

The Potential Impact of the Fetal Genotype on Maternal Blood Pressure during Pregnancy

Running Title: *Fetal Genotype & Maternal Blood Pressure*

Clive J. PETRY^{1*}, Kathryn BEARDSALL^{1, 2} and David B. DUNGER^{1, 3}

¹Department of Paediatrics, University of Cambridge, Cambridge, U.K.

²Neonatal Unit, Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge, U.K.

³Medical Research Laboratories, Institute of Metabolic Science, University of Cambridge, Cambridge, U.K.

Correspondence and Reprints: Dr. Clive J. Petry, Department of Paediatrics, Box 116, Addenbrooke's Hospital, Hills Road, Cambridge CB2 0QQ, U.K. E-mail: cjp1002@cam.ac.uk, Tel.: +44 (0)1223 762945, Fax.: +44 (0)1223 336996.

Conflicts of Interest and Source of Funding: None declared. Our studies that contributed to this review were funded by the Medical Research Council (G0500733), Diabetes UK (11/0004241), Wellbeing of Women (RG1644), and the Evelyn Trust.

Word Count: 8,450, Tables: 2, Figures: 0

Number of supplementary digital content files: none.

Abstract

The heritability of pregnancy-induced hypertension (encompassing both gestational hypertension and pre-eclampsia) is around 0.47 suggesting that there is a genetic component to its development. However the maternal genetic risk variants discovered so far only account for a small proportion of the heritability. Other genetic variants that may affect maternal blood pressure in pregnancy arise from the fetal genome, e.g. wild type pregnant mice carrying offspring with *Cdkn1c* or *Stox1* disrupted develop hypertension and proteinuria. In humans there is a higher risk for pre-eclampsia in women carrying fetuses with Beckwith Wiedemann syndrome (including those fetuses with *CDKN1C* mutations) and a lower risk for women carrying babies with trisomy 21. Other risk may be associated with imprinted fetal growth genes and genes that are highly expressed in the placenta such as *GCM1*. This manuscript reviews the current state of knowledge linking the fetal genotype with maternal blood pressure in pregnancy.

Condensed Abstract

Maternal genetic risk factors discovered so far only account for a small proportion of the heritability of pregnancy-induced hypertension (encompassing both gestational hypertension and pre-eclampsia). Other genetic variants that may affect maternal blood pressure in pregnancy arise from the fetal genome. Examples of this include the hypertension exhibited by wild type pregnant mice carrying offspring with *Cdkn1c* disrupted and the increased risk of pre-eclampsia in women carrying fetuses with Beckwith Wiedemann syndrome. This manuscript reviews the current state of knowledge linking the fetal genotype with maternal blood pressure in pregnancy.

Key Words: gestational hypertension, pre-eclampsia, genetics, imprinted

Introduction

Studies of the Swedish Twin Register and the Swedish Medical Birth Register suggest pregnancy-induced hypertension (raised blood pressure which originates in pregnancy and encompasses both gestational hypertension and pre-eclampsia) has a heritability of 0.47 (0.13-0.61), with a non-shared environmental effect of 0.53 [1]. This suggests that genetics plays an important part of the overall control of blood pressure in pregnant women and that polymorphic genetic variation can contribute towards changes in a woman's risk of developing gestational hypertension (with its heritability of 0.24 [1]) or pre-eclampsia (heritability of 0.54 [1]). Despite there being no shortage of family linkage studies, candidate gene association studies and genome wide (essentially hypothesis-free) association studies (GWASs), the maternal genetic variants linked or associated with gestational hypertension, pre-eclampsia or changes in blood pressure (reviewed in [2]) itself only account for a small fraction of the heritability of pregnancy-induced hypertension [3]. The reasons for this apparent discrepancy may relate to a combination of the effects of the lack of sensitivity of even large GWASs for detecting associations with small effect sizes and genetic variation that would not be picked up in such studies, such as the effects of copy number variation, epistasis, rare variants with large effect sizes and epigenetics (such as changes in methylation, histone and microRNA {miRNA} expression). However evidence from the literature suggests that a further genetic influence, i.e. additional to that imposed by the maternal genotype, on maternal blood pressure in pregnancy may relate to the fetal genotype. Indeed for one specific form of hypertension in pregnancy, pre-eclampsia, using the Swedish Birth and Multi-Generation Registries it was found that 35% of the variance in the liability of pre-eclampsia could be attributed to the maternal genotype, 20% to the fetal genetic effects (with maternal and paternal inheritance making similar contributions), 13%

to the so-called couple effect (caused by maternal and paternal genetic interactions), less than 1% to the shared sibling environment and 32% to other, unmeasured factors [4]. This descriptive review highlights the evidence for a relationship between the fetal genotype and maternal blood pressure in pregnancy, gained from both human and animal studies, and identifies groups of fetal genes that could emerge as potential effectors of maternal blood pressure in pregnancy and therefore risk of developing conditions such as gestational hypertension [5].

Fetal Effects on Maternal Blood Pressure in Pregnancy

The mechanism of how the fetal genotype may influence maternal blood pressure in pregnancy is unknown and probably varies according to the specific genes in question. In general, however, we hypothesised that one likely option would be via changes in placental function or secretion of vasoactive hormones and proteins [5] with the placenta largely being a fetal organ that expresses the fetal genotype [6], despite part of it being of maternal origin arising from the transformation of the uterine mucosa [7]. Relative to singleton pregnancies twin pregnancies are associated with increased total placental weight, whether one [8] or two [9] placentas are present. In a large American study of 684 twin pregnancies and 2,946 singleton pregnancies, the mean (95% confidence interval {95% CI}) relative risks for the development of both gestational hypertension (2.04 (1.60-2.59)) and pre-eclampsia (2.62 (2.03-3.38)) were both more than doubled in twin pregnancies [10]. Even higher relative risk for pregnancy induced hypertension (3.65 (2.11-6.30)) was observed in a Thai study of 305 twin and 298 singleton pregnancies [11]. Finally in an extremely large American study of 34,374 singleton, twin, triplet and quadruplet pregnancies it was found that the incidence of pregnancy-related hypertensive disorders increased according to the number

of fetuses up to triplets [12]. Similar results were evident for severe pregnancy-related hypertensive disorders such as pre-eclampsia and HELLP (haemolysis, elevated liver enzymes and low platelets: a specific, severe form of pre-eclampsia) [12].

A further influence of the fetus on maternal blood pressure in pregnancy is observed in relation to the fetal sex. Thus the risk of a woman developing pre-eclampsia and/or pregnancy-induced hypertension (which in different studies may include gestational hypertension with or without pre-eclampsia) has been observed to change according to whether the woman is carrying a male or a female baby [13-26]. Generally the higher risk is associated with carrying a male fetus [13-23], although some studies have observed a higher risk associated with carrying a female fetus [24-26]. The reason for this discrepancy is not clear, although it may relate to interactions with other risk factors as some studies have found that carrying a male fetus leads to a lower risk for the mother developing pre-eclampsia *that leads to preterm delivery* [27]. Indeed a recent study of women in Libya found that pre-eclampsia was more common among *preterm* females and *post-term* males (as well as male-bearing primigravids) [24]. Another study found an interaction with maternal age such that the proportion of women with pre-eclampsia that were carrying males dropped with age [22]. A molecular difference was observed in one prospective pregnancy study when it was found that in women that went on to develop either pre-eclampsia or gestational hypertension circulating angiotensin-(1-7) levels were raised at 15 weeks gestation, but only in those women who were female-bearing [28]. Finally fetal sex differences in maternal risk may be masked by factors such as a lack of statistical power or the influence of multifetal effects [29]. As well as direct associations between the risk of maternal hypertensive disorders and fetal sex, the fetal sex may also have an indirect

interactive effect with the maternal genotype. Thus in one of study of 2,089 Caucasian women with singleton pregnancies, whilst a maternal progesterone receptor polymorphism in isolation was not associated with maternal blood pressure, in A/A homozygotes those women carrying male fetuses had systolic blood pressures that were on average 9 mmHg lower than those of women carrying female fetuses in the first trimester [30]. Diastolic blood pressures were on average 5 mmHg lower.

