XVI CONGRESSO
REGIONALE
AMD MOLISE

14 OTTOBRE 2023
HOTEL CENTRUM PALACE
CAMPOBASSO

Influenze Bidirezionali fra Madre e Figlio sull'Outcome della Gravidanza

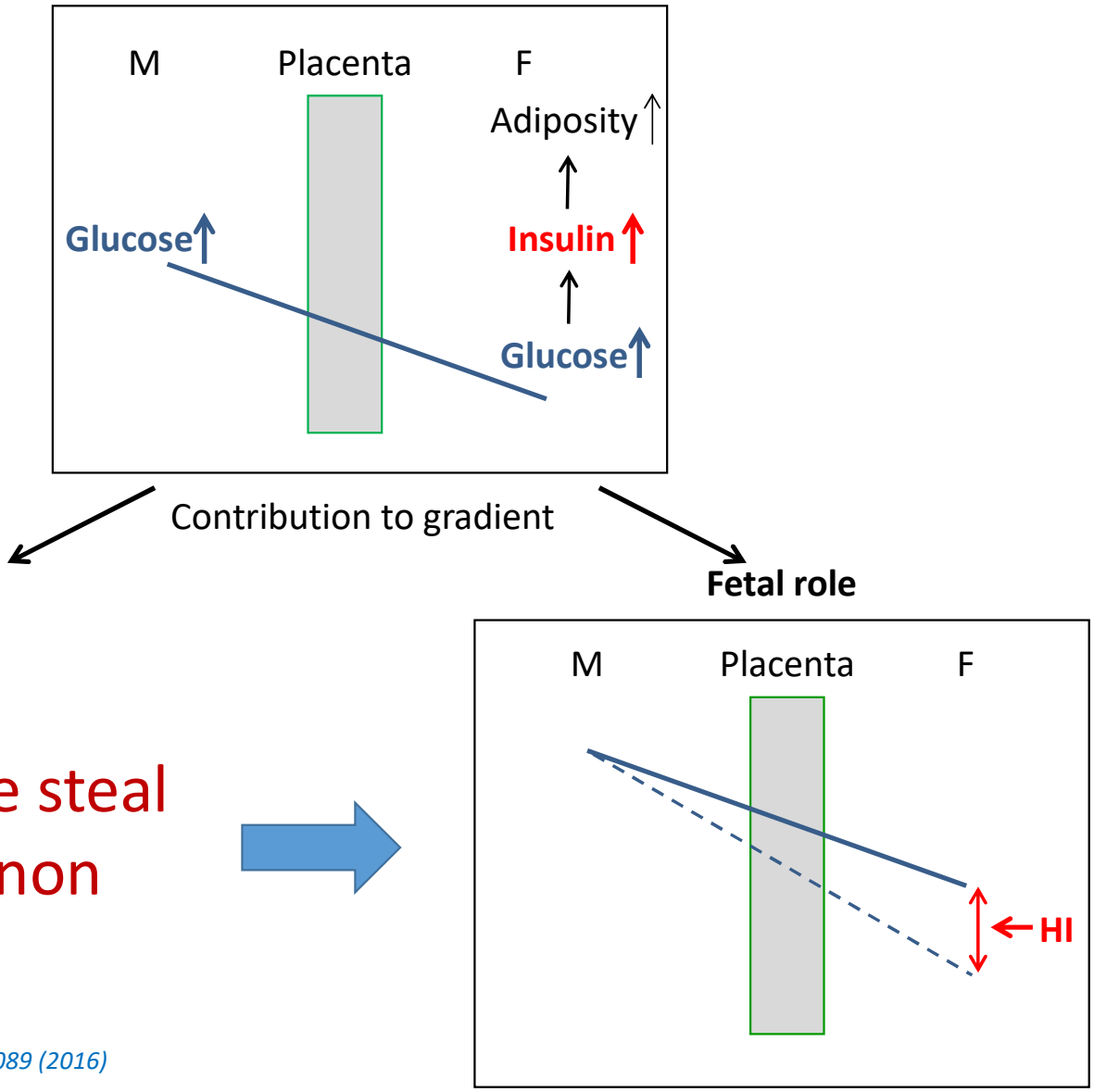
Angela Napoli

Gestational Diabetes

GDM arises in Women who have
a **chronic defect in pancreatic beta cell function** that

- first becomes **clinically apparent** as an **inability to sufficiently increase insulin secretion** in response to the metabolic challenge posed by the severe insulin resistance of late pregnancy, resulting in the hyperglycaemia by which GDM is diagnosed

- underlies an **elevated post partum Lifetime Risk of developing Type 2 diabetes**.



