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| Paper | Model | Exposure | Results |
| Placental Glucose Transporter Expression Is Regulated by Glucocorticoids <https://academic.oup.com/jcem/article/84/4/1445/2864464>  T.Hahn 1999 | Human placental extracts from term pregnancy treated with triamcinolone (TA)  E21 Rat placentas from rats injected with 0.38mg/kg TA once at E16  Mouse E17 placentas from GR transgenic mice using antisense RNA – this antisense is in the mother, but in placenta GR protein expression was reduced by 28% | TA in human cells and rats  GR KO model using antisense RNA in mice | Human TB cells had GLUT1 on MVM, GLUT3 on endothelial cells  GLUT1 mRNA and protein was reduced after TA  GLUT3 mRNA unaffected, but protein decreased  In rat and mouse, GLUT1 and GLUT3 localized in STB, CTB and endothelial cells(weakest in CTB)  In rats, fetal and placental wts were reduced by 73% and 53%, respectively at E21.  Implantation number unaffected  GLUT1 and GLUT3 mRNA and protein was reduced after TA  Placental wt of transgenic mice reduced by 28%, offspring of transgenic mice were 20% lighter  GLUT1 mRNA and protein was reduced  GLUT3 mRNA and protein increased  This suggests that GC may act via the GR to regulate GLUT expression in the placenta (since GC downregulates GR in placentas and other tissues) |
| Corticosterone alters materno-fetal glucose partitioning and insulin signaling in pregnant mice  Vaughan OR , 2015  <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4358686/> | 2 Mice cohorts given corticosterone in drinking water at two intervals:  1. E11-E16  2. E14-E19  The cort was designed to produce plasma cort levels that are high and similar to concentrations reported in heat/light stressed dams  Unidirectional materno-fetal clearance of non-metabolizable glucose was assessed | FIRST STUDY (ACCORDING TO THEM) TO DETERMINE *IN VIVO* GLUCOSE TRANSPORT IN CORT TREATED MICE IS REDUCED at E19  CORT in water given to mice | *Cool findings: Fetal glucose needs increase with pregnancy, maternal glucose passes to fetus through diffusion along concentration gradient*  *Transplacental glucose transport is not insulin-dependent since placental TBs do not express GLUT4 (Hay, 2006) Some have seen increased glucose placental transport in diabetic pregnant women so this is still not 100% confirmed. Localization of GLUT4 in human placentas remains unclear (from Hay 2006)*  Dams treated with cort where hyperinsulinemic but normoglycemic  On D19, transplacental 3Hmethyl-D-glucose clearance decreased by 33%, but this was normalized when mice were pair-fed (given food as much as controls eat to reduce increased food intake upon cort tx)  Cort reduced fetal weight by 8% and 19% at D16 and D19, respectively  Placental weight was reduced at both points  Number of viable pups was unaffected  At D19, materno-fetal clearance and fetal accumulation of glucose tracer was lower than controls at E19. No difference in clearance or accumulation at D16  Placental *Slc2a1&3* (GLUT 1 and 3) mRNA expression increased at E16, no change in expression on E19 🡪 THUS THE DECREASE IN TRASNPORT AT E19 WAS UNRELATED TO TRASNPORTER EXPRESSION CHANGE , SAME WITH E16 WHERE TRASNPORT WAS UNCHANGED BUT TRANSPORTER EXPRESSION DECREASED. HENCE OTHER TRASNPORTERS MAY BE INVOVLED  *Redd1* expression increased on D19 but not D16 with cort and was in sync with the reduced transplacental glucose transport at D19  No change in placental *Igf2* expression  On D16, pAkt was reduced 🡪 less active Akt |
| Maternal corticosterone regulates nutrient allocation to fetal growth in mice  Vaughan OR , 2012  <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3515836/> | 2 Mice cohorts given corticosterone in drinking water at two intervals:  1. E11-E16  2. E14-E19 | Corticosterone given in water | *Cool fndings: System A is for neutral amino acid transport which occurs via sodium-dependent active transport into the placenta then from the placenta they follow concentration gradient*  Fetal weight reduced in both  At D16, no effect on materno-fetal transfer of labeled amino acid  Fetal and placental weight reduced by 7% on D16  On D19, fetus weight decreased by 16% and placental