Rodent studies have also shown an influence of the unborn offspring on maternal blood pressure in pregnancy. Like in humans in inbred mice the mean arterial blood pressure usually drops in the early stages of pregnancy probably due to systemic vasodilation. However no such change was observed in a study of pseudopregnant randomly-bred CD1 mice where endometrial decidualisation was established, despite these mice having the usual endocrine changes, uterine neoangiogenesis and recruitment of immune cells [31]. These results therefore suggest that the presence of viable conceptus(es) appears to be vital for the drop in blood pressure usually observed in early pregnancy [31]. In other studies when stimulated by either exercise or angiotensin II administration, CBA/J female mice were found to have hypertension when mated with DBA/2 males in comparison to if the same females were mated with BALB/c males [32], reminiscent of the risk of maternal pre-eclampsia in humans being partially dependent on the father [2]. Female BPH/5 mice have been shown to have higher mean arterial blood pressures than C57Bl/6 mice even in the non-pregnant state, but the difference in blood pressures between the two strains of mice has been shown to be exacerbated during the final week of pregnancy prior to returning to normal within two days post-partum [33]. Spontaneous hypertension in pregnancy has also been observed in SHHF/Mcc-fa(cp) rats [34], although for a more prolonged period of the

pregnancy than was observed in the BPH/5 mice. The rise in blood pressure normalised post-partum in the SHHF model, and further study of the same strain of rats suggested that the increase in blood pressure was related to an abnormal pressor response to progesterone [35].

Fetal Genotype Effects on Maternal Blood Pressure

Human Studies

Whilst the above studies relate the unborn offspring to a mother's blood pressure in pregnancy additional studies relate the actual fetal genotype to either a mother's blood pressure or her risk of developing gestational hypertension or pre-eclampsia. Women who were pregnant with a child that had the genetic disorder Beckwith Wiedemann syndrome were found to be 5.7 (1.9-16.6 95% CI) times more likely to develop proteinuria and hypertension, and 2.4 (1.4-4.1 95% CI) times to develop non-proteinuric gestational hypertension [36] than when the same women were pregnant with a non-affected sibling. Case reports of the link between pre-eclampsia and babies with Beckwith Wiedemann syndrome had previously been published [37-39]. The actual genetic mutations that cause Beckwith Wiedemann syndrome are most commonly observed in a number of different loci in the 11p15.5 region such as in the *H19*, *KCNQ1OT1* (potassium channel, voltage-gated, KQT-like subfamily, member 1-overlapping transcript 1) and *CDKN1C* (cyclin-dependent kinase inhibitor 1C) genes [40]. A further series of case reports described three women with pre-eclampsia and/or HELLP syndrome where their babies had Beckwith Wiedemann syndrome caused by mutations in the *CDKN1C* gene (which caused expression of truncated, non-functional proteins) [41]. The mutations were inherited from their mothers in two cases and arose *de novo* in the third. One of the mothers who had the mutation was unaffected

due to having inherited the mutation in the paternally-imprinted, maternally-expressed *CDKN1C* gene from their father. The other mother who transmitted the mutated gene had a *de novo* mutation and was asymptomatic.

A fetal chromosomal effect on maternal blood pressure in pregnancy is suggested by studies of unaffected pregnant women carrying babies with trisomy 21. Whilst there was no detectable effect in multiparous pregnancies, in first pregnancies study of 7,763 affected pregnancies and 15,293 unaffected pregnancies from the U.S. Natality files showed that carrying a child with trisomy 21 was associated with a significantly reduced risk of developing pregnancy induced hypertension (adjusted risk 0.67 {0.53-0.85 95% CI}) [42]. The association was confirmed in a Californian case control study (665 affected pregnancies and 987 unaffected pregnancies) and it was suggested that the change in risk in first pregnancies was due to a lower chance of such women developing pre-eclampsia (adjusted risk 0.19 {0.04-0.88 95% CI}) rather than gestational hypertension (adjusted risk 0.83 {0.37-1.84 95% CI}) [42]. In a further study, this time using the Texas Birth Defects Registry for 1999-2003 the number of cases of pre-eclampsia in a cohort of pregnancies carrying a trisomy 21 fetus was 84 out of a total of 2,995 pregnancies (3.7%). The equivalent figure for pregnancies with fetal isolated oral clefts (which were used as controls) was 111 out of a total of 1,959 (5.7%) [43]. This gave a crude odds ratio for having pre-eclampsia in a trisomy 21-affected pregnancy of 0.63 (0.47-0.85 95% CI) ($p=4.1 \times 10^{-7}$), which remained broadly the same when adjusted for confounders. It is not currently known which actual genes on chromosome 21 may be responsible for this association, although it may relate to changes in placental development and function (reviewed in [44]).

Another fetal chromosomal association with changes in maternal blood pressure in pregnancy is the association between an increased risk of developing pre-eclampsia and fetal trisomy 13 which has been reported in both (modestly-sized) case-control [45-47] and case report form [48-52]. The emergence of pre-eclampsia in these pregnancies may relate to changes in placental development and function associated with the trisomy 13 [52, 53] such as a small placental volume and reduced placental vascularisation. Candidate genes from chromosome 13 that may be involved in pre-eclampsia include FMS-related tyrosine kinase 1 (the vascular endothelial growth factor receptor), the alpha-2 chain of type IV collagen and periostin [53].

There is also a single case report of a mother carrying a fetus with trisomy 18 who developed HELLP syndrome [54]. However the fetal trisomy 18 and the maternal HELLP syndrome may not have been directly related as a separate case-control study of 38 women bearing trisomy 18 offspring did not find any excess of hypertensive disorders in the mothers [46].

In terms of specific fetal genotypes and changes in maternal blood pressure in pregnancy there are not many published studies so far, although studies are ongoing. However in a small American study of predominantly Hispanic women, the fetal genotype for a single nucleotide polymorphism (SNP) (rs9349655) in the *GCM1* (glial cells missing, drosophila, homolog of) gene was associated with a reduced risk of the development of pre-eclampsia: odds ratio of 0.41 (0.20-0.85 95% CI) for group sizes of 136 with pre-eclampsia and 169 without any form of pregnancy-induced hypertension [55]. There was no such association between the maternal genotype and the risk of pre-eclampsia, however. This was

presumably related to the selective expression of *GCM1* in the placenta being where the modulation of risk emerges [56] and the fact that most of the placenta is of fetal origin [6]. The same group who found the fetal *GCM1* association had previously found an association between the risk of maternal pre-eclampsia and a fetal SNP in the transforming growth factor (TGF)- β 3 (*TGFB3*) gene in the same group of women [57]. The odds ratio for the mother developing pre-eclampsia when the fetus was carrying at least one of minor allele of the SNP rs11466414 was 0.32 (0.14-0.77 95% CI). Like for the *GCM1* finding there was no equivalent association with the maternal genotype. Other studies have observed increased placental expression of *TGFB3* in pregnancies affected by pre-eclampsia [58], suggesting a possible mechanism for the fetal rs11466414 association with this SNP being located in the upstream regulatory region of the *TGFB3* gene and therefore probably being associated with changes in gene expression.