Fetal glucose steal phenomenon

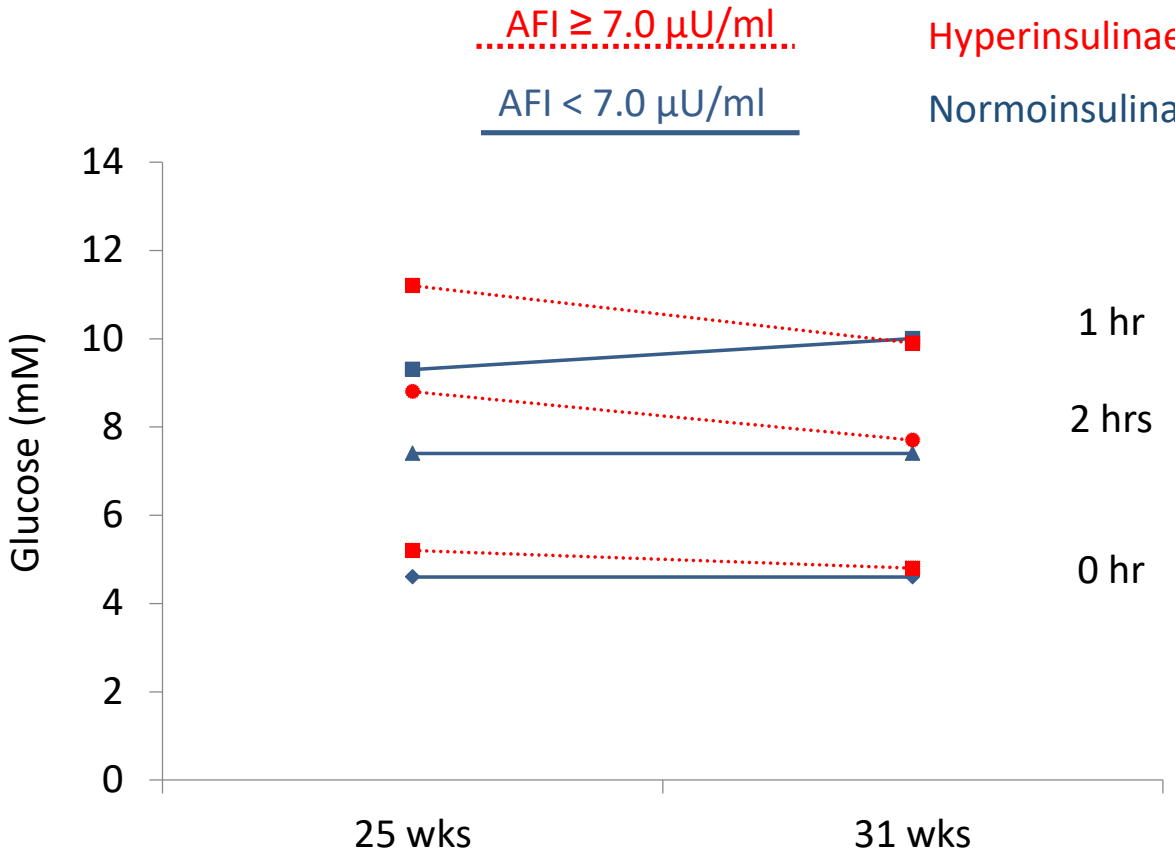
Desoye & Nolan Diabetologia 59: 1089 (2016)

Fetal Hyperinsulinism Blunts Maternal Glucose Levels after oGTT

OGTTs were performed in 34 mothers with GDM at 25 and 31 weeks prior to any commencing insulin therapy
Amniocentesis was also performed at week 31 and AFI levels were measured

In the mothers of the Normoinsulinaemic fetuses:

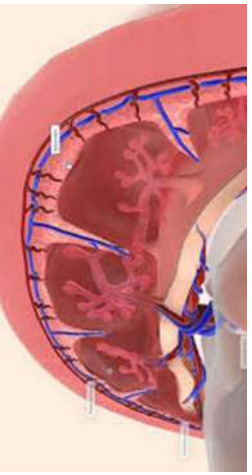
Maternal glucose tolerance deteriorated from the 1st to the 2nd time point with **higher 1 h post-load glucose value**

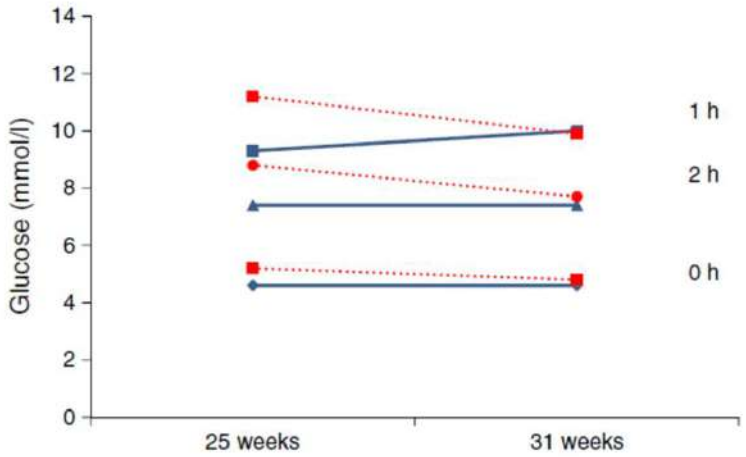


In the mothers of the Hyperinsulinaemic fetuses:

Maternal Glucose glucose tolerance improved from the 1st to the 2nd time point with **lower post load glucose values**

Weiss et al. Am J Obstet Gynecol 184: 470-475, 2001





The Placentas
of **Hyperinsulinaemic, Macrosomic fetuses** might also have been **Larger**, such **that increased Placental Glucose consumption** could also have contributed to **the blunting of the OGTT glucose rise** observed in the mothers

Thus, there is a **RISK that GDM will Not be diagnosed in Women with the most affected Fetuses**

33% of mothers of **Hyperinsulinemic Fetuses delivered Neonates** with a **weight >4.000g** v
0% of mothers of **Normoinsulinemic fetuses**

Desoye & Nolan Diabetologia 59: 1089 (2016)

Clinical Implications of Glucose Steal Phenomenon

Controlling Maternal Blood Glucose may not be enough to prevent Excessive Fetal Fat Accumulation

May blunt maternal Postload Plucose Peaks $\Rightarrow$ GDM may become Unrecognized

Weiss et al. Am J Obstet Gynecol 184: 470-475, 2001

Desoye & Nolan Diabetologia 59: 1089 (2016)

Can Tight Glycaemic Control Later in Pregnancy, reverse Fetal Hyperinsulinaemia and the Fetal Glucose Steal?