weight was 11% smaller  Fetal weight negatively correlated with maternal corticosteroid levels at E19 but not E16  Number of viable pups per litter was unchanged with maternal cort tx  Fetal accumulation of MeAIB was not changed at E16, but placental accumulation was 35% more (expression of placental transporters was up as well, mentioned below)  At E19, placental and fetal MeAIB accumulation was reduced by 40-50%, after tx from E14-E19 (although placental transporter snat1 increased and others did not change)  Oppositely at E19, from dams treated E11-E16 (3 days post tx), fetal accumulation and clearance were 38% higher but placental accumulation was unchanged 🡪 longer term effects of GC tx after cessation of tx  At E16, *Slc38a1 and 2* expression in placenta was increased, *Slc38a4* was unchanged  At E19, *Slc38a1*expression increased, but no change in *Slc38a2 or 4*  Placentas weighed less at E16 but volume of zones did not differ. No difference in zone at E19  Reduced vascularity shown by less fetal capillaries in the labyrinthine zone by 55% at E16 |
| Dexamethasone stimulates placental system A transport and trophoblast differentiation in term villous explants. Placenta. 2010;31(2):97–105.  Audette MC, 2010  <https://www.ncbi.nlm.nih.gov/pubmed/20045184> | Human placental explants from term-pregnancies in healthy women | Term placentas collected from healthy women  Placental explants incubated with radiolabeled 14C-MeAIB for different periods  Dex added at 10^-6 M | *Cool findings: Sodium-dependent system A transporters located on both MVM and BM and transports small neutral amino acids and the non-metabolized synthetic analogue, N-methylated aminoisobutyric acid (MeAIB), which is used to assess System A activity.*  *System A contains SNAT1,2 and 4 only encoded by Slc38a1,2 and 4.*  Dex treatment increased placental uptake of MeAIB at 10-6M but not at 10-8M 🡪 stimulated system A activity at 10-6M with 30% increase of MeAIB uptake 🡪 they hypothesize that this increase in system A activity after 48h incubation may be due to acute upregulation/compensation which does not reflect permanent placental changes in transport rate  No change in mRNA expression of SNAT1,2 or 4 with Dex tx. increased hCG secretion suggesting increased regeneration of cells  No effect on placental apoptosis |
| Cortisol stimulates system A amino acid transport and SNAT2 expression in a human placental cell line (BeWo) American The Journal of Physiology. 2006;291(3):E596–E603.  Jones HN,2006  <https://www.ncbi.nlm.nih.gov/pubmed/16621896> | BeWo choriocarcinoma cell line used with 14CMeAIB infusion to assess transport of system A aa  Mannitol was included to assess passive component of MeAIB transepithelial transport (they then calculated ration of mannitol to MeAIB) | Cortisol was added to incubated cells at concentrations 5nM-2.5uM for up to 24 hours | *Cool findings: system A insufficiency is implicated in development of IUGR*  *System A transports small non-branched AA like alanine and glycine*  *SNAT4 is not expressed in BeWo cells!*  Cortisol did not affect passive transport of mannitol 🡪 passive permeability of membranes is unchanged  **Replacing sodium cations with Lithium cation inhibited 60% of the MeAIB transfer indicating that 60% of placental amino acid transfer is sodium-dependent thus 🡪 majority of placental transport depends on system A**  BeWo cells incubated with 1000nM cortisol had higher MeAIB transfer from apical to basolateral chambers over 20 minutes  SNAT1 mRNA was unchanged with cortisol tx at multiple concentrations  SNAT2 mRNA levels increased by 21% at 24h incubation of 1uM cortisol. Cort exposure of 2.5uM for 24 hours increase SNAT2 mRNA expression by 30%  Protein expression of SNAT1 was not assessed  Protein expression of SNAT2 by florescence staining showed increased expression with 1uM of cortisol for 24 hours |