Other studies have found associations between fetal but not maternal polymorphisms and pre-eclampsia. A study of Chinese Han women found that a polymorphism in the fetal angiotensinogen gene was protective against the development of pre-eclampsia in the mother, with an adjusted odds ratio of 0.28 (0.14-0.59 95% CI) [59]. No such association was found with the maternal genotype. A polymorphism in the fetal *ERAP2* (endoplasmic reticulum aminopeptidase 2) gene (and not the maternal gene) has been associated with the development of pre-eclampsia in a population of African American women but not in Chilean women [60]. In a population of Caucasian women from Australia or New Zealand, when stratified by maternal body mass index, a polymorphism in the angiotensin II receptor type 2 (*AGTR2*) gene was associated with a two to three times increased risk of developing pre-eclampsia whether it was the maternal, paternal or fetal genotype that was analysed

[61]. The authors suggested that the mechanism behind the associations between all these genotypes and pre-eclampsia might involve variations in placentation at the maternal-fetal interface resulting from changes in trophoblast apoptosis, given the role of *AGTR2* in apoptosis in other tissues [61]. In a population of Caucasian women a polymorphism in the fetal and paternal but not the maternal *KDR* (kinase insert domain receptor) gene was found to be associated with the development of pre-eclampsia, with an adjusted odds ratio of 2.2 (1.0-4.4 95% CI) [62]. When the data were stratified by whether or not the mother smoked during pregnancy, the maternal *KDR* genotype was associated with the risk of pre-eclampsia. With most of the placenta being of fetal origin [6], again the authors suggested that the mechanism behind this pattern of association was likely to involve placentation and in particular placental angiogenesis [62]. Immune tolerance, or lack of it, may also play a part in regulating maternal blood pressure in pregnancy as one relatively small study of Malay women found the fetal HLA-G*0106 genotype to be associated with pre-eclampsia in multigravida pregnancies, with an odds ratio of developing the condition of 5.0 (1.8-13.8 95% CI) [63]. This study also found a higher occurrence of maternal/fetal HLA-G*0106 genotype mismatch in women with pre-eclampsia than in the controls, with an odds ratio of 9.6 (2.4-38.7 95% CI).

Animal Studies

Animal studies offer further specific fetal genetic associations with maternal blood pressure in pregnancy. Phenotypically wild type pregnant female mice carrying litters where half of the offspring have targeted disruption of *Cdkn1c* (also known as *p57^{kip2}*) genes develop a condition similar to pre-eclampsia with hypertension and proteinuria, as well as thrombocytopenia, decreased anti-thrombin III activity, and increased endothelin

concentrations during late pregnancy [64]. The environment modulates the risk of these signs developing [65]. Comparable to findings of pre-eclampsia in mothers carrying fetuses with *CDKN1C* mutations [41], in these mice the maternal blood pressure and proteinuria, as well as the other factors, return to normal post-partum [64]. During the pregnancy the placentas of those pups who do not express *Cdkn1c* exhibit trophoblastic hyperplasia, similar to the excess of intermediate trophoblasts observed in human pre-eclampsia [66]. We found that in a similar model where phenotypically wild type pregnant mice carrying litters where around half of the offspring had the *H19* gene and the nearby *Igf2* control element disrupted, hyperglycaemia and placentomegaly was evident in late pregnancy [67]. We then found similar associations between fetal *IGF2* SNPs and maternal glucose concentrations in humans [68], raised glucose concentrations themselves being associated with an increased risk of developing pre-eclampsia [69].

Gestational hypertension is also observed in wild type pregnant mice carrying litters where around half of the offspring have targeted disruption of one copy of their *Gcm1* gene [70]. This therefore shows similarities with the fetal *GCM1* association observed in humans [55] where reduced placental expression of the gene is found in pregnancies complicated by pre-eclampsia [71]. The targeted disruption of the gene in mice, however, is clearly more severe than the single SNP effect in humans as disruption of both copies of the fetal gene is embryonically lethal [70]. The exact mechanism of how the reduction in *Gcm1* expression of around 50% in affected placentas leads to maternal hypertension is unknown, but is likely to involve the changes in placental development such as defective syncytiotrophoblast differentiation and increased fetoplacental vascularity [70].

A further mouse model of gestational hypertension, with other features of pre-eclampsia, occurs when wild type female mice are mated with males that are heterozygotes for the transgenic overexpression of the *STOX1* (storkhead box 1) gene [72]. This is interesting given that *STOX1* is one of only two maternal genes that are confirmed to be associated with the development of pre-eclampsia at the genome-wide level in humans (reviewed in [73]) and is thought to exert its action through negatively regulating trophoblast invasion by upregulation of the cell-cell adhesion protein alpha-T-catenin [74]. The studies in mice suggest that rather than the maternal gene *per se* leading to the development of pre-eclampsia it is the transmission of the maternal genotype to the fetus that is important. A further mouse model of gestational hypertension arises through transgenic manipulation where female mice that express human angiotensinogen are mated with male mice that express human renin [75], although the relevance for human gestational hypertension might be quite limited due to the extensive manipulation.

Groups of Fetal Genes that may influence Maternal Blood Pressure in Pregnancy

Whilst neither extensive in number nor homogeneous enough to permit meta-analyses, there is enough evidence in the literature to suggest that the fetal genotype can be associated with changes in maternal blood pressure in pregnancy, particularly with the development of pre-eclampsia where there is more available evidence. Not many genes mediating this link have been found so far, and those studies that have found associations generally need further replication to validate them. Currently it is unclear if genes involved in cardiac risk inherited by the fetus either play a role in mediating or provide a link between the fetal genotype and maternal blood pressure in pregnancy. In one study of 162 women with pre-eclampsia and 521 controls early onset paternal hypertension and myocardial

infarctions were associated with severe maternal pre-eclampsia [76] but in another study of 14,130 families maternal hypertensive disorders of pregnancy were not associated with paternal cardiovascular risk factors such as blood pressure, body mass index, waist circumference, and circulating lipid and glucose concentrations [77]. Other genes that may well be involved in the fetal genotype modulation of maternal blood pressure are those that code for proteins that are involved in functions that are specific to pregnancy (otherwise their effects too would presumably become apparent in adult life). Given the fetal contribution to the development and functioning of the placenta [7] and the resulting carrying of the fetal genotype, one group of genes is those that are highly expressed in placenta or which are involved in its development and function. Examples of these would be *GCM1* and *STOX1* which have been shown to be associated with changes in pregnancy blood pressure in both humans [55, 73] and mouse models [70, 72].