Treatment of GDM from 24 to 28 weeks can **reduce the rate of LGA births** suggest

- can **reverse fetal hyperinsulinaemia**, at least when **hyperglycaemia** is **mild**

- does **not** reduce the **Rate** of elevated **cord C-peptide levels** whereas measured
- does **not significantly reduce Neonatal Hypoglycaemia** needing i.v. glucose therapy
- Despite **Normalisation of Birthweight**, has **not** been shown to **normalise excess fetal adiposity**

*unless treatment with insulin is initiated according to the presence or absence of an **elevated AFI** concentration, (the rate of elevated cord blood C-peptide levels in neonates was markedly reduced).*

Weiss et al. Am J Obstet Gynecol 184: 470-475, 2001

Desoye & Nolan Diabetologia 59: 1089 (2016)

Can Tight Glycaemic Control Later in Pregnancy, reverse Fetal Hyperinsulinaemia and the Fetal Glucose Steal?

Other Nutrients i.e Amino Acids & Fatty Acids &/or Hormones/Cytokines could also contribute, particularly in the pregnancies of Obese Mothers with Normal Glucose Tolerance but with ⇑ cord blood C-peptide levels at birth

Weiss et al. Am J Obstet Gynecol 184: 470-475, 2001

Desoye & Nolan Diabetologia 59: 1089 (2016)

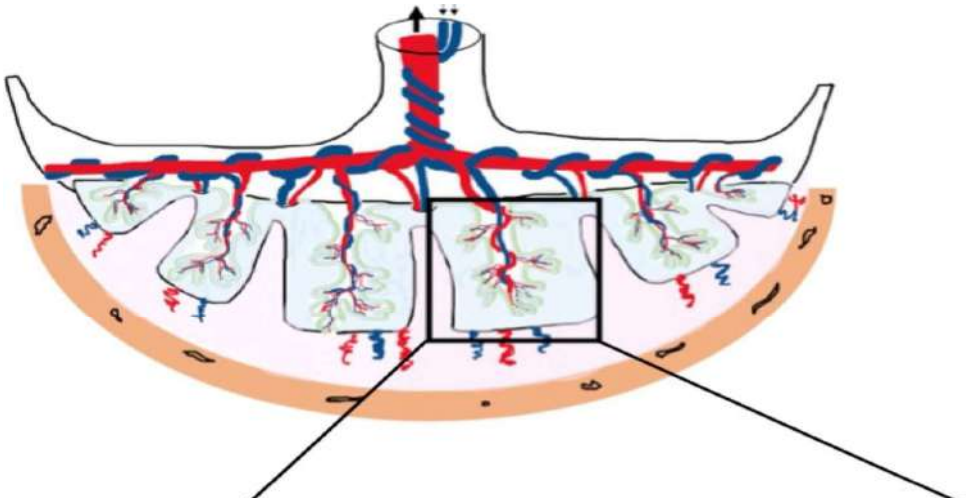
Evidence support the emerging concept of a

BI-DIRECTIONAL MATERNAL–FETAL METABOLIC INTERPLAY

in which the mother and the fetus each influence the metabolism of the other

DOES FETAL SEX MATTER?

D. Jaskolka, Diabetologia (2015) 58:2469–2475



Braun *et al. Biology of Sex Differences* 2022, **13**(1):50
https://doi.org/10.1186/s13293-022-00459-7

REVIEW

Sex at the interface: the origin and impact of sex differences in the developing human placenta

Amy E. Braun[1*]

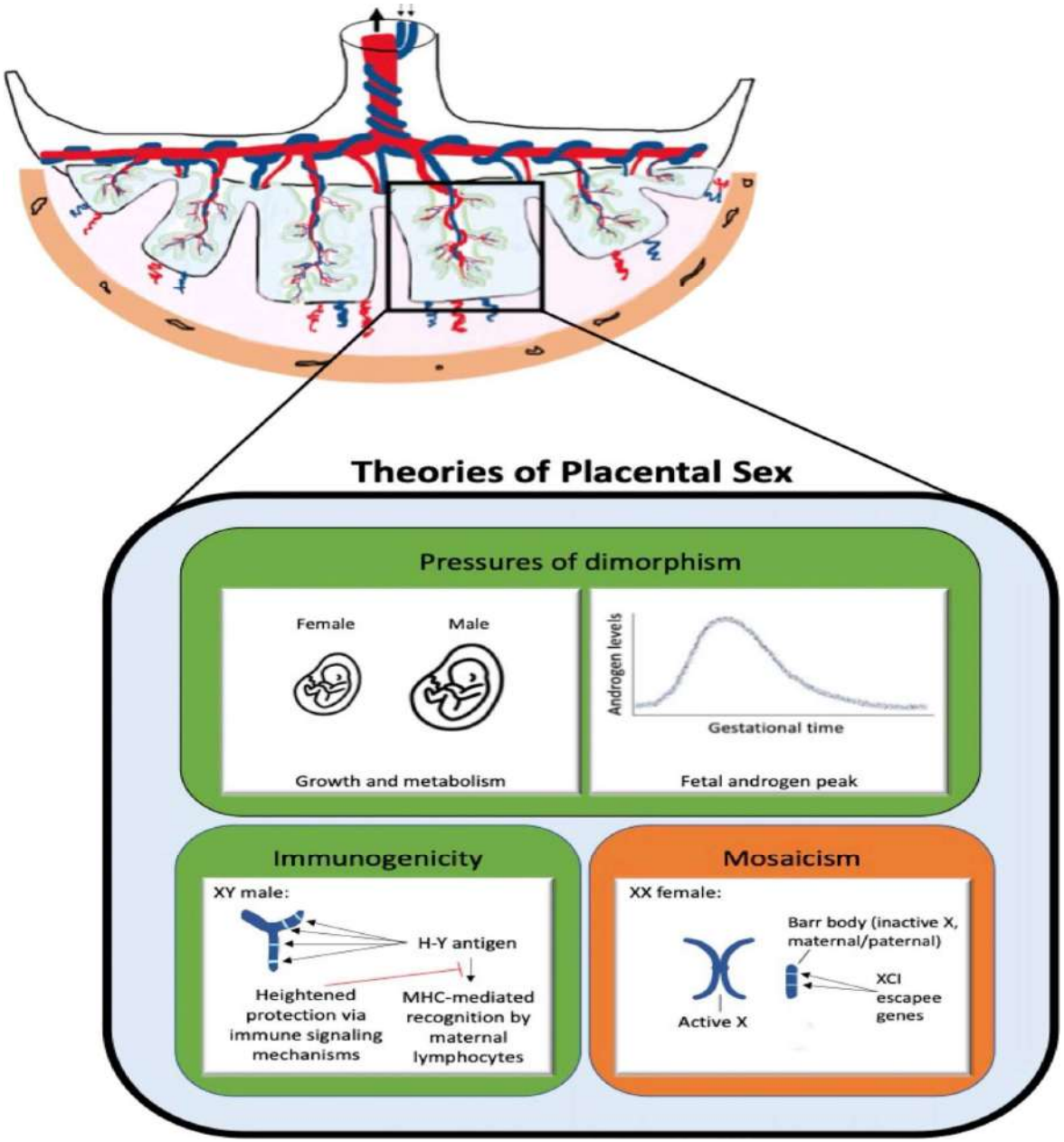
How does Sex manifest in the Human Placenta?

