoblast cells):          |                  | ↑ proliferation; invasion (MMP2, MMP9 and fetal fibronectin); migration; immunosuppression (HLA-G); testosterone production; hCG and IL6 release |            |
| Exogenous (human myometrial smooth muscle cells): |                  | ↑ proliferation                                                                  |            |
| Exogenous (human and bovine endothelial cells): |                  | ↑ proliferation; migration; tube formation; phosphorylation of transcription factor STAT3 |            |
| Exogenous (human and rat pancreatic islets):   |                  | ↓ insulin production and secretion                                                 |            |
| Relaxin High                                  |                  | In vitro, relaxin increases decidual cell insulin-like growth factor binding protein-1 expression, a marker of decidualization (Mazella et al., 2004). It also enhances survival and proliferation of cultured human trophoblast cells (Lodhi et al., 2013; Astuti et al., 2015). During early mouse pregnancy, relaxin modulates the uterine expression of genes involved in angiogenesis, steroid hormone action and remodeling (Marshall et al., 2016b). Indeed in pregnant maternal vascular function that serve to promote blood flow to the gravid uterus during pregnancy. |            |
marmosets, exogenous relaxin improves uterine and placental growth (Einspanier et al., 2009). Relaxin infusion also alters the endometrial lymphocyte number in vivo (Goldsmith et al., 2004), which suggests a possible role of relaxin in achieving immune tolerance of the allogenic conceptus. Relaxin impedes spontaneous contractility of myometrium in humans, rats and pigs (Mclennan and Grant, 1991; Longo et al., 2003), and is thus thought to play a role in regulating the onset of parturition (Vannuccini et al., 2016). In mice with a deficiency in relaxin signaling, obstructed deliveries occur at a higher rate due to poor maturation of the cervix (Zhao et al., 1999; Kamat et al., 2004; Krajnc-Franken et al., 2004; Kaftanovskaya et al., 2015). Conversely in hamsters, the rise in circulating relaxin toward term coincides with cervical ripening in preparation for delivery (O’byrne et al., 1976). Insufficient relaxin signaling also impedes mammary development through excessive duct dilation and reduces the nursing of offspring in mice (Zhao et al., 1999; Kamat et al., 2004; Krajnc-Franken et al., 2004). Conversely, overexpression leads to hypertrophy of the nipples in non-pregnant mice (Feng et al., 2006). Hence, relaxin is important in driving changes at the maternal-fetal interface that establish pregnancy, adapts the cardiovascular system of the mother to support the pregnancy and prepares the mother for lactation post-partum.

Parathyroid Hormone-Related Protein (PTHrP)  
During pregnancy, the placenta serves as an additional source of PTHrP (Bowden et al., 1994; Emly et al., 1994), a key hormone involved in bone metabolism (Table 7; PTHrP). PTHrP concentrations in the maternal blood rise throughout gestation in humans (Gallacher et al., 1994; Ardawi et al., 1997; Hirota et al., 1997) and correlate with the rise in maternal circulating calcium during pregnancy (Bertelloni et al., 1994). However, excessively high circulating PTHrP can lead to hypercalcaemia during pregnancy (Winter and Appelman-Dijkstra, 2017). PTHrP increases maternal bone resorption, thereby enabling calcium transfer from mother to fetus for bone development (Salles, 2016). Thus, it is perhaps not surprising that complete knockout of PTHrP in mice is lethal at birth in association with abnormal bone development (Karaplis et al., 1994). Carrying one defective PTHrP copy is enough to also impede bone development and reduce snout length in mice (Amizuka et al., 1996). Mammary-specific PTHrP deletion increases maternal bone mass and protects against lactation-associated bone loss by reducing bone turnover in mice (Williams et al., 1998; Vanhouten et al., 2003). However, deleting bone-specific PTHrP increases skeletal fragility, both in the non-pregnant and pregnant state (Kirby et al., 2011). PTHrP infusion of lactating goats increases mammary gland uptake calcium, phosphorous and magnesium for transfer in milk to the neonate (Barlet et al., 1992). These findings imply that a fine balance of PTHrP production by gestational and maternal tissues must be achieved for appropriate regulation of maternal bone metabolism and offspring calcium requirements during pregnancy and lactation.

Placental-derived PTHrP may also exert additional effects on the placenta and the mother which are beneficial for offspring development and growth. PTHrP stimulates the proliferation, differentiation, outgrowth and calcium uptake of trophoblast in vitro (Table 8; PTHrP; Hershberger and Tuan, 1998; El-Hashash and Kimber, 2006). In vivo, blocking PTHrP signaling during mouse pregnancy leads to excessive uterine growth and decidualization in association with a decrease in decidual cell apoptosis (Williams et al., 1998; Vanhouten et al., 2003). Moreover, over-expression of PTHrP impairs mammary gland branching morphogenesis (Wysolmerski et al., 1995; Dunbar et al., 2001). These studies highlight a possible important regulatory role of PTHrP in the control of decidualization and mammary gland development in vivo. In non-pregnant mice, PTHrP enhances pancreatic β-cells proliferation and insulin secretion whilst it inhibits islet cell apoptosis (Vasavada et al., 1996; Porter et al., 1998; Cebran et al., 2002; Fujinaka et al., 2004). It also increases renal plasma flow and glomerular filtration rate, and exerts proliferative effects on renal glomerular and tubule cells in rodents (Izquierdo et al., 2006; Romero et al., 2010). Additionally, in vitro studies show PTHrP can induce relaxation of uterine arteries (Meziani et al., 2005). However, the significance of PTHrP on glucose-insulin dynamics and renal and vascular function of the mother during pregnancy remains to be investigated.