Although only evident when interacting with the effects of maternal genes, a further group of candidate genes are those related to immune tolerance [78]. This may be especially apparent when there is a fetal/maternal mismatch in HLA genes as observed in a study of paternally-transmitted HLA-G*0106 which was associated with pre-eclampsia in multigravida pregnancies [63], consistent with the idea that pre-eclampsia has an immunological basis. Alternatively HLA-sharing between the mother and fetus, particularly of HLA class I and II molecules, has also been shown to be associated with pre-eclampsia [79]. Whether it is a fetal/maternal mismatch or HLA-sharing that is important for the development of pre-eclampsia, or even both with respect to different HLA genes, a role is suggested for the fetal HLA genotype in the process of modulating pre-eclampsia risk and therefore maternal blood pressure.

Fetal HLA genes may also modulate the effects of other maternal immune-related genes. In one study the risk of developing pre-eclampsia was associated with the fetal HLA-C genotype in pregnant women with an A/A KIR (killer immunoglobulin receptor) genotype [80]. The highest risk for pre-eclampsia was associated with mothers lacking all or most of the activating receptor (i.e. those with the A/A genotype) and carrying fetuses with the HLA-C2 genotype (odds ratio for pre-eclampsia in pregnancies carrying this genetic combination 2.38 {1.45–3.90 95% CI}). This association was presumably mediated via uterine natural killer cells which express HLA-C-binding KIR on their cell surface. As a way of validating these results differences in the population prevalences of the protective maternal A/A KIR genotype and the fetal HLA-C2 risk genotype by ethnicity would lead to the expectation that pregnancies of Japanese mothers (with a relatively high prevalence of A/A KIR genotypes) with Caucasian fathers (with a relatively high prevalence of HLA-C2 genotypes) would be particularly prone to the development of pre-eclampsia if the findings in this study were not just due to random chance. One study comparing the incidence of pre-eclampsia in such pregnancies with those from couples where both mother and father were Japanese failed to reveal any significant difference however [81]. In contrast a study testing the incidence of pre-eclampsia in pregnancies with a wider range of maternal and paternal ethnicities found Asian paternity to be associated with a lower risk of pre-eclampsia than Caucasian paternity (odds ratio 0.76 {0.68-0.85 95% CI}) and parental ethnic discordance to be associated with a modest increase in the risk of developing pre-eclampsia (odds ratio 1.13 {1.02-1.26 95% CI}) [82]. The discrepancy between these studies may [83] or may not [84] be explained by there being insufficient statistical power to detect parental ethnicity-related differences and the lack of maternal KIR and fetal HLA-C genotyping in the Japanese study [81] or it could result

from differences in other confounders between the studies such as the length of time elapsing between the start of the parents' sexual cohabitation and the conception [85]. Until the validity of the conclusions from the initial study can be confirmed in further (genotyped) populations the concept that mismatching between the paternal gene-affected trophoblast and maternal KIRs would lead to a susceptibility to pre-eclampsia must remain just an intriguing possibility.

An additional group of fetal genes that have specific roles in pregnancy and may be involved in modulating maternal blood pressure are genes involved in fetal and placental growth. Whilst pre-eclampsia is most well known to be associated with reduced birth weight it has also been associated with significantly increased birth weight [86]. Similarly gestational hypertension can be associated with both intrauterine growth restriction [87] and the baby being born large for gestational age [88]. Maternal blood pressure itself has a non-linear relationship with baby's birth weight, with rises in blood pressure in the pre-pathological range being associated with increases in birth weight and then rises above that being associated with a fall in birth weight [89, 90]. Independent of baseline blood pressure an increase in maternal blood pressure over the course of the pregnancy is associated with adverse birth outcomes including increased rates of preterm birth and low birth weight [91] suggesting that a change in pregnancy blood pressure has an important effect on fetal outcomes.

Of the fetal genes and chromosomes described so far that have been associated with changes in pregnancy-related hypertensive disorders, a number of them are also associated with changes in birth weight. Beckwith Wiedemann syndrome may be caused by a number

of different genetic mutations [40] but whatever causes it seems to be associated with placentomegaly [38, 39] and increased weight and length at birth [92]. Of the specific genes associated with Beckwith Wiedemann syndrome a polymorphisms in *CDKN1C* has been shown to be associated with increased birth weight [93] and in the mouse fetal *Cdkn1c* model of pre-eclampsia there is also increased fetal growth [94]. The *IGF2* gene has also been associated with the risk of Beckwith Wiedemann syndrome [95] and in other studies has been variably associated with changes in birth weight (reviewed in [96]). Similarly fetal trisomy 21, which causes Down's syndrome and is associated with a reduced risk of maternal pre-eclampsia [42, 43], is associated with lower birth weight [97]. Fetal trisomy 13, which causes Patau syndrome and is also associated with risk of maternal pre-eclampsia [45-47], may cause fetal growth restriction early in pregnancy [98]. Even fetal trisomy 18 which causes Edward's syndrome and may be associated with maternal HELLP syndrome [54], is also associated with reduced birth weight [99]. Most of the specific fetal genes that have been found to be associated with pregnancy-related hypertensive disorders in pregnancy have not been studied in relation to fetal growth. However a common polymorphism in fetal *angiotensinogen* has been found to be associated with changes in birth weight (and fetal glycated haemoglobin levels) [100], associations that were not previously observed when testing the maternal copies of the same polymorphism [101].

Fetal Imprinted Genes

The most characterised fetal growth genes are those that are imprinted [96, 102] such that only one copy of a gene is active and the other is inactivated, whether it is the copy inherited from the father or the mother that is active depending on such factors as the gene itself, the stage of development and the tissue in question. The majority of imprinted genes

are thought to be involved in fetal and placental growth and function [103]. The most quoted hypothesis for the evolution of genomic imprinting is Haig's Kinship theory [104], which was in turn derived from Trivers' parent-offspring conflict theory [105]. This suggests that the genetic influences on fetal growth relate to a conflict between the effects of maternal genes which tend to limit growth and paternally-transmitted fetal genes which tend to stimulate it [106]. Fetal growth would reflect the balance between imprinted gene-mediated fetal demand and nutrient supply, as shown in mouse models [107]. Haig suggested that fetal imprinted genes could mediate their effects through changes in maternal metabolism caused by placental hormones [108]. We suggested that fetal imprinted genes could influence the risk of the mother developing hypertensive disorders in pregnancy and gestational diabetes [5, 109]. We have published data consistent with this in terms of raised maternal glucose concentrations in late pregnancy and fetal (paternally-expressed) *IGF2* in both mice [67] and humans [68]. Preliminary analyses of results from our Cambridge Baby Growth Study cohort suggest that maternal blood pressure will also be associated with polymorphic variation in various fetal imprinted genes. Slight rises in blood pressure, in the normal range, are associated with increased fetal growth [89, 90] which could be advantageous to the fetus given that low birth weight is associated with increased perinatal morbidity and mortality. Indeed there must be some genetic advantage in the fetus being able to influence its mother's blood pressure as if the influence was purely detrimental to health and reproductive fitness, unless it were of relatively recent origin, it would likely have been removed by natural selection. Recent data pertaining to more than 750,000 births recorded in the Danish National Patient Registry, however suggest why this influence may have persisted [110]. Whilst pre-eclampsia in the final trimester of pregnancy was detrimental to maternal and fetal health, fetal exposure to raised maternal blood

pressure in the first trimester was associated with significantly reduced overall later-life disease risks when tracking the child over their first 27 years, as well as just the first year of life. Historically the advantage brought about by this may outweigh the disadvantage to health brought about by pre-eclampsia and hence natural selection may have favoured the trait.