The placenta is a critical determinant of both fetal & maternal health is

- the **interface** for the **exchange of nutrients and waste**
- the **source** of **hormones & immune factors** that facilitate pregnancy maintenance & fetal growth

During the process of **Human Placentation**, trophoblast cells from the outer trophectoderm layer of the blastocyst invade maternal decidua to form the placenta & chorionic membranes the resulting

EXTRAEMBRYONIC COMPARTMENT SHARES
THE **BIOLOGICAL SEX** OF THE DEVELOPING **EMBRYO**



Braun *et al. Biology of Sex Differences* 2022, **13**(1):50
https://doi.org/10.1186/s13293-022-00459-7

REVIEW

Sex at the interface: the origin and impact of sex differences in the developing human placenta

Amy E. Braun[1*]

- Placental Sex differences exist from Early Prenatal Development, and may help explain Sex differences in Pregnancy Outcomes

- Transcriptome Profiling of Early to Mid-gestation Placenta reveals that Immune signaling is a Hub of Early Prenatal Sex differences

GDM: does Fetal Sex matter?

Sex of the Baby and Risk of GDM in the Mother: a Systematic Review and Meta-analysis

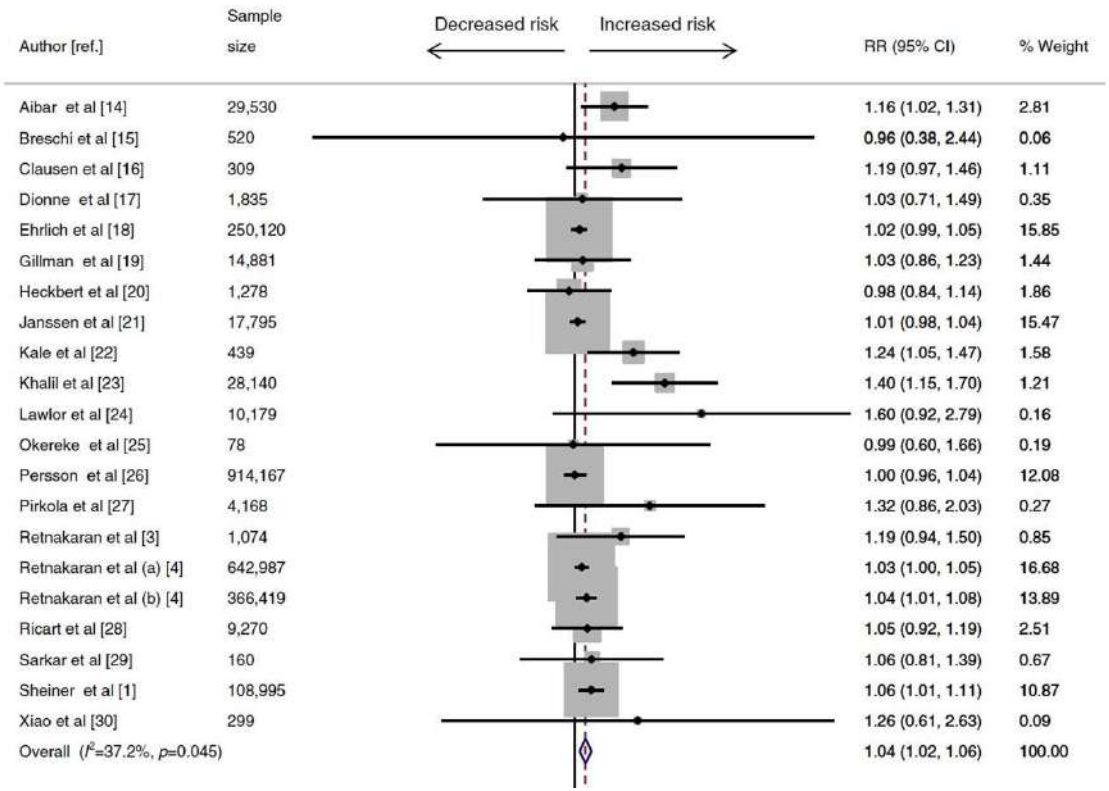
The **Sex of a Baby** has been associated with the **Risk** of **Adverse Obstetrical Outcomes** at **Delivery**