Leptin
Leptin is an abundant circulating hormone involved in regulating appetite. In the non-pregnant state, the adipose tissue is the exclusive source of circulating leptin. During pregnancy in humans, baboons and mice, concentrations of leptin rapidly rise throughout gestation, peaking toward term (Highman et al., 1998; Henson et al., 1999; Malik et al., 2005). The rise in leptin positively correlates with increases in maternal body fat (Highman et al., 1998). In humans, blood leptin rapidly falls to non-pregnant concentrations within 24 h of delivery, indicating that the placenta contributes to the main rise of leptin in pregnancy (Masuzaki et al., 1997). In particular, leptin is produced by the human placental trophoblast cells (Masuzaki et al., 1997). A similar post-pregnancy decline and placental trophoblast expression is seen in baboons (Henson et al., 1999). However, this is not the case for mice, as the murine placenta does not produce leptin (Malik et al., 2005). Nevertheless, leptin studies in mice still provide useful knowledge about pregnancy-related effects of leptin (Table 7; Leptin). For instance, leptin in pregnancy helps prepare the mother for lactation, as a deficiency results in impaired mammary gland development, which is detrimental for lactation post-delivery (Mounzih et al., 1998; Malik et al., 2001). Another significant effect of leptin in pregnancy observed through mouse studies is leptin resistance, whereby the dam increases her food intake in mid-pregnancy to meet increased energy demands despite an increase in circulating leptin, which in the non-pregnant state would lead to satiety (Mounzih et al., 1998). In contrast, excessive leptin significantly decreases maternal food intake and restricts feto-placental growth (Yamashita et al., 2001). Leptin exposure of rat and human islets and cultured insulinoma cells significantly decreases insulin production in vitro, demonstrating that leptin may be directly involved in glucose metabolism (Table 8; Leptin; Kulkarni et al., 1997). Indeed dysfunctional leptin signaling in
pregnancy leads to the spontaneous development of a gestational diabetic phenotype in db/+ mice, who are heterozygous for the leptin receptor (Table 7; Leptin; Yamashita et al., 2001). Further in vitro studies on placental explants or trophoblast cultures highlight a potential for leptin to be involved in immune modulation and placental hormone production, given its stimulatory effects on HLA-G and hCG expression (Table 8; Leptin; Chardonnens et al., 1999; Islami et al., 2003a,b; Barrientos et al., 2015). Additional effects of leptin on the placenta are thoroughly reviewed elsewhere (Schanton et al., 2018). Therefore, placental leptin can have systemic effects on the mother in pregnancy.

CONCLUSION

Pregnancy represents a unique physiological paradigm; there are dynamic and reversible changes in the function of many organ systems in the mother that are designed to support offspring development. In part, these changes are signaled via the placental secretion of hormones, which in turn, alter in abundance, interact with one another and exert wide effects on maternal tissues during pregnancy. For instance, steroid hormones modulate most systems of the mother throughout pregnancy. However, they also alter the production of other hormones, such as prolactin and placental lactogens, which in turn, may contribute to the physiological changes in the mother (Figure 2). However, further work is required to better define how placental hormones elicit their actions in the mother, as well as, identify the extent to which they interplay with hormones produced by maternal tissues. As the endocrine and metabolic state of the mother is also influenced by her environment, maternal conditions such as poor nutrition and obesity may modulate placental hormone production and pregnancy adaptations. Indeed, previous work has shown that an obesogenic diet during pregnancy alters the expression of PRL/PL genes in the placenta in association with mal-adaptations of maternal metabolism in mice (Musial et al., 2017). Further studies are nonetheless needed to assess the interaction of the maternal environment with placental endocrine function. Placental hormones are also released into the fetal circulation, where they may have direct impacts on fetal growth and development (Freemark, 2010). Investigations exploring the importance of placental endocrine function on fetal growth, independent of the mother, will require future examination. Collectively, further studies on the nature and role of placental endocrine function in maternal adaptations and fetal growth will undoubtedly provide novel insights into understanding of the potential causes of obstetrical syndromes such as gestational diabetes and preeclampsia that are marked by maternal physiological maladaptation.

AUTHOR CONTRIBUTIONS

TN and HY substantially contributed to the conception of the work, drafting and revision of the manuscript, preparation of the tables and approved of the final version. JL-T substantially contributed to the conception of the work, drafting and revision of the manuscript, preparation of the figures and approved of the final version. AS-P substantially contributed to the conception of the work, critical revision of the manuscript for intellectual content and approved of the final version.

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