| Antenatal dexamethasone treatment in midgestation reduces system A-mediated transport in the late-gestation murine placenta.  Audette MC , 2011  <https://www.ncbi.nlm.nih.gov/pubmed/21733830> | Pregnant mice treated with dex injected at E13.5 and E14.5 (midgestation exposure)  14C Mannitol was used as a negative control to ensure specificity of system  A transfer) | Dex 0.1mg/kg injection given to mice at E13.5 and E14.5  Transfer studies done at E12.5, E15.5 (24hr after tx) , E17.5 (72h after tx) and E18.5 (96h after tx)  Subset of dams were allowed to deliver their pups  First study to assess effects of antenatal GC on placental system A transport in vivo | In saline injected controls, placental and fetal weights increased from E12.5 to E15.5 to E18.5. Placental 14CMeAIB transfer also increased which was consistent with increases in system A gene expression of SNAT1, 2 and 4 as pregnancy progressed.  Mannitol transfer also increased from E15.5 to E18.5 in control and dex placentas as pregnancy progressed (makes sense)  Effects of Dex: Treatment from E13.5 and E14.5 did not alter 14CMeAIB transfer at E15.5 or E17.5, but **transfer was reduced at E18.5 in male and female placentas** (long-term after treatment cessation).  14C Mannitol transfer did not differ between control vs Dex male and female placentas on E15.5 and E18.5 🡪 passive diffusion was unaltered (they used mannitol to determine specificity of system A transport, negative control)  SNAT1,2 and 4 mRNA expression was unchanged with Dex tx in male and female placentas  Fetal weights at E15.5, E18.5 or at birth was unchanged.  No change on placental weight at E15.5, E17.5 and E18.5 in males. In females there was no change at E15.5 or E17.5, but placental weight was reduced at E18.5. 🡪 the reduced female placental weight at E18.5 increased the fetal:placental ratio at E18.5  No change in placental labyrinth or junctional zone proportions w.r.t. total placental area  No difference in maternal or ftal plasma corticosterone concentrations at E18.5 (mais c’est normal parce que it’s ages after the exposure, non? Oui oui) |
| Sex specific changes in placental growth and MAPK following short term maternal dexamethasone exposure in the mouse. Cuffe JS , 2011  <https://www.ncbi.nlm.nih.gov/pubmed/21974799> | Pregnant mice treated with Dex 1ug/kg/h for 60 hours (2.5 days) via a minipump at E12.5  Placentas collected at E14.5 (2 days- 48 hours) and at E17.5 (after 5 days of initial exposure, after 2.5 days from end of exposure) | Dex via minipump for 60 hours starting at E12.5 (so till E15) | Reduced fetal body weight at E14.5 in males and females, but not at E17.5.  Reduced female placental weight at E14.5 but not E17.5. Male placental weight was unchanged in both days.  HSD11B2 mRNA expression increased in females at E14.5, protein expression increased in females at E17.5. No change in mRNA or protein at other times and no change at all with male placentas. (not that I care about HSD11B2 since dex is not inactivated by it anyways)  *Igf2* expression not affected by Dex at either age.  MAPK  GLUT1, GLUT3, SNAT 1, SNAT2 and SNAT4 gene expression was unaltered after Dex at E14.5 and E17.5  No differences in placental areas or gross morphology  Female junctional zone cross sectional area was smaller at E14.5 (they used *in situ* hybridization to localize spongiotrophoblast marker, spongioTBs are expressed in junctional zone only) and whole placental cross sectional area was smaller |
| Synthetic Glucocorticoid Reduces Human Placental System A Transport in Women Treated With Antenatal TherapyAudette MC <https://academic.oup.com/jcem/article/99/11/E2226/2836194> | Used placental extracts from pregnancies treated with GC who delivered at various times during gestation. | Women recruited if they received 2 doses of celestone (betamethasone 12 mg intramuscular ~12 hours apart) at 23.6 and 33.9 weeks of gestation  Groups:  1. mom who delivered preterm 24h-14 days after tx  2. who delivered 14d-after treatment but still delivered before term  3.who received GC but delivered at term | Maternal age, pre-pregnancy BMI, and parity are available.  Fetuses born 24hours-14 days after the GC treatment (preterm delivery) had reduced birth weight compared to fetuses born 14days post treatment until term (term pregnancies).  