Indeed, **carrying a Male Fetus** confers **increased risks** of **Multiple Adverse Perinatal Outcomes**

- Premature rupture of membranes
- Pre-term delivery
- Failure to progress in the first and second stages of labour
- Non-reassuring fetal heart rate patterns
- Ombilical cord prolapse, true umbilical cord knot
- Caesarean delivery
- Lower Apgar Scores

D. Jaskolka, Diabetologia (2015) 58:2469–2475

Sex of the baby and risk of GDM in the mother: a systematic review and meta-analysis



In this study of **over 2.4 million pregnancies**, we demonstrate that

Women carrying a **MALE FETUS** have a **4% higher relative risk of GDM** than those carrying a girl

Meta-analysis of the association in women between carrying a **Male fetus vs Female fetus** & the **risk of GDM**

D. Jaskolka, Diabetologia (2015) 58:2469–2475

Sex of the baby and risk of GDM in the mother: a systematic review and meta-analysis

Women carrying a **MALE FETUS**

Poorer Maternal beta cell function

Higher Postprandial glycaemia and an **Elevated risk of GDM**

independently of classical Diabetes Risk Factors (i.e. Age, Ethnicity, BMI, Family history of diabetes)

the observed genotype-dependent effects of **fetal sex** on **maternal HbA1c** at delivery

*the recognition that women carrying a fetus with **Beckwith–Wiedemann syndrome** have>2 fold increase in their risk of developing Gestational Hypertension than when the same mothers carry non-affected siblings*

D. Jaskolka, Diabetologia (2015) 58:2469–2475

Fetal sex has implications for Maternal Risk of Diabetes both During Pregnancy and After Delivery

GDM is a major maternal medical complication of pregnancy where current **understanding** of its **pathophysiology does not** necessarily implicate **the fetus as a primary determinant**

Although the mechanism **underlying normal ßcell adaptation** has not been fully elucidated they involve

Placentally derived maternal hormones

*(i.e. Human Placental Lactogens & Prolactin) acting through downstream mediators (including the transcription **factor FoxMI**, the serotonin synthetic enzyme **Tph1** and the **cell cycle regulator menin**), ultimately **leading to the expansion of beta cell mass** and **enhanced insulin secretion***

Sex-specific selection in utero

Female fetuses** are more likely to undergo **Spontaneous Abortion** than male fetuses **in the presence of poorer prepregnancy beta cell function

D. Jaskolka, Diabetologia (2015) 58:2469–2475

The Impact of Fetal Sex on Risk Factors for GDM & related Adverse Pregnancy Outcomes

Regional database: all pregnancies occurring in Tuscany, Italy, (2010–2018)

Purpose

- confirm the relation between **Male fetal sex** and **GDM diagnosis**
- whether **fetal sex modifies the impact of some established clinical risk factors** on **GDM incidence**

Table 3 Effect of risk factors on adverse pregnancy outcomes in pregnancies with GDM, stratified by fetal sex. ORs were calculated after adjusting for all considered confounders

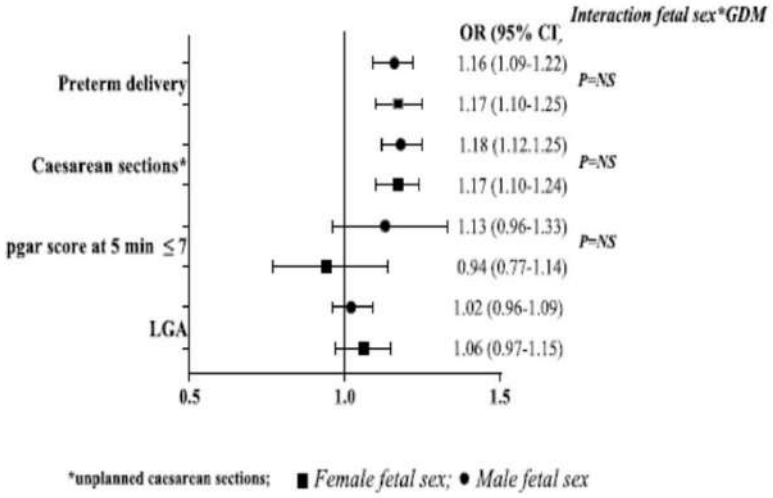
	Adverse pregnancy outcomes (Odds Ratio (95% CI))											
	LGA			Unplanned caesarean sections			5-min-Apgar ≤ 7			Preterm delivery		
Fetal sex	Male	Female	*p**	Male	Female	*p**	Male	Female	*p**	Male	Female	*p**
Age ≥ 35 year	0.93 (0.83–1.04)	0.934 (0.80–1.09)	NS	**1.37 (1.23–1.1.52)**	**1.59 (1.41–1.78)**	NS	1.00 (0.72–1.39)	**1.54 (1.04–2.27)**	NS	**1.26 (1.13–1.41)**	**1.22 (1.08–1.38)**	NS
Ethnicity	**1.22 (1.09–1.39)**	**1.46 (1.23–1.73)**	NS	**1.15 (1.01–1.30)**	**1.34 (1.17–1.54)**	NS	1.02 (0.70–1.49)	1.08 (0.68–1.70)	NS	**1.38 (1.22–1.56)**	**1.28 (1.12–1.47)**	NS
Primiparous	**0.57 (0.51–0.64)**	**0.47 (0.40–0.56)**	NS	**2.59 (2.33–2.89)**	**2.07 (1.83–2.33)**	0.004¶¶	1.30 (0.94–1.79)	**1.50 (1.01–2.20)**	NS	0.91 (0.82–1.02)	0.93 (0.82–1.04)	NS
BMI ≥ 30 kg/m^2	**1.68 (1.45–1.95)**	**2.44 (2.04–2.92)**	0.001¶	**1.51 (1.31–1.74)**	**1.49 (1.23–1.72)**	NS	**2.02 (1.39–2.95)**	1.50 (0.93–2.52)	NS	1.04 (0.89–1.22)	**1.21 (1.03–1.42)**	NS