Conclusions and Future Prospects

There are a growing number of studies that suggest that a fetus and its genotype can influence a mother's blood pressure and therefore likely risk of hypertensive disorders in pregnancy. Whilst there is not much data in the literature that refute this suggestion publication bias towards positive results and the fact that not many investigators have even considered it mean that this view must be held with a degree of caution. This influence may explain some of the currently unaccounted for apparent heritability of hypertensive disorders arising during pregnancy. The overall effect sizes of the associations between various fetal genotypes and maternal blood pressure cannot easily be judged at present due to the inability to perform meta-analyses on published data because of study heterogeneity. Another difficulty in relating the effect size of the fetal genotype on maternal blood pressure in pregnancy is that many of the cited studies relate to pre-eclampsia rather than to maternal blood pressure *per se* due to the potential increased severity of the phenotype. The problem with using pre-eclampsia as the clinical endpoint is that genetic influences on pre-eclampsia traits other than blood pressure, such as urinary albumin excretion, may show an association with the condition and therefore skew the overall fetal risk genotypes away from those that have a direct influence on (or even just an association with) maternal blood pressure. To resolve this future genetic studies need to use maternal blood pressure

as a continuous variable and/or non-proteinuric pregnancy-induced hypertension as a binary variable clinical endpoint.

It is likely that fetal genes that may exert an influence on maternal blood pressure in pregnancy will not be the same as maternal genetic variants that are associated with pregnancy-related hypertensive disorders. We hypothesise that they will be related to fetal and/or placental growth, development and function such as imprinted genes rather than cardiovascular function. If certain fetal genes affect placental function and secretion as well as maternal blood pressure, it may be possible in future to measure unique fetally-related biomarkers in maternal serum early in pregnancy that predict rises in maternal blood pressure in late pregnancy. Such biomarker concentrations may add to the assessment of factors that can predict the risk of the development of hypertensive disorders in pregnancy.

Acknowledgments

Our studies that contributed to this review were funded by the Medical Research Council (G0500733), Diabetes UK (11/0004241), Wellbeing of Women (RG1644), and the Evelyn Trust. Funding for other aspects of the Cambridge Baby Growth Study has come from the Medical Research Council, the European Union Framework 5, the World Cancer Research Fund, Newlife Birth Defects and the Mothercare Group Foundation. The authors also acknowledge the help provided by the Medical Research Council Centre for Obesity and Related metabolic Diseases and the National Institute for Health Research Cambridge Biomedical Research Centre.

References

- [1] Salonen Ros H, Lichtenstein P, Lipworth L, Cnattingius S. Genetic effects on the liability of developing pre-eclampsia and gestational hypertension. *Am J Med Genet* 2000; 91:256-260
- [2] Williams PJ, Broughton Pipkin F. The genetics of pre-eclampsia and other hypertensive disorders of pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2011; 25:405-417
- [3] Basson J, Simino J, Rao DC. Between candidate genes and whole genomes: time for alternative approaches in blood pressure genetics. *Curr Hypertens Rep* 2012; 14:46-61
- [4] Cnattingius S, Reilly M, Pawitan Y, Lichtenstein P. Maternal and fetal genetic factors account for most of familial aggregation of preeclampsia: a population-based Swedish cohort study. *Am J Med Genet A* 2004; 130A:365-371
- [5] Petry CJ, Ong KK, Dunger DB. Does the fetal genotype affect maternal physiology during pregnancy? *Trends Mol Med* 2007; 13:414-421
- [6] Baergen RN. The placenta as witness. *Clin Perinatol* 2007; 34:393–407
- [7] Benirschke K, Burton GJ, Baergen RN. Macroscopic features of a delivered fetus. In: *Pathology of the Human Placenta*. Sixth edition. Heidelberg: Springer Verlag; 2012. pp. 13-15
- [8] Gielen M, Lindsey PJ, Derom C, Loos RJ, Derom R, Nijhuis JG, et al. Curves of placental weights of live-born twins. *Twin Res Hum Genet* 2006; 9:664-672
- [9] Almog B, Shehata F, Aljabri S, Levin I, Shalom-Paz E, Shrim A. Placenta weight percentile curves for singleton and twins deliveries. *Placenta* 2011; 32:58-62
- [10] Sibai BM, Hauth J, Caritis S, Lindheimer MD, MacPherson C, Klebanoff M, et al. Hypertensive disorders in twin versus singleton gestations. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *Am J Obstet Gynecol* 2000; 182:938-942

- [11] Chittacharoen A, Wetchapruuekitak S, Suthutvoravut S. Pregnancy induced hypertension in twin pregnancy. *J Med Assoc Thai* 2005; 88 (suppl 2):S69-S74
- [12] Day MC, Barton JR, O'Brien JM, Istwan NB, Sibai BM. The effect of fetal number on the development of hypertensive conditions of pregnancy. *Obstet Gynecol* 2005; 106:927-931
- [13] Toivanen P, Hirvonen T. Sex ratio of newborns: preponderance of males in toxemia of pregnancy. *Science* 1970; 170:187-188
- [14] López-Llera M. Eclampsia and fetal sex. *Int J Gynaecol Obstet* 1990; 33:211-213
- [15] Naeye RL, Demers LM. Differing effects of fetal sex on pregnancy and its outcome. *Am J Med Genet Suppl* 1987; 3:67-74
- [16] Campbell DM, MacGillivray I, Carr-Hill R, Samphier M. Fetal sex and pre-eclampsia in primigravidae. *Br J Obstet Gynaecol* 1983; 90:26-27
- [17] Di Renzo GC, Rosati A, Sarti RD, Cruciani L, Cutuli AM. Does fetal sex affect pregnancy outcome? *Gend Med* 2007; 4:19-30
- [18] Hsu CD, Witter FR. Fetal gender effect on preterm and term preeclamptic pregnancies. *Int J Gynaecol Obstet* 1994; 47:53-54
- [19] Sanchez AR, Macho JE, Estrada HV, Gonzalez AL. Does the gender of the fetus determine the severity of preeclampsia-eclampsia? *Ginecol Obstet Mex* 1996; 64:18-20
- [20] Basso O, Olsen J. Sex ratio and twinning in women with hyperemesis or pre-eclampsia. *Epidemiology* 2001; 12:747-749
- [21] Elsmén E, Källén K, Marsál K, Hellström-Westas L. Fetal gender and gestational-age-related incidence of pre-eclampsia. *Acta Obstet Gynecol Scand* 2006; 85:1285-1291
- [22] Rueness J, Vatten L, Eskild A. The human sex ratio: effects of maternal age. *Hum Reprod* 2012; 27:283-287