No difference between birth weight of GC treated fetuses at term and term controls (not treated with GC)  Placentas of fetuses delivered between 24h-14d after the tx had significantly lower weights compared to placentas from 14d-term deliveries with GC tx. v  Uptake of 14CMeAIB by placental explants from GC treated moms who delivered 14d-term or at term after the treatment had reduced system A activity compared to placentas from preterm delivery (  Placentas from preterm delivery (24h-14d post GC) had no change in MeAIB uptake compared to control term placentas  Placentas of GC tx moms who delivered at term had significantly reduced system A transport compared to control term placentas.  Expression of placental AA transporters:  No effect of SNAT 1 or SNAT2  SNAT4 gene expression was reduced in placentas of GC treated moms at term compared to GC treated placentas of fetuses born 14d-term after GC treatment  Overall result 🡪 Delivering at term after having a GC tx earlier during pregnancy caused reduced MeAIB transfer compared to control untreated term placentas ; transport of MeAIB in GC treated placentas from 14-term or term deliveries was lower than 24h-14d deliveries. 🡪 GC may have a long-term effect on transport |
| Excess Hydrocortisone Hampers Placental Nutrient Uptake Disrupting Cellular Metabolism  Maria Mateos R , 2018  <https://www.hindawi.com/journals/bmri/2018/5106174/> | Placentas obtained from healthy women who delivered at term. Placental explants cultured with or without GC hydrocortisone 1mg/ml (2.75 mM) |  | Placentas incubated with 1mg/ml hydrocortisone had unchanged 3H-2DOG uptake, but higher concentrations of 2mg/ml and 20mg/ml showed reduced DOG uptake by 30-40%  Expression of GLUT1 was not changed with all concentrations  GLUT3 expression was increased with 2mg/ml incubation only  GLUT1 protein expression was increased at 1mg/ml, 2mg/ml and 20mg/ml of hydrocortisone  Fatty acid oxidation was reduced by 25%, 50% and 75% in explants treated with 1, 2 and 20 mg/ml, respectively  Fatty acid esterification (to make TG or to undergo oxidation ) was also reduced at all concentrations, consistent with the fact that there was less oxidation  Lipoprotein lipase activity was reduced significantly by 40% and 80% at 2 and 20 mg/ml doses, respectively (LPL is needed to allow uptake of fatty acids that will then become esterified and undergo oxidation or become TG)  Mitochondrial activity in placental explants was significantly reduced at 20mg/ml only, but TUNEL analysis showed no differences in apoptosis  MAPK-signaling pathway showed decrease ERK1,2 phosphorylation at 2 and 20 mg/ml doses  **Overall** 🡪 GC reduced DOG uptake at higher doses of GC, increased GLUT1 protein expression, increased GLUT3 mRNA expression 🡪 placental adaptive response in response to GC induced decrease in glucose uptake  Ovdrall 🡪 When glucose uptake is compromised, placenta can use lipid oxidation for energy! In this study, placental FAO was reduced and thus compensation failed. They assumed esterification will be increased since the placenta may be storing more lipids as TG if oxidation is reduced, but this was untrue. FA esterification was reduced.  Overall 🡪 When lipid storage and oxidation are reduced, lipid uptake was deemed to be reduced as well given the reduced LPL activity  Hence, glucose and lipid uptake were reduced in placentas despite available nutrients |
| Antenatal dexamethasone treatment leads to changes in gene expression in a murine late placentaBaisden B, 2008 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2040329/> | Pregnant mice injected with 0.5mg/kg intraperitoneal dexamethasone on E15, E16 and E17 | Mice injected with dex on 3 consecutive days to mimic multiple course of antenatal GC treatment | At E20, dex placentas were pale and weighed less.  Dex treatment was not associated with fetal death  Trophoblasts in labyrinth and junctional zones were swollen with loss of TB in junctional zone (marked by empty space in H&E stain)  Downregulation of 1212 genes and up-regulation of 1382 genes (shown in table 1) 🡪 decreased expression of genes involved in cell division with mixed responses on genes regulating glucose, cholesterol and steroid metabolism  No difference in gene expression of *Igf1 or 2* |