Acta Diabetologica G. Seghieri, G. Di Cianni, · et al

The Impact of Fetal Sex on Risk Factors for GDM & related Adverse Pregnancy Outcomes

Purpose

- confirm the relation between **male fetal sex** & **GDM**
- **Impact of fetal sex on established clinical risk factors** on **GDM incidence**



Results

GDM was **diagnosed** in 21,613 pregnancies (**10.5%**).

Male Fetal sex predicted **a higher adjusted risk of GDM** (~ **10%**)

Pre-pregnancy Obesity:
independent established clinical risk factor for GDM

LGA excess risk significantly increased in GDM giving birth to **a Female** newborn. (~ **45%**)

Primiparous pregnancies with **Male offspring** are associated with a modest but significantly higher risk of **Unplanned Caesarean Sections.**

Acta Diabetologica G. Seghieri, G. Di Cianni, · et al

The Impact of Fetal Sex on Risk Factors for GDM & related Adverse Pregnancy Outcomes

Evidence suggest that **Girls are more Insulin-resistant than boys at birth**
(⇑⇑ levels of Cord Insulin & C peptide observed in the deliveries of Female births)

In animal models, **both GDM** & **Pregestational Obesity** impact in a **Sex-dimorphic manner** on **Placental expression of some genes** involved in **key metabolic or infammatory pathways** modulating the **risk of LGA** as well as of **Diabetes** or **Obesity** in the **Offspring later in the adult life**

In the latter, compared to female fetal sex**, Male Fetal Sex was related to 20% increase in risk of Unplanned Caesarean Sections** partially explained by the greater trend of births with **LGA in Primiparous Pregnancies** with **Male fetus**

Gender diferences in insulin & C-peptide concentrations at birth using cord blood collection. Arch Endocrinol Metab (2016)
Measurement of cord insulin and insulinrelated peptides suggests that girls are more insulin resistant than boys at birth. Diabetes Care (2007)
Sex-specifc associations of insulin-like peptides in cord blood with size at birth. Clin Endocrinol (Oxf) (2018) Joshi A, Azuma R, Gestational diabetes and maternal obesity are associated with sexspecifc changes in miRNA and target gene expression in the fetus. Int J Obes (Lond) (2020)
Sex modifes placental gene expression in response to metabolic and infammatory stress. Placenta 78:1–9. (2019)

Sex of the baby and future maternal risk of Type 2 diabetes in women who had GDM

DIABETIC Medicine
DIABETES UK
KNOW DIABETES. FIGHT DIABETES.

It has recently emerged that carrying a male fetus is associated with poorer maternal β-cell function and an increased risk of gestational diabetes,
whereas the development of **GDM when carrying a girl** (as compared with a boy) **predicts a comparatively higher risk of early**

Among Women with GDM, those who are carrying a Girl have a slightly higher overall future risk of Type 2 Diabetes

carried a **Boy** (n = 12 134).

Results
Over median 5.5 years follow-up, **5483 women (23.5%) were diagnosed with diabetes**.
Compared with those who carried a boy, **women who had a girl** had an **elevated risk of subsequently developing diabetes (adjusted hazard ratio** = 1.06, 95% CI 1.01–1.12).

R. Retnakaran, B. R. Shah

Worldwide several studies have examined the associations of

- Fetal Sex
- *Paternal Age*
- *Maternal Age*

with

- Pregnancy Outcomes

Does Sex matter?
Association of fetal Sex and Parental Age with Pregnancy Outcomes in Taiwan: a cohort study

Besides fetal sex, the sex of the parents matters as well

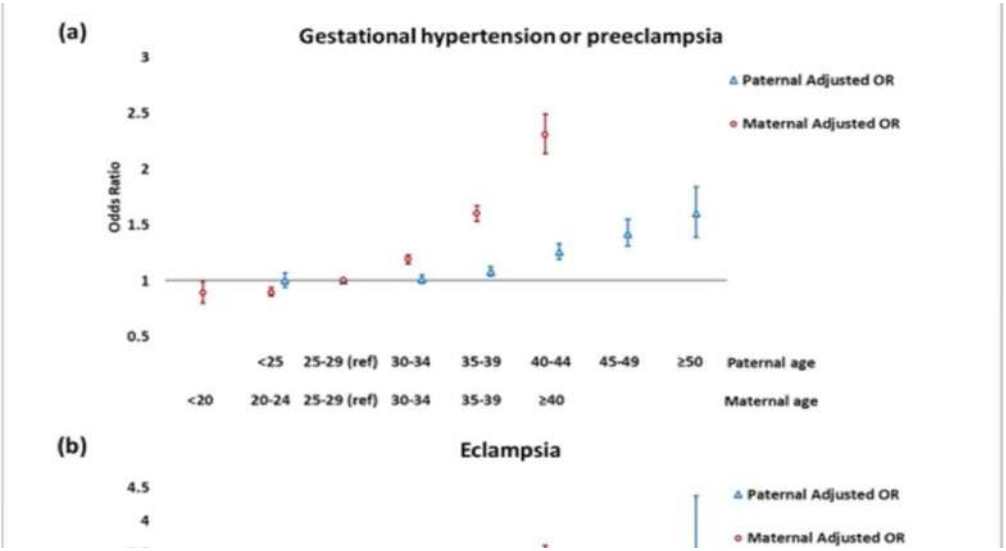
Advanced paternal age, while less influential on pregnancy outcomes than maternal age, is related to **chromosomal** & **non-chromosomal birth defects**, **autism spectrum disorder** & **childhood cancer**