- [23] Aliyu MH, Salihu HM, Lynch O, Alio AP, Marty PJ. Fetal sex and differential survival in preeclampsia and eclampsia. *Arch Gynecol Obstet* 2012; 285:361-365
- [24] Khalil MM, Alzahra E. Fetal gender and pregnancy outcomes in Libya: a retrospective study. *Libyan J Med*. 2013; 8:20008
- [25] Shiozaki A, Matsuda Y, Satoh S, Saito S. Impact of fetal sex in pregnancy-induced hypertension and preeclampsia in Japan. *J Reprod Immunol* 2011; 89:133-139
- [26] Shiozaki A, Matsuda Y, Satoh S, Saito S. Comparison of risk factors for gestational hypertension and preeclampsia in Japanese singleton pregnancies. *J Obstet Gynaecol Res* 2013; 39:492-499
- [27] Hsu CD, Johnson TR, Witter FR. Fetal gender effect on pre-eclampsia: a retrospective study of Baltimore area in the United States of America. *Int J Gynaecol Obstet* 1994; 45:160-161
- [28] Sykes SD, Pringle KG, Zhou A, Dekker GA, Roberts CT, Lumbers ER. Fetal sex and the circulating renin-angiotensin system during early gestation in women who later develop preeclampsia or gestational hypertension. *J Hum Hypertens* 2013 doi: 10.1038/jhh.2013.51
- [29] Makhseed M, Musini VM, Ahmed MA. Association of fetal gender with pregnancy-induced hypertension and pre-eclampsia. *Int J Gynaecol Obstet* 1998; 63:55-56
- [30] Hochar B, Chen YP, Schlemm L, Burdack A, Li J, Halle H, et al. Fetal sex determines the impact of maternal PROGINS progesterone receptor polymorphism on maternal physiology during pregnancy. *Pharmacogenet Genomics* 2009; 19:710-718
- [31] Barrette VF, Adams MA, Croy BA. Endometrial decidualization does not trigger the blood pressure decline of normal early pregnancy in mice. *Biol Reprod* 2012; 86:66
- [32] Ahmed A, Singh J, Khan Y, Seshan SV, Girardi G. A new mouse model to explore therapies for preeclampsia. *PLoS One* 2010; 5:e13663

- [33] Davisson RL, Hoffmann DS, Butz GM, Aldape G, Schlager G, Merrill DC, et al. Discovery of a spontaneous genetic mouse model of preeclampsia. *Hypertension* 2002; 39:337-342
- [34] Sharkey LC, McCune SA, Yuan O, Lange C, Fray J. Spontaneous pregnancy-induced hypertension and intrauterine growth restriction in rats. *Am J Hypertens* 2001; 14:1058-1066
- [35] Sharkey LC, Kirchain S, McCune SA, Simpson GI, Archambault EZ, Boatright NK, et al. Progesterone increases blood pressure in spontaneous gestational hypertension in rats. *Am J Hypertens* 2005; 18:36-43
- [36] Wangler MF, Chang AS, Moley KH, Feinberg AP, Debaun MR. Factors associated with preterm delivery in mothers of children with Beckwith-Wiedemann syndrome: a case cohort study from the BWS registry. *Am J Med Genet A* 2005; 134A:187-191
- [37] Irving I. Exomphalos with macroglossia: a study of 11 cases. *J Pediatr Surg* 1967; 2:499–507
- [38] Lage JM. Placentomegaly with massive hydrops of placental stem villi, diploid DNA content and fetal omphaloceles. Possible association with Beckwith–Wiedemann syndrome *Hum Pathol* 1991; 22:591–597
- [39] McCowan LM, Becroft DM. Beckwith-Wiedemann syndrome, placental abnormalities, and gestational proteinuric hypertension. *Obstet Gynecol* 1994; 83:813-817
- [40] Choufani S, Shuman C, Weksberg R. Molecular findings in Beckwith-Wiedemann syndrome. *Am J Med Genet C Semin Med Genet* 2013; 163:131-140
- [41] Romanelli V, Belinchón A, Campos-Barros A, Heath KE, García-Miñaur S, Martínez-Glez V, et al. CDKN1C mutations in HELLP/preeclamptic mothers of Beckwith-Wiedemann Syndrome (BWS) patients. *Placenta* 2009; 30:551-554

- [42] Zhang J, Christianson RE, Torfs CP. Fetal trisomy 21 and maternal preeclampsia. *Epidemiology* 2004; 15:195-201
- [43] Defant J, Gambello MJ, Monga M, Langlois PH, Noblin SJ, Vidaeff AC. Fetal trisomy 21 and the risk of preeclampsia. *J Matern Fetal Neonatal Med* 2010; 23:55-59
- [44] Pidoux G, Gerbaud P, Cocquebert M, Segond N, Badet J, Fournier T, et al. Human trophoblast fusion and differentiation: lessons from trisomy 21 placenta. *Placenta* 2012; 33 (suppl):S81-S86
- [45] Boyd PA, Lindenbaum RH, Redman C. Pre-eclampsia and trisomy 13: a possible association. *Lancet* 1987; 2:425-427
- [46] Tuohy JF, James DK. Pre-eclampsia and trisomy 13. *Br J Obstet Gynaecol* 1992; 99:891-894
- [47] Bower C, Stanley F, Walters BN. Pre-eclampsia and trisomy 13 (letter). *Lancet* 1987; 2:1032
- [48] Feinberg RF, Kliman HJ, Cohen AW. Preeclampsia, trisomy 13, and the placental bed. *Obstet Gynecol* 1991; 78:505-508
- [49] Boyd PA, Maher EJ, Lindenbaum RH, Hoogwerf AM, Redman C, Crocker M. Maternal 3;13 chromosome insertion, with severe pre-eclampsia. *Clin Genet* 1995; 47:17-21
- [50] Heydanus R, Defoort P, Dhont M. Pre-eclampsia and trisomy 13. *Eur J Obstet Gynecol Reprod Biol* 1995; 60:201-202
- [51] Pedersen BW, Grønlund A. Severe pre-eclampsia and fetal trisomy 13 in a multiparous woman. *Ugeskr Laeger* 2003; 165:2108-2109
- [52] Kakigano A, Mimura K, Kanagawa T, Nakayama M, Kanayama T, Fujita S, et al. Imbalance of angiogenic factors and avascular edematous cystic villi in a trisomy 13 pregnancy: a case report. *Placenta* 2013; 34:628-630

- [53] Chen CP. Placental abnormalities and preeclampsia in trisomy 13 pregnancies. *Taiwan J Obstet Gynecol* 2009; 48:3-8
- [54] Mueller MD, Brühwiler H. HELLP syndrome and trisomy 18 in a multi-parity patient. *Z Geburtshilfe Neonatol* 1996; 200:119-121
- [55] Wilson ML, Brueggmann D, Desmond DH, Mandeville JE, Goodwin TM, Ingles SA. A fetal variant in the GCM1 gene is associated with pregnancy induced hypertension in a predominantly hispanic population. *Int J Mol Epidemiol Genet* 2011; 2:196-206
- [56] Baczyk D, Kibschull M, Mellstrom B, Levytska K, Rivas M, Drewlo S, et al. DREAM mediated regulation of GCM1 in the human placental trophoblast. *PLoS One* 2013; 8:e51837
- [57] Wilson ML, Desmond DH, Goodwin TM, Miller DA, Ingles SA. Maternal and fetal variants in the TGF-beta3 gene and risk of pregnancy-induced hypertension in a predominantly Latino population. *Am J Obstet Gynecol* 2009; 201:295.e1-5
- [58] Caniggia I, Grisaru-Gravnosky S, Kuliszewsky M, Post M, Lye SJ. Inhibition of TGF-beta 3 restores the invasive capability of extravillous trophoblasts in preeclamptic pregnancies. *J Clin Invest* 1999; 103:1641-1650
- [59] Xiang P, Li Z, Di H, Nie S, Yan W. The associations between maternal and fetal angiotensinogen M235T polymorphism and pregnancy-induced hypertension in Chinese women. *Reprod Sci* 2011; 18:640-644
- [60] Hill LD, Hilliard DD, York TP, Srinivas S, Kusanovic JP, Gomez R, et al. Fetal ERAP2 variation is associated with preeclampsia in African Americans in a case-control study. *BMC Med Genet* 2011; 12:64
- [61] Zhou A, Dekker GA, Lumbers ER, Lee SY, Thompson SD, McCowan LM, et al. The association of AGTR2 polymorphisms with preeclampsia and uterine artery bilateral notching is modulated by maternal BMI. *Placenta* 2013; 34:75-81

