Uncomplicated carbohydrate transport

In state of pregnancy, maternal physiology undergoes changes to facilitate constant stream of glucose to the infant; including maternal insulin resistance and increased gluconeogenesis (Catalano et al, 1992). Glucose is the main substrate for fetal, and placental metabolism (Leonce et al 2006). Both the fetus and placenta create large glucose demand for mothers, with as much as 26% of tracer glucose in animal studies administered residing in fetal or placental tissues (sawatze 2014). The vast majority of glucose supplied to the uteroplacental unit is from maternal circulation (Gallo L.A. et al, 2017). The normal transfer of maternal glucose into the placenta is passive transport through GLUT family transporters (Leonce 2006). The most prominent glucose transporter for gestation is GLUT1 (Brett, 2014). GLUT1 expression is highest in the placenta (sawatze 2014) and increases as gestation progresses (Ericsson 2005). The GLUT1 transporter is in greater concentration on the maternal face of the placenta, in microvillus structures (Laugeu et al 2013) than the fetal facing basal membrane. This makes passage of substrates across the basal membrane the rate-limiting one step of fetal nutrient transport (Brett 2014)(Acosta 2015). Within the normal physiological range of blood glucose, there is more GLUT1 on the maternal villous side than on the basal/fetal side (laugue et al 2013)(Day 2013). The expression of GLUT1 at the basal membrane has been shown to be correlated with birthweight, suggesting that greater expression leads to greater glucose flux to the developing fetus (Acosta, 2015). There appears to be greater saturation of GLUT1 transporters early in the pregnancy, with expression stagnating as gestation progresses (Gallo 2017)(Brett 2014). Because maternal glycemia is greater than that of the fetus, even in uncomplicated pregnancy, and the transporters are of passive mechanism, it has been hypothesized that maternal blood glucose drives the rate of glucose transport out of maternal circulation. Fetal and placental metabolic needs, as well as fetal insulinemia play a role in determining the transfer of glucose (Gallo 2017), meaning that simple glucose concentration differences between maternal and fetal circulation do not fully explain glucose flux to the fetus. GLUT3 is also present in the microvillus membrane of the placenta to further facilitate glucose flux. Over the course of gestation, GLUT3 expression in the placenta decreases; with expression in the third trimester just 34 percent of baseline (1st trimester) levels (Brown 2011). GLUT4 is present in the placenta, so some insulin-dependent transportation of glucose does occur (laugue 2013). However, insulin-dependent transport of glucose appears crucial in transport during early gestation, further evidenced by a decline in expression of GLUT4 as gestation continues (Ericsson 2005). Other GLUT transporters, such as GLUT 9 (Acosta 2015) are present in the placenta, largely at the microvillous membrane. GLUT9 expression; however, it does not appear to play a major role in glucose flux, as it is not correlated with glucose uptake by the fetus or infant birthweight (Acosta 2015). In rat glucose tracer studies, it was found that the placenta sequestered more radio-labeled glucose than the fetus, and it nearly reached the same level of metabolic demand as the maternal brain (sawatze 2014). Fractional uptake of tracer glucose was 2-fold less in fetuses than placenta (sawatze 2014). The majority of the variance in accumulation of glucose was explained by fetal size, not placental size (sawatze 2014), demonstrating that the fetus creates much of the demand and sequesters majority of glucose provided in maternal circulation.

Other carbohydrate metabolism mechanisms take place in the placenta. Among them are the synthesis of glycogen, which is stored in the placenta. The concentration of placental glycogen is greatest early in the pregnancy, with steady decline in glycogen storage until term (Blows 1988)(Hugget 1961). Release of glucose from the placenta is controversial. Some studies state the placental expresses glucose 6 phosphatase, implying ability to dephosphorylate and release stored glucose into fetal circulation (Laugue, 2013). Still other state that the placenta does not release glucose into circulation as the term placenta does not demonstrate expression of G6Pase enzyme (Hugget 1961). Some evidence points to placental glucose release mechanisms activated only during starvation or extreme stress *in utero* (Leonce 2006). There is evidence that the placenta participates in the lactate-alanine cycle (Schaefer 1993). The placenta participates in this cycling with the fetus, producing alanine from glycolytic pyruvate and in turn utilizing lactate that is supplied by fetal liver (Schaefer 1993).

Pregnancy complicated with obesity

Pregnancies complicated by maternal obesity can have a myriad of effects in the placenta and its transfer of nutrients to the fetus. Women who are obese often present with greater insulin levels than their normal weight counterparts (Higgins, 2011). There is evidence of increased nutrient sensing in pregnancies of women who have obesity, there is increased insulin in maternal circulation. This insulin biding to its receptor activates mTORC1 signaling (laugue et al 2013). Still other studies have found evidence that obese mothers have reductions in placental mTOR expression (Martino 2016), accompanied by no changes in upstream (akt) or downstream (S6) expression. The explanation given was that a rise in mtor was only seen when a mother was not only obese, but hyperglycemic (martino 2016). Another group found that Mtor was increased, as well as enhanced IGF1 signaling in a Swedish cohort (Jansson 2013)In pregnancy, there is gathering evidence that flux of glucose to the fetus is determined by more than maternal glycemia. The presence of maternal obesity has been found to alter expression of GLUT1, increasing its expression in the microvillous membrane, and correlating with greater birthweight (Higgins 2011). This suggests that obesity may increase overall glucose flux to the fetus, however, few studies in humans have used tracer glucose models to definitively delineate increased flux of glucose in obese pregnancy. In a study of obese, non-diabetic mothers delivering at term, it was found that there was no correlation between fasting maternal glucose concentration and fetal umbilical vein glucose, meaning that determinants of flux of nutrients relies on more than simply maternal glycemia (Acosta et al, 2015). The effects of obesity on placental nutrient transfer of carbohydrate and placental carbohydrate metabolism may rely on gestational weight gain. Oxidative stress markers are demonstrated to be greater in the placentas of obese women, with greater expression of SIRT1 and UCP2 than non-obese controls (Martino 2016). Much more often, gestational diabetes is studied instead of obesity; however, maternal obesity outside of the effects of gestational diabetes or hyperglycemia warrants further research. Especially the use of tracer glucose and flux experiments.

Other things I found that I bet you included, but have sources for

* Non-GDM, obese moms more likely to give birth to children of greater birthweight, and larger placentas (Acosta 2015) (Martino 2016)
* Increased immune cell (monocyte)in plac. Of women who are obese (Martino 2016)
* Higher plasma leptin in obese moms (Martino 2016) increased cord blood leptin of children upon births
* Could we talk about difficulty in assessing flux because of ethical implications, difficulty of tissue access, and majority of flux papers being in vitro models or from primary cultured explants or trophoblast cell lines? Perhaps in the future directions section.

Works consulted- giving it to Noura