In 2018 the **mean Age for Mothers** and **Fathers was 32.0 years** & **34.5 years**, respectively

We focused on two types of adverse pregnancy outcomes:

- Hypertensive Disorders of Pregnancy (Gestational Hypertension, Preeclampsia & Eclampsia)
- Preterm delivery

Tsung Yu, *BMC Pregnancy and Childbirth* volume 20, Article number: 348 (2020)

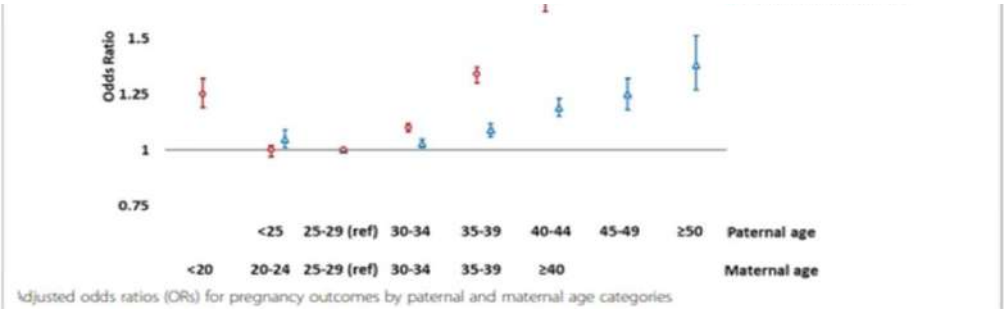


Gestational Hypertension/Preeclampsia

After considering other Parent's Age (paternal & maternal age) and covariates
a significantly **stepped increase in the risk** of all primary end points

Fathers aged ≥50 years ≅ ⇑ **risk of Gestational Hypertension/Preeclampsia** OR: 1.60

Preterm Delivery OR: 1.38



Preterm Delivery

Does sex matter? Association of Fetal Sex and Parental Age with pregnancy outcomes in Taiwan: a cohort study

Objective

the association of **Fetal Sex** & **Parental Age** with **Gestational Hypertension/Preeclampsia, Eclampsia** & **Preterm Delivery**

Nationwide study: 1.347.672 live births born between 2004 and 2011 in Taiwan

Results:

% Gestational Hypertension/Preeclampsia : 2.27%
% Eclampsia: 0.07%
% Preterm Delivery: 6.88%

Analysis on Fetal Sex

relatively more **Female Births** were linked to **Gestational Hypertension/Preeclampsia**
more **Male Births** linked to **Preterm Delivery**
compared to the whole population.

Conclusions

Both Paternal & Maternal Age, as well as Fetal Sex, were associated with the risk of pregnancy outcomes.

Tsung Yu, *BMC Pregnancy and Childbirth* volume 20, Article number: 348 (2020)

www.nature.com/pr

BASIC SCIENCE ARTICLE OPEN

Fetal sex and maternal fasting glucose affect neonatal cord blood-derived endothelial progenitor cells

Elisa Weiss[1], Barbara Leopold-Posch[1], Anna Schrüfer[1], Silvija Cvitic[2] and Ursula Hiden[1]✉

…we addressed the question whether, within **Healthy, Non-diabetic Pregnancy**, **Fetal Sex** & **Maternal Metabolic Hallmark**

FPG & Post-load Glycemia at Midpregnancy, Gestational Weight Gain, Pre-pregnancy BMI

affect Neonatal **ECFC Function**.

Elisa Weiss.., U Hiden 2022 Pediatric Research (2022) 92

Fetal Sex & Maternal Fasting Glucose Affect Neonatal Cordblood-derived Endothelial Progenitor Cells

Maternal Cardiovascular Risk Factors (**CVRF**) in pregnancy: obesity & hyperglycemia, transmit to the fetus & affect placental and fetal endothelial function

Moreover, a **sex dimorphism in endothelial function** and **susceptibility towards CVRF** exists already **in utero**. **Endothelial colony-forming cells** (**ECFC**) are **circulating endothelial progenitors** highly present in **neonatal cord blood** & sensitive to **CVRF**.

PURPOSE

whether **Fetal Sex** or **Subtle Maternal Metabolic Changes** within healthy range **alter fetal ECFC outgrowth**.