- [62] Andraweera PH, Dekker GA, Thompson SD, Roberts CT. Single-nucleotide polymorphisms in the KDR gene in pregnancies complicated by gestational hypertensive disorders and small-for-gestational-age infants. *Reprod Sci* 2012; 19:547-554
- [63] Tan CY, Ho JF, Chong YS, Loganath A, Chan YH, Ravichandran J, et al. Paternal contribution of HLA-G*0106 significantly increases risk for pre-eclampsia in multigravid pregnancies. *Mol Hum Reprod* 2008; 14:317-324
- [64] Kanayama N, Takahashi K, Matsuura T, Sugimura M, Kobayashi T, Moniwa N, et al. Deficiency in p57Kip2 expression induces preeclampsia-like symptoms in mice. *Mol Hum Reprod* 2002; 8:1129-1135
- [65] Falcao S, Solomon C, Monat C, Bérubé J, Gutkowska J, Lavoie JL. Impact of diet and stress on the development of preeclampsia-like symptoms in p57kip2 mice. *Am J Physiol Heart Circ Physiol* 2009; 296:H119-H126
- [66] Redline RW, Patterson P. Pre-eclampsia is associated with an excess of proliferative immature intermediate trophoblast. *Hum Pathol* 1995; 26:594-600
- [67] Petry CJ, Evans ML, Wingate DL, Ong KK, Reik W, Constância M, et al. Raised late pregnancy glucose concentrations in mice carrying pups with targeted disruption of H19delta13. *Diabetes* 2010; 59:282-286
- [68] Petry CJ, Seear RV, Wingate DL, Manico L, Acerini CL, Ong KK, et al. Associations between paternally transmitted fetal IGF2 variants and maternal circulating glucose concentrations in pregnancy. *Diabetes* 2011; 60:3090-3096
- [69] The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study: preeclampsia. *Am J Obstet Gynecol* 2010; 202:255.e1-7

- [70] Bainbridge SA, Minhas A, Whiteley KJ, Qu D, Sled JG, Kingdom JC, et al. Effects of reduced Gcm1 expression on trophoblast morphology, fetoplacental vascularity, and pregnancy outcomes in mice. *Hypertension* 2012; 59:732-739
- [71] Chen CP, Chen CY, Yang YC, Su TH, Chen H. Decreased placental GCM1 (glial cells missing) gene expression in pre-eclampsia. *Placenta* 2004; 25:413-421
- [72] Doridot L, Passet B, Méhats C, Rigourd V, Barbaux S, Ducat A, et al. Preeclampsia-like symptoms induced in mice by fetoplacental expression of STOX1 are reversed by aspirin treatment. *Hypertension* 2013; 61:662-668
- [73] van Dijk M, Oudejans CB. STOX1: Key player in trophoblast dysfunction underlying early onset preeclampsia with growth retardation. *J Pregnancy* 2011; 2011:521826
- [74] van Dijk M, van Bezu J, van Abel D, Dunk C, Blankenstein MA, Oudejans CB, et al. The STOX1 genotype associated with pre-eclampsia leads to a reduction of trophoblast invasion by alpha-T-catenin upregulation. *Hum Mol Genet* 2010; 19:2658-2667
- [75] Takimoto E, Ishida J, Sugiyama F, Horiguchi H, Murakami K, Fukamizu A. Hypertension induced in pregnant mice by placental renin and maternal angiotensinogen. *Science* 1996; 274:995-998
- [76] Rigó J Jr, Boze T, Derzsy Z, Derzbach L, Treszl A, Lázár L, et al. Family history of early-onset cardiovascular disorders is associated with a higher risk of severe preeclampsia. *Eur J Obstet Gynecol Reprod Biol* 2006; 128:148-151
- [77] Myklesstad K, Vatten LJ, Salvesen KÅ, Davey Smith G, Romundstad PR. Hypertensive disorders in pregnancy and paternal cardiovascular risk: a population-based study. *Ann Epidemiol* 2011; 21:407-412
- [78] Pfab T, Chen YP, Slowinski T, Richter CM, Godes M, Arck PC, et al. Impact of genes related to immune tolerance and inflammation (tumour necrosis factor-alpha, interleukin-6)

on blood pressure, protein excretion and oedema in pregnancy. *J Hypertens* 2005; 23:2187-2191

[79] Triche EW, Harland KK, Field EH, Rubenstein LM, Saftlas AF. Maternal-fetal HLA sharing and preeclampsia: variation in effects by seminal fluid exposure in a case-control study of nulliparous women in Iowa. *J Reprod Immunol* 2013. doi: pii: S0165-0378(13)00081-8

[80] Hiby SE, Walker JJ, O'Shaughnessy KM, Redman CW, Carrington M, Trowsdale J, Moffett A. Combinations of maternal KIR and fetal HLA-C genes influence the risk of preeclampsia and reproductive success. *J Exp Med* 2004; 200:957-965

[81] Saito S, Takeda Y, Sakai M, Nakabayahi M, Hayakawa S. The incidence of pre-eclampsia among couples consisting of Japanese women and Caucasian men. *J Reprod Immunol* 2006; 70:93-98

[82] Caughey AB, Stotland NE, Washington AE, Escobar GJ. Maternal ethnicity, paternal ethnicity, and parental ethnic discordance: predictors of preeclampsia. *Obstet Gynecol* 2005; 106:156-161

[83] Moffett A, Hiby S, Carrington M. The incidence of pre-eclampsia among couples consisting of Japanese women and Caucasian men (letter). *J Reprod Immunol* 2006; 71:132-133

[84] Saito S, Sakai M. The incidence of pre-eclampsia among couples consisting of Japanese women and Caucasian men (letter). *J Reprod Immunol* 2006; 71:134

[85] Robillard PY, Dekker G, Chaouat G, Hulsey TC, Saftlas A. Epidemiological studies on primipaternity and immunology in preeclampsia - a statement after twelve years of workshops. *J Reprod Immunol* 2011; 89:104-17

[86] Xiong X, Demianczuk NN, Buekens P, Saunders LD. Association of preeclampsia with high birth weight for age. *Am J Obstet Gynecol* 2000; 183:148-155