| Growth restricting effects of a single course of antenatal betamethasone treatment and the role of human placental lactogen.Braun T , 2013 <https://www.sciencedirect.com/science/article/pii/S0143400413000751?via%3Dihub> | Humans who received a single course of betamethasone treatment during pregnancy  Single course is 2 x 12 mg betamethasone in 2 consecutive days given intramuscularly  Collected maternal plasma at 4 timepoints:  1.prior to first GC administration  2. 24 hours after first GC administration and right before the second dose of 12mg betamethasone  3. 48 hours after the first GC tx (24h after second dose)  4. Finally one sample collected during delivery at 4-5cm cervical dilation |  | *Cool findings: Placental lactogen may play a role in regulating fetal growth through an indirect mechanism potentially by stimulating IGF release*  Single Betamethasone tx was associated with reduced fetal growth and reduced head circumference by -8.6%, reduced body length by 06% compared to control offspring.  Birth weight was reduced by -18.2% after bet tx.  Placental width was reduced by -5.5% with insignificant but reduced surface area by -14.7%  Birth weight was positively associated with placental surface area.  Bet increased STB cell circumference (swollen?) and cell surface  Placental lactogen stain showed similar intensity in BET placentas and control, no effect on lactogen protein levels |
| Enhanced placental GLUT1 and GLUT3 expression in dexamethasone-induced fetal growth retardation.  Langdown ML and Sugden MC , 2001  <https://www.ncbi.nlm.nih.gov/pubmed/11738800> | Pregnant rats given dexamethasone by subcutaneous infusion at E15 via a pump atr a dose of 100 or 200 ug/kg body wt/day  Sac at E21 |  | Reduced fetal and placental weights that was dose-dependent, the 200 dex dose had a larger impact on weight reduction  No effect of dex on gestation length or offspring number or viability  Maternal blood showed higher but insignificant blood glucose when dex treated at 200 dose.  Fetal hypoglycemia was evident and showed 36% and 49% reduction in fetal plasma glucose at 100 and 200 ug dex, respectively.  Increase in placental GLUT1 protein expression by 1.6 and 1.9 fold at 100 and 200 ug/kg/day dex doses, respectively.  Increased GLUT3 protein expression by 2.3 fold only with the 200 ug dex dose.  PPAR-y is needed for placental vascularization.  No change in placental PPAR-y protein expression.  Suppression of fetal cardiac PPAR-y protein expression at both doses with a marked decrease at the higher 200 ug dex dose. 🡪 PPAR-y is needed for heart function and thus this reduction may indicate heart failure in later life of offspring |
| **Effects of chronic maternal dexamethasone treatment on the hormones of the hypothalamo-pituitary-adrenal axis in the rat fetus**  DUPOUY JP 1987  <https://www.karger.com/Article/PDF/242712> | Dex treated rats at E15 till E21 with dexamethasone acetate n drinking water at 10ug/ml dose |  | 21 day old rats offspring from stressed dams showed reduced headless body weight (- 66%)  Lower offspring hypothalamic Corticotropin releasing factor (sam as CR hormone) content and concentration from 21-day old rats of stressed dams (-57 and -67%, respectively )  Lower pituitary ACTH content (-93 %) and lower plasma ACTH levels (below detected levels so ‘vraiment trop’ low) in 21d old offspring from stressed dams  Lower adrenal corticosterone concentrations (-74%) and lower plasma corticosterone levels (below sensitivity limit so vraiment low)  Severe atrophy of adrenals with reduced absolute adrenal weight (- 83%) and reduced relative adrenal to body weight  Overall 🡪 maternal GC tx has negative effects on offspring Hypothalamus, can casue a negative feedback mechanism since CRH, ACTH and cort are all reduced in offspring |
| Dexamethasone-induced intrauterine growth restriction impacts the placental prolactin family, insulin-like growth factor-II and the Akt signaling pathway.  Ain R , 2005  <https://www.ncbi.nlm.nih.gov/pubmed/15845918/> | Rats injected subcutaneously with 100ug dexamethasone acetate in 0.1% ethanol at E13.  Pump was then implanted to release 200ug dex acetate/kg body wt/day  Sac on E20 |  | Dex did not affect litter size or fetal viability  Significant reduction of fetal and placental weights  Reduced maternal body weight gain compared to controls  Prolactin family gene and protein expression was reduced in junctional zone but increased in labyrinth zone  Decrease of junctional zone. *Igf2* mRNA expression but no effect on it in labyrinth zone 🡪 can be a contributor to placental growth restriction  Decrease protein expression of phosphorylated/active Akt, but no effect on total Akt 🡪 attenuated Akt signaling  BAD (apoptosis marker) is phosphorylated by Akt to prevent apoptosis, showed decreased BAD phosphorylation but no effect on total BAD protein expression 🡪 increased placental apoptosis |