METHODS:

Outgrowth of ECFC from **Cord Blood** of **Male (n = 31)** & **Female (n = 26) Neonates**

Elisa Weiss.., U Hidene 2022 Pediatric Research (2022) 92

Days until Colony Outgrowth

Male

Female

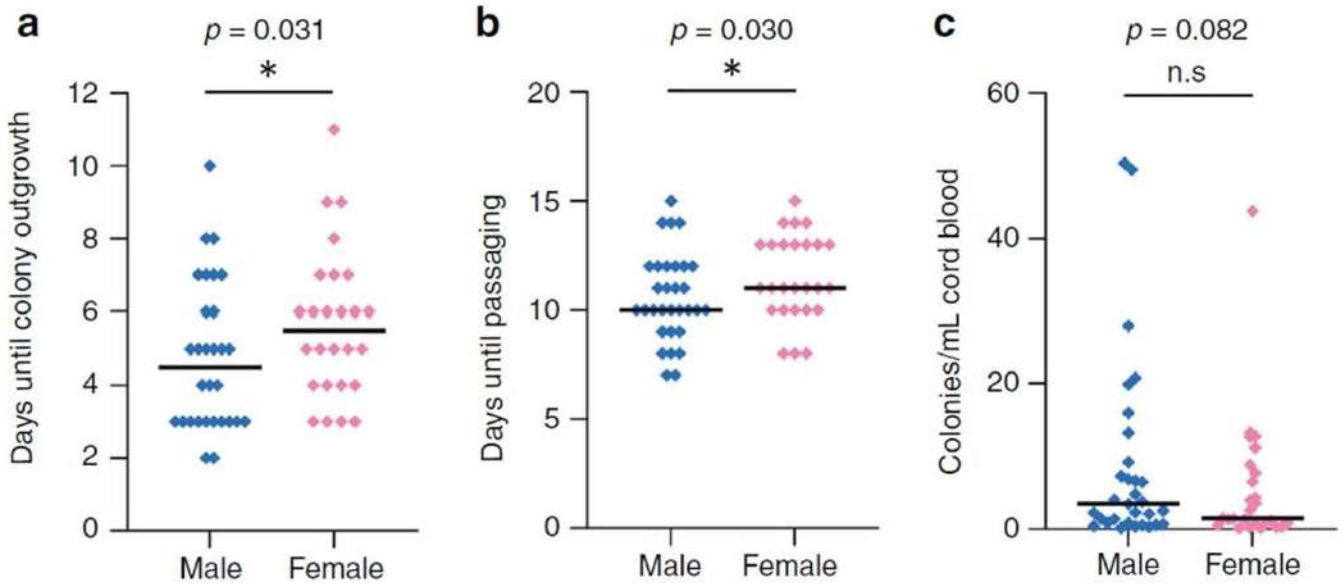


Fig. 3 Effect of neonatal sex on ECFC colony outgrowth. a Days required for colony outgrowth in ECFC of male and female neonates. **b** Days required for reaching confluency in ECFC of male and female neonates. **c** ECFC colony numbers of male and female neonates. Data were analyzed via ANCOVA adjusted for delivery mode after log-transformation of the dependent variable. Graphs represent untransformed and unadjusted data with median. *n* (male) = 31, *n* (female) = 26.

Elisa Weiss.., U Hidene 2022 Pediatric Research (2022) 92

Fetal Sex & Maternal Fasting Glucose Affect Neonatal Cord blood-derived Endothelial Progenitor Cells

RESULTS

Male ECFC grew out *earlier (−20.57% days) than female although all women were non-diabetic

Higher Levels of Fasting BG at Midpregnancy increased the Time required for Colony Outgrowth

FPG much stronger predictor for adverse pregnancy outcomes than elevated post-load glucose which, **after stratifying** for **Fetal Sex**, was **significant only in the Males**

Gestational weight gain and BMI	did not affect outgrowth
Colony number	unchanged by all parameters

CONCLUSIONS:

Fetal Sex & **Maternal FPG within normal range alter ECFC function in utero**

Elisa Weiss.., U Hidene 2022 Pediatric Research (2022) 92

Fetal Sex & Maternal Fasting Glucose Affect Neonatal Cord blood-derived Endothelial Progenitor Cells

IMPACT

Endothelial Cells Multifunctional Cells

Regulate Vascular Tone, Angiogenesis, formation of a Barrier, Blood Clotting, modulate the Inflammatory Response

Disturbance of these functions is regarded as Endothelial Dysfunction (ED)

ED is a precursor to cardiovascular disease (CVD)

Elisa Weiss.., U Hidene 2022 Pediatric Research (2022) 92

Sex matters together Other Factors

XVI CONGRESSO REGIONALE AMD MOLISE

14 OTTOBRE 2023
HOTEL CENTRUM PALACE
CAMPOBASSO

GRAZIE

Angela Napoli

Does Sex matter?
Association of fetal Sex and Parental Age with Pregnancy Outcomes in Taiwan: a cohort study

Besides fetal sex, the sex of the parents matters as well.

Hypertensive disorders induced by pregnancy may lead to

- stillbirth, Infant Death, and Maternal Death [18].
- women's long-term risk of developing Chronic Hypertension, Cardiovascular Ddisease, Stroke and Venous Thromboembolism [19].

Preterm delivery affects about **10% of newborns globally**.

Preterm delivery is associated

- **many adverse perinatal outcomes**
- **respiratory distress syndrome, sepsis, neurological impairment, bronchopulmonary dysplasia, perinatal mortality**
- ⇑ **cost** to the **healthcare system** and the **psychological burden** on families [22].

Tsung Yu, *BMC Pregnancy and Childbirth* volume 20, Article number: 348 (2020)

Fetal Sex & Maternal Fasting Glucose Affect Neonatal Cord blood-derived Endothelial Progenitor Cells

E**ndothelial function** is **subject** to **Sex Dimorphism**

A **Sexual Dimorphism** in ECFC function, as **cells of Female progeny** require a **Longer Period of Time until Colony Outgrowth** than **ECFC of Male Progeny**

ECFC function is **highly sensitive** and **affected** by **Maternal Glucose Levels** even in a Normal, nondiabetic range

CONCLUSIONS:

Fetal Sex & **Maternal FPG within normal range alter ECFC function in utero**

Elisa Weiss.., U Hidene 2022 Pediatric Research (2022) 92