- [87] Luo ZC, Simonet F, An N, Bao FY, Audibert F, Fraser WD. Effect on neonatal outcomes in gestational hypertension in twin compared with singleton pregnancies. *Obstet Gynecol* 2006; 108:1138-1144
- [88] Stella CL, O'Brien JM, Forrester KJ, Barton JR, Istwan N, Rhea D, et al. The coexistence of gestational hypertension and diabetes: influence on pregnancy outcome. *Am J Perinatol* 2008; 25:325-329
- [89] Naeye RL. Maternal blood pressure and fetal growth. *Am J Obstet Gynecol* 1981; 141:780-787
- [90] Steer PJ, Little MP, Kold-Jensen T, Chapple J, Elliott P. Maternal blood pressure in pregnancy, birth weight, and perinatal mortality in first births: prospective study. *BMJ* 2004; 329:1312
- [91] Bakker R, Steegers EA, Hofman A, Jaddoe VW. Blood pressure in different gestational trimesters, fetal growth, and the risk of adverse birth outcomes: the generation R study. *Am J Epidemiol* 2011; 174:797-806
- [92] Kawafuji A, Suda N, Ichikawa N, Kakara S, Suzuki T, Baba Y, et al. Systemic and maxillofacial characteristics of patients with Beckwith-Wiedemann syndrome not treated with glossectomy. *Am J Orthod Dentofacial Orthop* 2011; 139:517-525
- [93] Nielsen EM, Hansen L, Stissing T, Yanagisawa K, Borch-Johnsen K, Poulsen P, et al. Studies of variations of the cyclin-dependent kinase inhibitor 1C and the cyclin-dependent kinase 4 genes in relation to type 2 diabetes mellitus and related quantitative traits. *J Mol Med (Berl)* 2005; 83:353-361
- [94] Tunster SJ, Van de Pette M, John RM. Fetal overgrowth in the Cdkn1c mouse model of Beckwith-Wiedemann syndrome. *Dis Model Mech* 2011; 4:814-821

- [95] Murrell A, Heeson S, Cooper WN, Douglas E, Apostolidou S, Moore GE, et al. An association between variants in the IGF2 gene and Beckwith-Wiedemann syndrome: interaction between genotype and epigenotype. *Hum Mol Genet* 2004; 13:247-255
- [96] Dunger DB, Petry CJ, Ong KK. Genetics of size at birth. *Diabetes Care* 2007; 30 (suppl 2):S150-S155
- [97] Myrelid A, Gustafsson J, Ollars B, Annerén G. Growth charts for Down's syndrome from birth to 18 years of age. *Arch Dis Child* 2002; 87:97-103
- [98] Bahado-Singh RO, Lynch L, Deren O, Morroti R, Copel JA, et al. First-trimester growth restriction and fetal aneuploidy: the effect of type of aneuploidy and gestational age. *Am J Obstet Gynecol* 1997; 176:976-980
- [99] Boghossian NS, Horbar JD, Murray JC, Carpenter JH; Vermont Oxford Network. Anthropometric charts for infants with trisomies 21, 18, or 13 born between 22 weeks gestation and term: the VON charts. *Am J Med Genet A* 2012; 158A:322-332
- [100] Schlemm L, Haumann HM, Ziegner M, Stirnberg B, Sohn A, Alter M, et al. New evidence for the fetal insulin hypothesis: fetal angiotensinogen M235T polymorphism is associated with birth weight and elevated fetal total glycated hemoglobin at birth. *J Hypertens* 2010; 28:732-739
- [101] Pfab T, Stirnberg B, Sohn A, Krause K, Slowinski T, Godes M, et al. Impact of maternal angiotensinogen M235T polymorphism and angiotensin-converting enzyme insertion/deletion polymorphism on blood pressure, protein excretion and fetal outcome in pregnancy. *J Hypertens* 2007; 25:1255-1261
- [102] Abu-Amero S, Monk D, Apostolidou S, Stanier P, Moore G. Imprinted genes and their role in human fetal growth. *Cytogenet Genome Res* 2006; 113:262-270

- [103] Frost JM, Moore GE. The importance of imprinting in the human placenta. *PLoS Genet* 2010; 6:e1001015
- [104] Haig D, Westoby M. Parent-specific gene expression and the triploid endosperm. *Amer Natur* 1989; 134:147–155
- [105] Trivers RL. Parent-offspring conflict. *Amer Zool* 1974; 14: 249–264
- [106] Haig D. Genetic conflicts in human pregnancy. *Q Rev Biol* 1993; 68:495-553
- [107] Reik W, Constância M, Fowden A, Anderson N, Dean W, Ferguson-Smith A, et al. Regulation of supply and demand for maternal nutrients in mammals by imprinted genes. *J Physiol* 2003; 547:35-44
- [108] Haig D. Placental hormones, genomic imprinting, and maternal–foetal communication. *J Evol Biol* 1996; 9:357–380
- [109] Petry CJ. Gestational diabetes: risk factors and recent advances in its genetics and treatment. *Br J Nutr* 2010; 104:775-787
- [110] Hollegaard B, Byars SG, Lykke J, Boomsma JJ. Parent-offspring conflict and the persistence of pregnancy-induced hypertension in modern humans. *PLoS One* 2013; 8:e56821

Tables

Table 1 Estimates of genetic and environmental factors for gestational hypertension, pre-eclampsia and pregnancy-induced hypertension as a whole among female twins who were born before 1959 and who gave birth in Sweden between 1973 and 1993 [1]. Used with permission, copyright © 2000 Wiley-Liss, Inc.

<i>Measured</i>	<i>Parameter Estimates</i>			<i>Fit of Model^b</i>		
	<i>(95% CI)^a</i>			<i>χ²</i>	<i>df</i>	<i>P</i>
Pre-eclampsia	0.54	0	0.46	2.42	3	0.49
	(0~0.71)	(0~0.47)	(0.29~0.67)			
Gestational hypertension	0.24	0	0.76	6.81	3	0.08
	(0~0.53)	(0~0.33)	(0.47~1.00)			
Pregnancy-induced hypertension	0.47	0	0.53	28.50	25	0.28
	(0.13~0.61)	(0~0.26)	(0.39~0.69)			

95% CI = 95% confidence interval.

^a h^2 = heritability, c^2 = shared environment, e^2 = non-shared environment.

^b χ^2 = chi-squared, df = degrees of freedom, P = probability.

Table 2 The prevalence and odds ratios of maternal complications during pregnancy in probands with Beckwith Wiedemann syndrome [36]. Used with permission, copyright © 2005 Wiley-Liss, Inc.

Complication	Prevalence in Beckwith Wiedemann Group	Odds Ratio (95% CI)
Preterm delivery (< 38 weeks)	39.4 (109 of 277)	19.1 (9.1~40.2)
Delivery before 34 weeks	16.0 (43 of 268)	43.1 (5.9~316.3)
Polyhydramnios	40.0 (110 of 275)	31.6 (12.6~79.1)
Gestational hypertension	17.7 (49 of 277)	2.4 (1.4~4.1)
Proteinuria and hypertension	8.7 (24 of 277)	5.7 (1.9~16.6)
Vaginal bleeding	27.8 (77 of 277)	3.9 (2.3~6.4)
Gestational diabetes	5.1 (14 of 276)	2.1 (0.8~5.6)
Maternal infection	14.8 (41 of 277)	1.7 (0.96~2.8)
Caesarean birth	43.7 (121 of 277)	2.2 (1.5~3.2)
Preterm delivery without polyhydramnios, bleeding or hypertension	6.5 (18 of 277)	8.6 (3.1~24.0)

95% CI = 95% confidence interval.