| **Does in utero exposure to synthetic glucocorticoids influence birthweight, head circumference and birth length? A systematic review of current evidence in humans.**  Khan AA , 2011  <https://www.ncbi.nlm.nih.gov/pubmed/21133966/> | Systemic Review from human studies : Effects of GC on human birth wt, gestation age.. | Compiled studies from humans that used betamethasone during pregnancy.  Major differences:  1:different doses and timing of exposure | 10 out of 17 studies reported significant reduction in birthweight of infants exposed to antenatal GC, while other 7 studies reported no relation 🡪 studies methods varied largely!  All studies used betamethasone.  5 out of 9 studies reported reduced head circumference  Birth length and ponderal index: 2 out of 5 studies reported reductions in these  Overall 🡪 synthetic GCs contribute to reduced birth size but there is a lot unknown and studies conflict in their used methods, results and measured variables |
| Prenatal stress induces intrauterine growth restriction and programmes glucose intolerance and feeding behaviour disturbances in the aged rat.  Lesage J , 2004  <https://www.ncbi.nlm.nih.gov/pubmed/15128277> | Rats exposed to stress of being in a plastic cylinder in a lighted environment 3x/day for 45 minutes each during last week of gestation.  Sac at E20 | Stress by confinement in lighted environment exposure | Fetuses of stressed dams had reduced body weights in males and females 🡪 IUGR  Fetal plasma glucose and corticosterone levels were reduced but leptin was unchanged.  Effect of antenatal stress on offspring:  24-month old male rats had unchanged weights after antenatal exposure of stress  Basal plasma corticosterone levels were higher but not significant  Plasma leptin was reduced  OGTT showed higher plasma glucose levels in antenatally stressed rats at all timepoints (0, 60 and 120 minutes tested), but insulin secretion was similar  No effect of antenatal stress on adult food intake, but after fasting the rats for 24 hours, rats’ intake was increased in 3 hours post fast compared to offspring from unstressed dams. |
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| <https://www.ncbi.nlm.nih.gov/books/NBK279156/>  GREAT RESOURCE FOR GC EQUIVALENCIES AND POTENCY, TABLE 1  Nicolaides N , 2000 |  |  | Dex has long half-life, highest HPA suppressive capacity compared to other synthetic GCs |
| <https://www.ncbi.nlm.nih.gov/pubmed/9129953>  GOOD REVIEW ON PLACENTAL TRANSPORTERS ACTIVITY AND EXPRESSION  SIBLEY C , 1997 |  |  | Diffusion of nutrients and transport-mediated transport |
| Regulation of Nutrient Transport across the Placenta LAGER S AND POWELL TL 2012  <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3523549/>  REVIEW ON PLACENTAL TRASNPORT INFLUENCED BY MULTIPLE FACTORS/CONDITIONS |  |  |  |
| Endocrine Regulation of Feto-Placental Growth  FOWDEN AL AND FORHEAD AJ 2009  MINI REVIEW  <https://www.karger.com/Article/FullText/245927#ref35> |  |  |  |
| Prenatal glucocorticoids and long-term programming  Seckl JR , 2004  <https://www.ncbi.nlm.nih.gov/pubmed/15554887> |  |  |  |
| **Sex differences in plasma corticosterone in mouse fetuses are mediated by differential placental transport from the mother and eliminated by maternal adrenalectomy or stress.**  Montano MM 1993  <https://www.ncbi.nlm.nih.gov/pubmed/8107008> | Sex differences in maternal cort transfer ro fetus. Mouse female fetuses acquire more cort than males |  |  |
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| <https://www.glowm.com/pdf/Antenatal%20Corticosteroids%20to%20Reduce%20Neonatal%20Morbidity.pdf> |  |  | Guidelines for antenatal GC treatment, cool info |